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Insulin for the treatment of women with gestational diabetes (Review)

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[Intervention Review]

Insulin for the treatment of women with gestational diabetes

Julie Brown[1], Luke Grzeskowiak[2], Kathryn Williamson[3], Michelle R Downie[4], Caroline A Crowther[1,5]

[1]Liggins Institute, The University of Auckland, Auckland, New Zealand. [2]Adelaide Medical School, Robinson Research Institute, University of Adelaide, Adelaide, Australia. [3]Department of Paediatrics, University of Auckland, Auckland, New Zealand. [4]Department of Medicine, Southland Hospital, Invercargill, New Zealand. [5]ARCH: Australian Research Centre for Health of Women and Babies, Robinson Research Institute, Discipline of Obstetrics and Gynaecology, The University of Adelaide, Adelaide, Australia

Contact address: Julie Brown, Liggins Institute, The University of Auckland, Park Rd, Grafton, Auckland, 1142, New Zealand. j.brown@auckland.ac.nz.

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ABSTRACT

Background

Gestational diabetes mellitus (GDM) is associated with short- and long-term complications for the mother and her infant. Women who are unable to maintain their blood glucose concentration within pre-specified treatment targets with diet and lifestyle interventions will require anti-diabetic pharmacological therapies. This review explores the safety and effectiveness of insulin compared with oral anti-diabetic pharmacological therapies, non-pharmacological interventions and insulin regimens.

Objectives

To evaluate the effects of insulin in treating women with gestational diabetes.

Search methods

We searched Pregnancy and Childbirth's Trials Register (1 May 2017), ClinicalTrials.gov, WHO International Clinical Trials Registry Platform (ICTRP) (1 May 2017) and reference lists of retrieved studies.

Selection criteria

We included randomised controlled trials (including those published in abstract form) comparing:

a) insulin with an oral anti-diabetic pharmacological therapy;

b) with a non-pharmacological intervention;

c) different insulin analogues;

d) different insulin regimens for treating women with diagnosed with GDM.

We excluded quasi-randomised and trials including women with pre-existing type 1 or type 2 diabetes. Cross-over trials were not eligible for inclusion.

Data collection and analysis

Two review authors independently assessed study eligibility, risk of bias, and extracted data. Data were checked for accuracy.

Main results

We included 53 relevant studies (103 publications), reporting data for 7381 women. Forty-six of these studies reported data for 6435 infants but our analyses were based on fewer number of studies/participants.

Overall, the risk of bias was unclear; 40 of the 53 included trials were not blinded. Overall, the quality of the evidence ranged from *moderate to very low quality*. The primary reasons for downgrading evidence were imprecision, risk of bias and inconsistency. We report the results for our maternal and infant GRADE outcomes for the main comparison.

Insulin versus oral anti-diabetic pharmacological therapy

For the mother, insulin was associated with an increased risk for **hypertensive disorders of pregnancy (not defined)** compared to oral anti-diabetic pharmacological therapy (risk ratio (RR) 1.89, 95% confidence interval (CI) 1.14 to 3.12; four studies, 1214 women; *moderate-quality evidence)*. There was no clear evidence of a difference between those who had been treated with insulin and those who had been treated with an oral anti-diabetic pharmacological therapy for the risk of **pre-eclampsia** (RR 1.14, 95% CI 0.86 to 1.52; 10 studies, 2060 women; *moderate-quality evidence*); the risk of birth by **caesarean section** (RR 1.03, 95% CI 0.93 to 1.14; 17 studies, 1988 women; *moderate-quality evidence*); or the risk of **developing type 2 diabetes** (metformin only) (RR 1.39, 95% CI 0.80 to 2.44; two studies, 754 women; *moderate-quality evidence*). The risk of undergoing **induction of labour** for those treated with insulin compared with oral anti-diabetic pharmacological therapy may possibly be increased, although the evidence was not clear (average RR 1.30, 95% CI 0.96 to 1.75; three studies, 348 women; I^2 = 32%; *moderate-quality of evidence*). There was no clear evidence of difference in **postnatal weight retention** between women treated with insulin and those treated with oral anti-diabetic pharmacological therapy (metformin) at six to eight weeks postpartum (MD -1.60 kg, 95% CI -6.34 to 3.14; one study, 167 women; *low-quality evidence*) or one year postpartum (MD -3.70, 95% CI -8.50 to 1.10; one study, 176 women; *low-quality evidence*). The outcomes of perineal trauma/ tearing or postnatal depression were not reported in the included studies.

For the infant, there was no evidence of a clear difference between those whose mothers had been treated with insulin and those treated with oral anti-diabetic pharmacological therapies for the risk of being born **large-for-gestational age** (average RR 1.01, 95% CI 0.76 to 1.35; 13 studies, 2352 infants; *moderate-quality evidence*); the risk of **perinatal (fetal and neonatal death) mortality** (RR 0.85; 95% CI 0.29 to 2.49; 10 studies, 1463 infants; *low-quality evidence*);, for the risk of **death or serious morbidity composite** (RR 1.03, 95% CI 0.84 to 1.26; two studies, 760 infants; *moderate-quality evidence*); the risk of **neonatal hypoglycaemia** (average RR 1.14, 95% CI 0.85 to 1.52; 24 studies, 3892 infants; *low-quality evidence*); **neonatal adiposity at birth (% fat mass)** (mean difference (MD) 1.6%, 95% CI -3.77 to 0.57; one study, 82 infants; *moderate-quality evidence*); **neonatal adiposity at birth (skinfold sum/mm)** (MD 0.8 mm, 95% CI -2.33 to 0.73; random-effects; one study, 82 infants; *very low-quality evidence*); or **childhood adiposity (total percentage fat mass)** (MD 0.5%; 95% CI -0.49 to 1.49; one study, 318 children; *low-quality evidence*). Low-quality evidence also found no clear differences between groups for rates of **neurosensory disabilities in later childhood**: hearing impairment (RR 0.31, 95% CI 0.01 to 7.49; one study, 93 children), visual impairment (RR 0.31, 95% CI 0.03 to 2.90; one study, 93 children), or any mild developmental delay (RR 1.07, 95% CI 0.33 to 3.44; one study, 93 children). Later infant mortality, and childhood diabetes were not reported as outcomes in the included studies.

We also looked at comparisons for regular human insulin versus other insulin analogues, insulin versus diet/standard care, insulin versus exercise and comparisons of insulin regimens, however there was insufficient evidence to determine any differences for many of the key health outcomes. Please refer to the main results for more information about these comparisons.

Authors' conclusions

The main comparison in this review is insulin versus oral anti-diabetic pharmacological therapies. Insulin and oral anti-diabetic pharmacological therapies have similar effects on key health outcomes. The quality of the evidence ranged from very low to moderate, with downgrading decisions due to imprecision, risk of bias and inconsistency.

For the other comparisons of this review (insulin compared with non-pharmacological interventions, different insulin analogies or different insulin regimens), there is insufficient volume of high-quality evidence to determine differences for key health outcomes.

Long-term maternal and neonatal outcomes were poorly reported for all comparisons.

The evidence suggests that there are minimal harms associated with the effects of treatment with either insulin or oral anti-diabetic pharmacological therapies. The choice to use one or the other may be down to physician or maternal preference, availability or severity of GDM. Further research is needed to explore optimal insulin regimens. Further research could aim to report data for standardised GDM outcomes.

PLAIN LANGUAGE SUMMARY

Insulin for the treatment of women with gestational diabetes

What is the issue?

The aim of this Cochrane review was to find out the effectiveness and safety of insulin compared with oral medication or non-pharmacological interventions for the treatment of gestational diabetes mellitus (GDM, which is diabetes diagnosed in pregnancy). It also looked at different timings for taking insulin during the day. We collected all the relevant studies (May 2017) and analysed the data.

Why is this important?

GDM can lead to both short- and long-term complications for the mother and her baby.

Usually, diet and lifestyle advice is the first step, and women whose blood glucose remains too high may be treated with insulin, which is normally injected every day.

Finding out if other treatment options are as safe and effective as insulin, is important, as these other treatments may be preferred by women who do not want to inject themselves with insulin.

What evidence did we find?

We searched for evidence on 1 May 2017 and found 53 studies reporting data for 7381 mothers and 46 studies reported data for 6435 babies. Overall, the quality of the evidence ranged from very low to moderate. Studies were undertaken in a variety of countries, including low-, middle- and high-income countries. Three studies reported that financial support or drugs had been provided by a pharmaceutical company and 36 studies did not provide any statement about the source of funding.

For mothers with GDM, insulin was associated with an increased likelihood of hypertensive disorders of pregnancy (high blood pressure - not defined) although there was no evidence of any difference in pre-eclampsia (high blood pressure, swelling and protein in the urine), birth by caesarean section, developing type 2 diabetes, or postnatal weight when women who had been treated with insulin were compared with women who had been treated with oral anti-diabetic medication.

Insulin appeared to possibly increase the likelihood of induction of labour, when compared with oral anti-diabetic medication but these results are unclear. Damage to the perineum, return to pre-pregnancy weight or postnatal depression were not reported by the included studies. For the baby, there was no evidence of a clear difference between groups in the risk of being born large-for-gestational age, death or serious illness after birth, low blood sugar, being overweight as a baby or as a child, having a hearing or visual impairment, or mild developmental delay at 18 months. None of the included studies looked at the baby's health in childhood.

We also looked at comparisons for regular human insulin versus other insulin types, insulin versus dietary advice with standard care, insulin versus exercise, and we also looked at comparisons of different insulin dosages and frequency. However, there was not enough evidence for us to be certain of any differences for many of the key health outcomes.

What does this mean?

The available evidence suggests that there are very few differences in short-term outcomes for the mother and baby between treatment with injected insulin and treatment with oral medication. There is not enough evidence yet for the long-term outcomes. Decisions about which treatment to use could be based on discussions between the doctor and the mother. Further research is needed to explore optimal insulin regimens for women with GDM. Future studies could aim to report long-term as well short-term outcomes for mothers and their babies.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Insulin compared to anti-diabetic agent for the treatment of women with gestational diabetes (maternal outcomes)

Patient or population: the treatment of women (maternal outcomes) with gestational diabetes
Setting: primary and secondary care (Canada, Egypt, USA, Brazil, Finland, Iran, Australia, New Zealand, India)
Intervention: Insulin
Comparison: Oral anti-diabetic pharmacological therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with oral anti-diabetic agent	Risk with insulin				
Hypertensive disorders of pregnancy (pre-eclampsia)	77 per 1000	88 per 1000 (66 to 117)	RR 1.14 (0.86 to 1.52)	2060 (10 RCTs)	⊕⊕⊕◯ MODERATE [1]	No data were reported for eclampsia
Hypertensive disorders of pregnancy (not defined)	36 per 1000	69 per 1000 (42 to 114)	RR 1.89 (1.14 to 3.12)	1214 (4 RCTs)	⊕⊕⊕◯ MODERATE [1]	There were no definitions for hypertensive disorders in pregnancy in the trials reporting this outcome
Caesarean section	394 per 1000	405 per 1000 (366 to 449)	RR 1.03 (0.93 to 1.14)	1988 (17 RCTs)	⊕⊕⊕◯ MODERATE [1]	
Development of type 2 diabetes	52 per 1000	73 per 1000 (42 to 128)	RR 1.39 (0.80 to 2.44)	754 (2 RCTs)	⊕⊕⊕◯ MODERATE [2]	These 2 trials compared insulin with metformin. No other trials reported this long-term outcome

Perineal trauma/tearing - not measured	-	-	-	-	-	None of the included trials in this review prespecified or reported perineal trauma as an outcome
Postnatal weight retention or return to pre-pregnancy weight - Maternal weight six to eight weeks postpartum - Maternal weight one year postpartum	The mean weight at six to eight weeks postpartum was 80.8 kg The mean weight at one year postpartum was 81.8 kg	MD 1.6 kg lower (6.34 lower to 3.14 higher) MD 3.7 kg lower (8.5 lower to 1.1 higher)	MD 1.60 kg (-6.34 to 3.14) MD 3.70 kg (-8.50 to 1.10)	167 (1 RCT) 176 (1 RCT)	⊕⊕◯◯[2,3] LOW ⊕⊕◯◯[2,3] LOW	
Postnatal depression - not reported	-	-	-	-	-	None of the included trials in this review prespecified or reported postnatal depression as an outcome
Induction of labour	408 per 1000	535 per 1000 (424 to 669)	average RR 1.30, 95%CI 0.96,to 1.75	348 (3 RCTs)	⊕⊕⊕◯ MODERATE [2]	These 3 trials compared insulin with metformin. No other trials reported this outcome

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** mean difference; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Risk of bias: Most of the trials were not blinded - downgraded one level.

[2] Risk of bias: No blinding. Lacked methodological details to be able to judge randomisation or allocation concealment - downgraded one level.

[3] Imprecision: Wide confidence intervals and single study - downgraded one level.

BACKGROUND

The original review by Alwan 2009 has been split into three new reviews due to the complexity of the included interventions. The new review protocols include the following.

Lifestyle interventions for the treatment of women with gestational diabetes (Brown 2017a)

Oral anti-diabetic pharmacological therapies for the treatment of women with gestational diabetes (Brown 2017b)

Insulin for the treatment of women with gestational diabetes (this review).

There will be similarities in the background, methods and outcomes between these three systematic reviews. Portions of the methods section of this protocol are based on a standard template used by Cochrane Pregnancy and Childbirth.

Description of the condition

Gestational diabetes mellitus (GDM), often referred to as gestational diabetes can be defined as 'glucose intolerance or hyperglycaemia (high blood glucose concentration) with onset or first recognition during pregnancy' (WHO 1999). GDM occurs when the body is unable to make enough insulin to meet the extra needs in pregnancy. The high blood sugars associated with GDM will usually return to normal after the birth of the baby. However, there is currently no universally accepted diagnostic criteria (ACOG 2013; ADA 2013, Coustan 2010; HAPO 2008; Hoffman 1998; IADPSG 2010; Metzger 1998; NICE 2015) (Table 1). GDM may include previously undetected type 1 diabetes, type 2 diabetes, or diabetes presenting only during pregnancy depending on when the timing of when diagnosis is made (HAPO 2008; IADPSG 2010; Metzger 1998; Nankervis 2014; WHO 2014).

GDM is one of the most common pregnancy complications and the prevalence is rising worldwide with 1% to 36% of pregnancies being affected (Bottalico 2007; Cundy 2014; Duran 2014; Ferrara 2007; NICE 2015; Tran 2013). The prevalence of GDM is likely to continue to increase along with the increasing prevalence of maternal obesity and associated type 2 diabetes mellitus (Bottalico 2007; Mulla 2010; Petry 2010).

Screening and diagnosis of GDM

Regardless of whether universal or selective (risk factor) screening with a 50 gram (g) oral glucose challenge test is used, diagnosis of GDM is usually based on either a 75 g two-hour oral glucose tolerance test (OGTT) or a 100 g three-hour OGTT performed between 24 and 28 weeks' gestation (ADA 2013; IADPSG 2010; Nankervis 2014; NICE 2015; WHO 1999). Recommendations regarding diagnostic criteria vary nationally and internationally (Table 1), and these diagnostic criteria have changed over time, sometimes due to changing understanding about the effects of hyperglycaemia on pregnancy and infant outcomes (Coustan 2010), but also because of a lack of evidence clearly demonstrating the clinical and cost-effectiveness of one criterion over another.

The Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) study (HAPO 2008) was a large, international observational study which reported graded linear associations in the odds of several GDM-associated adverse outcomes and glucose levels at OGTT, with no clear threshold identified at which risk increased substantially. The International Association of the Diabetes and Pregnancy Study Groups (IADPSG) recommended diagnostic criteria using data from the HAPO study (IADPSG 2010). Applying the IADPSG criteria in most health environments will increase the number of women diagnosed with GDM. A study conducted in Vietnam showed that depending on the criteria used, the diagnosis of GDM varied between 5.9% (American Diabetes Association - ADA), 20.4% (International Association of Diabetes in Pregnancy Study Groups - IADPSG), 20.8% (Australasian Diabetes in Pregnancy Society - ADIPS), and up to 24.3% (World Health Organization - WHO) (Tran 2013). A Bulgarian study also reported differences in prevalence based on the diagnostic criteria ranging from 10.8% (European Association for the Study of Diabetes - EASD), 13.5% (ADA), 16.2% (New Zealand Society for the Study of Diabetes - NZSSD), 17.1% (WHO), 21.2% (ADIPS), 31.6% (IADPSG) (Boyadzhieva 2012).

Pathophysiology of GDM

Normal pregnancy is associated with significant changes in maternal metabolism (Lain 2007). In early pregnancy, oestrogen and progesterone stimulate maternal beta-cell hyperplasia and insulin secretion, which promotes maternal nutrient storage (adipose and hepatic glycogen) to support later fetal growth. At this stage, insulin sensitivity is maintained or may even increase. However, as pregnancy progresses whole-body insulin sensitivity steadily decreases, such that by the third trimester it is reduced by almost half (Barbour 2007). Several factors contribute to this, including placental hormones (human placental lactogen and placental growth hormone), cytokines released from adipocytes (IL-6, TNF-alpha), increased free fatty acids and lower adiponectin concentrations (Clapp 2006; Devlieger 2008). This results in decreased postprandial peripheral glucose disposal by up to 40% to 60% (Barbour 2007). In normal pregnancy, maternal glycaemia is maintained by a significant increase in insulin secretion of up to 200% to 250% (Barbour 2007; Lain 2007; Suman Rao 2013).

Regulation of fetal glucose metabolism requires (1) the maintenance of maternal glucose concentration through increasing maternal glucose production and at the same time developing maternal glucose intolerance and insulin resistance, (2) transfer of glucose to the fetus across the placenta, and (3) production of fetal insulin and uptake of glucose into adipose tissue and skeletal muscle (Suman Rao 2013).

Women with GDM have further reductions in insulin signalling and glucose uptake is decreased beyond that of normal pregnancy (Barbour 2007). This results in glucose intolerance, though glycaemia in pregnancy represents a continuum. In GDM, the steeper maternal-fetal glucose gradient, especially postprandial, leads to increased fetal glucose uptake, which stimulates fetal insulin secretion. Insulin is a key fetal anabolic hormone and hyperinsulinaemia promotes fetal overgrowth leading to large-for-gestational age (LGA) infants, macrosomia, and possible organ damage (Catalano 2003; Ju 2008; Metzger 2008; Reece 2009).

Women with GDM also have increased circulating inflammatory cytokines and lower adiponectin concentrations leading to increased lipolysis and fatty acid concentrations. Placental transfer of free fatty acids contributes to increased fetal adiposity, independent of glucose uptake (Knopp 1985). Thus, even women with well-controlled GDM still have increased risk of fetal macrosomia (Langer 2005).

Risk factors associated with GDM

A variety of factors have been associated with an increased risk of developing GDM. Non-modifiable risk factors include advanced maternal age (Chamberlain 2013; Morisset 2010), high parity, non-Caucasian race or ethnicity (in particular South Asian, Middle Eastern), family history of diabetes mellitus, maternal high or low birthweight, polycystic ovarian syndrome (Cypryk 2008; Petry 2010; Solomon 1997), a history of having a previous macrosomic infant (birthweight 4000 g or more), and a previous history of GDM (Petry 2010).

Modifiable risk factors include physical inactivity (Chasan-Taber 2008), having a low-fibre and high-glycaemic load diet (Zhang 2006), maternal overweight (body mass index (BMI) equal to or greater than 25 kg/m^2) or obesity (equal to or greater than 30 kg/m^2) (Kim S 2010), and excessive weight gain during pregnancy, especially for those who are already overweight or obese (Hedderson 2010).

Clinical outcomes for women with pregnancy hyperglycaemia

Adverse outcomes have been consistently reported at higher rates in women diagnosed with GDM and their infants compared to women without GDM (Crowther 2005; Landon 2009; Metzger 2008; Reece 2009).

Women with GDM have an increased risk of developing pre-eclampsia, are more likely to have their labour induced (Anderberg 2010; Crowther 2005; Ju 2008; Landon 2009; Metzger 2008), and are more likely to give birth by caesarean section (Landon 2009; Metzger 2008). The incidence of uterine rupture, shoulder dystocia and perineal lacerations is increased in women with GDM due to the increased likelihood of having a LGA or macrosomic baby (Jastrow 2010). Women who have experienced GDM are at a greater risk of metabolic dysfunction in later life (Shah 2008; Vohr 2008), with a crude cumulative incidence of type 2 diabetes of 10% to 20% within 10 years (Bellamy 2009; Kim 2002), but up to 50% when adjusted for retention and length of follow-up (Kim 2002).

Neonatal, infant and later outcomes related to pregnancy hyperglycaemia

A significant adverse health outcome for babies born to mothers with GDM is being born LGA or macrosomic (Catalano 2003; Crowther 2005; Landon 2009; Metzger 2008; Reece 2009). LGA or macrosomic infants are at increased risk of birth injury, such as shoulder dystocia, perinatal asphyxia, bone fractures and nerve palsies (Esakoff 2009; Henriksen 2008; Langer 2005; Metzger 2008).

Babies born to women with GDM, compared with babies born to women without GDM, have significantly greater skinfold measures and fat mass compared with infants of women with normal glucose tolerance (Catalano 2003). The offspring of women with GDM are heavier (adjusted for height) and have greater adiposity than the offspring of women with normal glycaemia during pregnancy (Pettitt 1985; Pettitt 1993) and are more likely to develop early overweight or obesity, type 2 diabetes (Hillier 2007; Pettitt 1993; Whincup 2008) or metabolic syndrome (a cluster of risk factors defined by the occurrence of three of the following: obesity, hypertension, hypertriglyceridaemia and a low concentration of high-density lipoprotein (HDL) cholesterol) in childhood, adolescence or adulthood (Guerrero-Romero 2010; Harder 2009).

The development of the metabolic syndrome during childhood is a risk factor for the development of adult type 2 diabetes at 25 to 30 years of age (Morrison 2008). These health problems repeat across generations (Dabelea 2005; Mulla 2010) and are important from a public health perspective, because with each generation the prevalence of diabetes increases. Other adverse outcomes which are increased for babies born to women with GDM include respiratory distress syndrome, hypoglycaemia (which if prolonged can cause brain injury), hyperbilirubinaemia, hypertrophic cardiomyopathy, hypocalcaemia, hypomagnesaemia, polycythaemia and admission to the neonatal nursery (Metzger 2008; Reece 2009).

Description of the intervention

While women with gestational diabetes still make insulin, their bodies are insensitive to it and do not produce enough insulin to maintain glycaemic control. Insulin is often the treatment of choice for women who are unable to maintain glycaemic treatment targets with medical nutrition therapy or other pharmacological therapies (NICE 2015). Insulin may be an alternative for women who are unable to tolerate the side effects (gastrointestinal upset for example) of oral anti-diabetic pharmacological therapies such as metformin. Glycaemic control is maintained by the replacement of insulin, which facilitates the transport of glucose from the

blood stream into the cells of the body for energy. Insulin in itself describes a group of heterogeneous preparations that are clinically differentiated by their course of action over time. Rapid-acting or short-acting insulin is used to mimic the response of endogenous insulin to food intake and is useful in correcting postprandial hyperglycaemia, without causing preprandial hypoglycaemia (bolus insulin) (Lambert 2013; Negrato 2012). In contrast, intermediate-acting and long-acting insulin is primarily used to provide a continuous supply of small amounts of insulin independent of food intake, over a longer period of time, which regulates lipolysis and the output of hepatic glucose (basal insulin) (Lambert 2013; Negrato 2012). At normal therapeutic doses all types of insulin do not cross the placenta (Lambert 2013; Negrato 2012).

Types of insulin used during pregnancy

Rapid-acting insulin

Insulin lispro, aspart and glulisine are commonly used rapid-acting insulin analogues. Their onset of action is within 15 minutes or less following administration. Peak concentrations are reached between 30 to 80 minutes and the maximum duration of action is between three to six hours (Lambert 2013; Negrato 2012).

Short-acting insulin

Regular human insulin - has an onset of action between 30 to 60 minutes and a time to peak concentration of 90 to 120 minutes with a maximum duration of action of five to 12 hours (Lambert 2013).

Intermediate-acting insulin

Neutral protamine Hagedorn insulin, also known as isophane insulin is a longer-acting form of regular human insulin, it has an onset of action of about 60 to 120 minutes and a time to peak action of 240 to 480 minutes. The maximum duration of action is about 16 to 18 hours (Lambert 2013).

Long-acting insulin

Insulin detemir - this analogue has an onset of action about 60 to 120 minutes after administration and action lasts for 18 to 20 hours. There is no peak of action (Negrato 2012).
Insulin glargine - this analogue has an onset of action about 60 to 120 minutes after administration and action lasts for 24 hours. There is no peak of action (Negrato 2012).
Pre-mixed insulin - contains a mixture of rapid-acting or short-acting insulin with intermediate-acting insulin. Provides a more rapid onset of action with a subsequent peak and prolonged duration of action.

Other formulations of insulin

Pharmaceutical companies are currently working on other routes of administration of insulin including inhaled and oral. These are still in early trial phases and may be available in the future. Newer analogues of ultra-long insulin are also being introduced.

Insulin regimens

As a result of the numerous types of insulin available, various regimens for insulin administration may be utilised. This may take the form of multiple injections throughout the day, or continuous administration by subcutaneous insulin infusion. The optimal insulin replacement regimen should be viewed in light of the need to provide appropriate basal insulin requirements across 24 hours, provide sufficient levels to cover food intake, have adequate provision for correction of blood glucose levels when needed, minimise blood glucose fluctuations, and therefore risk of hypoglycaemia and hyperglycaemia, and achieve optimal pregnancy outcomes. Insulin can be administered as:

- a once-daily dose which involves taking a single dose of insulin (intermediate- or long-acting insulin) each day. Individuals may also take oral anti-diabetic drugs in addition to insulin;
- a twice-daily regimen (basal-plus) which involves adding in one or two doses of rapid-acting insulin on to an intermediate or basal dose;
- a basal-bolus regimen which involves taking a long-acting or intermediate-acting dose and then separate injections of short- or rapid-acting insulin at each meal. This regimen is more common in those with type 1 diabetes. An advantage of this regimen is that it offers flexibility over timing of meals and variations based on different carbohydrate quantities in meals;
- a continuous subcutaneous infusion which involves delivery of a consistent amount of rapid-acting insulin via an insulin pump. At meal times a bolus of insulin can be delivered to maintain glycaemic control.

How the intervention might work

Insulin is a pancreatic hormone that regulates the movement of glucose from blood into cells. Insulin lowers blood glucose by stimulating peripheral glucose uptake and by inhibiting glucose production and release by the liver. Insulin inhibits lipolysis (breakdown of fat), proteolysis (breakdown of proteins), and gluconeogenesis (manufacture of glucose). It also increases protein synthesis and conversion of excess glucose into fat (Girard 2006).

Why it is important to do this review

With the rising prevalence of gestational diabetes (Bottalico 2007; Mulla 2010), it is likely that more women will require pharmacotherapy to maintain glycaemic control during their pregnancy

to reduce the associated maternal and neonatal short- and long-term effects of gestational diabetes. Adherence to medication is an important aspect of treatment for gestational diabetes (NICE 2015). Oral anti-diabetic agents may be an alternative to insulin. As more insulin analogues emerge on the market, it is important to establish their safety and efficacy for pregnant women with gestational diabetes and to identify the optimal regimen for administering insulin. This review will attempt to answer these important questions.

OBJECTIVES

To evaluate the effects of insulin in treating women with gestational diabetes.

METHODS

Criteria for considering studies for this review

Types of studies

We included published or unpublished randomised in full text or abstract format. We excluded quasi-randomised studies and cross-over trials. Cluster-randomised trials were eligible for inclusion but none were identified.

Types of participants

Participants were pregnant women diagnosed with gestational diabetes (diagnosis as defined by the individual trial). Women with type 1 or type 2 diabetes diagnosed prior to pregnancy were excluded.

Types of interventions

We considered the following interventions and comparisons.

- Insulin (any type) versus oral anti-diabetic agents
- Insulin type A versus insulin type B (e.g. rapid-acting versus short-acting; intermediate-acting versus long-acting insulin)
- Insulin (any type) versus diet/standard care
- Insulin (any type) versus exercise
- Insulin (any type) versus diet plus exercise
- Insulin regimen A versus insulin regimen B
- Insulin (any type) versus other treatment intervention not previously described

Types of outcome measures

These outcomes were identified from published Cochrane reviews of gestational diabetes, revised and selected by a group of Cochrane authors of systematic reviews related to the treatment of women with gestational diabetes. The outcomes were identified as being important to the mother, the infant and health service provision and included both short- and long-term outcomes.

Primary outcomes

Maternal

- Hypertensive disorders of pregnancy (including pre-eclampsia, pregnancy-induced hypertension, eclampsia, as defined by trialists)
- Caesarean section
- Development of type 2 diabetes (as defined by trialists, including results of postnatal testing)

Neonatal

- Perinatal (fetal and neonatal death) and later infant mortality
- Large-for-gestational age (LGA) (as defined by trialists)
- Death or serious morbidity composite (variously defined by trials, e.g. perinatal or infant death, shoulder dystocia, bone fracture or nerve palsy)
- Neurosensory disability in later childhood (as defined by trialists)

Secondary outcomes

Maternal

- Use of additional pharmacotherapy
- Maternal hypoglycaemia (as defined by trialists)
- Glycaemic control during/end of treatment (as defined by trialists)
- Weight gain in pregnancy
- Adherence to the intervention
- Induction of labour
- Placental abruption
- Postpartum haemorrhage (as defined by trialists)
- Postpartum infection
- Perineal trauma/tearing
- Breastfeeding at discharge, six weeks postpartum, six months or longer
- Maternal mortality
- Sense of well-being and quality of life
- Behavioural changes associated with the intervention
- Views of the intervention

- Relevant biomarker changes associated with the intervention (including adiponectin, free fatty acids, triglycerides, high-density lipoproteins (HDL), low-density lipoproteins (LDL), insulin)

Long-term outcomes for mother

- Postnatal depression
- Body mass index (BMI)
- Postnatal weight retention or return to pre-pregnancy weight
- Type 1 diabetes
- Type 2 diabetes
- Impaired glucose tolerance
- Cardiovascular health (as defined by trialists including blood pressure, hypertension, cardiovascular disease, metabolic syndrome)

Fetal/neonatal outcomes

- Stillbirth
- Neonatal death
- Macrosomia (greater than 4000 g; or as defined by individual study)
- Small-for-gestational age (SGA) (as defined by trialists)
- Birth trauma (shoulder dystocia, bone fracture, nerve palsy)
- Gestational age at birth
- Preterm birth (less than 37 weeks' gestation; and less than 32 weeks' gestation)
- Five-minute Apgar less than seven
- Birthweight and z score
- Head circumference and z score
- Length and z score
- Ponderal index
- Adiposity (including skinfold thickness measurements (mm); fat mass)
- Neonatal hypoglycaemia (as defined by trialists)
- Respiratory distress syndrome
- Neonatal jaundice (hyperbilirubinaemia) (as defined by trialists)
- Hypocalcaemia (as defined by trialists)
- Polycythaemia (as defined by trialists)
- Relevant biomarker changes associated with the intervention (including insulin, cord c-peptide)

Later infant/childhood outcomes

- Weight and z scores
- Height and z scores
- Head circumference and z scores
- Adiposity (including BMI, skinfold thickness, fat mass)
- Educational attainment
- Blood pressure
- Type 1 diabetes
- Type 2 diabetes
- Impaired glucose tolerance
- Dyslipidaemia or metabolic syndrome

Child as an adult outcomes

- Weight
- Height
- Adiposity (including BMI, skinfold thickness, fat mass)
- Cardiovascular health (as defined by trialists including blood pressure, hypertension, cardiovascular disease, metabolic syndrome)
- Employment, education and social status/achievement
- Dyslipidaemia or metabolic syndrome
- Type 1 diabetes
- Type 2 diabetes
- Impaired glucose tolerance

Health service use

- Number of antenatal visits or admissions
- Number of hospital or health professional visits (including midwife, obstetrician, physician, dietician, diabetic nurse)
- Admission to neonatal intensive care unit/nursery
- Duration of stay in neonatal intensive care unit or special care baby unit
- Length of antenatal stay
- Length of postnatal stay (maternal)
- Length of postnatal stay (baby)
- Cost of maternal care
- Cost of offspring care
- Costs associated with the intervention
- Costs to families associated with the management provided
- Cost of dietary monitoring (e.g. diet journals, dietician, nurse visits, etc)
- Costs to families - change of diet, extra antenatal visits
- Extra use of healthcare services (consultations, blood glucose monitoring, length and number of antenatal visits)
- Women's view of treatment advice

Search methods for identification of studies

The following methods section of this protocol were based on a standard template used by Cochrane Pregnancy and Childbirth.

Electronic searches

We searched Cochrane Pregnancy and Childbirth's Trials Register by contacting their Information Specialist (1 May 2017).
The Register is a database containing over 23,000 reports of controlled trials in the field of pregnancy and childbirth. For full search

methods used to populate Pregnancy and Childbirth's Trials Register including the detailed search strategies for CENTRAL, MEDLINE, Embase and CINAHL; the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service, please follow this link to the editorial information about the Cochrane Pregnancy and Childbirth in the Cochrane Library and select the '***Specialized Register***' section from the options on the left side of the screen.

Briefly, Cochrane Pregnancy and Childbirth's Trials Register is maintained by their Information Specialist and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. monthly searches of CINAHL (EBSCO);
5. handsearches of 30 journals and the proceedings of major conferences;
6. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Search results are screened by two people and the full text of all relevant trial reports identified through the searching activities described above is reviewed. Based on the intervention described, each trial report is assigned a number that corresponds to a specific Pregnancy and Childbirth review topic (or topics), and is then added to the Register. The Information Specialist searches the Register for each review using this topic number rather than keywords. This results in a more specific search set which has been fully accounted for in the relevant review sections (Included studies; Excluded studies; Studies awaiting classification; Ongoing studies).

In addition, we searched ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) for unpublished, planned and ongoing trial reports using search terms detailed in Appendix 1 (1 May 2017).

Searching other resources

We searched the reference lists of retrieved studies.

We did not apply any language or date restrictions.

Data collection and analysis

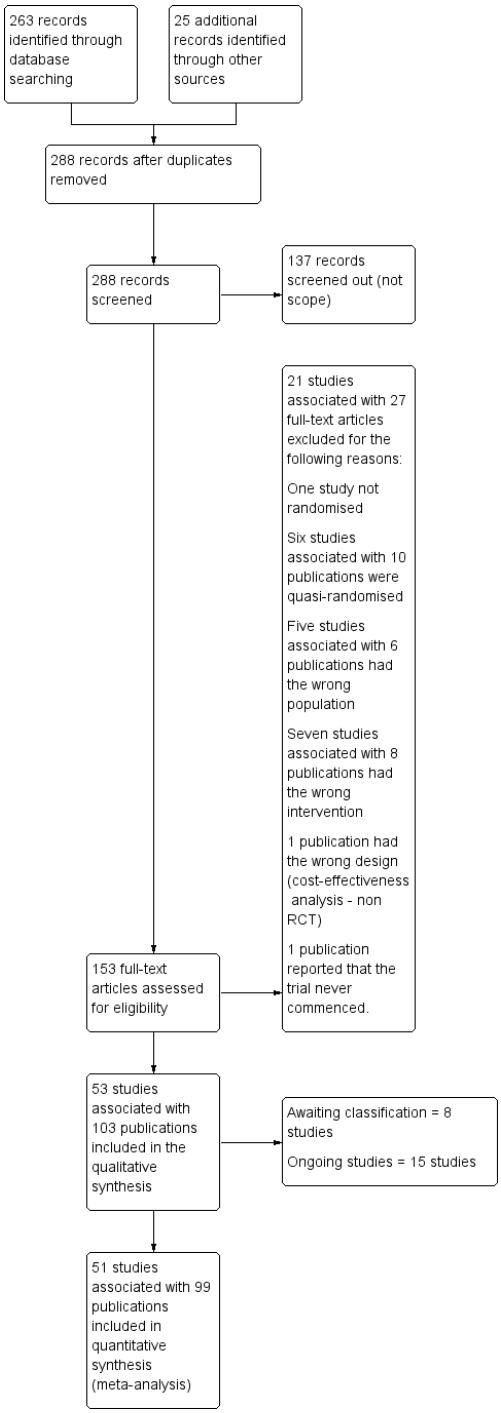
The following methods section of this protocol was based on a standard template used by Cochrane Pregnancy and Childbirth.

Selection of studies

Two review authors independently assessed for inclusion all the potential studies we identified as a result of the search strategy. We resolved any disagreement through discussion or, if required, we consulted a third person.

We created a study flow diagram to map out the number of records identified, included and excluded (Figure 1).

Figure 1. Study flow diagram.



Data extraction and management

We designed a form to extract data. For eligible studies, two review authors extracted the data using the agreed form. We resolved discrepancies through discussion or, if required, we consulted a third person. We entered data into Review Manager software (RevMan 2014) and checked for accuracy. When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreement by discussion or by involving a third assessor.

(1) Random sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.
We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.
We assessed the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at low risk of bias if they were blinded, or if we judged that the lack of blinding would be unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes. We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.
We assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we re-included missing data in the analyses which we undertook.
We assessed methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary

outcomes were not pre-specified; outcomes of interest were reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);

- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We described for each included study any important concerns we have about other possible sources of bias.

We assessed whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it was likely to impact on the findings. We explored the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Assessing the quality of the body of evidence using the GRADE approach

The quality of the evidence was assessed using the GRADE approach as outlined in the GRADE handbook in order to assess the quality of the body of evidence relating to the following outcomes. We selected a maximum of seven outcomes for the mother and seven for the infant/offspring covering both short- and long-term outcomes for the main comparisons.

Maternal outcomes

- Hypertensive disorders of pregnancy (including pre-eclampsia, pregnancy-induced hypertension, eclampsia as defined by trialists)
- Caesarean section
- Development of type 2 diabetes
- Perineal trauma/tearing
- Postnatal weight retention or return to pre-pregnancy weight
- Postnatal depression
- Induction of labour

Neonatal/child/adult outcomes

- Large-for-gestational age (LGA)
- Perinatal (fetal and neonatal death) and later infant mortality
- Death or serious morbidity composite (variously defined by trials, e.g. perinatal or infant death, shoulder dystocia, bone fracture or nerve palsy)
- Neonatal hypoglycaemia
- Adiposity (including BMI, skinfold thickness, fat mass)
- Diabetes (type 1, type 2 in childhood/adulthood)
- Neurosensory disability in later childhood (as defined by trialists)

Where data allowed we graded neonatal, child, and adult data for relevant outcomes.

We used the GRADEpro Guideline Development Tool to import data from Review Manager 5.3 (RevMan 2014) in order to create 'Summary of findings' tables. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias. A summary of the intervention effect and a measure of quality for each of the above outcomes was produced using the GRADE approach for the comparison of insulin versus oral anti-diabetic pharmacological therapies for the mother and for the infant and for the child/adult.

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we used the mean difference if outcomes are measured in the same way between trials. We used the standardised mean difference to combine trials that measure the same outcome, but used different methods.

Unit of analysis issues

Cluster-randomised trials

We did not identify any cluster-randomised trials. In future updates, if we identify any cluster-randomised trials we will include them in the analyses along with individually-randomised trials. We will make adjustments using the methods described in the *Handbook* [Section 16.3.4 or 16.3.6] using an estimate of the intra-cluster correlation co-efficient (ICC) derived from the trial (if

possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. We will consider it reasonable to combine the results from both cluster-randomised trials and individually-randomised trials if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely. If cluster-randomised trials are included, we will seek statistical advice on appropriate analysis to enable inclusion of data in the meta-analyses.

Other unit of analysis issues

Multiple pregnancy

There may be unit of analysis issues that arise when the women randomised have a multiple pregnancy. We presented maternal data as per woman randomised and neonatal data per infant.

Multiple-arm studies

Where a trial had multiple intervention arms (Bertini 2005), we avoided 'double counting' of participants by splitting the 'shared' group into two groups with smaller sample size and included two comparisons.

Dealing with missing data

For included studies, we noted levels of attrition. We explored the impact of including studies with high levels of missing data (more than 20%) in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses, and all participants were analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the Tau^2, I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if an I^2 is greater than 30% and either a Tau^2 was greater than zero, or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

If there were 10 or more studies in the meta-analysis, we investigated reporting biases (such as publication bias) using funnel plots Figure 2; Figure 3 . We assessed funnel plot asymmetry visually.

Figure 2. Funnel plot of comparison: 1 Insulin versus anti-diabetic agent, outcome: 1.3 Caesarean section.

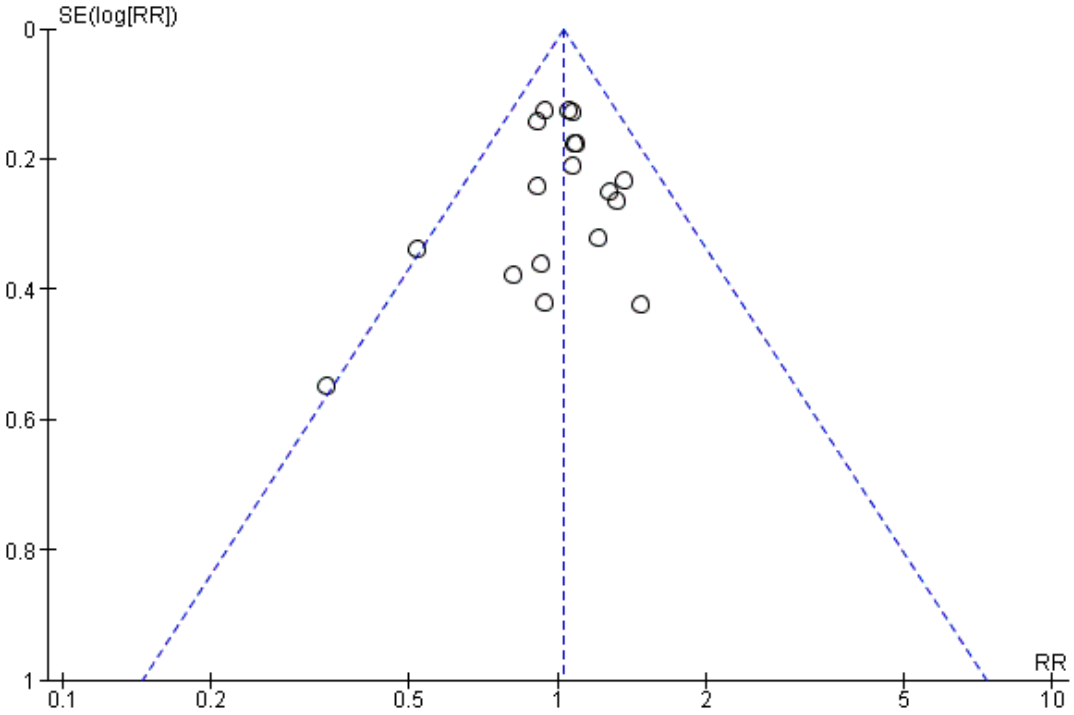
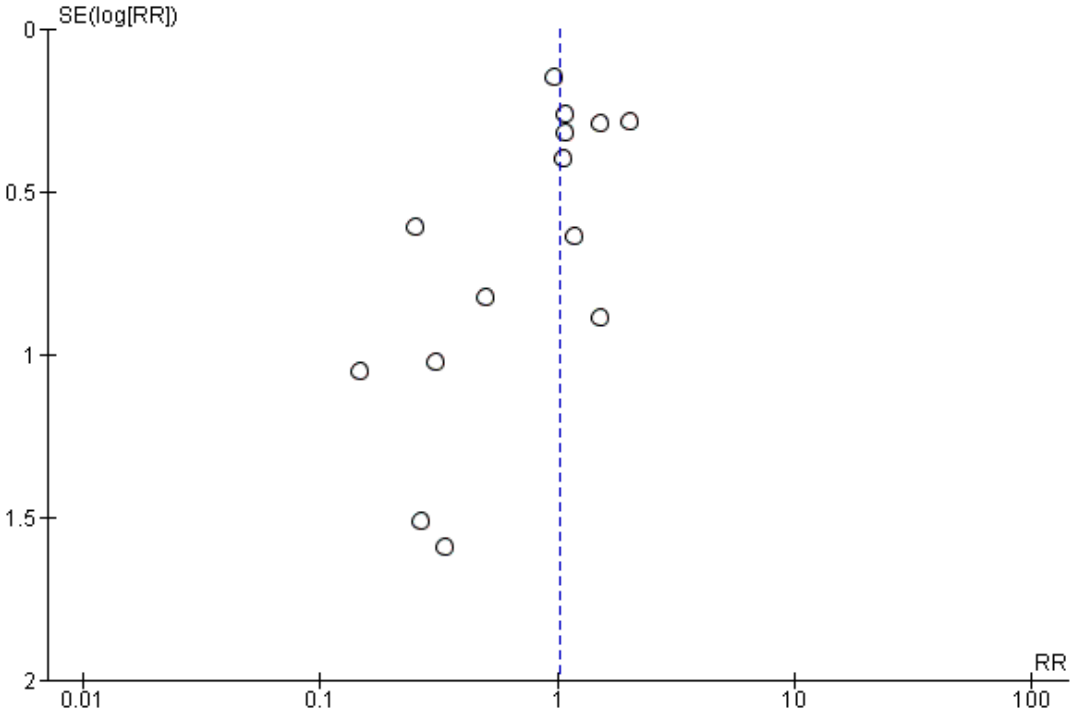


Figure 3. Funnel plot of comparison: 1 Insulin versus anti-diabetic agent, outcome: 1.6 Large-for-gestational age (Birthweight > 90th centile).



Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2014). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar. If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, we used random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials was considered clinically meaningful. The random-effects summary was treated as the average of the range of possible treatment effects and we discussed the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful, we did not combine trials.

Where we used random-effects analyses, the results were presented as the average treatment effect with 95% confidence intervals, and the estimates of Tau^2 and I^2.

Subgroup analysis and investigation of heterogeneity

Where we identified substantial heterogeneity, we investigated it using subgroup analyses and sensitivity analyses. We considered whether an overall summary was meaningful, and if it was, used random-effects analysis to produce it.

Diagnostic test used

ADA 2013, IADPSG 2010, Nankervis 2014 versus ACOG 2013 versus NICE 2008; WHO 1999; WHO 2014; Hoffman 1998 versus New Zealand Ministry of Health 2014 versus other not previously specified.

Timing of diagnosis

Early diagnosis (< 28 weeks' gestation) versus late diagnosis (≥ 28 weeks' gestation).

Comparator intervention

Metformin versus glibenclamide versus acarbose versus diet alone versus exercise alone versus diet plus exercise versus other intervention (not previously specified).
The following outcomes were used in subgroup analysis.

Maternal outcomes

- Hypertensive disorders of pregnancy (including pre-eclampsia, pregnancy-induced hypertension, eclampsia as defined by trialists)
- Caesarean section
- Development of type 2 diabetes

Neonatal outcomes

- Large-for-gestational age (LGA)
- Perinatal (fetal and neonatal death) and later infant mortality
- Death or serious morbidity composite (variously defined by trials, e.g. infant death, shoulder dystocia, bone fracture or nerve palsy)
- Neurosensory disability in later childhood (as defined by trialists)

We assessed subgroup differences by interaction tests available within RevMan (RevMan 2014). We reported the results of subgroup analyses quoting the Chi^2 statistic and P value, and the interaction test I^2 value. We were unable to look at timing of diagnosis due to insufficient details to be able to create subgroups. We did not look at differences in diagnostic criteria but have provided this detail, where reported, in Table 2. We did use comparator intervention for subgroup analysis.

Sensitivity analysis

We planned to conduct sensitivity analyses where there was substantive heterogeneity observed for the primary outcomes. We did not observe any substantive heterogeneity for the primary outcomes and therefore no sensitivity analyses were used. In future updates if we observe evidence of significant heterogeneity, we will explore this by using the quality of the included trials for the primary outcomes. We will compare trials with low risk of bias for allocation concealment with those judged to be of unclear or high risk of bias. We will exclude conference abstracts.

RESULTS

Description of studies

Results of the search

A total of 288 potential studies were identified. We assessed 153 full-text reports of 97 studies. We included 53 studies (103 reports) (Characteristics of included studies). We excluded 21 studies (27 reports) (Characteristics of excluded studies). Eight studies are awaiting classification (Characteristics of studies awaiting classification) (Afshari 2013; Dunne 2001; NCT00160485; Ibrahim 2014; Liang 2009; Shaikh 2013; Todorova 2007; Zhou 2012). There are 15 ongoing studies (Characteristics of ongoing studies).
NCT00414245 trial registration documentation states that the intervention is metformin but the comparison is not stated.
In subsequent updates of this review, we will check if these studies have been published and if they are eligible for inclusion in the review. Figure 1 illustrates the PRISMA flow diagram for this review.

Included studies

Fifty-three studies associated with 103 publications were included (Characteristics of included studies). The 53 included studies reported data for 7381 women and 46 of these studies reported data for 6435 infants (seven studies reported no neonatal data). Six studies did not contribute any data to this review (Hutchinson 2008; Martinez Piccole 2010; Notelovitz 1971; Riaz 2014; Waheed 2013; Wali 2015).

Design

All of the 53 included studies were parallel randomised controlled trials.

Sample sizes

Sample sizes ranged from a minimum of 10 (Balaji 2005) to a maximum of 733 (Rowan 2008) participants. Thirty-four studies had a sample size of 100 or less (Anjalakshi 2007; Ardilouze 2014; Ashoush 2016; Balaji 2005; Bertini 2005; Bung 1993; Castorino 2011; Coustan 1978; De Veciana 2002; Di Cianni 2007; Hague 2003; Hickman 2013; Ijas 2011; Ismail 2007; Jovanovic 1999; Lain 2009; Martinez Piccole 2010; Mecacci 2003; Mirzamoradi 2015; Mohamed 2014; Moore 2007; Mukhopadhyay 2012; Ogunyemi 2007; Pavithra 2016; Pettitt 2007; Poyhonen-Alho 2002; Prasad 2008; Ruholamin 2014; Silva 2007; Spaulonci 2013; Thompson 1990; Waheed 2013; Zangeneh 2014; Zawiejska 2016).

Setting and timing

Sixteen studies were conducted in the USA (Bung 1993; Castorino 2011; Coustan 1978; De Veciana 2002; Herrera 2015; Hickman 2013; Hutchinson 2008; Jovanovic 1999; Lain 2009; Langer 2000; Moore 2007; Ogunyemi 2007; O'Sullivan 1975a; O'Sullivan 1975b; Pettitt 2007; Thompson 1990); seven

from India (Anjalakshi 2007; Balaji 2005; Balaji 2012; Majeed 2015; Mukhopadhyay 2012; Pavithra 2016; Prasad 2008); six from Iran (Behrashi 2016; Mesdaghinia 2013; Mirzamoradi 2015; Niromanesh 2012; Ruholamin 2014; Zangeneh 2014) and three each from Egypt (Ashoush 2016; Mohamed 2014; Saleh 2016); Brazil (Bertini 2005; Silva 2007; Spaulonci 2013); Pakistan (Riaz 2014; Waheed 2013; Wali 2015); Finland (Ijas 2011; Poyhonen-Alho 2002; Tertti 2013); two from Italy (Di Cianni 2007; Mecacci 2003) and one each from Sweden (Persson 1985); Canada (Ardilouze 2014); Ghana (Beyuo 2015); Australia (Hague 2003); New Zealand and Australia (Rowan 2008); Turkey (Martinez Piccole 2010); Israel (Nachum 1999); Malaysia (Ismail 2007); South Africa (Notelovitz 1971); and Poland (Zawiejska 2016).

Thirteen studies were conducted in the 2010s (Ashoush 2016; Beyuo 2015; Herrera 2015; Majeed 2015; Mirzamoradi 2015; Mukhopadhyay 2012; Niromanesh 2012; Riaz 2014; Ruholamin 2014; Saleh 2016; Waheed 2013; Zangeneh 2014; Zawiejska 2016).

Ten studies were conducted in the 2000s (Bertini 2005; Hickman 2013; Ijas 2011; Lain 2009; Moore 2007; Ogunyemi 2007; Rowan 2008; Silva 2007; Spaulonci 2013; Tertti 2013).

Two studies were conducted in the 1990s (Mecacci 2003; Nachum 1999) and one study each in the 1990/80s (Thompson 1990); 1980s (Persson 1985); 1970s (Coustan 1978); 1960s (O'Sullivan 1975b) and 1950s (O'Sullivan 1975a).

The remaining studies provided no details on the timing of the studies (Anjalakshi 2007; Ardilouze 2014; Balaji 2005; Balaji 2012; Behrashi 2016; Bung 1993; Castorino 2011; De Veciana 2002; Di Cianni 2007; Hague 2003; Hutchinson 2008; Ismail 2007; Jovanovic 1999; Langer 2000; Martinez Piccole 2010; Mesdaghinia 2013; Mohamed 2014; Notelovitz 1971; Pavithra 2016; Pettitt 2007; Poyhonen-Alho 2002; Prasad 2008; Wali 2015).

Participants

Details including maternal age (years); ethnicity/race, maternal body mass index (BMI) at baseline (kg/m^2) and gestational age at start of intervention can be referred to in Table 3; Table 4; Table 5 and Table 6, respectively.

Diagnostic criteria for GDM

Multiple methods of diagnosing GDM were used in the included studies (Table 2).

The Carpenter and Coustan (1983) criteria were used in 12 studies (Behrashi 2016; Di Cianni 2007; Jovanovic 1999; Lain 2009; Langer 2000; Mecacci 2003; Mesdaghinia 2013; Mirzamoradi 2015; Mohamed 2014; Pavithra 2016; Niromanesh 2012; Zangeneh 2014). In the Herrera 2015 study, either the Carpenter and Coustan (1983) or IADPSG (2010) criteria could be used.

The World Health Organization (WHO) (1994) criteria were used in five studies (Anjalakshi 2007; Balaji 2012; Bertini 2005; Mukhopadhyay 2012; Silva 2007) and the American Diabetes Association (ADA) criteria were used in five studies, ADA (2012) was reported in one study (Beyuo 2015); one study used ADA (2011) (Spaulonci 2013), and three studies used earlier versions of ADA criteria (Ashoush 2016; Moore 2007; Thompson 1990).

Three studies (Hague 2003; Rowan 2008; Ruholamin 2014) used the Australian Diabetes in Pregnancy Society (Hoffman 1998) and two studies used the National Diabetes Data Group (1979) criteria (Hickman 2013; Nachum 1999).

One study reported using the Canadian Diabetes Association (CDA) criteria but no date/version was specified (Ardilouze 2014); IADPSG (2010) criteria was used in two studies (Saleh 2016; Wali 2015); one study reported using a modified O'Sullivan and Mahan criteria (Coustan 1978) and one study (Persson 1985) reported using Gillmer 1975.

Two used the Finnish National Guidelines (2008) (Poyhonen-Alho 2002; Tertti 2013).

Eighteen studies did not state the diagnostic criteria used for GDM (Balaji 2005; Bung 1993; Castorino 2011; De Veciana 2002; Hutchinson 2008; Ijas 2011; Ismail 2007; Majeed 2015; Martinez Piccole 2010; Notelovitz 1971; Ogunyemi 2007; O'Sullivan 1975a; O'Sullivan 1975b; Pettitt 2007; Prasad 2008; Riaz 2014; Waheed 2013; Zawiejska 2016).

Treatment targets

Treatment targets, where reported, are summarised in Table 7.

Interventions and comparisons

Insulin versus metformin

Nineteen studies compared insulin with metformin (Ashoush 2016; Beyuo 2015; Hague 2003; Hickman 2013; Ijas 2011; Majeed 2015; Martinez Piccole 2010; Mesdaghinia 2013; Moore 2007; Niromanesh 2012; Riaz 2014; Rowan 2008; Ruholamin 2014; Saleh 2016; Spaulonci 2013; Tertti 2013; Waheed 2013; Wali 2015; Zawiejska 2016) though four of these did not contribute data (Martinez Piccole 2010; Riaz 2014; Waheed 2013; Wali 2015).

Comparisons included the following.

- Regular insulin (no other details) Majeed 2015
- Regular human insulin plus Neutral Protamine Hagedorn insulin versus metformin (Ashoush 2016; Hickman 2013; Mesdaghinia 2013)
- Neutral Protamine Hagedorn insulin versus metformin (Niromanesh 2012; Spaulonci 2013)
- Insulin lispro plus Neutral Protamine Hagedorn insulin versus metformin (Ijas 2011)

- Insulin lispro/aspart plus Neutral Protamine Hagedorn insulin versus metformin (Tertti 2013)
- Soluble and premixed insulin (no other details) (Beyuo 2015)
- Actrapid and Mixtard versus metformin (Saleh 2016)

Nine studies did not report details on the insulin type used (Hague 2003; Martinez Piccole 2010; Moore 2007; Riaz 2014; Rowan 2008; Ruholamin 2014; Waheed 2013; Wali 2015; Zawiejska 2016).
Hickman 2013 included both women with GDM and pre-existing diabetes. The data could not be separated however as 50% of the women had GDM these data have been included. Authors have been contacted for further information.
Seven studies are ongoing (NCT01756105; IRCT2014010116025N1; CTRI/2013/10/004055; SLCTR/2011/009; CTRI/2011/08/001956; CTRI/2014/08/004835; NCT00681460). In the next update of this review we will check for publications from these studies and add data if available.

Insulin versus glibenclamide

Eleven studies compared insulin with glibenclamide (Anjalakshi 2007; Behrashi 2016; Bertini 2005; Lain 2009; Langer 2000; Mirzamoradi 2015; Mukhopadhyay 2012; Ogunyemi 2007; Pavithra 2016; Silva 2007; Zangeneh 2014).
Comparisons included the following.
- Long-acting and short-acting insulin (no details) versus glibenclamide (Lain 2009)
- Regular human insulin versus glibenclamide (Langer 2000)
- Regular human insulin plus Neutral Protamine Hagedorn insulin versus glibenclamide (Behrashi 2016; Bertini 2005; Mirzamoradi 2015; Silva 2007; Zangeneh 2014).

Four studies did not report any details on the insulin type that was used (Anjalakshi 2007; Mukhopadhyay 2012; Ogunyemi 2007; Pavithra 2016).
There are two ongoing studies (IRCT2013102315045N2; NCT01731431). In the next update of this review we will check for publications from these studies and add data if available.

Insulin versus acarbose

Two studies compared insulin with acarbose (Bertini 2005; De Veciana 2002).
Comparisons included the following.
- Regular human insulin plus Neutral Protamine Hagedorn insulin versus acarbose (Bertini 2005)
- Insulin lispro plus Neutral Protamine Hagedorn insulin versus acarbose (De Veciana 2002)

Combined metformin and glibenclamide

Three studies compared insulin with a combination of metformin and glibenclamide (Ardilouze 2014; Hutchinson 2008; Mohamed 2014). The data for Hutchinson 2008 cannot be separated out for GDM and type 2 diabetes and have not been included. Authors have been contacted.
Comparisons included the following.
- Insulin aspart or lispro plus Neutral Protamine Hagedorn insulin versus combined metformin and glibenclamide (Ardilouze 2014)
- Intermediate- and short-acting insulin (no details) versus combined metformin and glibenclamide (Mohamed 2014). This study recruited women with both GDM and type 2 diabetes and the data cannot be separated. However, 65 of the women recruited had a diagnosis of GDM and 19 with type 2 diabetes. As the majority of women have GDM (77%) we have included the data in the analyses.

One study is ongoing (NCT02080377). In the next update of this review we will check for publications from these studies and add data if available.

Insulin type A versus insulin type B

Ten studies compared one preparation of insulin with another preparation of insulin (Balaji 2005; Balaji 2012; Di Cianni 2007; Herrera 2015; Jovanovic 1999; Mecacci 2003; Ismail 2007; Pettitt 2007; Poyhonen-Alho 2002; Prasad 2008).
One ongoing study was identified (NCT01662921) that compares insulin glulisine versus insulin lispro. We will seek data for this study in subsequent updates of this review.
Comparisons included the following.
- Regular human insulin versus insulin aspart (Balaji 2005; Balaji 2012; Di Cianni 2007)
- Regular human insulin versus insulin lispro (Di Cianni 2007; Jovanovic 1999; Mecacci 2003)
- Regular human insulin versus Neutral Protamine Hagedorn insulin (Ismail 2007; Poyhonen-Alho 2002)
- Regular human insulin plus Neutral Protamine Hagedorn insulin versus insulin aspart (Prasad 2008)
- Neutral Protamine Hagedorn insulin plus regular human insulin versus Neutral Protamine Hagedorn insulin plus insulin aspart (Pettitt 2007)
- Insulin detemir plus and insulin aspart versus Neutral Protamine Hagedorn insulin and insulin aspart (Herrera 2015)

Insulin versus diet

Four studies compared insulin with diet (Coustan 1978; Notelovitz 1971; Persson 1985; Thompson 1990). One study did not provide details of the preparation of insulin that was used

(Notelovitz 1971). Two studies compared insulin (plus diet) with standard antenatal care (O'Sullivan 1975a; O'Sullivan 1975b). Coustan 1978 used regular human insulin plus Neutral Protamine Hagedorn insulin; Persson 1985 compared fast/intermediate-acting insulin (no details) with diet versus diet alone and Thompson 1990 compared regular human insulin plus Neutral Protamine Hagedorn insulin and diet with diet alone.

Insulin versus exercise

One study compared insulin with exercise (Bung 1993), the type of insulin used was not specified.

Regimens of insulin

Two studies compared different **regimens of insulin** (Castorino 2011; Nachum 1999).

One ongoing study was identified (NCT01613807) which compares three injections of Humalog® 50/50TM daily with Humalog® plus Humalin N® administered as six injections daily. In subsequent updates of this review we will seek data from this study, where possible.

Comparisons included the following.

- 50/50 combination of insulin lispro plus Neutral Protamine Hagedorn insulin given as either three pre-meal doses or as six distinct injections (Castorino 2011)
- A twice-daily regimen of human regular insulin plus human intermediate insulin with a four times daily regimen of regular human insulin (Nachum 1999)

Outcomes

Maternal primary outcomes

- Hypertensive disorders of pregnancy (any definition) was reported in 13 studies (Balaji 2012; Hague 2003; Ijas 2011; Langer 2000; Mirzamoradi 2015; Nachum 1999; Niromanesh 2012; Pavithra 2016; Rowan 2008; Saleh 2016; Spaulonci 2013; Tertti 2013; Zangeneh 2014).
- Caesarean section was reported in 25 studies (Ardilouze 2014; Ashoush 2016; Balaji 2012; Bertini 2005; Bung 1993; Castorino 2011; Coustan 1978; Hague 2003; Ijas 2011; Jovanovic 1999; Langer 2000; Mecacci 2003; Mirzamoradi 2015; Moore 2007; Nachum 1999; Niromanesh 2012; Ogunyemi 2007; Pavithra 2016; Ruholamin 2014; Saleh 2016; Silva 2007; Spaulonci 2013; Tertti 2013; Thompson 1990; Zangeneh 2014).
- Development of type 2 diabetes was reported in four studies (Coustan 1978; O'Sullivan 1975a; Rowan 2008; Tertti 2013).

Neonatal primary outcomes

- Perinatal (fetal and neonatal death) mortality was reported in 15 studies (Bertini 2005; Ijas 2011; Lain 2009; Langer 2000; Mesdaghinia 2013; Mohamed 2014; Mukhopadhyay 2012; Nachum 1999; Niromanesh 2012; O'Sullivan 1975a; O'Sullivan 1975b; Persson 1985; Silva 2007; Tertti 2013; Thompson 1990). Later infant mortality was not reported in any studies.
- Large-for-gestational age (LGA) was reported in 19 studies (Balaji 2012; Bertini 2005; Castorino 2011; Hickman 2013; Ijas 2011; Jovanovic 1999; Lain 2009; Langer 2000; Mecacci 2003; Mesdaghinia 2013; Mukhopadhyay 2012; Nachum 1999; Niromanesh 2012; Persson 1985; Rowan 2008; Saleh 2016; Silva 2007; Spaulonci 2013; Tertti 2013).
- Death or serious morbidity composite was reported in three studies (Hickman 2013; Nachum 1999; Rowan 2008).
- Neurosensory disability in later childhood was reported in one trial (Ijas 2011).

Maternal secondary outcomes

- Use of additional pharmacotherapy was reported in 23 studies (Ardilouze 2014; Ashoush 2016; Bertini 2005; Beyuo 2015; Di Cianni 2007; De Veciana 2002; Hickman 2013; Ijas 2011; Lain 2009; Langer 2000; Mecacci 2003; Mirzamoradi 2015; Moore 2007; Niromanesh 2012; Ogunyemi 2007; Pavithra 2016; Persson 1985; Poyhonen-Alho 2002; Rowan 2008; Ruholamin 2014; Silva 2007; Spaulonci 2013; Tertti 2013).
- Maternal hypoglycaemia was reported in 16 studies (Anjalakshi 2007; Ashoush 2016; Balaji 2012; Bertini 2005; Di Cianni 2007; Hickman 2013; Ismail 2007; Langer 2000; Moore 2007; Mukhopadhyay 2012; Nachum 1999; Ogunyemi 2007; Pettitt 2007; Silva 2007; Thompson 1990; Zangeneh 2014).
- Glycaemic control during/end of treatment (fasting) was reported in 25 studies (Ardilouze 2014; Ashoush 2016; Balaji 2005; Balaji 2012; Behrashi 2016; Bertini 2005; Beyuo 2015; Castorino 2011; De Veciana 2002; Herrera 2015; Lain 2009; Langer 2000; Mecacci 2003; Mirzamoradi 2015; Moore 2007; Mukhopadhyay 2012; Niromanesh 2012; Ogunyemi 2007; Pavithra 2016; Rowan 2008; Saleh 2016; Silva 2007; Spaulonci 2013;Thompson 1990; Zawiejska 2016).
- Glycaemic control during/end of treatment (postprandial) was reported in 23 studies (Anjalakshi 2007; Ardilouze 2014; Ashoush 2016; Balaji 2005; Balaji 2012; Bertini 2005; Beyuo 2015; Di Cianni 2007; De Veciana 2002; Herrera 2015; Lain 2009; Langer 2000; Mecacci 2003; Mirzamoradi 2015; Moore 2007; Mukhopadhyay 2012; Niromanesh 2012; Ogunyemi 2007; Pavithra 2016; Rowan 2008; Saleh 2016; Silva 2007; Spaulonci 2013).
- Glycaemic control during/end of treatment (HbA1c) was reported in 15 studies (Anjalakshi 2007; Balaji 2012; Castorino 2011; Jovanovic 1999; Langer 2000; Mecacci 2003;

Mesdaghinia 2013; Mohamed 2014; Mukhopadhyay 2012; Nachum 1999; Niromanesh 2012; Persson 1985; Rowan 2008; Tertti 2013; Zawiejska 2016).

- Weight gain in pregnancy was reported in 14 studies (Ashoush 2016; Balaji 2012; Bertini 2005; Coustan 1978; Herrera 2015; Ijas 2011; Langer 2000; Majeed 2015; Nachum 1999; Niromanesh 2012; Rowan 2008; Silva 2007; Spaulonci 2013; Tertti 2013).
- Induction of labour was reported in three studies (Hague 2003; Ijas 2011; Tertti 2013).
- Postpartum haemorrhage was reported in two studies (Hickman 2013; Moore 2007).
- Breastfeeding at discharge, six weeks postpartum, six months or longer was reported in two studies (Ijas 2011; Rowan 2008).
- Maternal mortality was reported in one study (Ismail 2007).
- Body mass index (BMI) was reported in one study (Rowan 2008).
- Impaired glucose tolerance was reported in three studies (Mirzamoradi 2015; Rowan 2008; Tertti 2013).
- Relevant biomarker changes associated with the intervention was reported in one study (Zawiejska 2016).

Neonatal secondary outcomes

- Stillbirth was reported in three studies (Hickman 2013; Langer 2000; Tertti 2013).
- Neonatal death was reported in three studies (Lain 2009; Langer 2000; O'Sullivan 1975a).
- Macrosomia was reported in 29 studies (Ashoush 2016; Balaji 2012; Behrashi 2016; Bertini 2005; Coustan 1978; Di Cianni 2007; Hague 2003; Hickman 2013; Ijas 2011; Ismail 2007; Lain 2009; Langer 2000; Mesdaghinia 2013; Mirzamoradi 2015; Moore 2007; Mukhopadhyay 2012; Nachum 1999; Niromanesh 2012; O'Sullivan 1975a; Pavithra 2016; Pettitt 2007; Poyhonen-Alho 2002; Prasad 2008; Ruholamin 2014; Silva 2007; Spaulonci 2013; Tertti 2013; Thompson 1990; Zangeneh 2014).
- Small-for-gestational age (SGA) was reported in 13 studies (Bertini 2005; Coustan 1978; Lain 2009; Mecacci 2003; Mesdaghinia 2013; Nachum 1999; Niromanesh 2012; Persson 1985; Rowan 2008; Ruholamin 2014; Saleh 2016; Spaulonci 2013; Tertti 2013).
- Birth trauma was reported in 16 studies (Bertini 2005; Coustan 1978; Hickman 2013; Ijas 2011; Lain 2009; Mesdaghinia 2013; Moore 2007; Nachum 1999; Niromanesh 2012; Poyhonen-Alho 2002; Rowan 2008; Ruholamin 2014; Saleh 2016; Silva 2007; Tertti 2013; Thompson 1990).
- Gestational age at birth was reported in 24 studies (Ardilouze 2014; Balaji 2012; Behrashi 2016; Bertini 2005; Bung 1993; Coustan 1978; De Veciana 2002; Hague 2003; Ijas 2011; Jovanovic 1999; Lain 2009; Langer 2000; Mirzamoradi 2015; Mohamed 2014; Moore 2007; Mukhopadhyay 2012; Nachum 1999; Niromanesh 2012; Ogunyemi 2007; Rowan 2008; Saleh 2016; Spaulonci 2013; Tertti 2013; Thompson 1990).
- Preterm birth was reported in 15 studies (Ashoush 2016; Balaji 2012; Ijas 2011; Lain 2009; Majeed 2015; Mesdaghinia 2013; Niromanesh 2012; O'Sullivan 1975a; Pavithra 2016; Prasad 2008; Poyhonen-Alho 2002; Rowan 2008; Saleh 2016; Spaulonci 2013; Tertti 2013).
- Congenital abnormality was reported in 17 studies (Ashoush 2016; Behrashi 2016; De Veciana 2002; Hickman 2013; Jovanovic 1999; Langer 2000; Mesdaghinia 2013; Mirzamoradi 2015; Mohamed 2014; Mukhopadhyay 2012; Niromanesh 2012; Ogunyemi 2007; Pettitt 2007; Rowan 2008; Saleh 2016; Tertti 2013; Zangeneh 2014).
- Five-minute Apgar score less than seven was reported in five studies (Mesdaghinia 2013; Nachum 1999; Rowan 2008; Ruholamin 2014; Saleh 2016).
- Birthweight was reported in 33 studies (Anjalakshi 2007; Ardilouze 2014; Ashoush 2016; Balaji 2005; Balaji 2012; Behrashi 2016; Bertini 2005; Bung 1993; Castorino 2011; De Veciana 2002; Hague 2003; Ijas 2011; Ismail 2007; Jovanovic 1999; Lain 2009; Langer 2000; Mecacci 2003; Mesdaghinia 2013; Mirzamoradi 2015; Mohamed 2014; Moore 2007; Mukhopadhyay 2012; Nachum 1999; Niromanesh 2012; Ogunyemi 2007; Pettitt 2007; Poyhonen-Alho 2002; Rowan 2008; Ruholamin 2014; Silva 2007; Spaulonci 2013; Tertti 2013; Thompson 1990).
- Head circumference at birth was reported in three studies (Lain 2009; Niromanesh 2012; Rowan 2008).
- Length at birth was reported in seven studies (Balaji 2012; Bung 1993; Jovanovic 1999; Lain 2009; Niromanesh 2012; Pettitt 2007; Rowan 2008).
- Ponderal index at birth was reported in five studies (Balaji 2012; Lain 2009; Mecacci 2003; Rowan 2008;Thompson 1990).
- Adiposity was reported using a number of measures including skin fold thickness and percentage fat mass in two studies (Lain 2009; Rowan 2008).
- Neonatal hypoglycaemia was reported in 31 studies (Ardilouze 2014; Ashoush 2016; Behrashi 2016; Bertini 2005; Coustan 1978; Hickman 2013; Ijas 2011; Jovanovic 1999; Lain 2009; Langer 2000; Majeed 2015; Mesdaghinia 2013; Mirzamoradi 2015; Mohamed 2014; Moore 2007; Mukhopadhyay 2012; Nachum 1999; Niromanesh 2012; Ogunyemi 2007; Pavithra 2016; Persson 1985; Poyhonen-Alho 2002; Prasad 2008; Rowan 2008; Ruholamin 2014; Saleh 2016; Silva 2007; Spaulonci 2013; Tertti 2013; Thompson 1990; Zangeneh 2014).
- Respiratory distress syndrome was reported in 13 studies (Balaji 2012; Behrashi 2016; Bung 1993; Mesdaghinia 2013; Moore 2007; Mukhopadhyay 2012; Nachum 1999; Niromanesh 2012; Pavithra 2016; Rowan 2008; Ruholamin 2014; Saleh 2016; Spaulonci 2013).

- Neonatal jaundice (hyperbilirubinaemia) was reported in 21 studies (Behrashi 2016; Bung 1993; Hague 2003; Ijas 2011; Langer 2000; Mesdaghinia 2013; Mirzamoradi 2015; Mohamed 2014; Moore 2007; Mukhopadhyay 2012; Nachum 1999; Niromanesh 2012; Pavithra 2016; Poyhonen-Alho 2002; Prasad 2008; Ruholamin 2014; Saleh 2016; Spaulonci 2013; Tertti 2013; Thompson 1990; Zangeneh 2014).
- Hypocalcaemia was reported in seven studies (Behrashi 2016; Jovanovic 1999; Langer 2000; Mirzamoradi 2015; Pavithra 2016; Thompson 1990; Zangeneh 2014).
- Polycythaemia was reported in five studies (Langer 2000; Mirzamoradi 2015; Nachum 1999; Persson 1985; Zangeneh 2014).
- Relevant biomarker changes associated with the intervention including cord blood c peptide and cord insulin were reported in four studies (Anjalakshi 2007; Lain 2009; Langer 2000; Persson 1985).
- Childhood - weight was reported in two studies (Ijas 2011; Rowan 2008).
- Childhood - height was reported in two studies (Ijas 2011; Rowan 2008).
- Childhood adiposity including ponderal index and total fat mass were reported in two studies (Ijas 2011; Rowan 2008).
- Childhood blood pressure was reported in one study (Rowan 2008).
- The number of antenatal visits or admissions was reported in one study (Langer 2000).
- Admission to neonatal intensive care unit/nursery was reported in 18 studies (Ashoush 2016; Behrashi 2016; Bertini 2005; Ijas 2011; Lain 2009; Langer 2000; Majeed 2015; Mesdaghinia 2013; Mirzamoradi 2015; Mohamed 2014; Moore 2007; Mukhopadhyay 2012; Niromanesh 2012; Rowan 2008; Ruholamin 2014; Saleh 2016; Tertti 2013; Zangeneh 2014).
- Duration of stay in neonatal intensive care unit was reported in three studies (Mirzamoradi 2015; Mohamed 2014; Tertti 2013).

Funding

Academic or governmental funding not related to pharmaceutic industry was reported in 10 studies (Ardilouze 2014; Hickman 2013; Ijas 2011; Lain 2009; Mesdaghinia 2013; Persson 1985; Rowan 2008; Tertti 2013; Wali 2015; Zawiejska 2016). In four studies the manuscript stated that there was no funding received (Behrashi 2016; Beyuo 2015; Mukhopadhyay 2012; Ruholamin 2014).

Jovanovic 1999 declared that drugs were supplied by Eli Lilly and the research was also part funded by this organisation. Notelovitz 1971 reported financial support received from Pfizer laboratories. Pettitt 2007 reported the study was funded in part through a contract with Novo Nordisk Inc.

There was no statement about funding in the manuscript in 36 studies (Anjalakshi 2007; Ashoush 2016; Balaji 2005; Balaji 2012; Bertini 2005; Bung 1993; Castorino 2011; Coustan 1978; De Veciana 2002; Di Cianni 2007; Hague 2003; Herrera 2015; Hutchinson 2008; Ismail 2007; Langer 2000; Majeed 2015; Martinez Piccole 2010; Mecacci 2003; Mirzamoradi 2015; Mohamed 2014; Moore 2007; Nachum 1999; Niromanesh 2012; O'Sullivan 1975a; O'Sullivan 1975b; Ogunyemi 2007; Pavithra 2016; Poyhonen-Alho 2002; Prasad 2008; Riaz 2014; Saleh 2016; Silva 2007; Spaulonci 2013; Thompson 1990; Waheed 2013; Zangeneh 2014).

Conflicts of interest

Authors make a statement that there were no conflicts of interest in 14 studies (Ashoush 2016; Balaji 2012; Behrashi 2016; Beyuo 2015; Herrera 2015; Ijas 2011; Mesdaghinia 2013; Moore 2007; Mukhopadhyay 2012; Niromanesh 2012; Ruholamin 2014; Saleh 2016; Tertti 2013; Zawiejska 2016).

There were no details of conflicts of interest stated in the manuscript of 36 studies (Anjalakshi 2007; Ardilouze 2014; Balaji 2005; Bertini 2005; Bung 1993; Castorino 2011; Coustan 1978; De Veciana 2002; Di Cianni 2007; Hague 2003; Hickman 2013; Hutchinson 2008; Ismail 2007; Lain 2009; Langer 2000; Majeed 2015; Martinez Piccole 2010; Mecacci 2003; Mirzamoradi 2015; Mohamed 2014; Nachum 1999; Notelovitz 1971; O'Sullivan 1975a; O'Sullivan 1975b; Ogunyemi 2007; Pavithra 2016; Persson 1985; Poyhonen-Alho 2002; Prasad 2008; Riaz 2014; Silva 2007; Spaulonci 2013; Thompson 1990; Waheed 2013; Wali 2015; Zangeneh 2014).

Jovanovic 1999 reported that two authors received research support from the Sansum Medical Research Institute as being a conflict of interest. Pettitt 2007 reported that one of the authors was an employee of the funding body (Novo Nordisk Inc). In the Rowan 2008 paper, conflicts are reported by Dr Moore for receiving speaking fees from Sanofi-Aventis. In the 2011 follow-up paper Dr Hague reports being a speaker at a Merck European Association for the Study of Diabetes symposium.

Excluded studies

Twenty-one studies associated with 26 full-text articles were excluded for the following reasons.

Six studies associated with 10 publications were quasi-randomised (Ainuddin 2015a; Hassan 2012; Maresh 1983; Munshi 2014; O'Sullivan 1971; Tempe 2013). Five studies associated with six publications had the wrong study population for this review (Ainuddin 2015; Fadl 2015; NCT00678080; Schuster 1998; Smith 2015). Seven studies associated with eight publications had the wrong intervention for this review (Coiner 2014; Hopp 1996; Landon 2015; Li 1987; Palatnik 2015; Pettitt 2003; Snyder 1998). One publication had the wrong design (cost-effectiveness analysis - non RCT) for this review (Brennan 2015) and one publication

(Kitzmiller 1990) reported that the study never commenced. One study (Li 1999) was not randomised.

Risk of bias in included studies

Refer to Figure 4 and Figure 5 for graphical representation of risk of bias of the included studies.

Figure 4. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

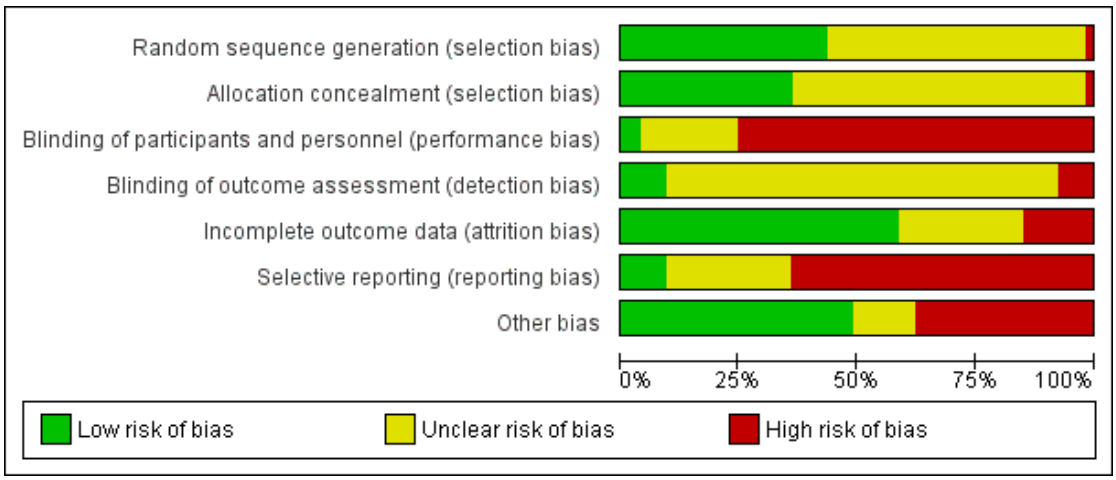
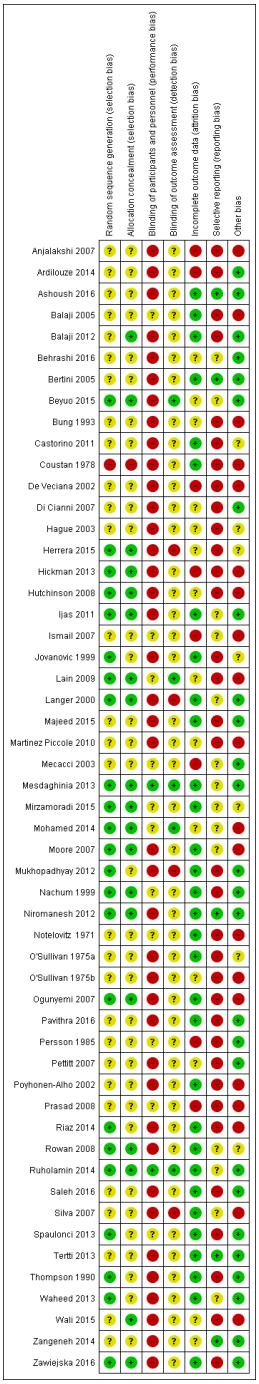


Figure 5. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Randomisation - Twenty-three studies were judged to be of low risk of bias for method of randomisation and used random number tables or permuted blocks (Beyuo 2015; Herrera 2015; Hickman 2013; Hutchinson 2008; Ijas 2011; Jovanovic 1999; Lain 2009; Langer 2000; Mesdaghinia 2013; Mirzamoradi 2015; Mohamed 2014; Moore 2007; Mukhopadhyay 2012; Nachum 1999; Niromanesh 2012; Ogunyemi 2007; Riaz 2014; Rowan 2008; Ruholamin 2014; Spaulonci 2013; Thompson 1990; Waheed 2013; Zawiejska 2016).

Twenty-nine studies were judged to be of unclear risk of bias for method of randomisation due to lack of methodological details (Anjalakshi 2007; Ardilouze 2014; Ashoush 2016; Balaji 2005; Balaji 2012; Behrashi 2016; Bertini 2005; Bung 1993; Castorino 2011; De Veciana 2002; Di Cianni 2007; Hague 2003; Ismail 2007; Majeed 2015; Martinez Piccole 2010; Mecacci 2003; Notelovitz 1971; O'Sullivan 1975a; O'Sullivan 1975b; Pavithra 2016; Persson 1985; Pettitt 2007; Poyhonen-Alho 2002; Prasad 2008; Saleh 2016; Silva 2007; Tertti 2013; Wali 2015; Zangeneh 2014).

One study was judged to be of high risk of bias for methods of randomisation (Coustan 1978) as the first 20 of 72 women were quasi-randomised and then the next 52 women were randomised to one of three groups with one new group added.

Allocation concealment - Nineteen studies were judged to be of low risk of bias for allocation concealment and had used serially numbered opaque envelopes (Balaji 2012; Beyuo 2015; Herrera 2015; Hickman 2013; Hutchinson 2008; Ijas 2011; Lain 2009; Langer 2000; Mirzamoradi 2015; Mohamed 2014; Moore 2007; Nachum 1999; Niromanesh 2012; Ogunyemi 2007; Wali 2015; Zawiejska 2016) or a third party (Mesdaghinia 2013; Ruholamin 2014) or centralised allocation (Rowan 2008).

Thirty-three studies were judged to be of unclear risk of bias for allocation concealment due to lack of methodological details (Anjalakshi 2007; Ardilouze 2014; Ashoush 2016; Balaji 2005; Behrashi 2016; Bertini 2005; Bung 1993; Castorino 2011; De Veciana 2002; Di Cianni 2007; Hague 2003; Ismail 2007; Jovanovic 1999; Majeed 2015; Martinez Piccole 2010; Mecacci 2003; Mukhopadhyay 2012; Notelovitz 1971; O'Sullivan 1975a; O'Sullivan 1975b; Pavithra 2016; Persson 1985; Pettitt 2007; Poyhonen-Alho 2002; Prasad 2008; Riaz 2014; Saleh 2016; Silva 2007; Spaulonci 2013; Tertti 2013; Thompson 1990; Waheed 2013; Zangeneh 2014).

One study was judged to be of high risk of bias for allocation concealment (Coustan 1978) because the first 20 of 72 women were quasi-randomised and then the next 52 women were randomised. There were no details for allocation concealment.

Blinding

Performance bias

Only two studies were judged to be low risk of performance bias as the care providers were blinded to treatment allocation (Mesdaghinia 2013) or the care providers and participants were not provided with actual OGTT results (Ruholamin 2014).

Eleven studies were judged to be of unclear risk of performance bias due to insufficient methodological information (Balaji 2005; Ismail 2007; Lain 2009; Mecacci 2003; Mirzamoradi 2015; Mohamed 2014; Nachum 1999; Notelovitz 1971; Persson 1985; Prasad 2008; Spaulonci 2013).

Forty studies were judged to be high risk of performance bias. Fifteen studies stated they were 'open-label' (Ardilouze 2014; Ashoush 2016; Balaji 2012; Beyuo 2015; Bertini 2005; Herrera 2015; Jovanovic 1999; Langer 2000; Mukhopadhyay 2012; Ogunyemi 2007; Pettitt 2007; Rowan 2008; Silva 2007; Thompson 1990; Wali 2015) and 25 studies were unlikely to have been blinded due to differences in mode of administration of the interventions (Anjalakshi 2007; Behrashi 2016; Bung 1993; Castorino 2011; Coustan 1978; De Veciana 2002; Di Cianni 2007; Hague 2003; Hickman 2013; Hutchinson 2008; Ijas 2011; Majeed 2015; Martinez Piccole 2010; Moore 2007; Niromanesh 2012; O'Sullivan 1975a; O'Sullivan 1975b; Pavithra 2016; Poyhonen-Alho 2002; Riaz 2014; Saleh 2016; Tertti 2013; Waheed 2013; Zangeneh 2014; Zawiejska 2016).

Detection bias

Five studies were judged to be low risk of detection bias as outcome assessors were blinded for one or more outcomes (Beyuo 2015; Lain 2009; Mesdaghinia 2013; Mohamed 2014; Ruholamin 2014).

Forty-four studies were judged to be of unclear risk of detection bias due to insufficient methodological details (Anjalakshi 2007; Ardilouze 2014; Ashoush 2016; Balaji 2005; Balaji 2012; Behrashi 2016; Bertini 2005; Bung 1993; Castorino 2011; Coustan 1978; De Veciana 2002; Di Cianni 2007; Hague 2003; Hickman 2013; Hutchinson 2008; Ijas 2011; Ismail 2007; Jovanovic 1999; Majeed 2015; Martinez Piccole 2010; Mecacci 2003; Mirzamoradi 2015; Moore 2007; Nachum 1999; Niromanesh 2012; Notelovitz 1971; Ogunyemi 2007; O'Sullivan 1975a; O'Sullivan 1975b; Pavithra 2016; Persson 1985; Pettitt 2007; Poyhonen-Alho 2002; Prasad 2008; Riaz 2014; Rowan 2008; Saleh 2016; Spaulonci 2013; Tertti 2013; Thompson 1990; Waheed 2013; Wali 2015; Zangeneh 2014; Zawiejska 2016).

Four studies were judged to be high risk of detection bias as the outcome assessors were aware of the allocation (Herrera 2015; Langer 2000; Mukhopadhyay 2012; Silva 2007).

Incomplete outcome data

Thirty-one studies were judged to be of low risk of attrition bias as minimal or no losses reported (Ashoush 2016; Balaji 2005; Balaji 2012; Bertini 2005; Castorino 2011; Coustan 1978; Ijas 2011; Jovanovic 1999; Langer 2000; Majeed 2015; Mesdaghinia 2013; Mirzamoradi 2015; Moore 2007; Mukhopadhyay 2012; Nachum 1999; Niromanesh 2012; Notelovitz 1971; Ogunyemi 2007; O'Sullivan 1975a; Pavithra 2016; Poyhonen-Alho 2002; Riaz 2014; Rowan 2008; Ruholamin 2014; Saleh 2016; Silva 2007; Spaulonci 2013; Tertti 2013; Thompson 1990; Waheed 2013; Zawiejska 2016).

Fourteen studies were judged to be of unclear risk of bias; eight as there was insufficient information to be able to make a judgement (Di Cianni 2007; Hague 2003; Hutchinson 2008; Martinez Piccole 2010; Mohamed 2014; O'Sullivan 1975b; Wali 2015; Zangeneh 2014) and three as there was relatively high attrition (16% loss to follow-up (87/104) - Beyuo 2015; 17% loss to follow-up or not completed intervention the reasons for losses are not explained Bung 1993; 18% (87/105) attrition (Herrera 2015). Lain 2009 did not analyse all of the women for all of the outcomes and the number of losses were reported in the Pettitt 2007 study but not the groups they were randomised to. Behrashi 2016 excluded women who had received insulin but these women were not excluded from other trials.

Eight studies were judged to be high risk of bias. Three studies reported preliminary data only in a conference abstract format. It is therefore unclear if these were all the women randomised and if there was any attrition at the end of data collection (Ardilouze 2014; De Veciana 2002; Prasad 2008). One study had high attrition (30%; 3/10) at follow-up in the glibenclamide group (Anjalakshi 2007). Hickman 2013 reported that only 31 of 230 women were randomised; Ismail 2007 reported that 68 women were randomised but only 61 women analysed; there is no explanation for the difference. One study reported excluding 16 of 65 women post hoc (Mecacci 2003) and one study reported that some data were not available for all women such as HbA1c at delivery and cord C peptide and other outcomes were not reported with total sample denominator. Persson 1985 reported that some data were not available for all women such as HbA1c at delivery and cord C peptide. Other outcomes not reported with total sample denominator.

Selective reporting

Five studies were judged to be of low risk of reporting bias as all outcomes pre-specified were reported (Ashoush 2016; Bertini 2005; Niromanesh 2012; Tertti 2013; Zangeneh 2014).

Fourteen studies were judged to be of unclear risk of reporting bias. Five studies reported one outcome that had not been pre-specified (Behrashi 2016; Langer 2000; Mecacci 2003; Mirzamoradi 2015; Mohamed 2014). Three studies reported only a limited number of outcomes that had not been pre-specified (Ismail 2007; Mesdaghinia 2013; Silva 2007). Moore 2007 did not report data for one of the trials' pre-specified outcomes and Ijas 2011 reported on data from subgroups that had not been pre-specified. Ruholamin 2014 did not provide data to support the findings reported in the text of the manuscript. Beyuo 2015 reported on data for women with GDM and with pre-existing diabetes, the majority of women had GDM 32 of 43 women in the metformin group and 23 of 40 women in the insulin group. Only glycaemic control data are reported although other neonatal outcomes were listed in the methods section of the report. The authors note in the results section that fasting blood glucose, one-hour postprandial glucose, maternal weight gain, pregnancy and neonatal outcomes were also recorded but were not discussed in this publication. In another study (Waheed 2013), it was unclear if the study includes women with pre-existing diabetes and what proportion they constituted. The two-year follow-up data for the Rowan 2008 study were only reported in two sites in Australia and New Zealand.

Thirty-four studies were judged to be high risk of reporting bias. Ten studies provided only preliminary data or data only reported in a conference abstract (Ardilouze 2014; Castorino 2011; De Veciana 2002; Hutchinson 2008; Martinez Piccole 2010; Ogunyemi 2007; Prasad 2008; Wali 2015), a brief report (Di Cianni 2007) or letter to the editor (Hague 2003). Five studies did not pre-specify any maternal or neonatal outcomes (Bung 1993; Notelovitz 1971; Persson 1985; Poyhonen-Alho 2002; Zawiejska 2016). Coustan 1978 only pre-specified diabetes postpartum as and outcome. Six studies had limited outcomes (Herrera 2015; Lain 2009; O'Sullivan 1975a; O'Sullivan 1975b; Pavithra 2016; Riaz 2014) and three studies did not report on all of the pre-specified outcomes (Balaji 2005; Lain 2009; Thompson 1990) or additional outcomes were reported that were not pre-specified (Majeed 2015). Seven studies reported additional outcomes (Balaji 2012; Hickman 2013; Jovanovic 1999; Mukhopadhyay 2012; Nachum 1999; Pettitt 2007; Spaulonci 2013). In the Anjalakshi 2007 study outcomes were not prespecified and were very limited. The evidence was published as correspondence only and no full publication could be identified.

Other potential sources of bias

Twenty-six studies were judged to be low risk of other sources of bias (Ardilouze 2014; Ashoush 2016; Balaji 2012; Behrashi 2016; Bertini 2005; Beyuo 2015; Di Cianni 2007; Ijas 2011; Langer 2000; Majeed 2015; Mecacci 2003; Mesdaghinia 2013; Mukhopadhyay 2012; Nachum 1999; Niromanesh 2012; Pavithra 2016; Persson 1985; Pettitt 2007; Ruholamin 2014; Saleh 2016; Spaulonci 2013; Tertti 2013; Thompson 1990; Waheed 2013;

Zangeneh 2014; Zawiejska 2016).

Seven studies were judged to be of unclear risk of other sources of bias. In the Mirzamoradi 2015 study more women were allocated to the insulin group (n = 59) compared with the glibenclamide group (n = 37) and the difference was not explained. There was insufficient detail to make a judgement for two studies (Hague 2003; O'Sullivan 1975a). Three studies reported some imbalance between groups at baseline (Castorino 2011; Jovanovic 1999 for age; Rowan 2008 for pregnancy losses (any reason)). One study noted that 33% of participants had type 2 diabetes and 67% had GDM. However, data for blood glucose are reported for GDM alone (Herrera 2015).

Twenty studies were judged to be high risk of other sources of bias. In the Coustan 1978 study data from quasi-randomised cannot be separated from randomised data. Ten studies only reported preliminary data and/or data in a conference abstract (Balaji 2005; De Veciana 2002; Hutchinson 2008; Martinez Piccole 2010; Prasad 2008; Wali 2015), correspondence (Anjalakshi 2007) or short communication (Ismail 2007; Poyhonen-Alho 2002; Riaz 2014). One study recruited women with both GDM and type 2 diabetes and did not report data separately, as 77% of the women had GDM we included the data in meta-analyses but what is not clear is the distribution of women with GDM between the intervention and control groups (Mohamed 2014). Another study recruited women with both GDM and type 2 diabetes and did not report data separately, as 50% of the women had GDM the data have been included (Hickman 2013). The Hickman 2013 study was unable to recruit the expected number of women and was therefore underpowered to detect differences in the outcomes. Notelovitz 1971 included women with both GDM and type 2 diabetes, the groups are not reported separately and the proportion of women with GDM is not reported. The data from this study have therefore not been included in any meta-analyses. The Lain 2009 study stopped early due to discontinuation of the maintenance equipment for the primary outcome. The O'Sullivan 1975b study stopped early due to lack of funding. Moore 2007 reported only half the sample that had been estimated to be statistically appropriate had been recruited after 32 months and as such an interim report on 63 women was undertaken. There is no evidence of a full report. Two studies reported multiple baseline differences in the relevant blood glucose levels (fasting, one-hour, two-hour and HbA1c levels), which were all higher in the insulin group (Ogunyemi 2007) or higher in the glibenclamide group (Silva 2007). Bung 1993 failed to report any baseline demographic data to determine if groups were balanced.

Effects of interventions

See: **Summary of findings for the main comparison** Insulin compared to anti-diabetic agent for the treatment of women with gestational diabetes (maternal outcomes); **Summary of findings 2** Insulin compared to anti-diabetic agent for the treatment of women with gestational diabetes (infant/child/adult outcomes)

Comparison 1 - Insulin versus oral anti-diabetic pharmacological therapy

Twenty-eight trials involving 4040 women contributed data to this comparison.

Maternal primary outcomes

1.1 and 1.2 Hypertensive disorders of pregnancy (including pre-eclampsia, pregnancy-induced hypertension, eclampsia)

Ten studies reported on hypertensive disorders of pregnancy; three compared insulin with glibenclamide (Langer 2000; Mirzamoradi 2015; Zangeneh 2014) and seven studies compared insulin with metformin (Hague 2003; Ijas 2011; Niromanesh 2012; Rowan 2008; Saleh 2016; Spaulonci 2013; Tertti 2013). Hypertensive disorders of pregnancy were reported as pre-eclampsia or hypertensive disorders of pregnancy (not defined). No studies reported eclampsia as an outcome.

There was no clear evidence of a difference for the risk of pre-eclampsia between women who had been treated with insulin and those who had been treated with an oral anti-diabetic pharmacological therapy (risk ratio (RR) 1.14, 95% CI 0.86 to 1.52; 10 studies, 2060 women; *moderate-quality evidence*) (Analysis 1.1). The quality of the evidence was downgraded for risk of bias as eight of the 10 studies were not blinded.

Treatment with insulin was associated with an increased risk for hypertensive disorders of pregnancy (not defined) compared with oral anti-diabetic pharmacological therapy (RR 1.89, 95% CI 1.14 to 3.12; four studies, 1214 women; *moderate-quality evidence,* Analysis 1.2). Three studies (Niromanesh 2012; Rowan 2008; Tertti 2013) had used metformin as the anti-diabetic pharmacological therapy and one study used glibenclamide (Pavithra 2016).

1.3 Caesarean section

Caesarean section was reported in 17 studies; seven compared insulin with glibenclamide (Bertini 2005; Langer 2000; Mirzamoradi 2015; Ogunyemi 2007; Pavithra 2016; Silva 2007; Zangeneh 2014); nine compared insulin with metformin (Ashoush 2016; Hague 2003; Ijas 2011; Moore 2007; Niromanesh 2012; Ruholamin 2014; Saleh 2016; Spaulonci 2013; Tertti 2013), and one study each compared insulin with acarbose (Bertini 2005) and a combination on metformin and glibenclamide (Ardilouze 2014).

There was no clear evidence of a difference for the risk of birth by caesarean section between women who had been treated with insulin and those who had been treated with an oral anti-diabetic pharmacological therapy (RR 1.03, 95% CI 0.93 to 1.14; 1988 women; 17 studies; *moderate-quality evidence*) (Analysis 1.3). The quality of the evidence was downgraded for risk of bias as 15 of the 17 studies were unblinded. Visual inspection of the funnel

plot associated with this outcome does not suggest any evidence of publication bias (Figure 2).

1.4 Development of type 2 diabetes

Development of type 2 diabetes was reported in two studies both comparing insulin and metformin (Rowan 2008; Tertti 2013). Rowan 2008 reported the outcome at the six to eight weeks postpartum oral glucose tolerance test and Tertti 2013 at up to one year postpartum. There was no evidence of a difference between groups (RR 1.39, 95% CI 0.80 to 2.44; two studies, 754 women; *moderate-quality evidence*) (Analysis 1.4). The quality of the evidence was downgraded for risk of bias as both studies were open-label.

Neonatal primary outcomes

1.5 Perinatal (fetal and neonatal death) and later infant mortality

Perinatal death was reported in 11 comparisons in 10 studies; five studies compared insulin with glibenclamide (Bertini 2005; Lain 2009; Langer 2000; Mukhopadhyay 2012; Silva 2007); four studies compared insulin with metformin (Ijas 2011; Mesdaghinia 2013; Niromanesh 2012; Tertti 2013), and one study each compared insulin with acarbose (Bertini 2005) and a combination of metformin and glibenclamide (Mohamed 2014).

There was no clear evidence of a difference for the risk of perinatal death between infants whose mothers had been treated with insulin and those treated with oral anti-diabetic pharmacological therapies (RR 0.85; 95% CI 0.29 to 2.49; 10 studies, 1463 infants; *low-quality evidence*). The quality of evidence was downgraded for risk of bias and imprecision. Six studies reported that there were no events of perinatal group in either the insulin or the oral anti-diabetic drug groups (Bertini 2005; Ijas 2011; Mesdaghinia 2013; Niromanesh 2012; Silva 2007; Tertti 2013). The studies were not powered to detect differences in perinatal mortality and event rates are very low 3/686 for the insulin-treated group and 3/693 for the oral anti-diabetic agent group (Analysis 1.5).

No data were reported for later infant mortality.

1.6 Large-for-gestational age (LGA)

LGA was reported in 14 studies of three comparisons; five studies compared insulin with glibenclamide (Bertini 2005; Lain 2009; Langer 2000; Mukhopadhyay 2012; Silva 2007); eight studies compared insulin with metformin (Hickman 2013; Ijas 2011; Mesdaghinia 2013; Niromanesh 2012; Rowan 2008; Saleh 2016; Spaulonci 2013; Tertti 2013) and one study (Bertini 2005) compared insulin with acarbose.

There was no clear evidence of a difference between infants whose mothers had been treated with insulin and those treated with oral anti-diabetic pharmacological therapies for the risk of being born LGA (average RR 1.01, 95% CI 0.76 to 1.35; 2352 infants; 13 studies; I^2 = 35%; *moderate-quality evidence;* Analysis 1.6). There was substantial heterogeneity present in this outcome so these result should be interpreted with caution (Heterogeneity: Tau^2 = 0.08; Chi^2 = 19.88 (P = 0.10)). Quality of evidence was downgraded for risk of bias and publication bias. The majority of studies were unblinded and visual inspection of the funnel plot (Figure 3) suggests asymmetry and therefore publication bias with those studies with larger effect sizes more likely to be published.

1.7 Death or serious morbidity composite (variously defined by trials, e.g. perinatal or infant death, shoulder dystocia, bone fracture or nerve palsy)

Two studies comparing insulin with metformin reported a composite outcome of serious infant morbidity (Hickman 2013; Rowan 2008). There was no evidence of a clear difference between those whose mothers had been treated with insulin and those treated with oral anti-diabetic pharmacological therapies (metformin) for the risk of a composite of serious infant morbidity (RR 1.03, 95% CI 0.84 to 1.26; two studies, 760 infants; *moderate-quality evidence;* Analysis 1.7). The quality of evidence was downgraded for risk of bias as both studies were not blinded.

1.8 Neurosensory disability in later childhood

At 18 months of age, there was no evidence of a clear difference in the risk of any mild developmental delay between infants whose mothers had been treated with insulin and those who had been treated with oral anti-diabetic agents (RR 1.07, 95% CI 0.33 to 3.44; one study, 93 children; *low-quality evidence*) (Ijas 2011). At 18 months of age, there was no evidence of a difference in the risk of hearing impairment (RR 0.31; 95% CI 0.01 to 7.49; one study, 93 children; *low-quality evidence*) or visual impairment (RR 0.31, 95% CI 0.03 to 2.90; one study, 93 children; *low-quality evidence*) between infants whose mothers had been treated with insulin and those who had been treated with oral anti-diabetic agents (Ijas 2011) (Analysis 1.8).

Maternal secondary outcomes

1.9 Use of additional pharmacotherapy

Where reported, for those women who were treated with oral anti-diabetic pharmacological therapy a total of 22% required supplementary insulin (RR 0.03, 95% CI 0.02 to 0.06; 19 studies; 2761 women). Seven studies reported using glibenclamide as the oral anti-diabetic (Bertini 2005; Lain 2009; Langer 2000; Mirzamoradi 2015; Ogunyemi 2007;Pavithra 2016; Silva 2007). In these studies 6.7% (29/433) of women required supplementary insulin. Ten studies reported using metformin as the oral anti-

diabetic (Ashoush 2016; Beyuo 2015; Hickman 2013; Ijas 2011; Moore 2007; Niromanesh 2012; Rowan 2008; Ruholamin 2014; Spaulonci 2013; Tertti 2013). For these studies, 30% (250/837) of women required supplementary insulin. These data are skewed by the Rowan 2008 study, which is the largest in this subgroup. In this study almost half of the women (46%, 168/363) received supplementary insulin. Acarbose was used in two studies (Bertini 2005; De Veciana 2002), for which 17% (11/64) women received supplementary insulin. It should be noted that women in the De Veciana 2002 study who were randomised to acarbose commenced insulin because they could not tolerate increasing doses of acarbose rather than an inability to maintain glycaemic control. One study reported comparing insulin with a combination on metformin and glibenclamide (Ardilouze 2014), 37% of the oral anti-diabetic agent group required additional insulin (Analysis 1.9).

1.10 Maternal hypoglycaemia

There was no evidence of a difference for the risk of maternal hypoglycaemia between women who had been treated with insulin and those who had been treated with an oral anti-diabetic pharmacological therapy (average RR 3.01, 95% CI 0.74 to 12.27; 10 studies, 998 women; I^2 = 84%) (Analysis 1.10). Five studies reported no events of maternal hypoglycaemia in either the insulin nor the oral anti-diabetic pharmacological therapy group (Anjalakshi 2007; Bertini 2005; Moore 2007; Mukhopadhyay 2012; Silva 2007). Heterogeneity may be due to lack of blinding reported in the studies reporting this outcome or to definitions of hypoglycaemia which are poorly report in the individual studies (Heterogeneity: Tau^2 = 1.91; Chi^2 = 24.87 (P = < 0.0001)).

1.11 to 1.13 Glycaemic control during/end of treatment

There was no evidence of a clear difference in fasting blood glucose (average standardised mean difference (SMD) 0.05, 95% CI -0.09 to 0.19; 19 studies, 2812 women; I^2 = 66%; Tau^2 = 0.06; Chi^2 = 56.67 (P <0.0001)) (Analysis 1.11), postprandial blood glucose (average SMD 0.12, 95% CI -0.05 to 0.29; 18 studies 2508 women; I^2 = 73%; Tau^2 = 0.09; Chi^2 = 67.85 (P < 0.00001)) (Analysis 1.12) or HbA1c (average SMD 0.01, 95% CI -0.12 to 0.15; nine studies, 1963 women; I^2 = 45%; Tau^2 = 0.02; Chi^2 = 14.42 (P <0.07)) (Analysis 1.13) between women who had been treated with insulin and those treated with oral anti-diabetic agents. Heterogeneity was substantial for all of these outcomes. Median data for fasting blood glucose concentration, one-hour postprandial glucose concentration and HbA1c were reported by Hickman 2013 (Table 8). Waheed 2013 and Riaz 2014 report data as the number of women who had values for glycaemic control within the treatment target (Table 8).

1.14 Weight gain in pregnancy

Insulin was associated with an increase in gestational weight gain compared with oral anti-diabetic pharmacological therapy (average mean difference (MD) 1.06 kg, 95% CI 0.63 to 1.48; 10 studies, 2336 women; I^2 = 65%, Tau^2 = 0.23) . The subgroup interaction test based on type of oral anti-diabetic pharmacological therapy was not significant suggesting no differential effect between glibenclamide, metformin, or acarbose (I^2 = 0%, Chi^2 = 0.69, P = 0.71) (Analysis 1.14). Median data for gestational weight gain were reported by Hickman 2013 (Table 8). None of the studies detailed wither the gestational weight gain was within, above or below acceptable standards, we suggest caution when interpreting these data.

1.15 Induction of labour

Insulin may possibly increase the risk of induction of labour compared with oral anti-diabetic pharmacological therapy although the evidence was not clear (average RR 1.30, 95%CI 0.96 to 1.75; three studies, 348 women; I^2 = 32%; Tau^2 = 0.02; *moderate quality of evidence;* Analysis 1.15). Quality of evidence was downgraded for risk of bias as all three studies were not blinded and there was insufficient detail to be able to judge allocation concealment and randomisation. All three studies reporting this outcome (Hague 2003; Ijas 2011; Tertti 2013) used metformin as the oral anti-diabetic agent.

1.16 Postpartum haemorrhage

There was no evidence of a difference for the risk of postpartum haemorrhage between women who had been treated with insulin and those who had been treated with an oral anti-diabetic pharmacological therapy (RR 0.34, 95% CI 0.01 to 8.13; two studies, 91 women; Analysis 1.16). One of the two studies reported no events in the insulin nor in the oral anti-diabetic group (Hickman 2013). There is evidence of imprecision with wide CIs, small sample size and low event rates.

1.17 Breastfeeding

Breastfeeding was poorly reported. There was no evidence of a difference for breastfeeding at six to eight weeks postpartum between women who had been treated with insulin and those who had been treated with an oral anti-diabetic pharmacological therapy (RR 1.03, 95% CI 0.86 to 1.23; two studies, 411 women) (Analysis 1.17). Both studies (Ijas 2011; Rowan 2008) used metformin as the oral anti-diabetic.

1.18 Relevant biomarker changes associated with the intervention

There was no clear evidence of a difference between insulin and oral anti-diabetic pharmacological therapy (metformin) for any of the reported biomarkers associated with the intervention: HOMA-IR (MD 0.00, 95% CI -2.92 to 2.92; one study, 78 women), total cholesterol (MD 0.10, 95% CI -0.49 to 0.69; one study, 78

women), high-density lipoprotein (HDL) cholesterol (MD 0.10, 95% CI -0.13 to 0.33; one study, 78 women) or triglycerides (MD -0.30, 95% CI -0.68 to 0.08; one study, 78 women).

Views of the intervention (data not shown)

Women in the Rowan 2008 trial were asked about the acceptability of the intervention one week postpartum. Of those treated with metformin, 76% said they would choose metformin if needed in a subsequent pregnancy whereas only 27% of women would choose insulin again. Women in the metformin group thought that taking medication was the easiest part of treatment compared with women taking insulin (59% versus 35%).

Adherence to the intervention (data not shown)

Sixty-nine per cent of women taking metformin in the Rowan 2008 trial reported that they never or rarely forgot to take their medication compared with 81% of women taking insulin.

No data were reported for *placental abruption, postpartum infection; perineal trauma/tearing; maternal mortality, sense of well-being or quality of life or behavioural changes associated with the intervention.*

Long-term outcomes for mother

A limited number of the included studies reported long-term data for women with GDM (Mirzamoradi 2015; Rowan 2008; Tertti 2013). Rowan 2008 and Tertti 2013 currently report up to two-years follow-up.

1.19 Body mass index (BMI)

There was no evidence of a difference between women who had been treated with insulin and those treated with oral anti-diabetic pharmacological therapy for BMI at six weeks postpartum (MD -0.20 kg/m^2, 95% CI -1.29 to 0.89; one study, 733 women) (Analysis 1.19).

1.20 Postnatal weight retention or return to pre-pregnancy weight

Maternal weight (kg) was reported from the Tertti 2013 study at six to eight weeks' postpartum and at one-year postpartum. There was no clear evidence of difference in postnatal weight between women treated with insulin and those treated with oral anti-diabetic pharmacological therapy (metformin) at six to eight weeks postpartum (MD -1.60 kg, 95% CI -6.34 to 3.14; one study, 167 women; *low-quality evidence*) or one year postpartum (MD -3.70 kg, 95% CI -8.50 to 1.10; one study, 176 women; *low-quality evidence*) (Analysis 1.20).

1.21 Impaired glucose tolerance

Three studies reported on impaired glucose tolerance at follow-up (Mirzamoradi 2015; Rowan 2008; Tertti 2013). At six weeks postpartum there was no clear evidence of a difference for impaired glucose tolerance between women who had been treated with insulin and those with oral anti-diabetic agents (RR 1.16, 95% CI 0.80 to 1.68; three studies, 841 women). Nor was there evidence of a difference between groups at one-year postpartum reported in one study (Tertti 2013) (RR 0.84, 95% CI 0.56 to 1.26; one study, 179 women). See Analysis 1.21.

No data were reported for *postnatal depression* or *cardiovascular health*.

Fetal/neonatal secondary outcomes

There was no clear difference between infants whose mothers had been treated with insulin and those treated with oral anti-diabetic agents for the following outcomes.

1.22 Stillbirth

There was no evidence of a clear difference between infants whose mothers had been treated with insulin and those treated with oral anti-diabetic pharmacological therapy for the risk of stillbirth (RR 0.60, 95% CI 0.08 to 4.52; three studies, 653 infants) (Analysis 1.22).

1.23 Neonatal death

There was no evidence of a clear difference between infants whose mothers had been treated with insulin and those treated with oral anti-diabetic pharmacological therapy for the risk of neonatal death (RR 0.99, 95% CI 0.06 to 15.72; two studies, 503 infants) (Analysis 1.23).

1.24 Macrosomia

There was no overall evidence of a clear difference between infants whose mothers had been treated with insulin and those treated with oral anti-diabetic pharmacological therapy for the risk of macrosomia (average RR 1.17, 95% CI 0.77 to 1.78; 19 studies, 2305 infants; I^2 = 42%, Tau^2 = 0.27; Chi^2 = 27.47 (P = 0.04)). The subgroup difference was not clear suggesting there was no differential effect between the type of oral anti-diabetic agent used. The Bertini 2005 study of 33 infants reported no events for macrosomia in either the insulin or the acarbose groups. See Analysis 1.24.

1.25 Small-for-gestational age (SGA)

There was no evidence of a clear difference between insulin and oral anti-diabetics for the risk of being born SGA (RR 1.16, 95% CI 0.79 to 1.69; nine studies, 1812 infants; Analysis 1.25). One study (Mesdaghinia 2013) reported no events in either the insulin or the oral anti-diabetic group.

1.26 Birth trauma

Birth trauma (not defined) was reported in five studies. There were no events reported in four studies (Bertini 2005; Lain 2009; Saleh 2016; Silva 2007). One study reported no differences for the risk of birth trauma (not specified) for insulin compared with metformin (Rowan 2008) (RR 1.04, 95% CI 0.53 to 2.03; one study, 733 infants) (Analysis 1.26).

There was no evidence of a clear difference for the risk of *shoulder dystocia* between insulin and oral antidiabetics groups (RR 1.44, 95% CI 0.62 to 3.34; eight studies, 968 infants; Analysis 1.26), the risk of *bone fracture* (RR 4.71, 95% CI 0.23 to 95.53; two studies, 196 infants) or *nerve palsy* (RR 5.05, 95% CI 0.24 to 103.90; two studies, 320 infants; Analysis 1.26).

1.27 Gestational age at birth

There was no evidence of a clear difference between insulin and oral anti-diabetics for gestational age at birth (average MD weeks -0.01, 95% CI -0.20 to 0.18; 18 studies, 2834 infants; I^2 = 59%, Tau^2 = 0.09; Chi^2 = 43.71 (P = 0.0006); Analysis 1.27). Median data for gestational age at birth were reported by Hickman 2013 (Table 9).

1.28 Preterm birth (less than 37 weeks' gestation)

For preterm birth less than 37 weeks' gestation, there was no evidence of a clear difference between insulin and oral anti-diabetics (average RR 1.10, 95% CI 0.64 to 1.88; 11 studies, 2417 infants; I^2 = 65%, Tau^2 = 0.45; Chi^2 = 28.57 (P = 0.001); Analysis 1.28). No data were presented for preterm birth less than 32 weeks' gestation.

1.29 Congenital abnormality (not pre-specified)

There was no evidence of a clear difference between insulin and oral anti-diabetics for the risk of congenital abnormality (RR 1.35, 95% CI 0.88 to 2.08; 15 studies, 2671 infants; Analysis 1.29). Three studies reported no events in either intervention group (De Veciana 2002; Hickman 2013; Zangeneh 2014).

1.30 Five-minute Apgar less than seven

There was no evidence of a clear difference between insulin and oral anti-diabetics for a five-minute Apgar score less than seven (RR 0.49, 95% CI 0.09 to 2.64; four studies, 1170 infants; Analysis 1.30) . There were no events in two of the studies (Mesdaghinia 2013; Ruholamin 2014).

1.31 Birthweight

Birthweight did not differ overall between infants whose mothers had been treated with insulin and those treated with oral anti-diabetic agents (MD -20.14 g, 95% CI -83.58 to 43.29; 22 studies, 3183 infants; I^2 = 67%, Tau^2 = 14034.8; Chi^2 = 67.47 (P < 0.00001)). The subgroup interaction test including glibenclamide, metformin and acarbose was not clear suggesting there was no differential effect between the oral anti-diabetic agents used (Analysis 1.31). Data for median birthweight were reported by Hickman 2013 (Table 9).

1.32 Head circumference at birth (cm)

There was no evidence of a difference between insulin and oral anti-diabetics for head circumference at birth (average MD 0.14 cm, 95% CI -0.26 to 0.53; three studies, 975 infants; I^2 = 65%, Tau^2 = 0.08; Chi^2 = 5.71 (P = 0.06); Analysis 1.32).

1.33 Length at birth (cm)

There was no evidence of a difference between insulin and oral anti-diabetics for length at birth (average MD 0.11 cm, 95% CI -0.50 to 0.71; three studies, 975 infants I^2 = 61%, Tau^2 = 0.17; Chi^2 = 5.10 (P = 0.08); Analysis 1.33).

1.34 Ponderal index at birth

Ponderal index did not differ overall between infants whose mothers had been treated with insulin and those treated with oral anti-diabetics (average MD 0.03 kg/m^3, 95% CI -0.13 to 0.19; two studies, 815 infants; I^2 = 78%; Tau^2 = 0.01; Chi^2 = 4.46 (P = 0.03); *very low-quality evidence*). The subgroup interaction test indicated a differential effect between these studies, one of which compared insulin with glibenclamide (Lain 2009) and showed no difference in ponderal index and one study that compared insulin with metformin (Rowan 2008), which showed a higher ponderal index for infants whose mothers had been treated with insulin (Analysis 1.34). Evidence is based on only two studies and caution should be taken when interpreting the data.

1.35 to 1.38 Adiposity at birth

Skinfold thickness measurements at birth (mm) - There was no clear difference between intervention groups for triceps (MD -0.07 mm, 95% CI -0.25 to 0.10; two studies, 815 infants; Analysis 1.35), subscapular (average MD -0.13 mm, 95% CI -0.50 to 0.24; two studies, 815 infants; I^2 = 52%, Tau^2 = 0.04; Chi^2 = 2.09, (P = 0.15); Analysis 1.36) or skinfold sum (MD -0.80 mm, 95% CI -2.33 to 0.73, one study, 82 infants; *very low-quality evidence*).

Percentage (%)fat mass - Percentage fat mass did not clearly differ between intervention groups (MD -1.60%, 95% CI -3.77 to 0.57; one study, n = 82 infants; *moderate-quality evidence;* Analysis 1.38).

1.39 Neonatal hypoglycaemia

Neonatal hypoglycaemia did not differ overall between infants whose mothers had been treated with insulin and those treated with oral anti-diabetic agents (RR 1.14, 95% CI 0.85 to 1.52;

24 studies; 3892 infants; I^2 = 47%; Tau^2 = 0.18; Chi^2 = 43.73 (P = 0.006); *low-quality evidence;* Analysis 1.39). The subgroup interaction test suggests a differential effect between the oral antidiabetic agents used (Chi^2 = 11.11, df = 3, P = 0.01, I^2 = 73%; Analysis 1.39). Insulin was associated with a decreased risk of neonatal hypoglycaemia compared with glibenclamide (RR 0.70, 95% CI 041 to ;1.19; 10 studies, 1283 infants) and an increased risk for neonatal hypoglycaemia when compared with metformin (RR 1.58, 95% CI 1.16 to 2.16; 12 studies, 2424 infants). There was no clear difference between groups for insulin compared with acarbose (RR 0.44, 95% CI 0.02 to 10.16; one study, 33 infants) or insulin compared with combined metformin and glibenclamide (RR 0.76, 95% CI 0.49 to 1.18; two studies, 152 infants; Analysis 1.39) although these latter two comparisons are based on small studies of participants and low event rates.

1.40 Respiratory distress syndrome

There was no evidence of a clear difference between intervention groups for the risk of respiratory distress syndrome (RR 1.29, 95% CI 0.83 to 1.99; 10 studies, 1894 infants; Analysis 1.40).

1.41 Neonatal jaundice (hyperbilirubinaemia)

There was no clear evidence of a difference between intervention groups for the risk of neonatal jaundice (RR 0.99, 95% CI 0.83 to 1.19; 16 studies, 2183 infants; Analysis 1.41) . The subgroup interaction test was not significant suggesting no differential effect between the oral antidiabetic pharmacological therapies.

1.42 Hypocalcaemia

For this outcome there was no evidence of a clear difference between exposure to insulin or oral anti-diabetic pharmacological therapy (glibenclamide) (RR 1.95, 95% CI 0.49 to 7.78; five studies, 939 infants; Analysis 1.42) . Caution is advised in interpreting the results due to wide CIs and low event rates (5/487 insulin group; 2/452 oral antidiabetic group).

1.43 Polycythaemia

For the outcome of polycythaemia, there was no evidence of a clear difference between exposure to insulin or oral anti-diabetic pharmacological therapy (glibenclamide) (RR 1.16, 95% CI 0.38 to 3.57; three studies, 590 infants) (Analysis 1.43). Caution is advised in interpreting the results due to wide CIs and low event rates (6/308 insulin group; 5/282 oral antidiabetic group).

1.44 to 1.45 Relevant biomarker changes associated with the intervention

There was no evidence of a clear difference between exposure to insulin or oral anti-diabetic pharmacological therapy (glibenclamide) for cord blood C-peptide concentration (MD -0.20 ng/mL, 95% CI -0.82 to 0.42; one study, 59 infants, Analysis 1.44) or cord blood insulin concentration (SMD 0.03, 95% CI -0.15 to 0.21; three studies, 486 infants; Analysis 1.45). Data were reported for median values for cord-C peptide by Hague 2003, Hickman 2013. The data were not included in the meta-analysis (Table 9). No data were reported in the included studies for perinatal death; z scores for birthweight, head circumference or length.

Later infant/childhood outcomes

Two studies reported on follow-up data into childhood (Ijas 2011; Rowan 2008). Both studies compared insulin with metformin. The offspring of the Ijas 2011 study were followed up at six months, 12 months and 18 months of age. Of the original 100 women randomised 97 (97%) completed the study. At 18 months; 93 children (93% of original cohort) were seen. The offspring from the Rowan 2008 study were followed up at two years of age (median age 29 months, range 22 to 38 months). Of the original 751 women randomised, 733 (98%) completed the study. At two years 577 (78%) were eligible to be seen of which 323 (56%) were seen at follow-up.

1.46 Childhood weight

At six months of age there was no evidence of a clear difference in weight between infants whose mothers had been treated with insulin and those who had been treated with oral anti-diabetic agents (MD -0.35 kg, 95% CI -0.75 to 0.05; one study, 93 children). At 12 months maternal treatment with insulin was associated with reduced weight compared with infants whose mothers had been treated with oral anti-diabetic pharmacological therapy (MD -0.62 kg, 95% CI -1.18 to -0.06; one study, 93 children). At 18 months to two years there continued to be reduced weight associated with maternal treatment with insulin compared with infants whose mothers had been treated with oral anti-diabetic agents (MD -0.44 kg, 95% CI -0.83 to -0.05, two studies, 411 children; Analysis 1.46).

1.47 Infant/Childhood height

There was no evidence of a clear difference in height between infants whose mothers had been treated with insulin and those who had been treated with oral anti-diabetic pharmacological therapy at six months of age (MD -0.70 cm, 95% CI -2.05 to 0.65, one study, 93 infants), 12 months (MD -1.30 cm, 95% CI 2.60 to 0.00; one study, 93 children) or at 18 months to two years (average MD -0.65 cm, 95% CI -2.61 to 1.31; two studies; 411 children; I^2 = 80%, Tau^2 = 1.61; Chi^2 = 5.10 (P = 0.02); Analysis 1.47).

1.48 to 1.49 Infant/childhood adiposity

There was no evidence of a clear difference in ponderal index between infants whose mothers had been treated with insulin and those who had been treated with oral anti-diabetic pharmacological therapy at six months (MD -1.00 kg/m^3, 95% CI -3.43 to 1.43; one study, 93 children); 12 months (MD -0.20 kg/m^3, 95% CI -1.12 to 0.72; one study, 93 children) or at 18 months to two years (MD -0.10 kg/m^3, 95% CI -0.88 to 0.68; one study, 93 children) (Analysis 1.48). There was no evidence of a clear difference in childhood total fat mass (%) at up to two years of age between infants whose mothers had been treated with insulin and those who had been treated with oral anti-diabetic pharmacological therapies (MD 0.50%, 95% CI -0.49 to 1.49; one study, 318 children;*low-quality evidence;* Analysis 1.49).

1.50 Childhood blood pressure (at two years)

The children of mothers randomised in the Rowan 2008 study were followed up at two years of age (median age 29 months, range 22 to 38 months). Of the original 751 women randomised, 733 (98%) completed the study. At two years 577 (78%) were eligible to be seen of which 323 (56%) were seen at follow-up. Blood pressure readings were obtained from 83/154 (54%) of children whose mother had been treated in the metformin arm and 87/164 (53%) who had been treated in the insulin arm. There was no evidence of a difference for systolic blood pressure (MD -2.24 mmHg, 95% CI -5.02 to 0.54; one study, 170 children) or diastolic blood pressure (MD -0.50 mmHg, 95% CI -16.75 to 15.75; one study, 170 children; Analysis 1.50).

No data were reported for z scores for height or weight, BMI, educational attainment, dyslipidaemia/metabolic syndrome or diabetes (type 1, type 2, or impaired glucose tolerance).

Child as an adult outcomes

None of the outcomes for the infant as an adult have been reported to date (weight, height, adiposity (including BMI, skinfold thickness, fat mass), cardiovascular health (as defined by trialists including blood pressure, hypertension, cardiovascular disease, metabolic syndrome), employment, education and social status/achievement, dyslipidaemia or metabolic syndrome, type 1 diabetes, type 2 diabetes, impaired glucose tolerance).

Health service use

1.51 Number of antenatal visits or admissions

There was no evidence of differences in the number of clinic visits between women treated with insulin and those treated with oral anti-diabetic pharmacological therapies (RR 1.00, 95% CI -0.08 to 2.08; one study, 404 women; Analysis 1.51).

1.52 Admission to neonatal intensive care unit/nursery

Maternal treatment with insulin was associated with an increased risk of the infant being *admitted to the neonatal intensive care unit or special care baby unit* compared with the infants of women treated with oral anti-diabetic pharmacological therapy (RR 1.38, 95% CI 1.19 to 1.59; 18 studies, 3441 infants; Analysis 1.52).

1.53 Duration of stay in neonatal intensive care unit or special care baby unit

There was no evidence of a difference in the duration of stay between the groups (average MD -0.20 days, 95% CI -1.79 to 1.39; three studies, 401 infants; I^2 = 72%; Tau^2 = 1.19; Chi^2 = 7.18 (P = 0.03); Analysis 1.53). Hague 2003 reported data for median duration of stay in the special care nursery and duration of hospital stay for the infant. The data were not in a suitable format to be included in a meta-analysis (Table 9).

Costs associated with the intervention

Costs of treatment were reported by one study (Ogunyemi 2007). They provide data on the cost of drugs per month which was US$20 for insulin and US$7 for glibenclamide. No other details are provided. Ashoush 2016 reported costs of 174.9 Egyptian pounds for insulin treatment and 89.66 Egyptian pounds for metformin only, or for combined metformin and insulin the cost was 159.48 Egyptian pounds. This did not include the cost of syringes for insulin treatment.

No data were reported for the following health service use outcomes: number of hospital or health professional visits (including midwife, obstetrician, physician, dietician, diabetic nurse); length of antenatal stay, length of postnatal stay (maternal), length of postnatal stay (baby), cost of maternal care, cost of offspring care, costs to families associated with the management provided, cost of dietary monitoring (e.g. diet journals, dietician, nurse visits, etc), costs to families - change of diet, extra antenatal visits, extra use of healthcare services (consultations, blood glucose monitoring, length and number of antenatal visits) or women's view of treatment advice.

Comparison 2 - Insulin type A versus insulin type B

Nine studies involving 909 women compared one insulin type with another (Balaji 2005; Balaji 2012; Herrera 2015; Ismail 2007; Jovanovic 1999; Mecacci 2003; Pettitt 2007; Poyhonen-Alho 2002; Prasad 2008).

Maternal primary outcomes

2.1 Hypertensive disorders of pregnancy (including pre-eclampsia, pregnancy-induced hypertension, eclampsia

There were no events of pre-eclampsia reported in one study comparing regular human insulin with insulin aspart in 320 women (Analysis 2.1) (Balaji 2012).

2.2 Caesarean section

There was no evidence of a clear difference in the caesarean section rate between women treated with regular human insulin compared with another insulin preparation (RR 1.00, 95% CI 0.91 to 1.09, three studies, 410 women). There was no evidence of a clear difference between regular human insulin and insulin aspart (RR 1.02, 95% CI 0.94 to 1.10; one study, 320 women) or insulin lispro (RR 0.81, 95% CI 0.42 to 1.56; two studies, 90 women). See Analysis 2.2.

Development of type 2 diabetes

No studies included in this review comparing one preparation of insulin with another reported on development of type 2 diabetes for the woman.

Neonatal primary outcomes

2.3 Large-for-gestational age (LGA)

There was no evidence of a cleat difference in the risk of being born LGA between women treated with human insulin compared with another insulin preparation (RR 1.21, 95% CI 0.58 to 2.55; three studies, 411 infants). There was no evidence of a clear difference between regular human insulin and insulin aspart (RR 1.14, 95% CI 0.50 to 2.61; one study, 320 infants) or insulin lispro (RR 1.56, 95% CI 0.29 to 8.55; two studies, 91 infants). See Analysis 2.3.

No studies included in this review comparing one preparation of insulin with another reported on **perinatal death (fetal and neonatal death) and later infant mortality**, **death or serious neonatal morbidity composite** or **neurosensory disability**.

Maternal secondary outcomes

2.4 Use of additional pharmacotherapy

There was no evidence of a clear difference between regular human insulin and other types of insulin for the use of additional pharmacotherapy (average RR 1.11, 95% CI 0.72 to 1.70; three studies, 168 women; I^2 = 56%; Tau^2 = 0.08; Chi^2 = 4.50 (P = 0.11)). There was no evidence of a clear difference for the use of additional pharmacotherapy between regular human insulin and insulin aspart (RR 1.33, 95% CI 0.83 to 2.14; one study, 47 women) insulin lispro (RR 1.38, 95% CI 0.90 to 2.09; two studies, 98 women) or Neutral Protamine Hagedorn insulin (RR 0.65, 95% CI 0.36 to 1.19; one study, 23 women). See Analysis 2.4.

2.5 Maternal hypoglycaemia

There was no evidence of a clear difference between regular human insulin and other types of insulin for the risk of maternal hypoglycaemia (RR 0.96, 95% CI 0.64 to 1.44; four studies, 504 women). There was no evidence of a clear difference for the risk of maternal hypoglycaemia between regular human insulin and insulin aspart (RR 0.90, 95% CI 0.59 to 1.35; three studies, 394 women), or Neutral Protamine Hagedorn insulin (RR 5.16, 95% CI 0.26 to 103.25; one study, 61 women). See Analysis 2.5. There were no events of maternal hypoglycaemia reported in the study by Di Cianni 2007 that compared regular human insulin with insulin lispro and with insulin aspart.

2.6 to 2.8 Glycaemic control during/after treatment

There was no evidence of a clear difference between human insulin and other insulin-treated women for maternal *HbA1c* at the end of treatment (average MD 0.04%, 95% CI -0.06 to 0.14; three studies, 411 women; I^2 = 46%; Tau^2 = 0.00; Chi^2 = 3.74 (P = 0.15); Analysis 2.6). We explored the heterogeneity by looking at the type of insulin used. The subgroup interaction test suggested there was not a differential effect between regular human insulin compared with either insulin lispro or insulin aspart. The Di Cianni 2007 study reported no differences for HbA1c between regular human insulin compared with insulin aspart or insulin lispro but did not tabulate the data.

There was no evidence of a clear difference between regular human insulin and other insulin-treated women for fasting plasma glucose (MD 0.15 mg/dL, 95% CI -2.02 to 2.32; four studies, 466 women) Analysis 2.7). The subgroup interaction test was not significant, suggesting there was not a differential effect between regular human insulin compared with either insulin lispro or insulin aspart. Herrera 2015 presented data for fasting plasma glucose, but combined GDM and type 2 diabetes which cannot be separated. This is a conference abstract only and we will wait for full publication to see if data are separated and will contact the authors. The Di Cianni 2007 study reported no differences for fasting plasma glucose between regular human insulin compared with insulin aspart or insulin lispro but did not tabulate the data.

There was no evidence of a clear difference between regular human insulin and other insulin preparations for postprandial glucose concentration (average SMD 0.08, 95% CI -0.25 to 0.42; five studies, 562 women; I^2 = 61%, Tau^2 = 0.10; Chi^2 = 12.89 (P = 0.02); Analysis 2.8). Subgroup analysis suggested no differential effect between regular human insulin and insulin aspart, insulin lispro or insulin detemir. Herrera 2015 presented data for postprandial plasma glucose but combined GDM and type 2 diabetes which cannot be separated. This is a conference abstract only and we will wait for full publication to see if data are separated and will contact authors.

Median data for HbA1c values were reported by Ismail 2007 (Table 8).

2.9 Weight gain in pregnancy

There was no evidence of a clear difference between regular human insulin and other insulin-treated (insulin aspart, Neutral Protamine Hagedorn insulin) women for weight gain in pregnancy (MD 0.46 kg, 95% CI -0.15 to 1.07; two studies, 407 women; Analysis 2.9). The Di Cianni 2007 study reported no differences for weight gain between regular human insulin compared with insulin aspart or insulin lispro but did not tabulate the data. Median data for gestational weight gain were reported by Mecacci 2003 (Table 8).

2.10 Maternal mortality

There were no events of maternal mortality in the one study, of 61 women, that reported this outcome (Analysis 2.10) (Ismail 2007)

Views of the intervention

Balaji 2005 reported that women were more comfortable with insulin aspart as it was administered just before a meal. No other data were reported.

No data were reported for adherence to the intervention; induction of labour; placental abruption, postpartum haemorrhage; postpartum infection; perineal trauma/tearing; breastfeeding at discharge, six weeks postpartum, six months or longer, quality of life, behavioural changes associated with the intervention or relevant biomarker changes associated with the intervention.

Long-term outcomes for mother

No data were reported for any of the long-term maternal outcomes (postnatal depression, BMI; postnatal weight retention or return to pre-pregnancy weight; type 1 diabetes, type 2 diabetes, impaired glucose tolerance or cardiovascular health).

Fetal/neonatal secondary outcomes

2.11 Stillbirth

Fetal death was reported in four studies including 508 infants (Balaji 2012; Ismail 2007; Pettitt 2007; Prasad 2008). One death due to umbilical cord strangulation was reported by the Pettitt 2007 study (human insulin versus insulin aspart). The other studies reported no deaths in either intervention or control groups (RR 0.36, 95% CI 0.02 to 8.06; four studies, 508 infants; Analysis 2.11).

2.12 Macrosomia

There was no evidence of an overall difference for the risk of being born macrosomic between infants whose mothers had been treated with regular human insulin and those treated with another insulin analogue (average RR 0.99, 95% CI 0.40 to 2.46, six studies, 627 infants; Analysis 2.12). There was evidence of a subgroup difference (Chi^2 = 5.83, df = 2, P = 0.05, I^2 = 65.7%). Regular human insulin was associated with reduced risk of macrosomia compared with Neutral Protamine Hagedorn insulin (RR 0.11, 95% CI 0.01 to 0.79; two studies, 84 infants), while there was no evidence of a clear difference between regular human insulin and insulin aspart (RR 1.47, 95% CI 0.71 to 3.05; four studies, 494 infants) or insulin lispro (RR 1.03, 95% CI 0.21 to 5.05; one study, 49 infants).

2.13 Small-for-gestational age (SGA)

There was no evidence of a clear difference between regular human insulin and insulin lispro in a single study reporting data for 49 infants (RR 1.04, 95% CI 0.07 to 15.73; one study, 49 infants, Analysis 2.13).

2.14 Birth trauma

There was no evidence of a clear difference between human insulin and Neutral Protamine Hagedorn insulin for the risk of nerve palsy in a single small study reporting data for 23 infants (RR 0.36, 95% CI 0.02 to 8.04; one study, 23 infants, Analysis 2.14). No data were reported for bone fracture or shoulder dystocia or birth trauma (not defined).

2.15 Gestational age at birth

Two studies reported data for gestational age at birth (Balaji 2012; Jovanovic 1999). Balaji 2012 compared regular human insulin with insulin aspart and Jovanovic 1999 compared regular human insulin with insulin lispro. The data were not combined in a meta-analysis as heterogeneity was I^2 = 92%, Tau^2 = 0.21 (data not shown). Balaji 2012 found that regular human insulin was associated with a lower gestational age at birth compared with insulin aspart (MD -0.67 weeks, 95% CI -1.01 to -0.33; one study, 320 infants; Analysis 2.15), there was no evidence of a clear difference reported between regular human insulin and insulin lispro in the Jovanovic 1999 study (MD 0.00 weeks, 95% CI -0.16 to 0.16; one study, 41 infants; Analysis 2.15). Median data for gestational age at birth were reported by Mecacci 2003 (Table 9).

2.16 Preterm birth (less than 37 weeks' gestation)

Three studies reported data for preterm birth (less than 37 weeks' gestation). Two studies compared regular human insulin with insulin aspart (Balaji 2012; Prasad 2008) and one study compared

regular human insulin with Neutral Protamine Hagedorn insulin (Poyhonen-Alho 2002). There was no evidence of a clear difference between regular human insulin and another insulin analogue (RR 2.29, 95% CI 0.52 to 10.05; three studies, 443 infants; Analysis 2.16). Caution is advised in interpreting these data as there are wide CIs and low event rates (5/218 for human insulin; 2/225 for other insulin). No data were reported for preterm birth < 32 weeks' gestation.

2.17 Congenital anomaly (not pre-specified)

Two studies including 69 infants reported data for congenital anomaly. There was no clear evidence of a difference between regular human insulin and other forms of insulin (RR 3.21, 95% CI 0.14 to 72.55; two studies, 69 infants). Pettitt 2007 compared regular human insulin with insulin aspart and Jovanovic 1999 compared regular human insulin with insulin lispro. Pettitt 2007 reported one event in the regular human insulin group. Jovanovic 1999 reported no events in either the regular human insulin or insulin lispro group (Analysis 2.17).

2.18 Birthweight

Overall, there was no evidence of a clear difference between regular human insulin and other insulin analogues for birthweight (average MD -0.04 g, 95% CI -0.17 to 0.08; seven studies, 531 infants; I^2 = 62%, Tau^2 = 0.01; Chi^2 = 15.68 (P = 0.02); Analysis 2.18). Three studies compared regular human insulin with insulin aspart (Balaji 2005; Balaji 2012; Pettitt 2007) (MD -0.01 g, 95% CI -0.11 to 0.09; three studies, 357 infants); two studies compared regular human insulin with insulin lispro (Jovanovic 1999; Mecacci 2003) (MD 0.04 g, 95% CI -0.07 to 0.14; two studies, 90 infants) and two studies compared regular human insulin with Neutral Protamine Hagedorn insulin (Ismail 2007; Poyhonen-Alho 2002) (MD -0.44 g; 95% CI -1.20 to 0.32; two studies, 84 infants, I^2 = 86%; Tau^2 = 0.26; Chi^2 = 7.28 (P = 0.007)). Di Cianni 2007 reported an increased birthweight in regular human insulin group compared with lispro and aspart groups but provided no data.

2.19 Length (cm) at birth

There was no clear evidence of a difference for length at birth between maternal treatment with regular human insulin compared with other insulin analogues (insulin lispro and aspart) (MD -0.11 cm, 95%CI -0.57 to 0.34; three studies, 388 infants) (Analysis 2.19).

2.20 Ponderal index

One study compared regular human insulin with insulin aspart (MD -0.10 kg/m^3, 95% CI -1.01 to 0.81; one study, 320 infants; Balaji 2012) and one study compared human insulin with insulin lispro (MD 0.03 kg/m^3, 95% CI -0.06 to 0.12; one study, 49 infants; Mecacci 2003). There was no evidence of a clear difference overall between regular human insulin and another insulin preparation for ponderal index (MD 0.03 kg/m^3, 95% CI -0.06 to 0.12; two studies, 369 infants; Analysis 2.20).

2.21 Neonatal hypoglycaemia

There was no clear evidence of an overall difference between regular human insulin and another insulin preparation for the risk of neonatal hypoglycaemia (RR 2.28, 95% CI 0.06 to 82.02; three studies, 165 infants; I^2 = 65%, Tau^2 = 4.37; Chi^2 = 2.89 (P = 0.09); Analysis 2.21). One study found no evidence of a clear difference in the risk for neonatal hypoglycaemia between infants whose mothers had been treated with regular human insulin plus Neutral Protamine Hagedorn insulin or insulin aspart (Prasad 2008) (RR 13.00, 95% CI 0.75 to 224.77; one study, 100 infants). One study that compared regular human insulin and insulin lispro (Jovanovic 1999) reported no events of neonatal hypoglycaemia in either the regular human insulin or the insulin lispro group. There was no evidence of a difference in the risk of neonatal hypoglycaemia between infants whose mothers had been treated with regular human insulin or Neutral Protamine Hagedorn insulin (RR 0.36, 95C% CI 0.02 to 8.04; one study, 23 infants). Data should be interpreted with caution due to low event rates, low sample size and wide CIs.

2.22 Respiratory distress syndrome

There was no evidence of a difference in the risk of respiratory distress syndrome between infants whose mothers had been treated with regular human insulin or insulin aspart (RR 0.52, 95% CI 0.10 to 2.79; one study, 320 infants, Analysis 2.22).

2.23 Neonatal jaundice (Hyperbilirubinaemia)

Overall there was no evidence of a difference in the risk of hyperbilirubinaemia between infants whose mothers had been treated with regular human insulin and those treated with another insulin analogue (average RR 0.48, 95% CI 0.05 to 4.93; two studies, 123 infants; I^2 = 57%; Tau^2 = 1.74; Chi^2 = 2.30, (P = 0.13); Analysis 2.23). There was no clear evidence of a difference between groups for regular human insulin plus Neutral Protamine Hagedorn insulin compared to insulin aspart reported by Prasad 2008 (RR 0.11, 95% CI 0.01 to 2.01; one study, 100 infants) or between regular human insulin compared with Neutral Protamine Hagedorn insulin reported by Poyhonen-Alho 2002 (RR 1.09, 95% CI 0.28 to 4.32, one study, 23 infants). Data should be interpreted with caution due to low event rates, low sample size and wide CIs.

2.24 Hypocalcaemia

No events of hypocalcaemia were reported in infants whose mothers had been treated with regular human insulin or insulin lispro

in a single small study of 42 infants (Jovanovic 1999) (Analysis 2.24) .

No data were reported for neonatal death; perinatal death; five-minute Apgar less than seven; head circumference; z scores for birthweight, head circumference, length; measures of adiposity; polycythaemia or relevant biomarker changes associated with the intervention cord blood measures.

Infant/childhood secondary outcomes

No data were reported for any of our pre-specified infant/childhood secondary outcomes for this review (weight, height, head circumference and z scores; adiposity; educational attainment; blood pressure; type 1 or type 2 diabetes, impaired glucose tolerance; dyslipidaemia or metabolic syndrome).

Child as an adult outcomes

No data were reported for any of our pre-specified infant as an adult secondary outcomes for this review (weight, height, adiposity, cardiovascular health, employment, education and social status/achievement; dyslipidaemia or metabolic syndrome, type 1 diabetes, type 2 diabetes, impaired glucose tolerance).

Health service use

No data were reported for any health service usage outcomes prespecified for this review (number of antenatal visits or admissions, umber of hospital or health professional visits, admission to neonatal intensive care unit/nursery, duration of stay in neonatal intensive care unit or special care baby unit, length of antenatal stay, length of postnatal stay (maternal), length of postnatal stay (baby), cost of maternal care, cost of offspring care, costs associated with the intervention, costs to families associated with the management provided, cost of dietary monitoring, costs to families, extra use of healthcare services, women's view of treatment advice).

Comparison 3 - Insulin versus diet

This comparison was reported in six studies involving 1226 women (Coustan 1978; Notelovitz 1971; O'Sullivan 1975a; O'Sullivan 1975b; Persson 1985; Thompson 1990). One study was not included in the meta-analysis as data for women with gestational diabetes could not be separated from women with pregestational diabetes (Notelovitz 1971).

Maternal primary outcomes

Hypertensive disorders of pregnancy (including pre-eclampsia, pregnancy-induced hypertension, eclampsia)

Pre-eclampsia, pregnancy-induced hypertension or eclampsia were not reported as outcomes in any of the included studies in this review.

3.1 Caesarean section

There was no evidence of a difference in the risk of birth by*caesarean section* between women treated with insulin and those treated with diet (RR 0.85, 95% CI 0.50 to 1.42, two studies, 133 women) (Analysis 3.1).

3.2 Development of type 2 diabetes

There was no evidence of a difference in the risk of developing type 2 diabetes postpartum between women treated with insulin and those treated with diet or standard antenatal care (RR 0.98, 95% CI 0.79 to 1.21; two studies, 653 women; Analysis 3.2). O'Sullivan 1975a reported follow-up to a maximum of 15 years. Coustan 1978 reported data for follow-up at five weeks postpartum.

Neonatal primary outcomes

3.3 Perinatal (fetal and neonatal)death and later infant mortality

There was no evidence of a difference in the risk of perinatal death between infants whose mothers had been treated with insulin and those who had been treated with diet/standard antenatal care (RR 0.74, 95% CI 0.41 to 1.33; four studies, 1137 infants; Analysis 3.3). No events of perinatal death were reported in two studies including 297 infants (Persson 1985; Thompson 1990).

3.4 Large-for-gestational age (LGA)

There was no difference in the risk of being born LGA between infants whose mothers had been treated with insulin or diet in one study including 202 infants (Persson 1985) (RR 0.85, 95% CI 0.41 to 1.78; one study, 202 infants, Analysis 3.4).

No data were reported for death or serious morbidity composite (variously defined by trials, e.g. perinatal or infant death, shoulder dystocia, bone fracture or nerve palsy) or neurosensory disability.

Maternal secondary outcomes

3.5 Use of additional pharmacotherapy

Use of additional pharmacotherapy was required by 14% (15/105) of women randomised to the dietary intervention groups reported in a single study including 202 women (Persson 1985). No analysis was conducted as the women in the insulin group all received insulin (data shown, see Analysis 3.5).

3.6 Maternal hypoglycaemia

There were no events of maternal hypoglycaemia reported on one study of 95 women (Thompson 1990) (Analysis 3.6).

3.7 Glycaemic control during/end of treatment

Insulin was associated with a slight increase in the mean HbA1c at the end of treatment (6.9 mmol/mol ± 0.2; 86 women) compared with diet only treatment (6.8 mmol/mol ± 0.2; 75 women) (MD 0.10 mmol/mol, 95% CI 0.04 to 0.16; one study, 161 women, Analysis 3.7) (Persson 1985). There was no evidence of a difference in the mean fasting blood glucose concentration (MD 1.60 mg/dL, 95% CI -2.97 to 6.17, one study, 68 women, Analysis 3.7) or two-hour postprandial glucose level (MD 0.30 mg/dL, 95% CI -5.32 to 5.92, one study, 68 women, Analysis 3.7) during treatment reported in a single study including 68 women (Thompson 1990). Persson 1985 reported maternal blood glucose in the insulin-treated group and diet-treated group, however the values are presented in a figure with median and 95% CI values. The data could not be included in a meta-analysis and authors were unable to provide original data. HbA1c values at birth were estimated from a bar graph (Persson 1985). Coustan 1978 reported data for fasting glucose concentration and two-hour postprandial glucose concentration at the end of treatment but the data are reported by the number of observations and not the number of women randomised. The data could not be included in a meta-analysis but indicate a reduced fasting glucose concentration in the insulin groups compared with the diet group (Table 8). O'Sullivan 1975a reported data as the number of samples rather than per woman randomised and the data have therefore not been included in the meta-analysis. Insulin was associated with reduced fasting blood glucose concentration (blood glucose concentration 80.1 mg/dL (SD 23); 295 samples) compared with routine antenatal care (blood glucose concentration 69.1 mg/dL (SD 16.9); 71 samples). At two to three hours postprandial, the authors report that insulin reduced blood glucose concentration (mean blood glucose concentration 80.1 mg/dL (SD 23); 295 samples) compared with routine antenatal care (mean blood glucose concentration 83.0 mg/dL (SD 21.2); 233 samples).

3.8 Weight gain during pregnancy

There was no evidence of a difference between insulin and dietary intervention groups for weight gain in pregnancy (MD 1.73 kg, 95% CI -3.31 to 6.77, one study, 38 women, Analysis 3.8) (Coustan 1978).

No data were reported in the included studies for the other maternal secondary outcomes pre-specified in this review (use of adherence to the intervention; induction of labour; placental abruption; postpartum haemorrhage; postpartum infection; perineal trauma/tearing; breastfeeding at discharge; six weeks postpartum, six months or longer; maternal mortality; sense of well-being and quality of life; behavioural changes associated with the intervention; views of the intervention or relevant biomarker changes associated with the intervention).

Long-term outcomes for mother

No data were reported for postnatal glycaemic level (HbA1c, glucose tolerance test); blood pressure; BMI; weight (kg); return to pre-pregnancy weight; or insulin sensitivity.

Fetal/neonatal outcomes

3.9 Neonatal death

There was no evidence of a difference for the risk of neonatal death between infants whose mothers had been treated with insulin and those who had been treated with standard antenatal care (RR 0.72, 95% CI 0.23 to 2.23; one study, 611 infants; Analysis 3.9).

3.10 Macrosomia

Maternal treatment with insulin was associated with a reduced risk of macrosomia in the infant compared with diet/standard antenatal care (RR 0.30, 95% CI 0.18 to 0.50; three studies, 717 infants; three studies; I^2 = 0%; Analysis 3.10). Of interest, these data differ from the single study reporting LGA which found no difference between groups. Two studies were undertaken in the 1970s (Coustan 1978; O'Sullivan 1975a) and one in 1990 (Thompson 1990). The insulin regimens may differ from those administered today and appear to be fixed doses of Neutral Protamine Hagedorn insulin, with or without regular human insulin rather than a weight adjusted dose which is seen in more recent studies. This may in part explain the reduced effectiveness of insulin for this outcome.

3.11 Small-for-gestational age (SGA)

There was no evidence of a difference between insulin-treated and diet-treated groups for the risk of the infant being born SGA (RR 0.35, 95% CI 0.05 to 2.40; two studies, 240 infants; Analysis 3.11).

3.12 Birth trauma (shoulder dystocia, bone fracture, nerve palsy)

There were no events of shoulder dystocia in the infants of mothers who had been treated with either insulin or the diet alone in two studies including 133 infants (Coustan 1978; Thompson 1990). There were no events of nerve palsy in either group reported from a single study including 38 infants (Coustan 1978). No data were reported for bone fracture in any of the included trials.

3.13 Gestational age at birth

There was no evidence of a difference for gestational age at birth between infants whose mothers had been treated with insulin or with diet (MD -0.66 weeks, 95% CI -1.37 to 0.06; two studies, 106 infants; Analysis 3.13).

3.14 Preterm birth (less than 37 weeks' gestation; and less than 32 weeks' gestation)

There was no evidence of a difference for the risk of preterm birth (less than 37 weeks' gestation) between infants whose mothers had been treated with insulin and those who had been treated with standard antenatal care (RR 1.09, 95% CI 0.64 to 1.85; one study, 611 infants, Analysis 3.14). No data were reported for preterm birth less than 32 weeks' gestation.

3.15 Birthweight

Maternal treatment with insulin was associated with a reduced birthweight compared with maternal treatment with diet alone (MD -342.85 g, 95% CI -561.11 to -124.60; two studies, 106 infants; Analysis 3.15).

3.16 Ponderal Index

Maternal treatment with insulin was associated with a reduced ponderal index compared with maternal treatment with diet alone (MD -0.18 kg/m^3, 95% CI -0.34 to -0.02; one study, 68 infants; Analysis 3.16).

3.17 Neonatal hypoglycaemia

There was no evidence of a difference between infants whose mothers had been treated with insulin and diet-treated groups for the risk of neonatal hypoglycaemia (RR 0.88, 95% CI 0.34 to 2.24; three studies, 176 infants; I^2 = 40%, Tau^2 = 0.24, Analysis 3.17).

3.18 Hyperbilirubinaemia

There were no events of hyperbilirubinaemia in a single study including 68 infants (Thompson 1990) (Analysis 3.18).

3.19 Hypocalcaemia

There were no events of hypocalcaemia in a single study including 68 infants (Thompson 1990) (Analysis 3.19).

3.20 Polycythaemia

There was no evidence of a difference between infants whose mothers had been treated with insulin and diet-treated groups for the risk of polycythaemia (RR 0.90, 95% CI 0.30 to 2.67; one study, 70 infants; Analysis 3.20).

3.21 Relevant biomarker changes associated with the intervention (including insulin, cord c-peptide)

Dietary interventions were associated with a reduction in cord blood C-peptide concentration compared with insulin-treated groups (MD 0.03 ng/mL, 95% CI 0.02 to 0.04; one study, 202 infants; Analysis 3.21).

No data were reported for other neonatal outcomes pre-specified in this review (stillbirth; five-minute Apgar less than seven; head circumference; length; z score for birthweight, head circumference and z score, length and z score; skinfold thickness measurements (mm); fat mass or respiratory distress syndrome).

Infant/childhood outcomes

No data were reported for any of the pre-specified infant/childhood secondary outcomes for this review (weight and z score; height and z score; head circumference and z score; adiposity; educational attainment; blood pressure; type 1 diabetes; type 2 diabetes; impaired glucose tolerance; dyslipidaemia or metabolic syndrome).

Child as an adult outcomes

No data were reported for any of the pre-specified infant as an adult secondary outcomes for this review (weight, height; adiposity; cardiovascular health; employment, education and social status/achievement; dyslipidaemia or metabolic syndrome; type 1 diabetes; type 2 diabetes; impaired glucose tolerance).

Health service use

No data were reported for any of the pre-specified health service usage outcomes for this review (number of antenatal visits or admissions; number of hospital or health professional visits; admission to neonatal intensive care unit/nursery; duration of stay in neonatal intensive care unit or special care baby unit; length of antenatal stay; length of postnatal stay (maternal); length of postnatal stay (baby); cost of maternal care; cost of offspring care; costs associated with the intervention; costs to families associated with the management provided; cost of dietary monitoring; costs to families; extra use of healthcare services or women's view of treatment advice).

Comparison 4 - Insulin versus exercise

This comparison was reported in a single study including 41 women but data only reported for 34 women (Bung 1993).

Maternal primary outcomes

Caesarean section

There was no evidence of a difference between treatment with insulin and treatment with exercise for the risk of birth by caesarean section (RR 1.50, 95% CI 0.29 to 7.87; one study, 34 women) (Analysis 4.1).
No data were reported for the outcomes of pre-eclampsia or development of type 2 diabetes.

Neonatal primary outcomes

No data were reported for any of the pre-specified neonatal primary outcomes for this review (perinatal death; LGA; a composite of serious infant death or morbidity or neurosensory disability).

Maternal secondary outcomes

No data were reported for any of the pre-specified maternal secondary outcomes for this review (use of additional pharmacotherapy, maternal hypoglycaemia, glycaemic control during/end of treatment, weight gain in pregnancy, adherence to the intervention, induction of labour, placental abruption, postpartum haemorrhage, postpartum infection, perineal trauma/tearing, breastfeeding at discharge, six weeks postpartum, six months or longer, maternal mortality, sense of well-being and quality of life, behavioural changes associated with the intervention, views of the intervention, relevant biomarker changes associated with the intervention).

Long-term outcomes for mother

No data were reported for any of the long-term outcomes for the mother pre-specified for this review (postnatal depression; BMI; postnatal weight retention or return to pre-pregnancy weight; type 1 diabetes; type 2 diabetes; impaired glucose tolerance or cardiovascular health).

Fetal/neonatal secondary outcomes

Macrosomia

There was no evidence of a difference for the risk of macrosomia between infants whose mothers had been treated with insulin and those treated with exercise (RR 2.00, 95% CI 0.42 to 9.50; one study, 34 infants) (Analysis 4.2).

Gestational age at birth

There was no evidence of a difference for the timing of gestational age at birth between infants whose mothers had been treated with insulin and those treated with exercise (MD -0.80 weeks, 95% CI -2.05 to 0.45, one study, 34 infants) (Analysis 4.3).

Birthweight (g)

There was no evidence of a difference in birthweight between infants whose mothers had been treated with insulin and those treated with exercise (MD 103.00 g, 95% CI -245.40 to 451.40; one study, 34 infants) (Analysis 4.4).

Length at birth (cm)

There was no evidence of a difference in length at birth (cm) between infants whose mothers had been treated with insulin or those treated with diet (MD 1.60 cm, 95% CI -0.01 to 3.21; one study, 34 infants) (Analysis 4.5).

Neonatal hypoglycaemia

There was no evidence of a difference for the risk of neonatal hypoglycaemia between infants whose mothers had been treated with insulin and those treated with exercise (RR 0.50, 95% CI 0.05 to 5.01; one study, 34 infants) (Analysis 4.6).

Respiratory distress syndrome

There were no events of respiratory distress reported in one study of 34 infants (Bung 1993).

Hyperbilirubinaemia

There were no events of hyperbilirubinaemia reported in one study of 34 infants (Bung 1993).

Hypocalcaemia

There were no events of hypocalcaemia reported in one study of 34 infants (Bung 1993).
There were no data reported for stillbirth; neonatal death; SGA, birth trauma, preterm birth, five-minute Apgar less than seven minutes, birthweight z score, head circumference and z score, length z score, ponderal index, adiposity, polycythaemia, relevant biomarker changes associated with the intervention.

Infant/childhood outcomes

No data were reported for any of the pre-specified infant/childhood secondary outcomes for this review (weight and z score; height and z score; head circumference and z score; adiposity; educational attainment; blood pressure; type 1 diabetes; type 2 diabetes; impaired glucose tolerance; dyslipidaemia or metabolic syndrome).

Child as an adult outcomes

No data were reported for any of the pre-specified infant as an adult secondary outcomes for this review (weight, height; adiposity; cardiovascular health; employment, education and social status/achievement; dyslipidaemia or metabolic syndrome; type 1 diabetes; type 2 diabetes; impaired glucose tolerance).

Health service use

No data were reported for any of the pre-specified health service usage outcomes for this review (number of antenatal visits or admissions; number of hospital or health professional visits; admission to neonatal intensive care unit/nursery; duration of stay in neonatal intensive care unit or special care baby unit; length of antenatal stay; length of postnatal stay (maternal); length of postnatal stay (baby); cost of maternal care; cost of offspring care; costs associated with the intervention; costs to families associated with the management provided; cost of dietary monitoring; costs to families; extra use of healthcare services or women's view of treatment advice).

Comparison 5 - Insulin regimen A versus Insulin regimen B (timing, number of injections)

One study compared twice-daily insulin with four times daily doses (Nachum 1999). One study compared three injections with six injections (Castorino 2011). In total the two studies involved 314 women.

Maternal primary outcomes

Pregnancy-induced hypertension

There was no evidence of a difference between a maternal insulin regimen twice daily or four times daily for the risk of pregnancy-induced hypertension (RR 1.11, 95% CI 0.51 to 2.42; one study, 274 women) (Analysis 5.1).

Caesarean section

There was no evidence of a difference between a maternal insulin regimen twice daily or four times daily for the risk of birth by caesarean section (RR 0.99, 95% CI 0.68 to 1.44; one study, 274 women). There was no evidence of a difference between a maternal regimen using three injections daily or six injections daily for the risk of birth by caesarean section (RR 1.06, 95% CI 0.17 to 6.72; one study, 37 women) (Analysis 5.2).
No data were reported for the *development of type 2 diabetes* in either of the included studies.

Neonatal primary outcomes

Perinatal (fetal and neonatal death) and later infant mortality

There was no evidence of a difference between a maternal insulin regimen twice daily or four times daily for the risk of perinatal death (RR 3.04, 95% CI 0.13 to 74.07; one study, 274 women) (Analysis 5.3).

Large-for-gestational age (LGA)

There was no evidence of a difference between a maternal insulin regimen twice daily or four times daily for the risk of being born LGA (RR 1.16, 95% CI 0.79 to 1.69; one study, 274 women). There was no evidence of a difference between a maternal regimen using three injections daily or six injections daily for the risk of being born LGA (RR 0.35, 95% CI 0.04 to 3.08; one study, 37 infants) (Analysis 5.4).

Composite of serious neonatal morbidity and mortality

A maternal regimen of insulin twice daily was associated with an increased risk of death or serious morbidity composite compared with a four times daily insulin regimen (RR 1.69, 95% CI 1.08 to 2.64; one study, 274 women) (Analysis 5.5).
No data were reported for *neurosensory disability*.

Maternal secondary outcomes

Maternal hypoglycaemia

There was no evidence of a difference between a maternal insulin regimen twice daily or four times daily for the risk of maternal hypoglycaemia (RR 1.01, 95% CI 0.06 to 16.06; one study, 274 women) (Analysis 5.6).

Glycaemic control (end of treatment)

There was no evidence of a difference for mean fasting blood glucose concentration between women using a regimen of three injections per day compared with six injections per day (MD 4.00 mg/dL, 95% CI -0.84 to 8.84; one study, 37 women) (Analysis 5.7). A maternal regimen of insulin four times daily was associated with a decrease in HbA1c at the end of treatment compared with a twice-daily regimen (MD 0.30%, 95% CI 0.06 to 0.54; one study, 274 women). There was no evidence of a difference for mean HbA1c between women using a regimen of three injections per day compared with six injections per day (MD -0.10%, 95% CI -0.29 to 0.09; one study, 37 women) (Analysis 5.8).

Weight gain in pregnancy

There was no evidence of a difference between a maternal insulin regimen twice daily or four times daily for weight gain in pregnancy (MD 0.70 kg, 95% CI -0.14 to 1.54; one study, 274 women) (Analysis 5.9). Castorino 2011 reported no evidence of a difference in gestational weight gain per week 0.2 +/- 0.3 in the three injection regimen and 0.3 +/- 0.2 in the six injection regimen.

No data were reported for other pre-specified maternal secondary outcomes for this review (use of additional pharmacotherapy, adherence to the intervention, induction of labour, placental abruption, postpartum haemorrhage, postpartum infection, perineal trauma/tearing, breastfeeding at discharge, six weeks postpartum, six months or longer, maternal mortality, sense of well-being and quality of life, behavioural changes associated with the intervention, views of the intervention, relevant biomarker changes associated with the intervention).

Long-term outcomes for mother

No data were reported for any of the long-term outcomes for the mother pre-specified for this review (postnatal depression; BMI; postnatal weight retention or return to pre-pregnancy weight; type 1 diabetes; type 2 diabetes; impaired glucose tolerance or cardiovascular health).

Fetal/neonatal outcomes

Macrosomia

There was no evidence of a difference between a maternal insulin regimen twice daily or four times daily for the risk of macrosomia (RR 1.20, 95% CI 0.72 to 2.01; one study, 274 women) (Analysis 5.10).

Small-for-gestational age (SGA)

There was no evidence of a difference between a maternal insulin regimen twice daily or four times daily for the risk of being born SGA (RR 1.78, 95% CI 0.53 to 5.93; one study, 274 women) (Analysis 5.11).

Birth trauma (not specified)

There was no evidence of a difference between a maternal insulin regimen twice daily or four times daily for the risk of birth trauma (RR 1.52, 95% CI 0.26 to 8.97; one study, 274 women) (Analysis 5.12).

Gestational age at birth

There was no evidence of a difference between a maternal insulin regimen twice daily or four times daily for the timing of gestational age at birth (MD -0.30 weeks, 95% CI -0.72 to 0.12; one study, 274 women) (Analysis 5.13).

Five-minute Apgar less than seven

There was no evidence of a difference between a maternal insulin regimen twice daily or four times daily for a five-minute Apgar score less than seven (RR 0.34, 95% CI 0.07 to 1.65; one study, 274 women) (Analysis 5.14).

Birthweight

There was no evidence of a difference between a maternal insulin regimen twice daily or four times daily for the outcome of birthweight (MD -1.00 g, 95% CI -150.49 to 148.49; one study, 274 women). There was no evidence of a difference between a maternal regimen of three injections of insulin daily compared with six injections for the outcome of birthweight (MD -197.00 g, 95% CI -495.43 to 101.43; one study, 37 infants) (Analysis 5.15).

Neonatal hypoglycaemia

A maternal regimen of insulin twice daily was associated with an increased risk of neonatal hypoglycaemia compared with a regimen of insulin four times daily (RR 8.12, 95% CI 1.03 to 64.03; one study, 274 infants) (Analysis 5.16). Data should be interpreted with caution due to large treatment effect and wide CIs suggesting imprecision.

Respiratory distress syndrome

There was no evidence of a difference between a maternal insulin regimen twice daily or four times daily for the risk of respiratory distress syndrome (RR 0.34, 95% CI 0.01 to 8.23; one study, 274 infants) (Analysis 5.17).

Hyperbilirubinaemia

A maternal regimen of insulin twice-daily insulin was associated with an increased risk of hyperbilirubinaemia compared with a four times a day regimen (RR 1.96, 95% CI 1.10 to 3.49; one study, 274 infants) (Analysis 5.18).

Polycythaemia

There was no evidence of a difference between a maternal insulin regimen twice daily or four times daily for the risk of polycythaemia (RR 0.43, 95% CI 0.11 to 1.65; one study, 274 infants) (Analysis 5.19).

There were no data reported for other secondary neonatal outcomes pre-specified for this review (stillbirth; neonatal death; preterm birth, birthweight z score, head circumference and z score, length z score, ponderal index, adiposity, relevant biomarker changes associated with the intervention).

Infant/childhood outcomes

No data were reported for any of the pre-specified infant/childhood secondary outcomes for this review (weight and z score; height and z score; head circumference and z score; adiposity; educational attainment; blood pressure; type 1 diabetes; type 2 diabetes; impaired glucose tolerance; dyslipidaemia or metabolic syndrome).

Child as an adult outcomes

No data were reported for any of the pre-specified infant as an adult secondary outcomes for this review (weight, height; adiposity; cardiovascular health; employment, education and social status/achievement; dyslipidaemia or metabolic syndrome; type 1 diabetes; type 2 diabetes; impaired glucose tolerance).

Health service use

No data were reported for any of the pre-specified health service usage outcomes for this review (number of antenatal visits or admissions; number of hospital or health professional visits; admission to neonatal intensive care unit/nursery; duration of stay in neonatal intensive care unit or special care baby unit; length of antenatal stay; length of postnatal stay (maternal); length of postnatal stay (baby); cost of maternal care; cost of offspring care; costs associated with the intervention; costs to families associated with the management provided; cost of dietary monitoring; costs to families; extra use of healthcare services or women's view of treatment advice).

ADDITIONAL SUMMARY OF FINDINGS [*Explanation*]

Insulin compared to anti-diabetic agent for the treatment of women with gestational diabetes

Patient or population: Infants of women with gestational diabetes.
Setting: Primary and secondary care (Canada, Egypt, USA, Brazil, Finland, Iran, Australia, New Zealand, India)
Intervention: Insulin
Comparison: Oral anti-diabetic pharmacological therapy.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with oral anti-diabetic agent	Risk with insulin				
Large-for-gestational age (birthweight > 90th centile)	159 per 1000	161 per 1000 (121 to 215)	Average RR 1.01 (0.76 to 1.35)	2352 (13 RCTs)	⊕⊕⊕◯ MODERATE [1]	
Perinatal (fetal and neonatal death) and later infant mortality	8 per 1000	7 per 1000 (2 to 20)	RR 0.85 (0.29 to 2.49)	1463 (10 RCTs)	⊕⊕◯◯ LOW [1,2]	Event rates are low 5/728 for the group whose mothers were treated with insulin and 6/735 for the group whose mothers were treated with anti-diabetic pharmacological therapies. No data were reported for later infant mortality
Death or serious morbidity composite	319 per 1000	329 per 1000 (268 to 402)	RR 1.03 (0.84 to 1.26)	760 (2 RCTs)	⊕⊕⊕◯ MODERATE [1]	These 2 trials compared insulin with metformin. No other trials reported this outcome One trial included: resuscitation in the deliv-

						ery room, preterm birth (< 37 weeks), neonatal intensive care unit admission, birth injury or diagnosis of neonatal complication, glucose infusion, antibiotics or phototherapy One trial included: hypoglycaemia -< 2.6 mmol/L, RDS, phototherapy, birth trauma, Apgar < 7 at 5 minutes, preterm birth (<37 weeks)
Neonatal hypoglycaemia	111 per 1000	126 per 1000 (94 to 169)	Average RR 1.14 (0.85 to 1.52)	3892 (24 RCTs)	⊕⊕◯◯ LOW [1,5]	
Adiposity at birth - percentage fat mass	The mean percentage fat mass was 12.8%	MD 1.6% lower (3.77 lower to 0.57 higher)	MD -1.60 (-3.77, 0.57)	82 (1 RCT)	⊕⊕⊕◯ MODERATE [4]	
Adiposity at birth - skinfold sum (mm)	The mean skinfold sum was 16 mm	MD 0.8 mm lower (0.49 lower to 0.73 higher)	MD -0.80 mm (-2.33, 0.73)	82 (1 RCT)	⊕◯◯◯ VERY LOW [2,4,7]	
Adiposity in childhood up to 2 years - total fat mass (%)	The mean childhood Total fat mass (%) - Metformin was 16.4%	MD 0.5% higher (0.49 lower to 1.49 higher)	MD 0.50 % (-0.49, 1.49)	318 (1 RCT)	⊕⊕◯◯ LOW [1,4]	
Childhood/adulthood diabetes (type 1, type 2) - not reported	-	-	-	-	-	No data were pre-specified or reported for type 1 or type 2 diabetes in childhood or adulthood in the included trials in this review

Neurosensory disability in later childhood (18 months) Mild developmental delay Hearing impairment Visual impairment	104 per 1000 0 per 1000 21 per 1000	111 per 1000 (34 to 358) 0 per 1000 (0 to 0) 6 per 1000 (1 to 60)	RR 1.07, (0.33 to 3.44) RR 0.31; (0.01 to 7.49) RR 0.31, (0.03 to 2.90)	93 (1 RCT)	⊕⊕◯◯ LOW [4,6]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

__CI:__ Confidence interval; __MD:__ mean difference; __RDS:__ respiratory distress syndrome; __RR:__ Risk ratio;

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Risk of bias: Most of the trials were not blinded. Downgraded one level.
[2] Imprecision: Event rates are low and confidence intervals are wide crossing the line of no effect. Downgraded one level.
[3] Inconsistency: I^2 = 78%. Downgraded one level.
[4] Evidence is based on a single trial. Downgraded one level.
[5] Inconsistency: I^2 = 51%. Downgraded one level.
[6] Imprecision: Wide confidence intervals. Downgraded one level.
[7] Risk of bias: Selective reporting and other bias detected. Downgraded one level.

DISCUSSION

Summary of main results

Insulin versus oral anti-diabetic pharmacological therapy

Twenty-eight studies reported the comparison of insulin with oral anti-diabetic pharmacological therapy. Insulin was associated with an increased risk of hypertensive disorders of pregnancy (not defined) compared with oral anti-diabetic pharmacological therapy and may possibly increase the risk for induction of labour although the evidence was not clear for this outcome. There was no evidence of a clear difference between groups for the risk of pre-eclampsia, caesarean section, or development of type 2 diabetes for the mother (Summary of findings for the main comparison). No data were reported for eclampsia. For the infant there was no evidence of a difference between groups for the risk of perinatal death, being born large-for-gestational age (LGA), a composite of serious neonatal outcomes or neurosensory disability in childhood (Summary of findings 2). For secondary maternal outcomes, there was no evidence of a difference between women who had been treated with insulin and those treated with oral anti-diabetic pharmacological therapies for the outcomes of maternal hypoglycaemia, glycaemic control, postpartum haemorrhage or breastfeeding. Insulin was associated with an increase in gestational weight gain compared with oral anti-diabetic pharmacological therapies. No other pre-specified maternal outcomes were reported. Long-term outcomes for the mother were poorly reported. There was no evidence of a difference between groups identified for body mass index (BMI) at six weeks postpartum or impaired glucose tolerance up to one year follow-up. There was no evidence of a difference for any of the reported neonatal outcomes in this review between infants whose mothers had been treated with insulin and those treated with oral anti-diabetic pharmacological therapies. Long-term outcomes were poorly reported with only two of 15 studies reporting data. There was no evidence of a difference between groups for height, adiposity or blood pressure up to 18 months follow-up. Maternal treatment with insulin was associated with a reduced childhood weight at 12 and 18 months of age compared with children whose mothers had been treated with oral anti-diabetic pharmacological therapies. Insulin treatment was associated with an increased risk for the infant being admitted to the neonatal intensive care unit although there was no evidence of a difference for the duration of stay in the neonatal intensive care unit.

One insulin versus another insulin

Data were included in meta-analyses from ten studies comparing regular human insulin with another insulin analogue. There was no evidence of an overall difference between the groups for any of the primary or secondary maternal or infant outcomes where data were reported. No data were reported for long-term infant outcomes into childhood or adulthood.

Insulin versus diet/standard care

Five of six included studies contributed data to meta-analyses to the comparison of insulin versus diet. Data for the pre-specified outcomes for this review were poorly reported. There was no evidence of a difference between women treated with insulin and those treated with diet for the risk of birth by caesarean section or development of type 2 diabetes. Hypertensive disorders of pregnancy (including pre-eclampsia, pregnancy-induced hypertension, eclampsia) was not reported as an outcome in any of the included studies of this comparison. There were no differences between groups for perinatal death or being born LGA. A composite of mortality and serious infant morbidity and the outcome of neurosensory disability were not reported in any of the included studies. There was a small, but clinically insignificant increase, in HbA1C at the end of treatment in women who had been treated with insulin compared to diet. Women treated with insulin were less likely to have a macrosomic infant compared to women treated with diet. Only one study reported on the number of women in the diet group who required supplementary insulin (14%). There were no long-term infant as a child or adult data reported in any of the included studies for this comparison.

Insulin versus exercise

Only one small study of 34 women reported a comparison of insulin with exercise. Data for the pre-specified outcomes for this review were poorly reported. There was no evidence of a difference between groups for the risk of birth by caesarean section and no data were reported for any of the other maternal or infant primary outcomes for this review. There was no evidence of a difference between groups for the limited number of neonatal outcomes reported in the study. No long-term data were reported for the mother or for the infant as a child or adult.

Regimen A versus Regimen B

Two studies examined different regimens of providing insulin. One study compared insulin four times a day with twice daily and the second study compared three injections daily with six injections. Data for the pre-specified outcomes for this review were poorly reported. Women treated with insulin four times daily were more likely to have a lower HbA1c at the end of treatment than women receiving insulin twice daily. No long-term data were reported for the mother or for the infant as a child or adult.

Overall completeness and applicability of evidence

The studies included in this review were conducted in women diagnosed with gestational diabetes. There were a variety of methods used to diagnose gestational diabetes mellitus although this is unlikely to influence the treatment effectiveness. The majority of the studies were conducted in high-resource contexts from developed countries.

Not all of the outcomes of interest for this review were addressed in the included studies in particular for the long-term maternal and infant as a child and adult health outcomes. Only two of 49 studies reported on follow-up into childhood.

Quality of the evidence

The method of random sequence generation was adequately reported in 23/53 studies (low risk of bias), we judged 29/53 studies to be of unclear risk of bias due to lack of methodological details. The method of allocation concealment was adequately reported in 19/53 studies (low risk of bias). Thirty-three of 53 studies provided insufficient methodological details to judge method of allocation concealment and were judged to be of unclear risk of bias. One study was judged to be of high risk of selection bias as the first 20 women were randomised using a quasi-randomised method (Figure 4; Figure 5).

Performance bias was judged to be of high risk in 40/53 studies which were open-label. Only two studies were judged to be of low risk of performance bias. Detection bias was judged to be of unclear risk of bias in 44/53 studies due to insufficient details being reported. Only five of 53 studies were judged to be of low risk of detection bias (Figure 4; Figure 5).

Attrition bias was judged to be low risk of bias in 31/53 studies, of unclear risk of bias in 14/53 studies and of high risk of bias in 8/53 studies (Figure 4; Figure 5). Reporting bias was judged to be of high risk of bias in 34/53 studies mainly due to lack of reporting of pre-specified outcomes or reporting of outcomes that had not been pre-specified. Fourteen of 53 studies were judged to be of unclear risk of reporting bias and only five studies were judged to be of low risk of reporting bias. Other sources of bias were judged to be of high risk of bias in 20/53 studies and of low risk of bias in 26/53 studies. Seven studies were judged to be of unclear risk of other bias due to insufficient information (Figure 4; Figure 5).

We examined the quality of the overall body of the evidence for the comparison of insulin with oral anti-diabetic pharmacological therapy using GRADE methodology (GRADEpro). The quality of the evidence ranged from *low quality* to *moderate quality.* The evidence was downgraded for imprecision (low event rates, wide confidence intervals, evidence based on a single study), risk of bias (lack of blinding, lack of details for method of randomisation/allocation concealment) and inconsistency ($I^2 > 50\%$) (Summary of findings for the main comparison; Summary of findings 2).

Potential biases in the review process

We made every attempt to minimise bias. We searched multiple databases without language or date restrictions to limit bias by identifying all relevant studies. We included published and unpublished studies. Where necessary, we made contact with authors to seek clarification or further information. Two review authors independently appraised studies for inclusion, and extracted data in order to minimise bias.

Agreements and disagreements with other studies or reviews

A systematic review and network meta-analysis (Jiang 2015) published in 2015 included eight studies comparing insulin with metformin and seven studies that compared insulin with glibenclamide or acabose. We excluded two of the studies (Hassan 2012; Tempe 2013) that had been included in the Jiang review as they were quasi-randomised and did not meet the inclusion criteria for this review. We identified an additional four studies, three that compared insulin with metformin (Ashoush 2016; Saleh 2016; Zawiejska 2016), and one that compared insulin with glibenclamide (Behrashi 2016).

Our conclusions concur for insulin being associated with an increased maternal weight gain during pregnancy compared with metformin. We found no clear evidence of a difference for birthweight associated with insulin compared with glibenclamide that had been identified in the Jiang 2015 review. Our conclusions differ for macrosomia, preterm birth and neonatal hypoglycaemia and this is likely to be reflective of the additional data we have included in our review with 18 studies comparing insulin and metformin and 10 studies comparing insulin and glibenclamide in addition to our exclusion of quasi-randomised studies.

Balsells 2015 summarised evidence on short-term outcomes for randomised trials comparing glibenclamide or metformin versus insulin in women with gestational diabetes. They included seven studies that compared glibenclamide with insulin and six studies that compared metformin with insulin. The Balsells 2015 review also included the quasi-randomised Tempe 2013 study that was excluded from our review. Results concur with those of our review for the outcomes of birthweight and macrosomia being reduced with insulin compared with glibenclamide; increased gestational weight gain and increased gestational age at birth with insulin compared with metformin. Balsells 2015 reported evidence of a difference between insulin and metformin for neonatal hypoglycaemia in six studies including 1360 infants, whereas our review found no evidence of a difference between groups in 10 studies including 2192 infants.

A review article by Lambert 2013 summarised evidence for the use of insulin analogues in pregnancy that included treating women with gestational diabetes. Six randomised studies were identified and all were also included in our review. There was no meta-

analysis conducted.

AUTHORS' CONCLUSIONS

Implications for practice

The data summarised in this systematic review suggests that overall maternal and neonatal outcomes, where reported, are comparable for insulin and oral anti-diabetic pharmacological therapies. Insulin and metformin have similar outcomes for mother and infant, however insulin does appear to have better outcomes than glibenclamide for reduced risk of being born large-for-gestational age (LGA) or macrosomic and reduced risk of neonatal hypoglycaemia. Current data have not yet fully explored the long-term effects of insulin or oral anti-diabetic pharmacological therapy for maternal and childhood outcomes and there is therefore insufficient evidence to be able to draw any definite conclusions on long-term benefits or harms.

The choice of insulin or oral anti-diabetic pharmacological therapies could be based on informed consultation with the woman and include, preference, compliance, cost, accessibility to medication and control of maternal hyperglycaemia.

There is no clear evidence of a difference between regular human insulin and other insulin analogues for treating women with gestational diabetes. The choice of analogue could be guided by clinician preference, cost and availability.

There is insufficient evidence to determine if insulin improves short- and long-term maternal and neonatal outcomes compared with diet/standard care or exercise.

There is insufficient evidence for different insulin treatment regimens to be able to draw any conclusions as to whether one is superior to another.

Implications for research

A network meta-analysis may help to identify the superiority of one treatment over another (insulin versus oral anti-diabetic pharmacological therapy; insulin analogue versus insulin analogue) using indirect rather than direct comparisons. Future studies could aim to report long-term as well short-term maternal and infant outcomes using standardised GDM outcomes.

Further trials are needed to identify the optimal treatment regimen/s for women with GDM being treated with insulin.

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- *Oral anti-diabetic pharmacological therapies for the treatment of women with gestational diabetes* - Julie Brown, Ruth Martis, Brenda Hughes, Janet Rowan, Caroline Crowther.

- *Lifestyle interventions for the treatment of women with gestational diabetes* - Julie Brown, Nisreen Alwan, Jane West, Stephen Brown, Christopher McKinlay, Diane Farrar, Caroline Crowther.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Anjalakshi 2007

Methods	Parallel randomised controlled trial. Single centre.
Participants	256 women were screened and 35 were eligible, 26 women were randomised and 23 were analysed **Inclusion criteria:** diagnosis of GDM using a 75g OGTT and diagnosis based on World Health Organization criteria of > 140 mg/dL at 2 hours, a singleton pregnancy and having failed to maintain blood glucose on medical nutrition therapy alone after 2 weeks **Exclusion criteria**: no details. **Setting:** women attending antenatal clinic in Chennai, India. **Timing:** dates not specified.
Interventions	Insulin (n = 13) starting dose 0.1 units/kg and increased weekly as required Glibenclamide (n = 10) starting dose 0.625 mg titrated weekly to maintain 2-hour plasma glucose ≤ 120 mg/dL
Outcomes	No outcomes were prespecified but reported on birthweight, glycaemic control and cord blood insulin
Notes	Published correspondence article only. Sample size calculation: none stated. ITT analysis: no. **Funding:** not stated. **Conflicts of interest:** no details were stated in the manuscript.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"assigned randomly" no other details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No evidence of blinding and it is unlikely to have occurred due to different modes of administration
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details.
Incomplete outcome data (attrition bias) All outcomes	High risk	3 women lost to follow-up all from the glibenclamide group. No details for losses were provided

Anjalakshi 2007 (*Continued*)

Selective reporting (reporting bias)	High risk	Outcomes were not prespecified and were very limited. The evidence is published as correspondence only and no full publication could be identified
Other bias	High risk	The evidence is published as correspondence only and no full publication could be identified

Ardilouze 2014

Methods	Parallel randomised controlled trial.
Participants	68 women diagnosed with GDM (Canadian Diabetes Association criteria) **Inclusion criteria:** ≥ 18 years, diagnosed with GDM between 24 and 28 weeks' gestation, failure to achieve glycaemic control with diet and exercise alone, able to understand and read French or English **Exclusion criteria:** known type 1 or type 2 diabetes, treatment interfering with glucose metabolism, allergies to 1 of the components of treatment, hepatic or haematologic diseases **Setting:** Quebec, Canada. **Timing**: no details in abstract.
Interventions	Combined metformin and glyburide - metformin 250 mg per day and glyburide 5 mg per day with an incremental increase in dosages to a maximum of 750 mg metformin and 10 mg glyburide. If treatment targets (capillary glucose fasting < 5.3 mmol/L; 2-hour postprandial < 6.7 mmol/L) not met over a 2-week period, then insulin was added versus Insulin (Insulin aspart/lispro and Neutral Protamine Hagedorn insulin)
Outcomes	Primary outcomes: glycaemic control at end of treatment. Secondary outcomes: acceptability of treatment.
Notes	Additional information was found from the NIH trials register NCT01215331 Estimated enrolment is for 275 women. **Funding:** Fonds de recherche sante Quebec **Conflicts of interest:** no details

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomised". No further details.
Allocation concealment (selection bias)	Unclear risk	No details.

Ardilouze 2014 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	"open label", masking is difficult due to insulin being given by subcutaneous injection and metformin and glyburide by oral medication
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details.
Incomplete outcome data (attrition bias) All outcomes	High risk	Interim report only.
Selective reporting (reporting bias)	High risk	Published as a conference abstract only.
Other bias	Low risk	No differences at baseline.

Ashoush 2016

Methods	Parallel randomised controlled trial
Participants	100 women enrolled **Inclusion criteria:** Women with GDM, singleton pregnancy, failure of satisfactory glycaemic control for at least one week after diagnosis **Exclusion criteria:** Presence of fetal anomaly, pregnancy complications other than GDM, known intolerance to metformin or risk of lactic acidosis **Setting:** Antenatal care clinics, Ain Shams University Maternity Hospital, Cairo; Egypt **Timing:** From January to November 2014
Interventions	Insulin (n = 50) Regular insulin and NPH insulin ratio of 3:7 at a starting dose of 0.7 units/kg/day, with two thirds before breakfast and one-third before dinner (evening) vs Metformin (n = 50) 1000 mg daily with meals and increased by 500 mg or 850 mg every 1 or 2 weeks up to maximum of 2500 mg until birth. Insulin could be added if required
Outcomes	Primary outcome - maternal glycaemic control Secondary outcomes - BMI, pre and post-prandial glucose concentration, supplemental insulin, birthweight, gestational weight gain, side effects of metformin, mode of birth, gestational age at birth, macrosomia, neonatal hypoglycaemia, admission to NICU, neonatal death, congential abnormalities,
Notes	**Funding:** No details. **Conflicts of interest:** The authors declare there were no conflicts of interest.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"selected randomly" no other details. Looks as though drawn by lots

Ashoush 2016 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	'200 closed, mixed and identical envelopes containing 50 'selected for insulin', 50 'selected for metformin' and '100 'non-selected cards, left in the office of the head nurse of the clinic No details on who placed details in envelopes or if envelopes were sealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label. Blinding not possible because of type of intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Five women excluded for discontinuing study and withdrawal of consent before starting treatment (two from insulin and three from metformin). Unrelated to treatment. 47 analysed in metformin group and 48 in the insulin group. No women were lost to follow-up
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes appear to be reported.
Other bias	Low risk	Groups seemed balanced at baseline.

Balaji 2005

Methods	Parallel randomised controlled trial.
Participants	10 women **Inclusion criteria:** Women with GDM failing to respond to diet alone. No details on diagnostic criteria **Exclusion criteria:** No details **Setting:** India **Timing:** Not stated
Interventions	Human insulin (n = 5) before breakfast, and lunch and pre-mixed insulin before dinner versus Insulin aspart (n = 5) before breakfast and lunch and 70/30 mixture of aspart protamine and soluble aspart before dinner
Outcomes	Fasting and 2-hour blood glucose levels, birthweight.
Notes	Sample size calculation - no details. ITT - yes. **Funding** - none stated. **Conflicts of interest** - no details in abstract.

Balaji 2005 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"randomly assigned", no other details.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data reported for all women.
Selective reporting (reporting bias)	High risk	Not all outcomes reported.
Other bias	High risk	Conference abstract only. Groups balanced at baseline.

Balaji 2012

Methods	Single-centre randomised controlled trial.
Participants	345 women eligible. 323 women randomised. **Inclusion criteria:** ≥ 20 and ≤ 30 years of age, 12 to 28 weeks' gestation. BMI ≤ 35 kg/m^2 at first visit, GDM confirmed by 75 g OGTT unable to maintain treatment targets after 2 weeks of medical nutrition therapy **Exclusion criteria:** pre-gestational diabetes, type 1 diabetes, ketoacidosis, severe kidney disease, cardiovascular disease, stroke, cancer, severe psychological disorder, hypothyroidism, anaemia,taking antibiotics or insulin **Setting:** Diabetes care and research institute, Chennai, India. **Timing:** April 2008 to September 2009.
Interventions	Biphasic insulin aspart BIAsp 30 (n = 163) initial dose 6 IU versus Biphasic human insulin BHI 30 (n = 160) initial dose 6 IU. Dosage adjusted after contact with women every 3 days; seen in clinic every 2 weeks or monthly depending on degree of glycaemic control. Self-monitoring 6 times daily before and 2 hours after each meal

Balaji 2012 (*Continued*)

Outcomes	Primary outcome: macrosomia (> 90^{th} percentile). Secondary outcome: achievement of FPG and PPG targets, adverse events, maternal hypoglycaemia, newborn length, birthweight and Apgar scores at 1 and 5 minutes
Notes	Sample size calculation - no details. ITT - yes. **Funding** - none stated. **Conflicts of interest** - authors declared no known conflicts of interest in manuscript

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomly allocated.
Allocation concealment (selection bias)	Low risk	Using sealed random allocation slips that were opened serially
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label as there were differences in injection devices.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details.
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 women in BHI group lost to follow-up as they moved out of area
Selective reporting (reporting bias)	High risk	More outcomes are reported in the results than listed in the methods section
Other bias	Low risk	Groups were balanced at baseline.

Behrashi 2016

Methods	Parallel randomised controlled trial.
Participants	258 women eligible. **Inclusion criteria:** 18-45 years, 11-33 weeks gestation, absence of diabetes before pregnancy, singleton pregnancy, absence of known kidney, hepatic, haematological and/or cardiovascular disease **Exclusion criteria:** Premature rupture of membranes, severe bleeding. Women assigned to the glibenclamide group who required insulin **Setting:** Gynaecology clinics, Kashan, Iran. **Timing:** No details

Behrashi 2016 (*Continued*)

Interventions	Insulin (NPH) - initial dose of 0.2 IU/kg. Two thirds in morning and one third in the evening (n = 129) versus Glibenclamide - 1.25 mg once daily increasing by 1.25 mg to 2.5 mg every 3 days to the maximum of 20 mg per day (n = 129) Self-monitoring of blood sugar four times daily.
Outcomes	Apgar scores, macrosomia (>4 kg), neonatal hypoglycaemia, hypocalcaemia, hyperbilirubinaemia, fetal anomalies, RDS, admission to NICU
Notes	**Funding:** The trial reports there was no funding. **Conflicts of interest:** The authors declare no conflicts of interest.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Block randomisation, no other details.
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not stated but unlikely due to differences in treatments
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	9 women in the metformin group required insulin and were therefore excluded from the study. This has not been a reason for exclusion in other studies
Selective reporting (reporting bias)	Unclear risk	Maternal glycaemic control was reported but was not clearly pre-specified as a maternal outcome
Other bias	Low risk	Groups were balanced at baseline.

Bertini 2005

Methods	Single-centre open-label randomised controlled trial.
Participants	70 women diagnosed with gestational diabetes using WHO criteria. **Inclusion criteria:** GDM diagnosed as $\geq$ 6.1 mmol/L or 110 mg/dL fasting plasma glucose and $\geq$ 7.8 mmol/L or 140 mg/dL OGTT after 2 hours 75 g of glucose **Exclusion criteria:** presence of a pathology requiring faster glucose control, such as

	corticoid therapy. Other concomitant pathologies that could affect therapy or perinatal results **Setting:** Maternity institution in Brazil. **Timing:** October 2003 to July 2004.
Interventions	1) Insulin as conventional therapy (n = 27), 0.7 IU/kg in the first trimester, 0.8 IU/kg in the 2nd trimester and 0.9 IU/kg in the 3rd trimester. Regular human insulin and Neutral Protamine Hagedorn insulin used 2) Glyburide (n = 24) initial dose 5 mg daily increasing every 7 days until glucose control achieved (max 20 mg), and 3) Acarbose (n = 19) initial dose 50 mg increasing by 50 mg every 7 days to a maximum dose of 300 mg All women received diet and exercise programmes. Treatment targets - fasting plasma glucose 5.0 mmol/L or 90 mg/dL and 2-hour postprandial 5.6 mmol/L or 100 mg/dL
Outcomes	Primary outcomes: neonatal hypoglycaemia, birthweight. Gestational age at birth, Apgar scores, neonatal hypoglycaemia, macrosomia (> 4000 g) , LGA (> 90th centile), fasting and postprandial glucose levels, severe maternal hypoglycaemia requiring admission, BMI, weight gain in pregnancy, mode of birth, other outcomes (not specified)
Notes	Gestational age at diagnosis range from 11 to 33 weeks'. All women had planned birth at 39 weeks' gestation. ITT analysis: 1 woman was excluded from the study data. Sample size calculation: no details. **Funding**: no details. **Conflicts of interest**: not reported in paper. See also Silva 2005.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomized". Telephone randomisation.
Allocation concealment (selection bias)	Unclear risk	"brown envelopes, containing outside the randomization number and in the inside a sheet defining which therapy, the patient was to be allocated to"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details.

Bertini 2005 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	1 woman was excluded due to severe asthma and data were not included in the analysis
Selective reporting (reporting bias)	Low risk	All outcomes were reported between both papers.
Other bias	Low risk	No evidence of other bias. Groups were balanced at baseline. The manuscript provides no acknowledgements or details of funding at yet in the text it is stated that acarbose was provided free of charge by the pharmaceutical company whereas insulin and glyburide were free of charge within the public health system

Beyuo 2015

Methods	Randomised controlled trial.
Participants	104 pregnant women. **Inclusion criteria:** age 18 to 45 years, singleton pregnancy, gestational age 20 to 30 weeks', diagnosed with type 2 diabetes or GDM, meeting hospital criteria for starting insulin therapy, not meeting treatment targets with diet and exercise **Exclusion criteria:** type 1 diabetes, type 2 diabetes who previously failed to meet treatment targets with metformin, allergic reaction to metformin **Setting:** Ghana. **Timing:** January 2013 to October 2013.
Interventions	Insulin (n = 52) soluble and premixed insulin used. Total daily dose of premixed insulin was usually calculated as 0.3 IU/kg body weight versus Metformin (n = 52) initial dose 500 mg daily and increased to a maximum daily dose of 2500 mg. Insulin was added if glycaemic targets not met
Outcomes	Glycaemic control, gestational age at birth, mode of birth, birthweight, neonatal intensive care admissions
Notes	Sample size calculation: yes. ITT analysis: yes. **Funding:** there was no source of funding. **Conflicts of interest:** authors declare no conflicts.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Beyuo 2015 (*Continued*)

Random sequence generation (selection bias)	Low risk	"randomized", ballot.
Allocation concealment (selection bias)	Low risk	Picking randomly 1 paper with an inscription from an opaque envelope. The sequencing of picking was in the order in which they reported to clinic
Blinding of participants and personnel (performance bias) All outcomes	High risk	"open-label."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No details, but glycaemic control was analysed by laboratories who were unlikely to be aware of the patients' allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	In the insulin group 6 women delivered outside the hospital area, 5 were lost to follow-up and 1 discharged from the clinic against advice (40 were analysed) In the metformin group 1 woman delivered outside the hospital area, 3 were lost to follow-up and 1 withdrew consent. 4 women who had been allocated metformin received insulin, they were analysed in the metformin group (47 were analysed)
Selective reporting (reporting bias)	Unclear risk	32 of the 43 women analysed had GDM in the metformin group and 23/40 in the insulin group had GDM. Only glycaemic control data is reported although other neonatal outcomes were listed in the methods section of the report. In the trial protocol viewed on ACTRN12614000942651 the primary outcome was glycaemic control and the secondary outcome was maternal weight gain. The authors note in the results section that fasting blood glucose, 1 hour postprandial glucose, maternal weight gain, pregnancy and neonatal outcomes were also recorded but were not discussed in this publication
Other bias	Low risk	Groups appear to be balanced at baseline.

Bung 1993

Methods	Randomised controlled trial.
Participants	41 women from USA. **Inclusion criteria:** pathological results on OGTT, failing to achieve glycaemic targets after 1 week of ADA diet **Exclusion criteria:** no details. **Setting**: high risk obstetric clinic Los Angeles, California.

Bung 1993 (*Continued*)

	Timing: not stated.
Interventions	41 women randomised but data only available on 34 women. No details on number of women in each group at time of randomisation Insulin plus diet (n = 20) no details of insulin type or regimen versus Exercise plus diet (n = 21) - An individual workload capacity that was 50% of VO2max was prescribed. Women attended an exercise session 3 times per week. They used a recumbent bicycle ergometer for 3x15 minute sessions with 5-minute rest periods between sessions
Outcomes	None prespecified apart fetal heart rate, uterine activity, pregnancy complications, perinatal morbidity, fetal outcome
Notes	Sample size calculation - no. ITT analysis - unclear. **Funding** - no funding stated. **Conflicts of interest** - not reported in paper.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomized" "double-stratified randomisation". No further details
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No details but unlikely.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	41 women were recruited and randomised but only 17 in the exercise group completed the trial, data are also reported for 17 women in the insulin group but unclear as to reasons for losses
Selective reporting (reporting bias)	High risk	No maternal or neonatal outcomes were prespecified.
Other bias	High risk	There is a lack of demographic information to determine if the groups were balanced at baseline

Castorino 2011

Methods	Randomised trial.
Participants	40 women with GDM unable to achieve fasting glucose < 90 mg/dL and 1-hour post-prandial glucose < 120 mg/dL after at least 1 week lifestyle intervention No other details available.
Interventions	50/50 mixture of Neutral Protamine Hagedorn insulin/lispro delivered as 3 pre-meal injections (n = 20) versus Neutral Protamine Hagedorn insulin and lispro as 6 injections pre-meal (n = 20)
Outcomes	Included fasting glucose and HbA1c.
Notes	Conference abstract only. **Funding:** No details **Conflicts of interest:** No details

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"randomised" no other details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No details but is unlikely to have occurred.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 women in the 50/50 mix group and 1 in the 6 injection group dropped out of the study
Selective reporting (reporting bias)	High risk	Conference abstract only, no full publication identified.
Other bias	Unclear risk	States that groups were balanced at baseline although the 50/50 mix group was younger. 86% of the included women were Mexican

Coustan 1978

Methods	Partly randomised and partly quasi-randomised controlled trial
Participants	72 women from USA. **Inclusion criteria:** women identified with GDM. **Exclusion criteria**: none stated. **Setting:** California, USA. **Timing:** July 1973 to February 1975.
Interventions	Insulin (n = 27) also received the diet advice plus 20 units of Neutral Protamine Hagedorn insulin and 10 units regular insulin given 30 minutes before breakfast versus Diet (n = 11) 30 to 35 calories/kg ideal body weight/day (24% at breakfast, 30% at lunch, 33% at dinner, 13% at bedtime snack). 125 g of protein but the rest equally divided between carbohydrates and fat versus No therapy (n = 34) - usual dietary counselling with 90 g of protein and a weight gain of 6.8 to 11.3 kg
Outcomes	No outcomes prespecified apart from testing for diabetes postpartum
Notes	Sample size calculation: not reported. ITT analysis: yes. **Funding:** not reported. **Conflicts of interest:** not reported.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	The first 20 women were assigned treatment based on time of gestation (10 diagnosed before 36 weeks' and given insulin and diet, 10 diagnosed after 35 weeks' and were control participants with no therapy). After this point women were randomly assigned to 1 of 3 groups (a diet group was added)
Allocation concealment (selection bias)	High risk	The first 20 women were assigned based on time of gestation and therefore there was no allocation, for the remaining 52 women there are no details
Blinding of participants and personnel (performance bias) All outcomes	High risk	No details but unlikely.
Blinding of outcome assessment (detection bias)	Unclear risk	No details.

Coustan 1978 (*Continued*)

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women randomised appear to have been analysed.
Selective reporting (reporting bias)	High risk	No outcomes were prespecified apart from diabetes postpartum
Other bias	High risk	The data for those women quasi-randomised cannot be separated from the truly randomised

De Veciana 2002

Methods	Parallel randomised controlled trial.
Participants	91 women with gestational diabetes. **Inclusion criteria** - women with GDM (no diagnostic criteria provided), failing to achieve treatment target on diet therapy at ≥ 20 weeks' gestation **Exclusion criteria** - not reported. **Setting** - Virginia, USA. **Timing** - not specified.
Interventions	Insulin (n = 46) initial dose 0.8 IU/kg in the second trimester and 0.9 IU/kg in the third trimester (split dose between Neutral Protamine Hagedorn insulin and insulin Lispro) versus Acarbose (n = 45) Initial dose 25 mg orally 3 times per day increased to a maximum of 100 mg 3 times per day
Outcomes	Glycaemic control (fasting and 1-hour postprandial), birthweight, gestational age at delivery
Notes	Conference abstract only with no definition of gestational diabetes. Unable to find contact details for authors and no evidence of full paper publication **Funding:** no details **Conflicts of interest:** no details

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"randomized" no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No details but unlikely.

De Veciana 2002 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details.
Incomplete outcome data (attrition bias) All outcomes	High risk	Presenting preliminary data only.
Selective reporting (reporting bias)	High risk	Presenting preliminary data only. Only primary outcome of glycaemic control was prespecified. Conference abstract only
Other bias	High risk	No baseline data to ascertain if groups comparable.

Di Cianni 2007

Methods	Randomised controlled trial.
Participants	96 women. **Inclusion criteria:** GDM diagnosed with Carpenter and Coustan criteria at 27.5±1.1 weeks' and who had failed to achieve postprandial glycaemic targets **Exclusion criteria**: not stated. **Setting:** Italy. **Timing**: not specified.
Interventions	Insulin aspart (n = 31). Insulin lispro (n = 33). Human insulin (n = 32). Self-monitoring 5 times per day. Seen by consultant weekly to adjust dose if required. No details on initial dosage
Outcomes	Weight gain, fasting plasma glucose, 1-hour post-prandial glucose, HbA1c, birthweight, maternal hypoglycaemia, macrosomia, cranial-thoracic circumference
Notes	Published a brief report only. **Funding:** no details **Conflicts of interest:** no details

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"randomly".
Allocation concealment (selection bias)	Unclear risk	No details.

Di Cianni 2007 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	No details.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details.
Selective reporting (reporting bias)	High risk	Data only reported as a brief report. No full paper was identified. Unclear if the outcomes were the only ones collected as no other record of the trial could be identified
Other bias	Low risk	Groups were comparable at baseline.

Hague 2003

Methods	Parallel, randomised controlled trial.
Participants	30 women. **Inclusion criteria:** GDM diagnosed by the criteria of the Australasian Diabetes in Pregnancy Society. **Exclusion criteria**: not stated. **Setting:** Australia, no further details. **Timing**: not stated.
Interventions	Insulin - n = 14 (no further details) versus Metformin - n = 16 (no further details).
Outcomes	Outcomes: mode of delivery, pre-eclampsia, gestational age at birth, cord C-peptide, cord glucose, birthweight, requiring intravenous dextrose, median time in SCBU, neonatal jaundice, need for neonatal phototherapy
Notes	This data comes from a letter to the editor. ITT analysis: not stated. **Funding:** not stated. **Conflicts of interest:** not reported in the letter to the editor.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"women randomised".

Hague 2003 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Unclear, no details.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not stated but unlikely to be blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient details provided.
Selective reporting (reporting bias)	High risk	This is a letter to a journal editor.
Other bias	Unclear risk	Unable to make judgements due to lack of data, groups appeared to be balanced at baseline

Herrera 2015

Methods	Parallel, randomised controlled trial.
Participants	105 women **Inclusion criteria:** women with GDM (100 g, 3-hour OGTT using 1 or more abnormal values by Carpenter and Coustan criteria 1982 or a 75 g 2-hour OGTT using IADPSG criteria) or type 2 diabetes in pregnancy 34 weeks' gestation or less. Singleton or twin pregnancy. Failing to maintain glycaemic targets on diet alone and/or hypoglycaemic agents and choosing to be on insulin **Exclusion criteria:** type 1 diabetes, < 18 years old, known allergy to insulin. **Setting:** New York, USA. **Timing:** March 2013 to January 2015.
Interventions	Insulin detemir + insulin aspart (n = 52) versus Neutral Protamine Hagedorn insulin + insulin aspart (n = 53) Self-monitoring of blood glucose 4 to 7 times daily. Glycaemic targets fasting blood glucose < 90 mg/dL, 2-hour postprandial blood glucose < 120 mg/dL
Outcomes	Primary outcome - mean blood glucose. Secondary outcomes - mean fasting blood glucose, mean post-prandial blood glucose, time to achieve glycaemic control, maternal weight gain, perinatal and neonatal outcomes, adverse effects including hypoglycaemia
Notes	Sample size calculation - yes, based on change in blood glucose level ITT - no per protocol analysis conducted, ITT done for primary outcome **Funding** - not stated. **Conflicts of interest** - authors state there are no conflicts of interest. Data is reported for GDM and type 2 diabetes combined and cannot be separated

Herrera 2015 (*Continued*)

	NCT01837680

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation.
Allocation concealment (selection bias)	Low risk	Sequentially number, opaque, sealed envelopes drawn in consecutive order
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label. Participants and researchers were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessors were not blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	In the detemir group 46/52 received the allocated intervention, 6 women had an allergic reaction; 2 women were lost to follow-up and 2 women switched to oral hypoglycaemic/diet. A total of 42 women were analysed In the Neutral Protamine Hagedorn insulin group 51/53 women received the allocated intervention, 2 women did not receive the intervention due to insurance coverage. 2 women were lost to follow-up and 4 women switched to oral hypoglycaemic/diet. A total of 45 women were analysed Attrition was reasonably high at 17%.
Selective reporting (reporting bias)	High risk	Neonatal and perinatal outcomes are not reported in the paper
Other bias	Unclear risk	33% of participants had type 2 diabetes and 67% had GDM. Data for blood glucose are reported for GDM alone

Hickman 2013

Methods	Randomised controlled trial - 2 centres.
Participants	31 women randomised. **Inclusion criteria:** presenting for antenatal care < 20 weeks' gestation, women with type 2 diabetes, GDM (A2) diagnosed < 20 weeks', failing to achieve glycaemic control with medical nutrition therapy

	Exclusion criteria: taking insulin before pregnancy, < 18 years of age at randomisation, not speaking fluent English or Spanish, having a triplet or higher order pregnancy, known fetal anomaly, evidence of end organ damage or major comorbidity associated with diabetes, contraindications to metformin including hepatic or renal disease, allergy, adverse reaction, history of diabetic ketoacidosis **Setting:** 2 hospitals in Carolina, USA. **Timing:** 2008 to 2010.
Interventions	Insulin - regular insulin (twice daily) and Neutral Protamine Hagedorn insulin. Insulin dose was weight based and initial dose was 0.7 U/kg per day given twice a day versus Metformin - initial dose 500 mg once or twice a day up to maximum daily dose of 2500 mg. If treatment targets not met then regular or Neutral Protamine Hagedorn insulin were added All women received dietary advice and were asked to self-monitor blood glucose fasting and 1-hour post-prandial
Outcomes	HbA1c, maternal hypoglycaemia, glycaemic control, c-peptide, neonatal hypoglycaemia, satisfaction
Notes	Sample size calculation - yes based on change in mean fasting blood glucose ITT analysis - yes. **Funding** - Bowles-Cefalo Young Researcher Award Grant. **Conflicts of interest** - no statement of conflicts of interest in the manuscript. Data are presented for type 2 diabetes and GDM combined and cannot be separated. However as 50% of the women had GDM these data have been included. The authors have been contacted to see if the GDM data alone are available

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated, block randomisation.
Allocation concealment (selection bias)	Low risk	A nurse not involved in the study prepared opaque, sequentially numbered envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants due to differences in administration of drugs
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	High risk	Due to only randomising 31 of 230 women the trial is underpowered to detect differences in primary outcome. Of the 31 randomised

Hickman 2013 (*Continued*)

		16 were allocated to insulin and 14 were analysed (1 inadequate mental capacity, 1 fetal demise). 15 were allocated to metformin 14 analysed (1 withdrew consent)
Selective reporting (reporting bias)	High risk	Several outcomes are reported that were not listed a priori.
Other bias	High risk	3 months after recruitment had started the authors became aware that they would not reach the target enrolment within the funded timeframe but continued to recruit and added another site. Trial includes GDM and pre-existing diabetes and data cannot be currently separated

Hutchinson 2008

Methods	Randomised controlled trial.
Participants	172 pregnant women. **Inclusion criteria:** GDM or type 2 diabetes not requiring insulin. **Exclusion criteria**: no details. **Setting:** Tennessee, USA. **Timing**: no details.
Interventions	Insulin (n = 80) versus Combined metformin-glyburide (n = 92).
Outcomes	Gestational age at birth, birthweight, cord glucose, fructosamine, HbA1c, neonatal 1-hour glucose, NICU admission and length of stay
Notes	Authors have been contacted in January 2016 and provided details to show that randomisation was by computer-generated number tables and that allocation concealment was done using opaque sealed envelopes maintained in a separate non-clinical area. They have agreed to provide us with additional information regarding the GDM and type 2 women in February 2016. No details have been provided at the time of publication of this review See Kipikasa 2008 for trial registration NCT00371306. **Funding:** no details **Conflicts of interest:** no details

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Hutchinson 2008 (*Continued*)

Random sequence generation (selection bias)	Low risk	"Computer generated table" (additional information from authors)
Allocation concealment (selection bias)	Low risk	"Opaque sealed envelopes" (additional information from authors)
Blinding of participants and personnel (performance bias) All outcomes	High risk	No details but unlikely.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if this is all women recruited in trial or interim data
Selective reporting (reporting bias)	High risk	Conference abstract, unclear if the outcomes reported all outcomes for the trial
Other bias	High risk	Conference abstract only. No full paper identified.

Ijas 2011

Methods	Multicentre (2 sites) randomised trial.
Participants	128 eligible women approached and 100 consented and randomised **Inclusion criteria:** singleton pregnancy, 12 to 34 weeks' gestation, normal liver and renal function. Diagnosis of GDM **Exclusion criteria:** pre-eclampsia, essential hypertension requiring medication, fetal growth restriction **Setting:** tertiary level hospitals in Finland. **Timing:** June 2005 to June 2009.
Interventions	1) Insulin (n = 50) - long acting insulin (Neutral Protamine Hagedorn insulin) according to hospital guidelines to normalise fasting and rapid-acting insulin lispro to normalise post-prandial glucose concentrations Self-monitoring twice a week (4 to 6 times in 1 day). Treatment targets were fasting < 5.3 mmol/L; 1.5 hours post-prandial < 6.7 mmol/L 2) Metformin (n = 50) 750 mg once daily for first week, twice daily for second week and 3 times daily from week 3 onwards ± supplementary insulin if normoglycaemia not achieved within 1 to 2 weeks versus All women were followed up until 6 to 8 weeks postpartum.
Outcomes	Primary outcome: macrosomia (birthweight > 4000 g or LGA). Secondary outcomes: admission to NICU, neonatal hypoglycaemia needing intravenous glucose, hyperbilirubinaemia treated with phototherapy, birth injury (clavicular fracture

Ijas 2011 (*Continued*)

	or brachial nerve injury), Apgar score, cord pH, need for supplementary insulin, preterm delivery, mode of birth, hypertension, weight gain during pregnancy, HbA1c
Notes	Power calculation: yes based on the outcome of macrosomia. ITT analysis: yes. **Funding:** Alma and K.A. Snellman, Oulu, Finland. **Conflicts of interest**: the authors declared there were no conflicts of interest associated with this trial Ijäs 2014 reported on follow-up of the cohort at 18 months of age in 45 children from the metformin group and 48 children from the insulin group

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation code generated manually in blocks of 10.
Allocation concealment (selection bias)	Low risk	Opaque, numbered, sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding due to different routes of administration of the interventions. "Open label"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding due to different routes of administration of the interventions
Incomplete outcome data (attrition bias) All outcomes	Low risk	Insulin: no losses in insulin group (50 randomised and 50 analysed) Metformin: 2 women withdrew consent, 1 woman was excluded as they had abnormal liver function, 3 women discontinued metformin due to gastrointestinal side effects (50 randomised and 47 analysed)
Selective reporting (reporting bias)	Unclear risk	The authors report on subgroups of the supplementary insulin group but this is not listed prospectively and the trial is not powered to look at the effects of this
Other bias	Low risk	There was no evidence of other sources of bias, groups did not differ at baseline

Ismail 2007

Methods	Randomised controlled trial.
Participants	68 women. **Inclusion criteria:** singleton pregnancy, < 34 weeks' gestation. **Exclusion criteria:** pre-existing hypertension, renal disease liver disease, autoimmune disorder **Setting:** combined clinic (obstetrician, endocrinologist, dietician) Kuala Lumpur, Malaysia **Timing**: not stated.
Interventions	2 weeks dietary control commenced, if targets not met then insulin started Short acting insulin (human insulin) Actrapid (n = 30) versus Intermediate acting insulin (Neutral Protamine Hagedorn insulin isophane insulin) Insulatard (n = 31) Home-monitoring of blood glucose started but frequency not detailed Insulin was titrated at each clinic visit. Target < 5.5 mmol/L preprandial; < 6.0 mmol/L before bed
Outcomes	None pre-specified. Reported on HbA1c, fructosamine and successful glycaemic control
Notes	Indirect evidence as includes women with GDM and pre-existing diabetes Infants were born at 38 weeks' according to hospital protocol Sample size calculation - no. ITT analysis - no. **Funding** - none reported. **Conflicts of interest** - none declared.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"randomized" no other details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details.
Incomplete outcome data (attrition bias) All outcomes	High risk	Report that 68 women were included but only provide data on 61, no other details provided

Ismail 2007 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Limited maternal outcomes and neonatal outcomes reported.
Other bias	High risk	Short communication, no full paper identified.

Jovanovic 1999

Methods	Randomised controlled trial.
Participants	42 women. **Inclusion criteria:** diagnosed at 14 to 32 weeks' gestation with GDM using Carpenter and Coustan criteria. Failing to maintain glycaemic control with diet and exercise alone during a 1-week period. Normal fetus on ultrasound scan **Exclusion criteria:** prior treatment with insulin, pre-gestational diabetes, demonstrated significant concurrent organic disease **Setting:** California, USA. **Timing**: not stated.
Interventions	Insulin lispro + Neutral Protamine Hagedorn insulin (n = 19) 3 times per day versus Regular human insulin + Neutral Protamine Hagedorn insulin (n = 23) 3 times per day Self-monitoring blood glucose 6 times per day.
Outcomes	HbA1c, insulin antibodies, maternal hypoglycaemia, cord blood insulin, birthweight, Apgar score, plasma glucose concentration, neonatal glucose concentration
Notes	Sample size calculation: no details. ITT analysis: **Funding:** drugs were supplied by Eli Lilly and the research was also part funded by this organisation **Conflicts of interest:** 2 authors received research support from the Sansum Medical Research Institute

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"randomised" "computer generated random numbers".
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"open-label" because of injecting at different times before meals

Jovanovic 1999 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 woman in the regular insulin group chose not to continue with trial
Selective reporting (reporting bias)	High risk	Some outcomes that were not prespecified were reported.
Other bias	Unclear risk	Women in insulin lispro group were significantly older than women in the regular insulin group at baseline

Lain 2009

Methods	Prospective randomised trial.
Participants	99 women randomised. **Inclusion criteria:** 24-34 weeks' gestation, singleton pregnancy, no fetal abnormality, no intrauterine growth restriction, no use of medication that could affect glycaemic control. Diagnosis of GDM using a 50 g 1-hour oral glucose challenge test. If > 7.5 mmol/L or 135 mg/dl then received a 100 g 3-hour OGTT. Diagnosis by 2 abnormal values (5.3 mmol/L or 95 mg/dL, 10.0 mmol/L or 180 mg/dL, 8.6 mmol/L or 155 mg/dL and 7.8 mmol/L or 140 mg/dL Carpenter and Coustan criteria), an elevated fasting value of 3-hour OGTT or 1-hour OGTT> 11.1 mmol/L or 200 mg/dL **Exclusion criteria**: no details. **Setting:** Magee Women's Hospital. Pittsburgh, USA. **Timing:** 2002 to 2005.
Interventions	Medical therapy was commenced if blood sugars were ≥ 5.3 mmol/L or 95 mg/dL (fasting) or 6.7 mmol/L or 120 mg/dL (2-hour postprandial). All women had education for diet and blood sugar monitoring 1) Insulin (n = 50) 0.8 U/kg in multiple daily injections with long-acting insulin and short-acting insulin and increased up to twice weekly versus 2) Glibenclamide (n = 49) 2.5 mg daily increasing to 2.5 to 5 mg increments weekly. Taken once or twice daily. Transitioned to insulin if maximum dose of 20 mg per day did not achieve therapeutic goal
Outcomes	Primary outcome: percentage fat mass. Secondary outcomes: glycaemic control, anthropometry, timing and mode of delivery, metabolic biomarkers (maternal and neonatal), gestational age, birthweight, fat free mass, neonatal complications
Notes	Power calculation: yes based on percentage fat mass. ITT analysis: yes but not for all outcomes. **Funding:** American Association of Obstetricians and Gynecologists Foundation, Magee Women's Health Foundation **Conflicts of interest:** not reported in the manuscript.

Lain 2009 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation using permuted block design.
Allocation concealment (selection bias)	Low risk	Sequentially numbered, opaque, sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unlikely that the women or the clinicians were blinded to the treatment but this is not stated
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assays performed in a blinded fashion. Research team performing neonatal measurements were masked to the group assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insulin: 2 withdrawals, no reasons specified. Glibenclamide: 4 withdrawals (no reasons specified) and 1 stillbirth Some outcomes were assessed by ITT but overall only analysed 41 women in each group and less for some outcomes
Selective reporting (reporting bias)	High risk	There were limited maternal outcomes and mode of delivery was not reported
Other bias	High risk	The trial was stopped early due to discontinuation of maintenance of equipment used for the primary outcome. No differences at baseline

Langer 2000

Methods	Randomised controlled trial.
Participants	404 women age 18 to 40 years. **Inclusion criteria:** singleton pregnancy, screened at 11 to 33 weeks with 50 g, 1-hour oral glucose challenge test. If above 7.3 mmol/L or 130 mg/dL then underwent 100 g OGTT. Diagnosis of GDM with fasting plasma glucose between 5.3 mmol/L or 95 mg/dL and 7.8 mmol/L or 130 mg/dL. 2 or more abnormal values required using Carpenter and Coustan criteria **Exclusion criteria**: none stated. **Setting:** maternal health clinics in Texas, USA. **Timing**: not specified.
Interventions	Treatment targets - fasting ≥ 5.3 mmol/L or 95 mg/dL; postprandial ≥ 6.7 mmol/L or 120 mg/dL All women had standard nutritional information for 3 meals and 4 snacks per day and

	weekly clinic visits. A nurse educator taught women how to self-monitor blood glucose which was done 7 times per day. Treatment targets were mean 5 to 5.9 mmol/L (90 mg/dL to 105 mg/dL), fasting blood glucose 3.4 mmol/L to 5.0 mmol/L (80 mg/dL to 95 mg/dL), preprandial 4.5 mmol/L to 5.3 mmol/L (80 mg/dL to 95 mg/dL) and postprandial (timing not stated) < 6.7 mmol/L (120 mg/dL) 1) Human insulin (n = 203) starting dose 0.7 units/kg subcutaneously 3 times daily and increased weekly as required versus 2) Glyburide (n = 201) 2.5 mg orally in the morning. Increased weekly by 2.5 mg and then 5 mg/week up to a maximum dose of 20 mg. If treatment targets not met for 2 weeks then switched to insulin therapy
Outcomes	Primary outcome: glycaemic control between 5 mmol/L to 5.9 mmol/L (mean) Secondary outcomes: insulin required, ≥ 90th percentile (LGA), SGA (≤ 10th percentile), macrosomia (≥ 4000 g), RDS, hypoglycaemia (≤ 2.2 mmol/L), hyperbilirubinaemia, hypocalcaemia (≤ 1.8 mmol/L), polycythaemia (> 60%), cord serum insulin, cord serum, capillary glucose
Notes	Power calculation: no details. ITT analysis: yes. **Funding:** no details. **Conflicts of interest:** no details included in the manuscript.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"randomly assigned" "computer generated list".
Allocation concealment (selection bias)	Low risk	Sequentialy-numbered opaque sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Obstetricians and neonatal teams were aware of the allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women randomised appear to have been analysed. No losses are reported. Report using ITT analysis
Selective reporting (reporting bias)	Unclear risk	Study reports both maternal and neonatal outcomes, although original protocol not sighted. Maternal hypoglycaemia was reported but not prespecified

Langer 2000 (*Continued*)

Other bias	Low risk	No evidence of any other bias. Groups were similar at baseline

Majeed 2015

Methods	Parallel randomised controlled trial.
Participants	500 pregnant women with GDM. **Inclusion criteria:** GDM (no details provided), 20 to 45 years of age, > 20 weeks' gestation **Exclusion criteria:** known diabetic, recent history of myocardial infarction or twin pregnancy **Setting:** Lahore; India. **Timing:** January 2014 to March 2015.
Interventions	Insulin (regular) s.c. no other details (n = 250) versus Metformin 500 mg orally no other details (n = 250). Blood sugars recorded fasting and 1-hour postprandial.
Outcomes	Preterm birth (< 37 weeks' gestation), neonatal hypoglycaemia (< 2.6 mmol/L; 46.8 mg/dL)
Notes	ITT analysis: all women randomised appear to be included in the analyses Sample size calculation: no. **Funding:** no details of funding. **Conflicts of interest:** not stated in the manuscript.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"randomized". Divided into 2 equal groups by randomisation.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No details but unlikely to be blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women randomised appear to have data reported.

Majeed 2015 (*Continued*)

Selective reporting (reporting bias)	High risk	Minimal outcomes reported for mother and infant. Maternal weight gain and admission to NICU were reported but were not pre-specified
Other bias	Low risk	Groups appear to be balanced at baseline.

Martinez Piccole 2010

Methods	Randomised trial no further details.
Participants	100 women treated for gestational diabetes. **Inclusion criteria**: no details. **Exclusion criteria**: no details. **Setting:** Turkey. **Timing**: no details.
Interventions	Insulin (no other details) versus Metformin (no other details).
Outcomes	Neonatal hypoglycaemia, birthweight, respiratory problems, admission to NICU
Notes	Conference abstract only. No details available to contact authors **Funding:** no details **Conflicts of interest:** no details

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"randomly assigned" no other details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No details but unlikely to be blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details.
Selective reporting (reporting bias)	High risk	No details, conference abstract only.

Martinez Piccole 2010 (*Continued*)

Other bias	High risk	Conference abstract only.

Mecacci 2003

Methods	Single-centre randomised controlled trial.
Participants	115 women screened and diagnosed with GDM using Carpenter and Coustan criteria between 25 and 32 weeks' gestation **Inclusion criteria:** Caucasian, singleton pregnancy, pre-gestational BMI between 19 and 25 kg/m^2. Being unable to meet treatment targets with diet alone (ADA recommendations) after 1 week **Exclusion criteria**: not reported. **Setting:** Perinatal Medicine Unit, University of Florence, Italy. **Timing:** June 1999 to December 2000.
Interventions	Insulin lispro (n = 32) administered immediately before each meal 3 times per day versus Regular insulin (n = 33) administered 15 minutes before each meal 3 times per day Initial dose of insulin was 1 unit per 10 g carbohydrates in the meal. Each dose was increased by 20% to 30% until glycaemic control was achieved. Self-monitoring 9 times per day
Outcomes	Blood glucose profiles, HbA1c, appropriate-for-gestational age, SGA, LGA, birthweight, ponderal index, cranial-thoracic circumference
Notes	Sample size calculation - no details. ITT - no. **Funding** - no details provided. **Conflicts of interest** - no declarations of interest in manuscript.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"randomly allocated".
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details.

Mecacci 2003 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	16 women were excluded post hoc (7 in the lispro group and 9 in the regular insulin group). 4 discontinued blood glucose self-monitoring, 4 received beta-mimetics or corticosteroids, 5 delivered in another clinic and 3 had a preterm birth
Selective reporting (reporting bias)	Unclear risk	One additional outcome reported.
Other bias	Low risk	Groups balanced at baseline.

Mesdaghinia 2013

Methods	Parallel, randomised controlled trial - single centre.
Participants	200 women. **Inclusion criteria:** 18 to 45 years, singleton pregnancy, no documented history of diabetes prior to pregnancy, gestational age 24 to 32 weeks' **Exclusion criteria**: no details. **Setting:** hospital in Isfahan, Iran. **Timing**: not stated.
Interventions	All women initially taught lifestyle modification. Treatment targets: fasting < 5.3 mmol/L or 95 mg/dL and 2-hour post-prandial < 6.7 mmol/L or 120 mg/dL. if failed to reach treatment targets then randomised to: Insulin (n = 100) initial dose 0.5 IU/kg/day divided as 2/3 of dose in morning (Neutral Protamine Hagedorn insulin) and 1/3 in the afternoon (regular insulin). Dose was increased in 1 IU intervals if treatment target levels not reached versus Metformin (n = 100) initial dose 500 mg daily and if required adjusted to a maximum of 2500 mg per day
Outcomes	Primary and secondary outcomes not specified. HbA1c, mode of birth, hypertension, pre-eclampsia, birthweight, shoulder dystocia, Apgar at 1 and 5 minutes, neonatal sepsis, jaundice, hypoglycaemia, respiratory distress, fetal anomalies, admission to NICU, neonatal liver function
Notes	Power calculation: yes but outcome that it was based on was not detailed ITT analysis: yes. **Funding**: funded by University. **Conflicts of interest**: manuscript states no conflicts of interest.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Mesdaghinia 2013 (*Continued*)

Random sequence generation (selection bias)	Low risk	"randomized"; "random number tables".
Allocation concealment (selection bias)	Low risk	Generated by a third party physician.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"blinded", Care providers were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Women who failed to maintain treatment targets on metformin and required insulin were excluded (n = 22) and replaced with new women. No further exclusions or losses
Selective reporting (reporting bias)	Unclear risk	Very few maternal outcomes reported. No raw data reported for cord liver function although this was not an outcome of the review
Other bias	Low risk	No other evidence of bias, the groups were matched at baseline

Mirzamoradi 2015

Methods	Randomised controlled trial - single centre.
Participants	96 women randomised. **Inclusion criteria:** age 18 to 45 years, singleton pregnancy, 24 to 36 weeks' gestation; diagnosed with GDM. Not meeting treatment targets for dietary control (fasting > 5.0 mmol/L or 90 mg/dL; 2-hour postprandial 6.66 mmol/L or 120 mg/dL **Exclusion criteria:** previous diabetes mellitus, fetal anomalies/aneuploidy, vascular disorders or substance/alcohol abuse **Setting:** tertiary teaching hospital, Iran. **Timing:** March 2012 to March 2013.
Interventions	All women had dietary advice and educated about how to measure blood glucose levels 4 times per day Insulin (n = 59) - initial dose 0.4 unit/kg. 50% from Neutral Protamine Hagedorn insulin and 50% from regular insulin in divided doses adjusted every 2 days Glyburide (n = 37) - initial dose of 1.25 mg with morning meal. If required dose was increased by 1.25 mg every 3 to 7 days up to a maximum dose of 20 mg per day. If treatment targets not met at maximum dose for 2 weeks then switched to insulin Self-monitoring of blood glucose 4 times daily. Treatment targets: fasting 5.0 to 5.8 mmol/L or 90 to 105 mg/dL, 2-hour postprandial < 6.7 mmol/L or 120 mg/dL

Outcomes	Primary outcome - effective glycaemic control. Secondary outcomes - LGA, SGA, macrosomia (≥ 4000 g), hypoglycaemia, hyperbilirubinaemia, hypocalcaemia, admission to NICU, need for oxygen therapy more than 1 hour after birth, need for assisted ventilation and intubation, RDS, transient tachypnoea, adverse effects associated with drug
Notes	ITT analysis: yes.. Power calculation: yes, unclear for which outcome this was based **Funding:** no details reported in manuscript. **Conflicts of interest**: no details reported in manuscript.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised by block randomisation method based on computer generated blocks of 4
Allocation concealment (selection bias)	Low risk	Sequentially coded sealed opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No evidence of blinding.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No evidence of blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women randomised had data reported.
Selective reporting (reporting bias)	Unclear risk	Some neonatal outcomes reported are not listed a priori and no data on adverse drug effects was reported
Other bias	Unclear risk	Groups were balanced at baseline. There are however more women randomised to insulin than glyburide and the reason is not clear

Mohamed 2014

Methods	Parallel randomised controlled trial.
Participants	84 women with GDM/type 2 diabetes. **Inclusion criteria:** GDM diagnosed according to WHO criteria (2-hour, 75 g OGTT with diagnosis if plasma glucose > 7.8 mmol/L; 140 mg/dL) or type 2 diabetes diagnosed before pregnancy **Exclusion criteria:** pre-existing type 1 diabetes, history of diabetic ketoacidosis, multiple pregnancy, hypersensitivity to used medications, underlying vascular disease or medical condition known to affect fetal growth or drug clearance, fetal anomalies identified by ultrasound before start of therapy, diagnosis of GDM after 32 weeks, refusal to participate **Setting:** outpatient clinic, Egypt. **Timing**: not stated.
Interventions	All women provided with standard nutritional instructions for 3 meals per day. Weekly clinic visits Insulin (n = 42) - combined dose of intermediate-acting and short-acting insulin given before breakfast and dinner. Starting dose was 0.7 U per kg and increased weekly as necessary versus Combined metformin-glyburide (n = 42) - starting dose was 500 mg metformin and 2.5 mg glyburide taken with the morning meal. Dosage increased if required to a maximum daily dose of 2 g metformin and 10 mg glyburide. If glycaemic control at maximum dose was not achieved for 2 weeks then insulin was added Treatment target mean blood glucose 5.0 mmol/L to 5.9 mmol/L (90 mg/dL to 105 mg/dL), fasting blood glucose 3.4 mmol/L to 5.0 mmol/L (60 mg/dL to 90 mg/dL), preprandial blood glucose 4.5 mmol/L to 5.3 mmol/L (80 mg/dL to 95 mg/dL), 2-hour postprandial glucose < 6.7 mmol/L (< 120 mg/dL) and HbA1c < 6%
Outcomes	Primary outcomes not specified. Glycaemic control, polyhydramnios, fetal well-being, gestational age at birth, mode of delivery, HbA1c, birthweight, macrosomia (≥ 4000 g), cord blood glucose, hyperbilirubinaemia, admission to NICU and length of NICU stay, neonatal outcome
Notes	Power calculation: yes but not detailed which outcome calculation is based on ITT analysis: no details. **Funding:** no details. **Conflicts of interest:** not detailed at all in the manuscript. The manuscript does not separate data for women with GDM (77%) and those with type 2 diabetes (23%). Authors have been contacted and we await a response

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"randomly allocated" using "random number tables".
Allocation concealment (selection bias)	Low risk	Serially numbered opaque envelopes.

Mohamed 2014 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear if there was blinding.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It is unclear if there were any losses.
Selective reporting (reporting bias)	Unclear risk	Congenital malformations are reported but not pre-specified.
Other bias	High risk	No differences between groups at baseline. However the group comprises one-third of women with type 2 diabetes diagnosed before pregnancy. The groups cannot be separated and unclear of the distribution of GDM and type 2 between groups. Authors contacted

Moore 2007

Methods	Single-centre, parallel, randomised controlled trial.
Participants	63 women. **Inclusion criteria:** women diagnosed with GDM. **Exclusion criteria:** insulin-dependent diabetes mellitus, liver/kidney disease, chronic hypertension or seizure disorders, less than 11 weeks or more than 36 weeks' gestation. **Setting:** Medical Centre in Mississippi, USA. **Timing:** 2001 to 2004.
Interventions	All women received dietary counselling. If they failed to maintain glycaemic control (fasting < 105 mg/dL, 2 hours postprandial < 120 mg/dL) then commenced on treatment 1) Insulin - 0.7 units/kg subcutaneously (n = 31). 2) Metformin - 500 mg twice daily (n = 32) -maximum dose 1000 mg twice daily (if glycaemic control not maintained then started on insulin) Target was postprandial glucose of < 120 mg/dL, or 60 to 90 mg/dL fasting
Outcomes	Primary: glycaemic control, mode of delivery, shoulder dystocia, PPH Gestational age at birth, birthweight, Apgar score at 5 minutes, NICU admission, hypoglycaemia, RDS, hyperbilirubinaemia, perinatal death
Notes	Sample size calculation: yes. ITT analysis: unclear but all women randomised were analysed **Funding**: no details. **Conflicts of interest:** authors state that there were no financial conflicts of interest

Moore 2007 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"randomized" "computer generated list".
Allocation concealment (selection bias)	Low risk	Sequentially numbered sealed opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unclear, no details but unlikely to be blinded due to different modes of administration. Neonatologist was not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear, no details.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no dropouts.
Selective reporting (reporting bias)	Unclear risk	All outcomes appear to be reported but there are some outcomes not listed and that have no data in the text of the paper such as induction of labour
Other bias	High risk	Report that groups equal at baseline. Only half the sample that had been estimated to be appropriate had been recruited after 32 months and as such an interim report on 63 women was undertaken. There is no evidence of a full report

Mukhopadhyay 2012

Methods	Prospective open-label parallel randomised trial.
Participants	60 women with singleton pregnancy, diagnosed with GDM, not maintaining glycaemic control with medical nutrition therapy **Inclusion criteria:** GDM diagnosed as above, singleton pregnancy. **Exclusion criteria:** pre-gestational diabetes, severe anaemia, heart disease, renal disease, taking steroids **Setting:** Department of Obstetrics and Gynecology, Kolkata, India. **Timing:** January 2010 to December 2010.
Interventions	All women received medical nutrition therapy for 2 weeks to include 3 meals and 3 snacks per day. If glycaemic control (fasting 5.0 mmol/L (90 mg/dL) and postprandial (timing not specified) 6.7 mmol/L (120 mg/dL) was not maintained then randomised

	to: Insulin (n = 30) commenced on 0.7 units per kg subcutaneously 3 times daily and increasing weekly as required versus Glibenclamide (n = 30) 2.5 mg orally in the morning, increased weekly by 2.5 mg up to a maximum of 20 mg. Women were switched to insulin if glycaemic targets not achieved in 2 weeks Self-monitoring of blood glucose occurred 7 times per day. Followed up for 7 days after delivery.
Outcomes	No primary outcomes specified. Birthweight, LGA (≥ 90th centile), macrosomia (≥ 4000 g), glycaemic control, hyperbilirubinaemia,maternal and neonatal hypoglycaemia (≤ 2.4 mmol/L), congenital abnormalities, perinatal death, respiratory distress, gestational age at delivery, HbA1c
Notes	Sample size calculation: no. ITT analysis: unclear but all women randomised were analysed **Funding**: no funding relating to this trial. **Conflicts of interest:** states that there were no conflicts of interest in the manuscript All deliveries were planned between 37 to 38 weeks' gestation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number tables.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	There was no blinding of staff or participants due to mode of delivery of drug
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessors were not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women appear to have been randomised and analysed. No losses to follow-up were reported
Selective reporting (reporting bias)	High risk	The original protocol was no viewed. Outcomes are not listed a priori in the methods section. Not all of the outcomes reported in the results were identified in the methods section

Other bias	Low risk	Unclear if there were other biases. No differences in baseline demographics

Nachum 1999

Methods	Randomised controlled trial.
Participants	Women with pre-gestational and gestational diabetes requiring insulin **Inclusion criteria:** singleton pregnancy, insulin treatment commenced before 35 weeks' gestation **Exclusion criteria**: not specified. **Setting:** University affiliated hospital Israel. **Timing:** January 1993 to December 1997
Interventions	Twice-daily regimen - (n = 136 GDM, n = 60 pre-gestational diabetes). Morning dose contained two-thirds of total daily insulin and afternoon dose one-third. Morning dose was one-third human regular insulin (Actrapid) and two-thirds human intermediate insulin (Insulatard). The evening dose was equal amounts of regular and intermediate insulin. Adjustments were made on an individual basis versus 4 times daily regimen - (n = 138 GDM, n = 58 pre-gestational diabetes). 3 doses of regular insulin given by insulin pen (Novopen 3) 30 minutes before each main meal and the 4th dose was given before bedtime Dietary advice and self-monitoring of blood glucose 7 times per day
Outcomes	Not clearly stated. Glycaemic control, maternal hypoglycaemia, neonatal blood glucose concentration, hyperbilirubinaemia, calcium levels
Notes	Sample size calculation - yes. ITT analysis - yes. **Funding** - none. **Conflicts of interest** - authors declare no conflicts.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated list of numbers.
Allocation concealment (selection bias)	Low risk	"...sealed in numbered opaque envelopes, which were opened sequentially"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No evidence of blinding due to different regimens.

Nachum 1999 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of attrition. Data are reported by GDM and pre-gestational diabetes separately
Selective reporting (reporting bias)	High risk	Outcomes were reported that were not prespecified.
Other bias	Low risk	No evidence of other bias.

Niromanesh 2012

Methods	Randomised single-blind parallel controlled trial.
Participants	172 women. **Inclusion criteria:** aged 18-40 years, singleton pregnancy with gestational age between 20 and 34 weeks. All women attending clinic were screened using a 50 g glucose challenge test **Exclusion criteria:** history of systemic disease, substance abuse, pre-gestational diabetes, major fetal malformation **Setting:** Women's Hospital Tehran, Iran. **Timing:** 2010 to 2012.
Interventions	All women received counselling and dietary and exercise advice with caloric restriction based on BMI. Women who failed to maintain glucose control for 1 week (FPG > 95 mg/dL or 2-hour postprandial blood glucose > 120 mg/dL) were randomised Insulin (n = 86) Neutral Protamine Hagedorn insulin with initial dose of 0.2 units/kg. Adjustments were made depending on whether fasting and or postprandial values were high versus Metformin (n = 86) initial dose of 500 mg twice daily and increased by 500 mg to 1000 mg weekly up to am maximum daily dose of 2500 mg divided by meals Insulin was added if glycaemic control was not achieved.
Outcomes	Side effects of treatment, HbA1c, weight gain, pre-eclampsia, pregnancy-induced hypertension, abruption, PPROM, shoulder dystocia, mode of delivery, preterm birth, neonatal anthropometry, birthweight, birthweight centile, macrosomia, admission to NICU, perinatal death, hospitalisation, umbilical artery PH, 5 minute Apgar, hyperbilirubinaemia, phototherapy, RDS, minor birth defects
Notes	Elective delivery was planned at 38.5 weeks by induction or caesarean section Sample size calculation: yes based on birthweight. ITT analysis: yes. **Funding:** none stated. **Conflicts of interest**: manuscript states that there were no conflicts of interest

Risk of bias

Niromanesh 2012 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"assigned randomly", "computer generated list".
Allocation concealment (selection bias)	Low risk	Sequentially-labelled, opaque, sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were not blinded but obstetricians were.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details on outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	160 out of 172 women who were randomised were analysed. In the metformin group, 1 woman withdrew consent, 2 were lost to follow-up, 3 discontinued due to adverse effects. In the insulin group there were 6 women lost to follow-up
Selective reporting (reporting bias)	Low risk	All important infant and maternal outcomes appear to have reported
Other bias	Low risk	No evidence of other bias.

Notelovitz 1971

Methods	Randomised parallel trial.
Participants	207 women from South Africa. **Inclusion criteria:** women who had been screened using a 2-hour 100 g OGTT with blood glucose values ≥ 7.8 mmol/L (140 mg/dL), remaining duration of pregnancy allowing for 6 weeks of intervention. Included women with known diabetes, glycosuria, family and obstetric histories suggestive of diabetes **Exclusion criteria:** established diabetics already on a specific treatment were not randomised **Setting:** Durban, South Africa. **Timing**: not stated.
Interventions	**Insulin (n = 47)** **Dietary restriction alone (n = 56)** Chlorpropramide (n = 58) Tolbutamide (n = 46)
Outcomes	None prespecified

Notelovitz 1971 (*Continued*)

Notes	Power calculation - not stated. ITT analysis - yes. **Funding** - financial support received from Pfizer laboratories. **Conflicts of interest** - not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"random sample basis", no other details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women randomised appear to have data.
Selective reporting (reporting bias)	High risk	There are no pre-specified outcomes for the mother or the infant
Other bias	High risk	Paper states that there were no differences between interventions at baseline. The data for GDM and other diabetes cannot be separated. The proportion of women with GDM cannot be determined and the data have therefore not been included in any meta-analysis

O'Sullivan 1975a

Methods	Randomised parallel controlled trial.
Participants	615 women. **Inclusion criteria:** women with GDM. **Exclusion criteria:** pre-gestational diabetes, blood sugar > 300 mg/100 mL, classic diabetic symptoms and abnormal blood sugars, enrolling after 37 weeks' gestation with GDM **Setting:** Boston, USA. **Timing:** April 1954 to June 1960.

O'Sullivan 1975a (*Continued*)

Interventions	Insulin plus diet (n = 307) - 10 Units Neutral Protamine Hagedorn insulin in the morning plus 30/cal/kg ideal body weight as 1.5 g to 2.0 g protein/kg with 40% total calories from carbohydrates versus Routine prenatal care (n = 308) - not defined further.
Outcomes	Perinatal death, LGA, subsequent maternal diabetes.
Notes	Also included a group of women without GDM who were selected at random at regular intervals. The data for these women are not included in this review Power calculation - no details. ITT - appears to be conducted. **Funding** - not stated. **Conflicts of interest** - not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"randomly allocated", no other details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not reported and unlikely to have occurred due to different treatment interventions
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women randomised appear to have data.
Selective reporting (reporting bias)	High risk	Outcomes very limited. Only report on LGA, perinatal death and subsequent maternal diabetes
Other bias	Unclear risk	No details of demographics at baseline, unable to judge. 12/305 (4%) did not receive insulin in the treatment group

O'Sullivan 1975b

Methods	Randomised parallel controlled trial.
Participants	229 women. **Inclusion criteria:** women with GDM. **Exclusion criteria:** pre-gestational diabetes, blood sugar > 300 mg/100 mL, classic diabetic symptoms and abnormal blood sugars, enrolling after 37 weeks' gestation with GDM **Setting:** Boston, USA. **Timing:** December 1962 to May 1970.
Interventions	Insulin plus diet (n = 111) - 10 Units Neutral Protamine Hagedorn insulin in the morning (increasing if required) plus 30/cal/kg ideal body weight as 1.5 g to 2.0 g protein/kg with 40% total calories from carbohydrates versus Routine prenatal care (n = 118) - not defined further.
Outcomes	Perinatal death.
Notes	Power calculation - no details. ITT - no. **Funding** -not stated. **Conflicts of interest** - not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"randomly assigned", no other details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not reported and unlikely to have occurred due to different treatment interventions
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	1 twin stillbirth that occurred in the routine care group was not included in the analysis
Selective reporting (reporting bias)	High risk	Outcomes very limited. Only report on perinatal death.
Other bias	High risk	Study ended early due to lack of funding.

Ogunyemi 2007

Methods	Randomised controlled trial, parallel design.
Participants	97 women with a diagnosis of GDM (1-hour 50 g glucose challenge test followed by a 3-hour OGTT). 80% were Hispanic and 15% African American **Inclusion criteria:** diagnosis of GDM, dietary interventions alone had not been effective in maintaining glycaemic control **Exclusion criteria**: not specified. **Setting:** prenatal clinics in Los Angeles, USA. **Timing:** 2002 to 2005.
Interventions	1) Insulin (n = 49) no other details versus 2) Glibenclamide (n = 48) no other details.
Outcomes	Primary outcomes: maternal glycaemic control and neonatal birthweight
Notes	Unable to contact authors by email. **Funding:** no details **Conflicts of interest:** no details

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer generated list."
Allocation concealment (selection bias)	Low risk	Sealed sequentially number opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of attrition. ITT analysis conducted.
Selective reporting (reporting bias)	High risk	Only published as a conference abstract and as a letter to the editor
Other bias	High risk	No evidence of other sources of bias. No differences reported at baseline for demographic variables but the fasting, 1-hour and 2-hour glucose levels from the OGTT and the HbA1c were all significantly higher

		in the insulin group

Pavithra 2016

Methods	Parallel randomised controlled trial.
Participants	100 women with GDM. **Inclusion criteria:** age 20 to 40 years, singleton pregnancy, gestation 24 to 34 weeks' **Exclusion criteria:** pre-gestational diabetes, any other medical disorders. **Setting:** India **Timing:** No details
Interventions	All women given dietary and lifestyle advice for 2 weeks. If unable to maintain glycaemic targets then randomised to: Insulin (no other details) versus Glibenclamide - initial dose 2.5 mg/day, increased in weekly increments if required up to 20 mg daily. If unable to meet treatment targets then switched to insulin
Outcomes	Macrosomia (> 4 kg), RDS, neonatal hypoglycaemia, hyperbilirubinaemia, preterm birth (< 37 weeks'), hypocalcaemia, hypomagnesaemia
Notes	Abstract of paper available only to review authors. Full paper requested from primary authors (February 2016) **Funding: n**o details **Conflicts of interest:** no details

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"randomized", no other details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No details but unlikely to have been blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women appear to have been analysed.

Pavithra 2016 (*Continued*)

Selective reporting (reporting bias)	High risk	Maternal outcomes were not pre-specified but were reported. Additional neonatal outcomes reported and some were not reported
Other bias	Low risk	Groups appear balanced at baseline.

Persson 1985

Methods	Randomised parallel trial.
Participants	202 of 239 women approached from Sweden. **Inclusion criteria:** impaired glucose tolerance. **Exclusion criteria:** no details. **Setting:** Stockholm, Sweden. **Timing:** November 1981 to May 1984.
Interventions	Insulin plus diet - (n = 97) 8 to 12 IU/day of a fast or intermediate-acting insulin. Dietary advice from a dietician. 50% of calories in dietary intake from carbohydrate, 20% from protein and 30% from fat versus Diet alone - (n = 105) Dietary advice from a dietician. 50% of calories in dietary intake from carbohydrate, 20% from protein and 30% from fat All women performed self-monitoring of blood glucose 3 days a week, 6 times per day before food and 1-hour postprandial
Outcomes	No primary outcomes prespecified. Glycaemic control, HbA1c, neonatal complications (no specified), C-peptide, SGA, LGA, AGA, skin fold thickness, neonatal glucose control, infant feeding, respiratory disorders
Notes	Sample size calculation - not reported. ITT analysis - no. **Funding** - Swedish Medical Research Council, Tielman Fund for Pediatric Research, Expressen Fund for Prenatal Research, Allmanna BB Minnesfond, Swedish Diabetic Association **Conflicts of interest** - not reported.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"randomized", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.

Persson 1985 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details.
Incomplete outcome data (attrition bias) All outcomes	High risk	Some data are not available for all women such as HbA1c at delivery and cord C peptide. Other outcomes not reported with total sample denominator
Selective reporting (reporting bias)	High risk	No maternal or infant primary outcomes were prespecified, the authors refer to neonatal complications but these are not prespecified
Other bias	Low risk	Groups appear to be balanced at baseline.

Pettitt 2007

Methods	Single-centre, randomised controlled trial.
Participants	27 women with GDM at 18 to 28 weeks' gestation. **Inclusion/exclusion criteria**: not stated. **Setting:** California USA. **Timing**: no details.
Interventions	Insulin aspart 5 minutes before a meal + Neutral Protamine Hagedorn insulin as the basal insulin versus Regular human insulin 30 minutes before a meal + Neutral Protamine Hagedorn insulin as the basal insulin Initial treatment was 2 daily doses (morning and bedtime) of Neutral Protamine Hagedorn insulin and 3 daily doses of either insulin aspart or regular human insulin. Initial dose of insulin was 0.8 U/kg per day if < 26 weeks' gestation or 0.9 U/kg if ≥26 weeks' gestation Given dietary advice and self-monitored 7 times per day.
Outcomes	HbA1c, maternal hypoglycaemia, insulin antibodies, blood glucose values, cord blood insulin and insulin antibody binding
Notes	Sample size calculation - no details. ITT analysis - yes. **Funding** - the study was funded in part through a contract with Novo Nordisk Inc **Conflicts of interest** - One of the authors was an employee of the funding body.
Risk of bias	

Pettitt 2007 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomized", no other details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"open label."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	13/14 women in the insulin aspart group completed the study and 9/13 in the human insulin group. 4 participants discontinued as they gave birth early and 1 participant due to the inability to complete the meal test. The authors do not specify which groups the participants belonged to
Selective reporting (reporting bias)	High risk	Data on birth outcome including weight and length, macrosomia and congenital anomalies were not prespecified
Other bias	Low risk	No differences at baseline.

Poyhonen-Alho 2002

Methods	Randomised controlled pilot trial, single-centre.
Participants	23 women. **Inclusion criteria:** insulin requiring GDM. **Exclusion criteria**: not stated. **Setting:** Department of Obstetrics and Gynaecology, Helsinki, Finland **Timing**: not stated.
Interventions	Individualised diet planned with a dietician. Daily energy intake 1800 kcal of which 50% was carbohydrates Short-acting insulin - Actrapid (human insulin). 3 daily injections with starting doses of 4, 6 and 4 IU before breakfast, lunch and dinner. Dose was increased if 1 of the postprandial glucose values > 7.8 mmol/L (n = 11) versus Long-acting insulin - Protaphan (Neutral Protamine Hagedorn insulin). 1 injection in the morning with an initial dose of 14 IU. Dose was increased if 2 of daily preprandial values > 5.5 mmol/L. (n = 12)

Poyhonen-Alho 2002 (*Continued*)

	Doses were individually adjusted and women followed up in clinics every 2 to 4 weeks. Self-monitoring of blood glucose before breakfast and pre- and postprandial at least twice a week
Outcomes	None prespecified but reported on insulin requirements,timing of birth, birthweight, macrosomia, nerve palsy, fetal hypoglycaemia, hyperbilirubinaemia, transient tachypnoea, need for insulin postpartum, mode of birth, malformations, Apgar < 7 at 1 minute, maternal HbA1c
Notes	Sample size calculation - no. ITT analysis - yes. **Funding:** not stated. **Conflicts of interest** - not reported in manuscript.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"randomized", no other details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No details but blinding unlikely due to different protocols and targets
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women randomised were analysed.
Selective reporting (reporting bias)	High risk	No outcomes were prespecified. A number of outcomes were reported in the results section. Some outcomes were not associated with any data and the authors state that there was no difference between groups
Other bias	High risk	These data are published as a brief report of a pilot study. There is no full publication and no indication that a larger trial was undertaken

Prasad 2008

Methods	Parallel randomised controlled trial.
Participants	100 women with GDM. **Inclusion criteria:** age 30 to 40 years diagnosed with GDM. **Exclusion criteria**: no details. **Setting:** India. **Timing**: no details.
Interventions	Insulin aspart - no details (n = 50) versus Regular insulin plus Neutral Protamine Hagedorn insulin - no details (n = 50)
Outcomes	Maternal hyperglycaemia, hypoglycaemia and other complications
Notes	Conference abstract only. **Funding:** no details **Conflicts of interest** : no details

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"randomised controlled trial."
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details.
Incomplete outcome data (attrition bias) All outcomes	High risk	Conference abstract only, unclear if any losses.
Selective reporting (reporting bias)	High risk	Minimal outcomes prespecified, report on outcomes not in methods
Other bias	High risk	Conference abstract only. No full publication identified.

Riaz 2014

Methods	Randomised controlled trial.
Participants	200 women with GDM. **Inclusion criteria:** diagnosis of GDM, having poor glycaemic control with diet alone **Exclusion criteria:** pre-gestational diabetes, already using insulin or contraindication to metformin use **Setting:** Rahim Yar Khan, Pakistan. **Timing:** January 2012 to June 2012.
Interventions	Insulin (type not specified) (n = 100) versus Metformin (n = 100).
Outcomes	Glycaemic control.
Notes	Sample size calculation - no. ITT analysis - yes. **Funding** - not stated. **Conflicts of interest** - the manuscript does not include any conflicts of interest

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Random number table", "Randomization".
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No details but unlikely.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis.
Selective reporting (reporting bias)	High risk	Only 1 outcome, glycaemic control, is reported as a frequency. No raw data for fasting or postprandial blood glucose levels are given. No neonatal data
Other bias	High risk	Data are presented as a brief report only.

Rowan 2008

Methods	Multicentre (n = 10 sites) randomised controlled trial.
Participants	**Inclusion criteria:** 18-45 years, singleton pregnancy, 20-33 weeks' gestation, meeting hospital criteria for insulin use, after lifestyle advice had more than on capillary blood glucose > 5.4 mmol/L (fasting), or > 6.7 mmol/L 2 hours postprandial. Diagnosis of GDM (ADIPS) - 75 g OGTT with 1 or more of the following being abnormal fasting plasma glucose level ≥ 5.1 mmol/L, 1-hour venous plasma glucose ≥ 10.0 mmol/L, or 2-hour venous plasma glucose ≥ 8.5 mmol/L **Exclusion criteria:** pre-pregnancy diagnosis of diabetes, contraindication to metformin, fetal anomaly, gestational hypertension, pre-eclampsia, fetal growth restriction or ruptured membranes **Setting:** New Zealand and Australian obstetric hospitals. **Timing:** October 2002 to November 2006.
Interventions	1) Insulin (n = 370) - administered as per usual practice. versus 2) Metformin (n = 363) - started at 500 mg once or twice daily increasing over 1 to 2 weeks to a maximum of 2500 mg daily +/- insulin. Treatment was stopped if there were maternal contraindications or intrauterine growth restriction
Outcomes	A composite of neonatal complications (hypoglycaemia -< 2.6 mmol/L, RDS, phototherapy, birth trauma, 5-minute Apgar < 7, preterm birth < 37 weeks) Maternal hypertension, acceptability of treatment, congenital abnormalities, anthropometry, diagnosis at hospital discharge, maternal and neonatal body composition, maternal glycaemic control, maternal glucose tolerance 6-8 weeks postpartum, adverse events, gestational weight gain Follow-up reported on neurodevelopmental outcomes.
Notes	ITT analysis: yes. Power calculation: yes. **Funding**: Auckland Medical Research Fund, Health Research Council, National Womens Evelyn Bond Charitable Trust, National Health and Medical Research Council, Australia **Conflicts of interest:** in the Rowan 2008 paper conflicts are reported by Dr Moore for receiving speaking fees from Sanofi-Aventis. In the 2011 follow-up paper Dr Hague reports being a speaker at a Merck European Association for the Study of Diabetes symposium Authors were contacted in August 2012 for additional information on allocation concealment. They have responded and this information has been included 2-year follow-up data were reported in Rowan 2011, Battin 2015, Wouldes 2016

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block size of 4 stratified by site and gestational age.

Rowan 2008 (*Continued*)

Allocation concealment (selection bias)	Low risk	Randomisation was central. Authors filled in a web-based form showing women met the randomisation criteria. It was submitted electronically and allocation to treatment and participant study number came back. This was organised centrally and independently of the trial
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Insulin: 8 excluded (2 withdrew consent, 2 moved away and 4 protocol violations) Metformin: 10 excluded (5 withdrew consent, 1 moved away and 4 protocol violations) 27 women in the metformin group stopped treatment before delivery (11 protocol violations, 7 gastrointestinal side effects, 5 personal choice, 4 advised to stop by another health professional)
Selective reporting (reporting bias)	Unclear risk	Maternal and neonatal outcomes reported. 2-year follow-up data are only reported for 2 sites in Australia and New Zealand
Other bias	Unclear risk	Metformin group had significantly more pregnancy losses for any reason compared to the insulin group

Ruholamin 2014

Methods	Parallel, randomised controlled trial - single-centre.
Participants	119 women. **Inclusion criteria:** 18 to 45 years, singleton pregnancy, 24 to 33 weeks' gestation, GDM diagnosis based on ADIPS criteria, no response to lifestyle modification after 1 week, providing consent **Exclusion criteria:** contraindication for receiving metformin (renal or hepatic failure), history of diagnosis of diabetes before pregnancy, history of severe drug reaction to drugs in study, serious medical condition that might interfere with safe participation in study **Setting:** Isfahan, Iran. **Timing:** 2011.

Interventions	Insulin (n = 59) initial dose 0.2 IU/kg/day versus Metformin (n = 60) initial dose 50 mg once or twice per day and increased if required over 1 to 2 weeks up to a maximum of 1500 mg per day. If treatment targets (fasting < 5.3 mmol/L or 95 mg/dL and 2-hour post-prandial < 6.7 mmol/L or 120 mg/dL) not met then insulin was added
Outcomes	Primary and secondary outcomes not specified. Pregnancy-induced hypertension, pre-eclampsia, birthweight, macrosomia (> 4500 g), SGA, preterm birth, Apgar score at 5 minutes, umbilical artery pH < 7.05, hypoglycaemia (< 2.6 mmol/L), hyperbilirubinaemia, need for intensive care treatment, RDS, shoulder dystocia
Notes	Power calculation: not stated. ITT analysis: no. **Funding:** nil. **Conflicts of interest**: manuscript states no conflicts of interest.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"randomized", simple randomisation with random number tables
Allocation concealment (selection bias)	Low risk	Third party performed randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind". Care providers blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Physician assessing outcomes was blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 women in the metformin group did not meet treatment targets and were excluded, 7 women were excluded because of pregnancy complications such as hypertension/ pre-eclampsia pre preterm birth 10 women in the insulin group were excluded because of pregnancy complications such as hypertension/pre-eclampsia pre preterm birth
Selective reporting (reporting bias)	Unclear risk	The results section states that fasting and 2-hour post-prandial blood sugar concentrations were similar between groups through-

		out treatment but these data are not reported anywhere in the paper
Other bias	Low risk	No other bias identified. Groups were similar at baseline.

Saleh 2016

Methods	Parallel randomised controlled trial
Participants	150 women **Inclusion criteria:** Women with GDM not responding to diet modifications alone after three weeks **Exclusion criteria:** type 1 or 2 diabetes, already on insulin treatment, fetal anomaly, hypersensitivity or intolerance to metformin, obstetric high risk **Setting:** Zagazig University Department, Zagazig; Egypt. **Timing:** November 2012 to December 2014
Interventions	Insulin - combination of short-acting (Actrapid) and intermediate-acting (Mixtard) human insulin as twice-daily injections. Dosage was estimated by maternal weight and trimester of pregnancy (n = 75). Blood sugar monitored three times daily versus Metformin initial dose of 500 mg/day increasing to a maximum of 3000 mg/day in divided doses. If glycaemic control not achieved then insulin commenced (n= 75)
Outcomes	Glycaemic control - fasting and two-hour postprandial blood glucose, medical complications (not specified), mode of birth, neonatal outcomes (none specified)
Notes	**Funding:** No details. **Conflicts of interest:** manuscript states no conflicts of interest.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Permuted block randomisation, no other details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unlikely due to differences in treatment interventions.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details.

Saleh 2016 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	150 randomised (75 insulin; 75 metformin), 137 competed and analysed (70 insulin; 67 metformin). Insulin group 3 withdrew consent and 2 lost to follow-up. In metformin group 4 withdrew consent, 2 lost to follow-up and 2 discontinued medication
Selective reporting (reporting bias)	High risk	Some maternal and all neonatal outcomes were not clearly prespecified
Other bias	Low risk	Groups balanced at baseline.

Silva 2007

Methods	Single-centre parallel, randomised controlled trial.
Participants	72 women randomised whose blood glucose was not controlled by diet alone. 68 analysed **Inclusion criteria:** ≥ 18 years, diagnosis of GDM using 75 g OGTT according to guidelines of the Ministry of Health, gestational age 11 to 33 weeks' gestation, singleton pregnancy, no evidence of malformations, no other pathologies that would affect therapy **Exclusion criteria**: not consenting, pathology that could affect treatment, childbirth in a different institution **Setting:** Maternity unit in Brazil. **Timing:** October 2003 to March 2005.
Interventions	All women saw a dietician for diet therapy. 1) Insulin - dose adjusted for current weight and gestation. Fast-acting human insulin (regular) before meals and slow-acting (Neutral Protamine Hagedorn insulin) at night (n = 36) versus 2) Glibencamide - 5 mg increasing weekly by 2.5 mg to 5 mg until glycaemic control. Maximum dose of 20 mg/day. If not controlled, had supplementary insulin (n = 32)
Outcomes	Glycaemic control, gestational age at delivery, mode of birth, birthweight, Apgar at 1 and 5 minutes, neonatal peripheral capillary blood glucose, macrosomia (> 4000 g), LGA (> 90th percentile)
Notes	Institutional policy required delivery before 39 weeks'. ITT analysis: no, not all those randomised were analysed. **Funding:** not stated. Power calculation: yes. **Conflicts of interest:** no details were specified in the manuscript.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Silva 2007 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	No details.
Allocation concealment (selection bias)	Unclear risk	Randomisation with envelopes that contained a sheet with the treatment group
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	Low risk	68/72 women analysed. 4 exclusions (birth in another hospital, moved out of area, requested exclusion, severe asthma requiring corticotherapy)
Selective reporting (reporting bias)	Unclear risk	Limited maternal outcomes.
Other bias	High risk	No evidence of other sources of bias. Demographics were balanced at baseline but the results of the OGTT were significantly higher in the glibenclamide group

Spaulonci 2013

Methods	Parallel randomised controlled trial.
Participants	**Inclusion criteria:** singleton pregnancy, use of diet and exercise for a minimum period of 1 week without satisfactory glycaemic control, absence of risk factors for lactic acidosis (renal failure, heart failure, chronic liver disease, severe chronic pulmonary disease, coronary insufficiency, history of thromboembolic phenomena), and absence of anatomic and/or chromosome anomalies of the conceptus detected by ultrasonography **Exclusion criteria:** lost to prenatal follow-up or performed less than 85% of the glucose tests **Setting:** Obstetric clinic in a university hospital in Sao Paolo, Brazil **Timing:** 2007-2010.
Interventions	Insulin (n = 47) Neutral Protamine Hagedorn insulin. Starting dose 0.4 units per kg body weight per day (half the dose in the morning, 1 quarter at lunchtime and one-quarter before bed). Doses adjusted based on glycaemic control versus Metformin (n = 47) initial dose of 1700 mg per day, increased after 1 week if necessary to 2550 mg/day. If glycaemic control not achieved then supplementary insulin was added

Spaulonci 2013 (*Continued*)

Outcomes	Pre-eclampsia, prematurity, neonatal hypoglycaemia, macrosomia, hyperbilirubinaemia, RDS, side effects, glycaemic control, gestational weight gain
Notes	ITT analysis: yes. **Funding:** not stated. Power calculation: yes based on glycaemic control. **Conflicts of interest:** no details

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Electronic randomisation lists.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 women withdrew. Analysis was by ITT.
Selective reporting (reporting bias)	High risk	There were outcomes reported in the paper that were not prespecified in the methods section
Other bias	Low risk	No evidence of other sources of bias.

Tertti 2013

Methods	Open-label randomised trial.
Participants	221 women from Finland. **Inclusion criteria:** singleton pregnancy, diagnosis of GDM (2-hour 75 g OGTT, screening criteria based on risk changed during the study. Diagnostic cut-off levels up to 2008 were fasting >/= 4.8 mmol/L 1 hour >/= 10.0 mmol/L, and 2 hour >/= 8.7 mmol/L and thereafter was fasting >/= 5.3 mmol/L, 1 hour >/= 10 mmo/L and 2 hour >/= 8.6 mmol/L. Between 22 to 34 weeks' gestation. Women who had failed to meet glucose targets with medical nutritional therapy (FPG >/= 5.5 mmol/L or postprandial >/= 7.8 mmol/L) **Exclusion criteria** - cardiac or renal insufficiency, liver disease metformin use within 3 months of pregnancy or during pregnancy before OGTT, self-measured FPG > 7.0 mmol/L or 1-hour post prandial glucose > 11.0 mmol/L

	Setting: University Central Hospital, Turku, Finland. **Timing:** June 2006 to December 2010.
Interventions	All women had dietary counselling at the hospital. Insulin (n = 110) Neutral Protamine Hagedorn insulin and/or rapid-acting insulin lispro or insulin aspart versus Metformin (n = 111) 500 mg once daily then increased to twice daily for first week. Dose increased to a maximum of 1 g twice daily if required. Additional insulin given if glucose targets not met. Also had vitamin B preparation containing 0.4 mg folic acid A third arm received only lifestyle and diet advice but these women were not randomised and therefore not used in this review
Outcomes	HbA1c, fructosamine, C-peptide, cord pH, birthweight, LGA (> 4500 g), pregnancy-induced hypertension, pre-eclampsia, maternal weight gain, induction of labour, mode of delivery, preterm birth, SGA, Apgar at 5 minutes, admission to NICU, neonatal hypoglycaemia requiring treatment, hyperbilirubinaemia requiring phototherapy, birth trauma
Notes	ITT analysis: no. **Funding:** Finnish Diabetes Association and EVO grants. **Conflicts of interest:** The authors declare no conflicts of interest. Power calculation: yes but did not reach sample target in each arm and may be under-powered Report on follow-up at 30 to 85 months on testicular size (Tertti 2016) Neurodevelopmental outcomes at 2-year old follow-up (Tertti 2015) Maternal weight and postpartum glucose tolerance (Tertti 2015) A further follow-up is planned at 9 years of age (Niinikoski NCT02417090)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised no other details.
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes, unclear if opaque or sequentially numbered
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of women or researchers due to mode of delivery of medication, unclear if this would affect outcomes
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Outcome assessors do not appear to be blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 women in insulin group excluded for protocol violation. In metformin group 1 woman moved away

Tertti 2013 (*Continued*)

Selective reporting (reporting bias)	Low risk	Original protocol not viewed but all outcomes listed a priori in the methods section have been reported in the results
Other bias	Low risk	No evidence of other sources of bias.

Thompson 1990

Methods	Single-centre randomised controlled trial.
Participants	108 women were enrolled and randomised. **Inclusion criteria**: diagnosis of GDM. Women were screened at or before 28 weeks with fasting capillary glucose and 1-hour capillary glucose following a 50 g loading dose. If 105 mg/dL for fasting or > 145 mg/dL for 1-hour result then underwent a 3-hour OGTT with a 100 g load. 2 or more results had to be abnormal for a diagnosis of GDM (fasting > 5.8 mmol/L or 105mg/dL, 1-hour 10.5 mmol/L or 190 mg/dL, 2-hour 9.2 mmol/L or 165 mg/dL, 3-hour > 8.1 mmol/L or 145 mg/dL) **Exclusion criteria:** 3-hour OGTT fasting result ≥ 7.8 mmol/L (140 mg/dL), refused to participate, diagnosed after 36 weeks' gestation, in study for less than 6 weeks before delivery **Setting:** Alabama, USA. **Timing:** October 1985 to June 1998.
Interventions	1) Diet plus insulin (n = 45) - same diet as above but with the addition of 20 units (Neutral Protamine Hagedorn insulin) and 10 units regular insulin 30 minutes before breakfast. If treatment targets not met then insulin dose increased versus 2) Diet alone (n = 50) a standard diet delivered by a nutritionist. 35 kcal/kg ideal body weight (50% carbohydrate, 30% fat, 20% protein) divided into 3 meals and 2 snacks per day. Supplementary insulin if glucose levels not maintained, 105 mg/dL fasting or < 120 mg/dL 2 hours post prandial
Outcomes	Ponderal index, perinatal mortality, birth trauma, caesarean section, macrosomia (> 4000 g), hypoglycaemia, hyperbilirubinaemia, hypocalcaemia
Notes	Power calculation: not stated. ITT analysis: for the majority of outcomes only reported women with good glycaemic control **Funding**: Not stated. **Conflicts of interest:** No details.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"randomly generated numbers."

Thompson 1990 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	"sealed envelopes" no other details as to whether opaque or handed out sequentially
Blinding of participants and personnel (performance bias) All outcomes	High risk	There was no blinding.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Neonatologists were aware of the treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	108 were randomised, 13 were excluded as they had treatment for less than 6 weeks. This was a prespecified exclusion. 95 were analysed
Selective reporting (reporting bias)	High risk	The authors included maternal and neonatal outcomes but only reported on those women maintaining acceptable glucose control. They do report no differences for ITT analysis but data not given
Other bias	Low risk	Groups appear to be balanced at baseline.

Waheed 2013

Methods	Randomised trial.
Participants	68 pregnant women. **Inclusion criteria:** > 14 weeks' gestation with diabetes in pregnancy (fasting blood sugar 100 mg/dL, 5.5 mmol/L and random blood sugar > 140 mg/dL, 7.7 mmol/L) **Exclusion criteria:** renal or hepatic impairment or type 1 diabetes. **Setting:** Department of obstetrics and Gynaecology, Maternal and Child Health Centre, Pakistan Institute of Medical Sciences, Islamabad **Timing:** May 2010 to January 2011.
Interventions	Insulin (n = 34) no details. versus Metformin starting dose 500 mg daily increasing to a maximum of 1500 mg (n = 34) Target for treatment was fasting blood sugar 63 mg to 100 mg (3.5 to 5.5 mmol/L) and random blood sugar < 140 mg/dL (7.7 mmol/L) and HbA1c < 6.1% (43.2 mmol/mol)
Outcomes	Fasting and postprandial glucose levels, HbA1c.
Notes	Power calculation: yes. ITT analysis: **Funding:** none. **Conflicts of interest:** no details

Waheed 2013 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"randomly divided in to 2 groups... based on table of random numbers"
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No details provided but unlikely to be blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There do not appear to be any losses and all women are accounted for
Selective reporting (reporting bias)	Unclear risk	Main introduction is around gestational diabetes but also report on women with diabetes in pregnancy and is unclear if this includes type 2 diabetes although blood sugars for inclusion are lower than that for women with type 2 diabetes. Data are not separated out so some evidence may be indirect
Other bias	Low risk	No other sources of bias identified.

Wali 2015

Methods	Randomised trial.
Participants	154 women. **Inclusion criteria:** women diagnosed with GDM, singleton pregnancy, consented to trial **Exclusion criteria:** pre-gestational type 1 or type 2 diabetes, overt diabetes, gestational age more than 30 weeks' at the time of recruitment, on steroid therapy, not tolerating OGTT **Setting:** Pakistan. **Timing**: not stated.
Interventions	Insulin (no details) (n = 71) versus Metformin +/- glibenclamide (n = 74).
Outcomes	Primary outcome - glycaemic control. Secondary outcome - acceptability of treatment, cost.

Wali 2015 (*Continued*)

Notes	**Funding:** Supported by Aga Kahn University Hospital **Conflicts of interest** - No details

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Block randomisation."
Allocation concealment (selection bias)	Low risk	"Sealed opaque envelope."
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Open label."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Conference abstract only. Unclear if reporting on total population
Selective reporting (reporting bias)	High risk	Conference paper only, unclear if all outcomes reported were pre-specified
Other bias	High risk	Unable to judge as conference abstract only. No full paper identified

Zangeneh 2014

Methods	Parallel, randomised controlled trial.
Participants	90 pregnant women from Kermanshah, Iran. **Inclusion criteria:** gestational diabetes, between 11 to 33 weeks' gestation, singleton pregnancy, failing to meet treatment targets with diet alone after 1 week **Exclusion criteria**: not agreeing to participate, multiple pregnancy, pre-gestational diabetes, infectious disease, cardiovascular disease, haematological disease **Setting:** Iran. **Timing:** March 2010 to March 2011.
Interventions	Insulin 0.5 U/kg twice daily increased weekly if required. Used regular insulin and Neutral Protamine Hagedorn insulin (n = 46) versus Glibenclamide 2.5 mg initially, increased if required to a maximum of 20 mg daily (n = 45) Self-monitoring of blood glucose 4 times daily.

Zangeneh 2014 (*Continued*)

Outcomes	Primary outcome - blood glucose level. Secondary outcomes - macrosomia, oligohydramnios, polyhydramnios, fetal death, intrauterine growth restriction, fetal anomaly, Apgar score, hypoglycaemia, hypocalcaemia, admission to NICU. caesarean section, pre-eclampsia
Notes	Sample size calculation - no. ITT analysis - yes. **Funding** - no details. **Conflicts of interest** - nothing in the manuscript about conflicts of interest.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomly assigned, no other details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No details but unlikely.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details, women randomised appear to be have been analysed
Selective reporting (reporting bias)	Low risk	All outcomes listed were reported.
Other bias	Low risk	No other evidence of risk of bias.

Zawiejska 2016

Methods	Parallel randomised controlled trial
Participants	**Inclusion criteria**: Maternal pre-pregnancy BMI of at least 25 kg/m^2, singleton pregnancy, no fetal abnormalities, gestational age 20 to 32 weeks, diagnosed with GDM and not responsive to dietary treatment, no pre-existing diabetes, normal liver and kidney function, no intravenous betamimetics given or intramuscular glucorticoids **Exclusion criteria:** no details. **Setting**: Tertiary academic centre, Ponzan, Poland. **Timing:** 2009 to 2011

Zawiejska 2016 (*Continued*)

Interventions	Insulin given using basal-bolus regimen starting at 0.3 IU/kg divided into two doses and prandial insulin in three doses (n = 43) versus Metformin starting dose 500 mg twice daily and titrated to achieve glycaemic control (n = 35)
Outcomes	Primary outcomes - fasting and mean daily glycaemia and HbA1c Secondary outcome - insulin resistance (HOMA-IR); triglycerides and HDL cholesterol to calculate the atherogenic plasma index; maternal weight gain
Notes	**Funding:** Polish Ministry of Science **Conflicts of interest**: Authors declare no conflicts of interest.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Drawn by lots.
Allocation concealment (selection bias)	Low risk	Allocation was contained in a sealed box until time of selection and were contained in sealed plain envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants or researchers.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details.
Incomplete outcome data (attrition bias) All outcomes	Low risk	78 women randomised. Data on birth not available for 9/35 women in metformin group or 3/43 in insulin group. Other outcome data were reported
Selective reporting (reporting bias)	High risk	No neonatal outcome data reported.
Other bias	Low risk	No evidence of other bias.

ADA: American Diabetes Association
AGA: Appropriate for gestational age
BMI: body mass index
FPG: fasting plasma glucose
GDM: gestational diabetes mellitus
HDL; high-density lipoprotein

HOMA-IR: homeostasis model assessment-estimated insulin resistance
IADPSG: International Association of the Diabetes and Pregnancy Study Groups
ITT: intention to treat
IU: international unit
LGA: large-for-gestational age
OGTT: oral glucose tolerance test
PPH: postpartum haemorrhage
PPROM: preterm prelabour rupture of membranes
NICU: neonatal intensive care unit
NPH: Neutral Protamine Hagedorn
RDS: respiratory distress syndrome
SGA: small-for-gestational age

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ainuddin 2015	Participants were women with pre-existing diabetes and women with overt diabetes in pregnancy. Wrong population
Ainuddin 2015a	This was a quasi-randomised trial using odd-even allocation as the means of randomisation
Brennan 2015	This is a cost-effectiveness analysis based on available data and is not a randomised trial. Wrong design
Coiner 2014	Trial compared metformin only, versus glibenclamide only versus metformin plus insulin. Wrong comparison
Fadl 2015	Participants did not meet the criteria for diagnosis with GDM in this trial
Hassan 2012	Quasi-randomised study with alternate allocation.
Hopp 1996	Trial where treatment was based on amniotic fluid insulin or maternal blood glucose. Wrong intervention
Kitzmiller 1990	Personal communication from Dr Kitzmiller indicated the trial never commenced
Landon 2015	Wrong comparison - lifestyle intervention versus usual care.
Li 1987	Wrong intervention. Intervention based on 2 different diagnostic criteria
Li 1999	Not randomised
Maresh 1983	Allocation was 'alternate'.
Munshi 2014	Participants were allocated using odd and even numbers. Quasi-randomised
NCT00678080	Type 2 diabetes only included.
O'Sullivan 1971	Quasi-randomised study with alternate allocation to treatment and control groups

(*Continued*)

Palatnik 2015	Wrong comparison. Secondary analysis of a trial of lifestyle intervention versus usual care
Pettitt 2003	Report on meal tests only not a treatment intervention.
Schuster 1998	Randomised trial of women with insulin dependant diabetes who were pregnant. Wrong population for this review
Smith 2015	Secondary analysis of a trial using metformin versus insulin postpartum to prevent type 2 diabetes
Snyder 1998	Trial comparing strict with less strict glycaemic control in women with GDM
Tempe 2013	This is a quasi-randomised trial using alternate allocation as the means of randomisation

GDM: gestational diabetes mellitus

Characteristics of studies awaiting assessment *[ordered by study ID]*

Afshari 2013

Methods	Unclear if this is randomised - 'The study was conducted in two groups'
Participants	The number of women allocated to groups is not provided. There are no inclusion and exclusion criteria listed. The study was conducted in Iran
Interventions	Insulin (no details) versus Diet (no details).
Outcomes	Maternal and neonatal blood sugar, birthweight, placental weight
Notes	Authors to be contacted regarding confirmation of randomisation and other methodological queries

Dunne 2001

Methods	Parallel randomised controlled trial.
Participants	200 women planned for recruitment. Inclusion criteria: women with GDM using WHO (75 g test); singleton pregnancy
Interventions	All women to receive dietary advice and to perform self-monitoring of blood glucose 7 times daily. Glycaemic targets - preprandial 3.5 to 5.6 mmol/L and 2-hour postprandial ≤ 7.8 mmol/L Insulin (n = 100 women planned) no details. Drug therapy (n = 100 planned) no details.

Dunne 2001 (*Continued*)

Outcomes	Glycaemic control, hypertensive disorders of pregnancy, maternal hypoglycaemia (< 3.3 mmol/L), caesarean section, macrosomia, respiratory distress syndrome, hypoglycaemia, polycythaemia, gestational age at birth, Apgar score, maternal lipids
Notes	Information obtained from Clinical Trials Registry only. No full paper or abstract could be identified. Study funded by Lilly Industries

Ibrahim 2014

Methods	Randomised controlled trial.
Participants	Women with diabetes in pregnancy including pre-existing and GDM
Interventions	Metformin plus insulin versus Metformin plus increased dose of insulin.
Outcomes	Glycaemic control, maternal hypoglycaemia, hospital admission, gestational age at birth, mode of delivery, birthweight, birth trauma, congenital anomalies, Apgar score, neonatal hypoglycaemia, admission to NICU, adverse neonatal outcomes
Notes	Authors contacted December 2015 regarding separation of data for GDM and pre-existing diabetes

Liang 2009

Methods	Unclear if this is a randomised controlled trial.
Participants	Women with GDM following insulin and diet for glycaemic control
Interventions	Insulin (n = 43) versus Astragalus plus insulin (n = 41).
Outcomes	Blood lipids, renal function, superoxide dismutase, malondialdehyde
Notes	Unclear if this is a randomised trial. Translation from Chinese required

NCT00160485

Methods	Glyburide compared to insulin in the management of White's classification A2 gestational diabetes
Participants	Randomised trial of treatment for gestational diabetes.
Interventions	Pregnant women over age 18 who fail to achieve adequate glucose control on diet therapy alone
Outcomes	Glyburide.

NCT00160485 (*Continued*)

Notes	Primary outcome measure: newborn birthweight. Secondary outcome measures: • gestational age at delivery; • method of delivery (caesarean, forceps, vacuum, spontaneous); complications of delivery (shoulder dystocia, birth injury, 4th degree vaginal laceration); • newborn intensive care unit admission; • congenital anomalies of the newborn; • incidence of neonatal metabolic derangement. Start date June 2004. Elizabeth C Golladay Spooner elizabeth.golladay@us.army.mil 31/1/12 - no new information 07/09/2012 Trial suspended due to primary investigator absence

Shaikh 2013

Methods	Randomised controlled trial.
Participants	450 women diagnosed with GDM. Setting: Dhaka, Bangladesh. Timing: December 2009 to December 2012.
Interventions	Insulin (n = 225) - no details versus Metformin (n = 225).
Outcomes	Primary outcome: perinatal and maternal outcome of metformin treatment (no details) Secondary outcomes: cost, satisfaction and acceptability.
Notes	Sample size calculation - no details in conference abstract. ITT analysis - no details in conference abstract. Funding - no details in conference abstract. Conflicts of interest - no details in conference abstract. The data are presented as a conference abstract and an e-poster. Numbers do not match and the event rates are much higher than expected. Authors to be contacted

Todorova 2007

Methods	Unclear - women were divided into 2 groups but these groups were not equal
Participants	Women diagnosed with GDM. Bulgaria.
Interventions	Insulin plus diet versus diet alone.
Outcomes	Blood glucose levels, HbA1c, caesarean section, birthweight, pre-eclampsia, macrosomia

Todorova 2007 (*Continued*)

Notes	Authors contacted by email 21/01/2016 regarding method of randomisation

Zhou 2012

Methods	Unclear if randomised. Participants were 'divided' into 2 groups
Participants	80 women with gestational diabetes mellitus.
Interventions	Human aspart insulin. Regular human insulin.
Outcomes	No details.
Notes	Information from Pubmed abstract only. Article in Chinese. Awaiting translation

ITT: intention to treat
GDM: gestational diabetes mellitus
NICU: neonatal intensive care unit

Characteristics of ongoing studies *[ordered by study ID]*

CTRI/2011/08/001956

Trial name or title	Can oral medication replace insulin injections in pregnant women with diabetes?
Methods	Randomised controlled trial.
Participants	120 women from India with gestational diabetes. **Inclusion criteria:** second trimester of pregnancy, singleton or twin pregnancy, able to give consent, no adverse obstetric history, no history of congenital abnormalities in previous babies **Exclusion criteria:** end organ complications of diabetes, prior adverse reaction to diabetes, liver disease, adverse obstetric complications, history of congenital abnormalities in previous babies
Interventions	Insulin versus Metformin
Outcomes	Primary outcome - glycaemic control. Secondary outcomes - need for additional insulin, pregnancy complications, acceptability and satisfaction, neonatal complications
Starting date	2011
Contact information	Dr Neeta Singh dneetasingh@yahoo.com

CTRI/2011/08/001956 (*Continued*)

Notes	

CTRI/2013/10/004055

Trial name or title	Metformin in management of diabetes in pregnancy: A randomised controlled study
Methods	Randomised controlled trial.
Participants	100 women with diabetes in pregnancy from India. **Inclusion criteria:** singleton pregnancy, abnormal blood glucose at 12 to 34 weeks' gestation, diabetes not controlled by medical nutrition therapy after 1 week **Exclusion criteria:** type 1 diabetes, severe hyperglycaemia, contraindications to metformin, in labour or with ruptured membranes, unwilling to participate
Interventions	Insulin versus Metformin
Outcomes	Primary outcome - glycaemic control. Secondary outcomes - composite of neonatal morbidity, insulin requirement, maternal complications, side effects
Starting date	2013.
Contact information	Dr Asmita Rathore asmita.rathore@yahoo.com
Notes	

CTRI/2014/08/004835

Trial name or title	A clinical trial to compare the effects of metformin versus insulin in patients with diabetes in pregnancy
Methods	Randomised controlled trial.
Participants	100 women with gestational diabetes. **Inclusion criteria:** diagnosis at 24 to 33 weeks'. **Exclusion criteria:** diagnosis of diabetes < 24 weeks', pre-gestational diabetes, HbA1c > 7.5%, renal, hepatic or cardiac failure, diabetic ketoacidosis, multiple pregnancy, intrauterine growth restriction, ruptured membranes, fetal anomaly, bad obstetric history, pre-eclampsia, chronic hypertension, other major comorbid illness, placental anomalies, oligohydramnios, polyhydramnios, unwilling to participate
Interventions	Insulin human regular insulin and Neutral Protamine Hagedorn insulin versus Metformin
Outcomes	Primary outcomes - birthweight, adjusted birthweight. Secondary outcomes - gestational hypertension, maternal weight gain, pre-eclampsia, mode of birth, gestational age at birth, induction of labour, shoulder dystocia, hyperbilirubinaemia, neonatal hypoglycaemia,

CTRI/2014/08/004835 (*Continued*)

	Apgar score, admission to NICU, respiratory distress, preterm birth, acceptability of treatment
Starting date	2014
Contact information	D Prahant Somani and Dr Pranab Sahana pranabsahana@gmail.com
Notes	

IRCT2013102315045N2

Trial name or title	Effect of glibenclamide in women with gestational diabetes on maternal and neonatal outcomes
Methods	Randomised controlled trial.
Participants	278 pregnant women from Isfahan, Iran. Inclusion: singleton pregnancy, no previous history of diabetes, 11 to 33 weeks' gestation Exclusion: cardiovascular disease, haematological disease, renal or liver disease, severe infectious disease, respiratory failure, premature rupture of membranes
Interventions	Insulin 0.2 U/kg twice daily. If needed then increased every 3 days to achieve normoglycaemia. Self-monitoring 4 times daily versus Glibenclamide 1.25 mg once daily and if required increased every 3 days to a maximum of 20 mg. If after 2 weeks' glycaemic control not met then treated with insulin Treatment targets fasting < 90 mg/dL, 2-hour postprandial < 120 mg/dL
Outcomes	Apgar score at 1 and 5 minutes, LGA, postpartum blood sugar, calcium level, hyperbilirubinaemia, macrosomia, intrauterine growth restriction, shoulder dystocia, perinatal mortality, and morbidity, respiratory distress, admission to NICU, pre-eclampsia, birth trauma, hypoglycaemia, fetal anomaly
Starting date	2013.
Contact information	Dr Gholam Ali Hamidi hamidi_gh@kaums.ac.ir
Notes	

IRCT2014010116025N1

Trial name or title	Comparing of the effectiveness of insulin and metformin in treating gestational diabetes
Methods	Randomised single-blind controlled trial.
Participants	400 women from Hormozgan, Iran. **Inclusion criteria:** age 18 to 45 years, diagnosed with gestational diabetes using ADIPS criteria, singleton pregnancy, gestation of 20 weeks' or more, meeting hospitals' criteria for treatment with insulin **Exclusion criteria:** pre-gestational diabetes,taking metformin, congenital anomaly, pregnancy associated hypertension, pre-eclampsia, intrauterine growth restriction, premature rupture of membranes, hepatic or renal

IRCT2014010116025N1 (*Continued*)

	disorders during the treatment period
Interventions	Insulin (n = 200) 0.5 to 1.0 unit/kg dose dependant on gestational age (regular and Neutral Protamine Hagedorn insulin) versus Metformin (n = 200) initial dose 500 mg to 2000 mg once or twice daily and increased if required after 2 weeks to a maximum of 2500 mg per day
Outcomes	Maternal blood glucose control, birthweight, length, head circumference, chest circumference, Apgar score
Starting date	2014.
Contact information	Dr Mojgan Rahbar rahbar_mojgan@yahoo.com
Notes	

NCT00414245

Trial name or title	Metformin for the treatment of diabetes in pregnancy.
Methods	Randomised controlled open-label trial.
Participants	200 women with diabetes in pregnancy from Israel. **Inclusion criteria:** pregnant, diagnosed with GDM or type 2 diabetes, singleton pregnancy **Exclusion criteria:** diabetic nephropathy or proliferative retinopathy, unable to swallow tablets
Interventions	Metformin versus Not stated.
Outcomes	Primary outcomes - glycaemic control, pregnancy complications Secondary outcomes - not listed.
Starting date	2007.
Contact information	Dr Boaz Sheizaf bsheizaf@bgu.ac.il
Notes	

NCT00681460

Trial name or title	Metformin in gestational diabetes mellitus (MetGDM).
Methods	Randomised controlled trial.
Participants	180 women with GDM. Inclusion - singleton pregnancy, ineffective dietary therapy

NCT00681460 (*Continued*)

	Exclusion - pre-gestational diabetes, fetal anomaly, multiple pregnancy, contraindications to using metformin
Interventions	Human recombined insulin versus Metformin.
Outcomes	Primary outcome - birthweight. Secondary outcomes - metabolic control in mother and newborn, insulin resistance, inflammatory reaction, oxidative stress, fetal growth
Starting date	2008.
Contact information	Hanna Mitowska Wozniak hanna.mitowska@onet.eu
Notes	

NCT00835861

Trial name or title	Effectiveness of metformin compared to insulin in pregnant women with mild pre-existing or early gestational diabetes (MIPOD)
Methods	Randomised controlled trial
Participants	31 women Inclusion criteria: Receiving care at participating hospital Diagnosis of diabetes prior to pregnancy or diagnosis of GDM prior to 20 weeks' gestation < 24 weeks' gestation at study enrolment Singleton or twin pregnancy English or Spanish speaking Able to give informed consent Exclusion criteria: End organ complications associated with diabetes prior need for insulin History of diabetic ketoacidosis or hyperosmolar state Prior adverse reaction to metformin Renal or liver disease Significant medical co-morbidities
Interventions	Insulin - regular and NPH insulin versus metformin 500 g to 2200 g per day
Outcomes	Blood glucose measurements, self-monitored blood glucose, obstetric complications, gestational weight gain, neonatal hypoglycaemia, HbA1c, meeting glycaemic treatment targets, maternal hypoglycaemia,adverse neonatal outcomes
Starting date	2008 to 2010

NCT00835861 (*Continued*)

Contact information	HIckman, University of North Carolina.
Notes	

NCT01613807

Trial name or title	Humalog® Mix50/50(tm) as a treatment for gestational diabetes
Methods	Randomised controlled trial.
Participants	40 women. Inclusion criteria: • Pregnant and at least 13 weeks' gestation • Diagnosed with GDM • Failed diet therapy Exclusion criteria: • < 18 years old or over 45 years old • urine dipstick > 2+ protein • blood pressure > 140/80 mmHg • haematocrit < 30% • refusal to take insulin • inability to understand instructions or to consent to participate.
Interventions	Mix 50/50: 3 doses of Mix 50/50 at mealtime versus Usual insulin regimen: 3 injections of Humalog(r) daily with meals; 3 injections of Humulin N (r) daily on rising, mid-afternoon, and at bedtime
Outcomes	Primary outcome listed as fasting self-monitored blood glucose measurements; no secondary outcomes listed
Starting date	October 2008.
Contact information	Lois Jovanovic, MD
Notes	

NCT01662921

Trial name or title	Comparator trial using insulin glulisine vs insulin lispro for treatment of gestational diabetes
Methods	Randomised controlled trial.
Participants	74 women diagnosed with gestational diabetes, aged 18 years or more, between 20 and 30 weeks' gestation failing to meet treatment targets following lifestyle and diet **Exclusion criteria:** < 18 years, blood pressure > 140/80 mm/Hg, A1c 6.5% or greater at enrolment, BMI > 40kg/m^2, fetal anomaly, currently using hypoglycaemic agent, refusal to use insulin before meals, inability to understand instructions or consent, history of type 1 or 2 diabetes, clinical judgement that patient is

NCT01662921 (*Continued*)

	inappropriate for trial
Interventions	Neutral Protamine Hagedorn insulin + insulin lispro versus Neutral Protamine Hagedorn insulin + insulin glulisine.
Outcomes	Primary outcome - 1-hour postprandial blood glucose. Secondary outcome - serum blood glucose area under the curve, HbA1c, maternal hypoglycaemia, birthweight > 90th percentile, caesarean section
Starting date	April 2013.
Contact information	ljovanovic@sansum.org
Notes	Collaborator listed as Sanofi.

NCT01731431

Trial name or title	Multicentre randomised trial of non-inferiority between glyburide and insulin for the treatment of gestational diabetes (INDAO)
Methods	Randomised controlled trial - multicentre.
Participants	900 Pregnant women from Paris, France. Inclusion: 24 to 34 weeks' gestation, failure to meet glycaemic targets after 10 days of dietary treatment alone Exclusion: multiple pregnancy, chronic hypertension, pre-eclampsia, renal or hepatic impairment, long time corticosteroid treatment, allergy to drugs, pre-gestational diabetes, abnormal result on screening test for GDM before 24 weeks', fasting glucose 1.26 g/L or more at diagnosis of diabetes, need for drug treatment that is contraindicated with glibenclamide, poor understanding of French, lack of social insurance
Interventions	Insulin versus Glibenclamide 2.5 mg initial dose increased as required to a maximum of 20 mg daily. If glycaemic targets not met then change to insulin
Outcomes	Primary - composite outcome of neonatal complications associated with gestational diabetes Secondary outcomes - caesarean section, preterm birth, neonatal mortality, birth trauma, respiratory distress, prenatal visits, number of days hospitalisation, maternal glycaemic control, maternal satisfaction
Starting date	2012.
Contact information	Dr Senat marie-victoire.senat@bct-aphp.fr
Notes	

NCT01756105

Trial name or title	Efficacy of metformin in achieving glycaemia goals as recommended for the treatment of gestational diabetes in non obese women
Methods	Randomised open-label controlled trial - multicentre.
Participants	600 women in France. **Inclusion criteria:** age 18 to 40 years, pre-pregnancy BMI < 30 kg/m^2, 22 to 28 weeks' gestation, diagnosed with GDM, social security affiliated person **Exclusion criteria:** contraindications to metformin, prior treatment with metformin, multiple pregnancy, pre-gestational diabetes, high blood pressure before pregnancy, pregnancy hepatic complication, pre-eclampsia, premature rupture of membranes
Interventions	Insulin rapid-acting analogue lispro and intermediate-acting Neutral Protamine Hagedorn insulin versus Metformin 500 mg to 2500 mg daily.
Outcomes	Primary outcome - maternal glycaemic control. Secondary outcomes - none listed.
Starting date	2012.
Contact information	Dr Nathalie Jeandidier nathalie.jeandidier@chru-strasbourg.fr
Notes	

NCT02080377

Trial name or title	A feasibility study looking at the use of glibenclamide and metformin versus standard care in gestational diabetes (GRACES)
Methods	Parellel randomised controlled trial.
Participants	44 women with GDM failing to achieve treatment targets on maximal dose of tolerated metformin
Interventions	Insulin plus metformin versus Metformin plus glibenclamide.
Outcomes	Adherence, glycaemic control, satisfaction, maternal weight gain, birthweight, neonatal hypoglycaemia
Starting date	April 2014.
Contact information	Sonai Whyte sonia.whyte@ed.ac.uk
Notes	Clinical trials register details NCT02080377.

NCT03106870

Trial name or title	Adding metformin to insulin in controlling pregestational and gestational diabetes mellitus
Methods	Randomised controlled trial
Participants	62 women Inclusion criteria: 20 to 35 years, 20 to 36 weeks' gestation, singleton pregnancy, pregestational or gestational diabetes Exclusion criteria: women with diabetes taking steroid therapy, hypertension, impaired renal or liver function, non compliant women
Interventions	Insulin mixtard plus metformin versus Insulin mixtard
Outcomes	Glycaemic control, macrosomia, neonatal hypoglycaemia
Starting date	June 2016
Contact information	Rehab Mohamed Abdelrahman, Ain Shams University
Notes	

SLCTR/2011/009

Trial name or title	Treatment with metformin to reduce insulin requirements in diabetes in pregnancy
Methods	Randomised controlled trial.
Participants	80 women from Sri Lanka. **Inclusion criteria:** diagnosed with GDM after 20 weeks' gestation. **Exclusion criteria:** GDM before 20 weeks', evidence of intrauterine growth restriction or hypertensive disease, multiple pregnancy, refusing consent, elevated liver or renal function tests
Interventions	Insulin versus metformin.
Outcomes	Primary outcome - reduction in insulin requirement. Secondary outcome - cost.
Starting date	2011.
Contact information	Dr Dhammiki Silva dammikasilva@yahoo.com
Notes	

ADIPS: Australasian Diabetes in Pregnancy Society
BMI: body mass index

GDM: gestational diabetes mellitus
LGA: large-for-gestational age
NICU: neonatal intensive care unit
NPH: Neutral Protamine Hagedorn

DATA AND ANALYSES

Comparison 1. Insulin versus oral anti-diabetic pharmacological therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hypertensive disorders of pregnancy - Pre-eclampsia	10	2060	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.86, 1.52]
1.1 Glibenclamide	3	590	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.62, 2.00]
1.2 Metformin	7	1470	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.83, 1.60]
2 Hypertensive disorders of pregnancy - not defined	4	1214	Risk Ratio (M-H, Fixed, 95% CI)	1.89 [1.14, 3.12]
2.1 Glibenclamide	1	100	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.38, 10.43]
2.2 Metformin	3	1114	Risk Ratio (M-H, Fixed, 95% CI)	1.88 [1.11, 3.18]
3 Caesarean section	17	1988	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.93, 1.14]
3.1 Glibenclamide	7	892	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.93, 1.28]
3.2 Metformin	9	995	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.87, 1.13]
3.3 Acarbose	1	33	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.39, 1.71]
3.4 Combined metformin-glibenclamide	1	68	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.41, 2.15]
4 Development of type 2 diabetes	2	754	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [0.80, 2.44]
5 Perinatal (fetal and neonatal death) and later infant mortality	10	1463	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.29, 2.49]
5.1 Glibenclamide	5	668	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.25, 3.91]
5.2 Metformin	4	678	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.3 Acarbose	1	33	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.4 Combined metformin/ glibenclamide	1	84	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.12, 3.79]
6 Large-for-gestational age	13	2352	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.76, 1.35]
6.1 Glibenclamide	5	651	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.19, 1.07]
6.2 Metformin	8	1668	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.94, 1.44]
6.3 Acarbose	1	33	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.01, 5.15]
7 Death or serious morbidity composite (variously defined by trials, e.g. perinatal or infant death, shoulder dystocia, bone fracture or nerve palsy)	2	760	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.84, 1.26]
8 Neurosensory disability in later childhood (18 to 24 months)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Hearing impairment	1	93	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.01, 7.49]
8.2 Visual impairment	1	93	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.03, 2.90]
8.3 Any mild developmental delay	1	93	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.33, 3.44]
9 Use of additional pharmacotherapy	19	2761	Risk Ratio (M-H, Fixed, 95% CI)	0.03 [0.02, 0.06]
9.1 Glibenclamide	7	893	Risk Ratio (M-H, Fixed, 95% CI)	0.10 [0.03, 0.31]
9.2 Metformin	10	1676	Risk Ratio (M-H, Fixed, 95% CI)	0.02 [0.01, 0.04]
9.3 Acarbose	2	124	Risk Ratio (M-H, Fixed, 95% CI)	0.10 [0.01, 0.74]

9.4 Metformin/glibenclamide	1	68	Risk Ratio (M-H, Fixed, 95% CI)	0.04 [0.00, 0.63]
10 Maternal hypoglycaemia	10	998	Risk Ratio (M-H, Random, 95% CI)	3.01 [0.74, 12.27]
10.1 Glibenclamide	7	779	Risk Ratio (M-H, Random, 95% CI)	2.80 [0.29, 26.99]
10.2 Metformin	3	186	Risk Ratio (M-H, Random, 95% CI)	3.01 [0.91, 9.94]
10.3 Acarbose	1	33	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11 Glycaemic control during/end treatment (fasting)	19	2812	Std. Mean Difference (IV, Random, 95% CI)	0.05 [-0.09, 0.19]
11.1 Glibenclamide	9	1185	Std. Mean Difference (IV, Random, 95% CI)	0.03 [-0.21, 0.27]
11.2 Metformin	8	1441	Std. Mean Difference (IV, Random, 95% CI)	0.03 [-0.18, 0.24]
11.3 Combined metformin-glyburide	1	68	Std. Mean Difference (IV, Random, 95% CI)	0.33 [-0.15, 0.81]
11.4 Acarbose	2	118	Std. Mean Difference (IV, Random, 95% CI)	0.10 [-0.60, 0.79]
12 Glycaemic control during/end treatment (postprandial)	18	2508	Std. Mean Difference (IV, Random, 95% CI)	0.12 [-0.05, 0.29]
12.1 Glibenclamide	9	959	Std. Mean Difference (IV, Random, 95% CI)	0.00 [-0.25, 0.26]
12.2 Metformin	7	1363	Std. Mean Difference (IV, Random, 95% CI)	0.33 [0.07, 0.59]
12.3 Combined metformin-glyburide	1	68	Std. Mean Difference (IV, Random, 95% CI)	0.20 [-0.28, 0.67]
12.4 Acarbose	2	118	Std. Mean Difference (IV, Random, 95% CI)	-0.30 [-0.67, 0.07]
13 Glycaemic control during/end of treatment (HbA1c)	9	1963	Std. Mean Difference (IV, Random, 95% CI)	0.01 [-0.12, 0.15]
13.1 Glibenclamide	3	487	Std. Mean Difference (IV, Random, 95% CI)	0.04 [-0.31, 0.39]
13.2 Metformin	5	1392	Std. Mean Difference (IV, Random, 95% CI)	0.05 [-0.14, 0.24]
13.3 Combined metformin/glibenclamide	1	84	Std. Mean Difference (IV, Random, 95% CI)	-0.13 [-0.55, 0.30]
14 Weight gain in pregnancy	10	2336	Mean Difference (IV, Random, 95% CI)	1.06 [0.63, 1.48]
14.1 Glibenclamide	3	509	Mean Difference (IV, Random, 95% CI)	0.63 [-0.42, 1.67]
14.2 Metformin	7	1794	Mean Difference (IV, Random, 95% CI)	1.11 [0.62, 1.61]
14.3 Acarbose	1	33	Mean Difference (IV, Random, 95% CI)	0.90 [-1.56, 3.36]
15 Induction of labour	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
15.1 Metformin	3	348	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.96, 1.75]
16 Postpartum haemorrhage	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 Metformin	2	91	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.13]
17 Breastfeeding at discharge, six weeks postpartum, six months or longer	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 Metformin	2	411	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.86, 1.23]
18 Relevant biomarker changes associated with the intervention	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
18.1 HOMA-IR	1	78	Mean Difference (IV, Fixed, 95% CI)	0.0 [-2.92, 2.92]
18.2 Total Cholesterol	1	78	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.49, 0.69]
18.3 HDL Cholesterol	1	78	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.13, 0.33]
18.4 Triglycerides	1	78	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-0.68, 0.08]
19 Body mass index (BMI)	1	733	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-1.29, 0.89]
19.1 Metformin	1	733	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-1.29, 0.89]
20 Postnatal weight retention	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
20.1 Six to eight weeks postpartum	1	167	Mean Difference (IV, Fixed, 95% CI)	-1.60 [-6.34, 3.14]
20.2 One year postpartum	1	176	Mean Difference (IV, Fixed, 95% CI)	-3.70 [-8.50, 1.10]
21 Impaired glucose tolerance	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
21.1 six weeks postpartum	3	841	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.80, 1.68]
21.2 one year postpartum	1	179	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.56, 1.26]

22 Stillbirth	3	653	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.08, 4.52]
22.1 Glibenclamide	1	404	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.06, 15.72]
22.2 Metformin	2	249	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.17]
23 Neonatal death	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
23.1 Glibenclamide	2	503	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.06, 15.72]
24 Macrosomia (> 4000 g)	19	2305	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.77, 1.78]
24.1 Glibenclamide	9	1186	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.31, 1.94]
24.2 Metformin	10	1086	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.88, 1.81]
24.3 Acarbose	1	33	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
25 Small-for-gestational age	9	1812	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.79, 1.69]
25.1 Glibenclamide	2	136	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.17, 4.20]
25.2 Metformin	7	1643	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.77, 1.71]
25.3 Acarbose	1	33	Risk Ratio (M-H, Fixed, 95% CI)	4.0 [0.17, 91.48]
26 Birth trauma	12		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
26.1 Birth trauma not defined	5	1107	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.53, 2.03]
26.2 Shoulder dystocia	8	968	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [0.62, 3.34]
26.3 Clavicular fracture	2	196	Risk Ratio (M-H, Fixed, 95% CI)	4.71 [0.23, 95.53]
26.4 Brachial nerve injury	2	320	Risk Ratio (M-H, Fixed, 95% CI)	5.05 [0.24, 103.90]
27 Gestational age at birth	18	2834	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.20, 0.18]
27.1 Glibenclamide	7	1025	Mean Difference (IV, Random, 95% CI)	-0.21 [-0.67, 0.26]
27.2 Metformin	8	1533	Mean Difference (IV, Random, 95% CI)	0.17 [0.04, 0.30]
27.3 Acarbose	2	124	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.52, 0.49]
27.4 Combined metformin/ glibenclamide	2	152	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.56, 0.42]
28 Preterm birth (< 37 weeks)	11	2417	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.64, 1.88]
28.1 Glibenclamide	2	182	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.51, 1.74]
28.2 Metformin	9	2235	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.58, 2.39]
29 Congenital abnormality	15	2671	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.88, 2.08]
29.1 Glibenclamide	6	922	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.50, 2.54]
29.2 Metformin	7	1574	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.81, 2.41]
29.3 Acarbose	1	91	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
29.4 Combined metformin/ glibenclamide	1	84	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.39, 10.34]
30 Five minute Apgar less than seven	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
30.1 Metformin	4	1170	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.09, 2.64]
31 Birthweight (g)	22	3183	Mean Difference (IV, Random, 95% CI)	-20.14 [-83.58, 43. 29]
31.1 Glibenclamide	9	1116	Mean Difference (IV, Random, 95% CI)	-75.73 [-230.46, 78. 99]
31.2 Metformin	10	1791	Mean Difference (IV, Random, 95% CI)	22.00 [-33.67, 77. 67]
31.3 Acarbose	2	124	Mean Difference (IV, Random, 95% CI)	22.17 [-154.08, 198. 42]
31.4 Combined metformin-glyburide	2	152	Mean Difference (IV, Random, 95% CI)	-46.17 [-199.60, 107.26]
32 Head circumference (cm) at birth	3	975	Mean Difference (IV, Random, 95% CI)	0.14 [-0.26, 0.53]
32.1 Glibenclamide	1	82	Mean Difference (IV, Random, 95% CI)	-0.40 [-1.08, 0.28]
32.2 Metformin	2	893	Mean Difference (IV, Random, 95% CI)	0.27 [-0.12, 0.65]
33 Length (cm) at birth	3	975	Mean Difference (IV, Random, 95% CI)	0.11 [-0.50, 0.71]
33.1 Glibenclamide	1	82	Mean Difference (IV, Random, 95% CI)	-0.60 [-1.64, 0.44]

33.2 Metformin	2	893	Mean Difference (IV, Random, 95% CI)	0.29 [-0.38, 0.97]
34 Ponderal index at birth	2	815	Mean Difference (IV, Random, 95% CI)	0.03 [-0.13, 0.19]
34.1 Glibenclamide	1	82	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.22, 0.08]
34.2 Metformin	1	733	Mean Difference (IV, Random, 95% CI)	0.10 [0.06, 0.14]
35 Adiposity at birth (Triceps skinfold (mm))	2	815	Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.25, 0.10]
35.1 Glibenclamide	1	82	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.35, 0.35]
35.2 Metformin	1	733	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.31, 0.11]
36 Adiposity at birth (Subscapular skinfold (mm))	2	815	Mean Difference (IV, Random, 95% CI)	-0.13 [-0.50, 0.24]
36.1 Glibenclamide	1	82	Mean Difference (IV, Random, 95% CI)	-0.40 [-0.90, 0.10]
36.2 Metformin	1	733	Mean Difference (IV, Random, 95% CI)	0.0 [-0.20, 0.20]
37 Adiposity at birth (Skin fold sum (mm))	1	82	Mean Difference (IV, Fixed, 95% CI)	-0.80 [-2.33, 0.73]
38 Adiposity at birth (Percentage fat mass)	1	82	Mean Difference (IV, Fixed, 95% CI)	-1.60 [-3.77, 0.57]
39 Neonatal hypoglycaemia	24	3892	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.85, 1.52]
39.1 Glibenclamide	10	1283	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.41, 1.19]
39.2 Metformin	12	2424	Risk Ratio (M-H, Random, 95% CI)	1.58 [1.16, 2.16]
39.3 Acarbose	1	33	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.02, 10.16]
39.4 Combined hypoglycaemia	2	152	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.49, 1.18]
40 Respiratory distress syndrome	10	1894	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.83, 1.99]
40.1 Glibenclamide	3	409	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.45, 3.91]
40.2 Metformin	7	1485	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.80, 2.06]
41 Neonatal jaundice (hyperbilirubinaemia)	16	2183	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.83, 1.19]
41.1 Glibenclamide	6	999	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.61, 1.02]
41.2 Metformin	9	1100	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.89, 1.56]
41.3 Combined metformin/ glibenclamide	1	84	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.69, 1.78]
42 Hypocalcaemia	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
42.1 Glibenclamide	5	939	Risk Ratio (M-H, Fixed, 95% CI)	1.95 [0.49, 7.78]
43 Polycythaemia	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
43.1 Glibenclamide	3	590	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.38, 3.57]
44 Relevant biomarker changes associated with the intervention (Cord blood C-peptide)	1	59	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.82, 0.42]
44.1 Glibenclamide	1	59	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.82, 0.42]
45 Relevant biomarker changes associated with the intervention (Cord blood insulin)	3		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
45.1 Glibenclamide	3	486	Std. Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.15, 0.21]
46 Childhood weight (kg)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
46.1 6 months	1	93	Mean Difference (IV, Fixed, 95% CI)	-0.35 [-0.75, 0.05]
46.2 12 months	1	93	Mean Difference (IV, Fixed, 95% CI)	-0.62 [-1.18, -0.06]
46.3 18 months to 2 years	2	411	Mean Difference (IV, Fixed, 95% CI)	-0.44 [-0.83, -0.05]
47 Childhood height (cm)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
47.1 6 months	1	93	Mean Difference (IV, Random, 95% CI)	-0.70 [-2.05, 0.65]
47.2 12 months	1	93	Mean Difference (IV, Random, 95% CI)	-1.30 [-2.60, 0.00]
47.3 18 to 24 months	2	411	Mean Difference (IV, Random, 95% CI)	-0.65 [-2.61, 1.31]

48 Childhood adiposity (ponderal index (kg/m^3))	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
48.1 6 months	1	93	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-3.43, 1.43]
48.2 12 months	1	93	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-1.12, 0.72]
48.3 18 months to 2 years	1	93	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.88, 0.68]
49 Childhood adiposity (Total fat mass (%))	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
49.1 Metformin	1	318	Mean Difference (IV, Fixed, 95% CI)	0.5 [-0.49, 1.49]
50 Childhood blood pressure (2 years)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
50.1 Systolic BP	1	170	Mean Difference (IV, Fixed, 95% CI)	-2.24 [-5.02, 0.54]
50.2 Diastolic BP	1	170	Mean Difference (IV, Fixed, 95% CI)	-0.5 [-16.75, 15.75]
51 Number of antenatal visits or admissions	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
51.1 Glibenclamide	1	404	Mean Difference (IV, Fixed, 95% CI)	1.0 [-0.08, 2.08]
52 Admission to neonatal care unit/nursery	18	3441	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [1.19, 1.59]
52.1 Glibenclamide	7	1018	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.74, 1.92]
52.2 Metformin	10	2306	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [1.22, 1.71]
52.3 Acarbose	1	33	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
52.4 Combined metformin/ glibenclamide	1	84	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.82, 1.52]
53 Duration of stay in neonatal intensive care unit or special care baby unit	3	401	Mean Difference (IV, Random, 95% CI)	-0.20 [-1.79, 1.39]

Comparison 2. One insulin versus another insulin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hypertensive disorders of pregnancy - Pre-eclampsia	1	320	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.1 Insulin aspart	1	320	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Caesarean section	3	410	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.91, 1.09]
2.1 Insulin aspart	1	320	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.94, 1.10]
2.2 Insulin lispro	2	90	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.42, 1.56]
3 Large-for-gestational age	3	411	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.58, 2.55]
3.1 Insulin aspart	1	320	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.50, 2.61]
3.2 Insulin lispro	2	91	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [0.29, 8.55]
4 Use of additional pharmacotherapy	3	168	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.72, 1.70]
4.1 Insulin aspart	1	47	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.83, 2.14]
4.2 Insulin lispro	2	98	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.90, 2.09]
4.3 NPH	1	23	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.36, 1.19]
5 Maternal hypoglycaemia	4	504	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.64, 1.44]
5.1 Insulin aspart	3	394	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.59, 1.35]
5.2 Insulin lispro	1	49	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.3 NPH	1	61	Risk Ratio (M-H, Fixed, 95% CI)	5.16 [0.26, 103.25]

6 Glycaemic control during/end of treatment (HbA1c) end of treatment	3	411	Mean Difference (IV, Random, 95% CI)	0.04 [-0.06, 0.14]
6.1 Insulin aspart	1	320	Mean Difference (IV, Random, 95% CI)	0.14 [-0.01, 0.29]
6.2 Insulin lispro	2	91	Mean Difference (IV, Random, 95% CI)	0.00 [-0.12, 0.12]
7 Glycaemic control during/end of treatment (Fasting plasma glucose)	4	466	Mean Difference (IV, Fixed, 95% CI)	0.15 [-2.02, 2.32]
7.1 Insulin aspart	2	330	Mean Difference (IV, Fixed, 95% CI)	2.05 [-1.53, 5.63]
7.2 insulin lispro	1	49	Mean Difference (IV, Fixed, 95% CI)	-1.80 [-6.84, 3.24]
7.3 Insulin detemir	1	87	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-3.85, 2.65]
8 Glycaemic control during/end of treatment (Postprandial glucose)	5	562	Std. Mean Difference (IV, Random, 95% CI)	0.08 [-0.25, 0.42]
8.1 Insulin aspart	3	377	Std. Mean Difference (IV, Random, 95% CI)	0.10 [-0.46, 0.65]
8.2 Insulin lispro	2	98	Std. Mean Difference (IV, Random, 95% CI)	0.22 [-0.87, 1.30]
8.3 Insulin detemir	1	87	Std. Mean Difference (IV, Random, 95% CI)	-0.14 [-0.56, 0.29]
9 Weight gain in pregnancy	2	407	Mean Difference (IV, Fixed, 95% CI)	0.46 [-0.15, 1.07]
9.1 Insulin aspart	1	320	Mean Difference (IV, Fixed, 95% CI)	0.47 [-0.15, 1.09]
9.2 NPH	1	87	Mean Difference (IV, Fixed, 95% CI)	0.10 [-3.48, 3.68]
10 Maternal mortality	1	61	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.1 NPH	1	61	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Fetal death	4	508	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.02, 8.06]
11.1 Insulin aspart	3	447	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.02, 8.06]
11.2 NPH	1	61	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Macrosomia	6	627	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.40, 2.46]
12.1 Insulin aspart	4	494	Risk Ratio (M-H, Random, 95% CI)	1.47 [0.71, 3.05]
12.2 Insulin lispro	1	49	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.21, 5.05]
12.3 NPH	2	84	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.01, 0.79]
13 Small-for-gestational age	1	49	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.07, 15.73]
13.1 Insulin lispro	1	49	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.07, 15.73]
14 Birth trauma (Nerve palsy)	1	23	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.02, 8.04]
14.1 NPH	1	23	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.02, 8.04]
15 Gestational age at birth	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
15.1 Insulin aspart	1	320	Mean Difference (IV, Random, 95% CI)	-0.67 [-1.01, -0.33]
15.2 Insulin lispro	1	41	Mean Difference (IV, Random, 95% CI)	0.0 [-0.16, 0.16]
16 Preterm birth (< 37 weeks)	3	443	Risk Ratio (M-H, Fixed, 95% CI)	2.29 [0.52, 10.05]
16.1 Insulin aspart	2	420	Risk Ratio (M-H, Fixed, 95% CI)	3.06 [0.49, 19.29]
16.2 NPH	1	23	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.08, 15.41]
17 Congenital anomaly	2	69	Risk Ratio (M-H, Fixed, 95% CI)	3.21 [0.14, 72.55]
17.1 Insulin aspart	1	27	Risk Ratio (M-H, Fixed, 95% CI)	3.21 [0.14, 72.55]
17.2 Insulin lispro	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18 Birthweight (kg)	7	531	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.17, 0.08]
18.1 Insulin aspart	3	357	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.11, 0.09]
18.2 Insulin lispro	2	90	Mean Difference (IV, Random, 95% CI)	0.04 [-0.07, 0.14]
18.3 NPH	2	84	Mean Difference (IV, Random, 95% CI)	-0.44 [-1.20, 0.32]
19 Length at birth (cm)	3	388	Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.57, 0.34]
19.1 Insulin aspart	2	347	Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.58, 0.42]
19.2 Insulin lispro	1	41	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-1.45, 0.85]
20 Ponderal Index kg/m3	2	369	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.06, 0.12]
20.1 Insulin aspart	1	320	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-1.01, 0.81]
20.2 Insulin lispro	1	49	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.06, 0.12]

21 Neonatal hypoglycaemia	3	165	Risk Ratio (M-H, Random, 95% CI)	2.28 [0.06, 82.02]
21.1 Insulin aspart	1	100	Risk Ratio (M-H, Random, 95% CI)	13.0 [0.75, 224.77]
21.2 Insulin lispro	1	42	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
21.3 NPH	1	23	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.02, 8.04]
22 Respiratory distress	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
22.1 Insulin aspart	1	320	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.10, 2.79]
23 Neonatal jaundice (hyperbilirubinaemia)	2	123	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.05, 4.93]
23.1 Insulin aspart	1	100	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.01, 2.01]
23.2 NPH	1	23	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.28, 4.32]
24 Hypocalcaemia	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
24.1 Insulin lispro	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 3. Insulin versus diet/standard care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Caesarean section	2	133	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.50, 1.42]
2 Development of type 2 diabetes	2	653	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.79, 1.21]
3 Perinatal (fetal and neonatal death) and later infant mortality	4	1137	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.41, 1.33]
4 Large-for-gestational age	1	202	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.41, 1.78]
5 Use of additional pharmacotherapy	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Maternal hypoglycaemia	1	95	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Glycaemic control during/end of treatment	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 HbA1c	1	161	Mean Difference (IV, Fixed, 95% CI)	0.10 [0.04, 0.16]
7.2 Fasting blood glucose	1	68	Mean Difference (IV, Fixed, 95% CI)	1.60 [-2.97, 6.17]
7.3 Postprandial blood glucose	1	68	Mean Difference (IV, Fixed, 95% CI)	0.30 [-5.32, 5.92]
8 Weight gain in pregnancy	1	38	Mean Difference (IV, Fixed, 95% CI)	1.73 [-3.31, 6.77]
9 Neonatal death	1	611	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.23, 2.23]
10 Macrosomia	3	717	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.18, 0.50]
11 Small-for-gestational age	2	240	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.05, 2.40]
12 Birth trauma	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 Shoulder dystocia	2	133	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.2 Nerve palsy	1	38	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13 Gestational age at birth	2	106	Mean Difference (IV, Fixed, 95% CI)	-0.66 [-1.37, 0.06]
14 Preterm birth (less than 37 weeks' gestation)	1	611	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.64, 1.85]
15 Birthweight	2	106	Mean Difference (IV, Fixed, 95% CI)	-342.85 [-561.11, -124.60]
16 Ponderal Index	1	68	Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.34, -0.02]
17 Neonatal hypoglycaemia	3	176	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.34, 2.24]
18 Neonatal jaundice (Hyperbilirubinaemia)	1	68	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
19 Hypocalcaemia	1	68	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

20 Polycythaemia	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.9 [0.30, 2.67]
21 Relevant biomarker changes associated with the intervention (Cord C-peptide)	1	202	Mean Difference (IV, Fixed, 95% CI)	0.03 [0.02, 0.04]

Comparison 4. Insulin versus exercise

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Caesarean section	1	34	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.29, 7.87]
2 Macrosomia	1	34	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.42, 9.50]
3 Gestational age at birth	1	34	Mean Difference (IV, Fixed, 95% CI)	-0.80 [-2.05, 0.45]
4 Birthweight (g)	1	34	Mean Difference (IV, Fixed, 95% CI)	103.0 [-245.40, 451.40]
5 Length at birth (cm)	1	34	Mean Difference (IV, Fixed, 95% CI)	1.60 [-0.01, 3.21]
6 Neonatal hypoglycaemia	1	34	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.05, 5.01]
7 Respiratory distress syndrome	1	34	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Neonatal jaundice (Hyperbilirubinaemia)	1	34	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Hypocalcaemia	1	34	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 5. Regimen A versus regimen B

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hypertensive disorders of pregnancy - Pregnancy-induced hypertension	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Twice v four times daily	1	274	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.51, 2.42]
2 Caesarean section	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Twice v four times daily	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.68, 1.44]
2.2 Three injections versus six injections	1	37	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.17, 6.72]
3 Perinatal (fetal and neonatal death) and later infant mortality	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Twice v four times daily	1	274	Risk Ratio (M-H, Fixed, 95% CI)	3.04 [0.13, 74.07]
4 Large-for-gestational age	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Twice v four times daily	1	274	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.79, 1.69]
4.2 Three injections versus six injections	1	37	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.04, 3.08]

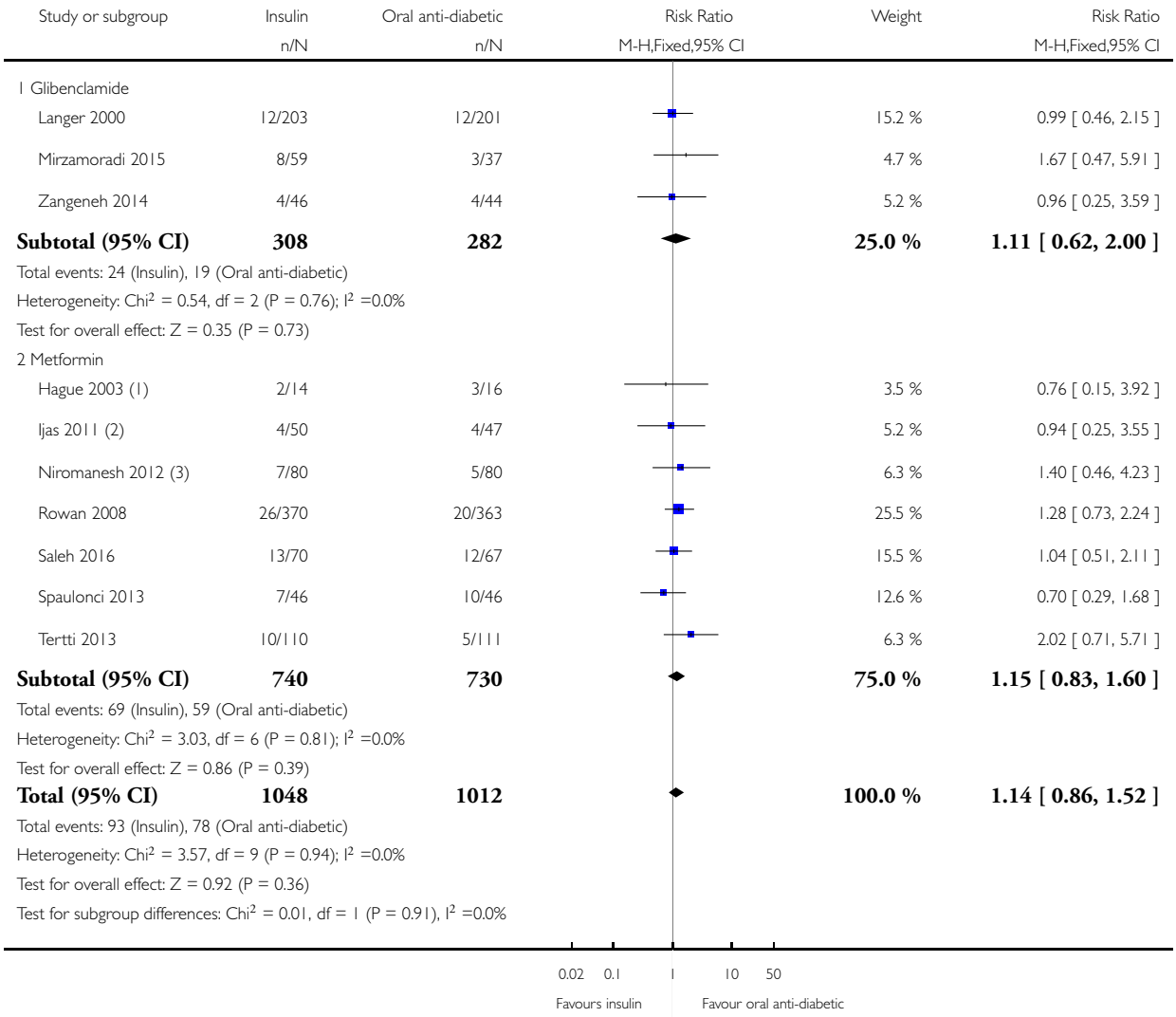
5 Death or serious morbidity composite (variously defined by trials, e.g. perinatal or infant death, shoulder dystocia, bone fracture or nerve palsy)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Twice v four times daily	1	274	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [1.08, 2.64]
6 Maternal hypoglycaemia	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Twice v four times daily	1	274	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.06, 16.06]
7 Glycaemic control during/end of treatment (Fasting)	1	37	Mean Difference (IV, Fixed, 95% CI)	4.0 [-0.84, 8.84]
7.1 Three injections versus six injections	1	37	Mean Difference (IV, Fixed, 95% CI)	4.0 [-0.84, 8.84]
8 Glycaemic control during/end of treatment (HbA1c)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 Twice v four times daily	1	274	Mean Difference (IV, Fixed, 95% CI)	0.30 [0.06, 0.54]
8.2 Three injections versus six injections	1	37	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.29, 0.09]
9 Weight gain in pregnancy	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 Twice v four times daily	1	274	Mean Difference (IV, Fixed, 95% CI)	0.70 [-0.14, 1.54]
10 Macrosomia	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Twice v four times daily	1	274	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.72, 2.01]
11 Small-for-gestational age	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 Twice v four times daily	1	274	Risk Ratio (M-H, Fixed, 95% CI)	1.78 [0.53, 5.93]
12 Birth trauma	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 Twice v four times daily	1	274	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [0.26, 8.97]
13 Gestational age at birth	1	274	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-0.72, 0.12]
13.1 Twice v four times daily	1	274	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-0.72, 0.12]
14 Five-minute Apgar less than 7	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 twice v four times daily	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.07, 1.65]
15 Birthweight (g)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
15.1 Twice v four times daily	1	274	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-150.49, 148.49]
15.2 Three injections versus six injections	1	37	Mean Difference (IV, Fixed, 95% CI)	-197.0 [-495.43, 101.43]
16 Neonatal hypoglycaemia	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 Twice daily v four times daily	1	274	Risk Ratio (M-H, Fixed, 95% CI)	8.12 [1.03, 64.03]
17 Respiratory distress syndrome	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 Twice v four times daily	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.23]
18 Neonatal jaundice (Hyperbilirubinaemia)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
18.1 Twice v four times daily	1	274	Risk Ratio (M-H, Fixed, 95% CI)	1.96 [1.10, 3.49]
19 Polycythaemia	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
19.1 Twice v four times daily	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.11, 1.65]

Analysis 1.1. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 1 Hypertensive disorders of pregnancy - Pre-eclampsia.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 1 Hypertensive disorders of pregnancy - Pre-eclampsia



(1) Not defined

(2) Not defined

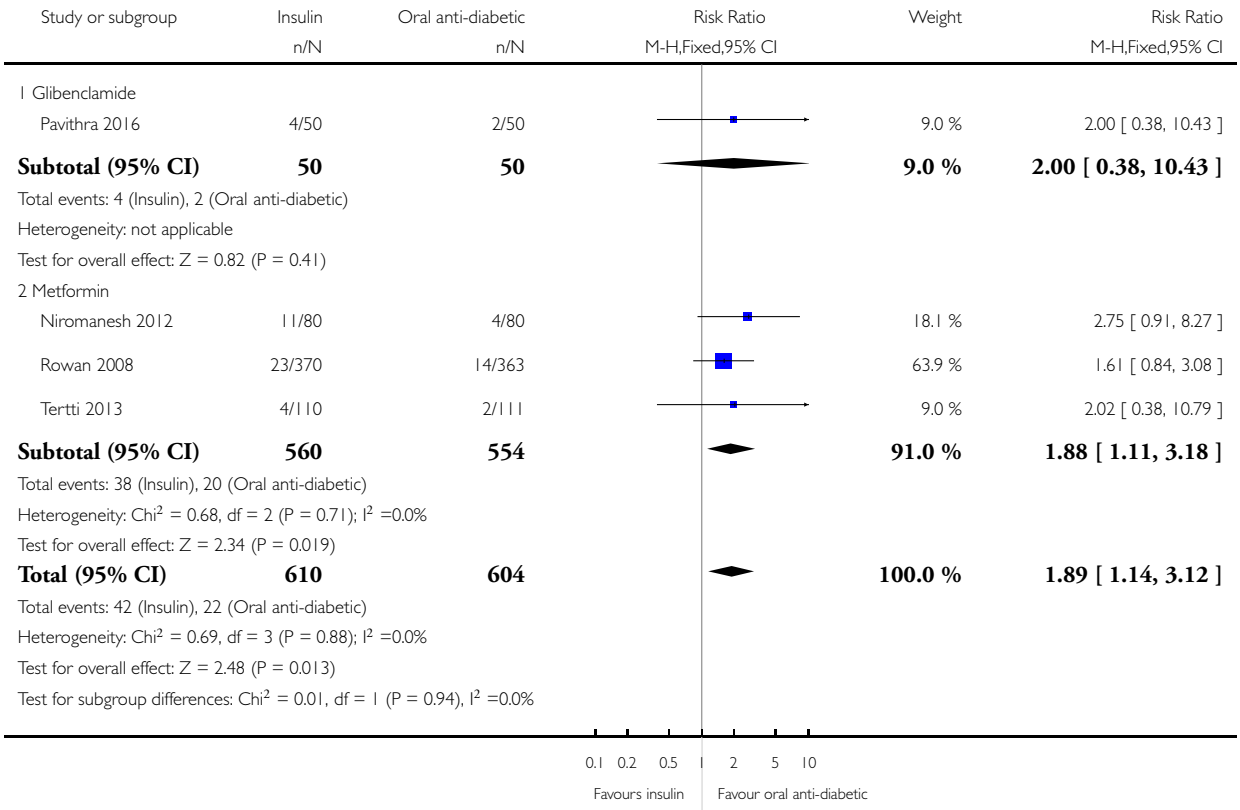
(3) BP > 140/90 mmHg with proteinuria > 0.3 g/24 hours.

Analysis 1.2. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 2 Hypertensive disorders of pregnancy - not defined.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 2 Hypertensive disorders of pregnancy - not defined

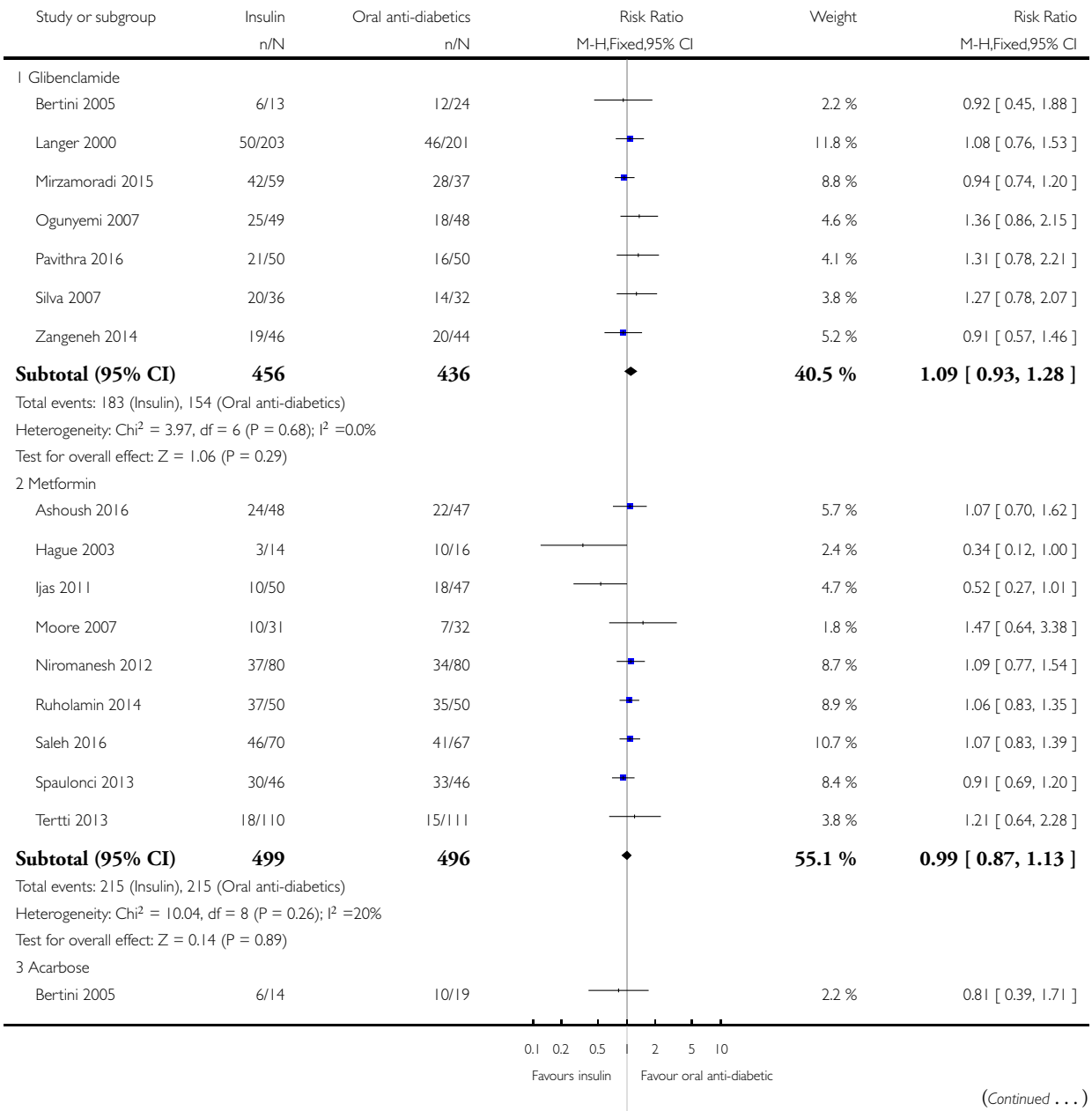


Analysis 1.3. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 3 Caesarean section.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 3 Caesarean section



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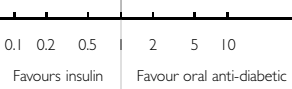
Study or subgroup	Insulin n/N	Oral anti-diabetics n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**14**	**19**		**2.2 %**	**0.81 [0.39, 1.71]**
Total events: 6 (Insulin), 10 (Oral anti-diabetics)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.54 (P = 0.59)					
4 Combined metformin-glibenclamide					
Ardilouze 2014	8/33	9/35		2.2 %	0.94 [0.41, 2.15]
Subtotal (95% CI)	**33**	**35**		**2.2 %**	**0.94 [0.41, 2.15]**
Total events: 8 (Insulin), 9 (Oral anti-diabetics)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.14 (P = 0.89)					
Total (95% CI)	**1002**	**986**		**100.0 %**	**1.03 [0.93, 1.14]**
Total events: 412 (Insulin), 388 (Oral anti-diabetics)					
Heterogeneity: Chi^2 = 14.43, df = 17 (P = 0.64); I^2 =0.0%					
Test for overall effect: Z = 0.52 (P = 0.61)					
Test for subgroup differences: Chi^2 = 1.25, df = 3 (P = 0.74), I^2 =0.0%					

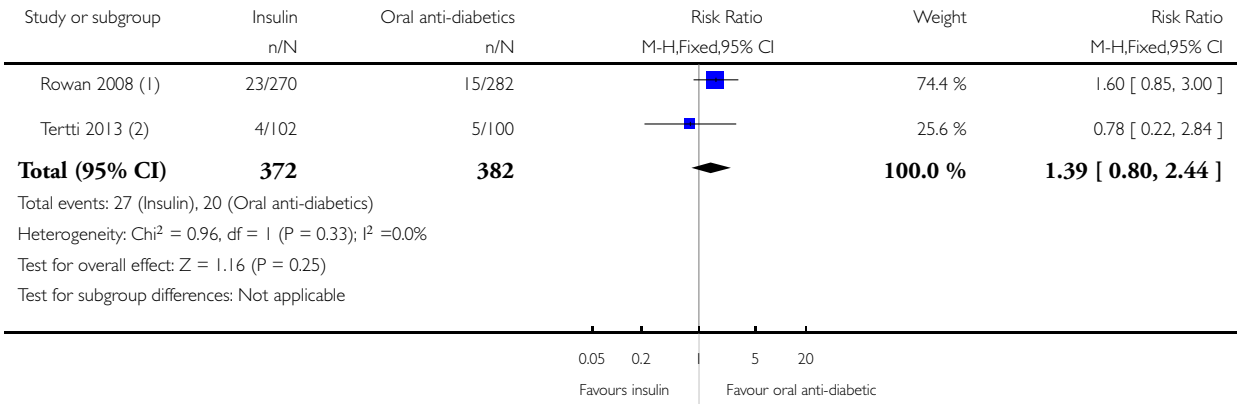


Analysis 1.4. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 4 Development of type 2 diabetes.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 4 Development of type 2 diabetes



(1) 6-8 weeks glucose tolerance test; metformin

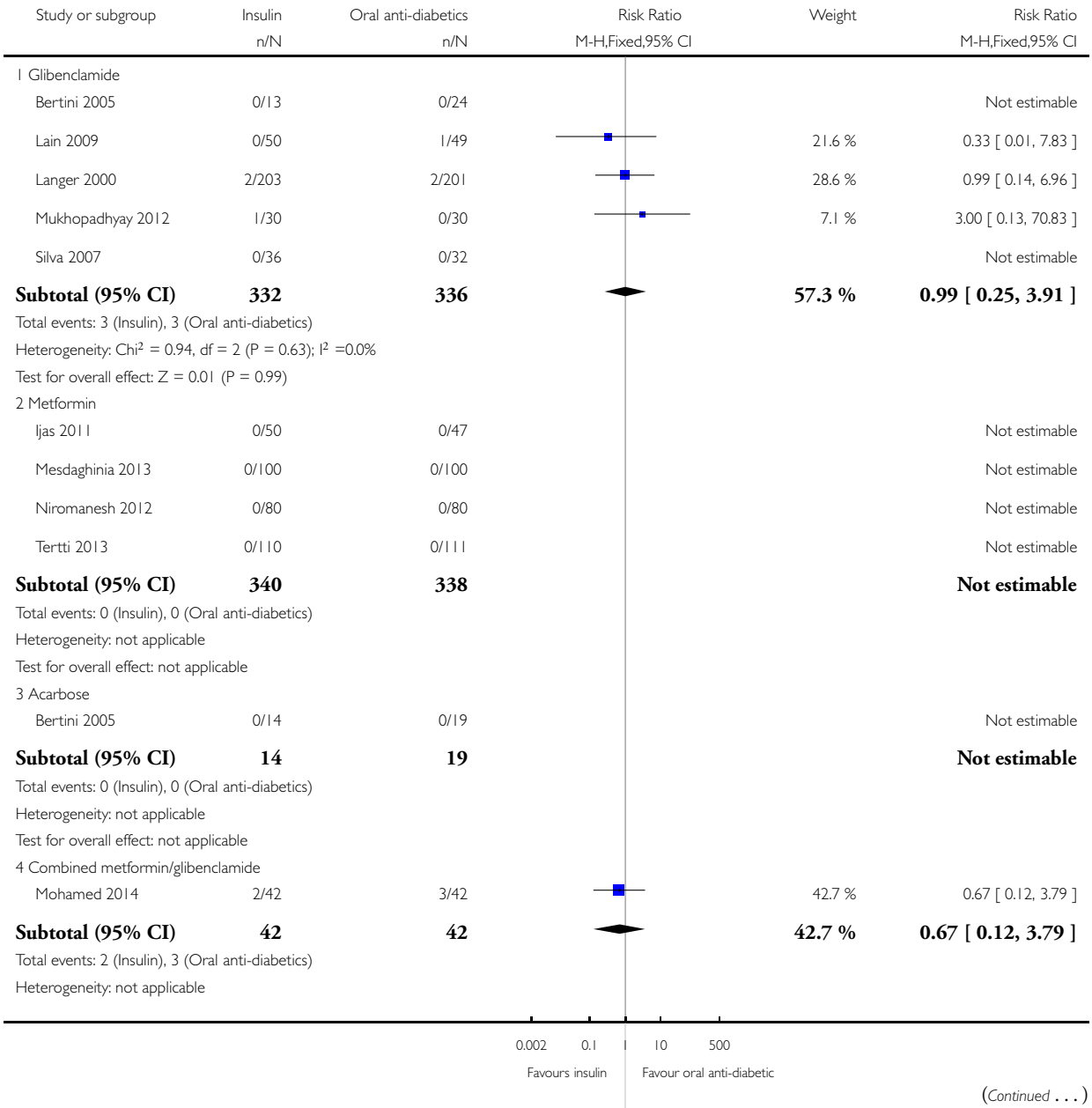
(2) up to 1 year postpartum; metformin

Analysis 1.5. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 5 Perinatal (fetal and neonatal death) and later infant mortality.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 5 Perinatal (fetal and neonatal death) and later infant mortality



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Study or subgroup	Insulin n/N	Oral anti-diabetics n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Test for overall effect: Z = 0.46 (P = 0.65)					
Total (95% CI)	**728**	**735**		**100.0 %**	**0.85 [0.29, 2.49]**
Total events: 5 (Insulin), 6 (Oral anti-diabetics)					
Heterogeneity: Chi^2 = 1.06, df = 3 (P = 0.79); I^2 =0.0%					
Test for overall effect: Z = 0.29 (P = 0.77)					
Test for subgroup differences: Chi^2 = 0.12, df = 1 (P = 0.73), I^2 =0.0%					

Analysis 1.6. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 6 Large-for-gestational age.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 6 Large-for-gestational age

Study or subgroup	Insulin n/N	Oral anti-diabetics n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Glibenclamide					
Bertini 2005	1/13	6/24		1.9 %	0.31 [0.04, 2.29]
Lain 2009	3/41	12/41		4.7 %	0.25 [0.08, 0.82]
Langer 2000	26/203	24/201		14.0 %	1.07 [0.64, 1.80]
Mukhopadhyay 2012	2/30	4/30		2.8 %	0.50 [0.10, 2.53]
Silva 2007	1/36	6/32		1.8 %	0.15 [0.02, 1.17]
Subtotal (95% CI)	**323**	**328**		**25.2 %**	**0.45 [0.19, 1.07]**
Total events: 33 (Insulin), 52 (Oral anti-diabetics)					
Heterogeneity: Tau^2 = 0.48; Chi^2 = 8.64, df = 4 (P = 0.07); I^2 =54%					
Test for overall effect: Z = 1.80 (P = 0.072)					
2 Metformin					
Hickman 2013	0/14	1/14		0.8 %	0.33 [0.01, 7.55]

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Study or subgroup	Insulin n/N	Oral anti-diabetics n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Ijas 2011	5/50	4/47		4.3 %	1.18 [0.34, 4.11]
Mesdaghinia 2013	24/100	16/100		12.8 %	1.50 [0.85, 2.65]
Niromanesh 2012	28/80	14/80		13.0 %	2.00 [1.14, 3.51]
Rowan 2008	69/370	70/363		20.3 %	0.97 [0.72, 1.30]
Saleh 2016	11/70	10/67		8.7 %	1.05 [0.48, 2.32]
Spaulonci 2013	3/46	2/46		2.4 %	1.50 [0.26, 8.56]
Tertti 2013	17/110	16/111		11.5 %	1.07 [0.57, 2.01]
Subtotal (95% CI)	**840**	**828**		**73.9 %**	**1.17 [0.94, 1.44]**
Total events: 157 (Insulin), 133 (Oral anti-diabetics)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 6.63$, df = 7 (P = 0.47); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.43 (P = 0.15)					
3 Acarbose					
Bertini 2005	0/14	2/19		0.9 %	0.27 [0.01, 5.15]
Subtotal (95% CI)	**14**	**19**		**0.9 %**	**0.27 [0.01, 5.15]**
Total events: 0 (Insulin), 2 (Oral anti-diabetics)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.87 (P = 0.38)					
Total (95% CI)	**1177**	**1175**		**100.0 %**	**1.01 [0.76, 1.35]**
Total events: 190 (Insulin), 187 (Oral anti-diabetics)					
Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 19.88$, df = 13 (P = 0.10); $I^2 = 35\%$					
Test for overall effect: Z = 0.09 (P = 0.93)					
Test for subgroup differences: $Chi^2 = 5.23$, df = 2 (P = 0.07), $I^2 = 62\%$					

Analysis 1.7. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 7 Death or serious morbidity composite (variously defined by trials, e.g. perinatal or infant death, shoulder dystocia, bone fracture or nerve palsy).

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 7 Death or serious morbidity composite (variously defined by trials, e.g. perinatal or infant death, shoulder dystocia, bone fracture or nerve palsy)

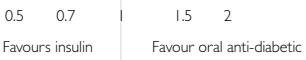
Study or subgroup	Insulin n/N	Oral anti-diabetics n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hickman 2013 (1)	7/14	4/13		3.4 %	1.63 [0.62, 4.28]
Rowan 2008 (2)	119/370	116/363		96.6 %	1.01 [0.82, 1.24]
Total (95% CI)	**384**	**376**		**100.0 %**	**1.03 [0.84, 1.26]**

Total events: 126 (Insulin), 120 (Oral anti-diabetics)

Heterogeneity: $Chi^2 = 0.90$, df = 1 (P = 0.34); $I^2 = 0.0\%$

Test for overall effect: Z = 0.26 (P = 0.80)

Test for subgroup differences: Not applicable



(1) Metformin; Rescuitation in the delivery room, preterm birth (< 37 weeks'), neonatal intensive care unit admission, birth injury or diagnosis of neonatal complication, glucose infusion, antibiotics or phototherapy

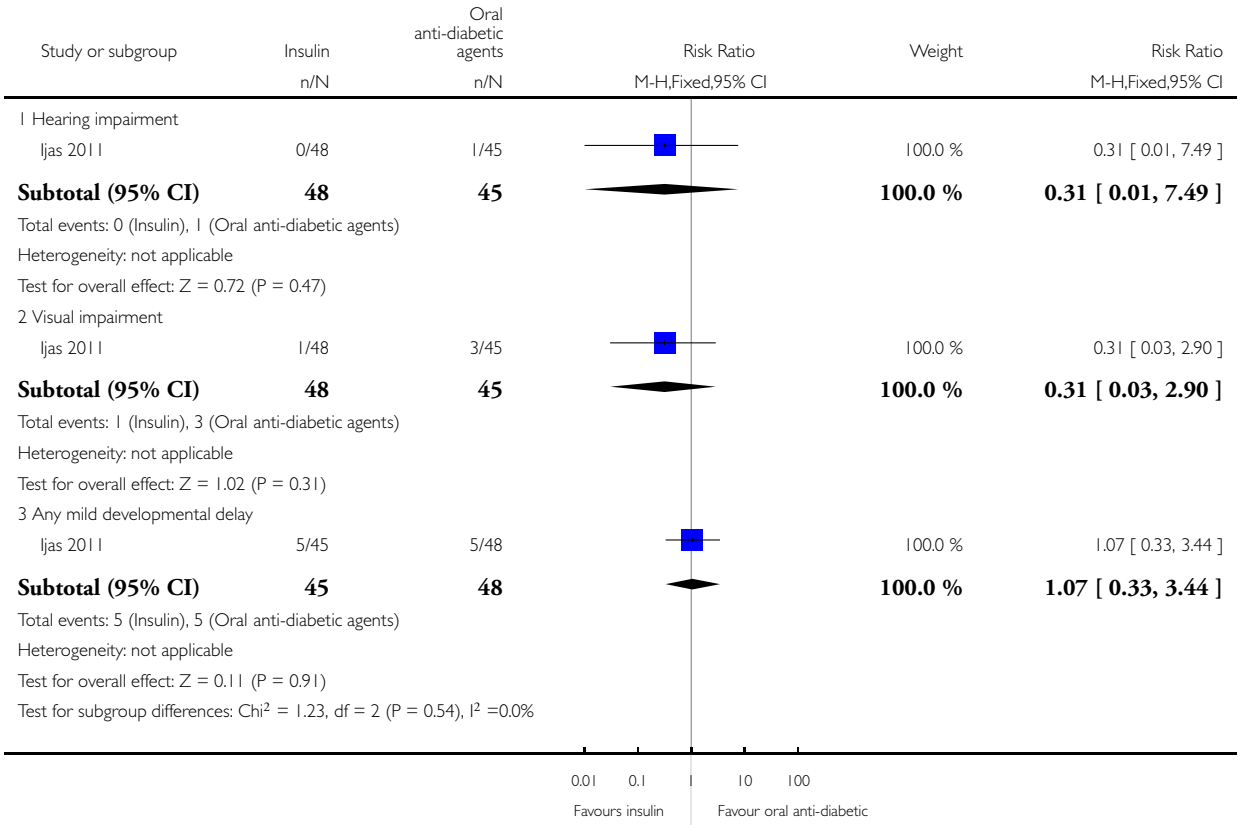
(2) Metformin; hypoglycaemia -< 2.6 mmol/L, RDS, phototherapy, birth trauma, 5 minute Apgar < 7, preterm birth < 37 weeks'

Analysis 1.8. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 8 Neurosensory disability in later childhood (18 to 24 months).

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 8 Neurosensory disability in later childhood (18 to 24 months)

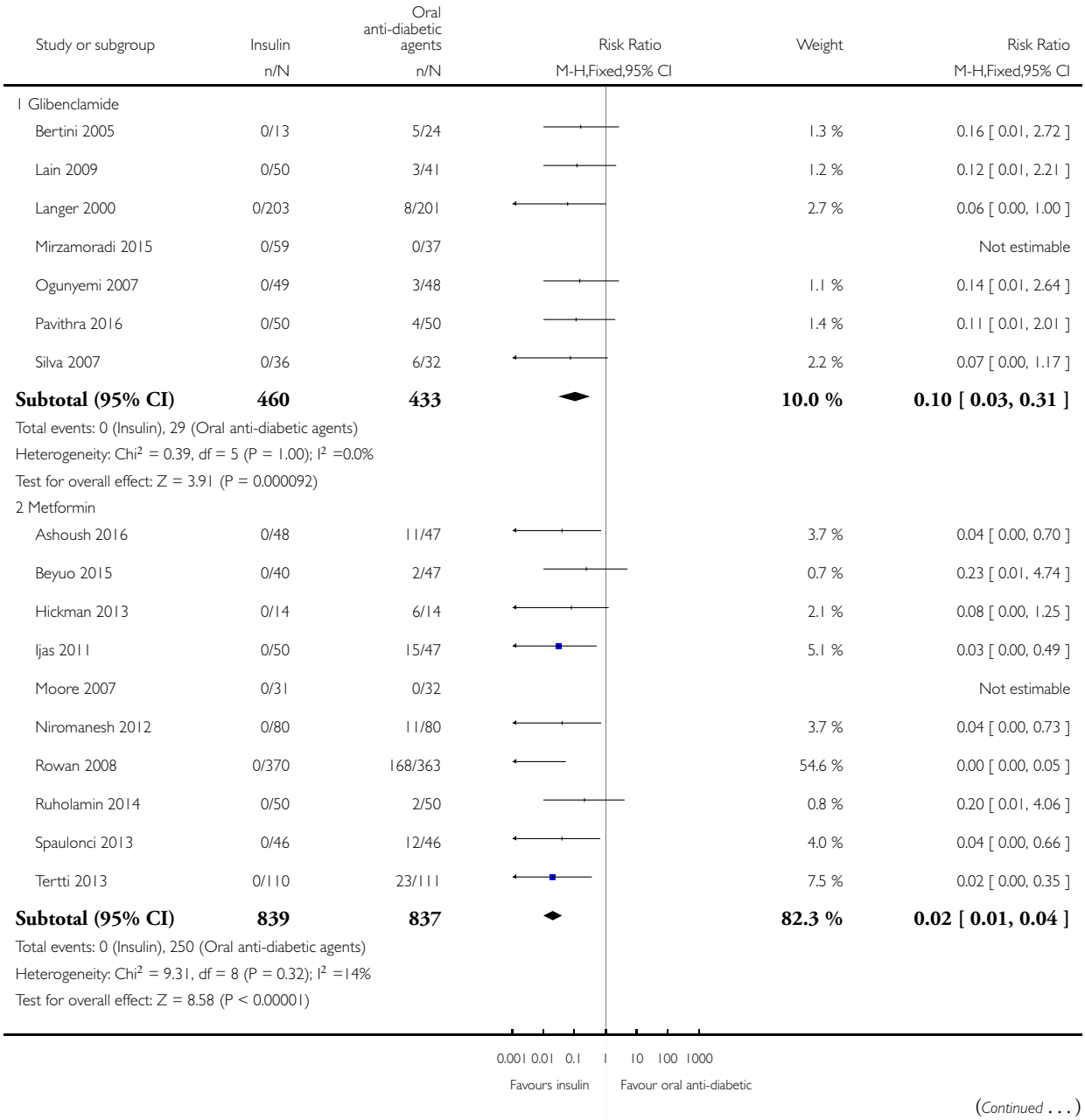


Analysis 1.9. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 9 Use of additional pharmacotherapy.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 9 Use of additional pharmacotherapy



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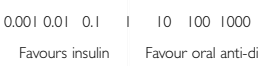
Study or subgroup	Insulin n/N	Oral anti-diabetic agents n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
3 Acarbose					
Bertini 2005	0/14	8/19		2.3 %	0.08 [0.00, 1.25]
De Veciana 2002 (1)	0/46	3/45		1.1 %	0.14 [0.01, 2.63]
Subtotal (95% CI)	**60**	**64**		**3.5 %**	**0.10 [0.01, 0.74]**
Total events: 0 (Insulin), 11 (Oral anti-diabetic agents)					
Heterogeneity: Chi^2 = 0.08, df = 1 (P = 0.78); I^2 =0.0%					
Test for overall effect: Z = 2.25 (P = 0.025)					
4 Metformin/glibenclamide					
Ardilouze 2014	0/33	13/35		4.2 %	0.04 [0.00, 0.63]
Subtotal (95% CI)	**33**	**35**		**4.2 %**	**0.04 [0.00, 0.63]**
Total events: 0 (Insulin), 13 (Oral anti-diabetic agents)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.28 (P = 0.023)					
Total (95% CI)	**1392**	**1369**		**100.0 %**	**0.03 [0.02, 0.06]**
Total events: 0 (Insulin), 303 (Oral anti-diabetic agents)					
Heterogeneity: Chi^2 = 13.10, df = 17 (P = 0.73); I^2 =0.0%					
Test for overall effect: Z = 10.59 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 6.05, df = 3 (P = 0.11), I^2 =50%					



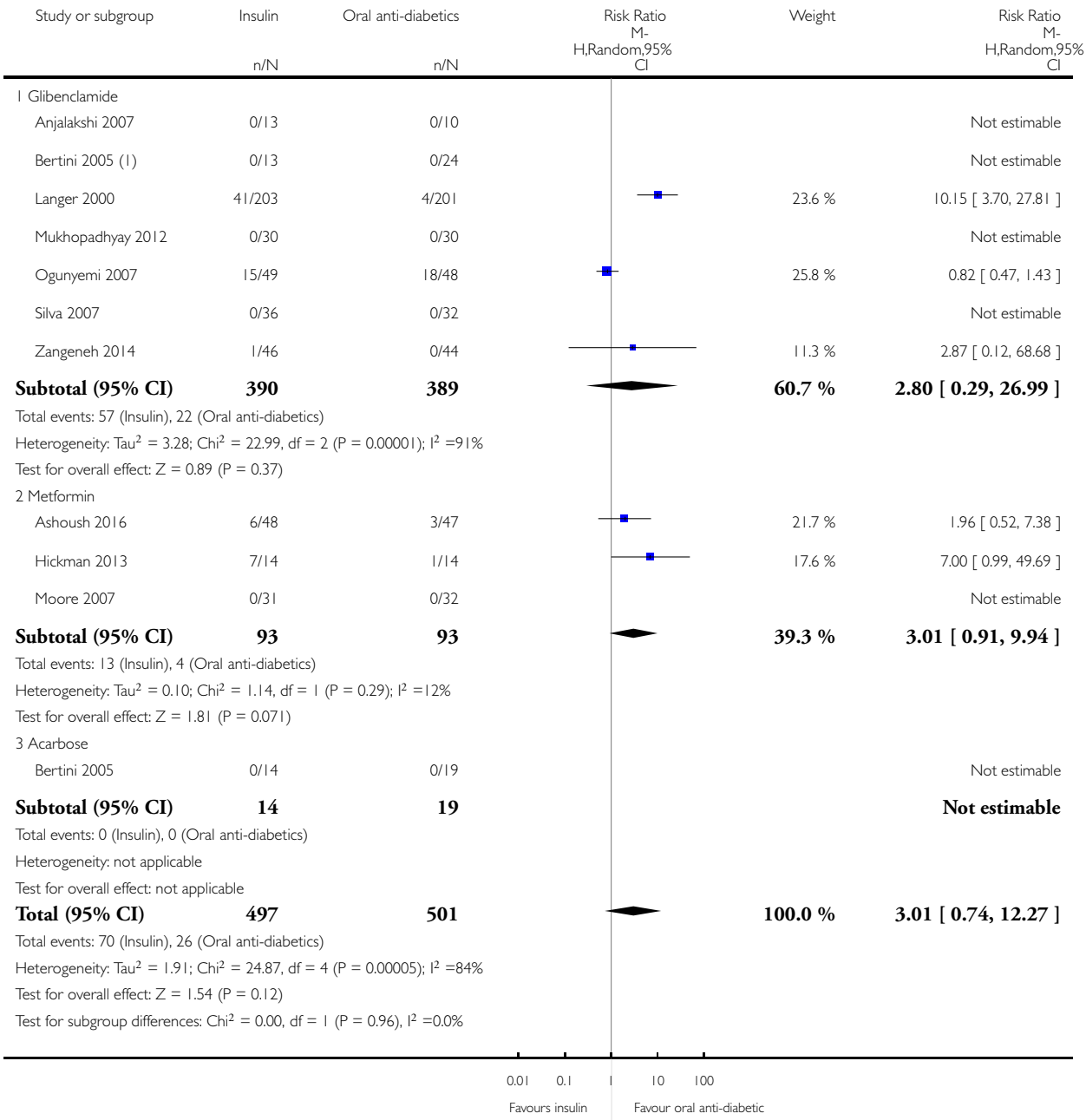
(1) Initiation of insulin for the women in the de Veciana 2002 trial was due to inability to tolerate increased dosage of acarbose rather than failure to meet glycaemic targets.

Analysis 1.10. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 10 Maternal hypoglycaemia.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 10 Maternal hypoglycaemia



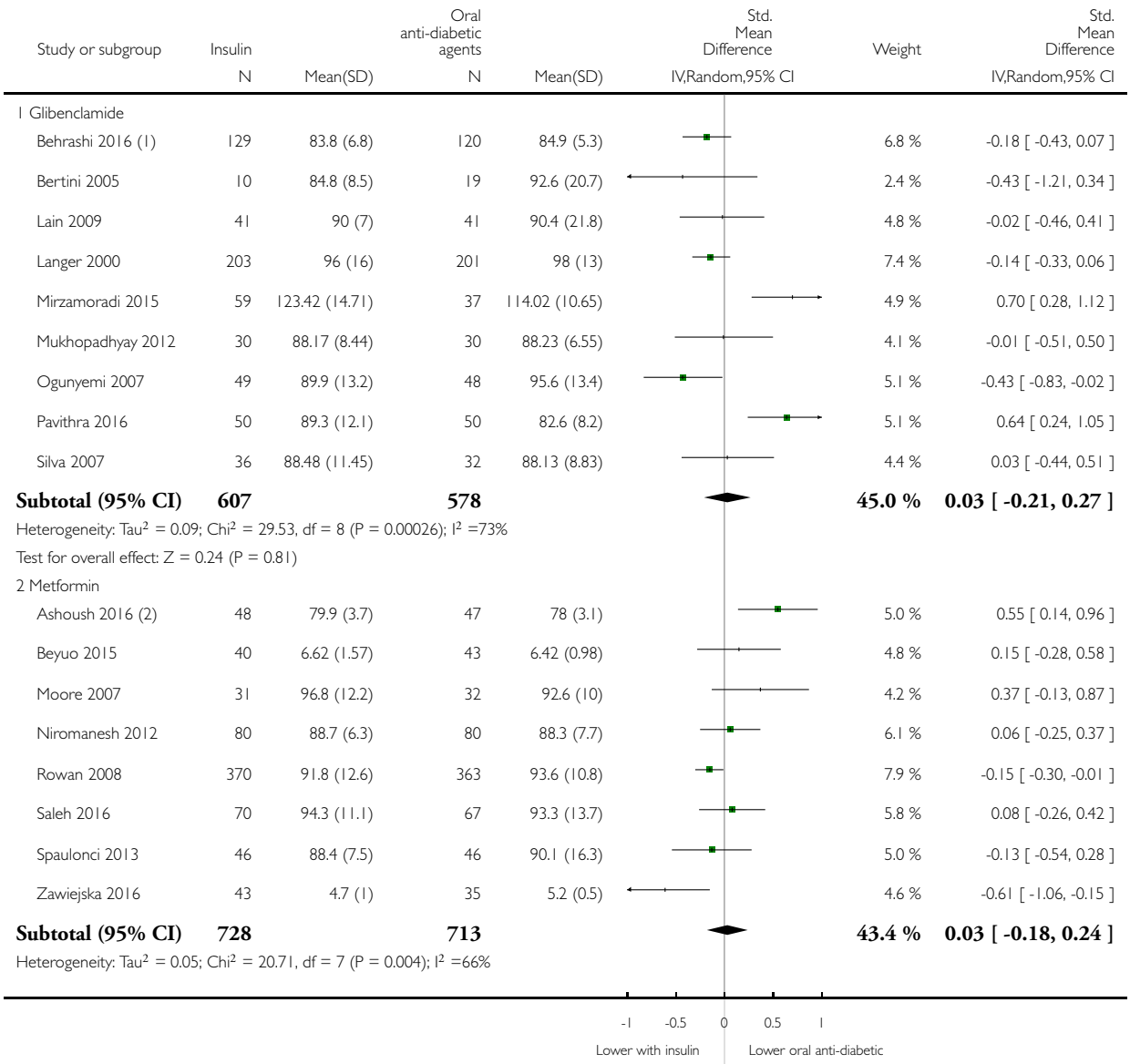
(1) Maternal hypoglycaemia requiring hospital admission

Analysis 1.11. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 11 Glycaemic control during/end treatment (fasting).

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 11 Glycaemic control during/end treatment (fasting)



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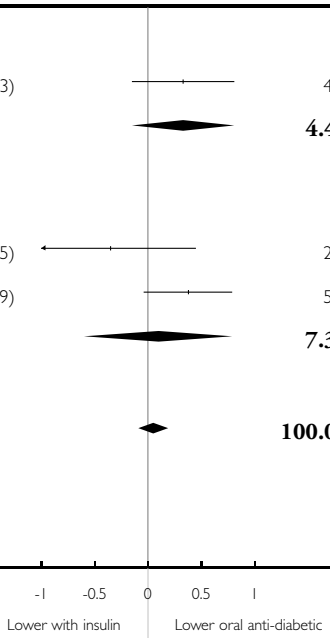
Study or subgroup	Insulin N	Mean(SD)	Oral anti-diabetic agents N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Test for overall effect: Z = 0.25 (P = 0.80)							
3 Combined metformin-glyburide							
Ardilouze 2014	33	4.8 (0.3)	35	4.7 (0.3)		4.4 %	0.33 [-0.15, 0.81]
Subtotal (95% CI)	**33**		**35**			**4.4 %**	**0.33 [-0.15, 0.81]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.35 (P = 0.18)							
4 Acarbose							
Bertini 2005	9	84.8 (8.5)	18	87.9 (8.5)		2.3 %	-0.35 [-1.16, 0.45]
De Veciana 2002	46	91 (8)	45	88.6 (3.9)		5.0 %	0.38 [-0.04, 0.79]
Subtotal (95% CI)	**55**		**63**			**7.3 %**	**0.10 [-0.60, 0.79]**
Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 2.49$, df = 1 (P = 0.11); $I^2 = 60\%$							
Test for overall effect: Z = 0.27 (P = 0.79)							
Total (95% CI)	**1423**		**1389**			**100.0 %**	**0.05 [-0.09, 0.19]**
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 56.67$, df = 19 (P = 0.00001); $I^2 = 66\%$							
Test for overall effect: Z = 0.69 (P = 0.49)							
Test for subgroup differences: $Chi^2 = 1.38$, df = 3 (P = 0.71), $I^2 = 0.0\%$							



(1) after treatment

(2) last week of treatment

Analysis 1.12. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 12 Glycaemic control during/end treatment (postprandial).

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 12 Glycaemic control during/end treatment (postprandial)

Study or subgroup	Insulin N	Mean(SD)	Oral anti-diabetics N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Glibenclamide							
Anjalakshi 2007 (1)	13	93 (9.8)	10	95.29 (7.4)		2.8 %	-0.25 [-1.08, 0.58]
Bertini 2005 (2)	10	100.6 (17.4)	19	101.8 (20)		3.1 %	-0.06 [-0.83, 0.71]
Lain 2009 (3)	41	115.7 (9.7)	41	124.8 (23.6)		5.3 %	-0.50 [-0.94, -0.06]
Langer 2000 (4)	203	112 (15)	201	113 (22)		7.4 %	-0.05 [-0.25, 0.14]
Mirzamoradi 2015 (5)	59	120.15 (9.56)	37	115.46 (8.21)		5.5 %	0.51 [0.10, 0.93]
Mukhopadhyay 2012 (6)	30	128 (12.38)	30	122.7 (10.3)		4.7 %	0.46 [-0.05, 0.97]
Ogunyemi 2007 (7)	49	116.3 (16.6)	48	132.6 (35)		5.6 %	-0.59 [-1.00, -0.19]
Pavithra 2016 (8)	50	111.5 (12.1)	50	107.3 (13.9)		5.7 %	0.32 [-0.07, 0.71]
Silva 2007	36	105.14 (17.91)	32	102.52 (24.89)		5.0 %	0.12 [-0.36, 0.60]
Subtotal (95% CI)	**491**		**468**			**45.1 %**	**0.00 [-0.25, 0.26]**
Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 25.36$, df = 8 (P = 0.001); $I^2 = 68\%$							
Test for overall effect: Z = 0.03 (P = 0.98)							
2 Metformin							
Ashoush 2016 (9)	48	113.3 (4.2)	47	109.9 (3.7)		5.5 %	0.85 [0.43, 1.27]
Beyuo 2015 (10)	40	9.1 (1.9)	43	7.8 (1.4)		5.2 %	0.78 [0.33, 1.22]
Moore 2007 (11)	31	109.2 (22.5)	32	108.1 (13.8)		4.9 %	0.06 [-0.44, 0.55]
Niromanesh 2012 (12)	80	111.1 (9)	80	113.3 (9.1)		6.4 %	-0.24 [-0.55, 0.07]
Rowan 2008 (13)	370	115.2 (16.2)	363	111.6 (10.8)		7.7 %	0.26 [0.12, 0.41]
Saleh 2016 (14)	70	117.1 (3.5)	67	116.5 (3.5)		6.2 %	0.17 [-0.17, 0.51]
Spaulonci 2013	46	119.1 (16.5)	46	110.8 (11.6)		5.5 %	0.58 [0.16, 0.99]
Subtotal (95% CI)	**685**		**678**			**41.4 %**	**0.33 [0.07, 0.59]**
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 25.80$, df = 6 (P = 0.00024); $I^2 = 77\%$							
Test for overall effect: Z = 2.47 (P = 0.013)							
3 Combined metformin-glyburide							
Ardilouze 2014 (15)	33	6.1 (0.5)	35	6 (0.5)		5.0 %	0.20 [-0.28, 0.67]
Subtotal (95% CI)	**33**		**35**			**5.0 %**	**0.20 [-0.28, 0.67]**

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Study or subgroup	Insulin N	Mean(SD)	Oral anti-diabetics N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Heterogeneity: not applicable							
Test for overall effect: Z = 0.81 (P = 0.42)							
4 Acarbose							
Bertini 2005 (16)	9	100.6 (17.4)	18	107.1 (19)		2.9 %	-0.34 [-1.15, 0.47]
De Veciana 2002 (17)	46	117 (4.3)	45	118.1 (3.2)		5.5 %	-0.29 [-0.70, 0.13]
Subtotal (95% CI)	**55**		**63**			**8.4 %**	**-0.30 [-0.67, 0.07]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.01, df = 1 (P = 0.91); I^2 =0.0%							
Test for overall effect: Z = 1.59 (P = 0.11)							
Total (95% CI)	**1264**		**1244**			**100.0 %**	**0.12 [-0.05, 0.29]**
Heterogeneity: Tau^2 = 0.09; Chi^2 = 67.85, df = 18 (P<0.00001); I^2 =73%							
Test for overall effect: Z = 1.40 (P = 0.16)							
Test for subgroup differences: Chi^2 = 8.15, df = 3 (P = 0.04), I^2 =63%							

(1) Two-hour postprandial

(2) Two-hour postprandial

(3) Two-hour postprandial (dinner)

(4) No details

(5) Two-hour postprandial

(6) Timing of postprandial measure not specified.

(7) Two-hour postprandial.

(8) Two-hour postprandial

(9) 2-hour postprandial, last week of treatment

(10) Two-hour postprandial.

(11) Two-hour postprandial (dinner).

(12) Two-hour postprandial.

(13) Two-hour postprandial.

(14) Two-hour postprandial

(15) Two-hour postprandial after supper

(16) Two-hour postprandial

(17) one-hour postprandial

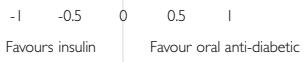
Analysis 1.13. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 13 Glycaemic control during/end of treatment (HbA1c).

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 13 Glycaemic control during/end of treatment (HbA1c)

Study or subgroup	Insulin N	Mean(SD)	Oral anti-diabetics N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Glibenclamide							
Anjalakshi 2007	13	5.5 (0.62)	10	5.3 (0.34)		2.4 %	0.37 [-0.46, 1.20]
Langer 2000	203	5.4 (0.6)	201	5.5 (0.7)		17.9 %	-0.15 [-0.35, 0.04]
Mukhopadhyay 2012	30	6.24 (0.57)	30	6.08 (0.55)		5.7 %	0.28 [-0.23, 0.79]
Subtotal (95% CI)	**246**		**241**			**26.0 %**	**0.04 [-0.31, 0.39]**
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 3.61$, df = 2 (P = 0.16); $I^2 = 45\%$							
Test for overall effect: Z = 0.25 (P = 0.80)							
2 Metformin							
Mesdaghinia 2013	100	5.12 (0.84)	100	4.86 (0.7)		12.9 %	0.34 [0.06, 0.61]
Niromanesh 2012	80	4.3 (0.4)	80	4.3 (0.5)		11.5 %	0.0 [-0.31, 0.31]
Rowan 2008	370	79.2 (12.6)	363	81 (10.8)		21.5 %	-0.15 [-0.30, -0.01]
Tertti 2013	110	5.69 (0.36)	111	5.68 (0.33)		13.7 %	0.03 [-0.23, 0.29]
Zawiejska 2016	43	5.7 (0.6)	35	5.6 (0.5)		7.0 %	0.18 [-0.27, 0.62]
Subtotal (95% CI)	**703**		**689**			**66.5 %**	**0.05 [-0.14, 0.24]**
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 10.35$, df = 4 (P = 0.03); $I^2 = 61\%$							
Test for overall effect: Z = 0.51 (P = 0.61)							
3 Combined metformin/glibenclamide							
Mohamed 2014	42	5.43 (0.5)	42	5.5 (0.6)		7.4 %	-0.13 [-0.55, 0.30]
Subtotal (95% CI)	**42**		**42**			**7.4 %**	**-0.13 [-0.55, 0.30]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.57 (P = 0.57)							
Total (95% CI)	**991**		**972**			**100.0 %**	**0.01 [-0.12, 0.15]**
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 14.42$, df = 8 (P = 0.07); $I^2 = 45\%$							
Test for overall effect: Z = 0.22 (P = 0.83)							
Test for subgroup differences: $Chi^2 = 0.55$, df = 2 (P = 0.76), $I^2 = 0.0\%$							

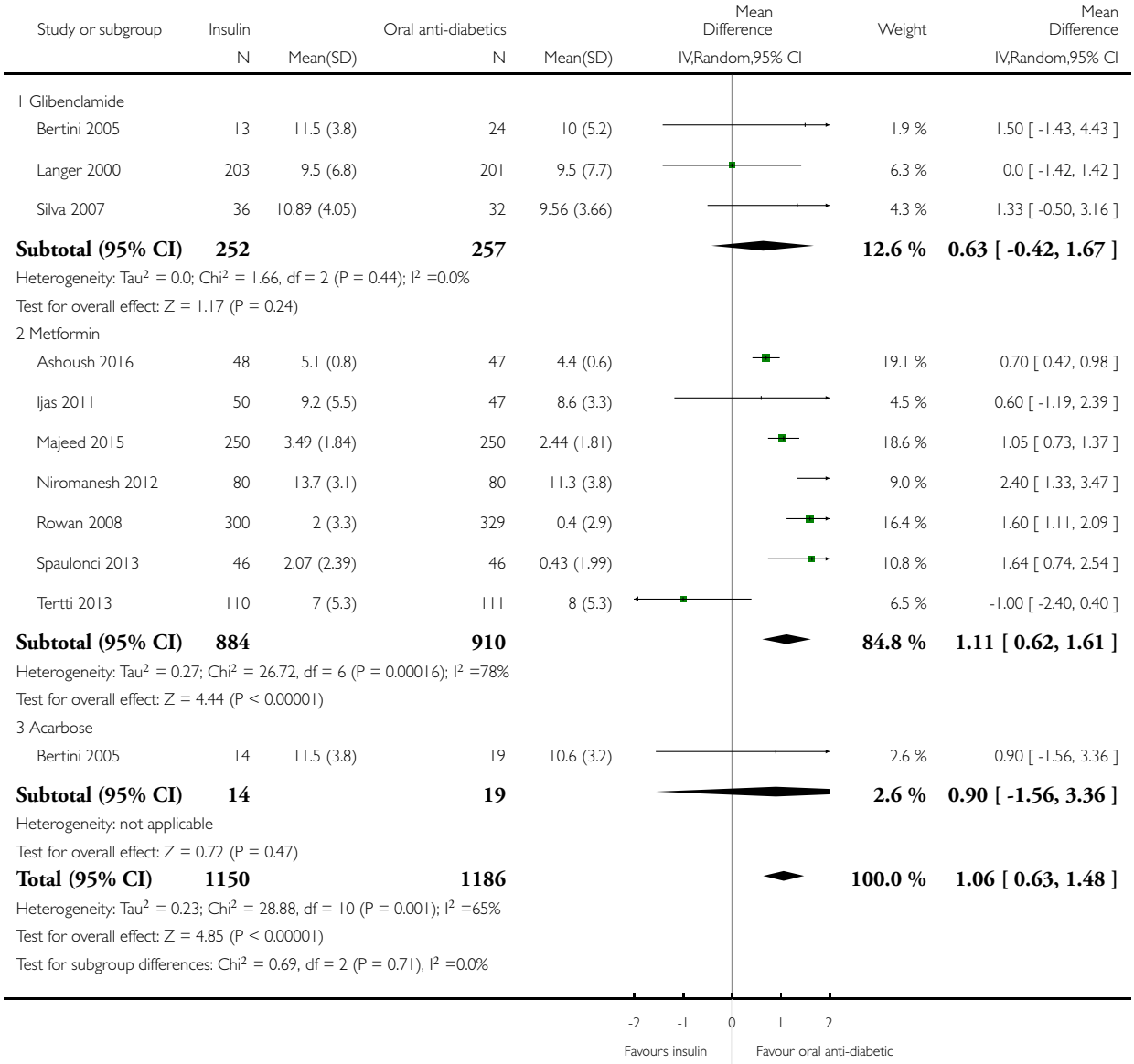


Analysis 1.14. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 14 Weight gain in pregnancy.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 14 Weight gain in pregnancy

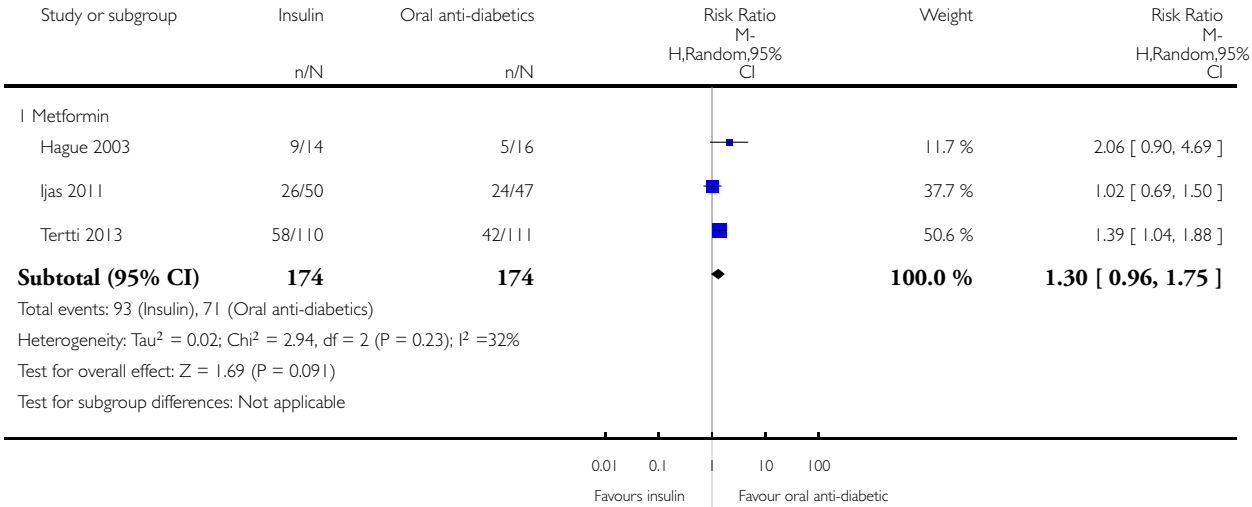


Analysis 1.15. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 15 Induction of labour.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 15 Induction of labour

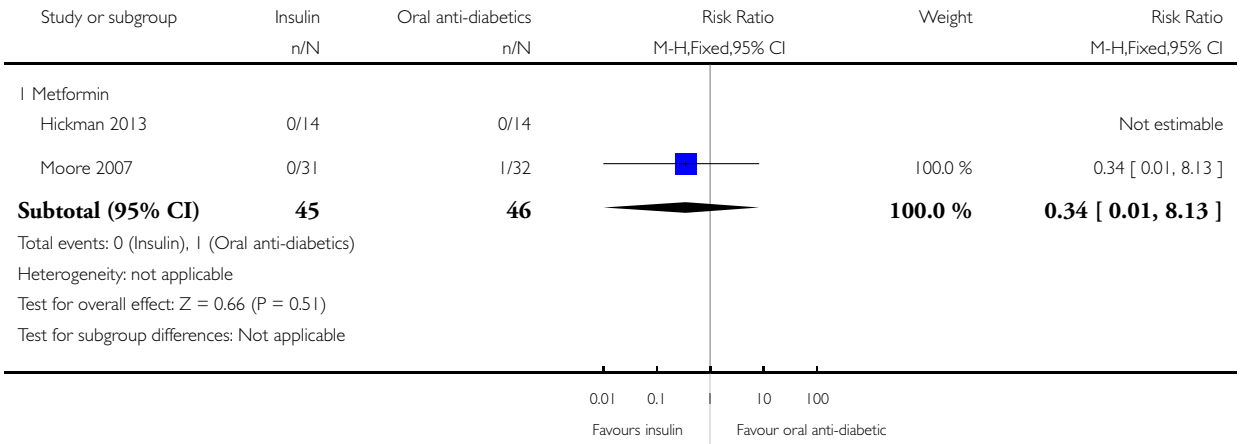


Analysis 1.16. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 16 Postpartum haemorrhage.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 16 Postpartum haemorrhage

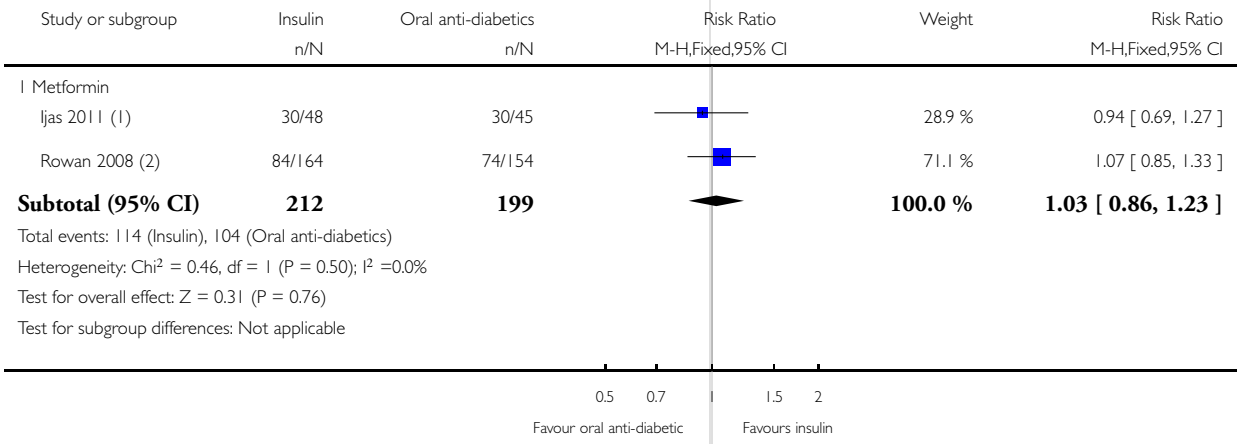


Analysis 1.17. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 17 Breastfeeding at discharge, six weeks postpartum, six months or longer.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 17 Breastfeeding at discharge, six weeks postpartum, six months or longer



(1) 6-8 weeks post-partum

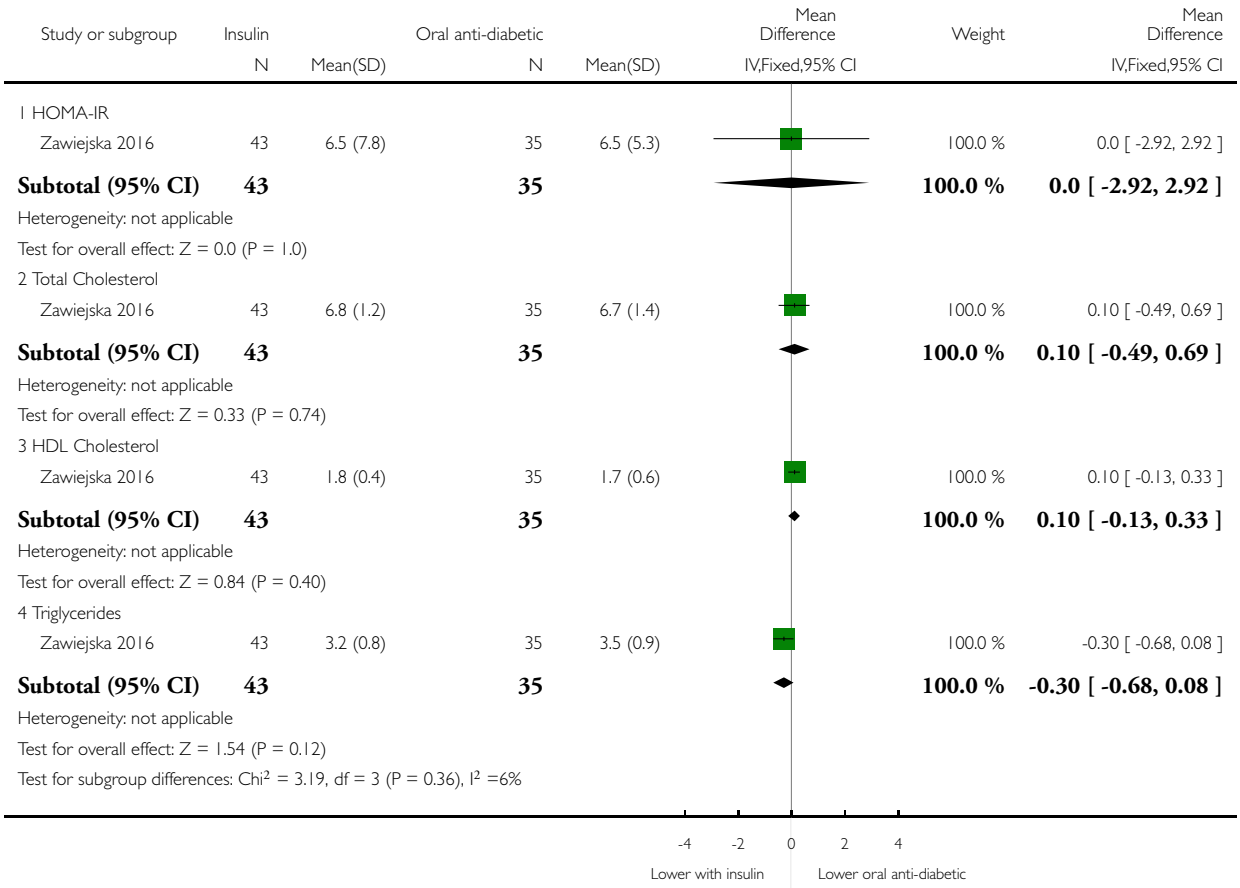
(2) 6-8 weeks post-partum

Analysis 1.18. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 18 Relevant biomarker changes associated with the intervention.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 18 Relevant biomarker changes associated with the intervention



Analysis 1.19. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 19 Body mass index (BMI).

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 19 Body mass index (BMI)

Study or subgroup	Insulin		Oral anti-diabetic agent		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
1 Metformin							
Rowan 2008 (1)	363	31.6 (7.6)	370	31.8 (7.5)		100.0 %	-0.20 [-1.29, 0.89]
Total (95% CI)	**363**		**370**			**100.0 %**	**-0.20 [-1.29, 0.89]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.36 (P = 0.72)

Test for subgroup differences: Not applicable

(1) 6 weeks postpartum

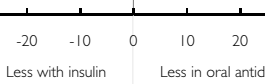
Analysis 1.20. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 20 Postnatal weight retention.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 20 Postnatal weight retention

Study or subgroup	Insulin N	Mean(SD)	Oral anti-diabetic N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Six to eight weeks postpartum							
Tertti 2013 (1)	83	79.2 (13.4)	84	80.8 (17.6)		100.0 %	-1.60 [-6.34, 3.14]
Subtotal (95% CI)	**83**		**84**			**100.0 %**	**-1.60 [-6.34, 3.14]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.66 (P = 0.51)							
2 One year postpartum							
Tertti 2013 (2)	91	78.1 (14.6)	85	81.8 (17.6)		100.0 %	-3.70 [-8.50, 1.10]
Subtotal (95% CI)	**91**		**85**			**100.0 %**	**-3.70 [-8.50, 1.10]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.51 (P = 0.13)							
Test for subgroup differences: Chi^2 = 0.37, df = 1 (P = 0.54), I^2 =0.0%							



(1) Postnatal weight (kg)

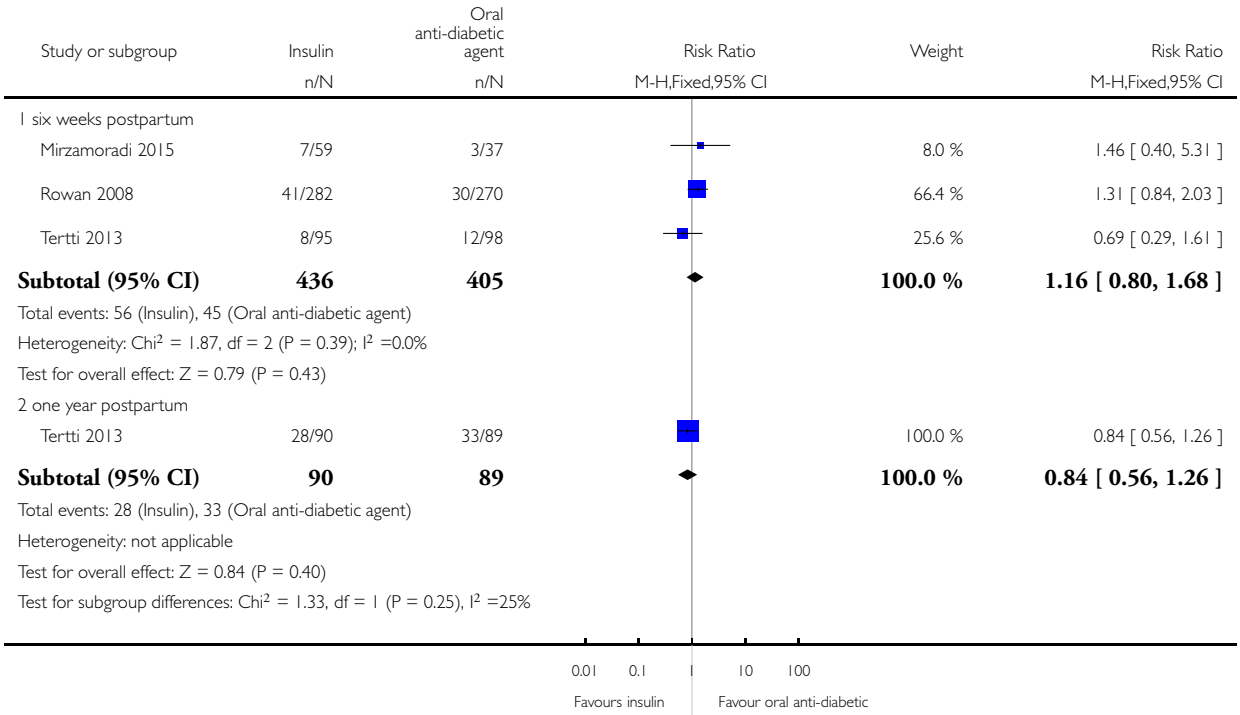
(2) Postnatal weight (kg)

Analysis 1.21. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 21 Impaired glucose tolerance.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 21 Impaired glucose tolerance

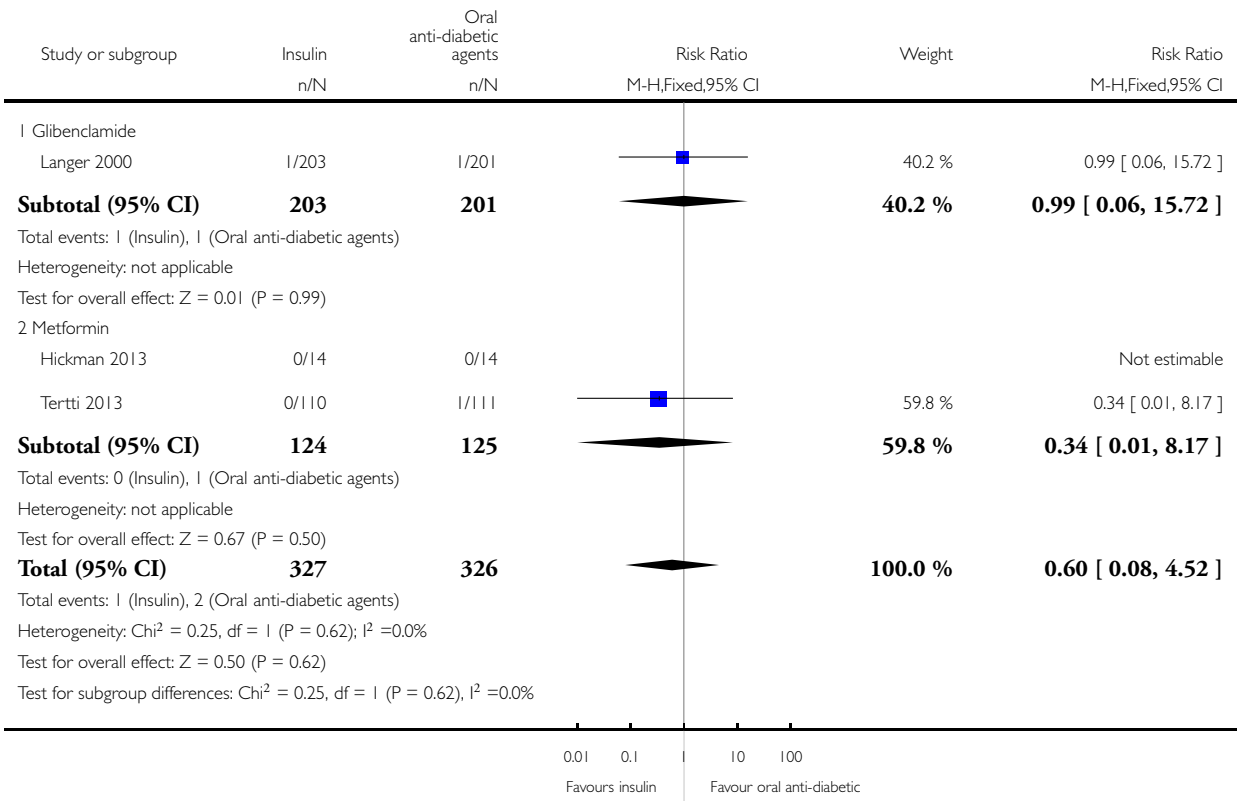


Analysis 1.22. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 22 Stillbirth.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 22 Stillbirth

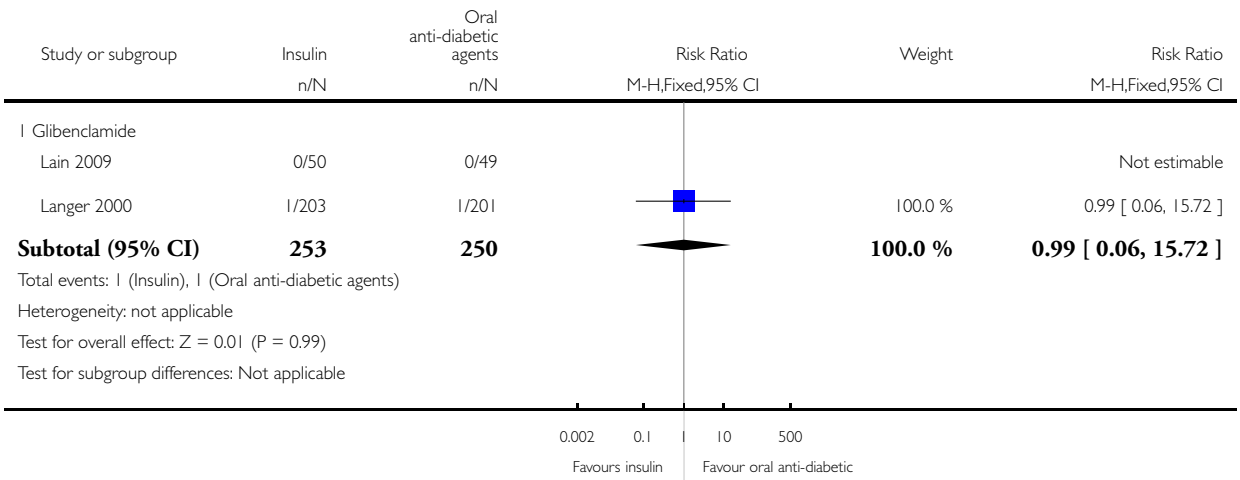


Analysis 1.23. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 23 Neonatal death.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 23 Neonatal death



Analysis 1.24. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 24 Macrosomia (> 4000 g).

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 24 Macrosomia (> 4000 g)

Study or subgroup	Insulin n/N	Oral anti-diabetic agents n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Glibenclamide					
Behrashi 2016	17/129	4/120		8.2 %	3.95 [1.37, 11.42]
Bertini 2005	0/13	4/24		1.9 %	0.20 [0.01, 3.42]
Lain 2009	1/41	9/41		3.5 %	0.11 [0.01, 0.84]
Langer 2000	9/203	14/201		10.4 %	0.64 [0.28, 1.44]
Mirzamoradi 2015	4/59	2/37		4.7 %	1.25 [0.24, 6.51]
Mukhopadhyay 2012	0/30	0/30			Not estimable
Pavithra 2016	4/50	1/50		3.1 %	4.00 [0.46, 34.54]
Silva 2007	0/36	5/32		1.9 %	0.08 [0.00, 1.41]
Zangeneh 2014	3/46	4/44		5.7 %	0.72 [0.17, 3.02]
Subtotal (95% CI)	**607**	**579**		**39.4 %**	**0.77 [0.31, 1.94]**
Total events: 38 (Insulin), 43 (Oral anti-diabetic agents)					
Heterogeneity: $Tau^2 = 0.96$; $Chi^2 = 18.29$, df = 7 (P = 0.01); $I^2 = 62\%$					
Test for overall effect: Z = 0.55 (P = 0.58)					
2 Metformin					
Ashoush 2016	5/48	2/47		5.0 %	2.45 [0.50, 12.00]
Hague 2003	2/14	2/16		4.0 %	1.14 [0.18, 7.08]
Hickman 2013	0/14	1/14		1.6 %	0.33 [0.01, 7.55]
Ijas 2011	11/50	9/47		10.7 %	1.15 [0.52, 2.52]
Mesdaghinia 2013	18/100	11/100		11.6 %	1.64 [0.82, 3.29]
Moore 2007	6/31	3/32		6.5 %	2.06 [0.57, 7.54]
Niromanesh 2012	8/80	3/80		6.5 %	2.67 [0.73, 9.69]
Ruholamin 2014	0/50	0/50			Not estimable
Spaulonci 2013	3/46	0/46		1.8 %	7.00 [0.37, 131.81]
Tertti 2013	16/110	22/111		12.8 %	0.73 [0.41, 1.32]

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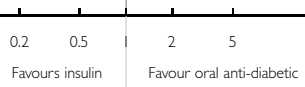
Study or subgroup	Insulin n/N	Oral anti-diabetic agents n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**543**	**543**		**60.6 %**	**1.26 [0.88, 1.81]**
Total events: 69 (Insulin), 53 (Oral anti-diabetic agents)					
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 8.44$, df = 8 (P = 0.39); $I^2 = 5\%$					
Test for overall effect: Z = 1.28 (P = 0.20)					
3 Acarbose					
Bertini 2005	0/14	0/19			Not estimable
Subtotal (95% CI)	**14**	**19**			**Not estimable**
Total events: 0 (Insulin), 0 (Oral anti-diabetic agents)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**1164**	**1141**		**100.0 %**	**1.17 [0.77, 1.78]**
Total events: 107 (Insulin), 96 (Oral anti-diabetic agents)					
Heterogeneity: $Tau^2 = 0.27$; $Chi^2 = 27.47$, df = 16 (P = 0.04); $I^2 = 42\%$					
Test for overall effect: Z = 0.73 (P = 0.47)					
Test for subgroup differences: $Chi^2 = 0.96$, df = 1 (P = 0.33), $I^2 = 0.0\%$					

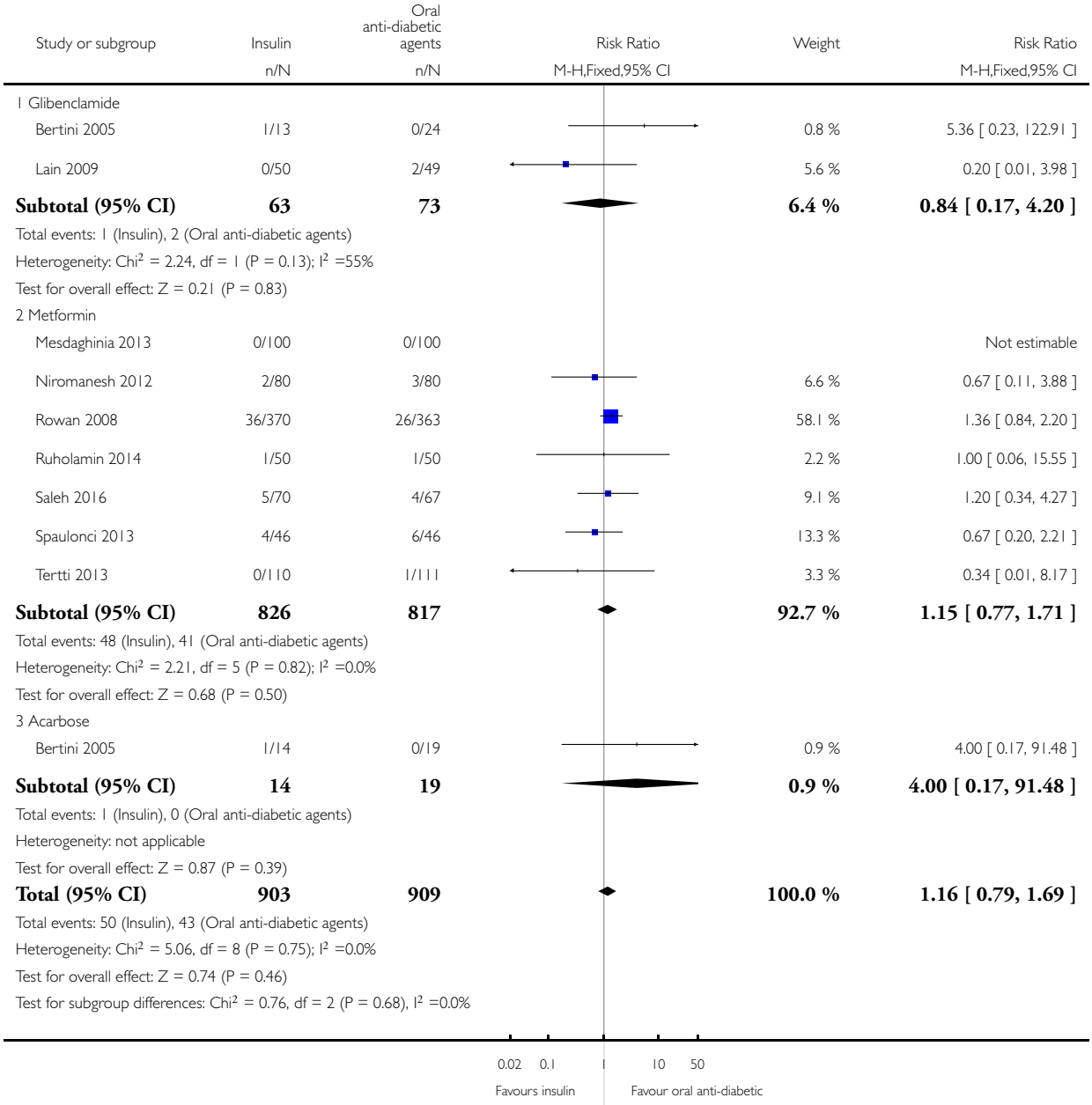


Analysis 1.25. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 25 Small-for-gestational age.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 25 Small-for-gestational age

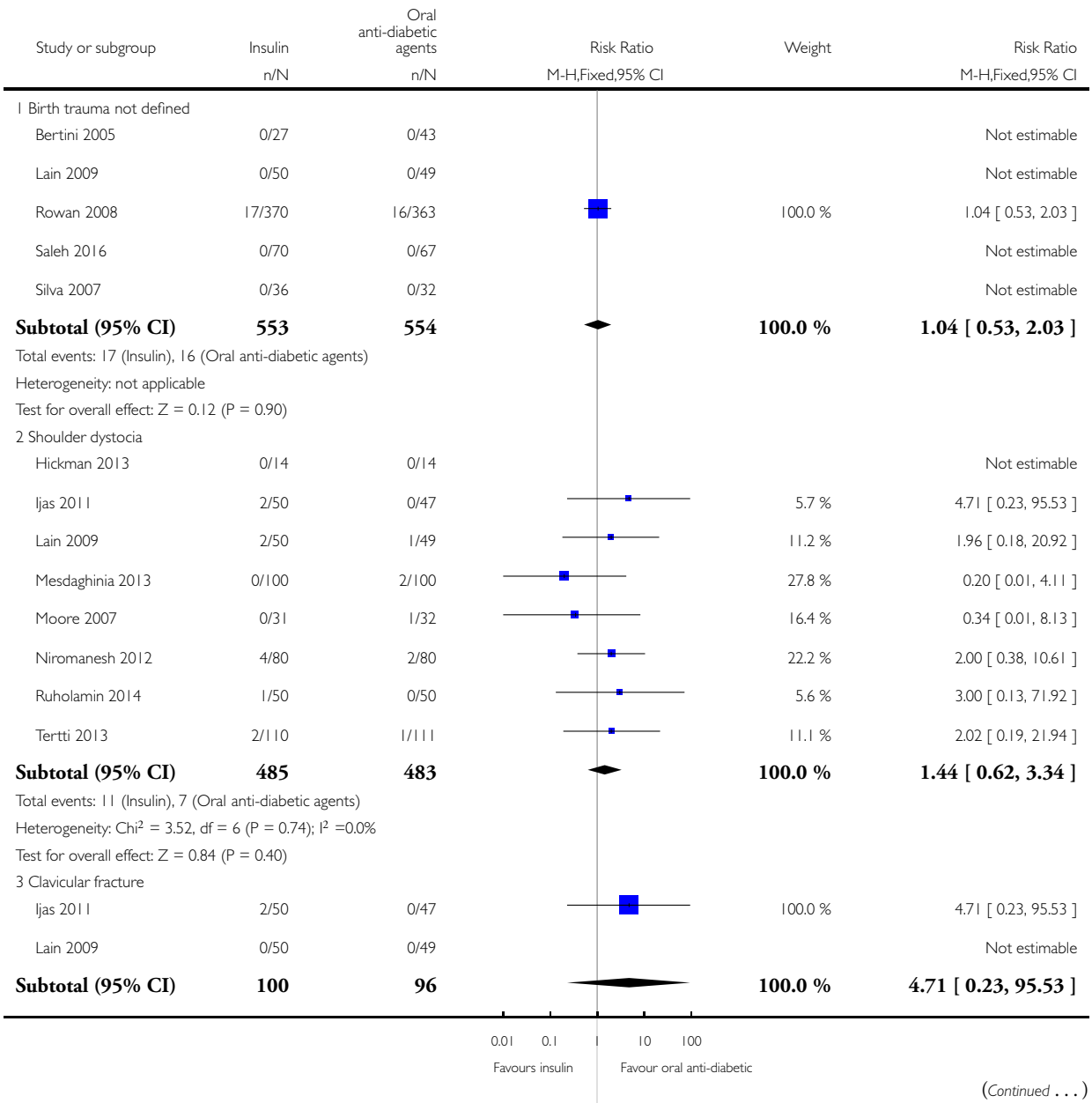


Analysis 1.26. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 26 Birth trauma.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 26 Birth trauma



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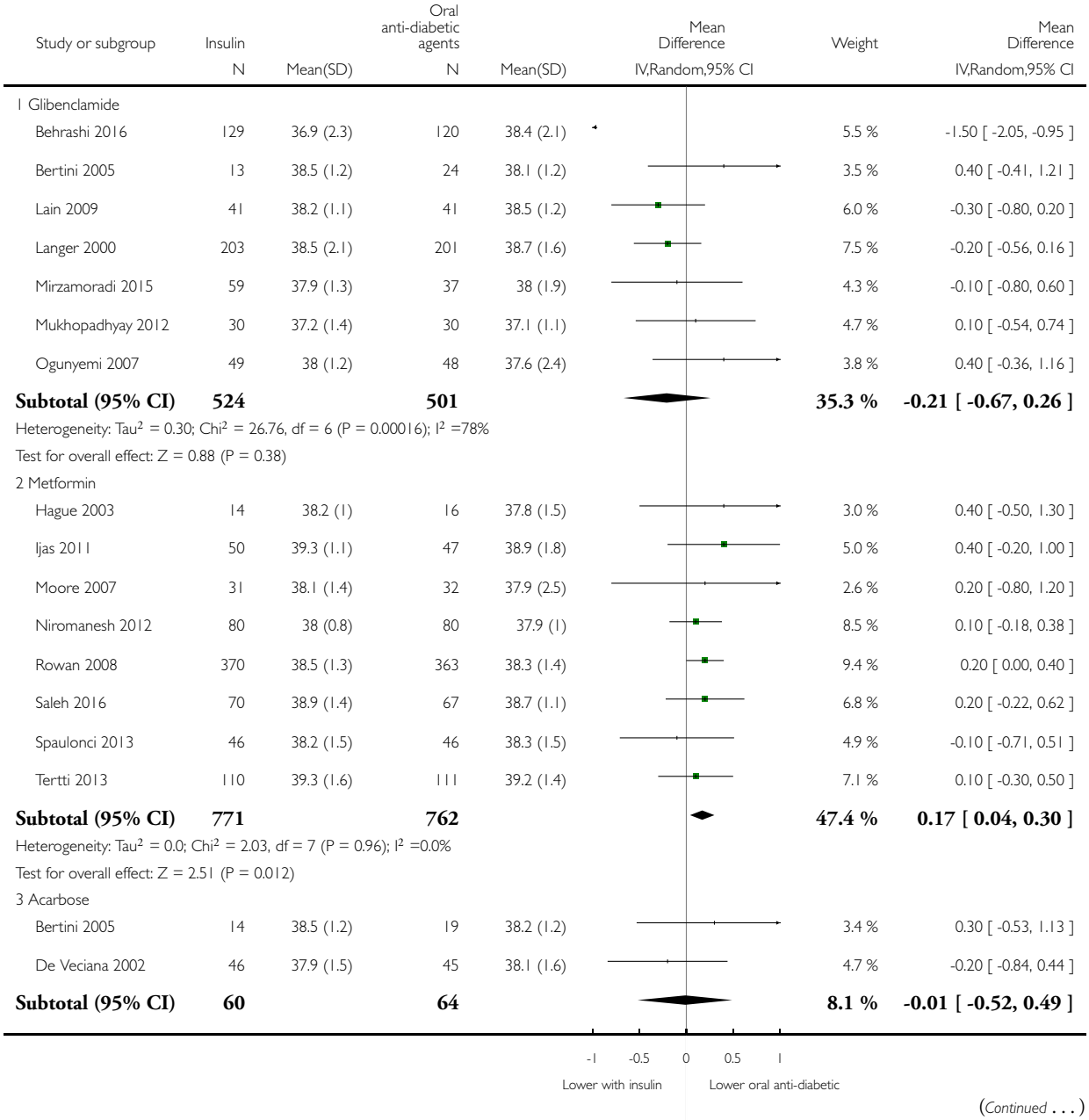
Study or subgroup	Insulin n/N	Oral anti-diabetic agents n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total events: 2 (Insulin), 0 (Oral anti-diabetic agents)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.01 (P = 0.31)					
4 Brachial nerve injury					
Lain 2009	0/50	0/49			Not estimable
Tertti 2013	2/110	0/111		100.0 %	5.05 [0.24, 103.90]
Subtotal (95% CI)	**160**	**160**		**100.0 %**	**5.05 [0.24, 103.90]**
Total events: 2 (Insulin), 0 (Oral anti-diabetic agents)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.05 (P = 0.29)					
Test for subgroup differences: Chi^2 = 1.94, df = 3 (P = 0.58), I^2 =0.0%					

Analysis 1.27. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 27 Gestational age at birth.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 27 Gestational age at birth



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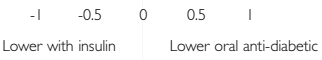
Study or subgroup	Insulin N	Mean(SD)	Oral anti-diabetic agents N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.88$, df = 1 (P = 0.35); $I^2 = 0.0\%$							
Test for overall effect: Z = 0.05 (P = 0.96)							
4 Combined metformin/glibenclamide							
Ardilouze 2014	33	38.4 (1.5)	35	38.7 (1.1)		4.8 %	-0.30 [-0.93, 0.33]
Mohamed 2014	42	38.3 (1.2)	42	38.1 (1.9)		4.4 %	0.20 [-0.48, 0.88]
Subtotal (95% CI)	**75**		**77**			**9.2 %**	**-0.07 [-0.56, 0.42]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 1.12$, df = 1 (P = 0.29); $I^2 = 11\%$							
Test for overall effect: Z = 0.27 (P = 0.79)							
Total (95% CI)	**1430**		**1404**			**100.0 %**	**-0.01 [-0.20, 0.18]**
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 43.71$, df = 18 (P = 0.00063); $I^2 = 59\%$							
Test for overall effect: Z = 0.10 (P = 0.92)							
Test for subgroup differences: $Chi^2 = 3.25$, df = 3 (P = 0.35), $I^2 = 8\%$							

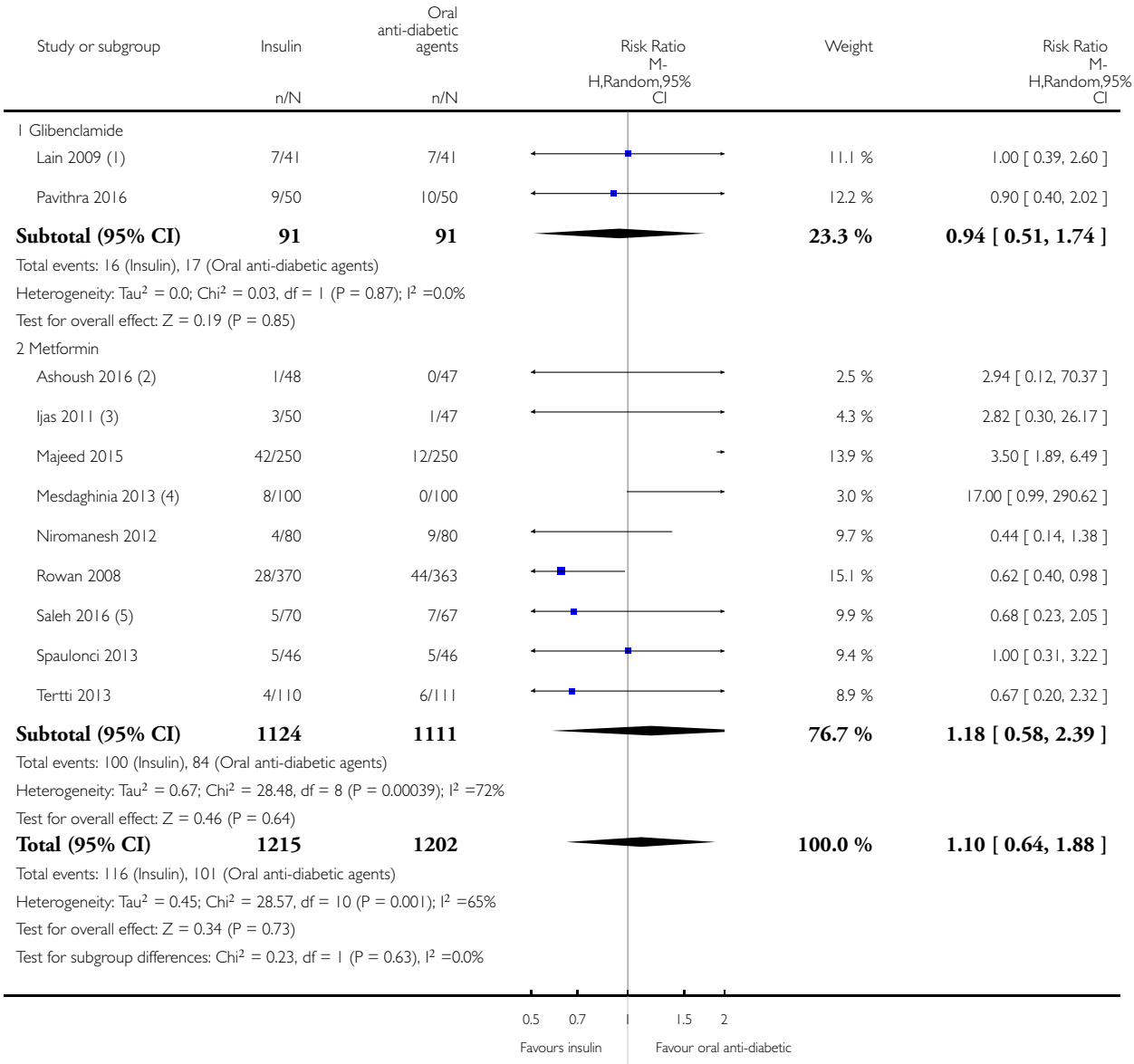


Analysis 1.28. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 28 Preterm birth (< 37 weeks).

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 28 Preterm birth (< 37 weeks)



(1) No details

(2) No details

(3) Birth at 31, 33 and 36 weeks' combined.

(4) No details

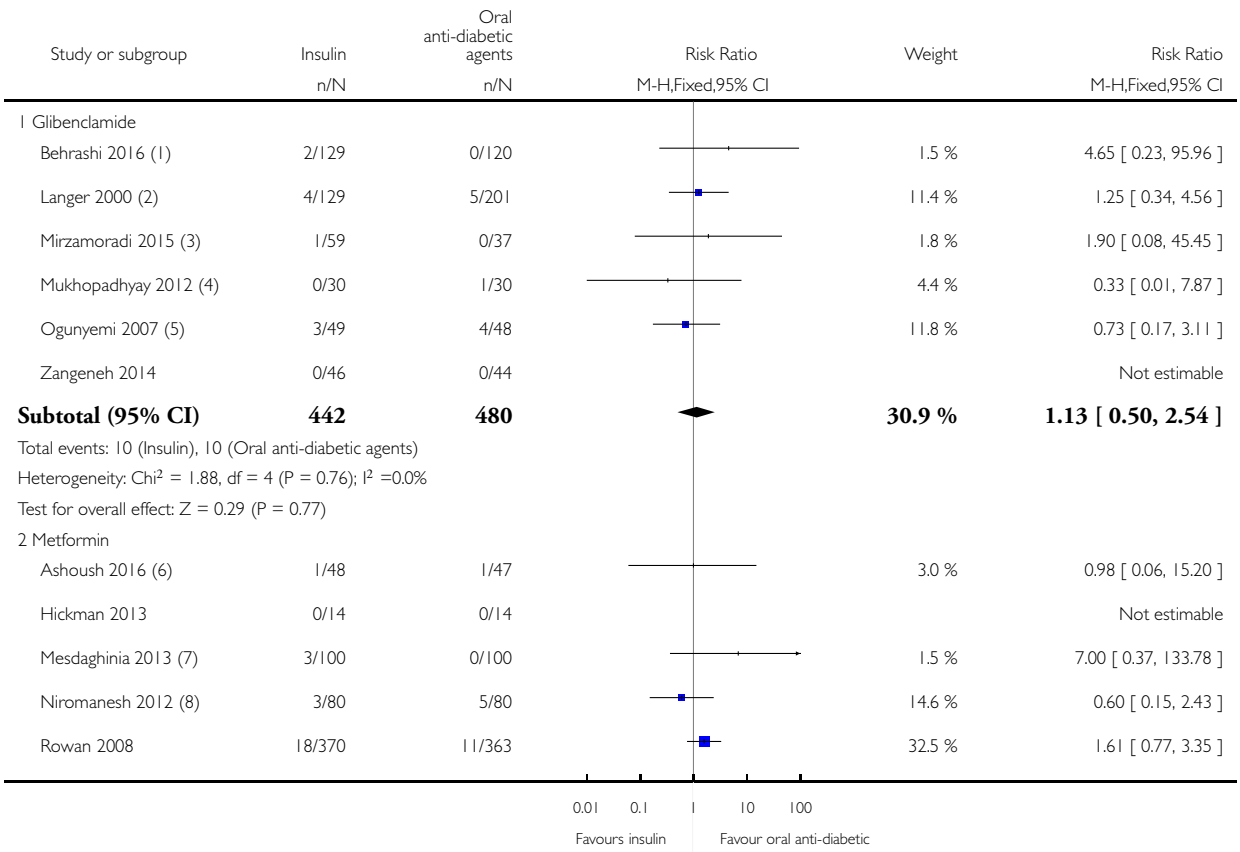
(5) No details

Analysis 1.29. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 29 Congenital abnormality.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 29 Congenital abnormality



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Study or subgroup	Insulin n/N	Oral anti-diabetic agents n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Saleh 2016	2/70	1/67		3.0 %	1.91 [0.18, 20.62]
Tertti 2013	3/110	3/111		8.7 %	1.01 [0.21, 4.89]
Subtotal (95% CI)	**792**	**782**		**63.2 %**	**1.40 [0.81, 2.41]**
Total events: 30 (Insulin), 21 (Oral anti-diabetic agents)					
Heterogeneity: Chi^2 = 2.99, df = 5 (P = 0.70); I^2 =0.0%					
Test for overall effect: Z = 1.22 (P = 0.22)					
3 Acarbose					
De Veciana 2002	0/46	0/45			Not estimable
Subtotal (95% CI)	**46**	**45**			**Not estimable**
Total events: 0 (Insulin), 0 (Oral anti-diabetic agents)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
4 Combined metformin/glibenclamide					
Mohamed 2014	4/42	2/42		5.8 %	2.00 [0.39, 10.34]
Subtotal (95% CI)	**42**	**42**		**5.8 %**	**2.00 [0.39, 10.34]**
Total events: 4 (Insulin), 2 (Oral anti-diabetic agents)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.83 (P = 0.41)					
Total (95% CI)	**1322**	**1349**		**100.0 %**	**1.35 [0.88, 2.08]**
Total events: 44 (Insulin), 33 (Oral anti-diabetic agents)					
Heterogeneity: Chi^2 = 5.33, df = 11 (P = 0.91); I^2 =0.0%					
Test for overall effect: Z = 1.36 (P = 0.17)					
Test for subgroup differences: Chi^2 = 0.43, df = 2 (P = 0.81), I^2 =0.0%					

(1) 1 heart disease , 1 polydactyl

(2) No details

(3) Limb anomaly

(4) Spina bifida occulta.

(5) No details

(6) 1 ventricular septal defect in insulin group; 1 unilateral cleft lip in metformin group

(7) No details

(8) No details

Analysis 1.30. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 30 Five minute Apgar less than seven.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 30 Five minute Apgar less than seven

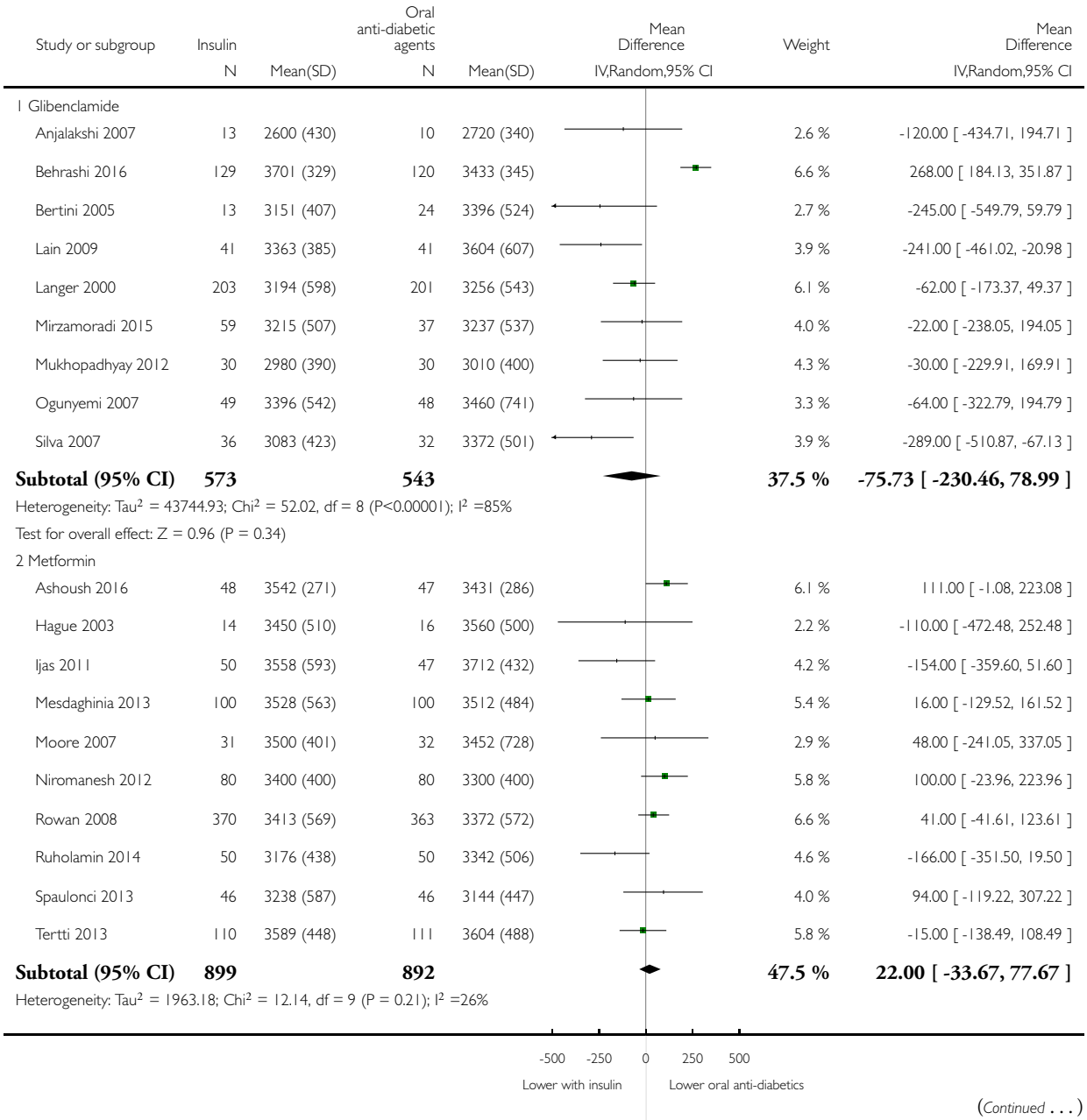
Study or subgroup	Insulin n/N	Oral anti-diabetic agents n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Metformin					
Mesdaghinia 2013	0/100	0/100			Not estimable
Rowan 2008	1/370	3/363		74.8 %	0.33 [0.03, 3.13]
Ruholamin 2014	0/50	0/50			Not estimable
Saleh 2016	1/70	1/67		25.2 %	0.96 [0.06, 14.99]
Subtotal (95% CI)	**590**	**580**		**100.0 %**	**0.49 [0.09, 2.64]**
Total events: 2 (Insulin), 4 (Oral anti-diabetic agents)					
Heterogeneity: Chi^2 = 0.35, df = 1 (P = 0.55); I^2 =0.0%					
Test for overall effect: Z = 0.84 (P = 0.40)					
Test for subgroup differences: Not applicable					

Analysis 1.31. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 31 Birthweight (g).

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 31 Birthweight (g)



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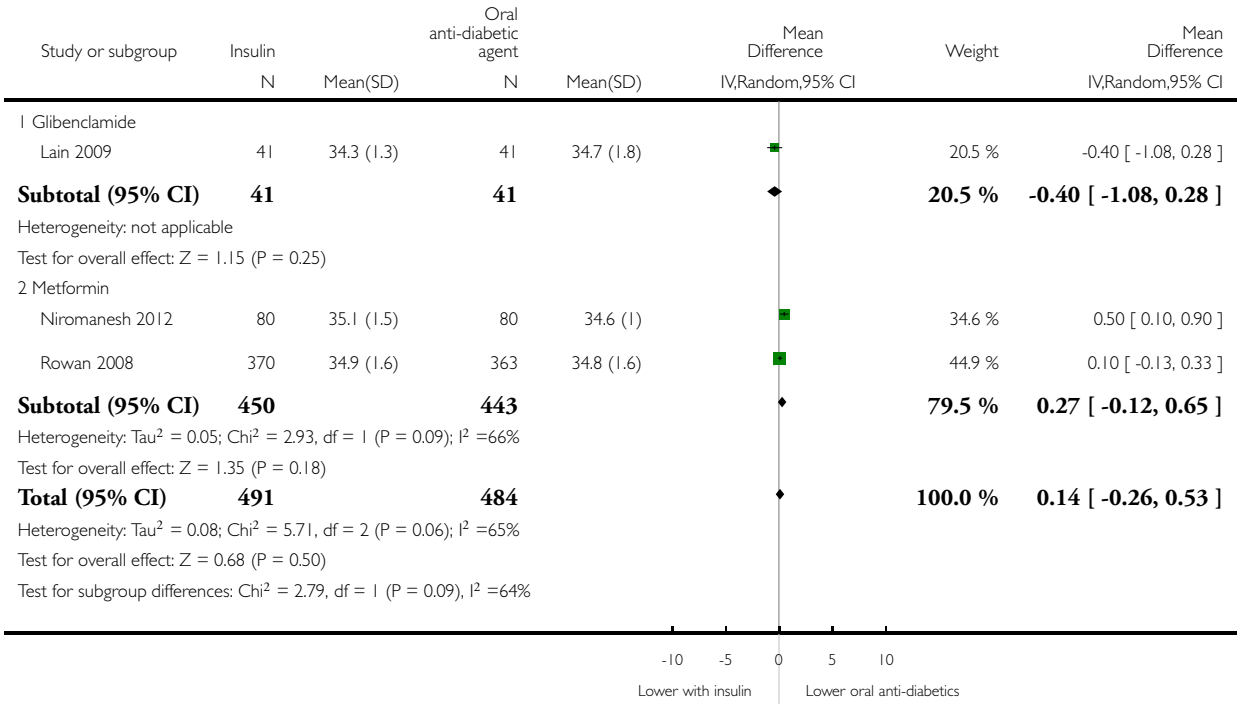
Study or subgroup	Insulin N	Mean(SD)	Oral anti-diabetic agents N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Test for overall effect: Z = 0.77 (P = 0.44)							
3 Acarbose							
Bertini 2005	14	3151 (407)	19	3243 (401)		3.1 %	-92.00 [-371.22, 187.22]
De Veciana 2002	46	3262 (501)	45	3169 (554)		4.0 %	93.00 [-124.17, 310.17]
Subtotal (95% CI)	**60**		**64**			**7.0 %**	**22.17 [-154.08, 198.42]**
Heterogeneity: Tau^2 = 826.41; Chi^2 = 1.05, df = 1 (P = 0.31); I^2 =5%							
Test for overall effect: Z = 0.25 (P = 0.81)							
4 Combined metformin-glyburide							
Ardilouze 2014	33	3227 (570)	35	3360 (389)		3.7 %	-133.00 [-366.30, 100.30]
Mohamed 2014	42	3527 (489)	42	3507 (463)		4.2 %	20.00 [-183.66, 223.66]
Subtotal (95% CI)	**75**		**77**			**7.9 %**	**-46.17 [-199.60, 107.26]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.94, df = 1 (P = 0.33); I^2 =0.0%							
Test for overall effect: Z = 0.59 (P = 0.56)							
Total (95% CI)	**1607**		**1576**			**100.0 %**	**-20.14 [-83.58, 43.29]**
Heterogeneity: Tau^2 = 14034.88; Chi^2 = 67.47, df = 22 (P<0.00001); I^2 =67%							
Test for overall effect: Z = 0.62 (P = 0.53)							
Test for subgroup differences: Chi^2 = 1.87, df = 3 (P = 0.60), I^2 =0.0%							

Analysis 1.32. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 32 Head circumference (cm) at birth.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 32 Head circumference (cm) at birth



Analysis 1.33. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 33 Length (cm) at birth.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 33 Length (cm) at birth

Study or subgroup	Insulin		Oral anti-diabetic agents		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
1 Glibenclamide							
Lain 2009	41	50.7 (2.2)	41	51.3 (2.6)		21.0 %	-0.60 [-1.64, 0.44]
Subtotal (95% CI)	**41**		**41**			**21.0 %**	**-0.60 [-1.64, 0.44]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.13 (P = 0.26)							
2 Metformin							
Niromanesh 2012	80	51.1 (2.3)	80	50.4 (2)		33.2 %	0.70 [0.03, 1.37]
Rowan 2008	370	50.3 (2.4)	363	50.3 (2.8)		45.9 %	0.0 [-0.38, 0.38]
Subtotal (95% CI)	**450**		**443**			**79.0 %**	**0.29 [-0.38, 0.97]**
Heterogeneity: $Tau^2 = 0.17$; $Chi^2 = 3.20$, df = 1 (P = 0.07); $I^2 = 69\%$							
Test for overall effect: Z = 0.85 (P = 0.40)							
Total (95% CI)	**491**		**484**			**100.0 %**	**0.11 [-0.50, 0.71]**
Heterogeneity: $Tau^2 = 0.17$; $Chi^2 = 5.10$, df = 2 (P = 0.08); $I^2 = 61\%$							
Test for overall effect: Z = 0.35 (P = 0.73)							
Test for subgroup differences: $Chi^2 = 1.99$, df = 1 (P = 0.16), $I^2 = 50\%$							

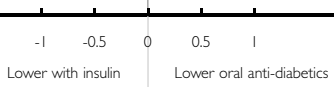
Analysis 1.34. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 34 Ponderal index at birth.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 34 Ponderal index at birth

Study or subgroup	Insulin N	Mean(SD)	Oral anti-diabetic agents N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Glibenclamide							
Lain 2009	41	2.59 (0.37)	41	2.66 (0.33)		40.5 %	-0.07 [-0.22, 0.08]
Subtotal (95% CI)	**41**		**41**			**40.5 %**	**-0.07 [-0.22, 0.08]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.90 (P = 0.37)							
2 Metformin							
Rowan 2008	370	2.7 (0.3)	363	2.6 (0.3)		59.5 %	0.10 [0.06, 0.14]
Subtotal (95% CI)	**370**		**363**			**59.5 %**	**0.10 [0.06, 0.14]**
Heterogeneity: not applicable							
Test for overall effect: Z = 4.51 (P < 0.00001)							
Total (95% CI)	**411**		**404**			**100.0 %**	**0.03 [-0.13, 0.19]**
Heterogeneity: Tau^2 = 0.01; Chi^2 = 4.46, df = 1 (P = 0.03); I^2 =78%							
Test for overall effect: Z = 0.37 (P = 0.71)							
Test for subgroup differences: Chi^2 = 4.46, df = 1 (P = 0.03), I^2 =78%							



Analysis 1.35. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 35 Adiposity at birth (Triceps skinfold (mm)).

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 35 Adiposity at birth (Triceps skinfold (mm))

Study or subgroup	Insulin		Oral anti-diabetic agents		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
1 Glibenclamide							
Lain 2009	41	3.9 (0.7)	41	3.9 (0.9)		25.7 %	0.0 [-0.35, 0.35]
Subtotal (95% CI)	**41**		**41**			**25.7 %**	**0.0 [-0.35, 0.35]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
2 Metformin							
Rowan 2008	370	5.1 (1.2)	363	5.2 (1.6)		74.3 %	-0.10 [-0.31, 0.11]
Subtotal (95% CI)	**370**		**363**			**74.3 %**	**-0.10 [-0.31, 0.11]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.96 (P = 0.34)							
Total (95% CI)	**411**		**404**			**100.0 %**	**-0.07 [-0.25, 0.10]**
Heterogeneity: Chi^2 = 0.23, df = 1 (P = 0.63); I^2 =0.0%							
Test for overall effect: Z = 0.82 (P = 0.41)							
Test for subgroup differences: Chi^2 = 0.23, df = 1 (P = 0.63), I^2 =0.0%							

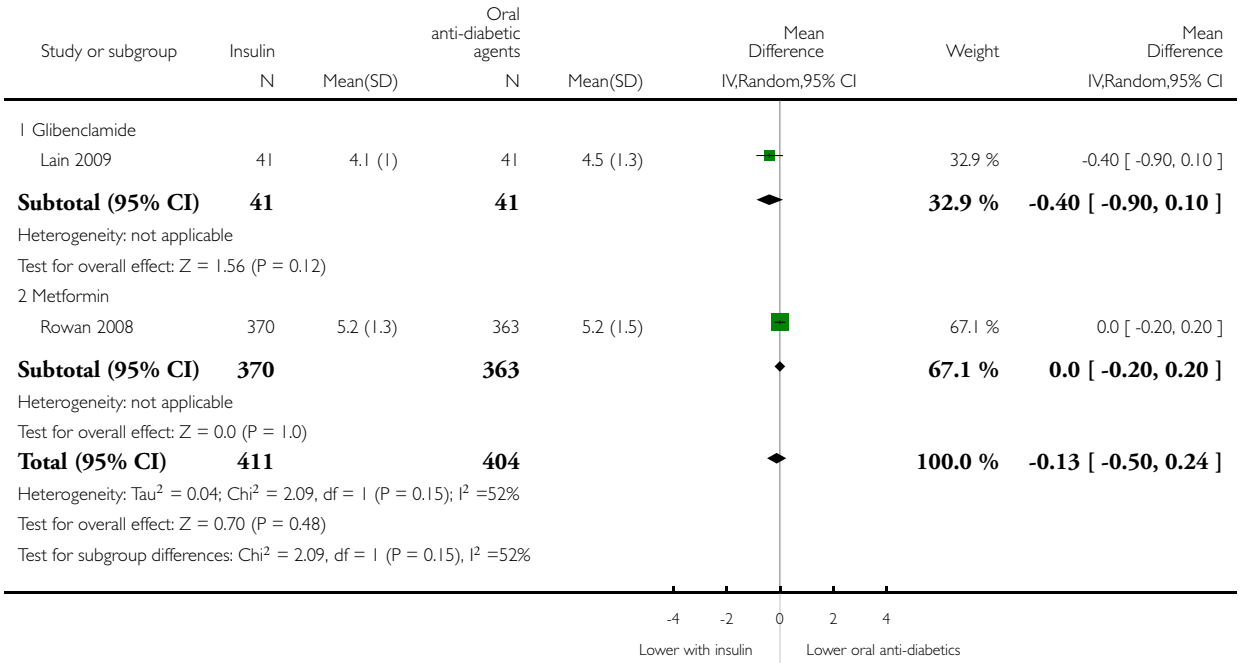
Analysis 1.36. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 36 Adiposity at birth (Subscapular skinfold (mm)).

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 36 Adiposity at birth (Subscapular skinfold (mm))

Study or subgroup	Insulin		Oral anti-diabetic agents		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
1 Glibenclamide							
Lain 2009	41	4.1 (1)	41	4.5 (1.3)		32.9 %	-0.40 [-0.90, 0.10]
Subtotal (95% CI)	**41**		**41**			**32.9 %**	**-0.40 [-0.90, 0.10]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.56 (P = 0.12)							
2 Metformin							
Rowan 2008	370	5.2 (1.3)	363	5.2 (1.5)		67.1 %	0.0 [-0.20, 0.20]
Subtotal (95% CI)	**370**		**363**			**67.1 %**	**0.0 [-0.20, 0.20]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
Total (95% CI)	**411**		**404**			**100.0 %**	**-0.13 [-0.50, 0.24]**
Heterogeneity: Tau^2 = 0.04; Chi^2 = 2.09, df = 1 (P = 0.15); I^2 =52%							
Test for overall effect: Z = 0.70 (P = 0.48)							
Test for subgroup differences: Chi^2 = 2.09, df = 1 (P = 0.15), I^2 =52%							

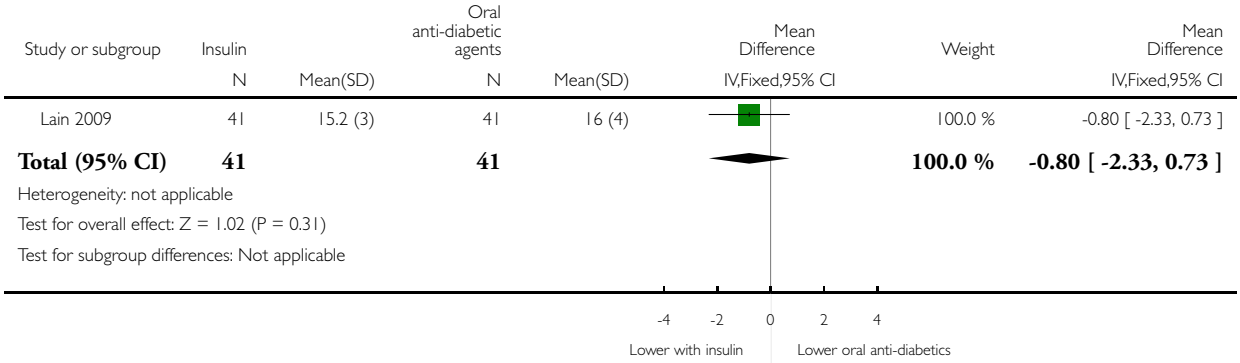


Analysis 1.37. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 37 Adiposity at birth (Skin fold sum (mm)).

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 37 Adiposity at birth (Skin fold sum (mm))

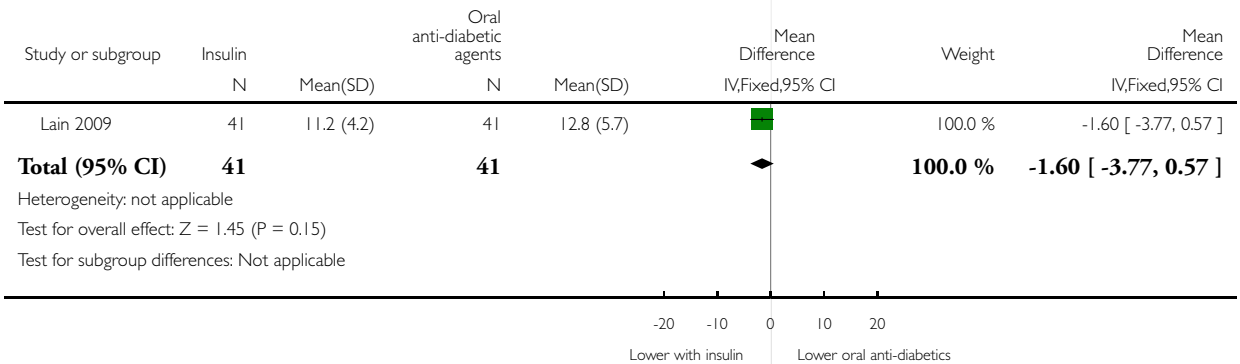


Analysis 1.38. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 38 Adiposity at birth (Percentage fat mass).

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 38 Adiposity at birth (Percentage fat mass)



Analysis 1.39. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 39 Neonatal hypoglycaemia.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 39 Neonatal hypoglycaemia

Study or subgroup	Insulin n/N	Oral anti-diabetic agents n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Glibenclamide					
Behrashi 2016	7/129	2/120		2.7 %	3.26 [0.69, 15.37]
Bertini 2005	1/13	8/24		1.9 %	0.23 [0.03, 1.65]
Lain 2009	0/41	4/41		0.9 %	0.11 [0.01, 2.00]
Langer 2000	12/203	18/201		7.1 %	0.66 [0.33, 1.33]
Mirzamoradi 2015	0/59	0/37			Not estimable
Mukhopadhyay 2012	3/30	4/30		3.2 %	0.75 [0.18, 3.07]
Ogunyemi 2007	6/49	12/48		5.7 %	0.49 [0.20, 1.20]
Pavithra 2016	6/50	4/50		3.9 %	1.50 [0.45, 4.99]
Silva 2007	0/36	3/32		0.9 %	0.13 [0.01, 2.38]
Zangeneh 2014	1/46	1/44		1.0 %	0.96 [0.06, 14.83]
Subtotal (95% CI)	**656**	**627**		**27.3 %**	**0.70 [0.41, 1.19]**
Total events: 36 (Insulin), 56 (Oral anti-diabetic agents)					
Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 10.13$, df = 8 (P = 0.26); $I^2 = 21\%$					
Test for overall effect: Z = 1.33 (P = 0.18)					
2 Metformin					
Ashoush 2016	7/48	6/47		4.9 %	1.14 [0.41, 3.15]
Hickman 2013 (1)	0/13	2/13		0.9 %	0.20 [0.01, 3.80]
Ijas 2011 (2)	7/50	4/47		4.1 %	1.65 [0.51, 5.26]
Majeed 2015 (3)	64/250	23/250		9.5 %	2.78 [1.79, 4.33]
Mesdaghinia 2013 (4)	15/100	10/100		6.7 %	1.50 [0.71, 3.18]
Moore 2007	2/31	0/32		0.9 %	5.16 [0.26, 103.27]
Niromanesh 2012	2/80	3/80		2.2 %	0.67 [0.11, 3.88]
Rowan 2008	69/370	55/363		10.6 %	1.23 [0.89, 1.70]

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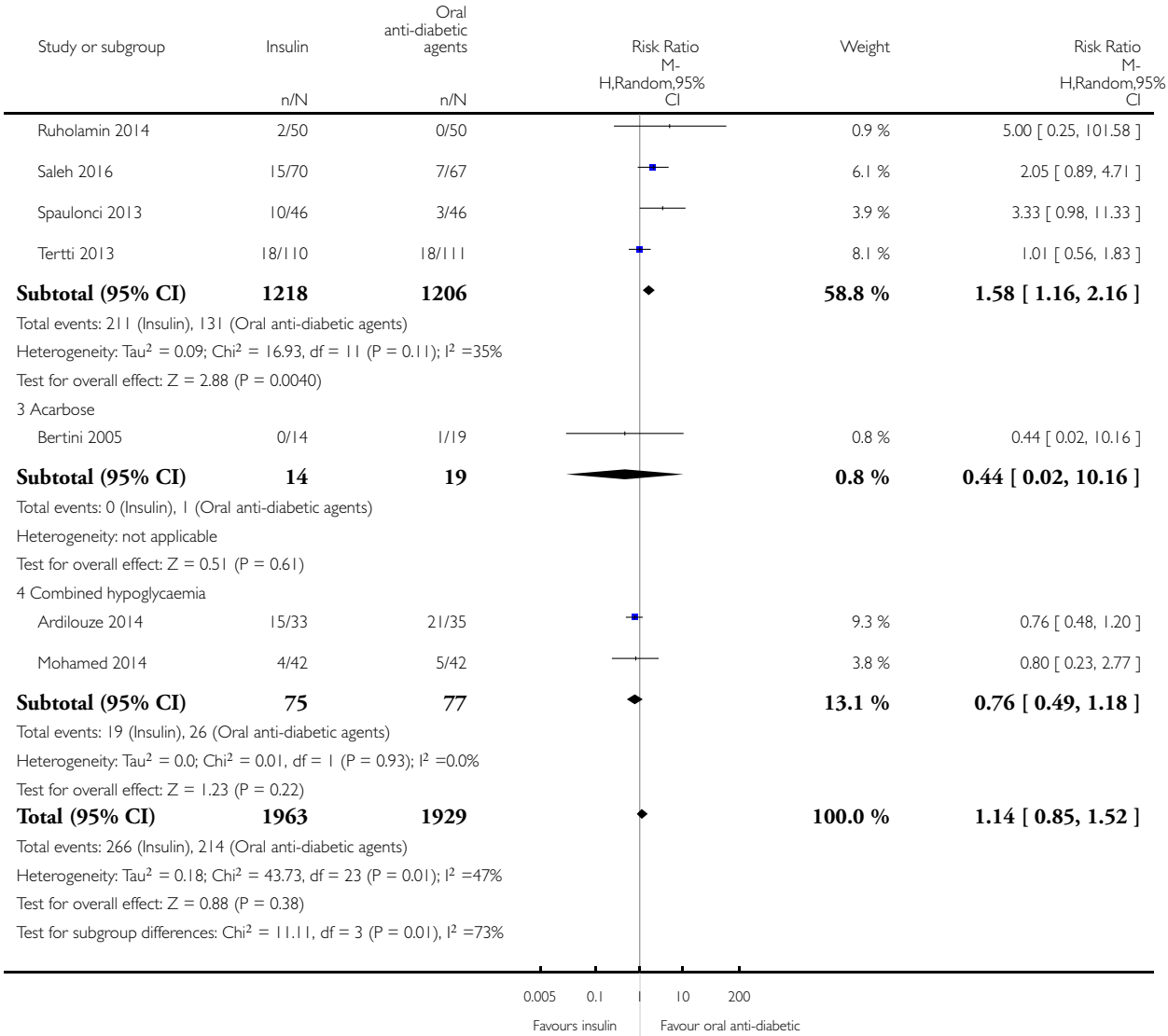


(1) </= 40 mg/dL

(2) Requiring intravenous glucose

(3) < 2.6 mmol/L

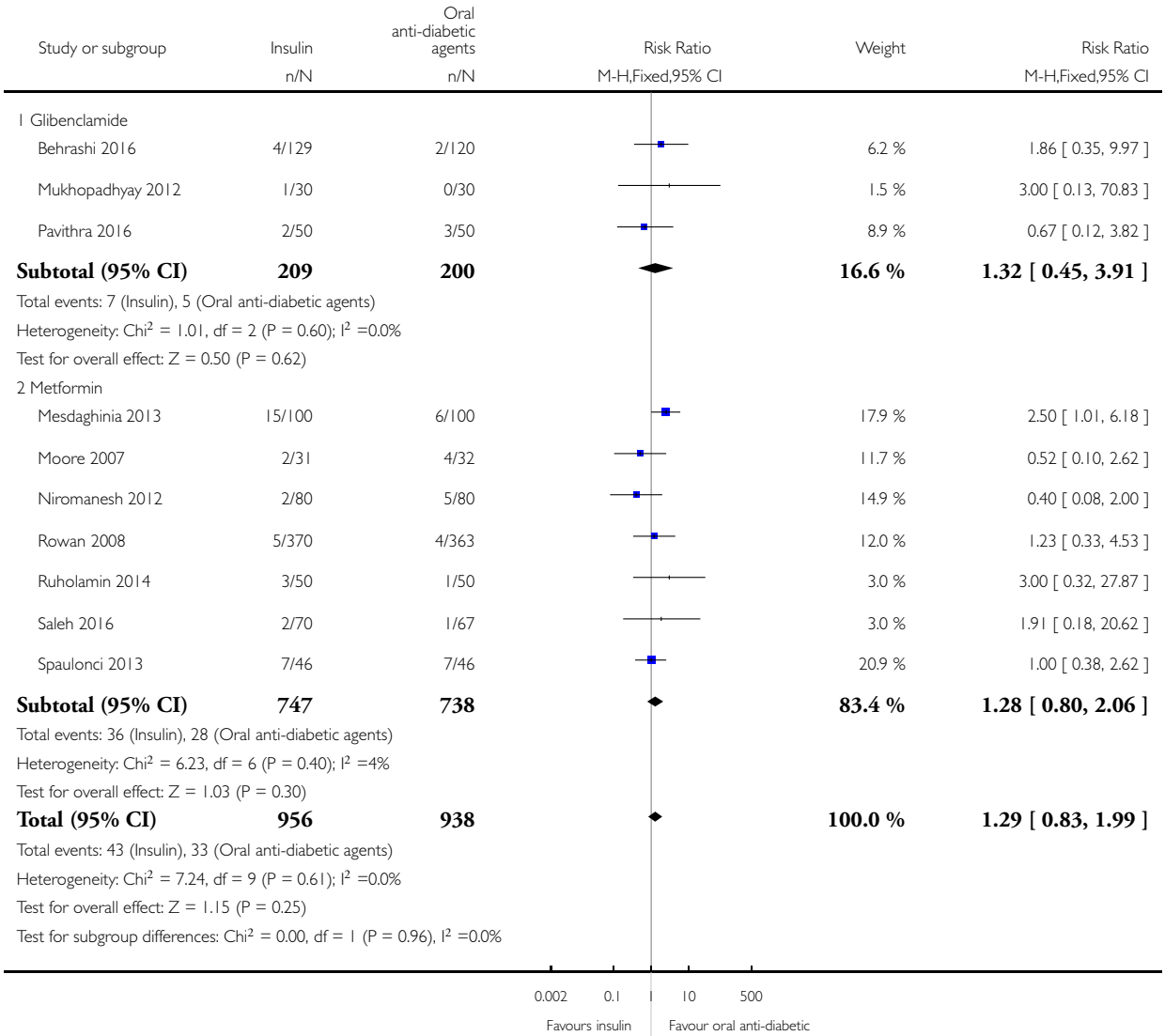
(4) Not defined

Analysis 1.40. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 40 Respiratory distress syndrome.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 40 Respiratory distress syndrome

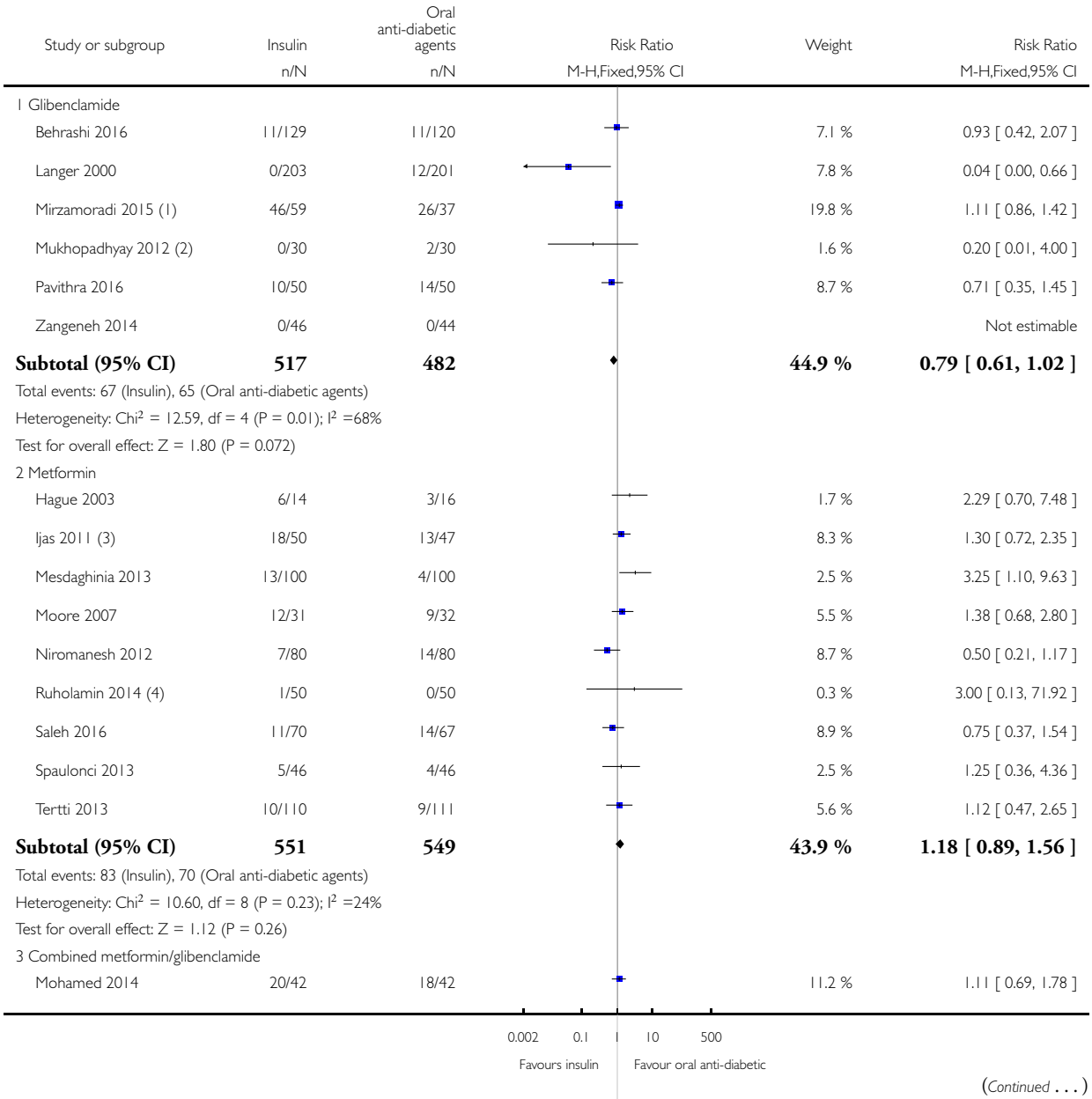


Analysis 1.41. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 41 Neonatal jaundice (hyperbilirubinaemia).

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 41 Neonatal jaundice (hyperbilirubinaemia)



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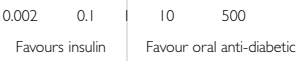
Study or subgroup	Insulin n/N	Oral anti-diabetic agents n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**42**	**42**		**11.2 %**	**1.11 [0.69, 1.78]**
Total events: 20 (Insulin), 18 (Oral anti-diabetic agents)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.44 (P = 0.66)					
Total (95% CI)	**1110**	**1073**		**100.0 %**	**0.99 [0.83, 1.19]**
Total events: 170 (Insulin), 153 (Oral anti-diabetic agents)					
Heterogeneity: Chi^2 = 19.74, df = 14 (P = 0.14); I^2 =29%					
Test for overall effect: Z = 0.06 (P = 0.95)					
Test for subgroup differences: Chi^2 = 4.54, df = 2 (P = 0.10), I^2 =56%					



(1) Infants requiring phototherapy

(2) Requiring phototherapy.

(3) Requiring phototherapy

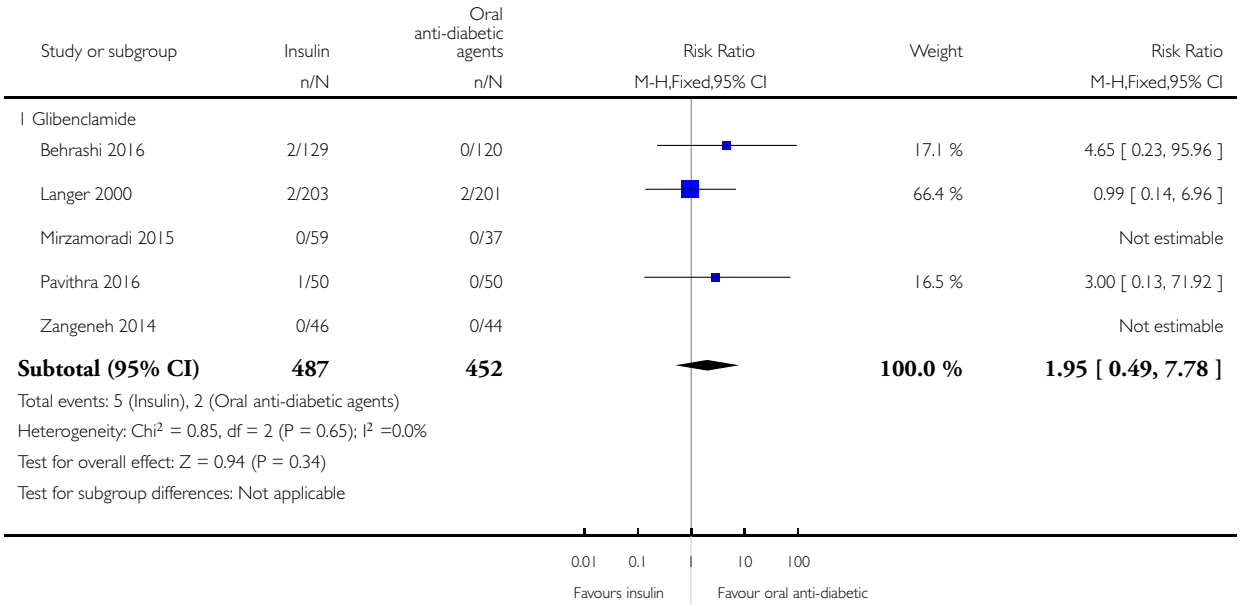
(4) Requiring phototherapy

Analysis 1.42. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 42 Hypocalcaemia.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 42 Hypocalcaemia



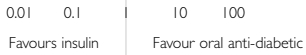
Analysis 1.43. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 43 Polycythaemia.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 43 Polycythaemia

Study or subgroup	Insulin n/N	Oral anti-diabetic agents n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Glibenclamide					
Langer 2000	6/203	4/201		72.4 %	1.49 [0.43, 5.18]
Mirzamoradi 2015	0/59	0/37			Not estimable
Zangeneh 2014	0/46	1/44		27.6 %	0.32 [0.01, 7.63]
Subtotal (95% CI)	**308**	**282**		**100.0 %**	**1.16 [0.38, 3.57]**
Total events: 6 (Insulin), 5 (Oral anti-diabetic agents)					
Heterogeneity: Chi^2 = 0.78, df = 1 (P = 0.38); I^2 =0.0%					
Test for overall effect: Z = 0.26 (P = 0.79)					
Test for subgroup differences: Not applicable					



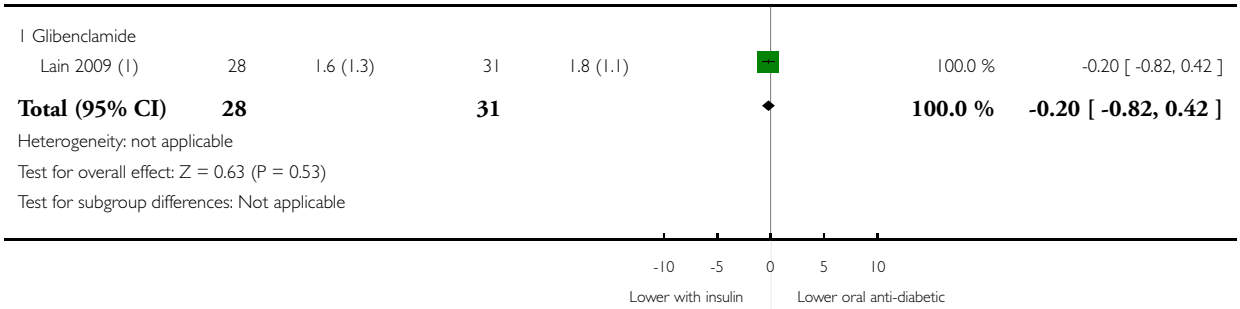
Analysis 1.44. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 44 Relevant biomarker changes associated with the intervention (Cord blood C-peptide).

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 44 Relevant biomarker changes associated with the intervention (Cord blood C-peptide)

Study or subgroup	Insulin		Oral anti-diabetic agents		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
1 Glibenclamide							
Lain 2009 (1)	28	1.6 (1.3)	31	1.8 (1.1)		100.0 %	-0.20 [-0.82, 0.42]
Total (95% CI)	**28**		**31**			**100.0 %**	**-0.20 [-0.82, 0.42]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.63 (P = 0.53)							
Test for subgroup differences: Not applicable							



(1) Glibenclamide

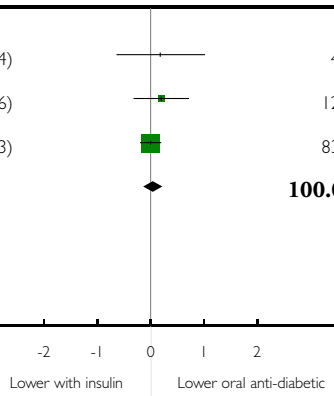
Analysis 1.45. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 45 Relevant biomarker changes associated with the intervention (Cord blood insulin).

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 45 Relevant biomarker changes associated with the intervention (Cord blood insulin)

Study or subgroup	Insulin		Oral anti-diabetic agents		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
1 Glibenclamide							
Anjalakshi 2007	13	5.5 (2.7)	10	4.72 (5.4)		4.6 %	0.18 [-0.64, 1.01]
Lain 2009	28	10.6 (15.6)	31	8.2 (7.6)		12.1 %	0.20 [-0.32, 0.71]
Langer 2000	203	15 (21)	201	15 (13)		83.3 %	0.0 [-0.20, 0.20]
Subtotal (95% CI)	**244**		**242**			**100.0 %**	**0.03 [-0.15, 0.21]**
Heterogeneity: Chi^2 = 0.63, df = 2 (P = 0.73); I^2 =0.0%							
Test for overall effect: Z = 0.35 (P = 0.72)							
Test for subgroup differences: Not applicable							



Analysis 1.46. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 46 Childhood weight (kg).

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 46 Childhood weight (kg)

Study or subgroup	Insulin N	Mean(SD)	Oral anti-diabetic agents N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 6 months							
Ijas 2011	48	7.93 (0.99)	45	8.28 (0.99)		100.0 %	-0.35 [-0.75, 0.05]
Subtotal (95% CI)	**48**		**45**			**100.0 %**	**-0.35 [-0.75, 0.05]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.70 (P = 0.088)							
2 12 months							
Ijas 2011	48	9.85 (1.26)	45	10.47 (1.49)		100.0 %	-0.62 [-1.18, -0.06]
Subtotal (95% CI)	**48**		**45**			**100.0 %**	**-0.62 [-1.18, -0.06]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.16 (P = 0.031)							
3 18 months to 2 years							
Ijas 2011	48	11.32 (1.45)	45	12.05 (1.87)		32.4 %	-0.73 [-1.41, -0.05]
Rowan 2008	164	14 (2.2)	154	14.3 (2.1)		67.6 %	-0.30 [-0.77, 0.17]
Subtotal (95% CI)	**212**		**199**			**100.0 %**	**-0.44 [-0.83, -0.05]**
Heterogeneity: Chi^2 = 1.03, df = 1 (P = 0.31); I^2 =3%							
Test for overall effect: Z = 2.21 (P = 0.027)							
Test for subgroup differences: Chi^2 = 0.59, df = 2 (P = 0.75), I^2 =0.0%							

Analysis 1.47. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 47 Childhood height (cm).

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 47 Childhood height (cm)

Study or subgroup	Insulin		Oral anti-diabetic agents		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
1 6 months							
Ijas 2011	48	67.4 (2.7)	45	68.1 (3.8)		100.0 %	-0.70 [-2.05, 0.65]
Subtotal (95% CI)	**48**		**45**			**100.0 %**	**-0.70 [-2.05, 0.65]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.02 (P = 0.31)							
2 12 months							
Ijas 2011	48	75.6 (3.1)	45	76.9 (3.3)		100.0 %	-1.30 [-2.60, 0.00]
Subtotal (95% CI)	**48**		**45**			**100.0 %**	**-1.30 [-2.60, 0.00]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.95 (P = 0.051)							
3 18 to 24 months							
Ijas 2011	48	82.2 (3.1)	45	83.9 (3.6)		47.6 %	-1.70 [-3.07, -0.33]
Rowan 2008	164	91 (4.8)	154	90.7 (4.9)		52.4 %	0.30 [-0.77, 1.37]
Subtotal (95% CI)	**212**		**199**			**100.0 %**	**-0.65 [-2.61, 1.31]**
Heterogeneity: Tau^2 = 1.61; Chi^2 = 5.10, df = 1 (P = 0.02); I^2 =80%							
Test for overall effect: Z = 0.65 (P = 0.51)							
Test for subgroup differences: Chi^2 = 0.50, df = 2 (P = 0.78), I^2 =0.0%							

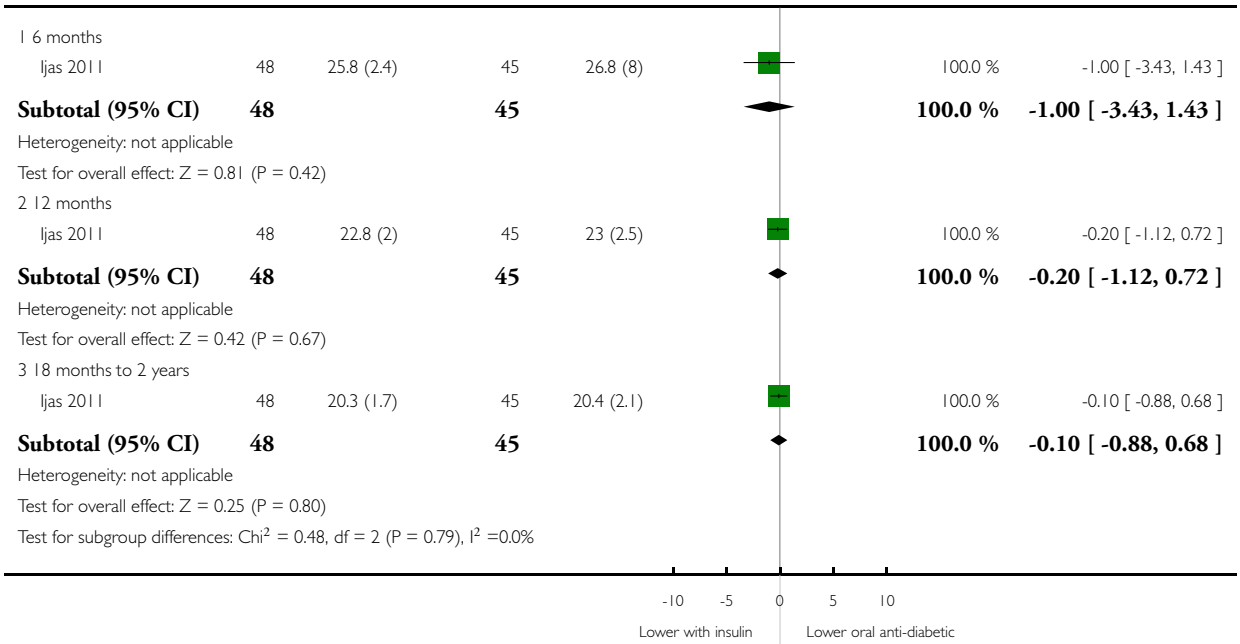
Analysis 1.48. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 48 Childhood adiposity (ponderal index (kg/m3)).

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 48 Childhood adiposity (ponderal index (kg/m^3))

Study or subgroup	Insulin N	Mean(SD)	Oral anti-diabetic agents N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 6 months							
Ijas 2011	48	25.8 (2.4)	45	26.8 (8)		100.0 %	-1.00 [-3.43, 1.43]
Subtotal (95% CI)	**48**		**45**			**100.0 %**	**-1.00 [-3.43, 1.43]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.81 (P = 0.42)							
2 12 months							
Ijas 2011	48	22.8 (2)	45	23 (2.5)		100.0 %	-0.20 [-1.12, 0.72]
Subtotal (95% CI)	**48**		**45**			**100.0 %**	**-0.20 [-1.12, 0.72]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.42 (P = 0.67)							
3 18 months to 2 years							
Ijas 2011	48	20.3 (1.7)	45	20.4 (2.1)		100.0 %	-0.10 [-0.88, 0.68]
Subtotal (95% CI)	**48**		**45**			**100.0 %**	**-0.10 [-0.88, 0.68]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.25 (P = 0.80)							
Test for subgroup differences: Chi^2 = 0.48, df = 2 (P = 0.79), I^2 =0.0%							



Analysis 1.49. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 49 Childhood adiposity (Total fat mass (%)).

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 49 Childhood adiposity (Total fat mass (%))

Study or subgroup	Insulin		Oral anti-diabetic agents		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
1 Metformin							
Rowan 2008	164	16.9 (4)	154	16.4 (4.9)		100.0 %	0.50 [-0.49, 1.49]
Subtotal (95% CI)	**164**		**154**			**100.0 %**	**0.50 [-0.49, 1.49]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.99 (P = 0.32)							
Test for subgroup differences: Not applicable							

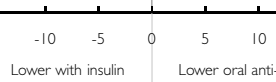
Analysis 1.50. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 50 Childhood blood pressure (2 years).

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 50 Childhood blood pressure (2 years)

Study or subgroup	Insulin N	Mean(SD)	Anti-diabetic N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Systolic BP							
Rowan 2008	87	89.86 (9.2)	83	92.1 (9.3)		100.0 %	-2.24 [-5.02, 0.54]
Subtotal (95% CI)	**87**		**83**			**100.0 %**	**-2.24 [-5.02, 0.54]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.58 (P = 0.11)							
2 Diastolic BP							
Rowan 2008	87	56.7 (77)	83	57.2 (7.1)		100.0 %	-0.50 [-16.75, 15.75]
Subtotal (95% CI)	**87**		**83**			**100.0 %**	**-0.50 [-16.75, 15.75]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.06 (P = 0.95)							
Test for subgroup differences: Chi^2 = 0.04, df = 1 (P = 0.84), I^2 =0.0%							



Analysis 1.51. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 51 Number of antenatal visits or admissions.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 51 Number of antenatal visits or admissions

Study or subgroup	Insulin		Oral anti-diabetic agents		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
1 Glibenclamide							
Langer 2000 (1)	203	12 (6)	201	11 (5)		100.0 %	1.00 [-0.08, 2.08]
Subtotal (95% CI)	**203**		**201**			**100.0 %**	**1.00 [-0.08, 2.08]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.82 (P = 0.069)							
Test for subgroup differences: Not applicable							

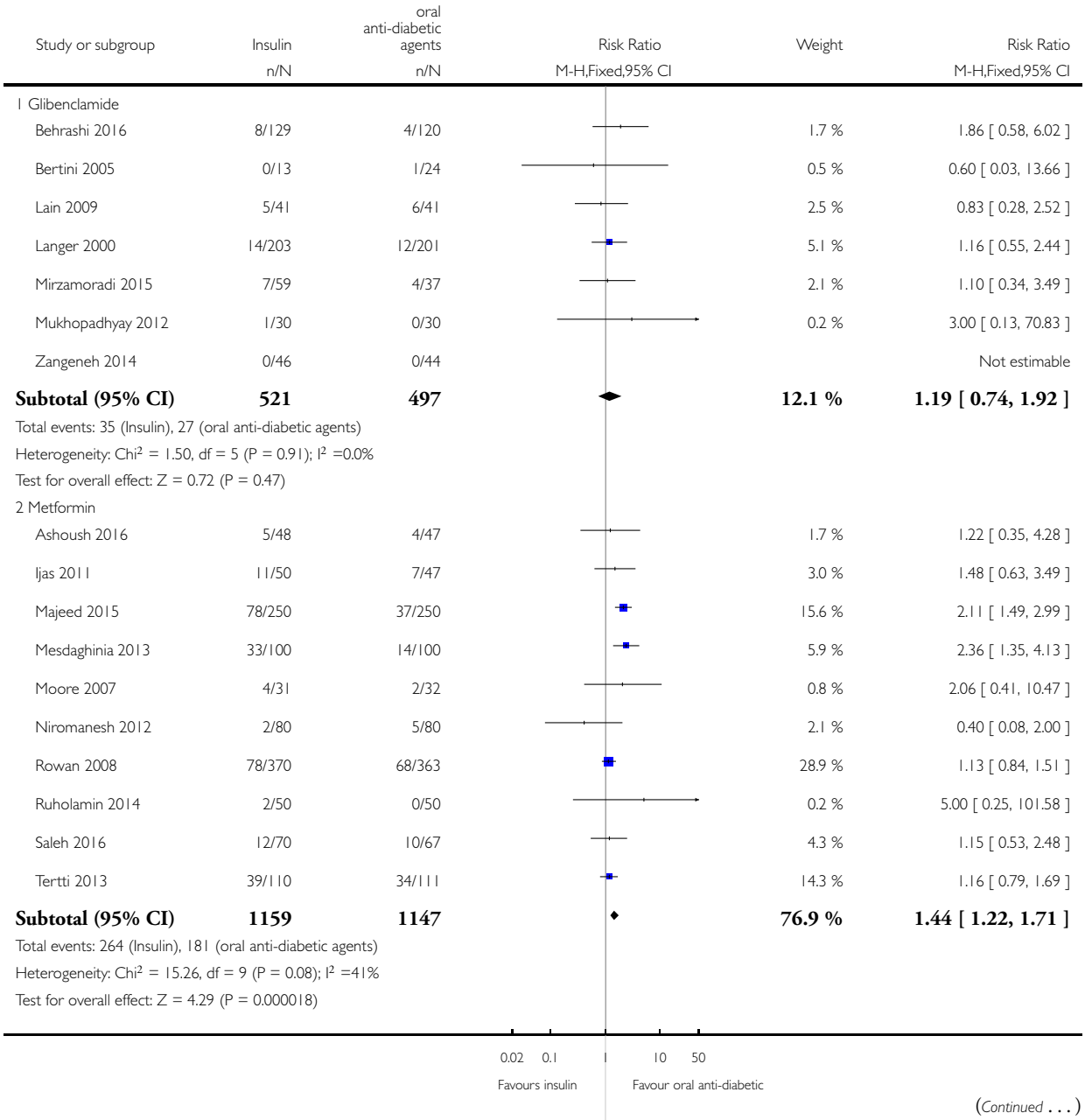
(1) Clinic visits

Analysis 1.52. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 52 Admission to neonatal care unit/nursery.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 52 Admission to neonatal care unit/nursery



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Study or subgroup	Insulin n/N	oral anti-diabetic agents n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
3 Acarbose					
Bertini 2005	0/14	0/19			Not estimable
Subtotal (95% CI)	**14**	**19**			**Not estimable**
Total events: 0 (Insulin), 0 (oral anti-diabetic agents)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
4 Combined metformin/glibenclamide					
Mohamed 2014	29/42	26/42		11.0 %	1.12 [0.82, 1.52]
Subtotal (95% CI)	**42**	**42**		**11.0 %**	**1.12 [0.82, 1.52]**
Total events: 29 (Insulin), 26 (oral anti-diabetic agents)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.69 (P = 0.49)					
Total (95% CI)	**1736**	**1705**		**100.0 %**	**1.38 [1.19, 1.59]**
Total events: 328 (Insulin), 234 (oral anti-diabetic agents)					
Heterogeneity: Chi^2 = 19.04, df = 16 (P = 0.27); I^2 =16%					
Test for overall effect: Z = 4.29 (P = 0.000018)					
Test for subgroup differences: Chi^2 = 2.31, df = 2 (P = 0.31), I^2 =14%					

Analysis 1.53. Comparison 1 Insulin versus oral anti-diabetic pharmacological therapy, Outcome 53 Duration of stay in neonatal intensive care unit or special care baby unit.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 1 Insulin versus oral anti-diabetic pharmacological therapy

Outcome: 53 Duration of stay in neonatal intensive care unit or special care baby unit

Study or subgroup	Insulin N	Mean(SD)	Oral anti-diabetic agents N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Mirzamoradi 2015	59	6.5 (4.3)	37	13.5 (16.44)		7.5 %	-7.00 [-12.41, -1.59]
Mohamed 2014	42	3.5 (2.7)	42	3.3 (1.8)		45.9 %	0.20 [-0.78, 1.18]
Tertti 2013	110	1.5 (4.5)	111	1 (2.2)		46.6 %	0.50 [-0.44, 1.44]
Total (95% CI)	**211**		**190**			**100.0 %**	**-0.20 [-1.79, 1.39]**

Heterogeneity: $Tau^2 = 1.19$; $Chi^2 = 7.18$, df = 2 (P = 0.03); $I^2 = 72\%$

Test for overall effect: Z = 0.25 (P = 0.81)

Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 One insulin versus another insulin, Outcome 1 Hypertensive disorders of pregnancy - Pre-eclampsia.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 2 One insulin versus another insulin

Outcome: 1 Hypertensive disorders of pregnancy - Pre-eclampsia

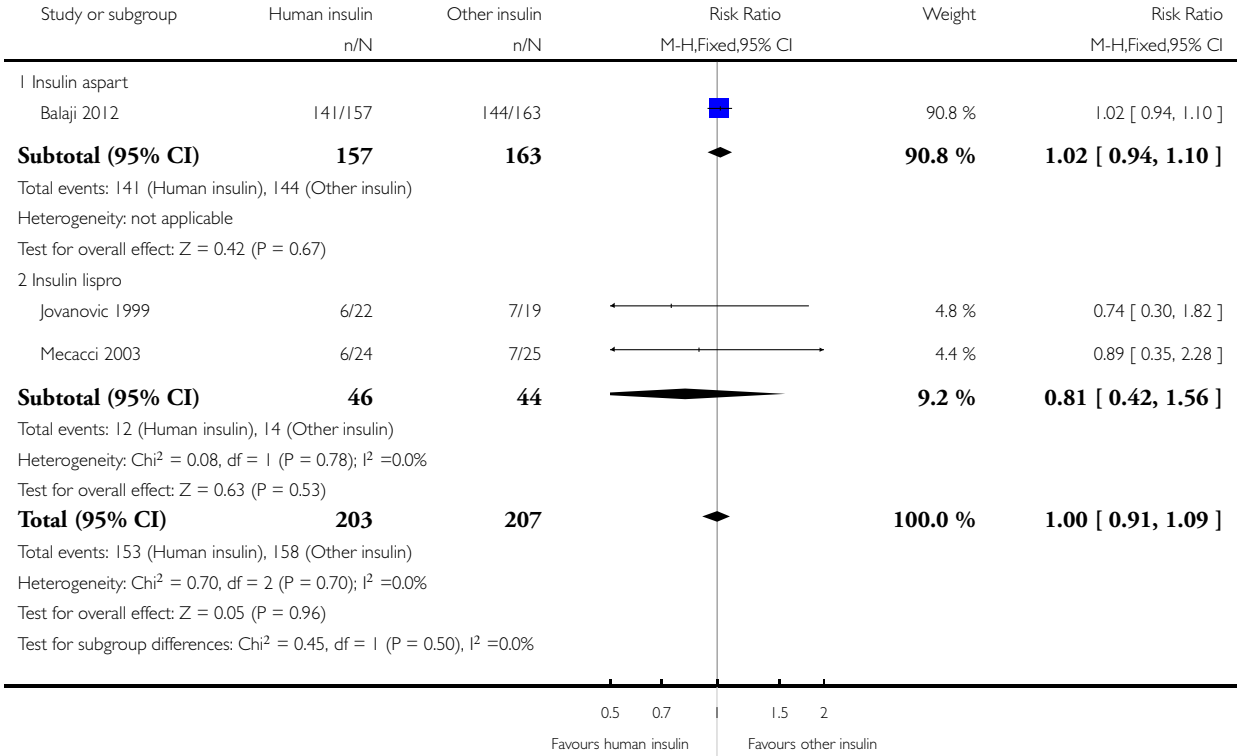
Study or subgroup	Human insulin n/N	Other insulin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Insulin aspart					
Balaji 2012	0/157	0/163			Not estimable
Total (95% CI)	**157**	**163**			**Not estimable**
Total events: 0 (Human insulin), 0 (Other insulin)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%					

Analysis 2.2. Comparison 2 One insulin versus another insulin, Outcome 2 Caesarean section.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 2 One insulin versus another insulin

Outcome: 2 Caesarean section

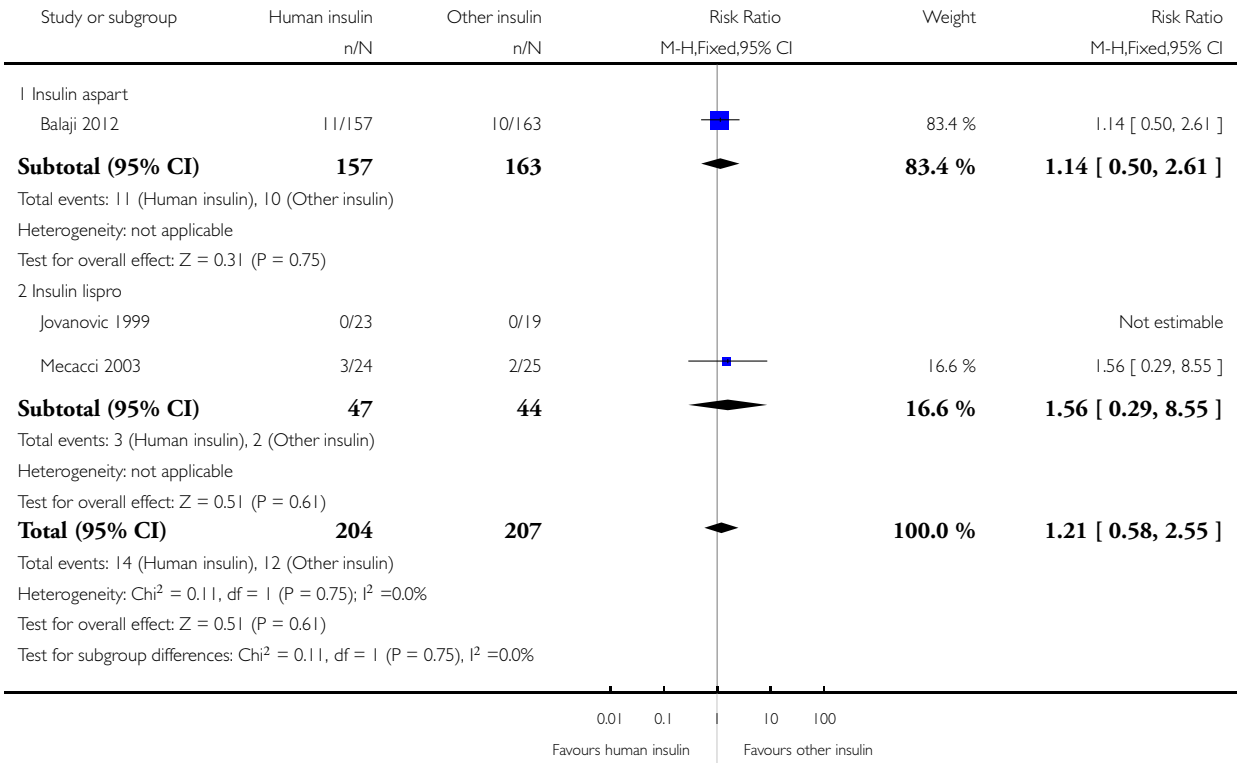


Analysis 2.3. Comparison 2 One insulin versus another insulin, Outcome 3 Large-for-gestational age.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 2 One insulin versus another insulin

Outcome: 3 Large-for-gestational age



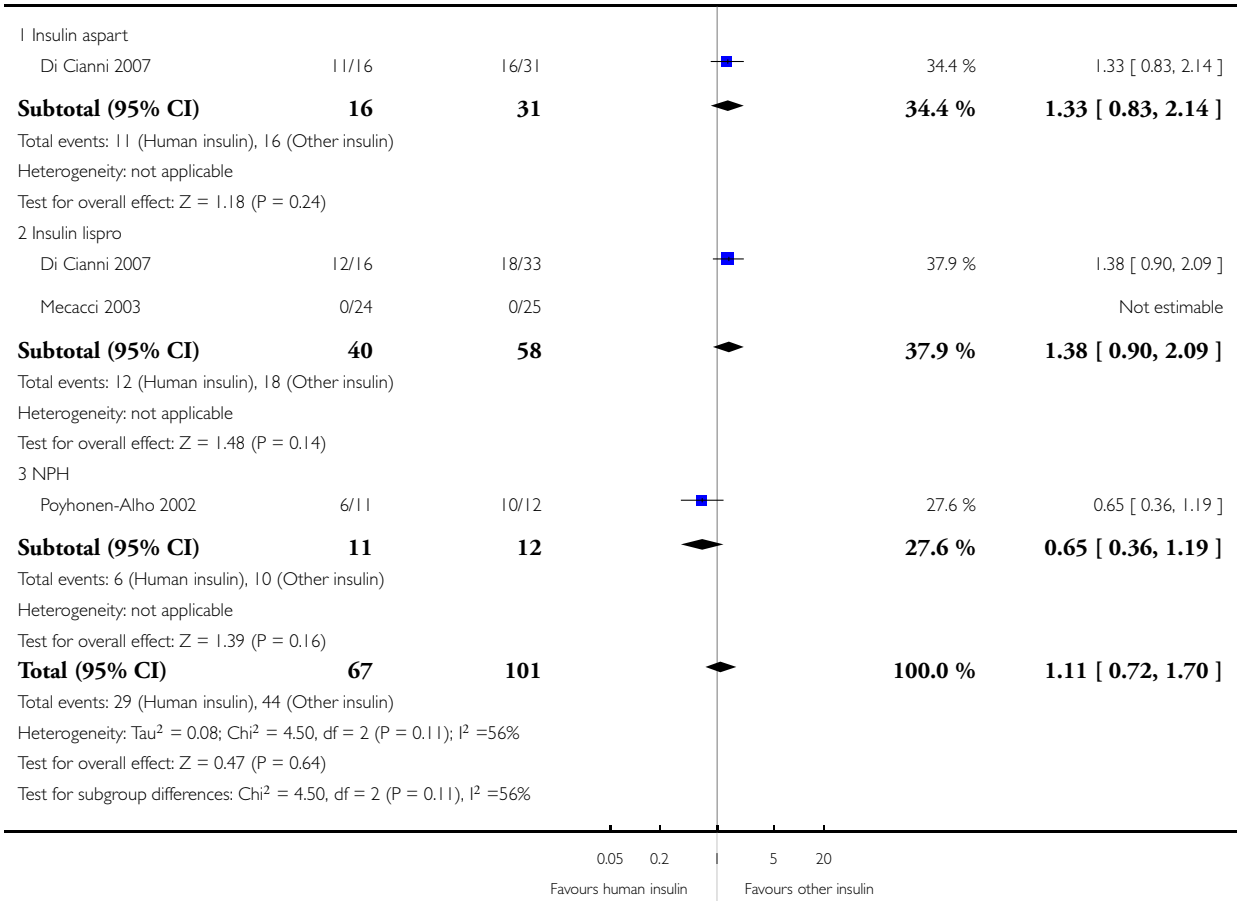
Analysis 2.4. Comparison 2 One insulin versus another insulin, Outcome 4 Use of additional pharmacotherapy.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 2 One insulin versus another insulin

Outcome: 4 Use of additional pharmacotherapy

Study or subgroup	Human insulin n/N	Other insulin n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Insulin aspart					
Di Cianni 2007	11/16	16/31		34.4 %	1.33 [0.83, 2.14]
Subtotal (95% CI)	**16**	**31**		**34.4 %**	**1.33 [0.83, 2.14]**
Total events: 11 (Human insulin), 16 (Other insulin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.18 (P = 0.24)					
2 Insulin lispro					
Di Cianni 2007	12/16	18/33		37.9 %	1.38 [0.90, 2.09]
Mecacci 2003	0/24	0/25			Not estimable
Subtotal (95% CI)	**40**	**58**		**37.9 %**	**1.38 [0.90, 2.09]**
Total events: 12 (Human insulin), 18 (Other insulin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.48 (P = 0.14)					
3 NPH					
Poyhonen-Alho 2002	6/11	10/12		27.6 %	0.65 [0.36, 1.19]
Subtotal (95% CI)	**11**	**12**		**27.6 %**	**0.65 [0.36, 1.19]**
Total events: 6 (Human insulin), 10 (Other insulin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.39 (P = 0.16)					
Total (95% CI)	**67**	**101**		**100.0 %**	**1.11 [0.72, 1.70]**
Total events: 29 (Human insulin), 44 (Other insulin)					
Heterogeneity: Tau^2 = 0.08; Chi^2 = 4.50, df = 2 (P = 0.11); I^2 =56%					
Test for overall effect: Z = 0.47 (P = 0.64)					
Test for subgroup differences: Chi^2 = 4.50, df = 2 (P = 0.11), I^2 =56%					

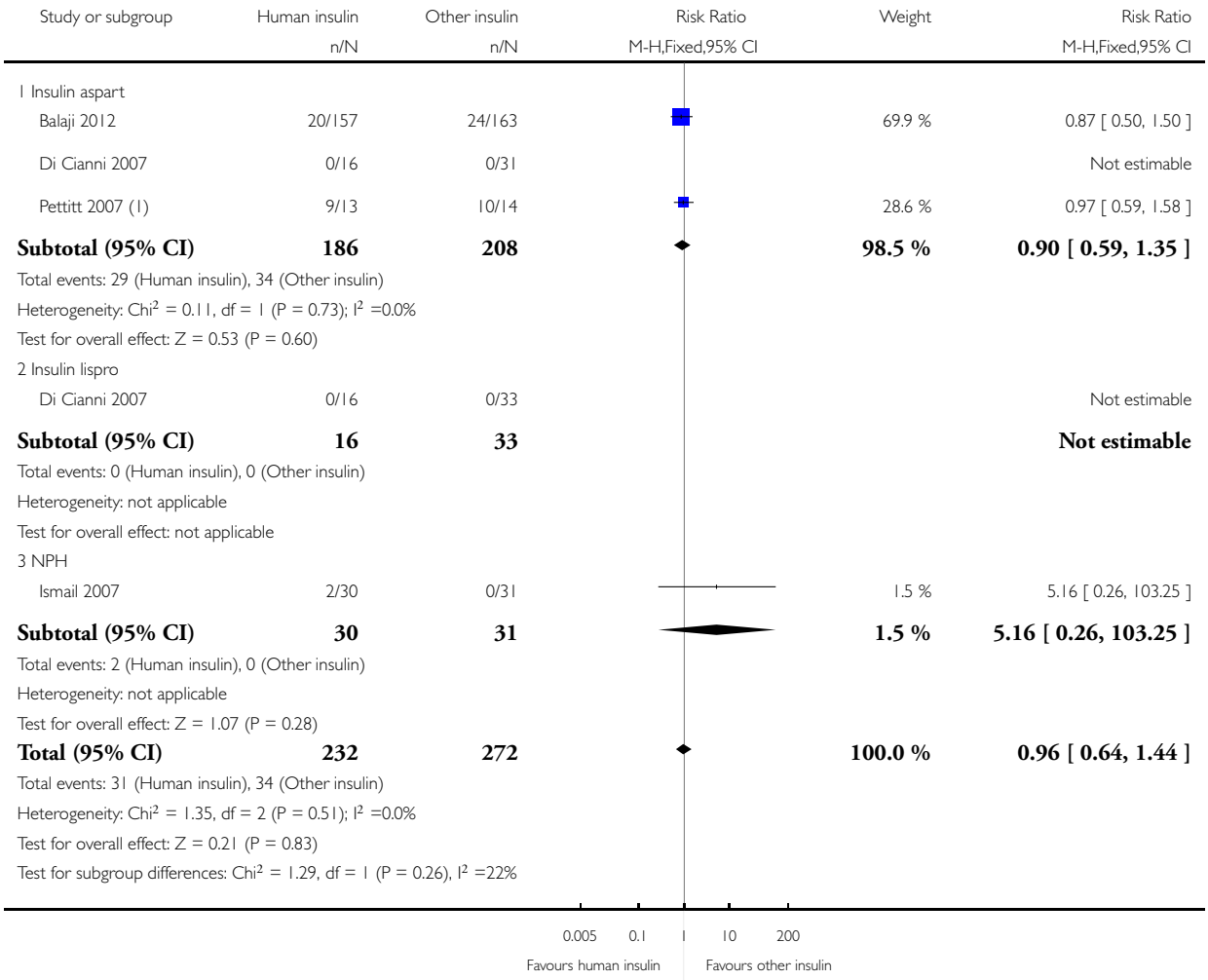


Analysis 2.5. Comparison 2 One insulin versus another insulin, Outcome 5 Maternal hypoglycaemia.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 2 One insulin versus another insulin

Outcome: 5 Maternal hypoglycaemia



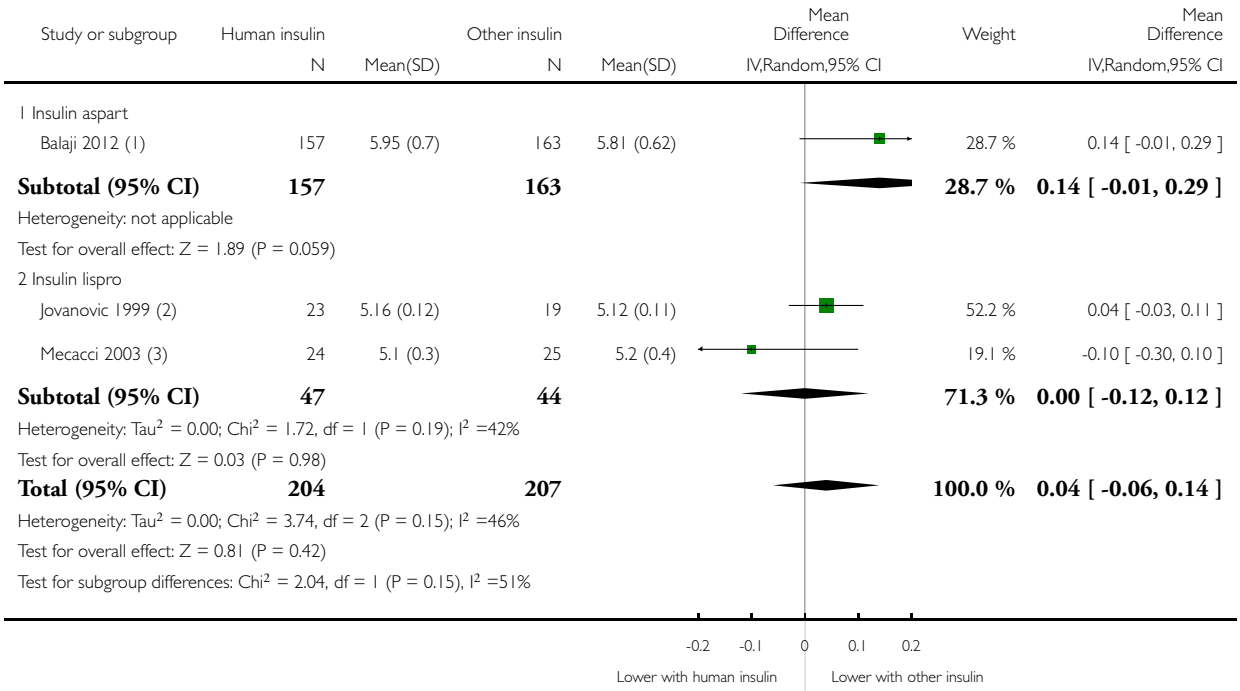
(1) Symptomatic events

Analysis 2.6. Comparison 2 One insulin versus another insulin, Outcome 6 Glycaemic control during/end of treatment (HbA1c) end of treatment.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 2 One insulin versus another insulin

Outcome: 6 Glycaemic control during/end of treatment (HbA1c) end of treatment



(1) end of treatment

(2) end of treatment

(3) end of treatment

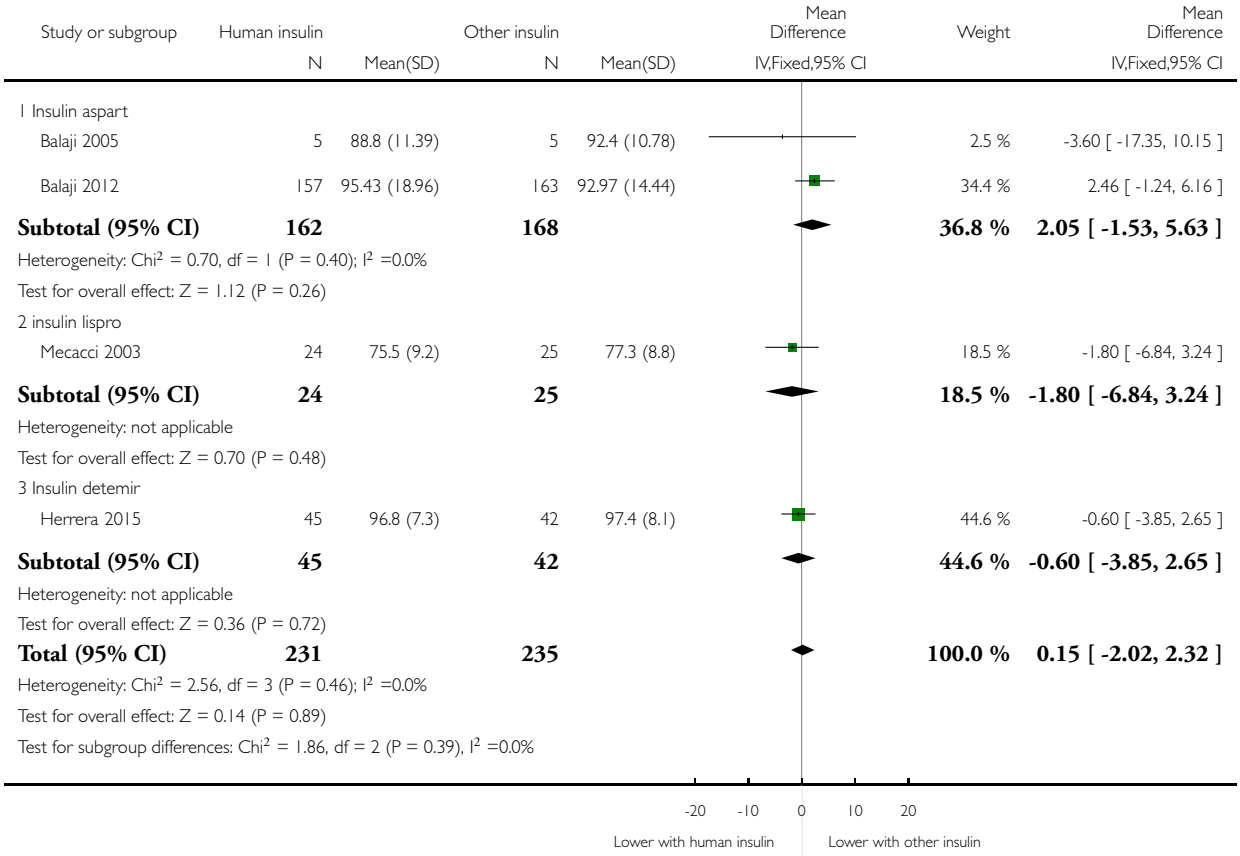
Analysis 2.7. Comparison 2 One insulin versus another insulin, Outcome 7 Glycaemic control during/end of treatment (Fasting plasma glucose).

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 2 One insulin versus another insulin

Outcome: 7 Glycaemic control during/end of treatment (Fasting plasma glucose)

Study or subgroup	Human insulin N	Mean(SD)	Other insulin N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Insulin aspart							
Balaji 2005	5	88.8 (11.39)	5	92.4 (10.78)		2.5 %	-3.60 [-17.35, 10.15]
Balaji 2012	157	95.43 (18.96)	163	92.97 (14.44)		34.4 %	2.46 [-1.24, 6.16]
Subtotal (95% CI)	**162**		**168**			**36.8 %**	**2.05 [-1.53, 5.63]**
Heterogeneity: Chi^2 = 0.70, df = 1 (P = 0.40); I^2 =0.0%							
Test for overall effect: Z = 1.12 (P = 0.26)							
2 insulin lispro							
Mecacci 2003	24	75.5 (9.2)	25	77.3 (8.8)		18.5 %	-1.80 [-6.84, 3.24]
Subtotal (95% CI)	**24**		**25**			**18.5 %**	**-1.80 [-6.84, 3.24]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.70 (P = 0.48)							
3 Insulin detemir							
Herrera 2015	45	96.8 (7.3)	42	97.4 (8.1)		44.6 %	-0.60 [-3.85, 2.65]
Subtotal (95% CI)	**45**		**42**			**44.6 %**	**-0.60 [-3.85, 2.65]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.36 (P = 0.72)							
Total (95% CI)	**231**		**235**			**100.0 %**	**0.15 [-2.02, 2.32]**
Heterogeneity: Chi^2 = 2.56, df = 3 (P = 0.46); I^2 =0.0%							
Test for overall effect: Z = 0.14 (P = 0.89)							
Test for subgroup differences: Chi^2 = 1.86, df = 2 (P = 0.39), I^2 =0.0%							

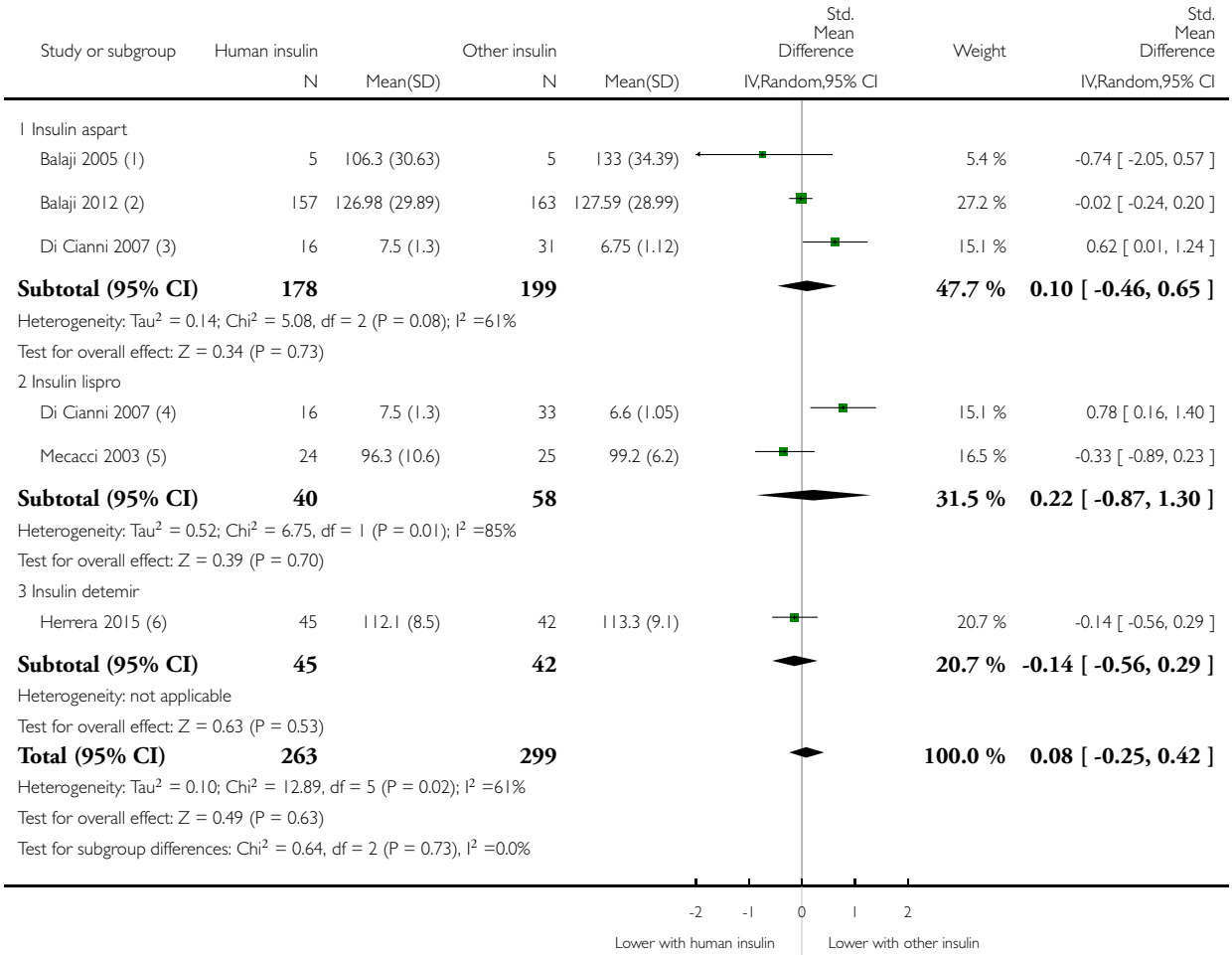


Analysis 2.8. Comparison 2 One insulin versus another insulin, Outcome 8 Glycaemic control during/end of treatment (Postprandial glucose).

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 2 One insulin versus another insulin

Outcome: 8 Glycaemic control during/end of treatment (Postprandial glucose)



(1) Two-hour postprandial

(2) 2 hour post-prandial (no details)

(3) 1 hour post-prandial (breakfast)

(4) 1 hour post-prandial (breakfast)

(5) 2-hour Mecacci 2003

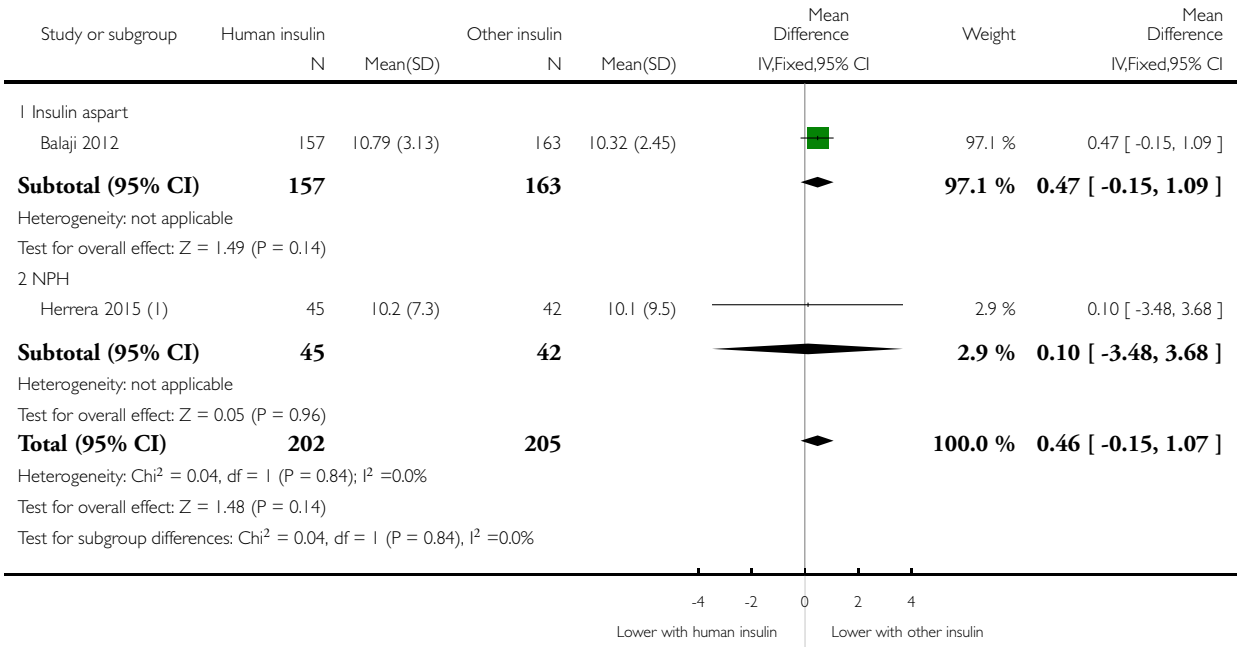
(6) Two-hour postprandial

Analysis 2.9. Comparison 2 One insulin versus another insulin, Outcome 9 Weight gain in pregnancy.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 2 One insulin versus another insulin

Outcome: 9 Weight gain in pregnancy



(1) Since trial entry (insulin detemir)

Analysis 2.10. Comparison 2 One insulin versus another insulin, Outcome 10 Maternal mortality.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 2 One insulin versus another insulin

Outcome: 10 Maternal mortality

Study or subgroup	Human insulin n/N	Other insulin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 NPH					
Ismail 2007	0/30	0/31			Not estimable
Total (95% CI)	**30**	**31**			**Not estimable**
Total events: 0 (Human insulin), 0 (Other insulin)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%					

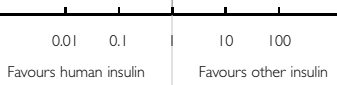
Analysis 2.11. Comparison 2 One insulin versus another insulin, Outcome 11 Fetal death.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 2 One insulin versus another insulin

Outcome: 11 Fetal death

Study or subgroup	Human insulin n/N	Other insulin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Insulin aspart					
Balaji 2012	0/157	0/163			Not estimable
Pettitt 2007 (1)	0/13	1/14		100.0 %	0.36 [0.02, 8.06]
Prasad 2008	0/50	0/50			Not estimable
Subtotal (95% CI)	**220**	**227**		**100.0 %**	**0.36 [0.02, 8.06]**
Total events: 0 (Human insulin), 1 (Other insulin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.65 (P = 0.52)					
2 NPH					
Ismail 2007	0/30	0/31			Not estimable
Subtotal (95% CI)	**30**	**31**			**Not estimable**
Total events: 0 (Human insulin), 0 (Other insulin)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**250**	**258**		**100.0 %**	**0.36 [0.02, 8.06]**
Total events: 0 (Human insulin), 1 (Other insulin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.65 (P = 0.52)					
Test for subgroup differences: Not applicable					



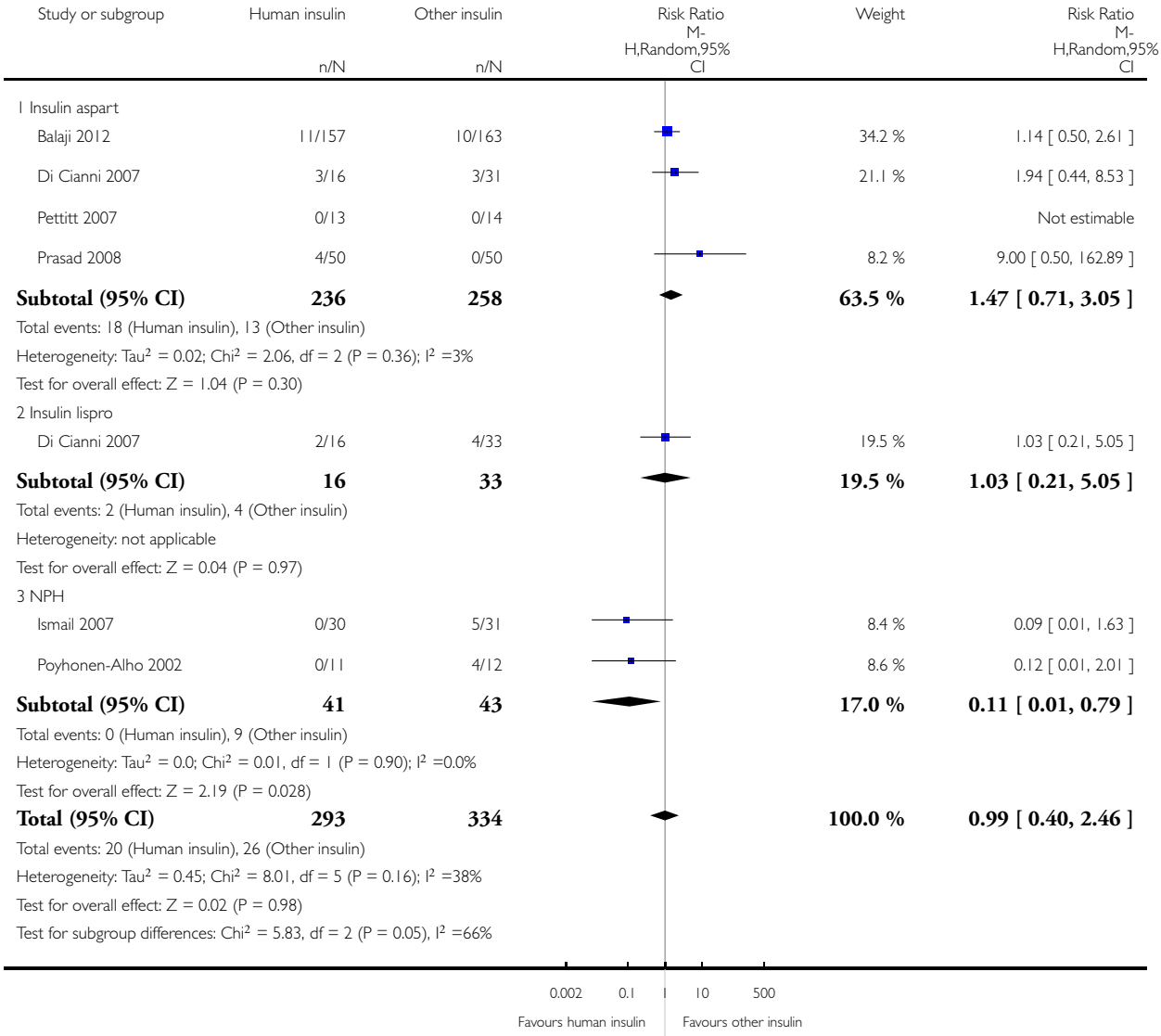
(1) Umbilical cord strangulation

Analysis 2.12. Comparison 2 One insulin versus another insulin, Outcome 12 Macrosomia.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 2 One insulin versus another insulin

Outcome: 12 Macrosomia

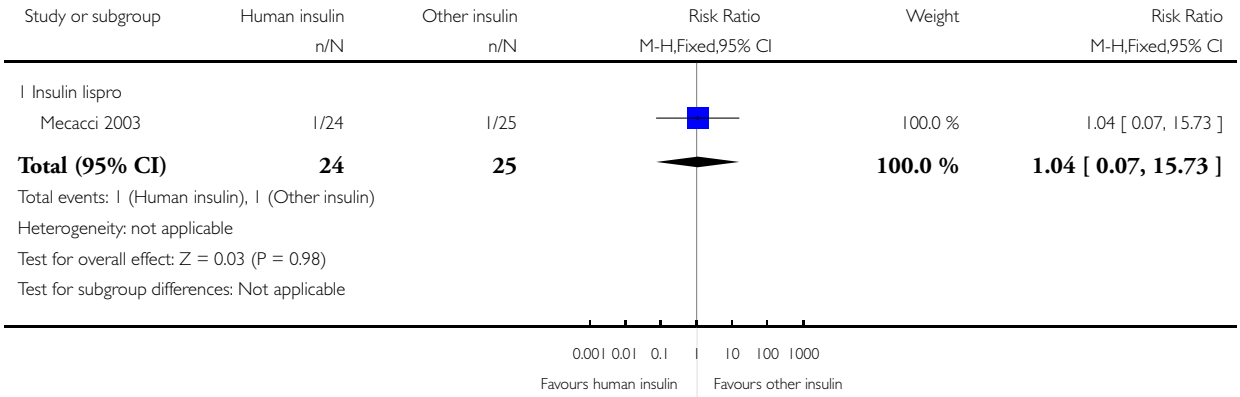


Analysis 2.13. Comparison 2 One insulin versus another insulin, Outcome 13 Small-for-gestational age.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 2 One insulin versus another insulin

Outcome: 13 Small-for-gestational age

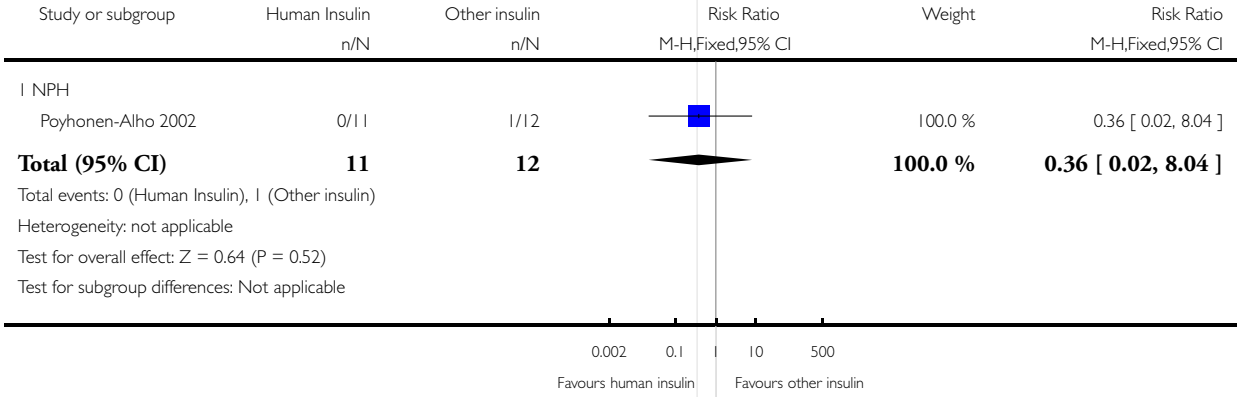


Analysis 2.14. Comparison 2 One insulin versus another insulin, Outcome 14 Birth trauma (Nerve palsy).

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 2 One insulin versus another insulin

Outcome: 14 Birth trauma (Nerve palsy)

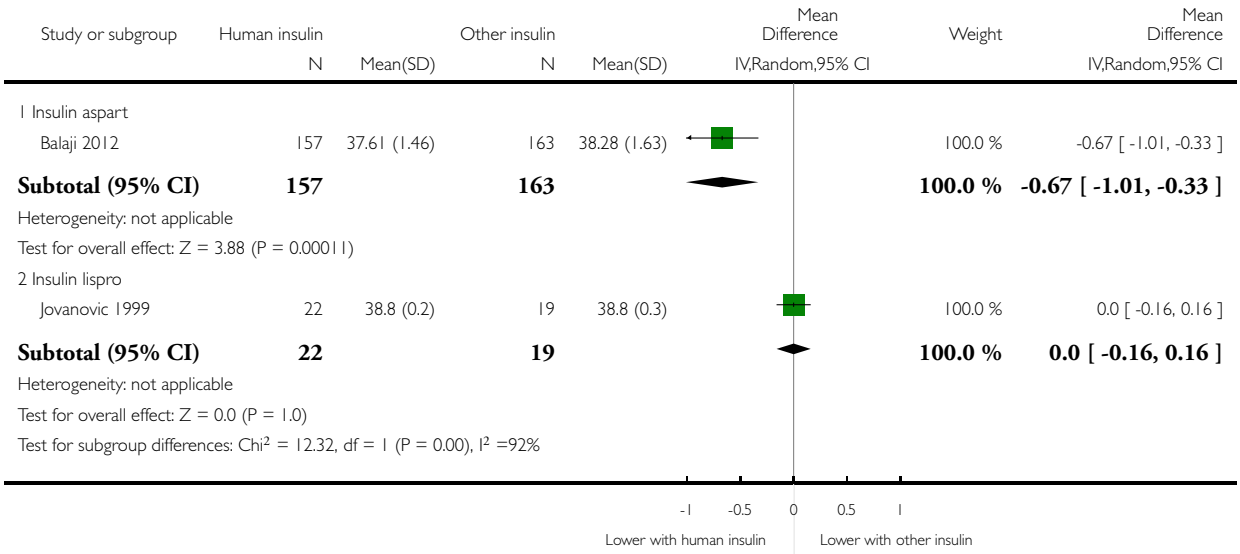


Analysis 2.15. Comparison 2 One insulin versus another insulin, Outcome 15 Gestational age at birth.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 2 One insulin versus another insulin

Outcome: 15 Gestational age at birth

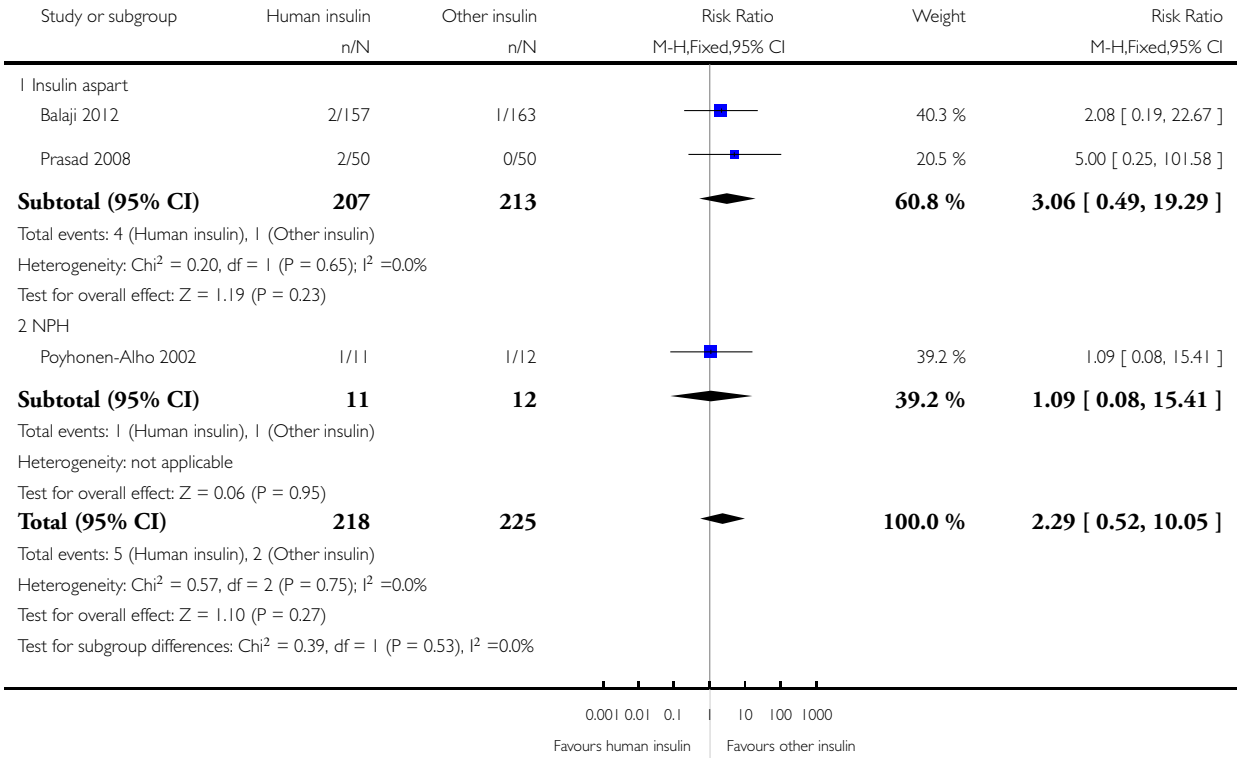


Analysis 2.16. Comparison 2 One insulin versus another insulin, Outcome 16 Preterm birth (< 37 weeks).

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 2 One insulin versus another insulin

Outcome: 16 Preterm birth (< 37 weeks)

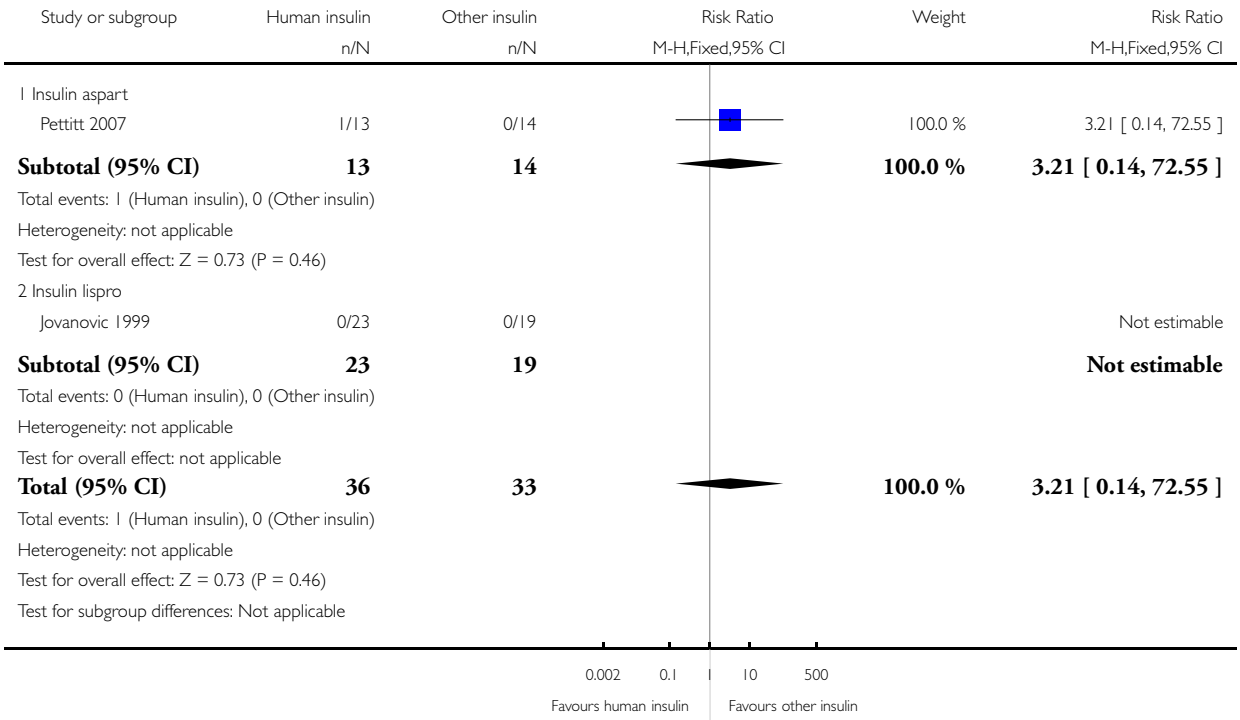


Analysis 2.17. Comparison 2 One insulin versus another insulin, Outcome 17 Congenital anomaly.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 2 One insulin versus another insulin

Outcome: 17 Congenital anomaly

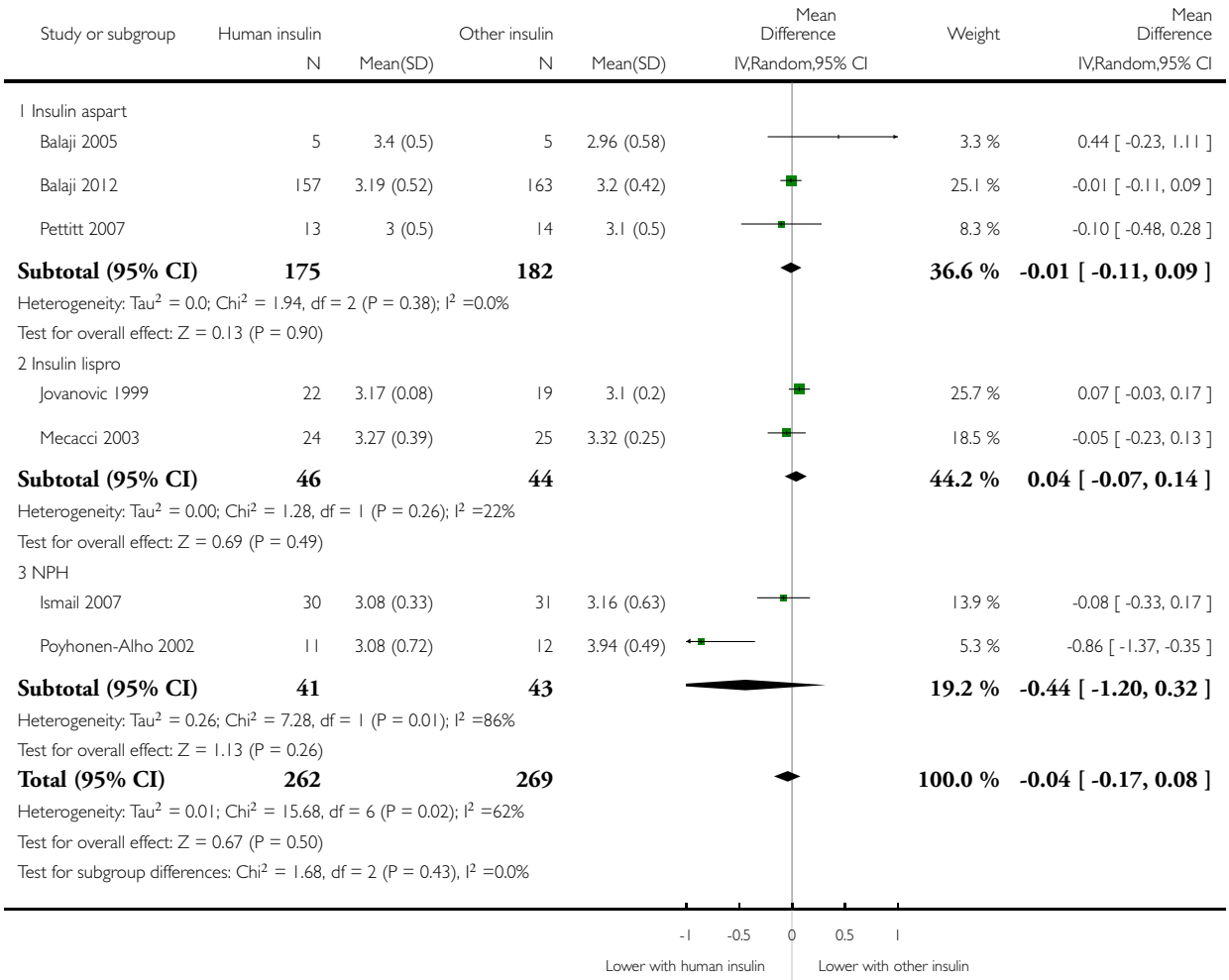


Analysis 2.18. Comparison 2 One insulin versus another insulin, Outcome 18 Birthweight (kg).

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 2 One insulin versus another insulin

Outcome: 18 Birthweight (kg)



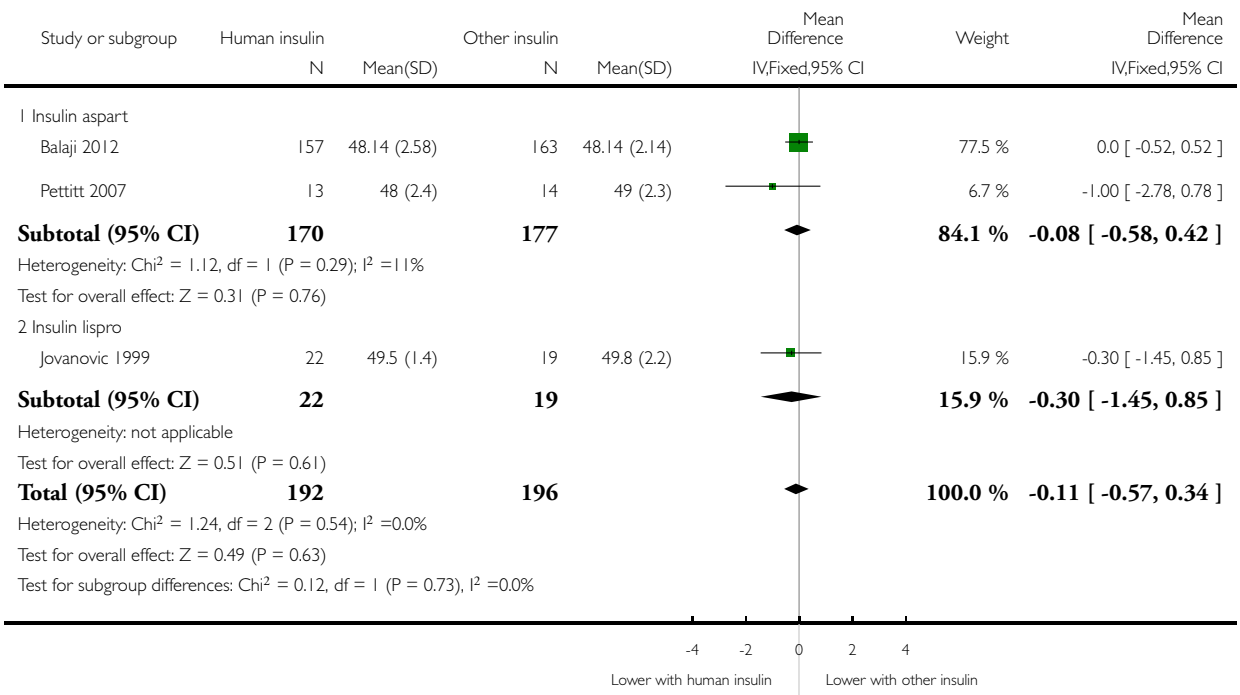
Analysis 2.19. Comparison 2 One insulin versus another insulin, Outcome 19 Length at birth (cm).

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 2 One insulin versus another insulin

Outcome: 19 Length at birth (cm)

Study or subgroup	Human insulin N	Mean(SD)	Other insulin N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Insulin aspart							
Balaji 2012	157	48.14 (2.58)	163	48.14 (2.14)		77.5 %	0.0 [-0.52, 0.52]
Pettitt 2007	13	48 (2.4)	14	49 (2.3)		6.7 %	-1.00 [-2.78, 0.78]
Subtotal (95% CI)	**170**		**177**			**84.1 %**	**-0.08 [-0.58, 0.42]**
Heterogeneity: Chi^2 = 1.12, df = 1 (P = 0.29); I^2 =11%							
Test for overall effect: Z = 0.31 (P = 0.76)							
2 Insulin lispro							
Jovanovic 1999	22	49.5 (1.4)	19	49.8 (2.2)		15.9 %	-0.30 [-1.45, 0.85]
Subtotal (95% CI)	**22**		**19**			**15.9 %**	**-0.30 [-1.45, 0.85]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.51 (P = 0.61)							
Total (95% CI)	**192**		**196**			**100.0 %**	**-0.11 [-0.57, 0.34]**
Heterogeneity: Chi^2 = 1.24, df = 2 (P = 0.54); I^2 =0.0%							
Test for overall effect: Z = 0.49 (P = 0.63)							
Test for subgroup differences: Chi^2 = 0.12, df = 1 (P = 0.73), I^2 =0.0%							

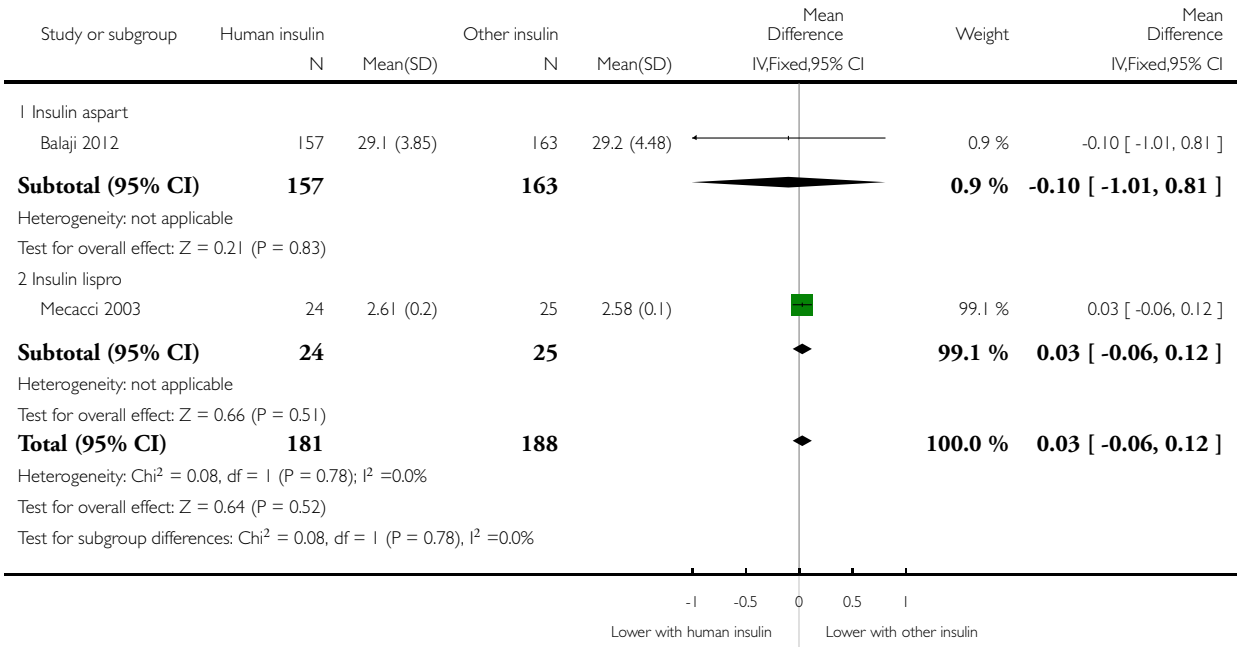


Analysis 2.20. Comparison 2 One insulin versus another insulin, Outcome 20 Ponderal Index kg/m3.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 2 One insulin versus another insulin

Outcome: 20 Ponderal Index kg/m3

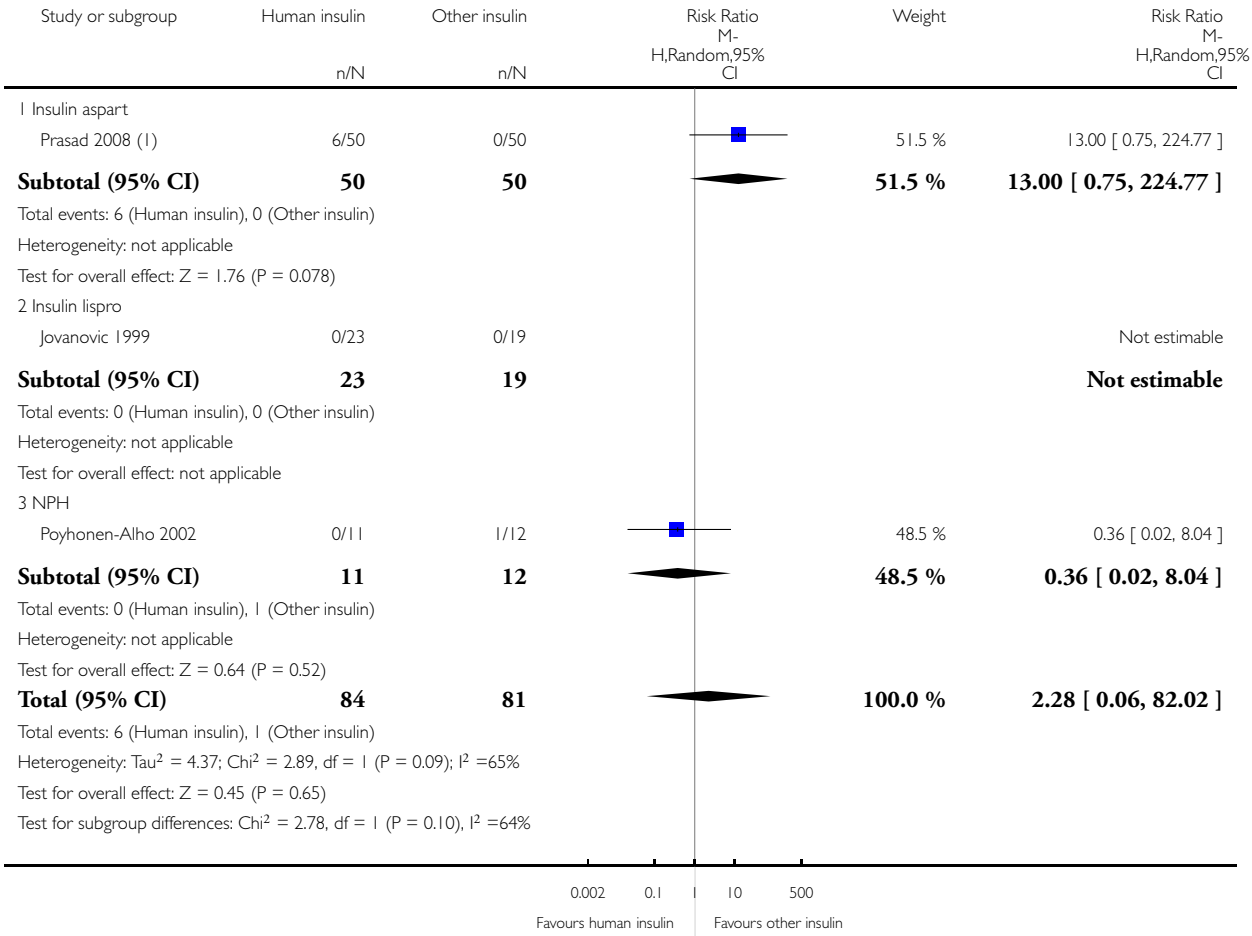


Analysis 2.21. Comparison 2 One insulin versus another insulin, Outcome 21 Neonatal hypoglycaemia.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 2 One insulin versus another insulin

Outcome: 21 Neonatal hypoglycaemia



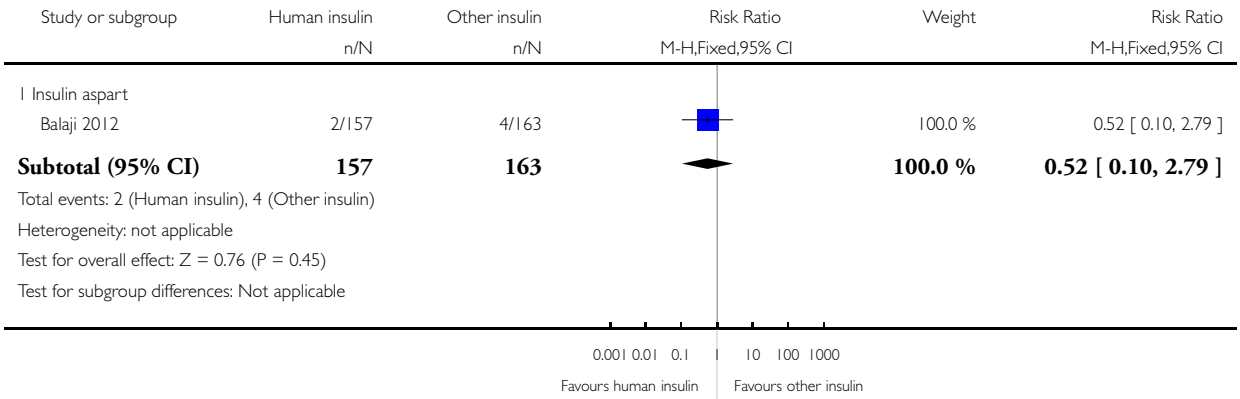
(1) Regular human insulin plus NPH

Analysis 2.22. Comparison 2 One insulin versus another insulin, Outcome 22 Respiratory distress.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 2 One insulin versus another insulin

Outcome: 22 Respiratory distress

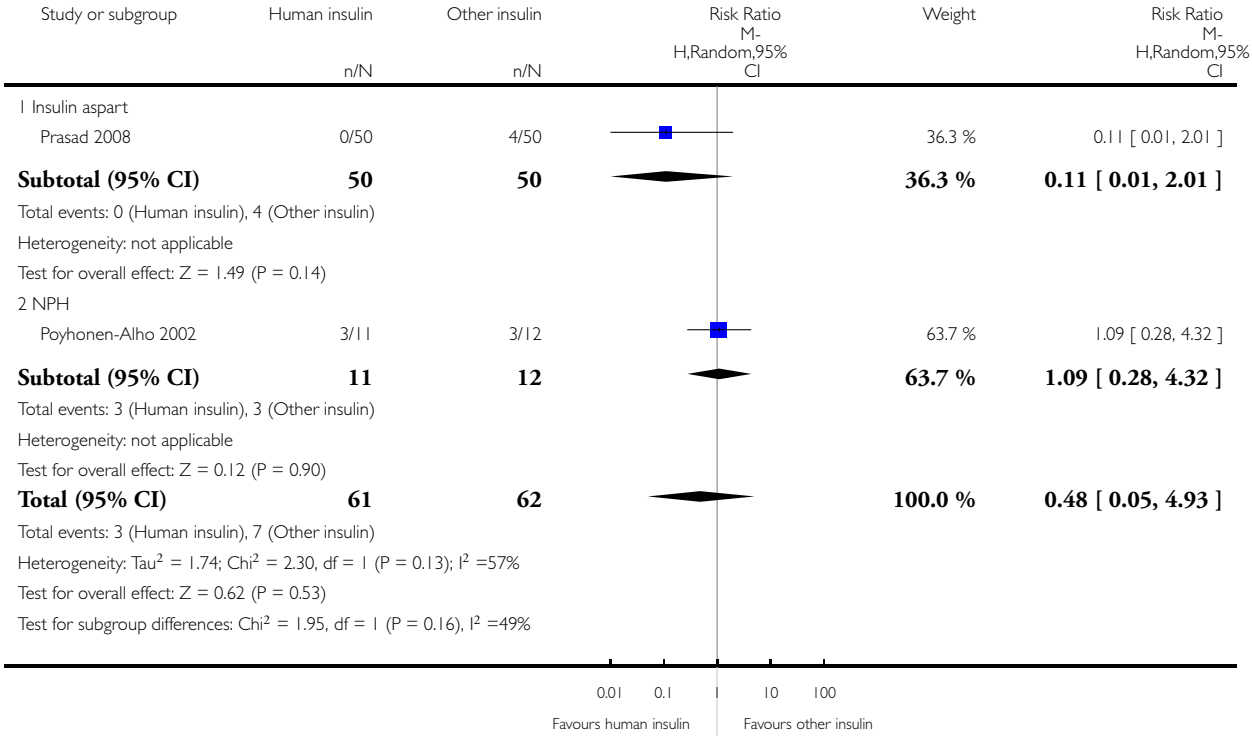


Analysis 2.23. Comparison 2 One insulin versus another insulin, Outcome 23 Neonatal jaundice (hyperbilirubinaemia).

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 2 One insulin versus another insulin

Outcome: 23 Neonatal jaundice (hyperbilirubinaemia)

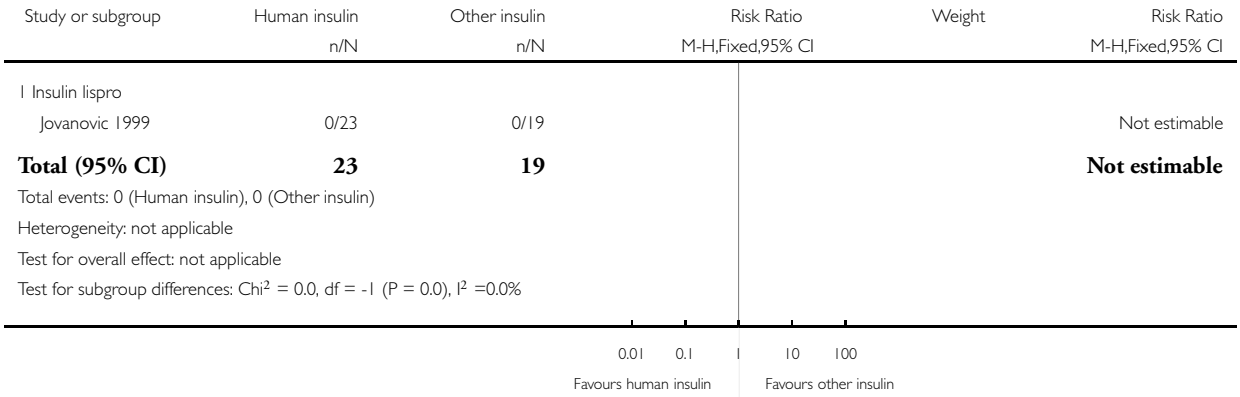


Analysis 2.24. Comparison 2 One insulin versus another insulin, Outcome 24 Hypocalcaemia.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 2 One insulin versus another insulin

Outcome: 24 Hypocalcaemia

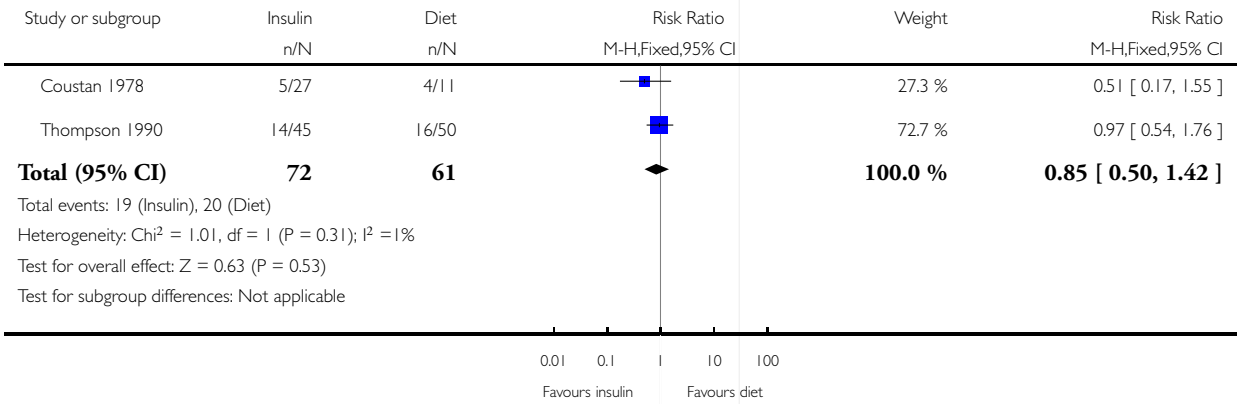


Analysis 3.1. Comparison 3 Insulin versus diet/standard care, Outcome 1 Caesarean section.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 3 Insulin versus diet/standard care

Outcome: 1 Caesarean section

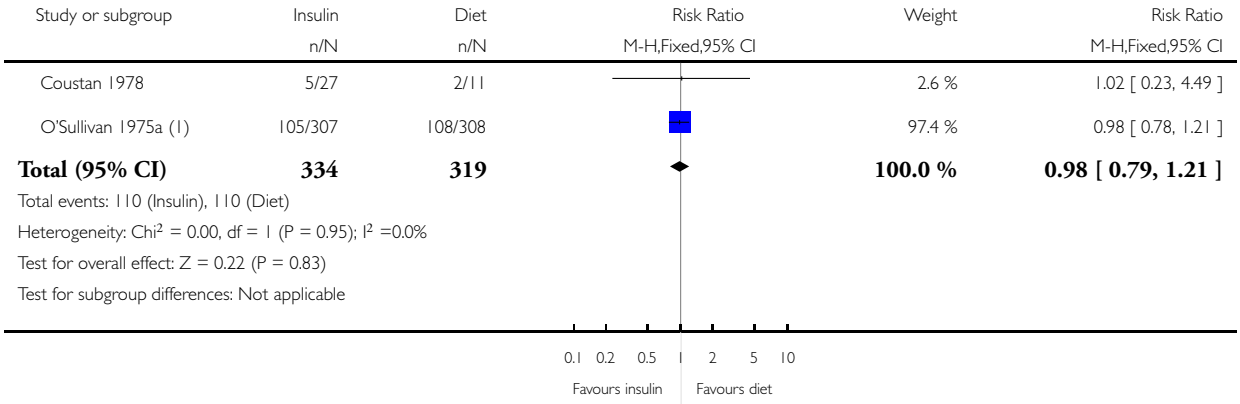


Analysis 3.2. Comparison 3 Insulin versus diet/standard care, Outcome 2 Development of type 2 diabetes.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 3 Insulin versus diet/standard care

Outcome: 2 Development of type 2 diabetes



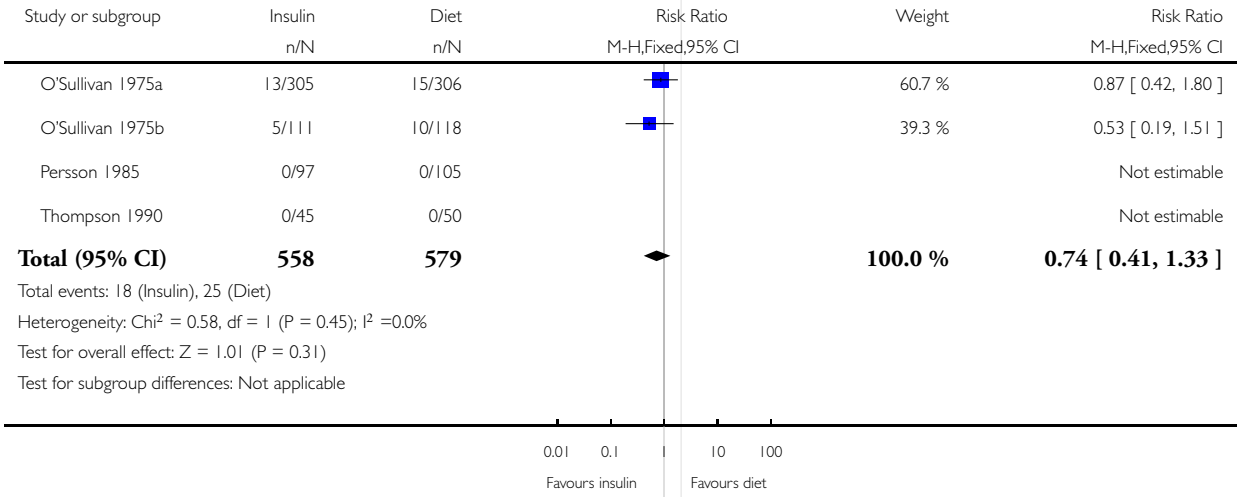
(1) up to 15 years follow-up

Analysis 3.3. Comparison 3 Insulin versus diet/standard care, Outcome 3 Perinatal (fetal and neonatal death) and later infant mortality.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 3 Insulin versus diet/standard care

Outcome: 3 Perinatal (fetal and neonatal death) and later infant mortality



Analysis 3.4. Comparison 3 Insulin versus diet/standard care, Outcome 4 Large-for-gestational age.

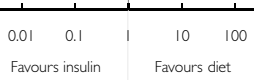
Review: Insulin for the treatment of women with gestational diabetes

Comparison: 3 Insulin versus diet/standard care

Outcome: 4 Large-for-gestational age

Study or subgroup	Insulin n/N	Diet n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Persson 1985	11/97	14/105		100.0 %	0.85 [0.41, 1.78]
Total (95% CI)	**97**	**105**		**100.0 %**	**0.85 [0.41, 1.78]**

Total events: 11 (Insulin), 14 (Diet)
Heterogeneity: not applicable
Test for overall effect: Z = 0.43 (P = 0.67)
Test for subgroup differences: Not applicable



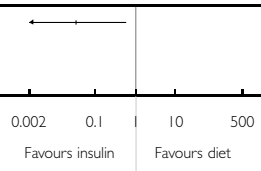
Analysis 3.5. Comparison 3 Insulin versus diet/standard care, Outcome 5 Use of additional pharmacotherapy.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 3 Insulin versus diet/standard care

Outcome: 5 Use of additional pharmacotherapy

Study or subgroup	Insulin n/N	Diet n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Persson 1985	0/97	15/105		0.03 [0.00, 0.58]



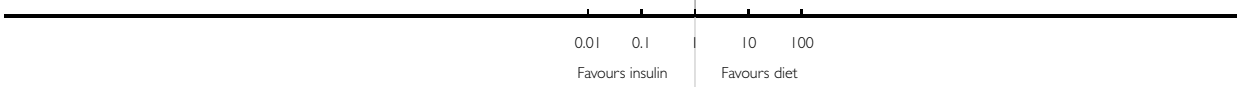
Analysis 3.6. Comparison 3 Insulin versus diet/standard care, Outcome 6 Maternal hypoglycaemia.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 3 Insulin versus diet/standard care

Outcome: 6 Maternal hypoglycaemia

Study or subgroup	Insulin n/N	Diet n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Thompson 1990	0/45	0/50			Not estimable
Total (95% CI)	**45**	**50**			**Not estimable**
Total events: 0 (Insulin), 0 (Diet)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					



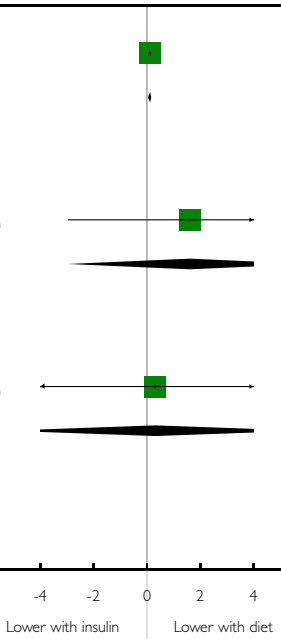
Analysis 3.7. Comparison 3 Insulin versus diet/standard care, Outcome 7 Glycaemic control during/end of treatment.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 3 Insulin versus diet/standard care

Outcome: 7 Glycaemic control during/end of treatment

Study or subgroup	Insulin N	Mean(SD)	Diet N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 HbA1c							
Persson 1985 (1)	86	6.9 (0.2)	75	6.8 (0.2)		100.0 %	0.10 [0.04, 0.16]
Subtotal (95% CI)	**86**		**75**			**100.0 %**	**0.10 [0.04, 0.16]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.16 (P = 0.0016)							
2 Fasting blood glucose							
Thompson 1990 (2)	34	81.3 (8)	34	79.7 (11)		100.0 %	1.60 [-2.97, 6.17]
Subtotal (95% CI)	**34**		**34**			**100.0 %**	**1.60 [-2.97, 6.17]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.69 (P = 0.49)							
3 Postprandial blood glucose							
Thompson 1990 (3)	34	94.1 (10.5)	34	93.8 (13)		100.0 %	0.30 [-5.32, 5.92]
Subtotal (95% CI)	**34**		**34**			**100.0 %**	**0.30 [-5.32, 5.92]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.10 (P = 0.92)							
Test for subgroup differences: Chi^2 = 0.42, df = 2 (P = 0.81), I^2 =0.0%							



(1) end of treatment

(2) During treatment

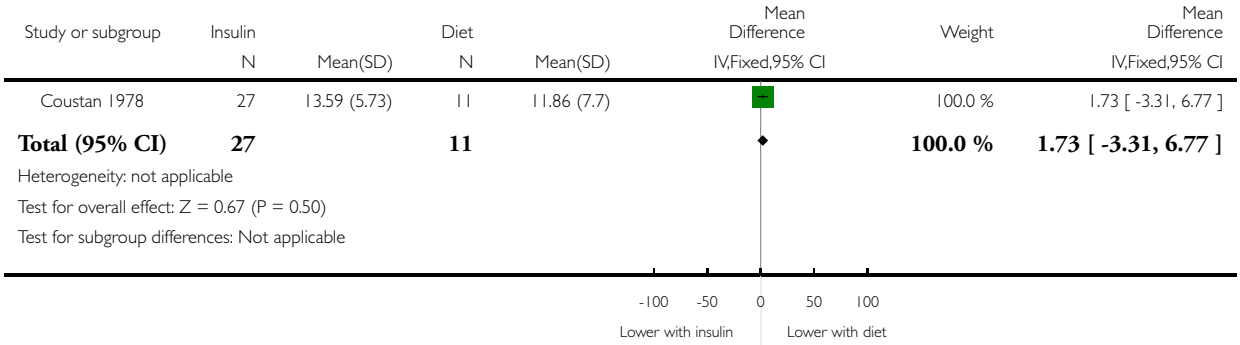
(3) During treatment, two-hour postprandial

Analysis 3.8. Comparison 3 Insulin versus diet/standard care, Outcome 8 Weight gain in pregnancy.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 3 Insulin versus diet/standard care

Outcome: 8 Weight gain in pregnancy

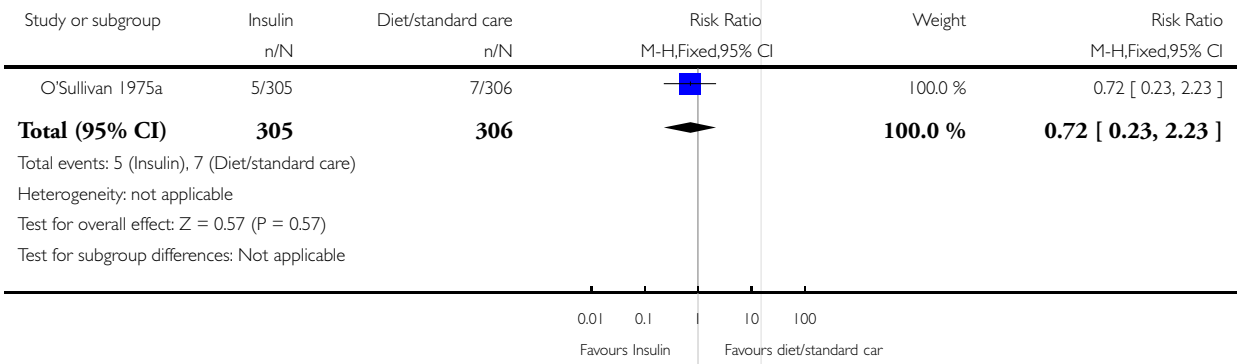


Analysis 3.9. Comparison 3 Insulin versus diet/standard care, Outcome 9 Neonatal death.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 3 Insulin versus diet/standard care

Outcome: 9 Neonatal death



Analysis 3.10. Comparison 3 Insulin versus diet/standard care, Outcome 10 Macrosomia.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 3 Insulin versus diet/standard care

Outcome: 10 Macrosomia

Study or subgroup	Insulin n/N	Diet n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Coustan 1978	2/27	4/11		10.4 %	0.20 [0.04, 0.96]
O'Sullivan 1975a	13/305	40/306		73.1 %	0.33 [0.18, 0.60]
Thompson 1990	2/34	9/34		16.5 %	0.22 [0.05, 0.95]
Total (95% CI)	**366**	**351**		**100.0 %**	**0.30 [0.18, 0.50]**

Total events: 17 (Insulin), 53 (Diet)

Heterogeneity: $Chi^2 = 0.47$, df = 2 (P = 0.79); $I^2 = 0.0\%$

Test for overall effect: Z = 4.53 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 3.11. Comparison 3 Insulin versus diet/standard care, Outcome 11 Small-for-gestational age.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 3 Insulin versus diet/standard care

Outcome: 11 Small-for-gestational age

Study or subgroup	Insulin n/N	Diet n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Coustan 1978	1/27	0/11		17.2 %	1.29 [0.06, 29.36]
Persson 1985	0/97	3/105		82.8 %	0.15 [0.01, 2.95]
Total (95% CI)	**124**	**116**		**100.0 %**	**0.35 [0.05, 2.40]**

Total events: 1 (Insulin), 3 (Diet)

Heterogeneity: $Chi^2 = 0.96$, df = 1 (P = 0.33); $I^2 = 0.0\%$

Test for overall effect: Z = 1.07 (P = 0.28)

Test for subgroup differences: Not applicable

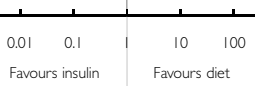
Analysis 3.12. Comparison 3 Insulin versus diet/standard care, Outcome 12 Birth trauma.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 3 Insulin versus diet/standard care

Outcome: 12 Birth trauma

Study or subgroup	Insulin n/N	Diet n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Shoulder dystocia					
Coustan 1978	0/27	0/11			Not estimable
Thompson 1990	0/45	0/50			Not estimable
Subtotal (95% CI)	**72**	**61**			**Not estimable**
Total events: 0 (Insulin), 0 (Diet)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Nerve palsy					
Coustan 1978	0/27	0/11			Not estimable
Subtotal (95% CI)	**27**	**11**			**Not estimable**
Total events: 0 (Insulin), 0 (Diet)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%					

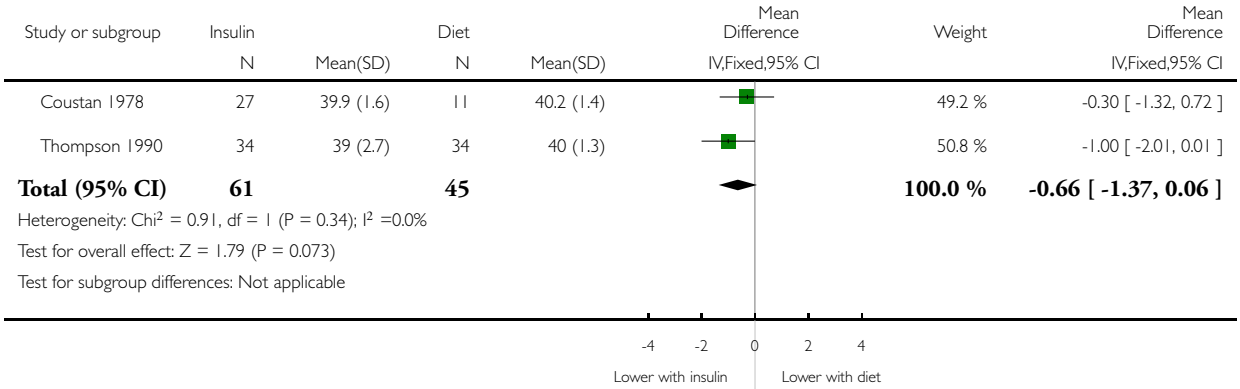


Analysis 3.13. Comparison 3 Insulin versus diet/standard care, Outcome 13 Gestational age at birth.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 3 Insulin versus diet/standard care

Outcome: 13 Gestational age at birth

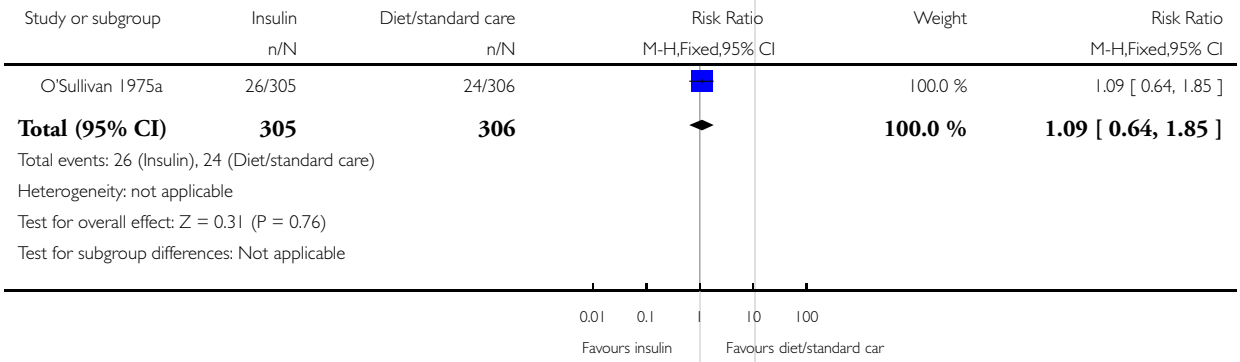


Analysis 3.14. Comparison 3 Insulin versus diet/standard care, Outcome 14 Preterm birth (less than 37 weeks' gestation).

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 3 Insulin versus diet/standard care

Outcome: 14 Preterm birth (less than 37 weeks' gestation)

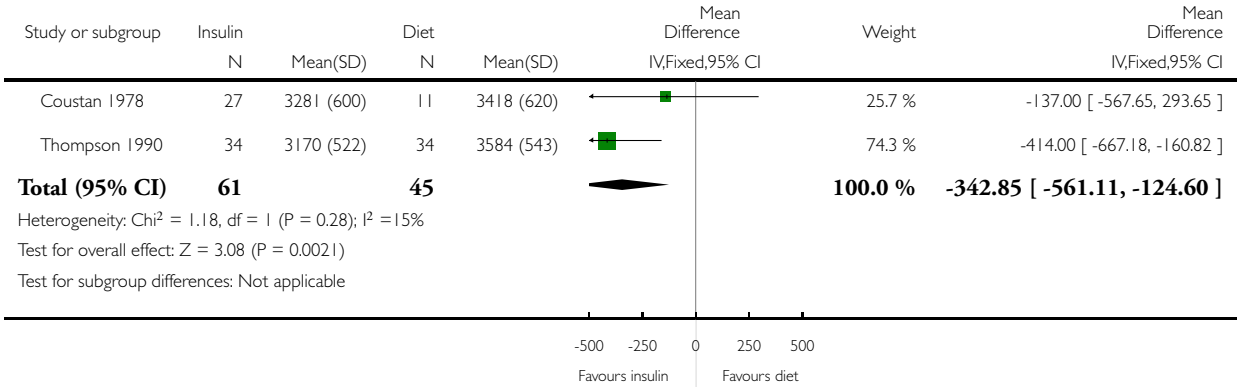


Analysis 3.15. Comparison 3 Insulin versus diet/standard care, Outcome 15 Birthweight.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 3 Insulin versus diet/standard care

Outcome: 15 Birthweight

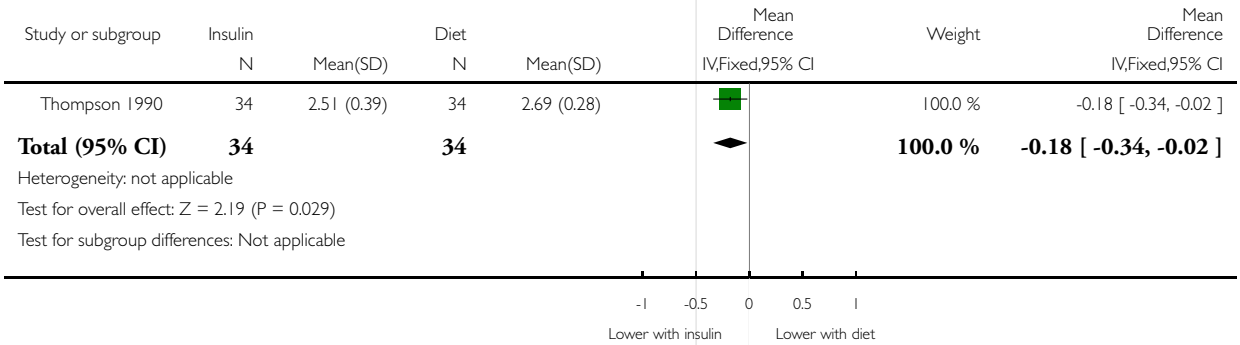


Analysis 3.16. Comparison 3 Insulin versus diet/standard care, Outcome 16 Ponderal Index.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 3 Insulin versus diet/standard care

Outcome: 16 Ponderal Index



Analysis 3.17. Comparison 3 Insulin versus diet/standard care, Outcome 17 Neonatal hypoglycaemia.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 3 Insulin versus diet/standard care

Outcome: 17 Neonatal hypoglycaemia

Study or subgroup	Insulin n/N	Diet n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Coustan 1978	0/27	0/11			Not estimable
Persson 1985	20/40	13/30		74.0 %	1.15 [0.69, 1.93]
Thompson 1990	2/34	5/34		26.0 %	0.40 [0.08, 1.92]
Total (95% CI)	**101**	**75**		**100.0 %**	**0.88 [0.34, 2.24]**

Total events: 22 (Insulin), 18 (Diet)

Heterogeneity: $Tau^2 = 0.24$; $Chi^2 = 1.68$, df = 1 (P = 0.20); I^2 =40%

Test for overall effect: Z = 0.28 (P = 0.78)

Test for subgroup differences: Not applicable

Analysis 3.18. Comparison 3 Insulin versus diet/standard care, Outcome 18 Neonatal jaundice (Hyperbilirubinaemia).

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 3 Insulin versus diet/standard care

Outcome: 18 Neonatal jaundice (Hyperbilirubinaemia)

Study or subgroup	Insulin n/N	Diet n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Thompson 1990	0/34	0/34			Not estimable
Total (95% CI)	**34**	**34**			**Not estimable**

Total events: 0 (Insulin), 0 (Diet)

Heterogeneity: not applicable

Test for overall effect: not applicable

Test for subgroup differences: Not applicable

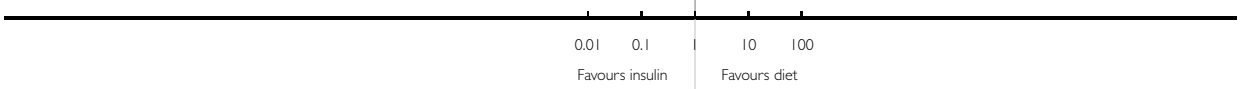
Analysis 3.19. Comparison 3 Insulin versus diet/standard care, Outcome 19 Hypocalcaemia.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 3 Insulin versus diet/standard care

Outcome: 19 Hypocalcaemia

Study or subgroup	Insulin n/N	Diet n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Thompson 1990	0/34	0/34			Not estimable
Total (95% CI)	**34**	**34**			**Not estimable**
Total events: 0 (Insulin), 0 (Diet)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					

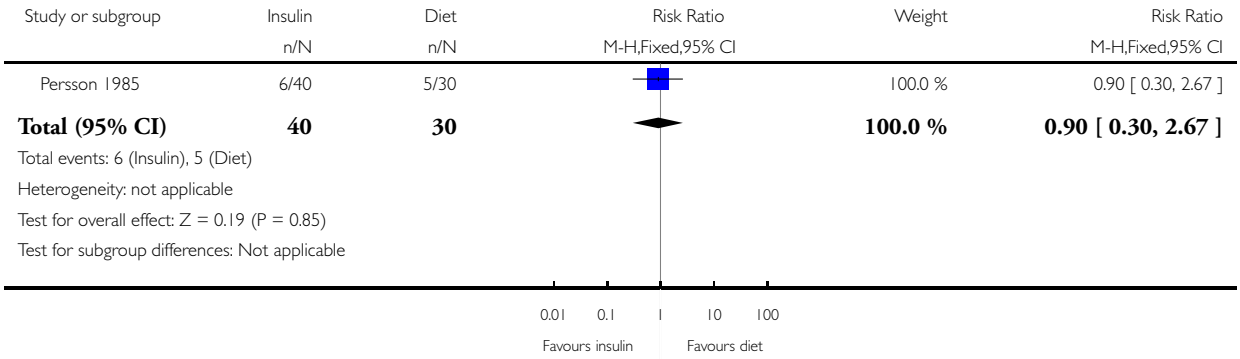


Analysis 3.20. Comparison 3 Insulin versus diet/standard care, Outcome 20 Polycythaemia.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 3 Insulin versus diet/standard care

Outcome: 20 Polycythaemia

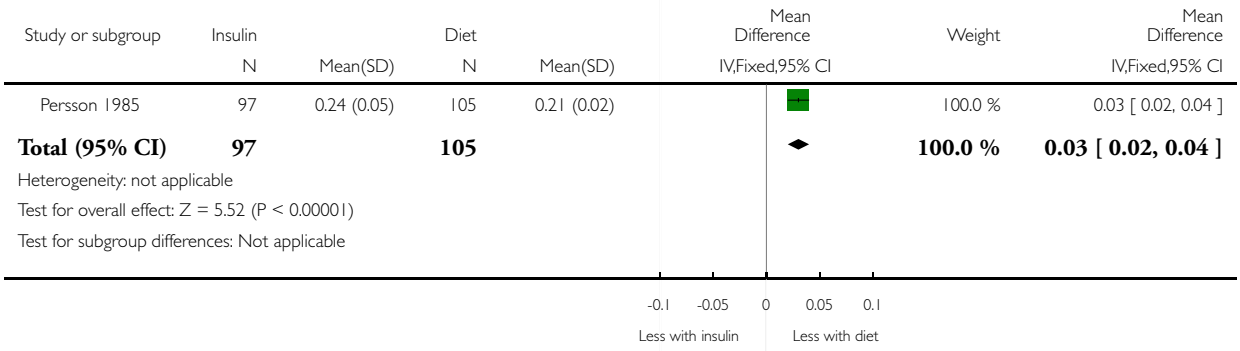


Analysis 3.21. Comparison 3 Insulin versus diet/standard care, Outcome 21 Relevant biomarker changes associated with the intervention (Cord C-peptide).

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 3 Insulin versus diet/standard care

Outcome: 21 Relevant biomarker changes associated with the intervention (Cord C-peptide)

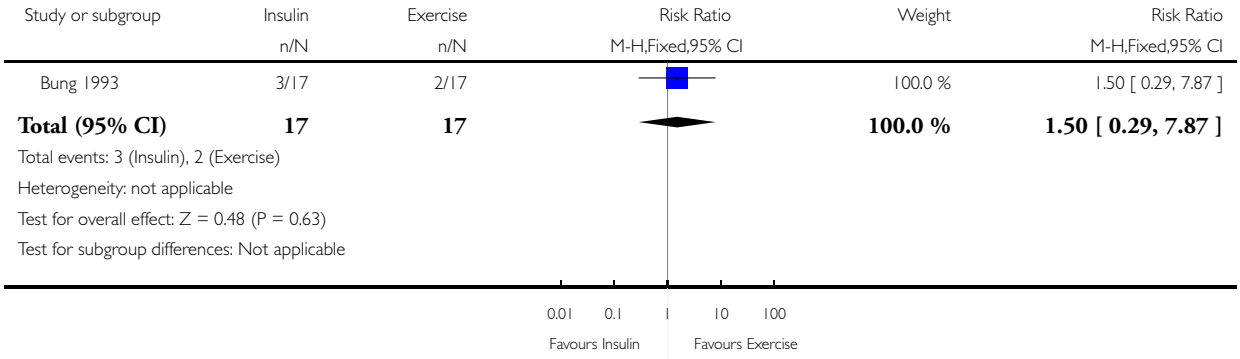


Analysis 4.1. Comparison 4 Insulin versus exercise, Outcome 1 Caesarean section.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 4 Insulin versus exercise

Outcome: 1 Caesarean section

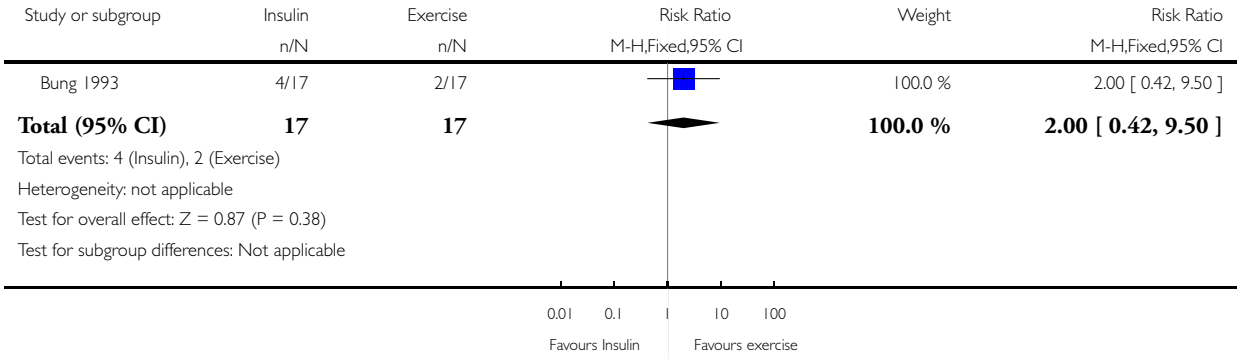


Analysis 4.2. Comparison 4 Insulin versus exercise, Outcome 2 Macrosomia.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 4 Insulin versus exercise

Outcome: 2 Macrosomia

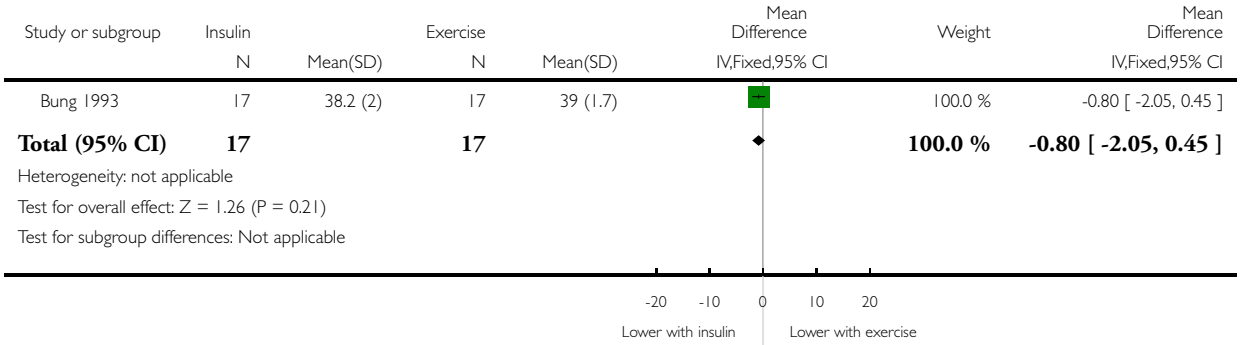


Analysis 4.3. Comparison 4 Insulin versus exercise, Outcome 3 Gestational age at birth.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 4 Insulin versus exercise

Outcome: 3 Gestational age at birth

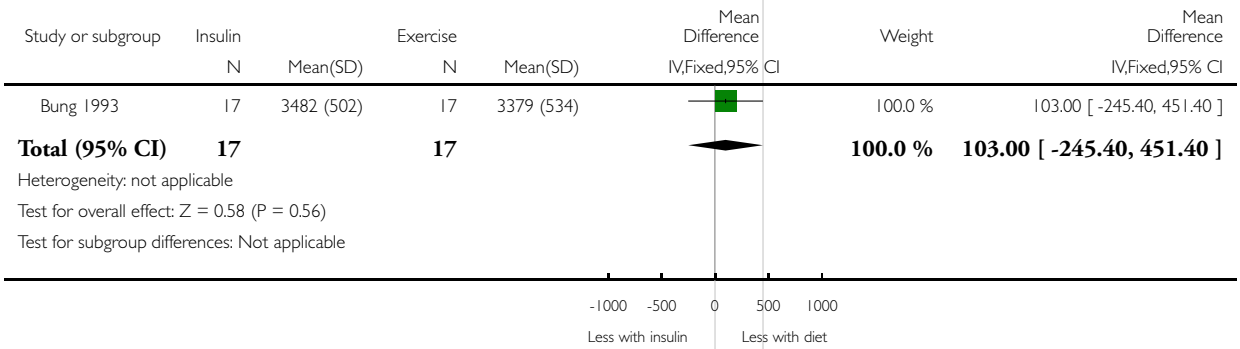


Analysis 4.4. Comparison 4 Insulin versus exercise, Outcome 4 Birthweight (g).

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 4 Insulin versus exercise

Outcome: 4 Birthweight (g)

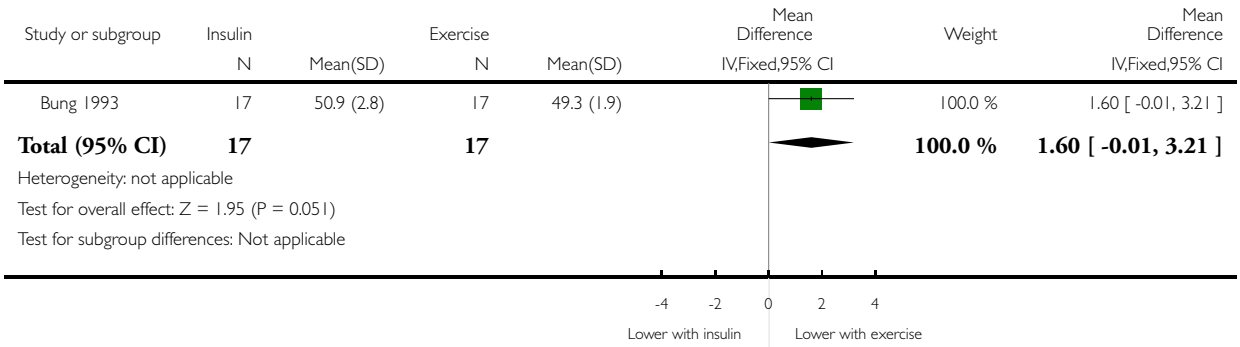


Analysis 4.5. Comparison 4 Insulin versus exercise, Outcome 5 Length at birth (cm).

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 4 Insulin versus exercise

Outcome: 5 Length at birth (cm)

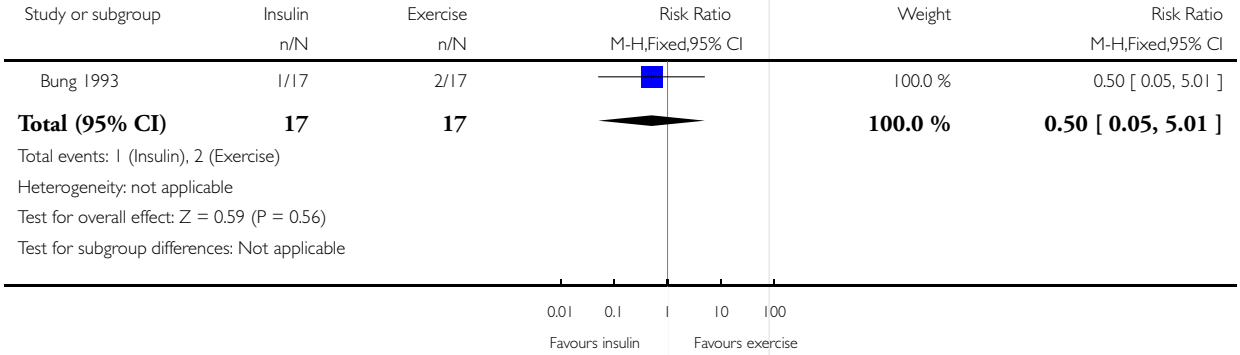


Analysis 4.6. Comparison 4 Insulin versus exercise, Outcome 6 Neonatal hypoglycaemia.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 4 Insulin versus exercise

Outcome: 6 Neonatal hypoglycaemia



Analysis 4.7. Comparison 4 Insulin versus exercise, Outcome 7 Respiratory distress syndrome.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 4 Insulin versus exercise

Outcome: 7 Respiratory distress syndrome

Study or subgroup	Insulin n/N	Exercise n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Bung 1993	0/17	0/17			Not estimable
Total (95% CI)	**17**	**17**			**Not estimable**

Total events: 0 (Insulin), 0 (Exercise)
Heterogeneity: not applicable
Test for overall effect: not applicable
Test for subgroup differences: Not applicable

Analysis 4.8. Comparison 4 Insulin versus exercise, Outcome 8 Neonatal jaundice (Hyperbilirubinaemia).

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 4 Insulin versus exercise

Outcome: 8 Neonatal jaundice (Hyperbilirubinaemia)

Study or subgroup	Insulin n/N	Exercise n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Bung 1993	0/17	0/17			Not estimable
Total (95% CI)	**17**	**17**			**Not estimable**

Total events: 0 (Insulin), 0 (Exercise)
Heterogeneity: not applicable
Test for overall effect: not applicable
Test for subgroup differences: Not applicable

Analysis 4.9. Comparison 4 Insulin versus exercise, Outcome 9 Hypocalcaemia.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 4 Insulin versus exercise

Outcome: 9 Hypocalcaemia

Study or subgroup	Insulin n/N	Exercise n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Bung 1993	0/17	0/17			Not estimable
Total (95% CI)	**17**	**17**			**Not estimable**
Total events: 0 (Insulin), 0 (Exercise)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					

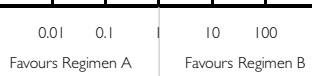
Analysis 5.1. Comparison 5 Regimen A versus regimen B, Outcome 1 Hypertensive disorders of pregnancy - Pregnancy-induced hypertension.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 5 Regimen A versus regimen B

Outcome: 1 Hypertensive disorders of pregnancy - Pregnancy-induced hypertension

Study or subgroup	Regimen A n/N	Regimen B n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Twice v four times daily					
Nachum 1999	12/136	11/138		100.0 %	1.11 [0.51, 2.42]
Subtotal (95% CI)	**136**	**138**		**100.0 %**	**1.11 [0.51, 2.42]**
Total events: 12 (Regimen A), 11 (Regimen B)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.25 (P = 0.80)					
Test for subgroup differences: Not applicable					

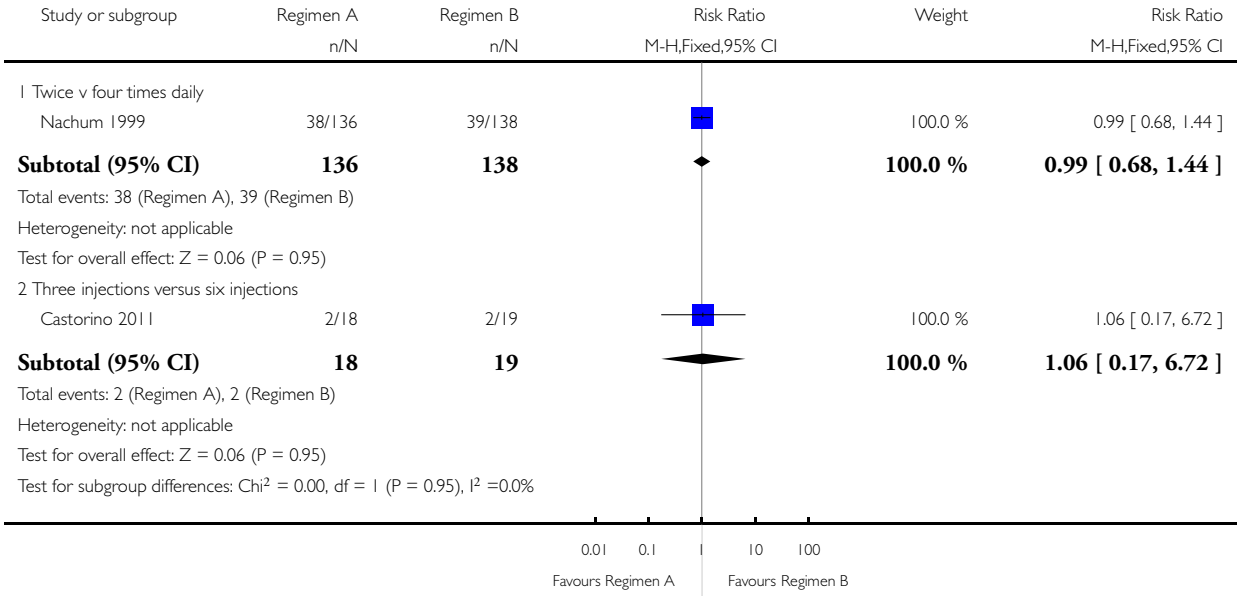


Analysis 5.2. Comparison 5 Regimen A versus regimen B, Outcome 2 Caesarean section.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 5 Regimen A versus regimen B

Outcome: 2 Caesarean section

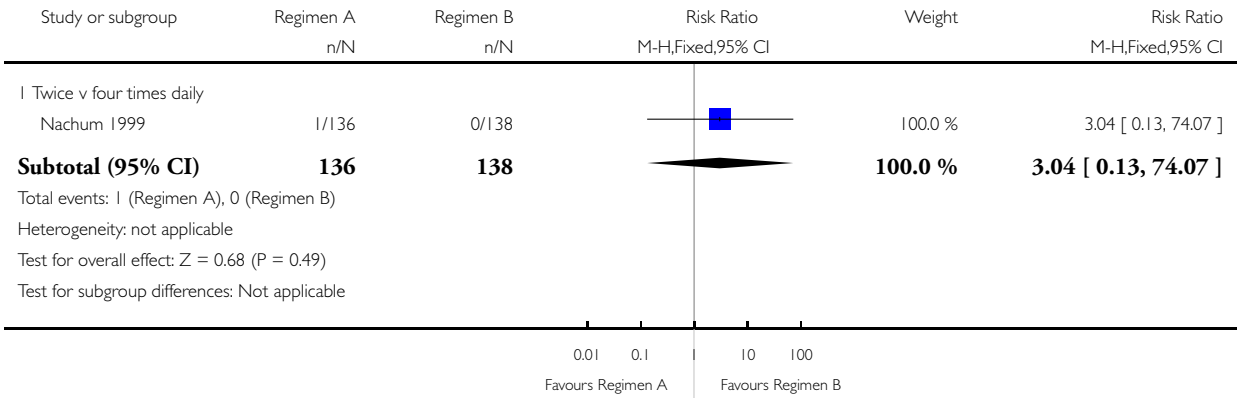


Analysis 5.3. Comparison 5 Regimen A versus regimen B, Outcome 3 Perinatal (fetal and neonatal death) and later infant mortality.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 5 Regimen A versus regimen B

Outcome: 3 Perinatal (fetal and neonatal death) and later infant mortality

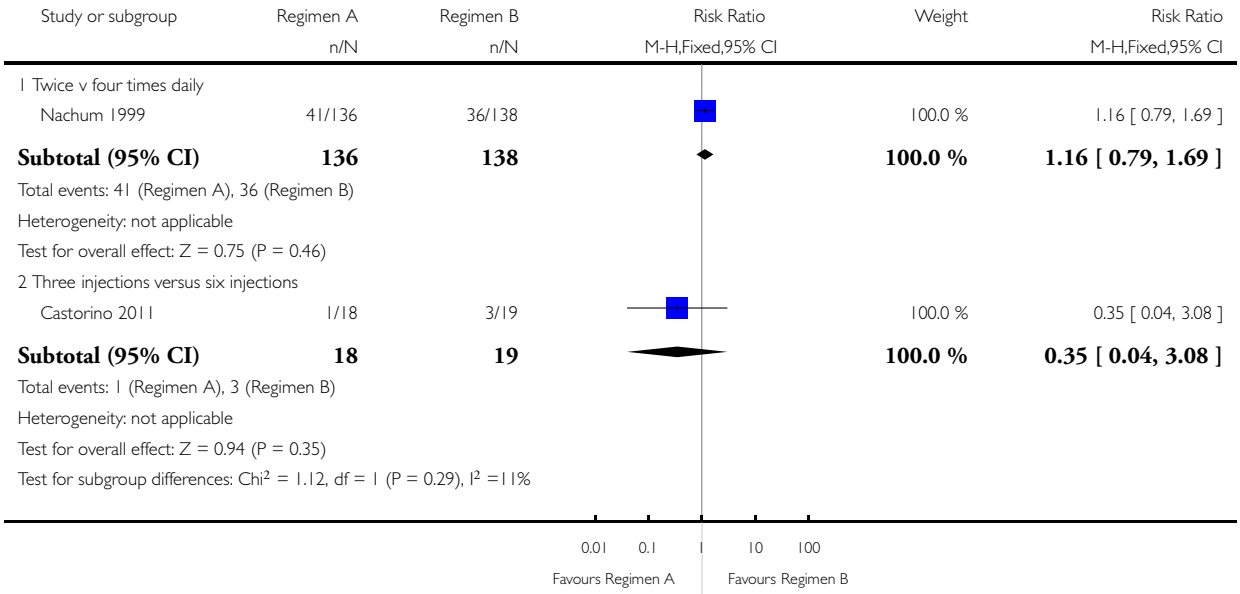


Analysis 5.4. Comparison 5 Regimen A versus regimen B, Outcome 4 Large-for-gestational age.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 5 Regimen A versus regimen B

Outcome: 4 Large-for-gestational age



Analysis 5.5. Comparison 5 Regimen A versus regimen B, Outcome 5 Death or serious morbidity composite (variously defined by trials, e.g. perinatal or infant death, shoulder dystocia, bone fracture or nerve palsy).

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 5 Regimen A versus regimen B

Outcome: 5 Death or serious morbidity composite (variously defined by trials, e.g. perinatal or infant death, shoulder dystocia, bone fracture or nerve palsy)

Study or subgroup	Regimen A n/N	Regimen B n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Twice v four times daily					
Nachum 1999	40/136	24/138		100.0 %	1.69 [1.08, 2.64]
Subtotal (95% CI)	**136**	**138**		**100.0 %**	**1.69 [1.08, 2.64]**
Total events: 40 (Regimen A), 24 (Regimen B)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.30 (P = 0.021)					
Test for subgroup differences: Not applicable					

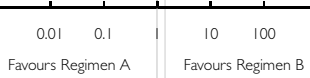
Analysis 5.6. Comparison 5 Regimen A versus regimen B, Outcome 6 Maternal hypoglycaemia.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 5 Regimen A versus regimen B

Outcome: 6 Maternal hypoglycaemia

Study or subgroup	Regimen A n/N	Regimen B n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Twice v four times daily					
Nachum 1999	1/136	1/138		100.0 %	1.01 [0.06, 16.06]
Subtotal (95% CI)	**136**	**138**		**100.0 %**	**1.01 [0.06, 16.06]**
Total events: 1 (Regimen A), 1 (Regimen B)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.01 (P = 0.99)					
Test for subgroup differences: Not applicable					



Analysis 5.7. Comparison 5 Regimen A versus regimen B, Outcome 7 Glycaemic control during/end of treatment (Fasting).

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 5 Regimen A versus regimen B

Outcome: 7 Glycaemic control during/end of treatment (Fasting)

Study or subgroup	Regimen A N	Mean(SD)	Regimen B N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Three injections versus six injections							
Castorino 2011	18	86 (7)	19	82 (8)		100.0 %	4.00 [-0.84, 8.84]
Total (95% CI)	**18**		**19**			**100.0 %**	**4.00 [-0.84, 8.84]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.62 (P = 0.11)							
Test for subgroup differences: Not applicable							

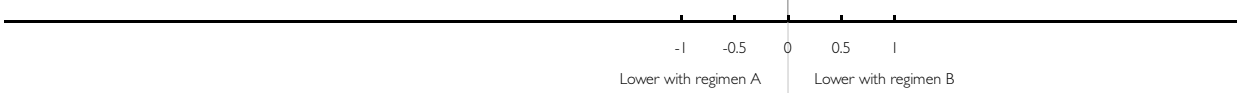
Analysis 5.8. Comparison 5 Regimen A versus regimen B, Outcome 8 Glycaemic control during/end of treatment (HbA1c).

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 5 Regimen A versus regimen B

Outcome: 8 Glycaemic control during/end of treatment (HbA1c)

Study or subgroup	Regimen A N	Mean(SD)	Regimen B N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Twice v four times daily							
Nachum 1999	136	5.8 (1)	138	5.5 (1)		100.0 %	0.30 [0.06, 0.54]
Subtotal (95% CI)	**136**		**138**			**100.0 %**	**0.30 [0.06, 0.54]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.48 (P = 0.013)							
2 Three injections versus six injections							
Castorino 2011	18	5.5 (0.3)	19	5.6 (0.3)		100.0 %	-0.10 [-0.29, 0.09]
Subtotal (95% CI)	**18**		**19**			**100.0 %**	**-0.10 [-0.29, 0.09]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.01 (P = 0.31)							
Test for subgroup differences: Chi^2 = 6.57, df = 1 (P = 0.01), I^2 =85%							

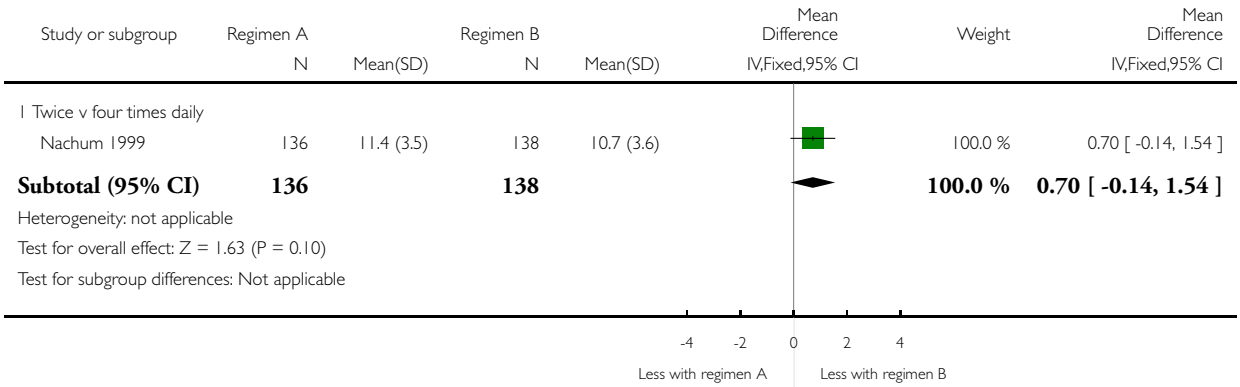


Analysis 5.9. Comparison 5 Regimen A versus regimen B, Outcome 9 Weight gain in pregnancy.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 5 Regimen A versus regimen B

Outcome: 9 Weight gain in pregnancy

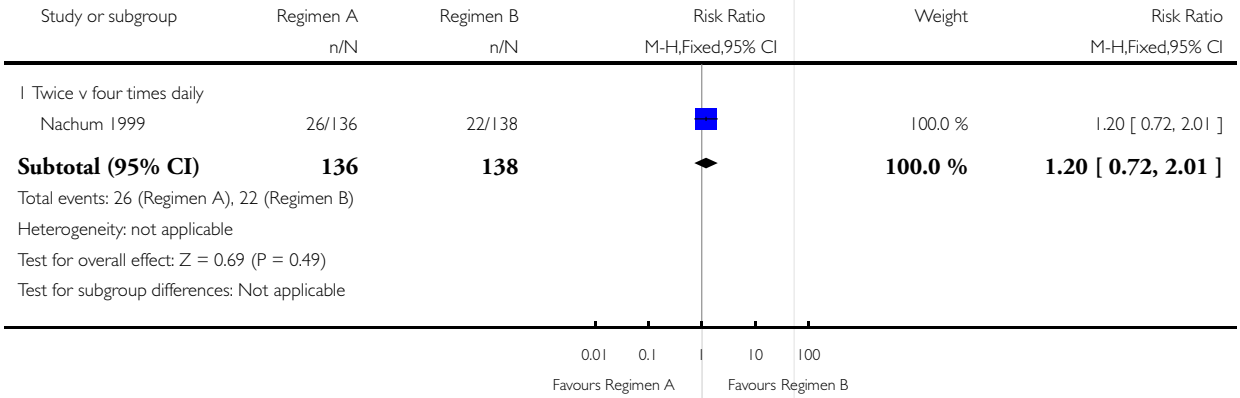


Analysis 5.10. Comparison 5 Regimen A versus regimen B, Outcome 10 Macrosomia.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 5 Regimen A versus regimen B

Outcome: 10 Macrosomia

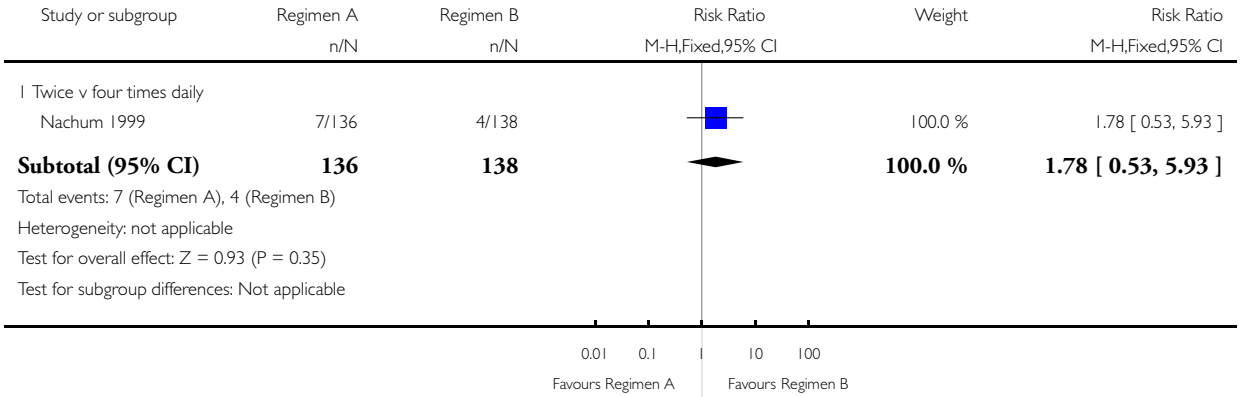


Analysis 5.11. Comparison 5 Regimen A versus regimen B, Outcome 11 Small-for-gestational age.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 5 Regimen A versus regimen B

Outcome: 11 Small-for-gestational age

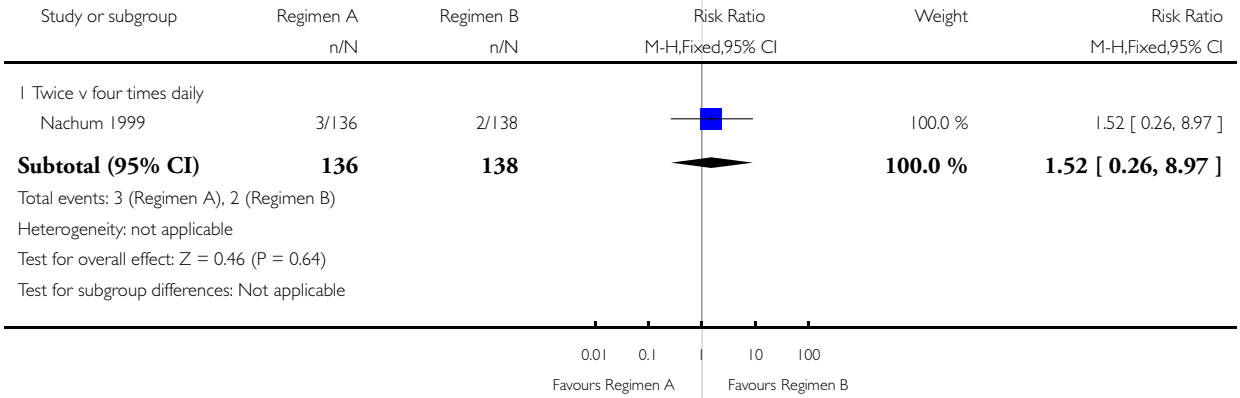


Analysis 5.12. Comparison 5 Regimen A versus regimen B, Outcome 12 Birth trauma.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 5 Regimen A versus regimen B

Outcome: 12 Birth trauma

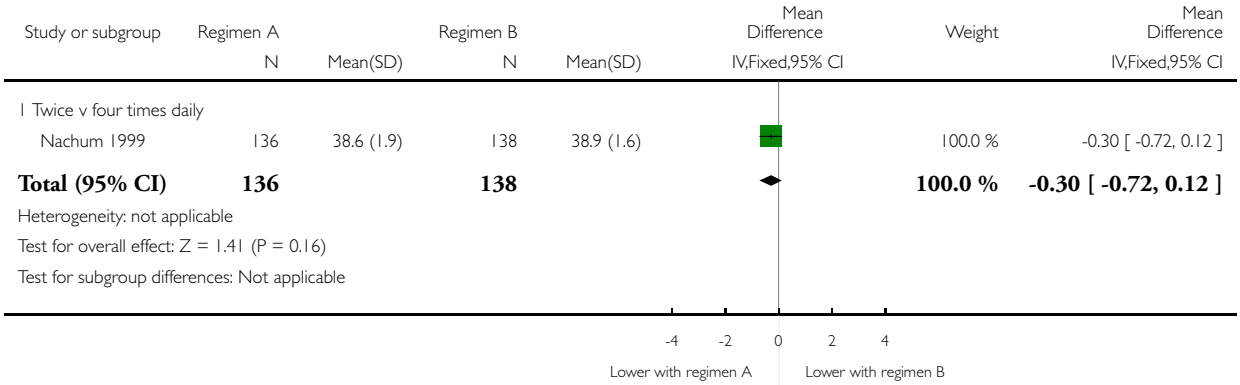


Analysis 5.13. Comparison 5 Regimen A versus regimen B, Outcome 13 Gestational age at birth.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 5 Regimen A versus regimen B

Outcome: 13 Gestational age at birth

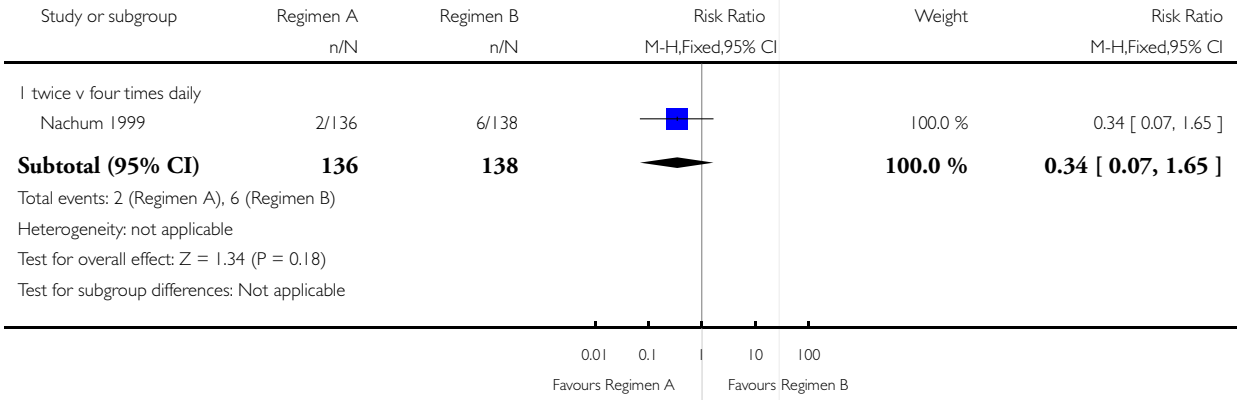


Analysis 5.14. Comparison 5 Regimen A versus regimen B, Outcome 14 Five-minute Apgar less than 7.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 5 Regimen A versus regimen B

Outcome: 14 Five-minute Apgar less than 7

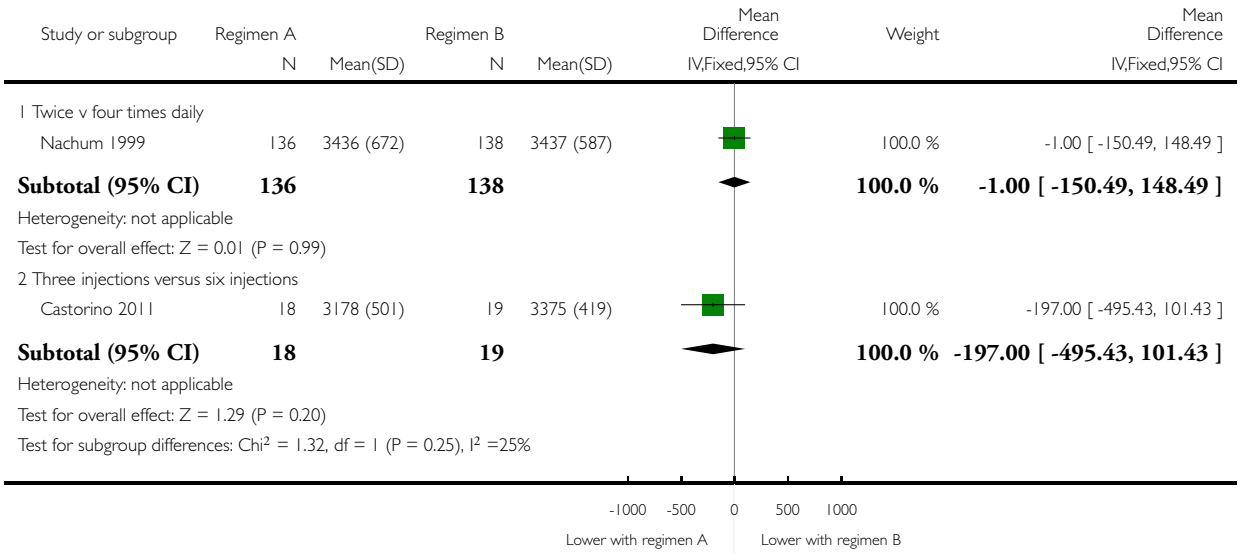


Analysis 5.15. Comparison 5 Regimen A versus regimen B, Outcome 15 Birthweight (g).

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 5 Regimen A versus regimen B

Outcome: 15 Birthweight (g)

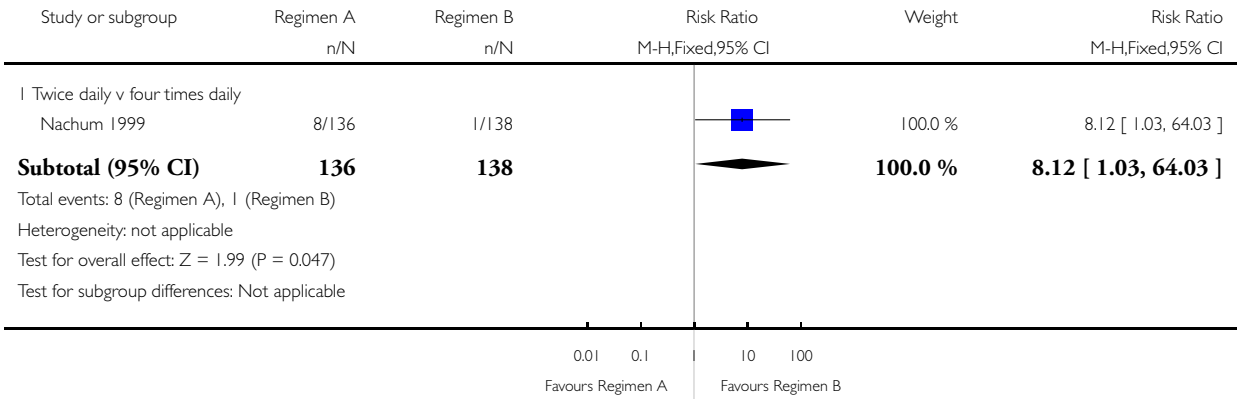


Analysis 5.16. Comparison 5 Regimen A versus regimen B, Outcome 16 Neonatal hypoglycaemia.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 5 Regimen A versus regimen B

Outcome: 16 Neonatal hypoglycaemia

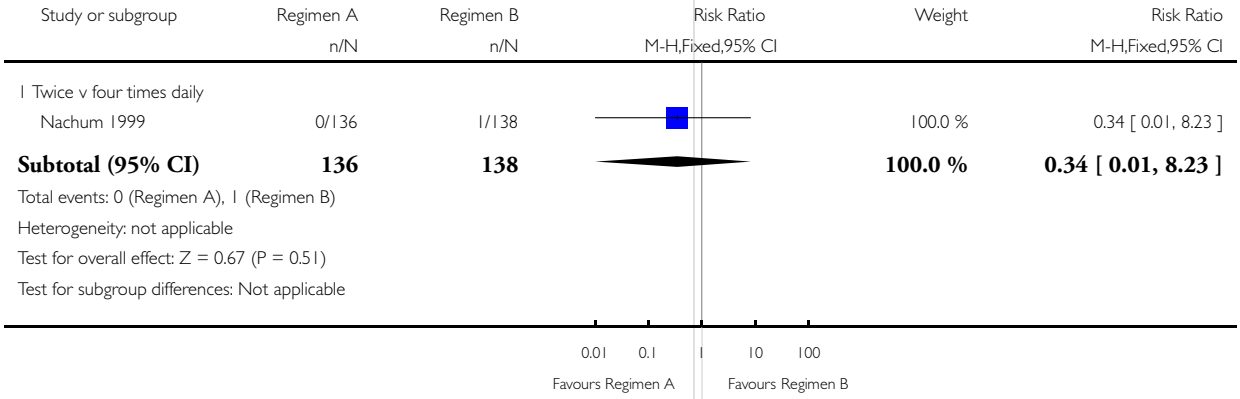


Analysis 5.17. Comparison 5 Regimen A versus regimen B, Outcome 17 Respiratory distress syndrome.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 5 Regimen A versus regimen B

Outcome: 17 Respiratory distress syndrome

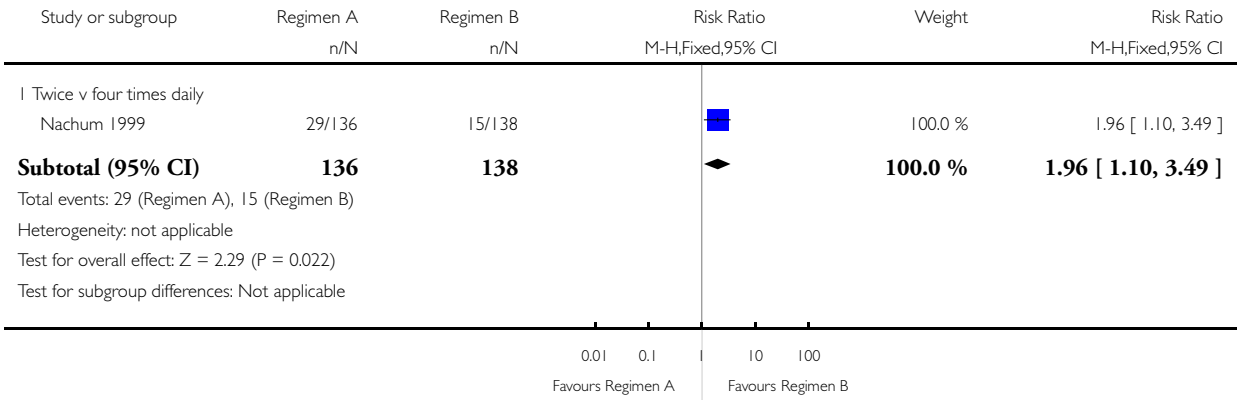


Analysis 5.18. Comparison 5 Regimen A versus regimen B, Outcome 18 Neonatal jaundice (Hyperbilirubinaemia).

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 5 Regimen A versus regimen B

Outcome: 18 Neonatal jaundice (Hyperbilirubinaemia)

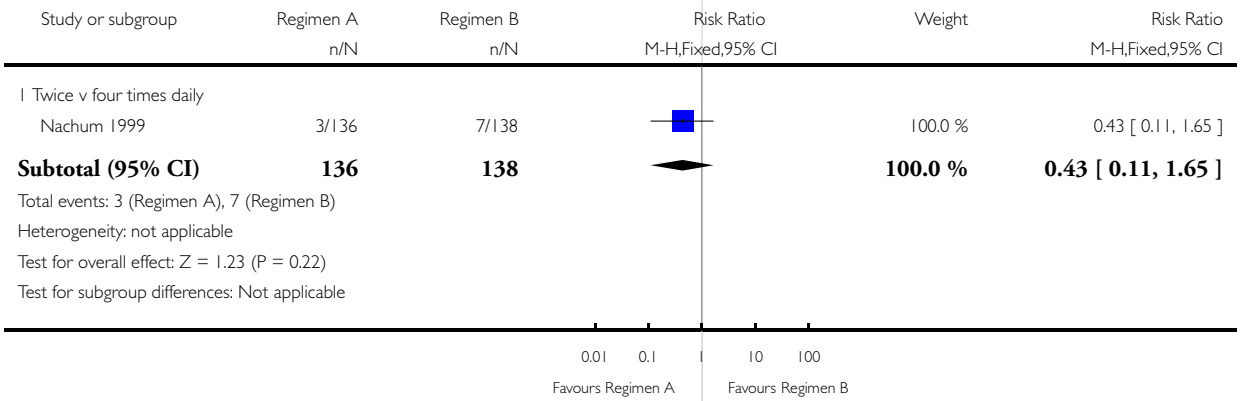


Analysis 5.19. Comparison 5 Regimen A versus regimen B, Outcome 19 Polycythaemia.

Review: Insulin for the treatment of women with gestational diabetes

Comparison: 5 Regimen A versus regimen B

Outcome: 19 Polycythaemia



ADDITIONAL TABLES

Table 1. Examples of diagnostic criteria for gestational diabetes mellitus

Organisation/ professional body	Screening criteria	Diagnostic criteria				
	One-hour oral glucose challenge test	Oral glucose tolerance test	Fasting	1-hour	2-hour	3-hour
ADA 2015b*, IADPSG 2010*, ADIPS 2014* (Nankervis 2014); WHO 2014*	-	75 g	≥ 5.1 mmol/L (≥ 92 mg/dL)	≥ 10 mmol/L (≥ 180 mg/dL)	≥ 8.5 mmol/L (≥ 153 mg/dL)	-
ADA 2015b	50 g (≥ 7.8 mmol/L; ≥ 140 mg/dL)	75 g	≥ 5.1 mmol/L (≥ 92 mg/dL)	≥ 10 mmol/L (≥ 180 mg/dL)	≥ 8.5 mmol/L (≥ 153 mg/dL)	-
ACOG 2013 Carpenter and Coustan^ or National Diabetes Data Group^	50 g (> 7.2 mmol/L; > 130 mg/dL)	100 g	≥ 5.3 mmol/L (95 mg/dL)	≥ 10 mmol/L (180 mg/dL)	≥ 8.6 mmol/L (155 mg/dL)	≥ 7.8 mmol/L (140 mg/dL)
	50 g (> 7.8 mmol/L; > 140 mg/dL)	100 g	≥ 5.8 mmol/L (105 mg/dL)	≥ 10.6 mmol/L (190 mg/dL)	≥ 9.2 mmol/L (165 mg/dL)	≥ 8.0 mmol/L (145 mg/dL)
NICE 2008; WHO 1999*; ADIPS 1998 (Hoffman 1998)		75 g	≥ 7.0 mmol/L (≥ 126 mg/dL)	-	≥ 11.1 mmol/L (≥ 200 mg/dL)	-
NICE 2015	-	75 g	≥ 5.6 mmol/L (≥ 101 mg/dL)	-	≥7.8 mmol/L (140 mg/dL)	-
New Zealand Ministry of Health 2014*	50 g if HbA1c < 41 mmol/mol (≥ 7.8 mmol/L; ≥ 140 mg/dL)	75 g	≥ 5.5 mmol/L (≥ 99 mg/dL)	-	≥ 9.0 mmol/L (≥ 162 mg/dL)	-

ADA: American Diabetes Association (recommends either the one step or two step strategy)
IADPSG: International Association of the Diabetes and Pregnancy Study Groups
ADIPS: Australasian Diabetes in Pregnancy Society
ACOG: American College of Obstetrics and Gynecology
NICE: National Institute for Health and Care Excellence
*1 abnormal result required for diagnosis
^2 or more abnormal results required for diagnosis
mmol/L - millimoles per litre
mg/dL - milligramme per decilitre

Table 2. Diagnostic criteria

		Screen	Diagnostic test	Diagnostic criteria	
Ashoush 2016	Not stated	Not stated	2-hour, 75 g OGTT	Not stated	ADA 2004
Anjalakshi 2007	Not stated	Not stated	75 g OGTT	2-hour ≥ 7.7 mmol/L (140 mg/dL)	WHO 1994
Ardilouze 2014	-	-	-	-	Canadian Diabetes Association (no details)
Balaji 2005	Not stated	Not stated	Not stated	Not stated	Not stated
Balaji 2012	12 to 28 weeks'	Not stated	2-hour, 75 g OGTT	2-hour ≥ 7.7 mmol/L (140 mg/dL)	WHO 1994
Behrashi 2016	11 to 33 weeks'	Not stated	3-hour, 100 g OGTT	2 abnormal values of: Fasting blood glucose ≥ 5.3 mmol/L (95 mg/dL), 1-hour glucose level 10.0 mmol/L (180 mg/dL), 2-hour glucose level 8.6 mmol/L (155 mg/dL) 3-hour glucose level 7.8 mmol/L (140 mg/dL),	Carpenter and Coustan criteria
Bertini 2005	11 to 33 weeks'	Not stated	2-hour, 75 g OGTT	Fasting blood glucose ≥ 6.1 mmol/L (110 mg/dL) and 2-hour glucose level ≥ 7.8 mmol/L (140 mg/dL)	WHO 1994
Beyuo 2015	20 to 28 weeks'	Not stated	2-hour, 75 g OGTT	1 or more abnormal value from: Fasting blood glucose ≥ 5.1 mmol/L (92 mg/dL), 1-hour glucose level 10.0 mmol/L (180	ADA 2012

Table 2. Diagnostic criteria (*Continued*)

				mg/dL), 2-hour glucose level 8.5 mmol/L (153 mg/dL).	
Bung 1993	Not stated	Not stated	Not stated	Not stated	Not stated
Castorino 2011	Not stated	Not stated	Not stated	Not stated	Not stated
Coustan 1978	Not stated	Women with risk factors for GDM	3-hour, 100 g OGTT	2 abnormal values of: Fasting blood glucose ≥ 5.3 mmol/L (95 mg/dL), 1-hour glucose level 10.0 mmol/L (180 mg/dL), 2-hour glucose level 8.9 mmol/L (160 mg/dL), 3-hour glucose level 7.5 mmol/L (135 mg/dL).	Modified O'sullivan and Mahan (1964)
De Veciana 2002	Not stated	Not stated	Not stated	Not stated	Not stated
Di Cianni 2007	No details				Carpenter and Coustan criteria
Hague 2003	-	-	-	-	ADIPS (old criteria)
Herrera 2015					Carpenter and Coustan 1983 or IADPSG 2010
Hickman 2013	< 20 weeks'	Not stated	3-hour 100 g OGTT	2 or more abnormal values	National Diabetes Data Group Criteria 1979
Hutchinson 2008	Not stated	Not stated	Not stated	Not stated	Not stated
Ijas 2011	Risk factor	Not stated	2-hour, 75 g OGTT	Fasting blood glucose 5.3 mmol/L (95 mg/dL), 1-hour glucose level 11.0 mmol/L, 2-hour glucose level 9.6 mmol/L. There were to be 1 or more abnormal values	Not stated

Table 2. Diagnostic criteria (*Continued*)

Ismail 2007	Not stated	Not stated	Not stated	Not stated	Not stated
Jovanovic 1999	14 to 32 weeks'				Carpenter and Coustan criteria modification of NDDG criteria
Lain 2009	24 to 34 weeks'	50 g 1-hour oral glucose challenge test > 7.5 mmol/L (135 mg/dL)	100 g 3-hour OGTT	2 abnormal values of: Fasting blood glucose 5.3 mmol/L (95 mg/dL), 1-hour glucose level 10.0 mmol/L (180 mg/dL) 2-hour glucose level 8.6 mmol/L (155 mg/dL) 3-hour glucose level 7.8 mmol/L (140 mg/dL), An elevated fasting value of 3-hour OGTT or 1-hour OGTT > 11.1 mmol/L or 200 mg/dL diagnostic of diabetes	Carpenter and Coustan criteria
Langer 2000	11 to 33 weeks'	50 g, 1-hour oral glucose challenge test > 7.3 mmol/L (130 mg/dL)	100 g OGTT	Fasting blood glucose between 5.3 mmol/L (95 mg/dL) and 7.8 mmol/L (130 mg/dL). 2 or more abnormal values required	Carpenter and Coustan criteria.
Majeed 2015	Not reported	Not reported	Not reported	Not reported	Not reported
Martinez Piccole 2010	Not reported	Not reported	Not reported	Not reported	Not reported
Mecacci 2003	25 to 32 weeks'				Carpenter and Coustan criteria
Mesdaghinia 2013	24 to 34 weeks'	50 g, 1-hour oral glucose challenge test	100 g 3-hour OGTT	2 or more abnormal results required from Fasting blood sugar	Carpenter and Coustan criteria

Table 2. Diagnostic criteria (*Continued*)

				> 5.3 mmol/L or 95 mg/dL; 1-hour glucose level > 9.99 mmol/L or 180 mg/dL; 2-hour glucose level > 8.6 mmol/L or 150 mg/dL; 3-hour glucose level > 7.8 mmol/L or 140 mg/dL.	
Mirzamoradi 2015	24 to 28 weeks'	Not stated	Not stated	Fasting blood glucose > 5.3 mmol/L or 95 mg/dL, 1-hour glucose level > 10.0 mmol/L or 180 mg/dL or 2-hour glucose level > 8.6 mmol/L or 150 mg/dL.	Carpenter and Coustan criteria
Mohamed 2014	-	-	-	Plasma glucose > 7.8 mmol/L (140 mg/dL)	Carpenter and Coustan criteria
Moore 2007	24 to 30 weeks'	1-hour 50 g glucose challenge test	100 g 3-hour OGTT	Fasting blood glucose > 105 mg/dL, 1-hour glucose level > 190 mg/dL, 2-hour glucose level > 165 mg/dL and 3-hour glucose level > 145 mg/dL. 2 or more abnormal values required for diagnosis.	ADA criteria (old)
Mukhopadhyay 2012	20 to 28 weeks'	Not stated	2-hour, 75 g OGTT	Fasting blood glucose ≥ 6.1 mmol/L (110 mg/dL) and 2-hour glucose level ≥ 7.8 mmol/L (140 mg/dL)	WHO 1994
Nachum 1999	Not stated	Not stated	100 g 3-hour OGTT	Fasting blood glucose 5.9 mmol/L 1-hour glucose level 10.6 mmol/L	NDDG 1979

Table 2. Diagnostic criteria (*Continued*)

				2-hour glucose level 9.2 mmol/L 3-hour glucose level 8.1 mmol/L	
Niromanesh 2012	20 to 34 weeks'	1-hour 50 g glucose challenge test	100 g 3-hour OGTT	-	Carpenter and Coustan criteria
Notelovitz 1971	Not reported	Not reported	2-hour, 100 g OGTT	2-hour glucose level ≥ 7.8 mmol/L (140 mg/dL)	Not reported
Ogunyemi 2007	Not reported	1-hour 50 g glucose challenge test	3-hour OGTT	Not reported	Not reported
O'Sullivan 1975a	Not reported	1-hour 50 g glucose challenge test - ≥ 130 mg/100 mL or presence of risk factors including history of macrosomia, fetal death, neonatal death, congenital anomaly	3-hour 100 g OGTT	2 or more abnormal readings from Fasting blood glucose ≥ 110 mg/100 mL 1-hour blood glucose level ≥ 170 mg/100 mL, 2-hour blood glucose level ≥ 120 mg/100 mL, 3-hour blood glucose level ≥ 110 mg/100 mL.	Not reported
O'Sullivan 1975b	Not reported	1-hour 50 g glucose challenge test - ≥ 130 mg/100 mL	3-hour 100 g OGTT	2 or more abnormal readings from Fasting blood glucose ≥ 110 mg/100 mL 1-hour blood glucose level ≥ 170 mg/100 mL, 2-hour blood glucose level ≥ 120 mg/100 mL, 3-hour blood glucose level ≥ 110 mg/100 mL.	Not reported
Pavithra 2016	24 to 28 weeks'	1-hour 50 g glucose challenge test	100 g OGTT	Fasting blood glucose > 5.3 mmol/L or 95 mg/dL, 1-hour glucose level	Carpenter and Coustan criteria

Table 2. Diagnostic criteria (*Continued*)

				> 10.0 mmol/L or 180 mg/dL or 2-hour glucose level > 8.6 mmol/L or 155 mg/dL. 3-hour glucose level > 7.7 mmol/L or 140 mg/dL	
Persson 1985	Not stated. Risk based selection	Not stated	3-hour, 50 g OGTT	Not stated values but note that 2SD above normal	Gillmer 1975
Pettitt 2007	Not stated	Not stated	Not stated	Not stated	Not stated
Poyhonen-Alho 2002	24 to 28 weeks'	OGTT based on risk factors (BMI > 25 kg/m2, age > 40 years, previous GDM, previous infant with macrosomia > 4500 g, glucosuria, current macrosomia)	2-hour, 75 g OGTT	2 or more abnormal values from: Fasting ≥ 4.8 mmol/L 1-hour glucose level ≥ 10.0 mmol/L 2-hour glucose value ≥ 8.7 mmol/L	Finnish national guidelines (2008)
Prasad 2008	Not stated	Not stated	Not stated	Not stated	Not stated
Riaz 2014	Not stated	Not stated	75 g OGTT	Not stated	Not stated
Rowan 2008	20 to 33 weeks'	Not stated	75 g OGTT	1 or more of the following being abnormal Fasting plasma glucose level ≥ 5.1 mmol/L, 1-hour venous plasma glucose ≥ 10.0 mmol/L (180 mg/dL), or 2-hour venous plasma glucose ≥ 8.5 mmol/L.	ADIPS (1998)
Ruholamin 2014	24 to 28 weeks'				ADIPS 1998
Saleh 2016	26 to 34 weeks'	Not stated	2-hour, 75 g OGTT	Fasting blood glucose ≥ 7.0 mmol/L (126 mg/dL) and 2-hour glucose level ≥ 7.8 mmol/L (140	IADPSG 2010

Table 2. Diagnostic criteria (*Continued*)

				mg/dL)	
Silva 2007	11 to 33 weeks'	Not stated	2-hour, 75 g OGTT	Fasting blood glucose ≥ 6.1 mmol/L (110 mg/dL) and 2-hour glucose level ≥ 7.8 mmol/L (140 mg/dL)	WHO 1994
Spaulonci 2013	Not reported	Not stated	2-hour 75 g or 3-hour 100 g OGTT	2 or more abnormal results Fasting blood glucose > 5.3 mmol/L (95 mg/dL) 1-hour glucose level ≥ 10.0 mmol/L (180 mg/dL) 2-hour glucose level ≥ 8.6 mmol/L (155 mg/dL) 3-hour glucose level ≥ 7.8 mmol/L (140 mg/dL)	ADA 2011
Tertti 2013	22 to 34 weeks'	Screening criteria based on risk changed during the study	2-hour 75 g OGTT	Diagnostic cut-off levels up to 2008 were: Fasting blood glucose ≥ 4.8 mmol/L (87 mg/dL) 1-hour glucose level ≥ 10.0 mmol/L (180 mg/dL) and 2-hour glucose level ≥ 8.7 mmol/L (157 mg/dL) and thereafter was fasting ≥ 5.3 mmol/L (95 mg/dL), 1-hour ≥ 10 mmo/L (180 mg/dL) and 2-hour ≥ 8.6 mmol/L (155 mg/dL).	Finnish national guidelines (2008)
Thompson 1990	28 weeks' or earlier	1-hour 50 g glucose challenge test	100 g 3-hour OGTT	Fasting blood glucose > 105 mg/dL, 1-hour glucose level > 190 mg/dL,	ADA criteria (old)

Table 2. Diagnostic criteria (*Continued*)

				2-hour glucose level > 165 mg/dL and 3-hour glucose level > 145 mg/dL. 2 or more abnormal values required for diagnosis.	
Waheed 2013	14 weeks' or more	No details	No details	Fasting blood glucose > 5.5 mmol/L (100 mg/dL), and random blood sugar > 7.7 mmol/L (140 mg/dL)	Not stated
Wali 2015					IADPSG (2010)
Zangeneh 2014	24 weeks'	1-hour 50 g glucose challenge test	100 g 3-hour OGTT	Fasting blood glucose between 5.3 mmol/L (95 mg/dL) and 7.8 mmol/L (130 mg/dL). 2 or more abnormal values required	Carpenter and Coustan criteria.
Zawiejska 2016	No details	No details	No details	No details	No details

OGTT: oral glucose tolerance test

Table 3. Maternal age (Years)

Trial ID		
	Insulin	Glibenclamide
Anjalakshi 2007	27.5 ± 5.8 (n = 13)	24.9 ± 3.7 (n = 10)
Behrashi 2016	29.9 ± 7.0 (n = 129)	30.7 ± 7.2 (n = 120)
Bertini 2005	28.7 ± 6.0 (n = 27)	31.2 ± 4.5 (n = 24)
Lain 2009	31.2 ± 5.9 (n = 41)	32.2 ± 5.0 (n = 41)
Langer 2000	30 ± 6 (n = 203)	29 ± 7 (n = 201)
Mirzamoradi 2015	31.2 ± 5.0 (n = 59)	29.5 ± 4.1 (n = 37)

Table 3. Maternal age (Years) (*Continued*)

Mukhopadhyay 2012	26 ± 4.3 (n = 30)	26.3 ± 4.6 (n = 30)
Ogunyemi 2007	Not reported	Not reported
Pavithra 2016	27.9 ± 3.6 (n = 50)	28.2 ± 3.1 (n = 50)
Silva 2007	29.9 ± 6.0 (n = 36)	31.6 ± 4.2 (n = 32)
Zangeneh 2014	32.6 ± 6.2 (n = 46)	31.4 ± 5 (n = 44)
	Insulin	Metformin
Ashoush 2016	32.1 ± 3.2 (n = 48)	31.6 ± 2.8 (n = 47)
Beyuo 2015	33.1 ± 4.6 (n = 40)	33.5 ± 4.7 (n = 43)
Hague 2003	34.1 ± 3.7 (n = 14)	33.7 ± 4.44 (n = 16)
Hickman 2013	Median 31 (IQR 26, 33) (n = 14)	Median 36 (IQR 35, 37) (n = 14)
Ijas 2011	31.7 ± 6.1 (n = 50)	32.3 ± 5.6 (n = 47)
Mesdaghinia 2013	30.2 ± 5.9 (n = 100)	29.6 ± 5.3 (n = 100)
Moore 2007	27.7 ± 6.7 (n = 31)	27.1 ± 4.7 (n = 32)
Majeed 2015	Not reported	Not reported
Martinez Piccole 2010	Not reported	Not reported
Niromanesh 2012	31.8 ± 5.1 (n = 80)	30.7 ± 5.5 (n = 80)
Riaz 2014	Not reported	Not reported
Rowan 2008	33 ± 5.1 years (n = 370)	33.5 ± 5.4 (n = 363)
Ruholamin 2014	23.4 ± 2.5 (n = 50)	24.6 ± 6.3 (n = 50)
Saleh 2016	29.8 ± 2.2 (n = 70)	31.0 ± 3.4 (n = 67)
Spaulonci 2013	32.76 ± 4.66 (n = 47)	31.93 ± 6.02 (n = 47)
Tertti 2013	32.1 ± 5.4 (n =107)	31.9 ± 5.0 (n = 110)
Waheed 2013	29.82 ± 4.58 (n = 34)	29.35 ± 4.97 (n = 34)

Table 3. Maternal age (Years) (*Continued*)

Wali 2015	Not reported	Not reported
Zawiejska 2016	35 (30 to 38) (n = 43)	22 (29 to 39) (n = 35)
	Insulin	Acarbose
Bertini 2005	28.7 ± 6.0 (n = 27)	31.5 ± 5.8 (n = 19)
De Veciana 2002	Not reported	Not reported
	Insulin	Glyburide/metformin combined
Ardilouze 2014	30.7 ± 4.4 (n = 33)	31.1 ± 4.7 (n = 35)
Hutchinson 2008	Not reported	Not reported
Mohamed 2014	32.1 ± 5.7 (n = 42)	33.2 ± 4.9 (n = 42)
	Human insulin	Insulin aspart
Balaji 2005	31.0 ± 2.7 (n = 5)	30.6 ± 5.0 (n = 5)
Balaji 2012	29.6 ± 4.5 (n = 157)	29.2 ± 4.0 (n = 163)
Di Cianni 2007	Not reported	Not reported
Pettitt 2007	29.7 ± 6.9 (n = 13)	31.6 ± 5.9 (n = 14)
Prasad 2008	Not reported	Not reported
	Human insulin	Insulin lispro
Di Cianni 2007	Not reported	Not reported
Jovanovic 1999	29.8 ± 1.0 (n = 23)	34.2 ± 1.3 (n = 19)
Mecacci 2003	median 35 (range 28 to 41) (n = 24)	Median 34.5 (range 28 to 41) (n = 25)

Table 3. Maternal age (Years) (*Continued*)

	Human insulin	Neutral Protamine Hagedorn insulin
Poyhonen-Alho 2002	Not reported	Not reported
Ismail 2007	Not reported	Not reported
Herrera 2015	Median 35 [31-38] (n = 42)	Median 35 [IQR 32-38] (n = 45)
	Insulin	Diet
Coustan 1978	Not reported	Not reported
Notelovitz 1971	31.8 (n = 47)	32.7 (n = 56)
Persson 1985	Median 30.5 (range 16 to 42) (n = 97)	Median 29 (range 18 to 46) (n = 105)
Thompson 1990	27 ± 5.4	26 ± 5.7
	Insulin	Exercise
Bung 1993	Not reported	Not reported
	Insulin	Standard care
O'Sullivan 1975a	Not reported	Not reported
O'Sullivan 1975b	Not reported	Not reported
	Insulin regimen A	Insulin regimen B
Castorino 2011	Not reported	Not reported
Nachum 1999	33 ± 5 (n = 136)	33 ± 5 (n = 138)

Table 4. Ethnicity/Race

Trial ID	Ethnicity
Ashoush 2016	Not reported
Anjalakshi 2007	Not reported but likely to be Indian
Ardilouze 2014	Not reported
Balaji 2005	Not reported but likely to be Indian
Balaji 2012	Not reported but likely to be Indian
Behrashi 2016	Not reported
Bertini 2005	Not reported but likely to be Brazilian
Beyuo 2015	Not reported
Bung 1993	Not reported
Castorino 2011	86% Mexican
Coustan 1978	Not reported
De Veciana 2002	Not reported
Di Cianni 2007	Not reported
Hague 2003	Not reported
Herrera 2015	33% White, 14% Black, 31% Hispanic, 21% Native American/Alaskan
Hickman 2013	79% Hispanic, 14% Black
Hutchinson 2008	Not reported
Ijas 2011	Not reported
Ismail 2007	Not reported
Jovanovic 1999	95% Hispanic
Lain 2009	13% Black (no other details)
Langer 2000	83% were Hispanic and 12% non-Hispanic Caucasian

Table 4. Ethnicity/Race (*Continued*)

Majeed 2015	Not reported but likely to be Indian
Martinez Piccole 2010	Not reported
Mecacci 2003	Caucasian
Mesdaghinia 2013	Not reported but likely to be Iranian
Mirzamoradi 2015	Not reported but likely to be Iranian
Mohamed 2014	Not reported
Moore 2007	50% African American, 44% Native American
Mukhopadhyay 2012	Not reported but likely to be Indian
Nachum 1999	56% were Jewish
Niromanesh 2012	Not stated but likely to be Iranian
Ismail 2007	Not reported
Notelovitz 1971	37% were Bantu (Zulu)
Ogunyemi 2007	80% were Hispanic and 15% African American
O'Sullivan 1975a	Not reported
O'Sullivan 1975b	Not reported
Pavithra 2016	Not reported
Persson 1985	Not reported
Pettitt 2007	75% were Hispanic and 19% were Caucasian
Poyhonen-Alho 2002	Not reported
Prasad 2008	Not reported
Riaz 2014	Not reported but likely to be Pakistani
Rowan 2008	47% Caucasian, 21% Polynesian, 13% Indian
Ruholamin 2014	Not reported but likely to be Iranian
Saleh 2016	Not reported

Table 4. Ethnicity/Race (*Continued*)

Silva 2007	Not reported but likely to be Brazilian
Spaulonci 2013	Not reported
Tertti 2013	Not reported
Thompson 1990	41% 'Black', 49% 'White'
Waheed 2013	Not reported but likely to be Pakistani
Wali 2015	Not reported but likely to be Pakistani
Zangeneh 2014	Not reported but likely to Iranian
Zawiejska 2016	Not reported

Table 5. Maternal BMI at baseline (kg/m2)

Trial ID		
	Insulin	Glibenclamide
Anjalakshi 2007	25.3 ± 5.1 (n = 13)	22.8 ± 3.5 (n = 10)
Behrashi 2016	22.6 ± 3.1 (n = 129)	21.9 ± 2.80 (n = 120)
Bertini 2005	27.0 ± 7.2 (n = 27)	27.5 ± 5.8 (n = 24)
Lain 2009	30.9 ± 5.7 (n = 41)	33.4 ± 12.9 (n = 41)
Langer 2000	Not reported	Not reported
Mirzamoradi 2015	31.8 ± 5.1 (n = 59)	30.8 ± 5.4 (n = 37)
Mukhopadhyay 2012	23.0 ± 2.9 (n = 30)	23.7 ± 2.7 (n = 30)
Ogunyemi 2007	30.8 ± 6.9 (n = 49)	32.0 ± 7.6 (n = 48)
Pavithra 2016	28.3 ± 3.8 (n = 50)	27.8 ± 4.0 (n = 50)
Silva 2007	27.9 ± 6.8 (n = 36)	27.5 ± 5.1 (n = 32)
Zangeneh 2014	27.8 ± 3 (n = 46)	27.5 ± 1.5 (n = 44)
	Insulin	Metformin

Table 5. Maternal BMI at baseline (kg/m2) (*Continued*)

Ashoush 2016	31.4 ± 1.5 (n = 48)	31.1 ± 1.3 (n = 47)
Beyuo 2015	32.6 ± 6.2 (n = 40)	33.5 ± 7.0 (n = 43)
Hague 2003	37.9 ± 6.87 (n = 14)	39.5 ± 6.94 (n = 16)
Hickman 2013	Median 33 (IQR 28, 41) (n = 14)	Median 29 (IQR 27,33) (n = 14)
Ijas 2011	30.8 ± 5.4 (n = 50)	31.5 ± 6.5 (n = 47)
Majeed 2015	Not reported	Not reported
Mesdaghinia 2013	28.5* (n = 100)	27.6* (n = 100)
Moore 2007	35.3 ± 6.7 (n = 31)	39.7 ± 9.0 (n = 32)
Niromanesh 2012	27.1 ± 2.1 (n = 80)	28.1 ± 4.0 (n = 80)
Martinez Piccole 2010	Not reported	Not reported
Riaz 2014	Not reported	Not reported
Rowan 2008	34.6 ± 7.2 (n = 370)	35.1 ± 8.3 (n = 363)
Ruholamin 2014	25.1 ± 3.4 (n = 50)	26.4 ± 2.8 (n = 50)
Saleh 2016	31.6 ± 31.1 (n = 70)	30.1 ± 3.2 (n = 67)
Spaulonci 2013	31.39 ± 5.71 (n = 47)	31.96 ± 4.75 (n = 47)
Tertti 2013	28.9 ± 4.7 (n = 107)	29.4 ± 5.9 (n = 110)
Waheed 2013	Not reported	Not reported
Wali 2015	Not reported	Not reported
Zawiejska 2016	32.0 ± 5.8 (n = 43)	32.2 ± 6.4 (n = 35)
	Insulin	Acarbose
Bertini 2005	27.0 ± 7.2 (n = 27)	25.7 ± 4.2 (n = 19)
De Veciana 2002	32.1 ± 5.6 (n = 46)	33.1 ± 6.4 (n = 45)

Table 5. Maternal BMI at baseline (kg/m2) (*Continued*)

	Insulin	Glyburide/metformin combined
Ardilouze 2014	32.2 ± 7.2 (n = 33)	32.0 ± 5.4 (n = 35)
Hutchinson 2008	Not reported	Not reported
Mohamed 2014	Not reported	Not reported
	Human insulin	Insulin aspart
Balaji 2005	25.6 ± 2.9 (n = 5)	28.6 ± 3.1 (n = 5)
Balaji 2012	25.8 ± 3.4 (n = 157)	26.0 ± 3.4 (n = 163)
Di Cianni 2007	Not reported	Not reported
Pettitt 2007	33.2 ± 5.7 (n = 13)	29.3 ± 4.7 (n = 14)
Prasad 2008	Not reported	Not reported
	Human insulin	Insulin lispro
Jovanovic 1999	33.3 ± 1.2 (n = 23)	31.5 ± 1.1 (n = 19)
Mecacci 2003	Median 22.3 (range 19.8 to 25.3) (n = 24)	Median 21.5 (range 19.2 to 25.1) (n = 25)
	Human insulin	Neutral Protamine Hagedorn insulin
Di Cianni 2007	Not reported	Not reported
Poyhonen-Alho 2002	Not reported	Not reported
Ismail 2007	Not reported	Not reported
	Insulin	Diet
Coustan 1978	Not reported	Not reported
Notelovitz 1971	Not reported	Not reported

Table 5. Maternal BMI at baseline (kg/m2) (*Continued*)

Persson 1985	Not reported	Not reported
Thompson 1990	Not reported	Not reported
	Insulin detemir	Neutral Protamine Hagedorn insulin
Herrera 2015	28.3 (IQR 24.9-33.8) (n = 42)	28.6 (IQR 24.4-31.1) (n = 45)
	Insulin	Exercise
Bung 1993	Not reported	Not reported
	Insulin	Standard care
O'Sullivan 1975a	Not reported	Not reported
O'Sullivan 1975b	Not reported	Not reported
	Insulin regimen A	Insulin regimen B
Castorino 2011	Not reported	Not reported
Nachum 1999	27.8 ± 2.7 (n = 136)	27.9 ± 2.6 (n = 138)

*SD not reported
IQR: interquartile ratio

Table 6. Gestational age at start of treatment/enrolment (weeks)

Trial ID		
	Insulin	Glibenclamide
Anjalakshi 2007	22.6 ± 5.6 (n = 13)	22.5 ± 4.7 (n = 10)
Behrashi 2016	24.5 ± 4.5 (n = 129)	24.9 ±3.9 (n = 120)
Bertini 2005	Not reported	Not reported

Table 6. Gestational age at start of treatment/enrolment (weeks) (*Continued*)

Lain 2009	30.6 ± 2.2 (n = 41)	30.8 ± 2.5 (n = 41)
Langer 2000	25.0 ± 7.0 (n = 203)	24.0 ± 7.0 (n = 201)
Mukhopadhyay 2012	27.4 ± 2.7 (n = 30)	28.3 ± 2.2 (n = 30)
Mirzamoradi 2015	30.3 ± 4.0 (n = 59)	29.9 ± 4.1 (n = 37)
Ogunyemi 2007	24.6 ± 8.0 (n = 49)	28.1 ± 7.6 (n = 48)
Pavithra 2016	Not reported	Not reported
Silva 2007	25.6 ± 5.9 (n = 36)	26.6 ± 4.3 (n = 32)
Zangeneh 2014	Not reported	Not reported
	Insulin	Metformin
Ashoush 2016	29.7 ± 1.9 (n = 48)	29.8 ± 1.4 (n = 47)
Beyuo 2015	Median 26 IQ range 23 to 28 (n = 40)	Median 28 IQ range 26 to 29 (n = 43)
Hague 2003	30.4 ± 4.67 (n = 14)	29.8 ± 4.49 (n = 16)
Hickman 2013	Median 14 (IQR 13, 19) (n = 14)	Median 17 (IQR 10, 22) (n = 14)
Ijas 2011	30.0 ± 4.0 (n = 50)	30.0 ± 4.9 (n = 47)
Majeed 2015	Not reported	Not reported
Mesdaghinia 2013	28.9 ± 3.8 (n = 100)	27.9 ± 3.2 (n = 100)
Moore 2007	28.9 ± 5.0 (n = 31)	27.8 ± 6.5 (n = 32)
Niromanesh 2012	28.6 ± 3.6 (n = 80)	28.7 ± 3.7 (n = 80)
Martinez Piccole 2010	Not reported	Not reported
Riaz 2014	Not reported	Not reported
Rowan 2008	30.1 ± 3.2 (n = 370)	30.2 ± 3.3 (n = 363)
Ruholamin 2014	26.7 ± 3.5 (n = 50)	27.6 ± 3.3 (n = 50)
Saleh 2016	Not reported	Not reported

Table 6. Gestational age at start of treatment/enrolment (weeks) (*Continued*)

Spaulonci 2013	32.05 ± 3.50 (n = 47)	32.18 ± 3.70 (n = 47)
Tertti 2013	30.4 ± 1.8 (n = 107)	30.3 ± 2.0 (n = 110)
Waheed 2013	Not reported	Not reported
Wali 2015	Not reported	Not reported
Zawiejska 2016	30 (28 to 31) (n = 43)	30 (28 to 32) (n = 35)
	Insulin	Acarbose
Bertini 2005	Not reported	Not reported
De Veciana 2002	30.2 ± 3.7 (n = 46)	30.5 ± 3.5 (n = 45)
	Insulin	Glyburide/metformin combined
Ardilouze 2014	30.1 ± 3.1 (n=33)	29.3 ± 3.8 (n=35)
Hutchinson 2008	Not reported	Not reported
Mohamed 2014	24.5 ± 6.3 (n = 42)	22.1 ± 7.3 (n = 42)
	Human insulin	Insulin aspart
Balaji 2005	Not reported	Not reported
Balaji 2012	22.4 ± 10.1 (n = 157)	21.7 ± 9.3 (n = 163)
Di Cianni 2007	Not reported	Not reported
Pettitt 2007	Not reported	Not reported
Prasad 2008	Not reported	Not reported
	Human insulin	Insulin lispro
Di Cianni 2007	Not reported	Not reported

Table 6. Gestational age at start of treatment/enrolment (weeks) (*Continued*)

Jovanovic 1999	25.6 ± 1.3 (n = 23)	27.3 ± 1.4 (n = 19)
Mecacci 2003	Median 29 (range 27 to 32) (n = 24)	Median 29 (range 26 to 32) (n = 25)
	Human insulin	Neutral Protamine Hagedorn insulin
Poyhonen-Alho 2002	Not reported	Not reported
Ismail 2007	Not reported	Not reported
	Insulin detemir	Neutral Protamine Hagedorn insulin
Herrera 2015	Median 27.3 (IQR 23.3 -28.5) (n = 42)	Median 28.1 (25.1 - 29.3) (n = 45)
	Insulin	Diet
Coustan 1978	Not reported	Not reported
Notelovitz 1971	Not reported	Not reported
Persson 1985	Not reported	Not reported
Thompson 1990	Not reported	Not reported
	Insulin	Exercise
Bung 1993	Not reported	Not reported
	Insulin	Standard care
O'Sullivan 1975a	Not reported	Not reported
O'Sullivan 1975b	Not reported	Not reported
	Insulin regimen A	Insulin regimen B

Table 6. Gestational age at start of treatment/enrolment (weeks) (*Continued*)

Castorino 2011	Not reported	Not reported
Nachum 1999	28 ± 6.9 (n = 136)	27.4 ± 6.8 (n = 138)

IQR Interquartile range

Table 7. Treatment targets

Study ID	Fasting	1-hour postprandial	2-hour postprandial
Ashoush 2016	< 5.5 mmol/L (100 mg/dL)		< 7.7 mmol/L (140 mg/dL)
Anjalakshi 2007	-	-	< 6.7 mmol/L (120 mg/dL)
Ardilouze 2014	< 5.3 mmol/L (95 mg/dL)	-	< 6.7 mmol/L (120 mg/dL)
Balaji 2005	< 5.0 mmol/L (90 mg/dL)		< 6.7 mmol/L (120 mg/dL)
Balaji 2012	> 4.4 mmol/L (> 80 mg/dL) and < 5.0 mmol/L (90 mg/dL)	-	< 6.7 mmol/L (120 mg/dL)
Behrashi 2016	< 5.0 mmol/L (90 mg/dL)	-	< 6.7 mmol/L (120 mg/dL)
Bertini 2005	< 5.0 mmol/L (90 mg/dL)	-	< 5.6 mmol/L (100 mg/dL)
Beyuo 2015	< 5.5 mmol/L (99 mg/dL)		< 7.0 mmol/L (126 mg/dL)
Bung 1993	> 5.8 mmol/L (105 mg/dL) to < 7.2 mmol/L (< 130 mg/dL)	-	-
Castorino 2011	< 5.0 mmol/L (90 mg/dL)	< 6.7 mmol/L (120 mg/dL	-
Coustan 1978	Not reported	Not reported	Not reported
De Veciana 2002	</= 5.3 mmol/L (95 mg/dL)		</= 6.7 mmol/L (120 mg/dL)
Di Cianni 2007	-	< 7.2 mmol/L (< 130 mg/dL)	-
Hague 2003	Not reported		
Herrera 2015	< 5.0 mmol/L (90 mg/dL)	-	< 6.7 mmol/L (120 mg/dL)
Hickman 2013	< 5.3 mmol/L (95 mg/dL)	< 7.2 mmol/L (< 130 mg/dL)	
Hutchinson 2008	Not reported	Not reported	Not reported

Table 7. Treatment targets (*Continued*)

Ijas 2011	< 5.3 mmol/L (95 mg/dL)	-	1.5 hours postprandial < 6.7 mmol/L (120 mg/dL)
Ismail 2007	< 5.5 mmol/L (100 mg/dL)	-	-
Jovanovic 1999	< 5.0 mmol/L (90 mg/dL)	-	< 6.7 mmol/L (120 mg/dL)
Lain 2009	< 5.3 mmol/L (95 mg/dL)	-	< 6.7 mmol/L (120 mg/dL)
Langer 2000	3.4 to 5.0 mmol/L (80 to 95 mg/dL)	-	< 6.7 mmol/L (120 mg/dL)
Majeed 2015	Not reported	-	Not reported
Martinez Piccole 2010	Not reported	-	Not reported
Mecacci 2003	< 5.0 mmol/L (90 mg/dL)	< 6.7 mmol/L (120 mg/dL)	-
Mesdaghinia 2013	< 5.3 mmol/L (95 mg/dL)		< 6.7 mmol/L (120 mg/dL)
Mirzamoradi 2015	3.3 to 5.0 mmol/L (60 to 90 mg/dL)	-	< 6.7 mmol/L (120 mg/dL)
Moore 2007	< 5.3 mmol/L (95 mg/dL)	-	< 6.7 mmol/L (120 mg/dL)
Mukhopadhyay 2012	< 5.0 mmol/L (90 mg/dL)	-	< 6.7 mmol/L (120 mg/dL)
Nachum 1999	3.3 to 5.3 mmol/L	</= 6.7	</= 6.7 mmol/L (120 mg/dL)
Niromanesh 2012	< 5.3 mmol/L (95 mg/dL)	-	< 6.7 mmol/L (120 mg/dL)
Ismail 2007	< 5.5 mmol/L		
Notelovitz 1971		8.3 mmol/L (150 mg/dL)	
Ogunyemi 2007	Not reported	Not reported	Not reported
O'Sullivan 1975a	Not reported	Not reported	Not reported
O'Sullivan 1975b	Not reported	Not reported	Not reported
Pavithra 2016	< 5.0 mmol/L (90 mg/dL)		</= 6.7 mmol/L (120 mg/dL)
Persson 1985	< 5.0 mmol/L	< 6.5 mmol/L	-
Poyhonen-Alho 2002	Not reported	Not reported	Not reported

Table 7. Treatment targets (*Continued*)

Pettitt 2007	Not reported	Not reported	Not reported
Prasad 2008	Not reported	Not reported	Not reported
Riaz 2014	Not reported	Not reported	Not reported
Rowan 2008	< 5.3 mmol/L (95 mg/dL)	-	< 6.7 mmol/L (120 mg/dL)
Ruholamin 2014	< 5.3 mmol/L (95 mg/dL)	-	< 6.7 mmol/L (120 mg/dL)
Saleh 2016	≤5.5mmol/L (<100 mg/dL)		< 7.0 mmol/L (126 mg/dL)
Silva 2007	< 5.0 mmol/L (90 mg/dL)	-	< 5.6 mmol/L (100 mg/dL)
Spaulonci 2013	≤ 5.3 mmol/L (95 mg/dL)	-	≤ 6.7 mmol/L (120 mg/dL)
Tertti 2013	≤5.5mmol/L (100 mg/dL)	-	≤ 7.8 mmol/L
Thompson 1990	< 5.8 mmol/L (105mg/dL)	-	< 6.7 mmol/L (120 mg/dL)
Waheed 2013	3.5 to 5.5 mmol/L (63 to 100 mg/dL)	-	-
Wali 2015	Not reported	-	Not reported
Zangeneh 2014	< 5.3 mmol/L (95 mg/dL)	-	< 6.7 mmol/L (120 mg/dL)
Zawiejska 2016	Not reported	-	Not reported

Table 8. Maternal outcomes

Study ID	Outcome	Insulin (A)	Comparison
Hickman 2013	Fasting blood glucose (mg/dL)	Median 85.2 (IQR 86, 115) (n = 8)	Metformin Median 89.5 (IQR 90, 98) (n = 10)
Coustan 1978	Fasting blood glucose (mg/dL)	86.8 ± 12.7 (n = 33 observations)	Diet 94.7 ± 9.1 (n = 14 observations)
Waheed 2013	Fasting blood glucose	30/34 women within treatment target	Metformin 27/34 women within treatment target
Hickman 2013	1-hour postprandial blood glucose (mg/dL)	Median 125.3 (IQR 112, 138) (n = 8)	Metformin Median 122.3 (IQR 118, 130) (n = 10)

Table 8. Maternal outcomes (*Continued*)

Coustan 1978	2-hour postprandial blood glucose (mg/dL)	99.9 ± 27.6 (n = 32 observations)	102.6 ± 12.4 (n = 13 observations)
Hickman 2013	HbA1c (%)	Median 5.6 (IQR 5.3, 6.4) (n = 13)	Metformin Median 5.9 (IQR 5.5, 6.0) (n = 13)
Ismail 2007	HbA1c (%)	Human insulin Median 6.0 (IQR 1. 20) (n = 30)	Neutral Protamine Hagedorn insulin Median 5.90 (IQR 0.80) (n = 31)
Waheed 2013	HbA1c (%)	27/34 women within treatment target	Metformin 28/34 women within treatment target
Hickman 2013	Gestational weight gain (kg)	Median 0.30 (IQR 0.18, 0.47) (n = 13)	Metformin Median 0.28 (IQR 0.11, 0.38) (n = 13)
Mecacci 2003	Gestational weight gain (kg)	Regular insulin - Median 11.1 (range 8 to 14) (n = 24)	Insulin lispro - Median 10.9 (range 7 to 17) (n = 25)
Riaz 2014	Glycaemic control	Insulin 56/100	Metformin 72/100

IQR: interquartile range

Table 9. Neonatal outcomes

Study ID	Outcome	Insulin	Comparison
Hague 2003	Cord C-peptide	Median 0.66 (range 0.45 to 1.71) pmol/mL (n = 14)	Metformin Median 0.53 (range 0.35 to 2.86) pmol/mL (n = 16)
Hague 2003	Duration in special care nursery	Median 24 (range 0 to 102) hours (n = 14)	Metformin Median 48 (range 0 to 360) hours (n = 16)
Niromanesh 2012	Duration of hospitalisation	Mean 2 days (range 1 to 4)	Metformin Mean 2 days (range 1 to 6)
Hickman 2013	Neonatal Cord C- peptide	Median 1.5 (IQR 1.1, 3.4) (n = 11)	Metformin Median 1.5 (IQR 0.9, 2.8) (n = 11)
Hickman 2013	Birthweight	Median 2986 (IQR 2822, 3630) (n = 14)	Metformin Median 3202 (IQR 3026, 3608) (n = 14)

Table 9. Neonatal outcomes (*Continued*)

Mecacci 2003	Gestational age at birth (weeks)	Regular insulin - Median 40 (range 37 to 41) (n = 24)	Insulin lispro - Median 40 (range 37 to 41) (n = 25)
Hickman 2013	Gestational age at birth (weeks)	Median 38 (IQR 36, 39) (n = 14)	Metformin Median 39 (IQR 37, 39) (n = 14)
		Insulin	Diet
Persson 1985	Gestational age at birth (days)	Median 277 (range 234 to 293) (n = 97)	Median 275 (range 234 to 297) (n = 105)
Persson 1985	Birthweight (g)	Median 3630 (range 1655 to 4830) (n = 97)	Median 3560 (range 2000 to 4700) (n = 105)
Persson 1985	Skinfold thickness triceps (mm) Skinfold thickness subscapular (mm)	Median 4.9 (range 3.3 to 9.4) (n = 97) Median 4.7 (range 3.1 to 7.4) (n = 97)	Median 5.1 (range 2.1 to 9.9) (n = 105) Median 4.9 (range 2.5 to 8.7) (n = 105)

IQR: interquartile range

APPENDICES

Appendix 1. Trial registry search terms

gestational diabetes OR GDM
diabetes AND pregnancy

CONTRIBUTIONS OF AUTHORS

Julie Brown guarantees this review.

Identification of studies, data extraction, assessment of risk of bias and GRADE was undertaken by Julie Brown and Tineke Crawford.

Julie Brown wrote the first version of this review.

Caroline Crowther acted a mediator for any potential disagreements and provided methodological and content expertise.

Luke Grzeskowiak provided content expertise and feedback to drafts as a pharmacist.

Kathryn Williamson and Michelle R Downie provided feedback to draft versions as paediatric and diabetes physician experts.

DECLARATIONS OF INTEREST

Julie Brown: Julie Brown has received a University of Auckland Departmental Grant to support the preparation of an overview of treatments for women with gestational diabetes. This review is one of the reviews to be included in the overview.

Luke Grzeskowiak: none known.

Michelle Downie: has received honorarium for lectures (and partial sponsorship to attend conferences) from Novo Nordisk and Sanofi Aventis.

Caroline A Crowther: none known.

Kathryn Williamson: has been awarded the Auckland Medical Research Foundation Ruth Spencer Fellowship in support of her doctoral studies at the University of Auckland.

SOURCES OF SUPPORT

Internal sources

- An internal University of Auckland Departmental Grant, New Zealand.

An internal University of Auckland grant from the Liggins Institute was awarded to Julie Brown to help with the preparation of several Cochrane systematic reviews as part of an overview of systematic reviews for the treatment of women with gestational diabetes. This current protocol/review will be one of the included reviews.

- Liggins Institute, New Zealand.

Support for infrastructure to support the preparation of this protocol is from the Liggins Institute, University of Auckland, New Zealand.

External sources

- National Institute for Health Research (NIHR), UK.

NIHR Cochrane Programme Grant Project: 13/89/05 - Pregnancy and childbirth systematic reviews to support clinical guidelines

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are some differences between the published protocol for this review (Brown 2016) and this full review - these are outlined below.

Methods/types of outcomes/long term secondary maternal outcomes - 'subsequent gestational diabetes' has been deleted as an outcome. This outcome was removed as we believe this outcome would be covered by impaired glucose tolerance which is already a maternal long term outcome.

We included the outcome of congenital abnormality in this review which was not pre-specified in the protocol. The reason for this is for the concerns about congential malformations with drugs including insulin, metformin and glibenclamide.

In our GRADE methods we edited the outcome names for consistency with those listed in the methods/types of outcomes and clarified whether outcomes relate to neonate/child, and child as adult.

NOTES

The original review Alwan N, Tuffnell DJ, West J. *Treatments for gestational diabetes*. Cochrane Database of Systematic Reviews 2009, Issue 3. Art. No.: CD003395. DOI: 10.1002/14651858.CD003395.pub2. has been split into three new review titles reflecting the complexity of treating women with gestational diabetes:

- *Lifestyle interventions for the treatment of women with gestational diabetes mellitus* (Brown 2017a);
- *Oral anti-diabetic pharmacological therapies for the treatment of women with gestational diabetes mellitus* (Brown 2017b);
- *Insulin for the treatment of women with gestational diabetes mellitus* (this review).

There will be similarities in the background, methods and outcomes between these three systematic reviews. Portions of the methods section of this protocol are based on a standard methods template used by the Cochrane Pregnancy and Childbirth Review Group.