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Different insulin types and regimens for pregnant women with pre-existing diabetes (Review)

O'Neill SM, Kenny LC, Khashan AS, West HM, Smyth RMD, Kearney PM

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[Intervention Review]

Different insulin types and regimens for pregnant women with pre-existing diabetes

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ABSTRACT

Background

Insulin requirements may change during pregnancy, and the optimal treatment for pre-existing diabetes is unclear. There are several insulin regimens (e.g. via syringe, pen) and types of insulin (e.g. fast-acting insulin, human insulin).

Objectives

To assess the effects of different insulin types and different insulin regimens in pregnant women with pre-existing type 1 or type 2 diabetes.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 October 2016), ClinicalTrials.gov (17 October 2016), the WHO International Clinical Trials Registry Platform (ICTRP; 17 October 2016), and the reference lists of retrieved studies.

Selection criteria

We included randomised controlled trials (RCTs) that compared different insulin types and regimens in pregnant women with pre-existing diabetes.

We had planned to include cluster-RCTs, but none were identified. We excluded quasi-randomised controlled trials and cross-over trials. We included studies published in abstract form and contacted the authors for further details when applicable. Conference abstracts were superseded by full publications.

Data collection and analysis

Two review authors independently assessed trials for inclusion, conducted data extraction, assessed risk of bias, and checked for accuracy. We assessed the quality of the evidence using the GRADE approach.

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Main results

The findings in this review were based on very low-quality evidence, from single, small sample sized trial estimates, with wide confidence intervals (CI), some of which crossed the line of no effect; many of the prespecified outcomes were not reported. Therefore, they should be interpreted with caution. We included five trials that included 554 women and babies (four open-label, multi-centre, two-arm trials; one single centre, four-arm RCT). All five trials were at a high or unclear risk of bias due to lack of blinding, unclear methods of randomisation, and selective reporting of outcomes. Pooling of data from the trials was not possible, as each trial looked at a different comparison.

1. One trial (N = 33 women) compared Lispro insulin with regular insulin and provided very low-quality evidence for the outcomes. There were seven episodes of pre-eclampsia in the Lispro group and nine in the regular insulin group, with no clear difference between the two groups (risk ratio (RR) 0.68, 95% CI 0.35 to 1.30). There were five caesarean sections in the Lispro group and nine in the regular insulin group, with no clear difference between the two groups (RR 0.59, 95% CI 0.25 to 1.39). There were no cases of fetal anomaly in the Lispro group and one in the regular insulin group, with no clear difference between the groups (RR 0.35, 95% CI 0.02 to 8.08). Macrosomia, perinatal deaths, episodes of birth trauma including shoulder dystocia, nerve palsy, and fracture, and the composite outcome measure of neonatal morbidity were not reported.

2. One trial (N = 42 women) compared human insulin to animal insulin, and provided very low-quality evidence for the outcomes. There were no cases of macrosomia in the human insulin group and two in the animal insulin group, with no clear difference between the groups (RR 0.22, 95% CI 0.01 to 4.30). Perinatal death, pre-eclampsia, caesarean section, fetal anomaly, birth trauma including shoulder dystocia, nerve palsy and fracture and the composite outcome measure of neonatal morbidity were not reported.

3. One trial (N = 93 women) compared pre-mixed insulin (70 NPH/30 REG) to self-mixed, split-dose insulin and provided very low-quality evidence to support the outcomes. Two cases of macrosomia were reported in the pre-mixed insulin group and four in the self-mixed insulin group, with no clear difference between the two groups (RR 0.49, 95% CI 0.09 to 2.54). There were seven cases of caesarean section (for cephalo-pelvic disproportion) in the pre-mixed insulin group and 12 in the self-mixed insulin group, with no clear difference between groups (RR 0.57, 95% CI 0.25 to 1.32). Perinatal death, pre-eclampsia, fetal anomaly, birth trauma including shoulder dystocia, nerve palsy, or fracture and the composite outcome measure of neonatal morbidity were not reported.

4. In the same trial (N = 93 women), insulin injected with a Novolin pen was compared to insulin injected with a conventional needle (syringe), which provided very low-quality evidence to support the outcomes. There was one case of macrosomia in the pen group and five in the needle group, with no clear difference between the different insulin regimens (RR 0.21, 95% CI 0.03 to 1.76). There were five deliveries by caesarean section in the pen group compared with 14 in the needle group; women were less likely to deliver via caesarean section when insulin was injected with a pen compared to a conventional needle (RR 0.38, 95% CI 0.15 to 0.97). Perinatal death, pre-eclampsia, fetal anomaly, birth trauma including shoulder dystocia, nerve palsy, or fracture, and the composite outcome measure of neonatal morbidity were not reported.

5. One trial (N = 223 women) comparing insulin Aspart with human insulin reported none of the review's primary outcomes: macrosomia, perinatal death, pre-eclampsia, caesarean section, fetal anomaly, birth trauma including shoulder dystocia. nerve palsy, or fracture, or the composite outcome measure of neonatal morbidity.

6. One trial (N = 162 women) compared insulin Detemir with NPH insulin, and supported the outcomes with very low-quality evidence. There were three cases of major fetal anomalies in the insulin Detemir group and one in the NPH insulin group, with no clear difference between the groups (RR 3.15, 95% CI 0.33 to 29.67). Macrosomia, perinatal death, pre-eclampsia, caesarean section, birth trauma including shoulder dystocia, nerve palsy, or fracture and the composite outcome of neonatal morbidity were not reported.

Authors' conclusions

With limited evidence and no meta-analyses, as each trial looked at a different comparison, no firm conclusions could be made about different insulin types and regimens in pregnant women with pre-existing type 1 or 2 diabetes. Further research is warranted to determine who has an increased risk of adverse pregnancy outcome. This would include larger trials, incorporating adequate randomisation and blinding, and key outcomes that include macrosomia, pregnancy loss, pre-eclampsia, caesarean section, fetal anomalies, and birth trauma.

PLAIN LANGUAGE SUMMARY

What is the best insulin type and regimen for pregnant women with pre-existing diabetes?

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What is the issue?

The insulin needs of pregnant women with type 1 or 2 diabetes change during pregnancy. Insulin is available in many forms, which affect how often and when the insulin is given. These forms vary in the time needed before the insulin has its effect, how long the effect may last, and whether it is made from animals or humans, which may be important personally or culturally. This review looked at the safest and most effective types and ways of giving insulin during pregnancy.

Why is this important?

Women with type 1 or 2 diabetes are at increased risk of complications during pregnancy and birth. They are more likely to experience pregnancy loss (stillbirth, miscarriage), high blood pressure and pre-eclampsia (high blood pressure associated with swelling and protein in the urine), and have large babies (called macrosomia, when the baby is 4 kg or more at birth) that result in injury to the mother or baby. The likelihood of having a caesarean is increased. Mothers and babies may have complications related to managing blood glucose levels. The baby is more likely to become overweight and develop type 2 diabetes. We wanted to find out the best type of insulin and regimen to use during pregnancy.

What evidence did we find?

We found five randomised trials (N = 554 women and 554 babies) in October 2016. Each trial looked at different insulin types and ways of giving the insulin. Different outcomes were looked at in each trial. One trial did not include any of the review's main outcomes. All five trials were small, and at a high or unclear risk of bias because of limitations in how the trials were conducted. The quality of the evidence was very low.

When rapid-acting human insulin (Lispro) was compared to regular insulin (N = 33), investigators found no clear differences between the groups for pre-eclampsia, abnormalities in the baby, or the need for a caesarean. Macrosomia, perinatal death, birth trauma including shoulder dystocia, nerve palsy, and fracture, and the composite measure of neonatal morbidity were not reported.

One trial (N = 43) that compared human insulin to animal insulin did not show any clear difference in the number of babies with macrosomia. Perinatal death, pre-eclampsia, caesarean section, fetal anomaly, birth trauma including shoulder dystocia, nerve palsy, and fracture, and the composite measure of neonatal morbidity were not reported.

One trial (N = 93) found no clear differences between pre-mixed and self-mixed insulin groups in the number of babies with macrosomia, and the number of women who had a caesarean section. This trial also compared insulin injected with a pen and a needle (syringe). Women in the insulin pen group were less likely to have a caesarean section, although the number of macrosomic babies was not clearly different. Perinatal death, pre-eclampsia, fetal anomaly, birth trauma including shoulder dystocia, nerve palsy, and fracture, and the composite measure of neonatal morbidity were not reported.

One trial (N = 223) comparing insulin Aspart to human insulin did not include any of the review's primary outcomes (macrosomia, perinatal death, pre-eclampsia, caesarean section, fetal anomaly, birth trauma including shoulder dystocia, nerve palsy, and fracture, or the composite measure of neonatal morbidity).

One trial (N = 162), which compared long-acting insulin Detemir with the intermediate-acting neutral protamine Hagedorn (NPH) insulin found the number of fetal abnormalities was not clearly different between groups. The trial did not measure macrosomia, perinatal death, pre-eclampsia, caesarean section, birth trauma including shoulder dystocia, nerve palsy, and fracture, or the composite outcome measure of neonatal morbidity.

What does this mean?

The trials did not provide sufficient evidence to identify clear differences between the various insulin types and regimens. Each study looked at a different type of insulin or regimen, so we could not combine the results. The studies were small, with overall high risk of bias. Therefore, we could not conclude which insulin type or regimen was best for pregnant women with pre-existing diabetes. More research is needed with larger groups of women, better reporting of how the trials were conducted, and more reported outcomes.

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SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Lispro versus regular insulin (Different insulin types within similar insulin regimens)

Patient or population: pregnant women with pre-existing diabetes
Setting: four centres in Sweden. The Departments of Obstetrics and Gynaecology in Huddinge Hospital, Karolinska Hospital, Södersjukhuset in Stockholm, and Örebro Regional Hospital
Intervention: Lispro
Comparison: regular insulin

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with regular insulin	Risk with Lispro				
Macrosomia				(0 studies)	Not reported	
Perinatal death	Study population		not estimable	33 (1 RCT)	⊕◯◯◯ VERY LOW [1,2,3]	
	0 per 1000	0 per 1000 (0 to 0)				
Pre-eclampsia	Study population		RR 0.68 (0.35 to 1.30)	33 (1 RCT)	⊕◯◯◯ VERY LOW [1,3,4,5]	
	647 per 1000	440 per 1000 (226 to 841)				
Caesarean section	Study population		RR 0.59 (0.25 to 1.39)	33 (1 RCT)	⊕◯◯◯ VERY LOW [1,3,4,5]	
	529 per 1000	312 per 1000 (132 to 736)				
Fetal anomaly	Study population		RR 0.35 (0.02 to 8.08)	33 (1 RCT)	⊕◯◯◯ VERY LOW [1,3,4,5]	
	59 per 1000	21 per 1000 (1 to 475)				

Birth trauma, including shoulder dystocia, nerve palsy, and fracture	Study population 0 per 1000	0 per 1000 (0 to 0)	Not estimable	33 (1 RCT)	⊕◯◯◯ VERY LOW [1,2,3]
Composite outcome measure of neonatal morbidity				(0 studies)	Not reported

*__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; **RR:** Risk ratio; **OR:** Odds 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] High or unclear risk of bias for allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other biases
[2] Small sample size and no events
[3] One study with design limitations
[4] Very wide 95% confidence intervals crossing the line of no effect
[5] Small sample size with few events

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BACKGROUND

Description of the condition

Diabetes mellitus

The term (DM) describes a metabolic disorder of multiple aetiology, characterised by chronic hyperglycaemia with disturbances of carbohydrate, fat, and protein metabolism that results from defects in insulin secretion, insulin action, or both (WHO 1999). Diabetes mellitus can occur during pregnancy in two forms, pre-gestational diabetes mellitus and gestational diabetes mellitus (GDM; Daflapurkar 2014). Pre-gestational diabetes refers to type 1 or type 2 diabetes and is diagnosed before conception. Historically, type 1 diabetes was considered a disorder of children and adolescents, generally occurring early in life, with a sudden onset of insulin deficiency. Age at onset of diagnosis is no longer a restricting factor (Atkinson 2014). Type 2 diabetes has been largely attributed to increasing obesity and socioeconomic status (Kothari 2014; Morton 2014). Gestational diabetes mellitus is a carbohydrate intolerance that results in hyperglycaemia (an excess of sugar in the blood) of variable severity, with onset or first recognition during pregnancy. It does not exclude the possibility that the glucose intolerance may antedate pregnancy but has been previously unrecognised. The definition applies regardless of whether or not insulin is used for treatment, or the condition persists after pregnancy (WHO 1999). This review will only include women with pre-existing DM (type 1 or 2).

Pathophysiology

Diabetes mellitus can be defined as abnormal glucose metabolism due to lack of, or relatively low, insulin production. It results in elevation of blood glucose levels with effects on all the vital organs. Type 1 DM describes a condition in which the pancreas is no longer able to produce sufficient insulin due to the destruction of the beta cells by an autoimmune process. According to the World Health Organization (WHO) definition, type 1 DM "includes those cases attributable to an autoimmune process, as well as those with beta-cell destruction, which are prone to ketoacidosis for which neither an aetiology nor a pathogenesis is known (idiopathic). It does not include those forms of beta-cell destruction or failure to which specific causes can be assigned (e.g. cystic fibrosis, mitochondrial defects, etc.)" (WHO 1999). Type 2 DM includes the common major form of diabetes that results from defects in insulin secretion, almost always with a major contribution from insulin resistance (Nolan 2011; WHO 1999).

Epidemiology

Diabetes mellitus is increasing globally and the number of adults with diabetes has more than doubled over nearly three decades, driven by both population growth and ageing, as well as the increasing levels of overweight and obesity (Danaei 2011). In Canada, the percentage of pregnant women with pre-existing DM rose from 0.7% to 1.5% between 1996 and 2010 (Feig 2014). Similar increasing trends of DM in pregnant women have been reported in the United States (Albrecht 2010; Lawrence 2008), and the United Kingdom (Bell 2008). Type 2 diabetes accounts for approximately 85% to 90% of all cases of diabetes in European countries, and is the driving force behind increasing diabetes rates (Wass 2011). Furthermore, DM is the most common pre-existing medical condition complicating pregnancy; the outcome for diabetic pregnancy remains poor, despite improvements in care (Kumareswaran 2013). Pre-existing DM complicates approximately 1.3% of pregnancies, one-third of these are type 1 DM, the remaining two thirds are type 2 DM (Bell 2008; Feghali 2012).

Risk factors associated with DM

Although the exact causes of type 1 DM are unknown, factors that may signal an increased risk include the following (Daneman 2006).

- Family history (risk increases if a parent or sibling has type 1 DM).
- Environmental factors (circumstances such as exposure to a viral illness likely play some role in type 1 DM).
- The presence of damaging immune system cells (autoantibodies). Sometimes family members of people with type 1 DM are tested for the presence of diabetes autoantibodies. The presence of these antibodies is associated with an increased risk of developing type 1 DM, but not everyone who has these autoantibodies develops DM.
- Dietary factors (including low vitamin D consumption, early exposure to cow's milk or cow's milk formula, and exposure to cereals before four months of age. None of these factors has been shown to directly cause type 1 DM).
- Geography. Certain countries, such as Finland and Sweden, have higher rates of type 1 DM.

It is not fully understood why some people develop type 2 DM and others do not. However, certain factors increase the risk, including the following (Kim 2002).

- Weight (the more fatty tissue present, the more resistant cells become to insulin).
- Inactivity (the less active a person is, the greater the risk. Physical activity helps control weight, uses up glucose as energy and makes cells more sensitive to insulin).
- Family history (risk increases if a parent or sibling has type 2 DM).
- Race (certain races - including blacks, Hispanics, American Indians, and Asian-Americans are at higher risk, although it is not clear why).

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- Age (risk increases as you get older, perhaps due to less exercise, lost muscle mass, and weight gain as you age, however, type 2 DM is also increasing dramatically among children, adolescents, and younger adults).
- GDM (if a woman developed gestational diabetes when pregnant, her risk of developing prediabetes and type 2 DM later increases. If a woman gave birth to a baby weighing more than nine pounds (four kilograms), the risk of type 2 DM also increases).
- Polycystic ovary syndrome (a common condition characterised by irregular menstrual periods, excess hair growth, and obesity) increases the risk of DM).
- High blood pressure, over 140/90 millimetres of mercury (mmHg), is linked to an increased risk of type 2 DM.
- Abnormal cholesterol and triglyceride levels (low levels of high-density lipoprotein (HDL), or 'good' cholesterol, result in an increased risk of type 2 DM, as does a high level of triglycerides).
- Gender (higher prevalence of diabetes among men, and men develop diabetes at lower body mass index (BMI) levels than women).

Possible complications in pregnant women with DM and their offspring

Diabetes in pregnancy is associated with risks to the woman and the developing fetus (Adam 2014; Ali 2011; Bartz 2012; Billionnet 2014; Carter 2012; Feig 2014; Fraser 2014; Holman 2014; Kapoor 2007; Krane 2014; Morken 2014; Øverland 2014; Ryu 2014; Tennant 2014; Yessoufou 2011).

- Increased risk of complications of DM, including ketoacidosis, hypoglycaemia, retinopathy, and nephropathy.
- Increased risk of obstetric complications, including pregnancy-induced hypertension, thromboembolism, obstructed labour, polyhydramnios, maternal infection, caesarean section, pre-eclampsia, and preterm labour.
- Increased risk of fetal and neonatal complications, including miscarriage, stillbirth, congenital malformations, macrosomia, birth injury, perinatal mortality, postnatal adaptation problems (e.g. hypoglycaemia (reduced levels of blood sugar)), fetal distress, respiratory distress syndrome, and jaundice.
- Long-term outcomes of offspring born to diabetic mothers include an increased risk of obesity, impaired cognitive ability, and type 2 diabetes.

Management of DM in pregnancy

The management of pregnant women with type 1 diabetes involves the use of insulin to control blood glucose levels. During pregnancy, a woman's insulin requirements may increase by up to three to four times her pre-pregnancy dose; insulin management is tailored to the individual (McCance 2010). In type 2 diabetes, lifestyle changes, including a healthy diet and regular exercise, are the first line of treatment, with the use of oral hypoglycaemic agents or insulin to lower blood glucose, if necessary. Therefore, the management of diabetes in pregnancy is complex, and includes a combination of preconception care, glycaemic control and monitoring, obtaining target blood glucose levels, monitoring glycated haemoglobin (HbA1c) levels, retinal assessment, carefully tailored insulin treatment, ketone testing, renal assessment, monitoring fetal growth and well-being, and postnatal care (Balaji 2011; Ballas 2012; NICE 2015).

Description of the intervention

Insulin is a hormone made naturally in the body by pancreatic beta cells. This hormone controls the level of glucose in the blood. There are different types of insulin available, which are classified according to how quickly and for how long they work on various parts of the body. There are also many different methods of administering insulin, referred to as 'regimens'. This review focuses on the efficacy and safety of different insulin types and the various regimens of insulin delivery during pregnancy. The appropriate insulin type and regimen for each woman will depend on a number of factors, including the type of diabetes, previous control, age, dexterity, eyesight, and personal and cultural preferences (Greuter 2012).

Types of insulin

Insulins can be classified into various types, according to their duration of action (Mooradian 2006; NICE 2015).

- **Short-acting insulin** (e.g. Humulin, Novolin): should be injected 15 to 30 minutes before a meal, to cover the rise in blood glucose levels that occurs after eating. This insulin has a peak action of two to six hours, and can last for up to eight hours.
- **Rapid-acting insulin analogues** (e.g. Aspart, Lispro): genetically engineered analogues of human insulin, which work like insulin that is normally produced with a meal. Onset of action is approximately 15 minutes, peaking at one hour, and lasting three to four hours. They can be injected shortly before, during, or immediately after meals.
- **Long-acting insulin analogues** (e.g. Detemir, Glargine): genetically modified analogues, with an onset of action at one to three hours; they plateau and last for 20 to 24 hours. Generally used once- or twice-daily to produce a constant flow of insulin, they are physiologically similar to normal endogenous basal insulin secretion.
- **Intermediate-acting** (medium-acting) insulins (e.g. isophane or neutral protamine Hagedorn (NPH)): these have an onset of action of two to four hours, peak at six to seven hours, and last 20 hours. Isophane insulin is ideal for twice-daily insulin regimens, and can be mixed with soluble insulin.
- **Mixed insulin** (Biphasic insulin): a combination of medium-acting and rapid-acting or short-acting insulin.

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- **Mixed analogue**: a combination of medium-acting insulin and rapid-acting analogue.

Insulin regimens

In this review, the term 'insulin regimen' refers to an overall strategy for insulin delivery that typically specifies:

- the frequency of insulin injections (e.g. once, twice daily);
- the type of insulin administered (e.g. intermediate-, long-acting); and
- the timing of insulin injections (e.g. bedtime, before breakfast).

The main insulin regimens are as follows.

Once-daily regimen

- Long- or intermediate-acting insulin administered at bedtime in people with type 2 diabetes only.
- It may be used in addition to oral hypoglycaemic agents.
- This regimen is generally used when starting insulin in type 2 diabetes and when it is necessary for others to administer the injections.

Twice-daily regimen

- A biphasic insulin is injected twice a day (before breakfast and before the evening meal).
- Assumes three meals a day are consumed, and peak action varies according to the amount of soluble insulin in the mixture.
- Optimal glycaemic control can be difficult to maintain, resulting in hypoglycaemic episodes.
- Additional snacks are often required between meals, given the overlap between short-acting and long-acting insulin.

Basal-bolus regimen

- Intermediate- or long-acting insulin is administered at bedtime to cover overnight insulin requirements, and is combined with rapid- or short-acting insulin injections to cover mealtimes.

When intensified insulin therapy is used to provide optimal glycaemic control, this is the most commonly used insulin regimen, and is also known as multiple daily injections (MDI).

Continuous subcutaneous insulin infusion, or insulin pump therapy

- Continuous subcutaneous insulin infusion (CSII) or insulin pump therapy is when basal insulin is given via a catheter, supplied from a syringe reservoir worn under clothing.
- The woman can activate pre-meal boluses, and the pump can be deactivated for up to one hour to facilitate activities, such as swimming.
- The pump can be pre-programmed, and as a result, the insulin absorption is more predictable than multiple daily injections.
- CSII provides some advantages over multiple daily injections in type 1 diabetes for children and adults who have recurrent hypoglycaemia, delayed meals, or pre-breakfast hyperglycaemia.

Continuous subcutaneous insulin infusion regimens have been covered extensively in two previous Cochrane reviews, and will not be included in the current review (Farrar 2016; Misso 2010).

Insulin dosage

Insulin dosage should be individualised to achieve and maintain a target blood glucose level, and is determined by various factors, including body weight, body fat, physical activity, insulin sensitivity, blood glucose levels, and target blood glucose. Insulin dosage is usually based on body weight (insulin unit per kilogram of body weight). One international unit of insulin (1 IU) is defined as the 'biological equivalent' of 34.7 μg of pure crystalline insulin (Beals 2013). Daily insulin requirements may be higher during illness, stress, pregnancy, in obese people, trauma, during concurrent use with medications having hyperglycaemic effects, or after surgery, and may be lower with exercise, weight loss, calorie restricted diets, or during concurrent use of medications having hypoglycaemic effects. Total daily doses should not be adjusted by more than 10% increments. Supplemental doses may be prescribed during illness, or to correct high preprandial blood glucose. In addition, dosage adjustments may be required when the brand, type, or species of insulin is changed (Teuscher 2007).

How the intervention might work

Insulin, a hormone made by beta cells of the pancreas, works on various parts of the body when it is chemically released into the bloodstream. This process results in the control of glucose (sugar) levels in the blood. Normally, after you have eaten, various foods are broken down into sugars, the main one being glucose, which pass through the gut wall into the bloodstream. To remain healthy, the blood glucose level should be neither too high nor too low. For example, if the blood glucose level rises (after eating), then the insulin level should also rise. Insulin works on the cells to make them absorb glucose from the bloodstream, some of which is used for energy, some of which is converted into glycogen or fat (energy stores). When blood glucose levels fall (between meals), insulin levels fall, and the glycogen or fat is converted back into glucose, which is released into the cells of the bloodstream. People with diabetes need to control the level of glucose in their blood; this is usually tailored to their individual needs and is dependent on the type of diabetes present. Overall, there is a lack of clear evidence regarding the benefits and risks of the various insulin types and

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regimens, particularly the newer insulin therapies. The evidence so far suggests that:

- rapid-acting insulin analogues may improve postprandial hyperglycaemia and reduce hypoglycaemia (Siebenhofer 2006);
- long-acting insulin analogues may reduce nocturnal hypoglycaemia and weight gain (Gough 2007), but some studies found them no better than conventional NPH insulin (Home 2005; Horvath 2007);
- the newer treatments seem to be safe so far (Siebenhofer 2004);
- the rapid-acting insulin analogues (Aspart and Lispro) do not seem to adversely affect pregnancy or the health of the fetus or newborn baby (Negrato 2012);
- use of isophane insulin (NPH insulin) as the first choice for long-acting insulin during pregnancy is recommended, and insulin Detemir or Glargine in women with diabetes who have established good blood glucose control before pregnancy (NICE 2015);
- twice-daily regimens using isophane insulin (NPH insulin) or long-acting insulin analogues (insulin Glargine) may be more suitable for those who require assistance, or have a dislike of injecting (Barnett 2008);
- multiple injection regimens using unmodified or soluble insulin or rapid-acting insulin analogues, are suitable for well-motivated individuals with a good understanding of disease control, or those with active or erratic lifestyles (NICE 2015).

The current review interventions may result in a better understanding of the following outcomes in pregnant women with pre-existing diabetes.
Improved glycaemic control: Improvement in glycaemic control levels (i.e. optimum HbA1c levels, fasting plasma glucose).
Reduction of hypoglycaemic or hyperglycaemic episodes: A reduction or absence in the number of hyperglycaemic or hypoglycaemic episodes reported in the trials.
Safety and efficacy: Measurement of the safety and efficacy of various insulin types and regimens.
Other: Satisfaction and quality of life reported by women; maternal and infant outcomes.

Why it is important to do this review

Several Cochrane reviews have evaluated the effects of various interventions for managing pre-existing diabetes in pregnancy, including: early pregnancy screening to improve maternal and child health; CSII versus MDI of insulin; glycaemic control; monitoring blood glucose during pregnancy; and oral anti-diabetic agents for impaired glucose tolerance (Allnutt 2015; Farrar 2016; Middleton 2012; Moy 2014; Tieu 2010a). In addition, there are other Cochrane reviews that cover various aspects of diabetes management around conception, pregnancy, and birth (e.g. elective delivery, exercise, antenatal breast milk expression, preconception care, and contraceptive advice (Boulvain 2001; Ceysens 2006; East 2014; Tieu 2010b; Visser 2013)).
Our review assessed evidence related to different insulin types and regimens, and aimed to contribute to knowledge that will ultimately be used by pregnant women with pre-existing diabetes and their clinicians, to minimise the risk of adverse birth outcomes and complications of diabetes for mothers. This review was timely, since currently, pregnant women with diabetes have significantly worse outcomes than women without diabetes. Achieving improved pregnancy outcomes for women with diabetes needs to be prioritised, particularly given that the prevalence of diabetes among women of childbearing age is increasing. Furthermore, while there have been advances in the different insulin types and regimens available that have crossed into the field of obstetrics, further research is needed to address the safety and efficacy of these new drugs on the market to improve compliance and glycaemic control, especially during pregnancy.

OBJECTIVES

To assess the effects of different insulin types and different insulin regimens in pregnant women with pre-existing type 1 or type 2 diabetes.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials and cluster-randomised trials, regardless of the number of trial arms that reported data that evaluated different insulin types or regimens. We excluded quasi-randomised controlled trials and trials using a cross-over design. We included studies published in abstract form and contacted the authors for further details where applicable. Conference abstracts were superseded by full publications.

Types of participants

Women with a singleton pregnancy who had pre-existing diabetes (type 1 or type 2) and were randomised to receive different insulin types or regimens. Trials were excluded if women were randomised prior to pregnancy. Women who met the diagnostic criteria for GDM were not included. Diagnostic criteria for DM and GDM were based on various definitions as reported by individual trialists, according to local health authorities and professional organisations. Women were eligible regardless of gestation, age, or parity.

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Types of interventions

We included randomised controlled trials that examined any of the following comparisons.

Comparisons between different insulin types used within similar insulin regimens

For example:

1. basal bolus regimen of NPH insulin given at bedtime, combined with Aspart to cover mealtimes versus basal bolus regimen of Glargine given at bedtime, combined with Aspart to cover mealtimes (i.e. a comparison of the effects of different insulin types [NPH versus Glargine] when used within a basal bolus regimen).

Comparisons between different insulin regimens with similar insulin types used within the regimens

For example:

1. twice-daily insulin regimen versus four times daily insulin regimen:

- twice-daily regimen: morning dosage = one-third human regular insulin and two-thirds human intermediate insulin; afternoon dosage = equal parts regular and intermediate insulin;
- four-times daily regimen: first three dosages of regular insulin 30 minutes before a meal; final dosage: bedtime, intermediate insulin.

Comparisons between different insulin regimens with different insulin types used within the regimens

For example:

1. a biphasic insulin injected twice a day (pre-breakfast and pre-evening meal) versus basal bolus regimen of NPH insulin given at bedtime, combined with Aspart to cover mealtimes.

Types of outcome measures

Primary outcomes

Infant

1. Macrosomia (birthweight greater than 4000 g, birthweight greater than 90% for gestational age at delivery after correcting for neonatal sex and ethnicity).
2. Perinatal death.

Maternal

1. Caesarean section (emergency or elective).
2. Pre-eclampsia.

Secondary outcomes

Infant

1. Fetal anomaly divided into major and minor.
2. Birth trauma including shoulder dystocia, nerve palsy, and fracture.
3. Preterm birth less than 37 weeks.
4. Small-for-gestational age at delivery (weight below the 10th percentile for gestational age at delivery).
5. Five-minute Apgar score less than seven.
6. Birthweight centile corrected for gestational age at delivery, parity, ethnicity, maternal weight, and fetal sex (Z scores used where available).
7. Admission and length of stay in neonatal intensive care unit.
8. Mechanical ventilation.
9. Neonatal infection.
10. Neonatal hypoglycaemia.
11. Insulin sensitivity (cord insulin, C-peptide).
12. Jaundice requiring therapy.
13. Respiratory distress syndrome.
14. Hyperbilirubinaemia.
15. Necrotising enterocolitis.
16. Intracranial haemorrhage.
17. Artifical tube feeding.
18. Composite outcome measure of neonatal morbidity (admission and length of stay in neonatal intensive care unit, mechanical ventilation, neonatal infection, neonatal hypoglycaemia, insulin sensitivity (cord insulin, C-peptide), jaundice requiring therapy, respiratory distress syndrome, hyperbilirubinaemia, necrotising enterocolitis, intracranial haemorrhage, artificial (tube) feeding).
19. Neonatal anthropometry (length, head circumference, ponderal index).
20. Neonatal adiposity (fat mass, skinfold thickness, body weight percentile).
21. Measures of growth and neurodevelopment at childhood follow-up.

Maternal

1. Vaginal delivery (spontaneous, ventouse, forceps).
2. Postpartum haemorrhage.
3. Severe perineal trauma (third- and fourth-degree tear).
4. Measures of diabetic metabolic control (levels of HbA1c, daily mean self-monitored blood glucose, postprandial and fasting, continuous glucose monitoring).
5. Maternal hypoglycaemia and hyperglycaemia episodes requiring intervention.
6. Weight gain in pregnancy.
7. Induction of labour (reasons related to diabetes).
8. Postpartum infection.
9. Breastfeeding.

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10. Retinopathy.
11. Quality of life (psychological impact of management, assessed by psychometric testing with a reliable standardised questionnaire).
12. Use of healthcare resources (rate of antenatal clinic visits and admission for treatment relating to control of diabetes, ultrasound growth scans, biophysical scans, dopplers, cardiotocograph's, maternal hospital days).
13. Woman's preference and satisfaction with treatment.
14. Economic evaluation.

Outcomes not prespecified in protocol (but added to review)

Infant

1. Birthweight.
2. Infant fasting C-peptide level at three months (pmol/mL).
3. Infant C-peptide level one hour after glucose-amino acid challenge at three months (pmol/mL).
4. Infant glucose fasting level at three months (pmol/mL).
5. Infant glucose level one hour after glucose-amino acid challenge at three months (pmol/mL).
6. Gestational age at delivery.

Maternal

1. Ventouse delivery.
2. Maternal ketonuria.
3. Maternal compliance with treatment score (1 = best compliance, 5 = worst compliance).

Search methods for identification of studies

The following methods section of this protocol is 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 (30 October 2016).
The Register is a database containing over 22,000 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).
In addition, we searched ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) for unpublished, planned, and ongoing trial reports on 17 October 2016 (see: Appendix 1 for the terms we used).

Searching other resources

We examined the reference lists of included studies and any relevant studies identified. Where studies could only be accessed as abstracts, we contacted the authors for more details.
We did not apply any language or date restrictions.

Data collection and analysis

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

Selection of studies

Two review authors (SON, HW) independently assessed all the potential studies identified as a result of the search strategy for inclusion. We resolved any disagreement through discussion, or if required, we consulted a third person (ASK).
We created a study flow diagram mapping out the number of records identified, included, and excluded.

Data extraction and management

We designed a form to extract data. For eligible studies, two review authors (SON, HW) independently extracted the data using the agreed form. We resolved discrepancies through discussion, or if required, we consulted a third person (LK). SON entered the data into Review Manager 5 software (RevMan 5 2014) and HW checked them for accuracy. When information regarding any of

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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 (SON, HW) 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 (PK).

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

For each included study, we described 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); or
- unclear risk of bias.

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

For each included study, we described 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)

For each included study, we described 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 was 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)

For each included study, we described 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)

For each included study, and for each outcome or class of outcomes, we described 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 included missing data in the analyses that 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)

For each included study, we described 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 was clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review had been reported);
- high risk of bias (where not all the study's pre-specified outcomes had been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest were reported incompletely and so could not be used; study failed 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)

For each included study, we described any important concerns we had about other possible sources of bias.

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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 *Cochrane Handbook of Systematic Reviews of Interventions* (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 the findings. We explored the impact of the level of bias by undertaking sensitivity analyses - *see* Sensitivity analysis.

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

We created 'Summary of findings' tables for all comparisons made in the review by importing data from Review Manager 5 (RevMan 5 2014) into the GRADEpro Guideline Development Tool. The following outcomes were included in the 'Summary of findings' tables.

- Macrosomia.
- Perinatal death.
- Pre-eclampsia.
- Caesarean section (emergency or elective).
- Fetal anomaly.
- Birth trauma, including shoulder dystocia, nerve palsy, and fracture.
- Composite outcome measure of neonatal morbidity (admission and length of stay in neonatal intensive care unit, mechanical ventilation, infection, jaundice requiring therapy, respiratory distress syndrome, necrotising enterocolitis, intracranial haemorrhage, artificial (tube) feeding).

The quality of the evidence for each outcome was assessed using the GRADE approach as outlined in the GRADE Handbook. We downgraded the evidence from high quality by one level for serious (or by two levels for very serious) limitations, depending on our assessments of the risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates, or potential publication bias.

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratios (RR) with 95% confidence intervals (CI).

Continuous data

For continuous data, we used the mean difference (MD) if outcomes were measured in the same way between trials. We had planned to use the standardised mean difference (SMD) to combine trials that measured the same outcome, but used different methods, but there were no such trials in this review.

Unit of analysis issues

Cluster-randomised trials

We did not include any cluster-randomised trials in this review. In future updates, if we identify eligible cluster-randomised trials, we will include their data in the analyses along with individually-randomised trials. We will adjust their sample sizes using the methods described in the *Cochrane Handbook of Systematic Reviews of Interventions* (Sections 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. If we identify both cluster-randomised trials and individually-randomised trials, we will synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs, and we consider it unlikely that there will be an interaction between the effect of the intervention and the choice of randomisation unit. We will also acknowledge heterogeneity in the randomisation unit and perform a subgroup analysis to investigate the effects of the randomisation unit.

Multi-armed trials

We included multi-armed trials and recorded all outcome data in the review as two-arm comparisons. We included the data for different arms in independent two-arm comparisons in separate meta-analyses where possible. If we were unable to include the data in separate comparisons, we combined them to create a single pair-wise comparison (Higgins 2011). If the control group was shared by two or more study arms, we divided the control group between relevant subgroup categories to avoid double counting the participants. For dichotomous data, we divided the events and the total population, while for continuous data, we assumed the same mean and standard deviation (SD) divided by the total population.

Cross-over trials

Cross-over trials were not eligible for inclusion in this review.

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Dealing with missing data

We noted levels of attrition in the included studies. If more eligible studies are included In future updates, we will explore the impact of including studies with high levels of missing data in the overall assessment of the treatment effect by using sensitivity analyses.
Analyses were carried out for all outcomes, 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 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 was greater than 30%, and either a Tau^2 was greater than zero, or the P was less than 0.10 in the Chi^2 test for heterogeneity.

Assessment of reporting biases

In future updates, if there are 10 or more studies in the meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will first visually assess funnel plot asymmetry. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager 5 software (RevMan 5 2014). We did not combine the results from different trials as each trial looked at a different comparison. If we had pooled the data in a meta-analysis, we would have used a fixed-effect model 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 to be sufficiently similar. If there was sufficient clinical heterogeneity to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, we had planned to use a random-effects model to produce an overall summary, if an average treatment effect across trials was considered clinically meaningful. The random-effects summary would have been treated as the average of the range of possible treatment effects, and we had planned to discuss the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful, we had planned not to combine trials.
If we had used random-effects analyses, the results would have been 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

It is very unlikely that an investigation of heterogeneity will produce useful findings unless there is a substantial number of studies (at least 10 studies for each characteristic in the meta-analysis), according to section 9.6.5.1 in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Had we identified substantial heterogeneity, we had planned to investigate it using subgroup analyses and sensitivity analyses, to consider whether an overall summary was meaningful, and if it was, to use the random-effects model to produce it.
We had planned to carry out the following subgroup analyses on the review's primary outcomes, but there were insufficient data to do so:

1. by type of diabetes (type 1 versus type 2);
2. gestational age when women were recruited to the trial (less than 12 weeks versus more than 12 weeks);
3. maternal age (younger than 35 years versus older than 35 years);
4. body mass index (at or before trial entry), overweight (more than 25 kg/m^2) versus normal weight (25 kg/m^2 or less), and obese (more than 30 kg/m^2) versus normal weight (25 kg/m^2 or less);
5. by unit of randomisation (randomised by individual participant versus randomised by cluster).

In future updates, we plan to assess subgroup differences by interaction tests available in RevMan 5 (RevMan 5 2014). We will report the results of subgroup analyses quoting the Chi^2 statistic and P value, and the interaction test, I^2 value.

Sensitivity analysis

We had planned to carry out the following sensitivity analyses for the reviews primary outcomes, but there were insufficient data to do so. In future updates, we will compare trials judged as having a low risk of bias for allocation concealment with trials judged to have unclear or high risk of bias, in order to assess any substantive differences in the overall result. We will also carry out a sensitivity analysis to explore the fixed-effect model or random-effects model analyses for primary outcomes with statistical heterogeneity. If ICCs from other sources are used, we will conduct sensitivity analyses to investigate the effect of variation in the ICC.
As noted in Section 9.7 of the *Cochrane Handbook for Systematic Reviews of Interventions*, "many issues suitable for sensitivity analysis are only identified during the review process when the individual peculiarities of the studies under investigation are identified" (Higgins 2011). If it is deemed appropriate in updates of the review to conduct further sensitivity analyses (in addition to the pre-specified analyses outlined above), we will explain the reasons for conducting these additional analyses in our review, and the analyses will be clearly labelled as 'non-prespecified analyses'.

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RESULTS

Description of studies

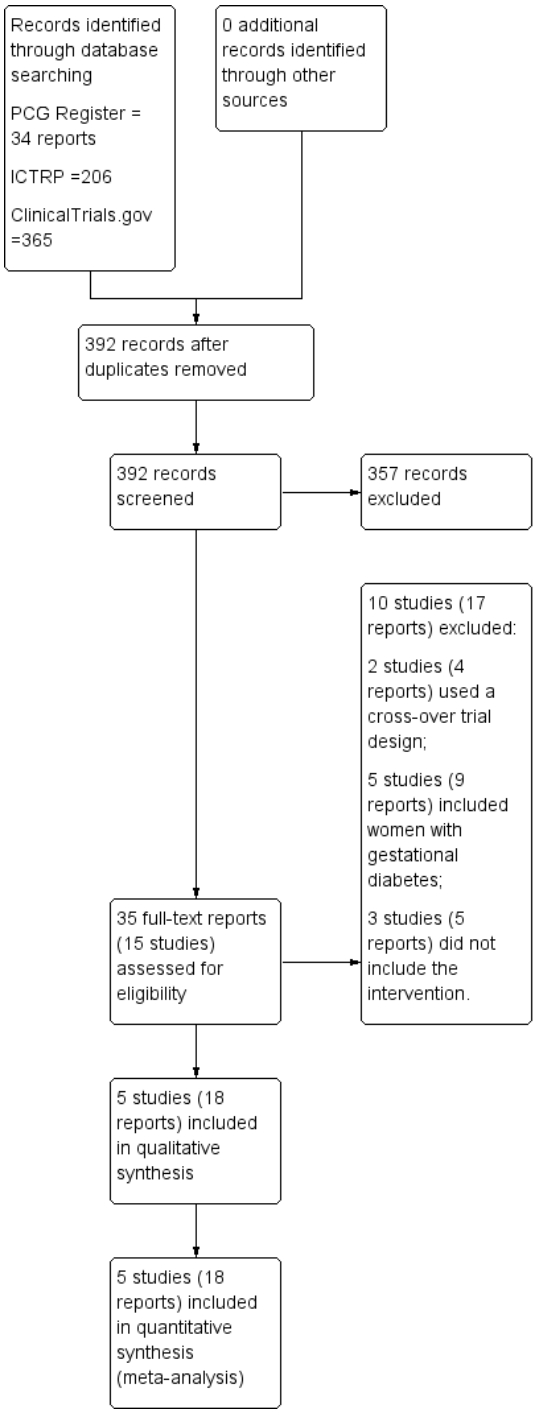
See Characteristics of included studies.

Results of the search

From the search of the Cochrane Pregnancy and Childbirth Group's Trials Register (October 2016), we retrieved 34 full-text reports. We also found two additional reports by searching ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP; 17 October 2016). When we assessed these reports for eligibility, by applying the inclusion and exclusion criteria, we were left with five trials eligible to be included in the review (see Figure 1).

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Figure 1. Study flow diagram.



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Included studies

Design

Four trials were open-label, multi-centre, two-armed RCTs (Jovanovic-Peterson 1992; Mathiesen 2007; Mathiesen 2012; Persson 2002). One trial was a single centre, four-armed RCT (Schuster 1998).

Sample sizes

There were 43 women included in the trial by Jovanovic-Peterson 1992 (N = 20 intervention arm, N = 23 control arm), 33 women in the trial by Persson 2002 (N = 16 intervention arm, N = 17 control arm), 223 women in the trial by Mathiesen 2007 (N = 113 intervention arm, N = 110 control arm), 162 women in the trial by Mathiesen 2012 (N = 79 intervention arm, N = 83 control arm) and 93 women in the trial by Schuster 1998 (N = 24 intervention arm1, N = 22 intervention arm2, N = 23 intervention arm3, N = 24 control arm).

Setting

Two trials were conducted in the USA (Jovanovic-Peterson 1992; Schuster 1998), one trial was conducted in Sweden (Persson 2002), and the remaining two trials were conducted in 63 sites in 18 countries, and 79 sites in 17 countries respectively, mainly within Europe (Mathiesen 2007, Mathiesen 2012).

Participants

Participants included pregnant women with type 1 DM (Jovanovic-Peterson 1992; Mathiesen 2007; Mathiesen 2012; Persson 2002; Schuster 1998), or type 2 DM (Jovanovic-Peterson 1992), recruited from hospitals in each specific region.

Interventions and comparisons

Different insulin types within similar insulin regimens

Four trials compared different insulin types within similar insulin regimens (Jovanovic-Peterson 1992; Mathiesen 2007; Mathiesen 2012; Persson 2002).

Persson 2002 compared the rapid-acting insulin analogue Lispro (Humalog®) plus the intermediate-acting insulin NPH (within a MDI basal bolus regimen) to regular short-acting insulin (Humulin Regular®/Actrapid®) plus the intermediate-acting insulin NPH.

Jovanovic-Peterson 1992 compared short-acting human insulin (recombinant deoxyribonucleic acid - Humulin®) to animal insulin.

Mathiesen 2007 compared rapid-acting insulin Aspart (plus the intermediate-acting insulin NPH) to human insulin (plus the intermediate-acting insulin NPH).

Mathiesen 2012 compared long-acting insulin Detemir (plus rapid-acting insulin Aspart) to intermediate-acting NPH insulin (plus rapid-acting insulin Aspart).

Different insulin regimens with similar insulin types used within the regimens

One trial compared three different interventions; for the purpose of this review, we combined the data as follows (Schuster 1998).

1. We compared pre-mixed (70 NPH/30 REG) insulin to self-mixed split dose insulin.
2. We compared insulin injected with a Novolin pen to insulin injected with a conventional needle or syringe.

Outcomes

Primary outcomes

Infant

1. Macrosomia was reported in two trials (Jovanovic-Peterson 1992; Schuster 1998).
2. Perinatal death was reported in one trial (Persson 2002).

Maternal

1. Caesarean section (emergency or elective) was reported in two trials (Persson 2002; Schuster 1998).
2. Pre-eclampsia was reported in one trial (Persson 2002).

Secondary outcomes

Infant

1. Fetal anomaly divided into major and minor was reported in two trials (Mathiesen 2012; Persson 2002).
2. Birth trauma, including shoulder dystocia, nerve palsy, and fracture was reported in one trial (Persson 2002).

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3. Preterm birth, at less than 37 weeks, was reported in one trial (Jovanovic-Peterson 1992).
4. Small-for-gestational age at delivery (weight below the 10th percentile for gestational age at delivery) was reported in one trial (Jovanovic-Peterson 1992).
5. Birthweight centile, corrected for gestational age at delivery, parity, ethnicity, maternal weight, and fetal sex (Z scores used where available) was reported in one trial (Jovanovic-Peterson 1992).
6. Neonatal anthropometry (length, head circumference, ponderal index): Infant length and head circumference were reported in one trial (Jovanovic-Peterson 1992).
7. Neonatal adiposity (fat mass, skinfold thickness, body weight percentile): skinfold thickness and body weight percentile were reported in one trial (Jovanovic-Peterson 1992).

Maternal

1. Vaginal delivery (spontaneous, ventouse, forceps) was reported in one trial (Persson 2002).
2. Measures of diabetic metabolic control (levels of HbA1c, daily mean self-monitored blood glucose, post-prandial and fasting, continuous glucose monitoring): levels of HbA1c at the third trimester visit were reported in one trial (Mathiesen 2007); blood glucose at week 14 (after lunch), was reported in one trial (Persson 2002); blood glucose at weeks 21, 28, and 34 combined (after lunch), was reported in one trial (Persson 2002); postprandial increase of blood glucose before week 14 (after lunch) was reported in one trial (Persson 2002); postprandial increase of blood glucose during weeks 21, 28 and 34 combined (after lunch) was reported in one trial (Persson 2002); antepartum capillary glucose measure (mg/dL), two hours post prandial (after lunch) was reported in one trial (Schuster 1998); insulin requirement during pregnancy (U/kg/24 hour) was reported in one trial (Jovanovic-Peterson 1992).
3. Maternal hypoglycaemia and hyperglycaemia episodes requiring intervention were reported in two trials (Mathiesen 2007; Persson 2002).
4. Postpartum infection was reported in one trial (Schuster 1998).
5. Retinopathy was reported in one trial (Persson 2002).
6. Use of healthcare resources (rate of antenatal clinic visits and admission for treatment relating to control of diabetes, ultrasound growth scans, biophysical scans, dopplers, cardiotocograph's, maternal hospital days): maternal hospital days were reported in one trial (Schuster 1998).

Outcomes not prespecified in protocol

Infant

1. Birthweight was reported in two trials (Jovanovic-Peterson 1992; Schuster 1998).
2. Infant fasting C-peptide level at three months (pmol/mL) was reported in one trial (Jovanovic-Peterson 1992).
3. Infant C-peptide level 1 hour after glucose-amino acid challenge at three months (pmol/mL) was reported in one trial (Jovanovic-Peterson 1992).
4. Infant glucose fasting level at three months (pmol/mL) was reported in one trial (Jovanovic-Peterson 1992).
5. Infant glucose level 1 hour after glucose-amino acid challenge at three months (pmol/mL) was reported in one trial (Jovanovic-Peterson 1992).
6. Gestational age at delivery was reported in one trial (Jovanovic-Peterson 1992).

Maternal

1. Ventouse delivery was reported in one trial (Persson 2002).
2. Maternal compliance with treatment score (1 = best compliance, 5 = worst compliance) was reported in one trial (Schuster 1998).
3. Maternal ketonuria was reported in one trial (Jovanovic-Peterson 1992).

Prespecified outcomes not reported

Infant

1. Five-minute Apgar score less than seven.
2. Admission and length of stay in neonatal intensive care unit.
3. Mechanical ventilation.
4. Neonatal infection.
5. Neonatal hypoglycaemia.
6. Insulin sensitivity (cord insulin, C-peptide).
7. Jaundice requiring therapy.
8. Respiratory distress syndrome.
9. Hyperbilirubinaemia.
10. Necrotising enterocolitis.
11. Intracranial haemorrhage.
12. Artificial (tube) feeding.
13. Composite outcome measure of neonatal morbidity (admission and length of stay in neonatal intensive care unit, mechanical ventilation, neonatal infection, neonatal hypoglycaemia, insulin sensitivity (cord insulin, C-peptide), jaundice requiring therapy, respiratory distress syndrome, hyperbilirubinaemia, necrotising enterocolitis, intracranial haemorrhage, artificial (tube) feeding).
14. Measures of growth and neurodevelopment at childhood follow-up.

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Maternal

1. Postpartum haemorrhage.
2. Severe perineal trauma (third- and fourth-degree tear).
3. Weight gain in pregnancy.
4. Induction of labour (reasons related to diabetes).
5. Breastfeeding.
6. Quality of life (psychological impact of management, assessed by psychometric testing with a reliable standardised questionnaire).
7. Woman's preference and satisfaction with treatment.
8. Economic evaluation.

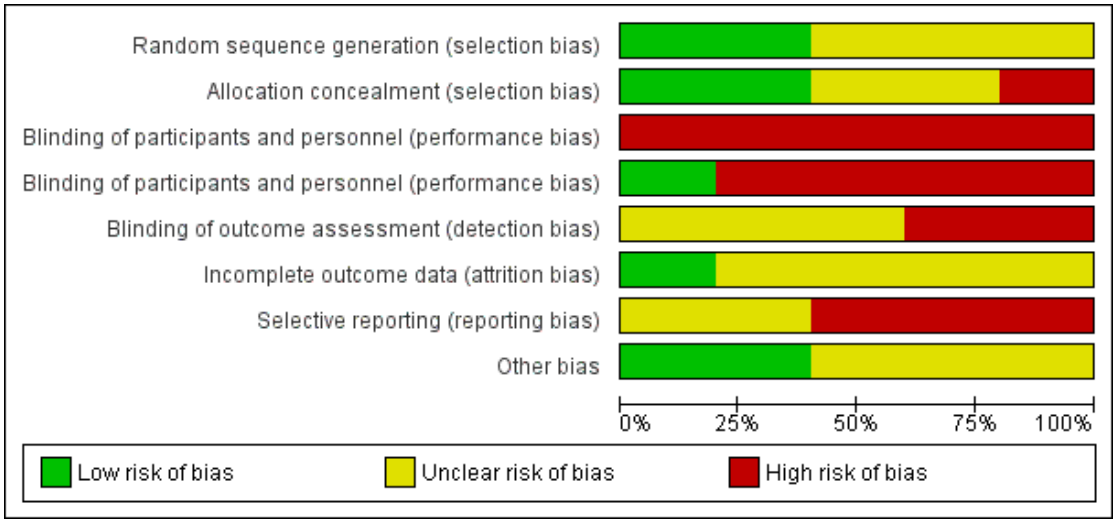
Excluded studies

We excluded Carr 2004 and Murphy 2011 because they used a cross-over study design. We excluded Herrera 2015b; Kipikasa 2008; Mohd 2012; Nachum 1999; and Nor 2007 because they included women with gestational diabetes. Porta 2011; Reller 1985; and Secher 2012 did not include suitable interventions. See Characteristics of excluded studies.

Risk of bias in included studies

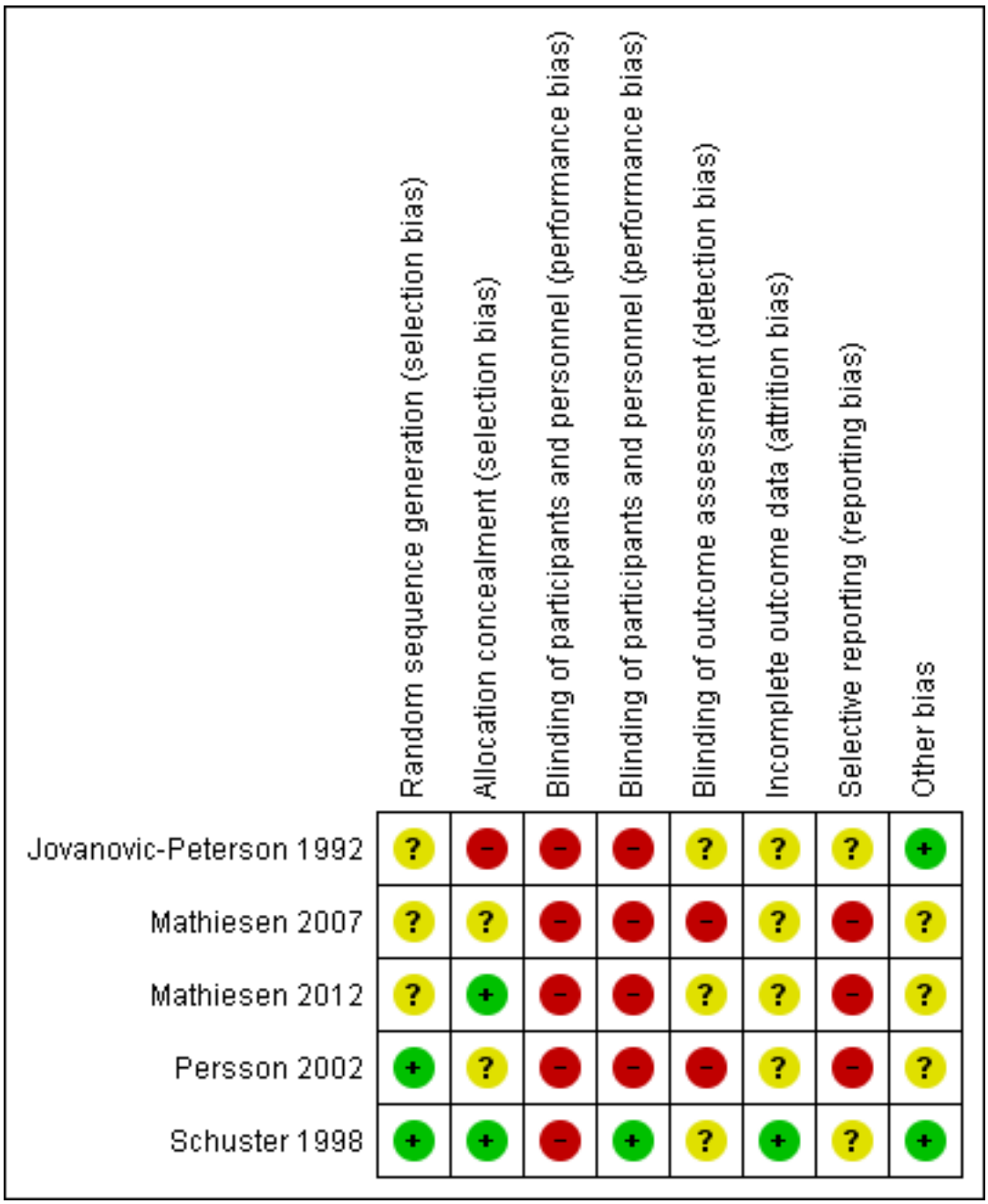
Overall, the five trials had a high risk of bias, due to lack of allocation concealment, lack of blinding, incomplete outcome data, and selective reporting of outcomes (Figure 2, Figure 3).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



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Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



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Allocation

Random sequence generation

Two trials described the method of sequence generation used (computer-generated randomisation (Persson 2002; Schuster 1998)). Three trials had an unclear risk of bias, as the method of random sequence generation was not described (Jovanovic-Peterson 1992; Mathiesen 2007; Mathiesen 2012).

Allocation concealment

Two trials provided sufficient details on the method of allocation concealment (sealed opaque envelopes (Mathiesen 2012; Schuster 1998)). One trial had a high risk of bias for allocation concealment (open-label (Jovanovic-Peterson 1992)). Two trials had an unclear risk of allocation concealment, which was not reported in the trials (Mathiesen 2007; Mathiesen 2012).

Blinding

Performance bias

It was difficult to blind the women and staff to the interventions of insulin types or insulin regimens. All five trials had a high risk of performance bias, as the participants were aware of the treatment they were receiving. For personnel, one trial reported blinding personnel to the intervention, so this was deemed to have a low risk of bias (Schuster 1998), whilst the other four trials (Jovanovic-Peterson 1992; Mathiesen 2007; Mathiesen 2012; Persson 2002) did not blind personnel, and these were deemed to have a high risk of bias.

Detection bias

Two trials had a high risk of detection bias (open-label (Mathiesen 2007; Persson 2002)), Three trials had an unclear risk of detection bias, which was not described in two of them (Jovanovic-Peterson 1992; Schuster 1998), and one trial reported blinding of outcome assessment for only one outcome (congenital malformations (Mathiesen 2012)).

Incomplete outcome data

Only one trial adequately described losses to follow-up, and women were equally distributed between the four groups in this study (Schuster 1998). Details regarding attrition bias were not reported in the other four trials (Jovanovic-Peterson 1992; Mathiesen 2007; Mathiesen 2012; Persson 2002).

Selective reporting

Two trials had an unclear risk of bias, as no protocol for either trial was available, and therefore, it was not clear whether all prespecified outcomes were reported (Jovanovic-Peterson 1992; Schuster 1998). Three trials were deemed to have high risk of reporting bias (Mathiesen 2007; Mathiesen 2012; Persson 2002). In the trial by Persson 2002, some outcomes were described as showing no differences, but these figures are not given. For two trials, we included a subgroup of women who were pregnant at randomisation, and for these women, very few outcomes were reported (Mathiesen 2007; Mathiesen 2012). Contact with the authors to gain information on this subgroup proved unsuccessful.

Other potential sources of bias

Three trials had unclear risk of bias (Mathiesen 2007; Mathiesen 2012; Persson 2002). One trial reported that there were no significant differences between the two treatment groups with regard to baseline characteristics, however, significantly more women in the Lispro group had aneurysms (Persson 2002), and two trials were funded by the pharmaceutical company Novo Nordisk© (Mathiesen 2007; Mathiesen 2012). Two trials had a low risk of bias as it was reported that there was no difference in baseline characteristics between the two groups, which was clear from the tables (Jovanovic-Peterson 1992; Schuster 1998).

Effects of interventions

See: **Summary of findings for the main comparison** Lispro versus regular insulin (Different insulin types within similar insulin regimens); **Summary of findings 2** Human insulin versus animal insulin (Different insulin types within similar insulin regimens); **Summary of findings 3** Pre-mixed insulin (70 NPH/30 REG) versus self-mixed split dose insulin (Different insulin regimens with similar insulin types used within the regimen); **Summary of findings 4** Insulin injected with a Novolin pen versus insulin injected with a needle or syringe (Different insulin regimens with similar insulin types used within the regimen); **Summary of findings 5** Insulin Aspart (+ NPH) compared to human insulin (+ NPH insulin) for pregnant women with pre-existing diabetes (Different insulin types within similar insulin regimens); **Summary of findings 6** Insulin Detemir + prandial insulin Aspart versus NPH insulin + prandial insulin Aspart (Different insulin types within similar insulin regimens)

See: Summary of findings for the main comparison, Lispro versus regular insulin (Different insulin types within similar insulin regimens); Summary of findings 2, Human insulin (recombinant deoxyribonucleic acid - Humulin) versus animal insulin (Different insulin types within similar insulin regimens); Summary of

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findings 3, Pre-mixed insulin (70 NPH/30 REG) versus self-mixed split dose insulin (Different insulin regimens with similar insulin types used within the regimen); Summary of findings 4, Insulin injected with a Novolin pen versus insulin injected with a needle/syringe (Different insulin regimens with similar insulin types used within the regimen); Summary of findings 5, Insulin Aspart plus NPH insulin versus Human insulin plus NPH insulin (Different insulin types within similar insulin regimens); Summary of findings 6, Insulin Detemir plus prandial insulin Aspart versus NPH insulin plus prandial insulin Aspart (Different insulin types within similar insulin regimens).

1. Lispro versus regular insulin (*Different* insulin *types* within *similar* insulin *regimens*)

See Summary of findings for the main comparison. We included one trial in this comparison, involving a total of 33 women (Persson 2002). The evidence was downgraded to very low-quality for all the outcomes supported by this trial for the following reasons: study limitations (there was a high or unclear risk of bias for allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other biases), and sparse data (one small study, few events for the outcomes, very wide confidence intervals often crossing the line of no effect).

Primary outcomes

Infant

There were no perinatal deaths in the Lispro or regular insulin group (Analysis 1.1).

Maternal

There was very low-quality evidence from one study (33 women) of no clear difference between insulin Lispro and regular insulin in the primary maternal outcomes of caesarean section (risk ratio (RR) 0.59, 95% confidence interval (CI) 0.25 to 1.39; 33 women; Analysis 1.2), and pregnancy-induced hypertension or pre-eclampsia (RR 0.68, 95% CI 0.35 to 1.30; Analysis 1.3).

Secondary outcomes

Infant

There was very low-quality evidence from one study (33 infants) of no clear difference between insulin Lispro and regular insulin in the secondary infant outcomes of fetal anomaly (RR 0.35, 95% CI 0.02 to 8.08; Analysis 1.4). There were no cases of birth trauma, including shoulder dystocia, nerve palsy, and fracture in either group (Analysis 1.5).

Maternal

There was very low-quality evidence from one study (33 women) of no clear differences between insulin Lispro and regular insulin in the secondary maternal outcomes of vaginal delivery (spontaneous, ventouse, forceps (RR 1.46, 95% CI 0.80 to 2.67; Analysis 1.6), and measures of diabetic metabolic control: blood glucose at week 14 after lunch (mean difference (MD) -1.09 mmol/L, 95% CI -3.60 to 1.42; Analysis 1.7); blood glucose after lunch at weeks 21, 28, and 34 combined (MD -0.04 mmol/L, 95% CI -2.10 to 2.02; Analysis 1.8); increase of blood glucose after lunch before week 14 (MD 1.00 mmol/L, 95% CI -1.52 to 3.52; Analysis 1.9); increase of blood glucose after lunch during weeks 21, 28, and 34 combined (MD 0.10 mmol/L, 95% CI -2.12 to 2.32; Analysis 1.10); maternal hypoglycaemia and hyperglycaemia episodes requiring intervention (RR 0.21, 95% CI 0.01 to 4.10; Analysis 1.11); and retinopathy (RR 1.06, 95% CI 0.17 to 6.67; Analysis 1.12). Caution is advised in interpreting the data where there are wide confidence intervals, small sample size, and low event rates in this comparison.

Outcomes not prespecified in protocol

Maternal

There was very low-quality evidence from one study (33 women) of no clear difference between insulin Lispro and regular insulin for ventouse delivery (RR 3.19, 95% CI 0.37 to 27.58; Analysis 1.13).

Outcomes not reported

Infant

Macrosomia, preterm birth at less than 37 weeks; small-for-gestational age at delivery; five-minute Apgar score less than seven; birthweight centile corrected for gestational age at delivery, parity, ethnicity, maternal weight, and fetal sex; admission and length of stay in neonatal intensive care unit; mechanical ventilation; neonatal infection; jaundice requiring therapy; respiratory distress syndrome; necrotising enterocolitis; intracranial haemorrhage; artificial (tube) feeding; and the composite outcome measure of neonatal morbidity (admission and length of stay in neonatal intensive care unit; mechanical ventilation; neonatal infection; jaundice requiring therapy; respiratory distress syndrome; necrotising enterocolitis; intracranial haemorrhage; artificial (tube) feeding); neonatal anthropometry (length, head circumference, ponderal index); neonatal adiposity (fat mass, skinfold thickness); measures

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of growth and neurodevelopment at childhood follow-up; birthweight; infant fasting C-peptide level at three months; infant C-peptide level one hour after glucose-amino acid challenge at three months; infant glucose fasting level at three months; infant glucose level one hour after glucose-amino acid challenge at three months; gestational age at delivery.

Maternal

Postpartum haemorrhage; severe perineal trauma (third- and fourth-degree tear); weight gain in pregnancy; induction of labour (reasons related to diabetes); postpartum infection; breastfeeding; quality of life (psychological impact of management, assessed by psychometric testing with a reliable standardised questionnaire); use of healthcare resources (rate of antenatal clinic visits and admission for treatment relating to control of diabetes, ultrasound growth scans, biophysical scans, dopplers, cardiotocograph's); women's preference and satisfaction with treatment; an economic evaluation; maternal ketonuria; maternal compliance with treatment score (1 = best compliance, 5 = worst).

2. Human insulin (recombinant deoxyribonucleic acid - Humulin) versus animal insulin (*Different* insulin *types* within *similar* insulin *regimens*)

See Summary of findings 2. We included one trial in this comparison (Jovanovic-Peterson 1992) involving a total of 42 women. The evidence supporting outcomes was downgraded to very low for the following reasons: study limitations (high or unclear risk of bias for allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other biases), and sparse data (one small study, few events for the outcomes, very wide confidence intervals often crossing the line of no effect).

Primary outcomes

Infant

There was very low-quality evidence from one study (42 infants) of no clear difference between human insulin and animal insulin in the primary infant outcome of macrosomia (RR 0.22, 95% CI 0.01 to 4.30; Analysis 2.8).

Maternal

None reported.

Secondary outcomes

Infant

There was very low-quality evidence from one study (42 infants) of no clear differences between human insulin and animal insulin for: preterm birth less than 37 weeks (RR 7.67, 95% CI 0.42 to 139.83, Analysis 2.2), birthweight centile (MD -6.70%, 95% CI -23.64% to 10.24%; Analysis 2.3), infant length (MD -3.30 cm, 95% CI -6.74 to 0.14; Analysis 2.4), skinfold thickness (MD -4.10 mm, 95% CI -13.28 to 5.08; Analysis 2.5), or body weight percentile (MD -6.70%, 95% CI -23.64 to 10.24; Analysis 2.6). The infants of women who were in the human insulin group had a smaller mean head circumference than those in the animal insulin group (MD -5.10 cm, 95% CI -9.52 to -0.68; Analysis 2.7). There were no cases of babies who were small-for-gestational age at delivery (Analysis 2.1).

Maternal

There was very low-quality evidence from one study (42 women) that for the measure of diabetic metabolic control, women in the human insulin group had a lower mean insulin requirement during pregnancy (MD -0.33 U/kg/24 hour, 95% CI -0.45 to -0.21; Analysis 2.9) compared to women in the animal insulin group.

Outcomes not prespecified in protocol

Infant

There was very low-quality evidence from one study (42 infants) that infants in the human group had a lower mean birthweight (MD -591.00 g, 95% CI -1066.27 to -115.73; Analysis 2.10), a very slightly lower infant fasting C-peptide level at three months (MD -0.07 pmol/mL, 95% CI -0.13 to -0.01; Analysis 2.11), and a lower infant C-peptide level one hour after glucose amino acid challenge at three months (MD -0.11 pmol/mL, 95% CI -0.19 to -0.03; Analysis 2.12). No clear difference was found for infant glucose fasting level at three months (MD -0.20 pmol/mL, 95% CI -0.62 to 0.22; Analysis 2.13); infant glucose level one hour after glucose amino acid challenge at three months (MD 0.50 pmol/mL, 95% CI -0.04 to 1.04; Analysis 2.14), or gestational age at delivery (MD 0.50 weeks, 95% CI -3.70 to 4.70; Analysis 2.15).

Maternal

There was very low-quality evidence from one study (42 women) that the human insulin group had an unclear lower risk of maternal ketonuria (RR 0.37, 95% CI 0.08 to 1.61; Analysis 2.16).

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Outcomes not reported

Infant

Perinatal death; fetal anomaly; birth trauma including shoulder dystocia, nerve palsy and fracture; five-minute Apgar score less than seven; birthweight centile corrected for gestational age at delivery, parity, ethnicity, maternal weight and fetal sex; admission and length of stay in neonatal intensive care unit; mechanical ventilation; neonatal infection; jaundice requiring therapy; respiratory distress syndrome; necrotising enterocolitis; intracranial haemorrhage; artificial (tube) feeding; a composite outcome measure of neonatal morbidity (admission and length of stay in neonatal intensive care unit, mechanical ventilation, neonatal infection, jaundice requiring therapy, respiratory distress syndrome, necrotising enterocolitis, intracranial haemorrhage, artificial (tube) feeding) and measures of growth and neurodevelopment at childhood follow-up.

Maternal

Caesarean section; pre-eclampsia; vaginal delivery (spontaneous, ventouse, forceps); postpartum haemorrhage; severe perineal trauma (third- and fourth-degree tear); maternal hypoglycaemia and hyperglycaemia episodes requiring intervention; weight gain in pregnancy; induction of labour (reasons related to diabetes); postpartum infection; breastfeeding; retinopathy; quality of life; use of healthcare resources; women's preference and satisfaction with treatment; an economic evaluation; ventouse delivery; and maternal compliance with treatment score (1 = best, 5 = worst compliance).

3. Pre-mixed insulin (70 NPH/30 REG) versus self-mixed split dose insulin (*Different* insulin *regimens* with *similar* insulin *type*s used within the regimen)

See Summary of findings 3. We included one trial in this comparison (Schuster 1998) involving a total of 93 women. The evidence supporting the outcomes was downgraded to very low for the following reasons: study limitations (high or unclear risk of bias for allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other biases), and sparse data (one small study, few events for the outcomes, very wide confidence intervals often crossing the line of no effect).

Primary outcomes

Infant

There was very low-quality evidence from one study (93 infants) of no clear difference between pre-mixed insulin and self-mixed insulin for **macrosomia** (RR 0.49, 95% CI 0.09 to 2.54; Analysis 3.1)

Maternal

There was very low-quality evidence from one study (93 women) of no clear difference between pre-mixed insulin and self-mixed insulin for caesarean section (RR 0.57, 95% CI 0.25 to 1.32; Analysis 3.2)

Secondary outcomes

Infant

None reported.

Maternal

There was very low-quality evidence from one study (93 women) that the pre-mixed insulin group had significantly lower measures of diabetic metabolic control, measured by antepartum capillary glucose taken two hours after lunch (MD -11.25 mg/dL, 95% CI -12.55 to -9.95; 10,218 tests performed on 93 women; Analysis 3.3) compared to the self-mixed insulin group. There was no clear difference between the pre-mixed insulin and self-mixed insulin groups for postpartum infection (endometritis; RR 0.52, 95% CI 0.26 to 1.04; Analysis 3.4); and use of healthcare resources (maternal hospital days; MD -0.50, 95% CI -1.40 to 0.41; Analysis 3.5)

Outcomes not prespecified in protocol

Infant

There was very low-quality evidence from one study (93 infants) that there was no clear difference between the pre-mixed and self-mixed insulin groups for birthweight (MD -116.56 g, 95% CI -391.81 to 158.69; Analysis 3.6).

Maternal

There was very low-quality evidence from one study (93 women) that there was no clear difference between the two groups in terms of the women's compliance score (ranges from 1 to 5, 1 = best, 5 = worst; MD 0.00, 95% CI -0.87 to 0.87; Analysis 3.7).

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Outcomes not reported

Infant

Perinatal death; fetal anomaly; birth trauma including shoulder dystocia, nerve palsy and fracture; preterm birth at less than 37 weeks; small-for-gestational age at delivery; five-minute Apgar score less than seven; birthweight centile corrected for gestational age at delivery, parity, ethnicity, maternal weight and fetal sex; admission and length of stay in neonatal intensive care unit; mechanical ventilation; neonatal infection; neonatal hypoglycaemia; insulin sensitivity (cord insulin, C-peptide); jaundice requiring therapy; respiratory distress syndrome; hyperbilirubinaemia; necrotising enterocolitis; intracranial haemorrhage; artificial (tube) feeding; a composite outcome of neonatal morbidity (admission and length of stay in neonatal intensive care unit, mechanical ventilation, neonatal infection, neonatal hypoglycaemia, insulin sensitivity (cord insulin, C-peptide), jaundice requiring therapy, respiratory distress syndrome, hyperbilirubinaemia, necrotising enterocolitis, intracranial haemorrhage, artificial (tube) feeding); neonatal anthropometry (length, head circumference, ponderal index); neonatal adiposity (fat mass, skinfold thickness) and measures of growth and neurodevelopment at childhood follow-up; infant fasting C-peptide level at three months; infant C-peptide level one hour after glucose-amino acid challenge at three months; infant glucose fasting level at three months; infant glucose level one hour after glucose-amino acid challenge at three months; gestational age at delivery.

Maternal

Pre-eclampsia; vaginal delivery (spontaneous, ventouse, forceps); postpartum haemorrhage; severe perineal trauma (third- and fourth-degree tear), maternal hypoglycaemia and hyperglycaemic episodes requiring intervention; weight gain in pregnancy; induction of labour (reasons related to diabetes); breastfeeding; retinopathy; quality of life (psychological impact of management assessed by psychometric testing using a reliable standardised questionnaire); women's preference and satisfaction with treatment; an economic evaluation; ventouse delivery; maternal ketonuria.

4. Insulin injected with a Novolin pen versus insulin injected with a needle/syringe (*Different* insulin *regimens* with *similar* insulin *type*s used within the regimen)

See Summary of findings 4. We included one trial in this comparison (Schuster 1998) involving a total of 93 women. The evidence for the outcomes was downgraded to very low for the following reasons: study limitations (high or unclear risk of bias for allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other biases) and sparse data (one small study, few events for the outcomes, very wide confidence intervals often crossing the line of no effect).

Primary outcomes

Infant

There was very low-quality evidence from one study (93 infants) of no clear difference between injecting with the Novolin pen and a conventional needle or syringe for macrosomia (RR 0.21, 95% CI 0.03 to 1.76; Analysis 4.1).

Maternal

There was very low-quality evidence from one study (93 women) of a difference between the two groups for caesarean section (RR 0.38, 95% CI 0.15 to 0.97; Analysis 4.2).

Secondary outcomes

Infant

None reported.

Maternal

There was very low-quality evidence from one study (93 women) that the Novolin pen group had a lower mean measure of diabetic metabolic control, measured by antepartum capillary glucose, taken two hours after lunch (MD -7.23 mg/dL), 95% CI -8.51 to -5.95; 10,218 tests performed on 93 women; Analysis 4.3) compared to the conventional syringe or needle group. There was no clear difference between injecting with the Novolin pen and a conventional needle or syringe for postpartum infection (endometritis; RR 0.56, 95% CI 0.28 to 1.14; Analysis 4.4) and use of healthcare resources (maternal hospital days; MD -0.56, 95% CI -1.45 to 0.33; Analysis 4.5).

Outcomes not prespecified in protocol

Infant

There was very low-quality evidence from one study (93 infants) of no clear difference between injecting with the Novolin pen and a conventional needle or syringe for birthweight (MD -162.36 g, 95% CI -438.25 to 113.53; Analysis 4.6).

Maternal

There was very low-quality evidence from one study (93 women) of no clear difference between the two groups in the women's compliance score (ranges from 1 to 5, 1 = best compliance, 5 = worst compliance; MD -0.21, 95% CI -0.83 to 0.41; Analysis 4.7).

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Outcomes not reported

Infant

Perinatal death; fetal anomaly; birth trauma including shoulder dystocia, nerve palsy and fracture; preterm birth at less than 37 weeks; small-for-gestational age at delivery; five-minute Apgar score less than seven; birthweight centile corrected for gestational age at delivery, parity, ethnicity, maternal weight and fetal sex; admission and length of stay in neonatal intensive care unit; mechanical ventilation; neonatal infection; neonatal hypoglycaemia; insulin sensitivity (cord insulin, C-peptide); jaundice requiring therapy; respiratory distress syndrome; hyperbilirubinaemia; necrotising enterocolitis; intracranial haemorrhage; artificial (tube) feeding; a composite outcome of neonatal morbidity (admission and length of stay in neonatal intensive care unit, mechanical ventilation, neonatal infection, neonatal hypoglycaemia, insulin sensitivity (cord insulin, C-peptide), jaundice requiring therapy, respiratory distress syndrome, hyperbilirubinaemia, necrotising enterocolitis, intracranial haemorrhage, artificial (tube) feeding); neonatal anthropometry (length, head circumference, ponderal index); neonatal adiposity (fat mass, skinfold thickness) and measures of growth and neurodevelopment at childhood follow-up; infant fasting C-peptide level at three months; infant C-peptide level one hour after glucose-amino acid challenge at three months; infant glucose fasting level at three months; infant glucose level one hour after glucose-amino acid challenge at three months; gestational age at delivery.

Maternal

Pre-eclampsia; vaginal delivery (spontaneous, ventouse, forceps); postpartum haemorrhage; severe perineal trauma (third- and fourth-degree tear), maternal hypoglycaemia and hyperglycaemic episodes requiring intervention; weight gain in pregnancy; induction of labour (reasons related to diabetes); breastfeeding; retinopathy; quality of life (psychological impact of management, assessed by psychometric testing using a reliable standardised questionnaire); women's preference and satisfaction with treatment; an economic evaluation; ventouse delivery; maternal ketonuria.

5. Insulin Aspart + NPH insulin versus Human insulin + NPH insulin (*Different* insulin *types* within *similar* insulin *regimens*)

See Summary of findings 5. We included one trial in this comparison (Mathiesen 2007) involving a total of 223 women. This is an empty 'summary of findings' table with no evidence or quality assessment as none of the primary outcomes were included in this trial.

Primary outcomes

Infant

None reported.

Maternal

None reported.

Secondary outcomes

Infant

None reported.

Maternal

There was very low-quality evidence from one study (223 women) of no difference between insulin Aspart and human insulin for diabetic metabolic control, measured by A1c at third trimester visits (MD -0.10%, 95% CI -0.28 to 0.08; Analysis 5.1, average plasma glucose at third trimester visits (MD -0.20 mmol/L, 95% CI -0.53 to 0.13; Analysis 5.2); and maternal hypoglycaemic episodes (RR 1.06, 95% CI 0.99 to 1.14; Analysis 5.3);

Outcomes not prespecified in protocol

Infant

None.

Maternal

None.

Outcomes not reported

Infant

Macrosomia; perinatal death; fetal anomaly; birth trauma including shoulder dystocia, nerve palsy and fracture; preterm birth less than 37 weeks; small-for-gestational age at delivery; five-minute Apgar score less than seven; birthweight centile corrected for gestational age at delivery, parity, ethnicity, maternal weight and fetal sex; admission and length of stay in neonatal intensive care unit; mechanical ventilation; neonatal infection; neonatal hypoglycaemia; insulin sensitivity (cord insulin, C-peptide); jaundice requiring therapy; respiratory distress syndrome; hyperbilirubinaemia; necrotising enterocolitis; intracranial haemorrhage; artificial (tube) feeding; a composite outcome measure of neonatal morbidity (admission and length of stay in neonatal intensive care

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unit, mechanical ventilation, neonatal infection, neonatal hypoglycaemia, insulin sensitivity (cord insulin, C-peptide), jaundice requiring therapy, respiratory distress syndrome, hyperbilirubinaemia, necrotising enterocolitis, intracranial haemorrhage, artificial (tube) feeding); neonatal anthropometry (length, head circumference, ponderal index); neonatal adiposity (fat mass, skinfold thickness) and measures of growth and neurodevelopment at childhood follow-up; birthweight; infant fasting C-peptide level at three months; infant C-peptide level one hour after glucose-amino acid challenge at three months; infant glucose fasting level at three months; infant glucose level one hour after glucose-amino acid challenge at three months; gestational age at delivery.

Maternal

Caesarean section; pre-eclampsia; vaginal delivery (spontaneous, ventouse, forceps); postpartum haemorrhage; severe perineal trauma (third- and fourth-degree tear); weight gain in pregnancy; induction of labour (reasons related to diabetes); postpartum infection; breastfeeding; retinopathy; quality of life (psychological impact of management, assessed by psychometric testing using a reliable standardised questionnaire); use of healthcare resources (rate of antenatal clinic visits and admission for treatment relating to diabetic control, ultrasound growth scans, biophysical scans, dopplers, cardiotocograph's); women's preference and satisfaction with treatment; an economic evaluation; ventouse delivery; maternal ketonuria; maternal compliance with treatment score (1 = best, 5 = worst compliance).

6. Insulin Detemir + Aspart versus NPH insulin + Aspart (*Different* insulin *types* within *similar* insulin *regimens*)

See Summary of findings 6. We included one trial in this comparison (Mathiesen 2012) involving a total of 162 women. The evidence for the outcomes supported by this study was downgraded to very low for study limitations (high or unclear risk of bias for allocation concealment, blinding of participants and personnel, incomplete outcome data, selective outcome reporting, and other biases) and sparse data (one small study, few events for the outcomes, very wide confidence intervals often crossing the line of no effect).

Primary outcomes

Infant

None reported.

Maternal

None reported.

Secondary outcomes

Infant

There was very low-quality evidence from one study (162 infants) of no clear difference in the number of major fetal anomalies in the insulin Detemir group compared to the NPH insulin group (RR 3.15, 95% CI 0.33 to 29.67; Analysis 6.1), major fetal anomalies (RR 2.10, 95% CI 0.19 to 22.72; Analysis 6.2); minor fetal anomalies (RR 0.35, 95% CI 0.01 to 8.47; Analysis 6.3), and minor fetal anomalies (RR 1.05, 95% CI 0.22 to 5.05; Analysis 6.4). Outcome assessors were blinded for Analyses 6.1 and 6.3 and unblinded for Analyses 6.2 and 6.4.

Maternal

Outcomes not prespecified in protocol

Infant

None.

Maternal

None.

Outcomes not reported

Infant

Macrosomia; perinatal death; birth trauma including shoulder dystocia, nerve palsy and fracture; preterm birth less than 37 weeks; small-for-gestational age at delivery; five-minute Apgar score less than seven; birthweight centile corrected for gestational age at delivery, parity, ethnicity, maternal weight and fetal sex; admission and length of stay in neonatal intensive care unit; mechanical ventilation; neonatal infection; neonatal hypoglycaemia; insulin sensitivity (cord insulin, C-peptide); jaundice requiring therapy; respiratory distress syndrome; hyperbilirubinaemia; necrotising enterocolitis; intracranial haemorrhage; artificial (tube) feeding; a composite outcome measure of neonatal morbidity (admission and length of stay in neonatal intensive care unit, mechanical ventilation, neonatal infection, neonatal hypoglycaemia, insulin sensitivity (cord insulin, C-peptide), jaundice requiring therapy, respiratory distress syndrome, hyperbilirubinaemia, necrotising enterocolitis, intracranial haemorrhage, artificial (tube) feeding); neonatal anthropometry (length, head circumference, ponderal index); neonatal adiposity (fat mass, skinfold thickness) and measures of growth and neurodevelopment at childhood follow-up; birthweight; infant fasting C-peptide level at three months;

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infant C-peptide level one hour after glucose-amino acid challenge at three months; infant glucose fasting level at three months; infant glucose level one hour after glucose-amino acid challenge at three months; gestational age at delivery.

Maternal

Caesarean section; pre-eclampsia; vaginal delivery (spontaneous, ventouse, forceps); postpartum haemorrhage; severe perineal trauma (third- and fourth-degree tear); measures of diabetic metabolic control (levels of HbA1c, daily mean self-monitored blood glucose, post-prandial and fasting, continuous glucose monitoring); maternal hypoglycaemia and hyperglycaemic episodes requiring intervention; weight gain in pregnancy; induction of labour (reasons related to diabetes); postpartum infection; breastfeeding; retinopathy; quality of life (psychological impact of management, assessed by psychometric testing using a reliable standardised questionnaire); use of healthcare resources (rate of antenatal clinic visits and admission for treatment relating to diabetic control, ultrasound growth scans, biophysical scans, dopplers, cardiotocograph's); women's preference and satisfaction with treatment; an economic evaluation; ventouse delivery; maternal ketonuria; maternal compliance with treatment score (1 = best, 5 = worst compliance).

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ADDITIONAL SUMMARY OF FINDINGS [*Explanation*]

Human insulin versus animal insulin (Different insulin types within similar insulin regimens)

Patient or population: pregnant women with pre-existing diabetes
Setting: The Children's Hospital of San Francisco and Cornell University Medical College, New York
Intervention: human insulin (recombinant deoxyribonucleic acid - Humulin)
Comparison: animal insulin

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with animal insulin	Risk with human insulin (Humulin)				
Macrosomia	Study population		RR 0.22 (0.01 to 4.30)	42 (1 RCT)	⊕◯◯◯ VERY LOW [1234]	
	91 per 1000	20 per 1000 (1 to 391)				
Perinatal death				(0 studies)	Not reported	
Pre-eclampsia				(0 studies)	Not reported	
Caesarean section				(0 studies)	Not reported	
Fetal anomaly				(0 studies)	Not reported	
Birth trauma including shoulder dystocia, nerve palsy, and fracture				(0 studies)	Not reported	
Composite outcome measure of neonatal morbidity				(0 studies)	Not reported	

*__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; __RR:__ Risk ratio; __OR:__ Odds 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 was high or unclear for random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting
[2] One study with serious design limitations including lack of blinding for allocation concealment
[3] Very wide 95% confidence intervals crossing the line of no effect
[4] Small sample size and few events

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Pre-mixed insulin (70 NPH/30 REG) versus self-mixed split dose insulin (Different insulin regimens with similar insulin types used within the regimen)

Patient or population: pregnant women with pre-existing diabetes
Setting: University of Mississippi Medical Centre, USA
Intervention: pre-mixed insulin (70 NPH/30 REG)
Comparison: self-mixed split dose insulin

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with self-mixed split dose insulin	Risk with pre-mixed insulin (70 NPH/30 REG)				
Macrosomia	Study population		RR 0.49 (0.09 to 2.54)	93 (1 RCT)	⊕◯◯◯ VERY LOW [1,2,3]	
	87 per 1000	43 per 1000 (8 to 221)				
Perinatal death				(0 studies)	Not reported	
Pre-eclampsia				(0 studies)	Not reported	
Caesarean section [4]	Study population		RR 0.57 (0.25 to 1.32)	93 (1 RCT)	⊕◯◯◯ VERY LOW [123]	
	261 per 1000	149 per 1000 (65 to 344)				
Fetal anomaly				(0 studies)	Not reported	
Birth trauma including shoulder dystocia, nerve palsy, or fracture				(0 studies)	Not reported	
Composite outcome measure of neonatal morbidity				(0 studies)	Not reported	

*__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; __RR:__ Risk ratio; __OR:__ Odds 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] Very wide 95% confidence intervals crossing the line of no effect
[2] Small sample size and few events
[3] One study with serious design limitations
[4] Caesarean section for cephalo-pelvic disproportion

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Insulin injected with a Novolin pen versus insulin injected with a needle or syringe (Different insulin regimens with similar insulin types used within the regimen)

Patient or population: pregnant women with pre-existing diabetes
Setting: University of Mississippi Medical Centre, USA
Intervention: insulin injected with a Novolin pen
Comparison: insulin injected with a needle or syringe

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with insulin injected with a needle or syringe	Risk with insulin injected with a Novolin pen				
Macrosomia	Study population		RR 0.21 (0.03 to 1.76)	93 (1 RCT)	⊕◯◯◯ VERY LOW [1,2,3]	
	104 per 1000	22 per 1000 (3 to 183)				
Perinatal death				(0 studies)	Not reported	
Pre-eclampsia				(0 studies)	Not reported	
Caesarean section [4]	Study population		RR 0.38 (0.15 to 0.97)	93 (1 RCT)	⊕◯◯◯ VERY LOW [1,2,3]	
	292 per 1000	111 per 1000 (44 to 283)				
Fetal anomaly				(0 studies)	Not reported	
Birth trauma including shoulder dystocia, nerve palsy, or fracture				(0 studies)	Not reported	

Composite outcome measure of neonatal morbidity		(0 studies)	Not reported

*__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; **RR:** Risk ratio; **OR:** Odds 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] Very wide 95% confidence intervals crossing the line of no effect
[2] Small sample size with few events
[3] One study with serious design limitations
[4] Caesarean section for cephalo-pelvic disproportion

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Insulin Aspart (+ NPH) compared to human insulin (+ NPH) for pregnant women with pre-existing diabetes (Different insulin types within similar insulin regimens)

Patient or population: pregnant women with pre-existing diabetes
Setting: 63 different sites in 18 countries
Intervention: insulin Aspart (+ NPH insulin)
Comparison: human insulin (+ NPH insulin)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with human insulin (+ NPH)	Risk with insulin Aspart (+ NPH)				
Macrosomia	-	-	-	-	-	Not reported
Perinatal death	-	-	-	-	-	Not reported
Pre-eclampsia	-	-	-	-	-	Not reported
Caesarean section	-	-	-	-	-	Not reported
Fetal anomaly	-	-	-	-	-	Not reported
Birth trauma including shoulder dystocia, nerve palsy and fracture	-	-	-	-	-	Not reported
Composite outcome measure of neonatal morbidity	-	-	-	-	-	Not reported

*__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; **RR:** Risk ratio; **OR:** Odds 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

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Insulin Detemir + prandial insulin Aspart versus NPH insulin + prandial insulin Aspart (Different insulin types within similar insulin regimens)

Patient or population: pregnant women with pre-existing diabetes
Setting: 79 sites in 17 countries, mainly within Europe
Intervention: insulin Detemir (+ Aspart)
Comparison: NPH (+ Aspart)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with NPH (+ Aspart)	Risk with insulin Detemir (+ Aspart)				
Macrosomia				(0 studies)	Not reported	
Perinatal death				(0 studies)	Not reported	
Pre-eclampsia				(0 studies)	Not reported	
Caesarean section				(0 studies)	Not reported	
Fetal anomaly (major) [1]	Study population		RR 3.15 (0.33 to 29.67)	162 (1 RCT)	⊕◯◯◯ VERY LOW [2,3,4,5]	
	12 per 1000	38 per 1000 (4 to 357)				
Birth trauma including shoulder dystocia, nerve palsy, or fracture				(0 studies)	Not reported	
Composite outcome measure of neonatal morbidity				(0 studies)	Not reported	

*__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; __RR:__ Risk ratio; __OR:__ Odds 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] Assessed by an expert who was blinded to the outcome
[2] One study with design limitations
[3] Very wide 95% confidence intervals crossing the line of no effect
[4] Large effect estimate
[5] Small sample size with few events

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DISCUSSION

There are many different types of insulin (e.g. human, animal), and many different insulin regimens (e.g. injection of insulin via a pen or injection of insulin with a conventional needle or syringe). This review sought to investigate whether any particular type of insulin or any particular regimen was safer or more effective for improving maternal and fetal health and well-being in pregnant women with pre-existing type 1 or type 2 diabetes.

Summary of main results

This review included five trials, with a total of 554 women and 554 babies. We could not determine whether there were any clear differences for the primary infant outcomes (macrosomia and perinatal death) or primary maternal outcomes (caesarean section and pregnancy-induced hypertension or pre-eclampsia) for each of the comparisons of different insulin types (Lispro versus regular insulin Summary of findings for the main comparison; Human insulin versus animal insulin Summary of findings 2; Insulin Aspart versus human insulin Summary of findings 5; and Insulin Detemir versus NPH insulin Summary of findings 6), or for the different insulin regimens (Pre-mixed insulin versus self-mixed insulin Summary of findings 3; and Insulin injected with a Novolin pen versus insulin injected with a conventional needle or syringe Summary of findings 4), since many were not reported in the trials, and secondly, where they were reported, the data were from a single, small trial. There were also no clear differences found for the secondary infant and maternal outcomes. In one trial, human insulin was associated with a lower mean insulin requirement during pregnancy, compared with the animal insulin group. In another trial, pre-mixed insulin was associated with a lower antepartum capillary glucose measurement two hours postprandial (after lunch) when compared with self-mixed insulin. The same was found when the Novolin pen was compared with the conventional needle or syringe. In addition, there were fewer caesarean sections in the Novolin pen group compared with the conventional needle or syringe group. Many important outcomes were not reported in these trials including most primary outcomes and secondary infant and maternal outcomes. There was no long-term follow-up of infants in these studies, and information on healthcare use and satisfaction with insulin treatments was lacking.

Overall completeness and applicability of evidence

Overall, we only included five trials in this review that included pregnant women with pre-existing diabetes. It was difficult to draw any firm conclusions from the trials, or to say that they were generalisable to the general pregnant population for many reasons. First of all, the sample sizes in the trials were small. Second, many of the review's primary prespecified outcomes were not reported, for example, perinatal death and pre-eclampsia were each reported in only one trial, and macrosomia and caesarean section were each reported in only two trials. Further trials in pregnant women are required that are adequately powered, and that report all outcomes suggested in this review, to evaluate the different insulin types and regimens.

Quality of the evidence

The trials included in this review were small. Overall, the quality of reporting was poor, and therefore, risk of bias in all trials was either high or unclear. All of the trials were open trials, as it is difficult to blind participants or clinicians to the intervention allocation in trials such as those included in this review. However, outcome assessors could have been blinded but were not in the majority of the trials. We do not know if the pregnant women included in these trials were representative of the general population of women with pre-existing type 1 or type 2 diabetes, but researchers should try to ensure that their trial populations reflect the general obstetric population as much as possible.

Most primary outcomes were not reported. For those that were reported, our GRADE assessment was that the quality of the evidence was very low (caesarean section, pregnancy-induced hypertension or pre-eclampsia, fetal anomaly, birth trauma, and macrosomia). This was because there was only a single study for each comparison, so pooling of the data was not possible, there were design limitations in the included trials (high or unclear risk of bias for allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other biases) and sparse data (small sample sizes, wide confidence intervals that crossed the line of no effect, and few or no events). These judgements are shown in the Summary of findings for the main comparison, Summary of findings 2, Summary of findings 3, Summary of findings 4, and Summary of findings 6. We were unable to populate Summary of findings 5, because our primary outcomes were not reported for this comparison. Therefore, we could not conclude whether one type of insulin or one insulin regimen was better in pregnant women with pre-existing diabetes for improving maternal and infant outcomes.

Potential biases in the review process

Risk of bias assessment is a subjective process. This can be minimised by following the procedures outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), whereby two or more review authors independently assess studies and resolve any disagreement through discussion, involving a third assessor to reach consensus as required. In this review, we undertook a comprehensive and systematic search of databases to

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reduce the potential for publication bias, and did not apply any language, date, or publication status restrictions.

Agreements and disagreements with other studies or reviews

Our findings, that the limited number of trials that provided very low-quality evidence, restricted us from drawing any meaningful or scientific conclusions regarding the safety and effectiveness of one type of insulin over the other, or one insulin regimen over the other, in pregnant women with pre-existing type 1 or type 2 diabetes. This was also the case in other reviews (Farrar 2016; Horvath 2007; Siebenhofer 2006). All reported that there was no evidence of any clear benefit of one insulin type or regimen over the other, and that large, randomised trials of better methodological quality are required. One review found that long-acting insulin preparations seemed to have a beneficial effect on nocturnal glucose levels; their overall diabetes control was described as clinically unremarkable (Vardi 2008). This review included three very large randomised controlled trials but concluded that the findings warranted further substantiation. This review was not in pregnant women.

AUTHORS' CONCLUSIONS

Implications for practice

At present, insufficient data exist to allow the review authors to make any substantial or concrete conclusions about the effectiveness of one insulin type or regimen over another in pregnant women with pre-existing type 1 or type 2 diabetes. Therefore, decisions about the use of different types of insulin and different insulin regimens for pregnant women with pre-existing type 1 or type 2 diabetes should be made according to individual needs and available resources.

Implications for research

Large, multi-centred trials, which are adequately randomised, sufficiently powered, and clearly reported are needed to assess the safety and effectiveness of different insulin types and regimens in pregnant women with pre-existing type 1 or type 2 diabetes. It would be very helpful if outcomes across trials were consistently defined and reported. In addition, it is difficult to blind women and caregivers to their randomised allocation because of the nature of the intervention of interest. However, it is possible to blind the outcome assessor to treatment allocation, which is strongly recommended. Any blinding should be clearly stated in the trial report. Future trials should undertake a longer period of follow-up of women and their infants, as well as the cost-effectiveness of various insulin types and regimens.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

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

Jovanovic-Peterson 1992

Methods	RCT (open-label, 2-centre, 2-arm).
Participants	43 insulin-requiring pregnant women with diabetes (type 1 or 2) Recruited between 1983 and 1985. Setting: The Children's Hospital of San Francisco and Cornell University Medical College, New York Inclusion criteria: pregnant women with type 1 or 2 diabetes; < 20 weeks' gestation; aged > 18 years old; treated with animal insulin for at least 24 months; bodyweight within 20% of ideal body weight as determined by the Metropolitan Life tables Exclusion criteria: women with hypertension (blood pressure > 140/90 mmHg); serum creatine higher than the upper range of normal; advanced cardiovascular disease; history of Addison's disease or pituitary insufficiency; local or systemic allergy to animal source insulin; pre-pregnancy insulin dose greater than 1.5 U/kg per 24 hours, history of treatment human insulin or an insulin infusion device
Interventions	Human insulin (recombinant deoxyribonucleic acid - Humulin); N = 20
Outcomes	**Infant** Gestational age at delivery Percentile body weight Skinfold thickness Length Weight Head circumference Large-for-gestational age at delivery Small-for-gestational age at delivery C-peptide level (pmol/mL) Glucose level (mmol) Preterm delivery Appropriate-for-gestational age at delivery Macrosomia (birthweight > 4000 g) **Maternal** Temperature Systolic blood pressure Diastolic blood pressure Resting heart rate Edema Renal function Complete blood cell count Chemistry profile Calories consumed Weight gain Glycohemoglobin levels Maternal ketonuria

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	Mean insulin dose requirement	
Notes		

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Women were randomly assigned to treatment with either human or their current animal insulin. However, there was no description of the method used
Allocation concealment (selection bias)	High risk	Open-label trial.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants: no. Open-label trial.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Personnel: no. Open-label trial.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	1 woman (out of 23) randomised to the animal insulin group did not complete the admission visit or return for follow-up. She was excluded from the statistical analysis. Not all babies were included in the reporting of large-for-gestational age at delivery
Selective reporting (reporting bias)	Unclear risk	This study was assessed from the published report. No protocol was available, so we do not know if all pre-specified outcomes were reported
Other bias	Low risk	It was reported that the baseline characteristics of groups showed a remarkably similar population of women in both groups

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Mathiesen 2007

Methods	2 arm RCT (open-label, parallel group, multi-centre).
Participants	Setting: 63 sites in 18 countries, mainly within Europe. Inclusion criteria: women ≥ 18 years with insulin-treated type 1 diabetes for ≥ 12 months. Women were either pregnant with a singleton pregnancy (gestational age at delivery ≤ 10 weeks; N = 223, included in this review), or planning to become pregnant (N = 99, excluded from this review). A1c was ≤ 8% at confirmation of pregnancy Exclusion criteria: women with multiple pregnancy, fertility treatment, clinically significant gynaecological conditions, diabetic nephropathy or medical problems, a previous child born with major congenital malformations, multiple miscarriage, or stillbirths (more than 2). Women not pregnant within 12 months of randomisation
Interventions	Experimental: prandial insulin Aspart (100 units/mL: Novo Nordisk, Basvaerd, Denmark) + NPH insulin. 1 to 4 subcutaneous injections per day (lowest available at centre) using the Novo pen. N = 113 (randomised when pregnant) Comparison: prandial human insulin (100 IU/mL; Novo Nordisk) + NPH insulin. 1 to 4 subcutaneous injections per day (lowest available at centre) using the Novo pen. N = 110 (randomised when pregnant)
Outcomes	Many outcomes were reported for all women in the study: major hypoglycaemia requiring third-party assistance, minor hypoglycaemia, maternal death, hypoglycaemic coma, inadequate glycaemic control, hyperglycaemia, pre-eclampsia, preterm labour, emergency caesarean section, glycaemic control, A1c, plasma glucose profile breakfast, lunch, dinner, mean insulin dose), abortion, caesarean section, induced abortion, stillbirth, QoL assessments However, few of these were reported separately for women randomised during pregnancy
Notes	SON contacted the authors to request additional data. A web site link was received, but did not allow access to the data. We received no responses to further requests

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	States that women were 'randomised', but no further description of method was given
Allocation concealment (selection bias)	Unclear risk	No description.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants: no. Open-label trial.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Personnel: no. Open-label trial.

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Mathiesen 2007 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All women in the subgroup included in the review were accounted for. Women who were not pregnant ≤ 12 months after randomisation were withdrawn from the study: potential bias in conception rates between groups affected the overall study, but not the subgroup included in the review
Selective reporting (reporting bias)	High risk	Very few outcomes were reported for the subgroup of women who were randomised during pregnancy
Other bias	Unclear risk	The report declared that the trial was sponsored by Novo Nordisk. It was unclear whether this conflict of interest introduced any bias

Mathiesen 2012

Methods	2-arm RCT, open label, parallel group, multi-centre.
Participants	Setting: 79 different sites in 17 countries. Inclusion criteria: Women ≥ 18 years with insulin-treated type 1 diabetes for ≥ 12 months before randomisation. They were either pregnant with a singleton pregnancy (gestational age at delivery 8 to 12 weeks; N = 162, included in this review), or planning to become pregnant (N = 148, excluded from this review). A1c was ≤ 8% at confirmation of pregnancy Exclusion criteria: women with impaired hepatic or renal function or uncontrolled hypertension (systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or both), undergoing medical infertility treatment, or who had been previously randomised in this trial. Women not pregnant within 12 months of randomisation
Interventions	Experimental intervention: Insulin Detemir (100 units/mL) with prandial insulin Aspart (100 units/mL) in a basal bolus regimen (1:1), subcutaneous injections administered from randomisation until termination or 6 weeks postdelivery. N = 79 (randomised when pregnant) Control/Comparison intervention: NPH insulin (100 IU/mL) with prandial insulin Aspart (100 units/mL) in a basal bolus regimen (1:1), subcutaneous injections administered from randomisation until termination or 6 weeks postdelivery. N = 83 (randomised when pregnant) Basal insulin dose was titrated according to fasting or pre-dinner capillary plasma glucose values. All bolus insulin doses were titrated according to pre- and postprandial plasma glucose values. Preprandial PG target of 72 to 108 mg/dL (4.0-6.0 mmol/L) and 2-hour postprandial glucose target < 126 mg/dL (< 7.0 mmol/L)

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Mathiesen 2012 (*Continued*)

Outcomes	Many outcomes were reported for all women in the study: hypoglycaemia, glycaemic control including A1c, insulin dose, adverse events, pregnancy outcomes However, few of these were reported separately for women randomised during pregnancy
Notes	SON contacted the authors to request additional data. A web site link was received, but did not allow access to the data. We received no responses to further requests

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Low risk	"Subjects were randomised 1:1 (using Interactive Voice/Web Response System)."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants: no. Open-label trial.
Blinding of participants and personnel (performance bias) All outcomes	High risk	.Personnel: no. Open-label trial.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Open-label. Congenital malformations were assessed by 2 independent experts, 1 of whom was blinded to group allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All women in the subgroup included in the review were accounted for. Women who were not pregnant $\leq$ 12 months after randomisation were withdrawn from the study: potential bias in conception rates between groups affected the overall study, but not the subgroup included in the review
Selective reporting (reporting bias)	High risk	Very few outcomes were reported for the subgroup of women who were randomised during pregnancy
Other bias	Unclear risk	The report declared that the trial was sponsored by Novo Nordisk. It was unclear whether this conflict of interest introduced any bias

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Persson 2002

Methods	RCT (open-label, multi-centre, 2-arm).
Participants	33 pregnant women with type 1 diabetes recruited at 6 to 8 weeks' gestation and entered into the study at 15 weeks' gestation Setting: 4 centres in Sweden. The Departments of Obstetrics and Gynaecology in Huddinge Hospital, Karolinska Hospital, Södersjukhuset in Stockholm, and Örebro Regional Hospital Inclusion criteria: pregnant women with type 1 diabetes; duration of diabetes for a minimum of 2 years; aged 20 years or more; multiple dose regimen with regular and NPH insulin; Initial HbA1c value below 9% Exclusion criteria: gestational or type 2 diabetes; duration of diabetes less than 2 years; aged younger than 20 years; In receipt of insulin lispro (intervention); HbA1c value greater than 9%
Interventions	Preprandial rapid-acting insulin lispro (Humalog®) in combination with NPH in a MDI regimen with administration of lispro or regular insulin immediately before or 30 minutes before meals, respectively. Medium-acting NPH insulin was administered at bedtime and when needed before breakfast. All women were given dietary instruction by a dietician. Blood glucose targets were pre- and postprandial levels of < 5.0 and < 6.5 mmol/l respectively. N = 16
Outcomes	**Infant** Gestational age at delivery Birthweight Length Appropriate-for-gestational age at delivery Small-for-gestational age at delivery Large-for-gestational age at delivery Malformation Birth trauma Asphyxia Respiratory distress Hypoglycaemia Hyperbilirubinemia Perinatal death **Maternal** Micoangiopathy Glycaemic control (HbA1c, blood glucose, hypoglycaemia) Retinopathy Mode of delivery Hypertension Pre-eclampsia Polyhydamniosis
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

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Persson 2002 (*Continued*)

Random sequence generation (selection bias)	Low risk	Randomisation was conducted at a central site according to 4-patient block model (AABB, etc.)
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants: no. Open-label trial.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Personnel: no. Open-label trial.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The report indicated that 7 women did not satisfy the inclusion criteria and 2 were unwilling to participate. These appeared to be in addition to those randomised, but it was unclear if these women were randomised and then withdrawn from the study
Selective reporting (reporting bias)	High risk	The trial was assessed from the published report, with no protocol available. It was not clear whether all prespecified outcomes were reported. Some outcomes were described as showing no differences, but these figures were not given: gestational age at delivery, birthweight, rate of large-for-gestational-age infants, neonatal complications
Other bias	Unclear risk	It was reported that there were no significant differences between the 2 treatment groups with regard to baseline characteristics, however, significantly more women in the lispro group had aneurysms

Schuster 1998

Methods	RCT (single-blinded, 1 centre, 4-arm).
Participants	93 pregnant women with type 1 or 2 diabetes. Setting: University of Mississippi Medical Centre, USA. Inclusion criteria: insulin-dependent diabetes; maternal age 15 to 44 years; < 20 weeks' gestation at entry; willingness to sign an informed consent form

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Schuster 1998 (*Continued*)

	Exclusion criteria: additional pregnancy complications which might affect maternal or infant outcome (hypertension, placenta praevia, fetal malformations, and glucose intolerance not requiring insulin); unwillingness to comply with prenatal care or aggressive glucose control; women's refusal to participate
Interventions	Women were enrolled into 4 groups. Intervention 1: pre-mixed insulin (70 NPH/30 REG) administered with a needle or syringe (N = 24) Intervention 2: self-mixed split dose regular and NPH insulin administered with a Novolin® pen (N = 22) Intervention 3: pre-mixed insulin (70 NPH/30 REG) administered with a Novolin® pen (N = 23) Control: self-mixed split dose regular and NPH insulin administered with a needle or syringe (N = 24)
Outcomes	**Infant** Gestational age at delivery Preterm delivery Infant birthweight Macrosomia 1- and 5-minute Apgar score Hyperbilirubinemia Hypoglycaemia Hypocalcemia Incidence of admission to the neonatal unit **Maternal** Caesarean delivery for cephalo-pelvic disproportion Pregnancy-induced hypertension Capillary glucose measurements (mg/DL) Abruption Chorioamnionitis Endometritis Maternal hospital days Number of prenatal visits Overall patient compliance (based on dietary assessment, adequate glucose monitoring, insulin usage, appropriate follow-up with physician instructions, and visits) scored from 1 to 5, with 1 implying good compliance and 5 implying poor compliance
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was carried out by selecting an opaque, consecutively-numbered envelope in which computer-generated randomisation cards were placed, to assign women into 1 of 4 groups

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Schuster 1998 (*Continued*)

Allocation concealment (selection bias)	Low risk	Randomisation was carried out by selecting an opaque, consecutively-numbered envelope in which computer-generated randomisation cards were placed, to assign women into 1 of 4 groups
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants: no. Open-label trial.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Personnel: yes. Staff managing the women were unaware of the treatment regimen to which the women were assigned, during the antepartum period
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of the 100 women enrolled, 93 were available for outcome analysis. 2 women suffered spontaneous abortions, 2 underwent elective terminations and 3 were lost to follow-up. These 7 women were equally distributed between the 4 groups
Selective reporting (reporting bias)	Unclear risk	This trial was assessed from the published report, with no protocol available. It was not clear whether all prespecified outcomes were reported. Some outcomes were described as showing no differences, but the figures were not given: caesarean section for any indication, incidence of pregnancy-induced hypertension, preterm labour, infant hyperbilirubinaemia, and hypoglycaemia. It was unclear whether caesarean section for cephalo-pelvic disproportion was a pre-specified outcome, or included because it showed a significant difference between groups
Other bias	Low risk	There were no significant differences between the treatment groups with regard to baseline characteristics

RCT: randomised controlled trial

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

Study	Reason for exclusion
Carr 2004	Cross-over trial design.
Herrera 2015b	Included women with gestational diabetes.
Kipikasa 2008	Included women with gestational diabetes.
Mohd 2012	Included women with gestational diabetes.
Murphy 2011	Cross-over trial design.
Nachum 1999	Included women with gestational diabetes.
Nor 2007	Included women with gestational diabetes.
Porta 2011	Did not include the intervention: randomisation prior to pregnancy
Reller 1985	Did not include the intervention: not a randomised controlled trial
Secher 2012	Did not include the intervention: a trial of glucose monitoring not insulin regimen

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DATA AND ANALYSES

Comparison 1. Lispro versus regular insulin (Different insulin types within similar insulin regimens)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Perinatal death	1	33	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Caesarean section	1	33	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.25, 1.39]
3 Pregnancy-induced hypertension and pre-eclampsia	1	33	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.35, 1.30]
4 Fetal anomaly	1	33	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.02, 8.08]
5 Birth trauma, including shoulder dystocia, nerve palsy, and fracture	1	33	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Vaginal delivery (spontaneous, ventouse, forceps)	1	33	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [0.80, 2.67]
7 Blood glucose (mmol/L) week 14 (after lunch)	1	33	Mean Difference (IV, Fixed, 95% CI)	-1.09 [-3.60, 1.42]
8 Blood glucose (mmol/L) weeks 21, 28, and 34 combined (after lunch)	1	33	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-2.10, 2.02]
9 Postprandial increase of blood glucose (mmol/L) before week 14 (lunch)	1	33	Mean Difference (IV, Fixed, 95% CI)	1.0 [-1.52, 3.52]
10 Postprandial increase of blood glucose (mmol/L) during weeks 21, 28, and 34 combined (lunch)	1	33	Mean Difference (IV, Fixed, 95% CI)	0.10 [-2.12, 2.32]
11 Maternal hypoglycaemia and hyperglycaemia episodes requiring intervention	1	33	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.01, 4.10]
12 Retinopathy	1	33	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.17, 6.67]
13 Ventouse delivery	1	33	Risk Ratio (M-H, Fixed, 95% CI)	3.19 [0.37, 27.58]

Comparison 2. Human insulin (recombinant deoxyribonucleic acid - Humulin) versus animal insulin (Different insulin types within similar insulin regimens)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Small-for-gestational age at delivery	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Preterm birth (< 37 weeks)	1	42	Risk Ratio (M-H, Fixed, 95% CI)	7.67 [0.42, 139.83]
3 Birthweight centile (%)	1	42	Mean Difference (IV, Fixed, 95% CI)	-6.70 [-23.64, 10.24]
4 Infant length (cm)	1	42	Mean Difference (IV, Fixed, 95% CI)	-3.30 [-6.74, 0.14]

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5 Skinfold thickness (mm)	1	42	Mean Difference (IV, Fixed, 95% CI)	-4.10 [-13.28, 5.08]
6 Body weight percentile (%)	1	42	Mean Difference (IV, Fixed, 95% CI)	-6.70 [-23.74, 10.34]
7 Head circumference (cm)	1	42	Mean Difference (IV, Fixed, 95% CI)	-5.10 [-9.52, -0.68]
8 Macrosomia	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.01, 4.30]
9 Insulin requirement during pregnancy (U/kg/24 hour)	1	42	Mean Difference (IV, Fixed, 95% CI)	-0.33 [-0.45, -0.21]
10 Birthweight (g)	1	42	Mean Difference (IV, Fixed, 95% CI)	-591.0 [-1066.27, -115.73]
11 Infant fasting C-peptide level at 3 months (pmol/mL)	1	42	Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.13, -0.01]
12 Infant C-peptide level 1 hour after glucose-amino acid challenge at 3 months (pmol/mL)	1	42	Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.19, -0.03]
13 Infant glucose fasting level at 3 months (pmol/mL)	1	42	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.62, 0.22]
14 Infant glucose level 1 hour after glucose-amino acid challenge at 3 months (pmol/mL)	1	42	Mean Difference (IV, Fixed, 95% CI)	0.5 [-0.04, 1.04]
15 Gestational age at delivery (weeks)	1	42	Mean Difference (IV, Fixed, 95% CI)	0.5 [-3.70, 4.70]
16 Maternal ketonuria	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.08, 1.61]

Comparison 3. Pre-mixed insulin (70 NPH/30 REG) versus self-mixed split dose insulin (Different insulin regimens with similar insulin types used within the regimen)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Macrosomia	1	93	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.09, 2.54]
2 Caesarean section	1	93	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.25, 1.32]
3 Antepartum capillary glucose measurement (mg/dL), 2 hours postprandial (after lunch)	1	10218	Mean Difference (IV, Fixed, 95% CI)	-11.25 [-12.55, -9.95]
4 Postpartum infection: endometritis	1	93	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.26, 1.04]
5 Use of healthcare resources (maternal hospital days)	1	94	Mean Difference (IV, Fixed, 95% CI)	-0.50 [-1.40, 0.41]
6 Birthweight (g)	1	93	Mean Difference (IV, Fixed, 95% CI)	-116.56 [-391.81, 158.69]
7 Compliance score	1	49	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.87, 0.87]

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Comparison 4. Insulin injected with a Novolin pen versus insulin injected with a needle (syringe) (Different insulin regimens with similar insulin types used within the regimen)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Macrosomia	1	93	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.03, 1.76]
2 Caesarean section	1	93	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.15, 0.97]
3 Antepartum capillary glucose measurement (mg/dL) 2 hours postprandial (after lunch)	1	10218	Mean Difference (IV, Fixed, 95% CI)	-7.23 [-8.51, -5.95]
4 Postpartum infection: endometritis	1	93	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.28, 1.14]
5 Use of healthcare resources (maternal hospital days)	1	93	Mean Difference (IV, Fixed, 95% CI)	-0.56 [-1.45, 0.33]
6 Birthweight (g)	1	93	Mean Difference (IV, Fixed, 95% CI)	-162.36 [-438.25, 113.53]
7 Compliance score	1	93	Mean Difference (IV, Fixed, 95% CI)	-0.21 [-0.83, 0.41]

Comparison 5. Insulin Aspart + NPH insulin versus Human insulin + NPH insulin (Different insulin types within similar insulin regimens)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 A1c (%) third trimester visit	1	223	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.28, 0.08]
2 Average plasma glucose (mmol/L) third trimester visit	1	223	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.53, 0.13]
3 Maternal hypoglycaemic episodes	1	223	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.99, 1.14]

Comparison 6. Insulin Detemir + prandial insulin Aspart versus NPH insulin + prandial insulin Aspart (Different insulin types within similar insulin regimens)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Major congenital malformation	1	162	Risk Ratio (M-H, Fixed, 95% CI)	3.15 [0.33, 29.67]
2 Major congenital malformation	1	162	Risk Ratio (M-H, Fixed, 95% CI)	2.10 [0.19, 22.72]
3 Minor congenital malformation	1	162	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.01, 8.47]
4 Minor congenital malformation	1	162	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.22, 5.05]

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Analysis 1.1. Comparison 1 Lispro versus regular insulin (Different insulin types within similar insulin regimens), Outcome 1 Perinatal death.

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 1 Lispro versus regular insulin (Different insulin types within similar insulin regimens)

Outcome: 1 Perinatal death

Study or subgroup	Lispro insulin n/N	Regular insulin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Persson 2002	0/16	0/17			Not estimable
Total (95% CI)	**16**	**17**			**Not estimable**

Total events: 0 (Lispro insulin), 0 (Regular insulin)
Heterogeneity: not applicable
Test for overall effect: not applicable
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1 Lispro versus regular insulin (Different insulin types within similar insulin regimens), Outcome 2 Caesarean section.

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 1 Lispro versus regular insulin (Different insulin types within similar insulin regimens)

Outcome: 2 Caesarean section

Study or subgroup	Lispro insulin n/N	Regular insulin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Persson 2002	5/16	9/17		100.0 %	0.59 [0.25, 1.39]
Total (95% CI)	**16**	**17**		**100.0 %**	**0.59 [0.25, 1.39]**

Total events: 5 (Lispro insulin), 9 (Regular insulin)
Heterogeneity: not applicable
Test for overall effect: Z = 1.21 (P = 0.23)
Test for subgroup differences: Not applicable



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Analysis 1.3. Comparison 1 Lispro versus regular insulin (Different insulin types within similar insulin regimens), Outcome 3 Pregnancy-induced hypertension and pre-eclampsia.

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 1 Lispro versus regular insulin (Different insulin types within similar insulin regimens)

Outcome: 3 Pregnancy-induced hypertension and pre-eclampsia

Study or subgroup	Lispro insulin n/N	Regular insulin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Persson 2002	7/16	11/17		100.0 %	0.68 [0.35, 1.30]
Total (95% CI)	**16**	**17**		**100.0 %**	**0.68 [0.35, 1.30]**

Total events: 7 (Lispro insulin), 11 (Regular insulin)
Heterogeneity: not applicable
Test for overall effect: Z = 1.17 (P = 0.24)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1 Lispro versus regular insulin (Different insulin types within similar insulin regimens), Outcome 4 Fetal anomaly.

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 1 Lispro versus regular insulin (Different insulin types within similar insulin regimens)

Outcome: 4 Fetal anomaly

Study or subgroup	Lispro insulin n/N	Regular insulin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Persson 2002	0/16	1/17		100.0 %	0.35 [0.02, 8.08]
Total (95% CI)	**16**	**17**		**100.0 %**	**0.35 [0.02, 8.08]**

Total events: 0 (Lispro insulin), 1 (Regular insulin)
Heterogeneity: not applicable
Test for overall effect: Z = 0.65 (P = 0.51)
Test for subgroup differences: Not applicable



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Analysis 1.5. Comparison 1 Lispro versus regular insulin (Different insulin types within similar insulin regimens), Outcome 5 Birth trauma, including shoulder dystocia, nerve palsy, and fracture.

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 1 Lispro versus regular insulin (Different insulin types within similar insulin regimens)

Outcome: 5 Birth trauma, including shoulder dystocia, nerve palsy, and fracture

Study or subgroup	Lispro insulin n/N	Regular insulin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Persson 2002	0/16	0/17			Not estimable
Total (95% CI)	**16**	**17**			**Not estimable**
Total events: 0 (Lispro insulin), 0 (Regular insulin)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					



Analysis 1.6. Comparison 1 Lispro versus regular insulin (Different insulin types within similar insulin regimens), Outcome 6 Vaginal delivery (spontaneous, ventouse, forceps).

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 1 Lispro versus regular insulin (Different insulin types within similar insulin regimens)

Outcome: 6 Vaginal delivery (spontaneous, ventouse, forceps)

Study or subgroup	Lispro insulin n/N	Regular insulin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Persson 2002	11/16	8/17		100.0 %	1.46 [0.80, 2.67]
Total (95% CI)	**16**	**17**		**100.0 %**	**1.46 [0.80, 2.67]**
Total events: 11 (Lispro insulin), 8 (Regular insulin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.23 (P = 0.22)					
Test for subgroup differences: Not applicable					



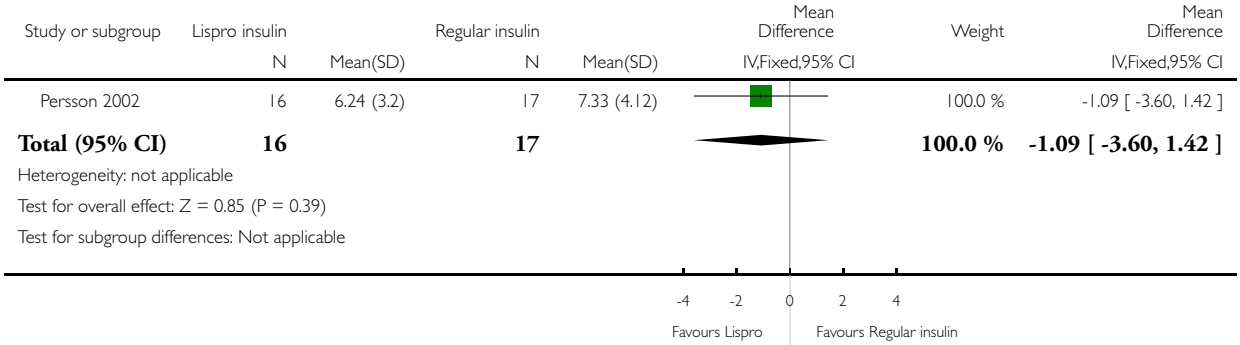
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Analysis 1.7. Comparison 1 Lispro versus regular insulin (Different insulin types within similar insulin regimens), Outcome 7 Blood glucose (mmol/L) week 14 (after lunch).

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 1 Lispro versus regular insulin (Different insulin types within similar insulin regimens)

Outcome: 7 Blood glucose (mmol/L) week 14 (after lunch)

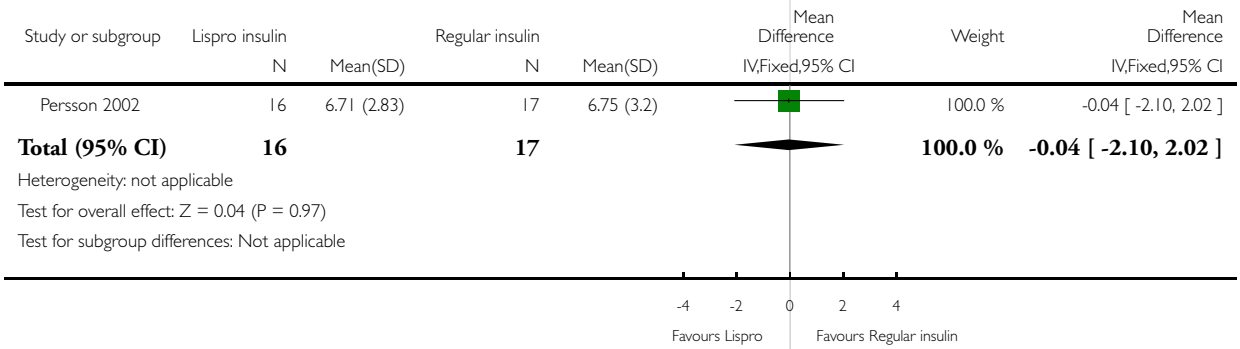


Analysis 1.8. Comparison 1 Lispro versus regular insulin (Different insulin types within similar insulin regimens), Outcome 8 Blood glucose (mmol/L) weeks 21, 28, and 34 combined (after lunch).

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 1 Lispro versus regular insulin (Different insulin types within similar insulin regimens)

Outcome: 8 Blood glucose (mmol/L) weeks 21, 28, and 34 combined (after lunch)



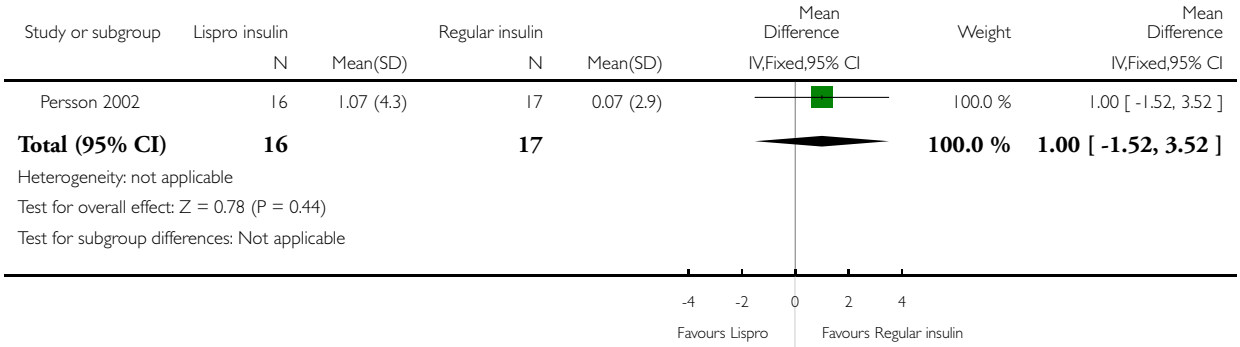
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Analysis 1.9. Comparison 1 Lispro versus regular insulin (Different insulin types within similar insulin regimens), Outcome 9 Postprandial increase of blood glucose (mmol/L) before week 14 (lunch).

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 1 Lispro versus regular insulin (Different insulin types within similar insulin regimens)

Outcome: 9 Postprandial increase of blood glucose (mmol/L) before week 14 (lunch)

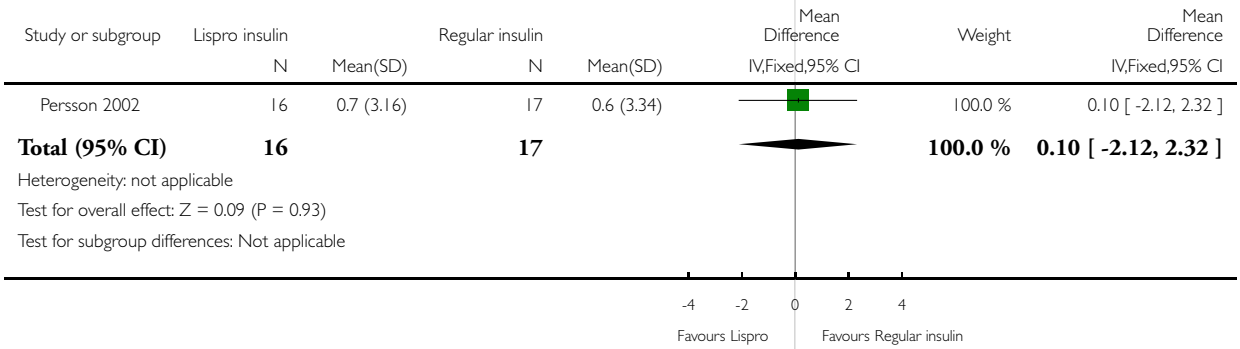


Analysis 1.10. Comparison 1 Lispro versus regular insulin (Different insulin types within similar insulin regimens), Outcome 10 Postprandial increase of blood glucose (mmol/L) during weeks 21, 28, and 34 combined (lunch).

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 1 Lispro versus regular insulin (Different insulin types within similar insulin regimens)

Outcome: 10 Postprandial increase of blood glucose (mmol/L) during weeks 21, 28, and 34 combined (lunch)



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Analysis 1.11. Comparison 1 Lispro versus regular insulin (Different insulin types within similar insulin regimens), Outcome 11 Maternal hypoglycaemia and hyperglycaemia episodes requiring intervention.

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 1 Lispro versus regular insulin (Different insulin types within similar insulin regimens)

Outcome: 11 Maternal hypoglycaemia and hyperglycaemia episodes requiring intervention

Study or subgroup	Lispro insulin n/N	Regular insulin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Persson 2002 (1)	0/16	2/17		100.0 %	0.21 [0.01, 4.10]
Total (95% CI)	**16**	**17**		**100.0 %**	**0.21 [0.01, 4.10]**
Total events: 0 (Lispro insulin), 2 (Regular insulin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.03 (P = 0.30)					
Test for subgroup differences: Not applicable					



(1) Authors did not state that intervention was required for episodes of hypoglycaemia/hyperglycaemia but it is assumed

Analysis 1.12. Comparison 1 Lispro versus regular insulin (Different insulin types within similar insulin regimens), Outcome 12 Retinopathy.

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 1 Lispro versus regular insulin (Different insulin types within similar insulin regimens)

Outcome: 12 Retinopathy

Study or subgroup	Lispro insulin n/N	Regular insulin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Persson 2002	2/16	2/17		100.0 %	1.06 [0.17, 6.67]
Total (95% CI)	**16**	**17**		**100.0 %**	**1.06 [0.17, 6.67]**
Total events: 2 (Lispro insulin), 2 (Regular insulin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.06 (P = 0.95)					
Test for subgroup differences: Not applicable					



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Analysis 1.13. Comparison 1 Lispro versus regular insulin (Different insulin types within similar insulin regimens), Outcome 13 Ventouse delivery.

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 1 Lispro versus regular insulin (Different insulin types within similar insulin regimens)

Outcome: 13 Ventouse delivery

Study or subgroup	Lispro insulin n/N	Regular insulin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Persson 2002	3/16	1/17		100.0 %	3.19 [0.37, 27.58]
Total (95% CI)	**16**	**17**		**100.0 %**	**3.19 [0.37, 27.58]**
Total events: 3 (Lispro insulin), 1 (Regular insulin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.05 (P = 0.29)					
Test for subgroup differences: Not applicable					



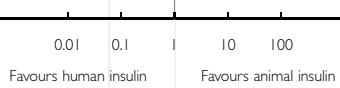
Analysis 2.1. Comparison 2 Human insulin (recombinant deoxyribonucleic acid - Humulin) versus animal insulin (Different insulin types within similar insulin regimens), Outcome 1 Small-for-gestational age at delivery.

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 2 Human insulin (recombinant deoxyribonucleic acid - Humulin) versus animal insulin (Different insulin types within similar insulin regimens)

Outcome: 1 Small-for-gestational age at delivery

Study or subgroup	Human insulin n/N	Animal insulin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Jovanovic-Peterson 1992	0/20	0/22			Not estimable
Total (95% CI)	**20**	**22**			**Not estimable**
Total events: 0 (Human insulin), 0 (Animal insulin)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					



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Analysis 2.2. Comparison 2 Human insulin (recombinant deoxyribonucleic acid - Humulin) versus animal insulin (Different insulin types within similar insulin regimens), Outcome 2 Preterm birth (< 37 weeks).

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 2 Human insulin (recombinant deoxyribonucleic acid - Humulin) versus animal insulin (Different insulin types within similar insulin regimens)

Outcome: 2 Preterm birth (< 37 weeks)

Study or subgroup	Human insulin n/N	Animal insulin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Jovanovic-Peterson 1992	3/20	0/22		100.0 %	7.67 [0.42, 139.83]
Total (95% CI)	**20**	**22**		**100.0 %**	**7.67 [0.42, 139.83]**

Total events: 3 (Human insulin), 0 (Animal insulin)
Heterogeneity: not applicable
Test for overall effect: Z = 1.37 (P = 0.17)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2 Human insulin (recombinant deoxyribonucleic acid - Humulin) versus animal insulin (Different insulin types within similar insulin regimens), Outcome 3 Birthweight centile (%).

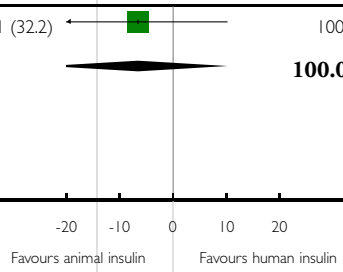
Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 2 Human insulin (recombinant deoxyribonucleic acid - Humulin) versus animal insulin (Different insulin types within similar insulin regimens)

Outcome: 3 Birthweight centile (%)

Study or subgroup	Human insulin N	Mean(SD)	Animal insulin N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Jovanovic-Peterson 1992	20	47.4 (23.5)	22	54.1 (32.2)		100.0 %	-6.70 [-23.64, 10.24]
Total (95% CI)	**20**		**22**			**100.0 %**	**-6.70 [-23.64, 10.24]**

Heterogeneity: not applicable
Test for overall effect: Z = 0.77 (P = 0.44)
Test for subgroup differences: Not applicable



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Analysis 2.4. Comparison 2 Human insulin (recombinant deoxyribonucleic acid - Humulin) versus animal insulin (Different insulin types within similar insulin regimens), Outcome 4 Infant length (cm).

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 2 Human insulin (recombinant deoxyribonucleic acid - Humulin) versus animal insulin (Different insulin types within similar insulin regimens)

Outcome: 4 Infant length (cm)

Study or subgroup	Human insulin N	Mean(SD)	Animal insulin N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Jovanovic-Peterson 1992	20	47.5 (7.1)	22	50.8 (3.5)		100.0 %	-3.30 [-6.74, 0.14]
Total (95% CI)	**20**		**22**			**100.0 %**	**-3.30 [-6.74, 0.14]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.88 (P = 0.060)

Test for subgroup differences: Not applicable



Analysis 2.5. Comparison 2 Human insulin (recombinant deoxyribonucleic acid - Humulin) versus animal insulin (Different insulin types within similar insulin regimens), Outcome 5 Skinfold thickness (mm).

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 2 Human insulin (recombinant deoxyribonucleic acid - Humulin) versus animal insulin (Different insulin types within similar insulin regimens)

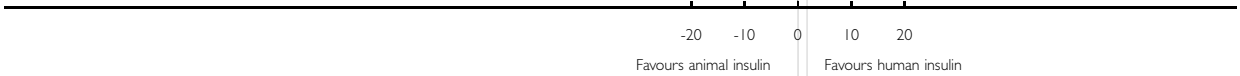
Outcome: 5 Skinfold thickness (mm)

Study or subgroup	Human insulin N	Mean(SD)	Animal insulin N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Jovanovic-Peterson 1992	20	17.2 (12.8)	22	21.3 (17.4)		100.0 %	-4.10 [-13.28, 5.08]
Total (95% CI)	**20**		**22**			**100.0 %**	**-4.10 [-13.28, 5.08]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.88 (P = 0.38)

Test for subgroup differences: Not applicable



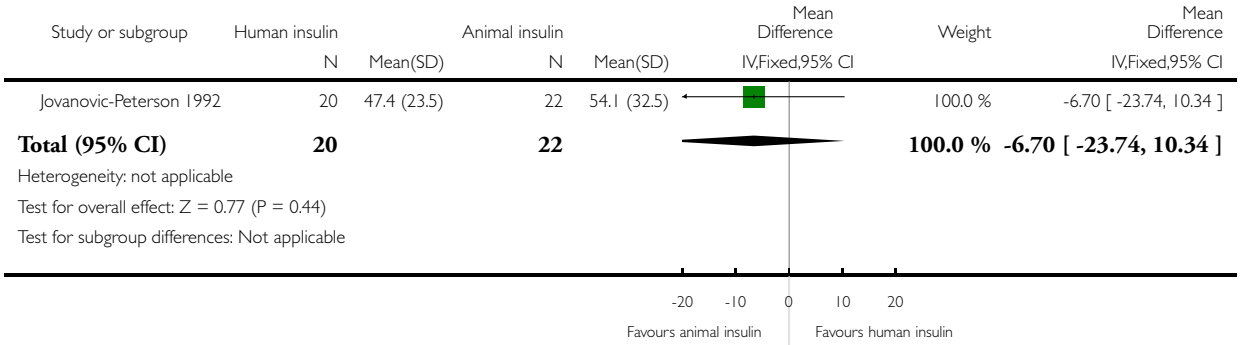
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Analysis 2.6. Comparison 2 Human insulin (recombinant deoxyribonucleic acid - Humulin) versus animal insulin (Different insulin types within similar insulin regimens), Outcome 6 Body weight percentile (%).

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 2 Human insulin (recombinant deoxyribonucleic acid - Humulin) versus animal insulin (Different insulin types within similar insulin regimens)

Outcome: 6 Body weight percentile (%)

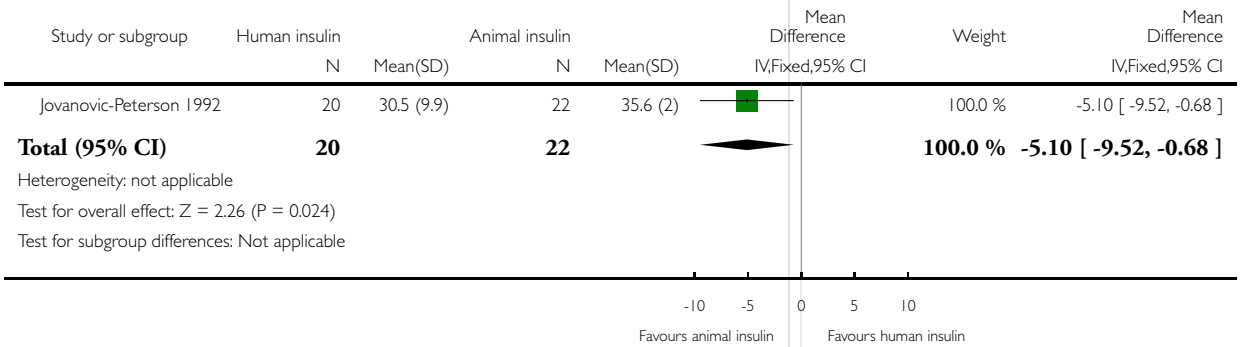


Analysis 2.7. Comparison 2 Human insulin (recombinant deoxyribonucleic acid - Humulin) versus animal insulin (Different insulin types within similar insulin regimens), Outcome 7 Head circumference (cm).

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 2 Human insulin (recombinant deoxyribonucleic acid - Humulin) versus animal insulin (Different insulin types within similar insulin regimens)

Outcome: 7 Head circumference (cm)



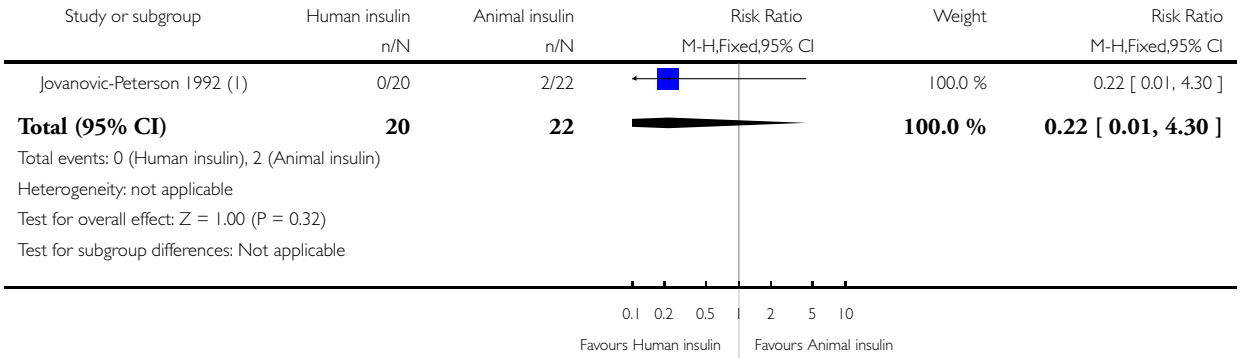
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Analysis 2.8. Comparison 2 Human insulin (recombinant deoxyribonucleic acid - Humulin) versus animal insulin (Different insulin types within similar insulin regimens), Outcome 8 Macrosomia.

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 2 Human insulin (recombinant deoxyribonucleic acid - Humulin) versus animal insulin (Different insulin types within similar insulin regimens)

Outcome: 8 Macrosomia



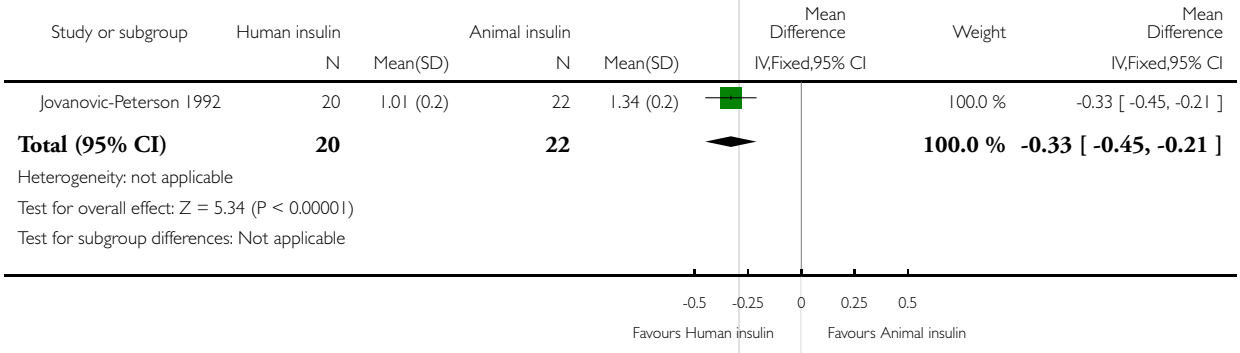
(1) birthweight > 4000g

Analysis 2.9. Comparison 2 Human insulin (recombinant deoxyribonucleic acid - Humulin) versus animal insulin (Different insulin types within similar insulin regimens), Outcome 9 Insulin requirement during pregnancy (U/kg/24 hour).

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 2 Human insulin (recombinant deoxyribonucleic acid - Humulin) versus animal insulin (Different insulin types within similar insulin regimens)

Outcome: 9 Insulin requirement during pregnancy (U/kg/24 hour)



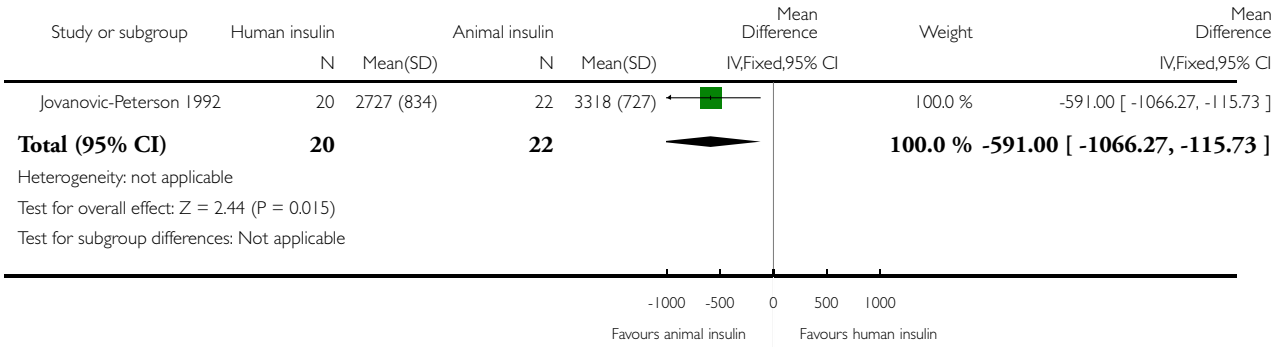
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Analysis 2.10. Comparison 2 Human insulin (recombinant deoxyribonucleic acid - Humulin) versus animal insulin (Different insulin types within similar insulin regimens), Outcome 10 Birthweight (g).

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 2 Human insulin (recombinant deoxyribonucleic acid - Humulin) versus animal insulin (Different insulin types within similar insulin regimens)

Outcome: 10 Birthweight (g)

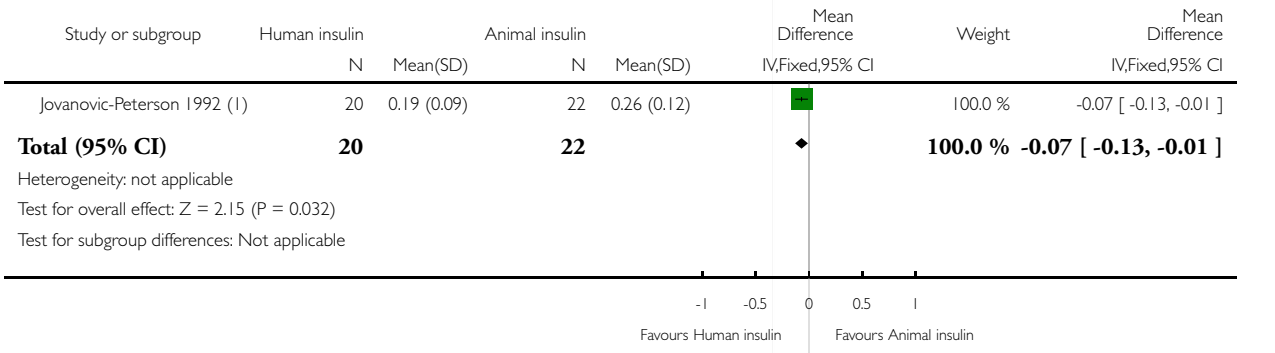


Analysis 2.11. Comparison 2 Human insulin (recombinant deoxyribonucleic acid - Humulin) versus animal insulin (Different insulin types within similar insulin regimens), Outcome 11 Infant fasting C-peptide level at 3 months (pmol/mL).

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 2 Human insulin (recombinant deoxyribonucleic acid - Humulin) versus animal insulin (Different insulin types within similar insulin regimens)

Outcome: 11 Infant fasting C-peptide level at 3 months (pmol/mL)



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(1) Note the review has included a SD of 0.09 for the human insulin group. In the original paper by Jovanovic Peterson (1992) the figure entered for the SD in this group was '09' with no decimal place.

Analysis 2.12. Comparison 2 Human insulin (recombinant deoxyribonucleic acid - Humulin) versus animal insulin (Different insulin types within similar insulin regimens), Outcome 12 Infant C-peptide level 1 hour after glucose-amino acid challenge at 3 months (pmol/mL).

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 2 Human insulin (recombinant deoxyribonucleic acid - Humulin) versus animal insulin (Different insulin types within similar insulin regimens)

Outcome: 12 Infant C-peptide level 1 hour after glucose-amino acid challenge at 3 months (pmol/mL)

Study or subgroup	Human insulin N	Mean(SD)	Animal insulin N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Jovanovic-Peterson 1992	20	0.21 (0.13)	22	0.32 (0.13)		100.0 %	-0.11 [-0.19, -0.03]
Total (95% CI)	**20**		**22**			**100.0 %**	**-0.11 [-0.19, -0.03]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.74 (P = 0.0062)							
Test for subgroup differences: Not applicable							



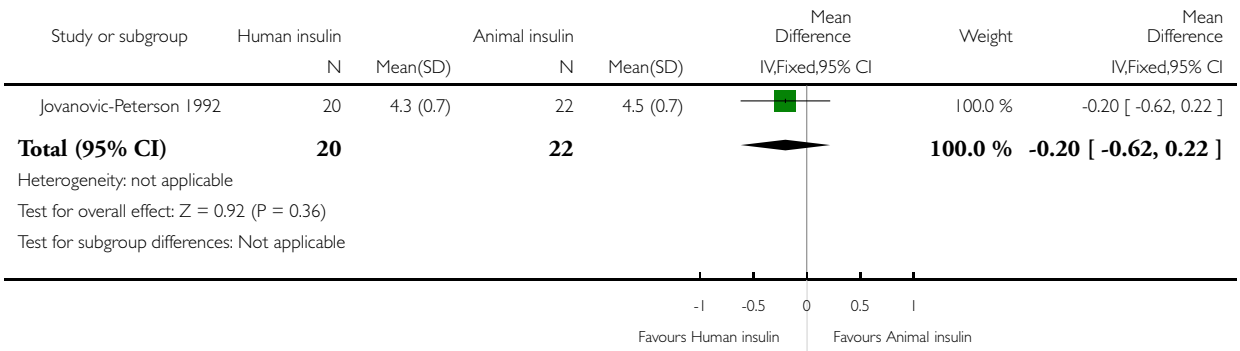
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Analysis 2.13. Comparison 2 Human insulin (recombinant deoxyribonucleic acid - Humulin) versus animal insulin (Different insulin types within similar insulin regimens), Outcome 13 Infant glucose fasting level at 3 months (pmol/mL).

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 2 Human insulin (recombinant deoxyribonucleic acid - Humulin) versus animal insulin (Different insulin types within similar insulin regimens)

Outcome: 13 Infant glucose fasting level at 3 months (pmol/mL)

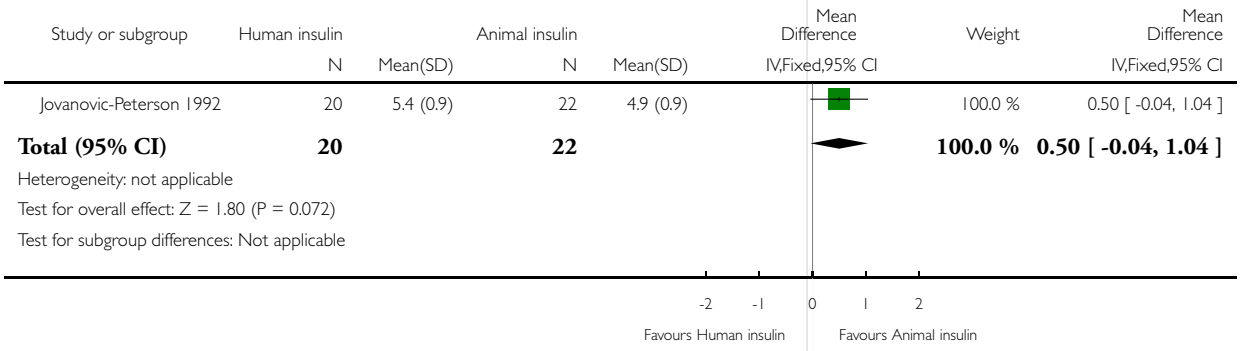


Analysis 2.14. Comparison 2 Human insulin (recombinant deoxyribonucleic acid - Humulin) versus animal insulin (Different insulin types within similar insulin regimens), Outcome 14 Infant glucose level 1 hour after glucose-amino acid challenge at 3 months (pmol/mL).

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 2 Human insulin (recombinant deoxyribonucleic acid - Humulin) versus animal insulin (Different insulin types within similar insulin regimens)

Outcome: 14 Infant glucose level 1 hour after glucose-amino acid challenge at 3 months (pmol/mL)



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Analysis 2.15. Comparison 2 Human insulin (recombinant deoxyribonucleic acid - Humulin) versus animal insulin (Different insulin types within similar insulin regimens), Outcome 15 Gestational age at delivery (weeks).

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 2 Human insulin (recombinant deoxyribonucleic acid - Humulin) versus animal insulin (Different insulin types within similar insulin regimens)

Outcome: 15 Gestational age at delivery (weeks)

Study or subgroup	Human insulin		Animal insulin		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Jovanovic-Peterson 1992	20	38.6 (9.4)	22	38.1 (1.9)		100.0 %	0.50 [-3.70, 4.70]
Total (95% CI)	**20**		**22**			**100.0 %**	**0.50 [-3.70, 4.70]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.23 (P = 0.82)

Test for subgroup differences: Not applicable



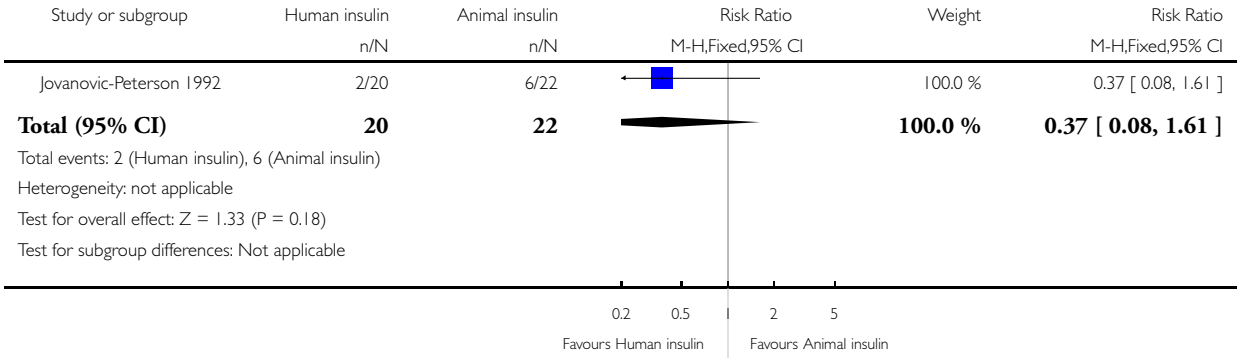
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Analysis 2.16. Comparison 2 Human insulin (recombinant deoxyribonucleic acid - Humulin) versus animal insulin (Different insulin types within similar insulin regimens), Outcome 16 Maternal ketonuria.

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 2 Human insulin (recombinant deoxyribonucleic acid - Humulin) versus animal insulin (Different insulin types within similar insulin regimens)

Outcome: 16 Maternal ketonuria

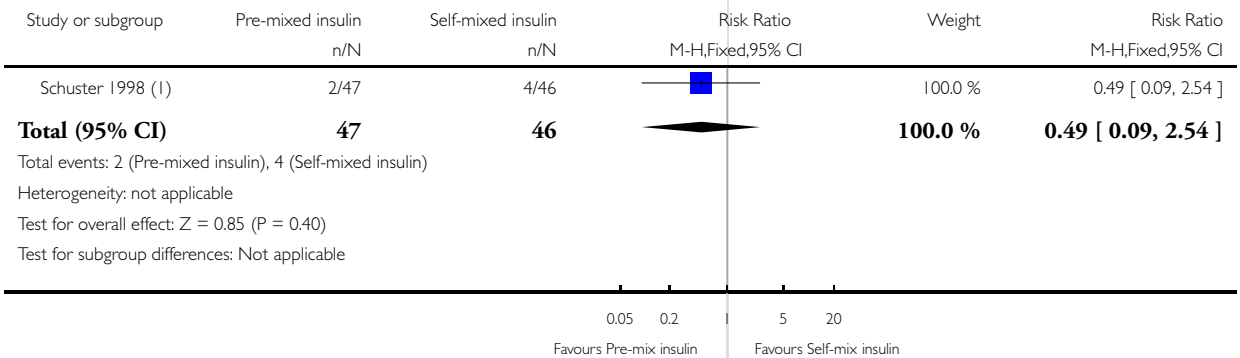


Analysis 3.1. Comparison 3 Pre-mixed insulin (70 NPH/30 REG) versus self-mixed split dose insulin (Different insulin regimens with similar insulin types used within the regimen), Outcome 1 Macrosomia.

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 3 Pre-mixed insulin (70 NPH/30 REG) versus self-mixed split dose insulin (Different insulin regimens with similar insulin types used within the regimen)

Outcome: 1 Macrosomia



(1) birthweight > 4000g

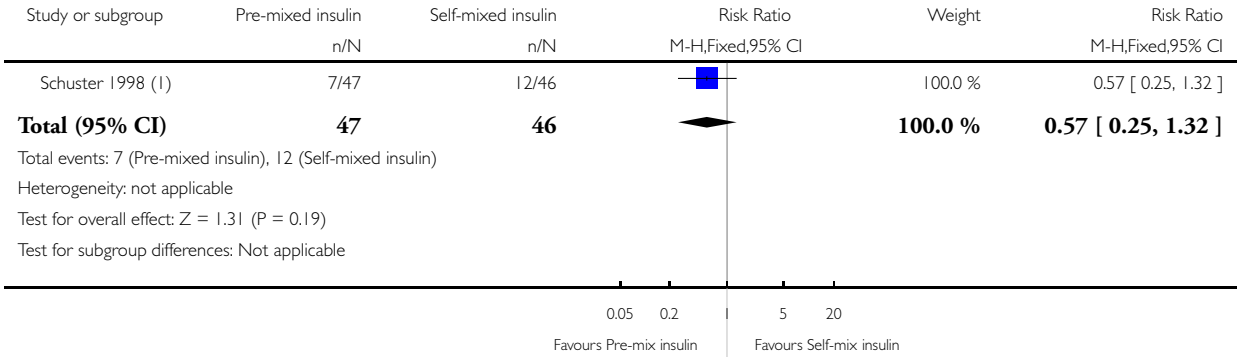
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Analysis 3.2. Comparison 3 Pre-mixed insulin (70 NPH/30 REG) versus self-mixed split dose insulin (Different insulin regimens with similar insulin types used within the regimen), Outcome 2 Caesarean section.

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 3 Pre-mixed insulin (70 NPH/30 REG) versus self-mixed split dose insulin (Different insulin regimens with similar insulin types used within the regimen)

Outcome: 2 Caesarean section



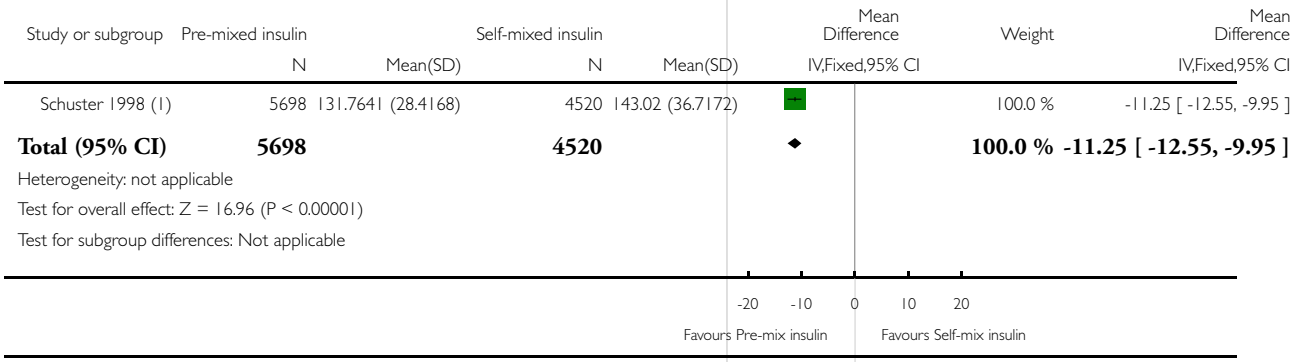
(1) Caesarean section for cephalopelvic disproportion only

Analysis 3.3. Comparison 3 Pre-mixed insulin (70 NPH/30 REG) versus self-mixed split dose insulin (Different insulin regimens with similar insulin types used within the regimen), Outcome 3 Antepartum capillary glucose measurement (mg/dL), 2 hours postprandial (after lunch).

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 3 Pre-mixed insulin (70 NPH/30 REG) versus self-mixed split dose insulin (Different insulin regimens with similar insulin types used within the regimen)

Outcome: 3 Antepartum capillary glucose measurement (mg/dL), 2 hours postprandial (after lunch)



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(1) Denominator for this outcome is the number of tests performed and not the number of women in each group

Analysis 3.4. Comparison 3 Pre-mixed insulin (70 NPH/30 REG) versus self-mixed split dose insulin (Different insulin regimens with similar insulin types used within the regimen), Outcome 4 Postpartum infection: endometritis.

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 3 Pre-mixed insulin (70 NPH/30 REG) versus self-mixed split dose insulin (Different insulin regimens with similar insulin types used within the regimen)

Outcome: 4 Postpartum infection: endometritis

Study or subgroup	Pre-mixed insulin n/N	Self-mixed insulin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Schuster 1998	9/47	17/46		100.0 %	0.52 [0.26, 1.04]
Total (95% CI)	**47**	**46**		**100.0 %**	**0.52 [0.26, 1.04]**
Total events: 9 (Pre-mixed insulin), 17 (Self-mixed insulin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.85 (P = 0.065)					
Test for subgroup differences: Not applicable					



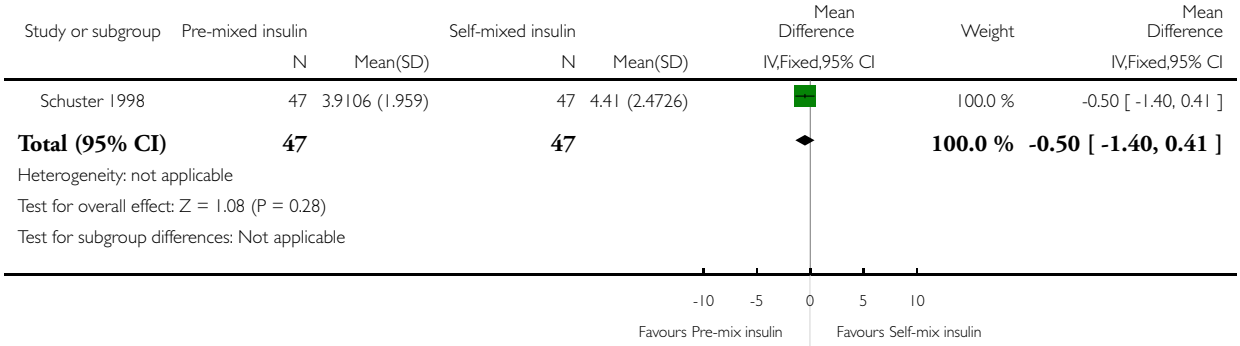
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Analysis 3.5. Comparison 3 Pre-mixed insulin (70 NPH/30 REG) versus self-mixed split dose insulin (Different insulin regimens with similar insulin types used within the regimen), Outcome 5 Use of healthcare resources (maternal hospital days).

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 3 Pre-mixed insulin (70 NPH/30 REG) versus self-mixed split dose insulin (Different insulin regimens with similar insulin types used within the regimen)

Outcome: 5 Use of healthcare resources (maternal hospital days)

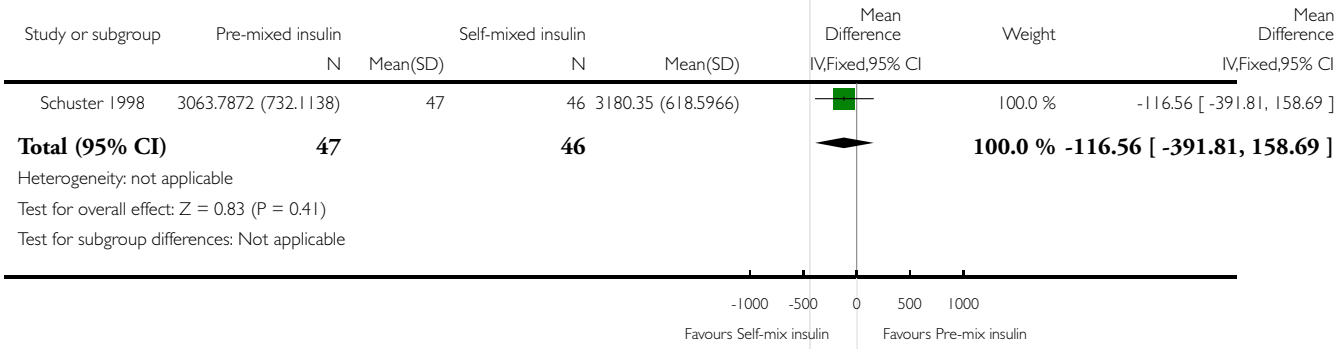


Analysis 3.6. Comparison 3 Pre-mixed insulin (70 NPH/30 REG) versus self-mixed split dose insulin (Different insulin regimens with similar insulin types used within the regimen), Outcome 6 Birthweight (g).

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 3 Pre-mixed insulin (70 NPH/30 REG) versus self-mixed split dose insulin (Different insulin regimens with similar insulin types used within the regimen)

Outcome: 6 Birthweight (g)



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Analysis 3.7. Comparison 3 Pre-mixed insulin (70 NPH/30 REG) versus self-mixed split dose insulin (Different insulin regimens with similar insulin types used within the regimen), Outcome 7 Compliance score.

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 3 Pre-mixed insulin (70 NPH/30 REG) versus self-mixed split dose insulin (Different insulin regimens with similar insulin types used within the regimen)

Outcome: 7 Compliance score

Study or subgroup	Pre-mixed insulin N	Mean(SD)	Self-mixed insulin N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Schuster 1998 (1)	24	3 (1.4)	25	3 (1.7)		100.0 %	0.0 [-0.87, 0.87]
Total (95% CI)	**24**		**25**			**100.0 %**	**0.0 [-0.87, 0.87]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P = 1.0)

Test for subgroup differences: Not applicable



(1) score ranges from 1 to 5, 1 = best, 5 = worst

Analysis 4.1. Comparison 4 Insulin injected with a Novolin pen versus insulin injected with a needle (syringe) (Different insulin regimens with similar insulin types used within the regimen), Outcome 1 Macrosomia.

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 4 Insulin injected with a Novolin pen versus insulin injected with a needle (syringe) (Different insulin regimens with similar insulin types used within the regimen)

Outcome: 1 Macrosomia

Study or subgroup	Novolin Pen n/N	Needle/Syringe n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Schuster 1998 (1)	1/45	5/48		100.0 %	0.21 [0.03, 1.76]
Total (95% CI)	**45**	**48**		**100.0 %**	**0.21 [0.03, 1.76]**

Total events: 1 (Novolin Pen), 5 (Needle/Syringe)

Heterogeneity: not applicable

Test for overall effect: Z = 1.44 (P = 0.15)

Test for subgroup differences: Not applicable



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(1) birthweight > 4000g

Analysis 4.2. Comparison 4 Insulin injected with a Novolin pen versus insulin injected with a needle (syringe) (Different insulin regimens with similar insulin types used within the regimen), Outcome 2 Caesarean section.

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 4 Insulin injected with a Novolin pen versus insulin injected with a needle (syringe) (Different insulin regimens with similar insulin types used within the regimen)

Outcome: 2 Caesarean section

Study or subgroup	Novolin Pen n/N	Needle/Syringe n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Schuster 1998 (1)	5/45	14/48		100.0 %	0.38 [0.15, 0.97]
Total (95% CI)	**45**	**48**		**100.0 %**	**0.38 [0.15, 0.97]**
Total events: 5 (Novolin Pen), 14 (Needle/Syringe)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.02 (P = 0.043)					
Test for subgroup differences: Not applicable					



(1) Caesarean section for cephalopelvic disproportion only

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Analysis 4.3. Comparison 4 Insulin injected with a Novolin pen versus insulin injected with a needle (syringe) (Different insulin regimens with similar insulin types used within the regimen), Outcome 3 Antepartum capillary glucose measurement (mg/dL) 2 hours postprandial (after lunch).

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 4 Insulin injected with a Novolin pen versus insulin injected with a needle (syringe) (Different insulin regimens with similar insulin types used within the regimen)

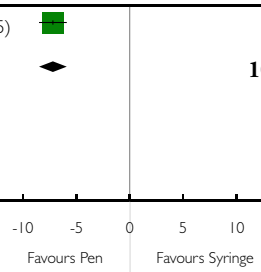
Outcome: 3 Antepartum capillary glucose measurement (mg/dL) 2 hours postprandial (after lunch)

Study or subgroup	Novolin Pen N	Mean(SD)	Needle/Syringe N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Schuster 1998 (1)	5425	133.3514 (29.834)	4793	140.58 (35.5355)		100.0 %	-7.23 [-8.51, -5.95]
Total (95% CI)	**5425**		**4793**			**100.0 %**	**-7.23 [-8.51, -5.95]**

Heterogeneity: not applicable

Test for overall effect: Z = 11.05 (P < 0.00001)

Test for subgroup differences: Not applicable



(1) Denominator for this outcome is the number of tests performed and not the number of women in each group

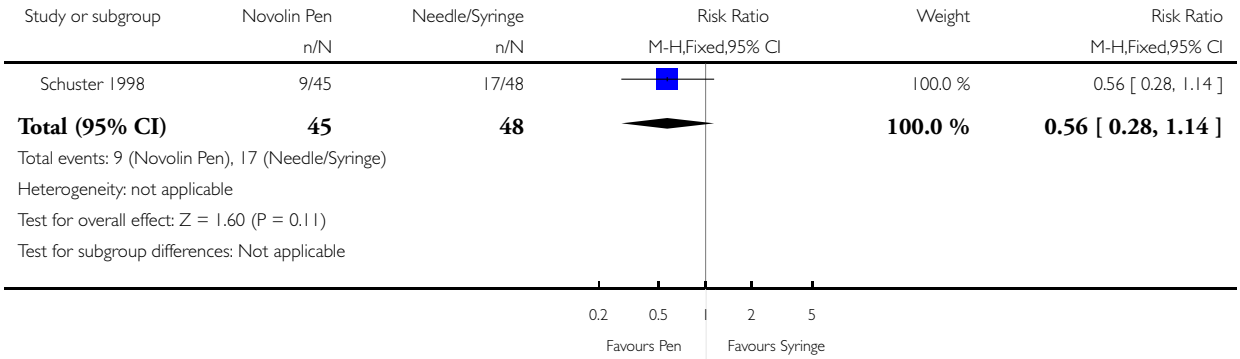
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Analysis 4.4. Comparison 4 Insulin injected with a Novolin pen versus insulin injected with a needle (syringe) (Different insulin regimens with similar insulin types used within the regimen), Outcome 4 Postpartum infection: endometritis.

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 4 Insulin injected with a Novolin pen versus insulin injected with a needle (syringe) (Different insulin regimens with similar insulin types used within the regimen)

Outcome: 4 Postpartum infection: endometritis

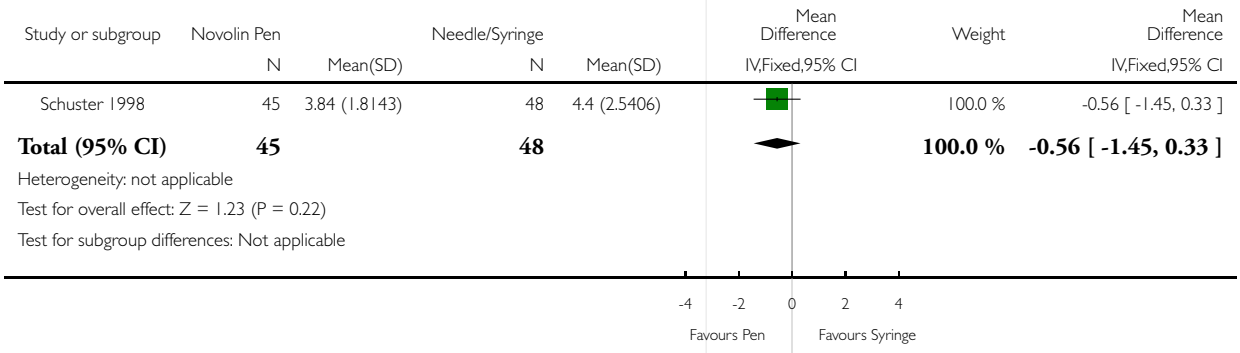


Analysis 4.5. Comparison 4 Insulin injected with a Novolin pen versus insulin injected with a needle (syringe) (Different insulin regimens with similar insulin types used within the regimen), Outcome 5 Use of healthcare resources (maternal hospital days).

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 4 Insulin injected with a Novolin pen versus insulin injected with a needle (syringe) (Different insulin regimens with similar insulin types used within the regimen)

Outcome: 5 Use of healthcare resources (maternal hospital days)



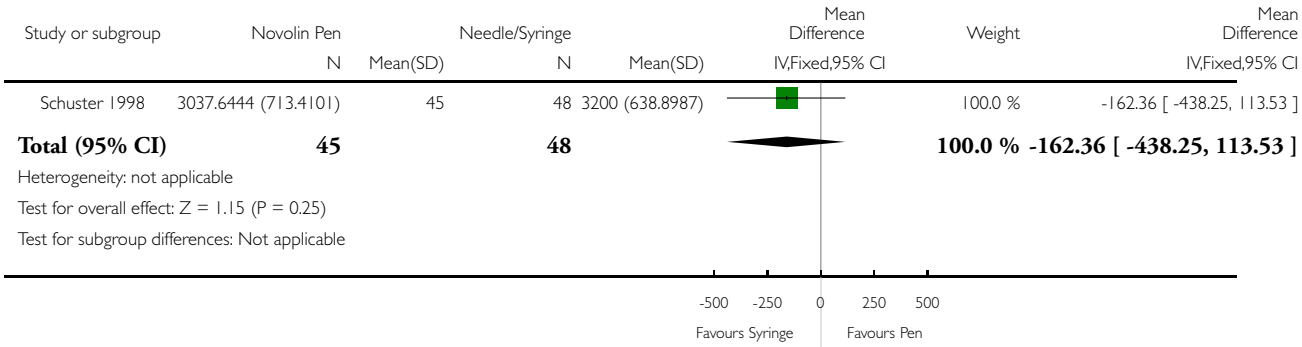
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Analysis 4.6. Comparison 4 Insulin injected with a Novolin pen versus insulin injected with a needle (syringe) (Different insulin regimens with similar insulin types used within the regimen), Outcome 6 Birthweight (g).

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 4 Insulin injected with a Novolin pen versus insulin injected with a needle (syringe) (Different insulin regimens with similar insulin types used within the regimen)

Outcome: 6 Birthweight (g)



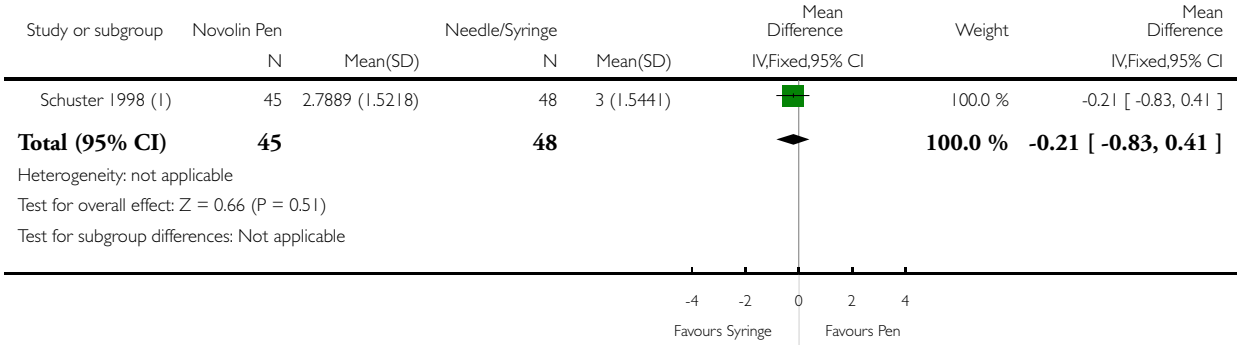
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Analysis 4.7. Comparison 4 Insulin injected with a Novolin pen versus insulin injected with a needle (syringe) (Different insulin regimens with similar insulin types used within the regimen), Outcome 7 Compliance score.

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 4 Insulin injected with a Novolin pen versus insulin injected with a needle (syringe) (Different insulin regimens with similar insulin types used within the regimen)

Outcome: 7 Compliance score



(1) score ranges from 1 to 5, 1 = best, 5 = worst

Analysis 5.1. Comparison 5 Insulin Aspart + NPH insulin versus Human insulin + NPH insulin (Different insulin types within similar insulin regimens), Outcome 1 A1c (%) third trimester visit.

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 5 Insulin Aspart + NPH insulin versus Human insulin + NPH insulin (Different insulin types within similar insulin regimens)

Outcome: 1 A1c (%) third trimester visit



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(1) which way round should the forest plot labels go? Is high % A1C better or worse?

Analysis 5.2. Comparison 5 Insulin Aspart + NPH insulin versus Human insulin + NPH insulin (Different insulin types within similar insulin regimens), Outcome 2 Average plasma glucose (mmol/L) third trimester visit.

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 5 Insulin Aspart + NPH insulin versus Human insulin + NPH insulin (Different insulin types within similar insulin regimens)

Outcome: 2 Average plasma glucose (mmol/L) third trimester visit

Study or subgroup	Aspart insulin N	Mean(SD)	Human insulin N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Mathiesen 2007	113	6.2 (1.2)	110	6.4 (1.3)		100.0 %	-0.20 [-0.53, 0.13]
Total (95% CI)	**113**		**110**			**100.0 %**	**-0.20 [-0.53, 0.13]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.19 (P = 0.23)

Test for subgroup differences: Not applicable



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Analysis 5.3. Comparison 5 Insulin Aspart + NPH insulin versus Human insulin + NPH insulin (Different insulin types within similar insulin regimens), Outcome 3 Maternal hypoglycaemic episodes.

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 5 Insulin Aspart + NPH insulin versus Human insulin + NPH insulin (Different insulin types within similar insulin regimens)

Outcome: 3 Maternal hypoglycaemic episodes

Study or subgroup	Aspart insulin n/N	Human insulin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Mathiesen 2007	108/113	99/110		100.0 %	1.06 [0.99, 1.14]
Total (95% CI)	**113**	**110**		**100.0 %**	**1.06 [0.99, 1.14]**
Total events: 108 (Aspart insulin), 99 (Human insulin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.60 (P = 0.11)					
Test for subgroup differences: Not applicable					



Analysis 6.1. Comparison 6 Insulin Detemir + prandial insulin Aspart versus NPH insulin + prandial insulin Aspart (Different insulin types within similar insulin regimens), Outcome 1 Major congenital malformation.

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 6 Insulin Detemir + prandial insulin Aspart versus NPH insulin + prandial insulin Aspart (Different insulin types within similar insulin regimens)

Outcome: 1 Major congenital malformation

Study or subgroup	Detemir insulin n/N	NPH insulin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Mathiesen 2012 (1)	3/79	1/83		100.0 %	3.15 [0.33, 29.67]
Total (95% CI)	**79**	**83**		**100.0 %**	**3.15 [0.33, 29.67]**
Total events: 3 (Detemir insulin), 1 (NPH insulin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.00 (P = 0.32)					
Test for subgroup differences: Not applicable					



(1) blinded outcome assessment

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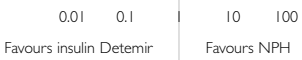
Analysis 6.2. Comparison 6 Insulin Detemir + prandial insulin Aspart versus NPH insulin + prandial insulin Aspart (Different insulin types within similar insulin regimens), Outcome 2 Major congenital malformation.

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 6 Insulin Detemir + prandial insulin Aspart versus NPH insulin + prandial insulin Aspart (Different insulin types within similar insulin regimens)

Outcome: 2 Major congenital malformation

Study or subgroup	Detemir insulin n/N	NPH insulin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Mathiesen 2012 (1)	2/79	1/83		100.0 %	2.10 [0.19, 22.72]
Total (95% CI)	**79**	**83**		**100.0 %**	**2.10 [0.19, 22.72]**
Total events: 2 (Detemir insulin), 1 (NPH insulin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.61 (P = 0.54)					
Test for subgroup differences: Not applicable					



(1) unblinded outcome assessment

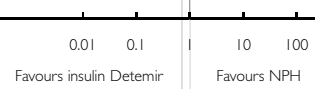
Analysis 6.3. Comparison 6 Insulin Detemir + prandial insulin Aspart versus NPH insulin + prandial insulin Aspart (Different insulin types within similar insulin regimens), Outcome 3 Minor congenital malformation.

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 6 Insulin Detemir + prandial insulin Aspart versus NPH insulin + prandial insulin Aspart (Different insulin types within similar insulin regimens)

Outcome: 3 Minor congenital malformation

Study or subgroup	Detemir insulin n/N	NPH insulin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Mathiesen 2012 (1)	0/79	1/83		100.0 %	0.35 [0.01, 8.47]
Total (95% CI)	**79**	**83**		**100.0 %**	**0.35 [0.01, 8.47]**
Total events: 0 (Detemir insulin), 1 (NPH insulin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.65 (P = 0.52)					
Test for subgroup differences: Not applicable					



(1) blinded outcome assessment

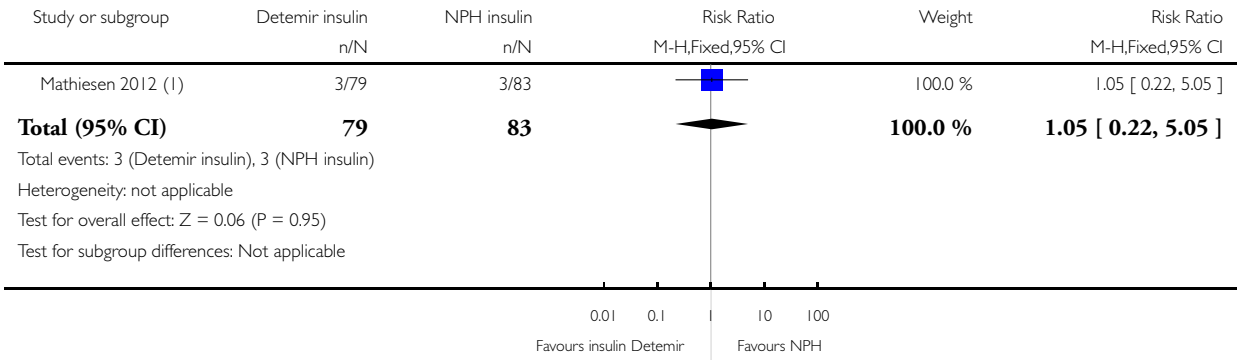
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Analysis 6.4. Comparison 6 Insulin Detemir + prandial insulin Aspart versus NPH insulin + prandial insulin Aspart (Different insulin types within similar insulin regimens), Outcome 4 Minor congenital malformation.

Review: Different insulin types and regimens for pregnant women with pre-existing diabetes

Comparison: 6 Insulin Detemir + prandial insulin Aspart versus NPH insulin + prandial insulin Aspart (Different insulin types within similar insulin regimens)

Outcome: 4 Minor congenital malformation



(1) unblinded outcome assessment

APPENDICES

Appendix 1. Search terms for ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform

type 1 diabetes AND pregnancy
type 2 diabetes AND pregnancy
insulin AND diabetes AND pregnancy

CONTRIBUTIONS OF AUTHORS

All six review authors were involved in the development of this review. Sinéad O'Neill co-ordinated and drafted the review with the help of Helen West, and is the guarantor of the review. Louise Kenny, Rebecca Smyth, and Patricia Kearney assisted in the conception of the review, and offered a clinical perspective. Ali Khashan provided statistical advice, as well as general advice on the review. Paul Beirne assisted with securing fellowship funding, and provided detailed comments on the protocol, but was not involved in the full review.

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DECLARATIONS OF INTEREST

SON: received support from a Health Research Board Cochrane Fellowship in order to prepare this review.

AK: none known.

LK: is As Director of the Irish Centre for Fetal and Neonatal Translational Research, and as such, has numerous grant applications under review at any given time. She has been paid by Alere to give invited symposia on a proprietary screening test for preeclampsia. She is the editor of Te Teachers and received royalties from the publishers. LK is also a limited share holder in Metabolomic Diagnostics, an SME who have licensed technology she has developed pertaining to the screening of preeclampsia.

HW: Helen West is paid to work on Cochrane reviews by a grant to Cochrane Pregnancy and Childbirth. The views and opinions expressed therein are those of the authors, and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

RS: none known.

PK: none known.

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Internal sources

- The Irish Centre for Fetal and Neonatal Translational Research (INFANT), University College Cork (UCC), Ireland.

LK is a Science Foundation Ireland (SFI) Principal Investigator (08/IN/.1/B2083) and the Director of the SFI funded centre INFANT (12/RC/2272)

- University College Cork (UCC), Ireland.

PB, SON, AK, and LK are employees of UCC and receive support from the University in the form of a salary.

- Cochrane Pregnancy and Childbirth Group, Department of Women's and Children's Health, The University of Liverpool, Liverpool, UK.

External sources

- Health Research Board (HRB), Ireland.

SON is the recipient of a full Cochrane Fellowship (Grant no: CTF-2014-884) from the HRB, Ireland

- NIHR Cochrane Programme Grant Project: 13/89/05 - Pregnancy and childbirth systematic reviews to support clinical guidelines, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. HW has been added as an author.

2. We added additional outcomes and labelled these as 'not prespecified outcomes'. For infants, these included: birthweight (g); infant fasting C-peptide level at three months (pmol/mL); infant C-peptide level one hour after glucose-amino acid challenge at three months (pmol/mL)); infant fasting glucose level at three months (pmol/mL); infant glucose level one hour after glucose-amino acid challenge at three months (pmol/mL), and gestational age at delivery. Additional maternal outcomes included: ventouse delivery; maternal ketonuria, and a maternal compliance with treatment score (1 = best, 5 = worst compliance).

3. We have reworded other outcomes to be in line with the list of core outcomes for diabetes in pregnancy (use of healthcare resources now includes maternal hospital days, pre-eclampsia includes pregnancy-induced hypertension, neonatal adiposity includes body weight percentile).

4. SON and HW performed the screening for eligibility, data extraction, and risk of bias for the included studies

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INDEX TERMS

Medical Subject Headings (MeSH)

Diabetes Mellitus, Type 1 [*drug therapy]; Diabetes Mellitus, Type 2 [*drug therapy]; Hypoglycemic Agents [administration & dosage; *therapeutic use]; Insulin [administration & dosage; *therapeutic use]; Insulin Aspart [therapeutic use]; Insulin Detemir [therapeutic use]; Insulin Lispro [therapeutic use]; Pregnancy Complications [*drug therapy]; Pregnancy in Diabetics [*drug therapy]

MeSH check words

Female; Humans; Pregnancy

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