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Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes (Review)

Farrar D, Tuffnell DJ, West J, West HM

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Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes.

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[Intervention Review]

Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes

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ABSTRACT

Background

Diabetes results in a rise in blood glucose above normal physiological levels; if untreated this may cause damage to many systems including the cardiovascular and renal systems. Pregnancy increases resistance to insulin action; for those women who have pre-gestational diabetes, this results in an increasing insulin requirement. There are several methods of administering insulin. Conventionally, insulin has been administered subcutaneously, formally referred to as intensive conventional treatment, but now more usually referred to as multiple daily injections (MDI). An alternative method of insulin administration is the continuous subcutaneous insulin infusion pump (CSII).

Objectives

To compare CSII with MDI of insulin for pregnant women with pre-existing and gestational diabetes.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (31 March 2016) and reference lists of retrieved studies.

Selection criteria

Randomised trials comparing CSII with MDI for pregnant women with diabetes.

Data collection and analysis

Three review authors independently assessed studies and two review authors extracted data. Disagreements were resolved through discussion with the third author. We assessed the quality of the evidence using the GRADE approach.

Main results

We included five single-centre trials (undertaken in Italy) with 153 women and 154 pregnancies in this review.

There were no clear differences in the primary outcomes reported between CSII and MDI in the included trials: **caesarean section** (risk ratio (RR) 1.09, 95% confidence interval (CI) 0.66 to 1.77; three trials, 71 women, *evidence graded very low*), **large-for-gestational**

Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes (Review)

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age (RR 4.15, 95% CI 0.49 to 34.95; three trials, 73 infants; *evidence graded very low*), and **perinatal mortality** (RR 2.33, 95% CI 0.38 to 14.32; four trials, 83 infants, *evidence graded very low*). Other primary outcomes were not reported in these trials (**hypertensive disorders of pregnancy, development of type 2 diabetes, composite outcome of serious neonatal outcomes, and neurosensory disability**).

There was no clear evidence of differences in the maternal secondary outcomes: **maternal weight gain during pregnancy, 24 hour mean blood glucose** in each trimester, **mean maternal HbA1c** in each trimester, **maternal hypoglycaemia**, and **maternal hyperglycaemia**. The included studies did not report several GRADE outcomes: **perineal trauma, return to pre-pregnancy weight, postnatal depression, induction of labour**. Many maternal secondary outcomes were also not reported.

In two trials, including a total of 61 infants, CSII was associated with an increase in **mean birthweight** compared with MDI (mean difference (MD) 220.56 g, 95% CI -2.09 g to 443.20 g; $P = 0.05$). However, the large CI including anything from a small reduction to an increase in mean birthweight and the lack of a difference in **macrosomia** rate (RR 3.20, CI 0.14 to 72.62; two trials, 61 infants) suggests uncertainty. **Large-for-gestational age** (see above), and **small-for-gestational age** also suggests uncertainty of effect. No significant differences were found in: **gestation at delivery, preterm birth < 37 weeks' gestation, preterm birth < 32 weeks' gestation, neonatal hypoglycaemia** (*evidence graded very low*), **respiratory distress syndrome, neonatal hyperbilirubinaemia**, and **fetal anomaly**. There were no data reported on many important infant outcomes, including the GRADE outcomes **adiposity** and **diabetes**. There was no follow-up of infants in childhood or adulthood, so longer-term outcomes were not reported.

The only outcome reported for use of health service resources was **maternal days hospitalised**, which did not show a difference between groups in the small number of women included (MD 9.40, CI -6.04 to 24.84; one trial, 10 women).

The methods used by the trials were poorly reported, for example although blinding of participants and clinicians regarding intervention allocation is impossible, it is possible to blind assessors and this along with other aspects of trial methods was not reported, which means that the trials are at an unclear or high risk of bias. We do not know if the women who participated were representative, and therefore if the results can be generalised. Most GRADE outcomes were not reported. For the GRADE outcomes that were reported, our assessment was that the evidence is *very low quality* (**caesarean section, large-for-gestational age, perinatal mortality, and neonatal hypoglycaemia**). This was due to design limitations in the included trials, small sample sizes in the trials contributing data, wide CIs crossing both the line of no effect and the line of appreciable benefit and/or harm, and often few events. We are therefore uncertain whether CSII or MDI improves outcomes for pregnant women with diabetes and their infants, and the results of further studies may differ substantially from those presented in this review.

Authors' conclusions

There is no evidence to support the use of one particular form of insulin administration over another for pregnant women with diabetes. There are only a small number of trials appropriate for meta-analysis, a small number of women included and questionable generalisability of the trial population.

Pump technology has progressed since these trials were undertaken. Well-designed randomised trials are required to evaluate comparisons such as patch pumps against MDI and more conventional CSII against MDI. These trials should be adequately powered to assess the effect of interventions, and report the core set of outcomes used in Cochrane reviews of diabetes in pregnancy. Trials to assess the effects of pumps on birthweight and macrosomia rates are needed. It would be beneficial for future trials to undertake longer-term follow-up of participants and their infants, assess women's preferences, and conduct an economic evaluation.

PLAIN LANGUAGE SUMMARY

Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes

What is the issue?

Diabetes is a condition in which glucose (sugar) in the blood is too high because the body does not respond to insulin or not enough insulin is made. Insulin is a hormone made by the pancreas, which allows glucose to enter the cells where it is used as fuel by the body.

Controlling blood sugar levels is important because levels that are too high or too low can affect the brain and other organs of the body. Poor blood sugar control in pregnant women with diabetes can lead to large babies who may then have a difficult birth. It also increases the chance of abnormalities in the baby, miscarriage, or stillbirth.

Traditionally, insulin is given as multiple daily injections (MDI), however a small pump can continuously give insulin through a fine tube under the skin (CSII).

Why is this important?

An insulin pump may help pregnant women keep their blood glucose more stable than multiple injections. It might stop the woman's blood sugar level going too high or too low, which would be better for the mother and her baby and it may be more acceptable to women. This review compared the positive and negative effects of CSII and MDI to work out which is best for mothers and infants.

What evidence did we find?

Five randomised trials involving 153 women (154 pregnancies) were included.

These trials did not report many of the outcomes we had hoped to look at. The evidence was judged to be very low quality for important outcomes (caesarean section, large-for-gestational age, perinatal mortality, and neonatal hypoglycaemia). This was because the trials were small, may not have been fair tests, and did not show a clear difference between MDI and CSII.

There were no clear differences in any of the reported outcomes between women who had insulin via a pump rather than as multiple injections. For mothers, this included caesarean section, weight gain during pregnancy, and blood sugar levels. For babies, this included the baby's weight, if they were born premature, and problems such as difficulty breathing, a low Apgar score at birth, low blood sugar, jaundice, or physical abnormalities.

In one small trial, there was no difference in the number of days mothers spent in hospital. This was the only measure of cost or use of health service resources reported.

What does this mean?

The trials did not provide enough information to know whether an insulin pump or multiple injections are better for a pregnant woman with diabetes or her baby. More research is needed, with bigger groups of women, good reporting of how the trials were undertaken, more outcomes assessed and reported, and using the latest pump technology and insulins.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [\[Explanation\]](#)

Continuous subcutaneous insulin infusion (CSII) versus multiple daily injections (MDI) of insulin for pregnant women with diabetes					
Patient or population: pregnant women with diabetes Setting: 3 studies in Italy Intervention: CSII Comparison: MDI					
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with MDI	Risk with GRADE CSII			
Hypertensive disorders of pregnancy (including pre-eclampsia, pregnancy-induced hypertension, eclampsia)				(0 studies)	outcome not reported
Caesarean section	Study population		RR 1.09 (0.66 to 1.77)	71 (3 RCTs)	⊕○○○ VERY LOW ¹²
	444 per 1000	484 per 1000 (293 to 787)			
	Moderate				
	438 per 1000	477 per 1000 (289 to 774)			
Development of Type 2 diabetes				(0 studies)	outcome not reported
Perineal trauma				(0 studies)	outcome not reported
Return to pre-pregnancy weight				(0 studies)	outcome not reported

Postnatal depression		(0 studies)	outcome not reported
Induction of labour		(0 studies)	outcome 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			
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 All studies contributing data had design limitations.

² Wide confidence interval crossing the line of no effect, and small sample size.

BACKGROUND

Description of the condition

Diabetes is a major disease affecting a growing proportion of pregnant women. Diabetes occurs when there is insufficient insulin in the blood. Given that insulin controls blood glucose levels, inadequate circulating insulin levels lead to a rise in blood glucose. Increased blood glucose levels can cause damage to many systems, including the cardiovascular and renal systems and during pregnancy, are associated with increased risk of adverse perinatal outcomes. There are two main types of diabetes that exist prior to pregnancy: type 1 diabetes occurs due to a lack of pancreatic islet b cells, caused by autoimmune destruction and resulting in an absence of insulin; type 2 diabetes occurs due to insulin resistance or b cell dysfunction, or both, and is likely to be the result of interactions between genetic, environmental and immunological factors; including diet, physical activity and obesity (Zaccardi 2016).

Physiological insulin resistance increases during pregnancy to facilitate glucose transfer across the placenta to the fetus, to ensure growth and development. This physiological insulin resistance leads to increasing Insulin requirements for women who have pre-gestational diabetes and who manage their diabetes with insulin; for those who manage their diabetes with diet and/or oral anti-diabetic agents, insulin may be required and for some women without pre-existing diabetes, gestational diabetes may develop. Recent studies have reported graded linear associations between maternal glucose and adverse perinatal outcomes across the whole glucose spectrum, with no clear threshold where risk increases (HAPO 2008; Farrar 2015), therefore interventions to reduce glucose levels for women with lower glucose levels, than were previously diagnostic of gestational diabetes, are likely to reduce associated perinatal risks. Similarly to maternal glucose, maternal obesity, which is a common 'co-condition' with type 2 diabetes, has been identified as being independently associated with adverse perinatal outcomes, however when maternal obesity is combined with hyperglycaemia (high blood sugar) the adverse impact on perinatal outcomes is greater than either one alone (HAPO 2010; Catalano 2012).

Since the introduction of insulin as a treatment for diabetes, maternal mortality and morbidity rates have improved; however, they remain significantly higher than those of the general obstetric population (Knight 2014). Perinatal mortality rates amongst babies of women with pre-existing diabetes have also declined over recent years, however population-based studies suggest that rates are still 2.5 to nine times higher than in the general obstetric population (Melamed 2009). In 2010 CEMACE reported that 27% of mothers with recorded pre-existing medical conditions had a stillbirth and that 3% of these had diabetes. Twenty-eight per cent of mothers whose infants died in the neonatal period also had a pre-existing medical condition and 2% of these had diabetes, making diabetes one of the commonest conditions associated with still-

birth and neonatal death (CMACE 2010). Complications associated with pre-existing diabetes include: higher rates of miscarriage, stillbirth and congenital anomaly. Recent congenital anomaly rates reported for infants of women with diabetes range from 42 to 94 per 1000 births, compared to a rate of between 10 and 21 per 1000 births in the general population (Hawthorne 1997; Penney 2003; CEMACH 2005).

A potential problem in the assessment of the management of diabetes has been reported by John 1997; Kilpatrick 1997; Kilpatrick 1998 and Marshall 2000, who suggest that differences have been found in the ranges and results produced by laboratories using the same methods of assessment to measure the same glycaemic index. Thus, a degree of caution should be used when interpreting multicentre studies using several laboratories to analyse specimens.

Continuous glucose monitoring systems are used selectively and provide a dynamic picture of interstitial glucose levels, converting these levels to an electrical signal, which produces an average recording of glucose level every five minutes. Studies using the continuous glucose monitoring system in conjunction with other methods of assessment such as glycated haemoglobin (HbA1c) and intermittent glucose monitoring, have found it useful in providing additional information in relation to hypo/hyperglycaemia, which is of particular importance during pregnancy (Buhling 2004; Kerssen 2004; Porter 2004; Hirsch 2005). The addition of continuous glucose monitoring should provide a more accurate picture of control over a 24-hour period and reduce the impact of anomalies associated with HbA1c monitoring, leading to improved glucose control.

Many women manage their type 2 diabetes with oral anti-diabetic agents such as metformin. Metformin improves insulin sensitivity and is not associated with hypoglycaemia (low blood sugar). During pregnancy, the use of oral anti-diabetic agents may be supplemented or substituted with insulin in order to achieve optimum glucose control. There is limited evidence evaluating the effects of oral anti-diabetic agents on maternal and infant outcomes. Results from the metformin in gestational diabetes (MIG) trial however reported no increase in perinatal complications with metformin compared with insulin (Rowan 2008). A Cochrane protocol has recently been published which aims to examine oral anti-diabetic pharmacological therapies for the treatment of women with gestational diabetes (Brown 2015). A Cochrane review investigating the use of oral anti-diabetic agents for women with pre-existing diabetes/impaired glucose tolerance or previous gestational diabetes however was unable to include any trials, though one trial is ongoing (Tieu 2010). The current Cochrane review evaluating treatments for gestational diabetes (which has now been divided into types of treatments, with protocols being published: Brown 2015; Brown 2015a; Brown 2016) reported that treatment of gestational diabetes reduces the risk of a range of perinatal adverse outcomes (Alwan 2009). Alwan 2009 found that women with gestational diabetes mellitus (GDM) when treated with oral hypoglycaemics compared with insulin were significantly less likely

to have a caesarean section and their infants significantly less likely to develop neonatal hypoglycaemia; there were however, no differences in other important outcomes including induction of labour and shoulder dystocia (difficulty in delivering a baby's shoulders). There remains controversy regarding the degree to which blood glucose level should be controlled in pregnancies complicated by diabetes. Though it is generally agreed that the optimal HbA1c level (retrospective glucose measure) should be between 4 mmol/L and 8 mmol/L (Hawthorne 2002; Williams 2003), though this may be difficult to achieve for women with refractory pre-existing or gestational diabetes (Maresh 2001). A Cochrane review has examined different intensities of glycaemic control for pregnant women with pre-existing diabetes (Middleton 2016). This review includes three trials (223 women with type 1 diabetes and their infants) and concluded that although evidence is limited and the included trials were assessed as being at high risk of bias, there is little difference in outcomes between very tight and tight-to-moderate glycaemic control. There is however evidence of harm with loose control. A recently published Cochrane review (Martis 2016) has examined trials evaluating different intensities of glycaemic control for women with gestational diabetes. The one eligible trial was published as a conference abstract, includes 171 women, methods were unclear and outcomes reported were few, therefore evidence is insufficient to suggest what intensity of glycaemic control is superior.

Description of the intervention

There are several methods of administering insulin to women who require it in pregnancy. Conventionally, insulin has been administered subcutaneously in the form of a basal/bolus regimen, often referred to as multiple daily injections (MDI). This consists of pre-meal boluses of rapid-acting insulin (RAI) and a later evening basal injection of long-acting insulin, usually given with pen injection devices. The advantage of MDI is that blood sugar levels can be tightly controlled by frequent, self-regulated adjustment of dose, necessary because of the dynamic insulin requirements of pregnancy, but frequent injections can be painful and may interfere with daily living activities. An alternative insulin administration method is the continuous subcutaneous insulin infusion pump (CSII). Modern pumps are small and lightweight, are battery operated and hold enough insulin for several days (Pozzilli 2016). A more recent advance is the development of the patch pump (tubing-free pumps in which the reservoir and integrated infusion set adhere to the skin) (Thabit 2012). Different basal rates can be preset and boluses given as required. Potentially CSII maintains the basal rate of insulin and reduces the risk of hypoglycaemia, decreases the risk of fasting hyperglycaemia (the dawn phenomenon) and can improve compliance, as frequent injection of insulin is not required (as with MDI) (Gonzalez 2002; Pozzilli 2016). Hadden 1996, however, suggests that although insulin pumps offer the treatment effects of conventional regimens (and may be preferred

by some women), they may be overly complex for routine use. Selective use of pumps for those who are motivated, or with refractory diabetes is an alternative to widespread use.

How the intervention might work

Despite widespread use of CSII pumps in some high-income countries such as Norway, Germany, France and the USA, they are used infrequently in the other high-income countries such as the UK and Spain and most low- to middle-income countries (Pozzilli 2016). Reasons for this are unclear, but may be due to conservatism, costs and lack of evidence on effectiveness and safety (Colquitt 2004). Brink 1986, Knight 1985 and Mecklenburg 1984 report improved glycaemic control with CSII compared to MDI, however both Knight 1985 and Mecklenburg 1984, also report an increased incidence of ketoacidosis. Group allocation was not random in the Knight 1985 study and generally ketoacidosis was precipitated by illness. Brink 1986 found no increased incidence in diabetic ketoacidosis using CSII compared to MDI. Both studies (Knight 1985; Brink 1986) report the incidence of ketoacidosis reduced with time, suggesting learning or familiarity played a part. A recent review and meta-analyses comparing CSII compared with MDI reported that more women in the CSII group had hypoglycaemic spells and ketoacidotic episodes (requiring treatment), however the differences for both these outcomes were non-significant (Mukhopadhyay 2007).

Both rapid-acting insulin analogues (RAIA) and regular human insulin can be given via CSII and MDI. RAIAs provide a more physiological time course of action. It has been suggested by some authors that the use of RAIAs, compared to regular human insulin, reduces episodes of hypoglycaemia and improves metabolic control (Anderson 1997; Johansson 2000). This improved control is thought to be due to RAIAs' ability to achieve peak plasma concentrations approximately twice as high and in approximately half the time compared to regular insulin (Siebenhofer 2004). A Cochrane review of RAIA versus regular human insulin in patients with diabetes (Siebenhofer 2006) however, concluded (and taking into account the low quality of trials included in the meta-analysis), that there seemed to be only a negligible benefit with RAIA over regular human insulin. The authors suggest a cautious response to the vigorous promotion of RAIAs and that more robust trials needed to be carried with longer-term follow-up of both mother and child.

Why it is important to do this review

Diabetes affects a significant and growing proportion of women in pregnancy. Hyperglycaemia is associated with increased risk of important perinatal outcomes across the whole spectrum of glucose. Treatments to reduce glucose levels however, in both women with pre-existing diabetes and gestational diabetes reduce adverse out-

come risk. Different methods of administering insulin may have different effects in terms of achieving optimal glucose control and may influence the risk of maternal and infant outcomes. This review will examine the effects of CSII and MDI for women with diabetes in pregnancy.

OBJECTIVES

The objective was to conduct a systematic review of randomised trials comparing continuous subcutaneous insulin infusion (CSII) with multiple daily injections (MDI) of insulin for pregnant women with diabetes.

METHODS

Criteria for considering studies for this review

Types of studies

We included published and unpublished randomised trials comparing CSII with MDI of insulin for pregnant women with diabetes. We excluded quasi-randomised trials and cross-over trials. Cluster-randomised trials were eligible for inclusion.

Types of participants

Women with pre-existing and gestational diabetes and randomised to receive either CSII or MDI.

Types of interventions

Any comparisons of CSII with MDI of insulin for pregnant women with diabetes.

Types of outcome measures

For this update, we used the core outcome set agreed by consensus between review authors of Cochrane Pregnancy and Childbirth systematic reviews for prevention and treatment of gestational diabetes mellitus (GDM) and pre-existing diabetes.

Primary outcomes

Mother

1. Hypertensive disorders of pregnancy (including pre-eclampsia, pregnancy-induced hypertension, eclampsia)
2. Caesarean section
3. Development of type 2 diabetes

Neonatal/infant

1. Large-for-gestational age
2. Perinatal mortality (stillbirth and neonatal mortality)
3. Mortality or morbidity composite (e.g. perinatal mortality, shoulder dystocia, bone fracture, and admission to the neonatal unit)
4. Neurosensory disability

Secondary outcomes

Mother

1. Induction of labour
2. Perineal trauma
3. Placental abruption
4. Postpartum haemorrhage
5. Postpartum infection
6. Weight gain during pregnancy
7. Adherence to the intervention
8. Behaviour changes associated with the intervention
9. Relevant biomarker changes associated with the intervention (e.g. adiponectin, free fatty acids, triglycerides, high-density lipoproteins, low-density lipoproteins, insulin)
10. Sense of well-being and quality of life
11. Views of the intervention
12. Breastfeeding (e.g. at discharge, six weeks postpartum)
13. Use of additional pharmacotherapy
14. Glycaemic control during/end of treated (as defined by trialists)
15. Maternal hypoglycaemia
16. Maternal mortality

Long-term maternal outcomes

1. Postnatal depression
2. Postnatal weight retention or return to pre-pregnancy weight
3. Body mass index (BMI)
4. Gestational diabetes mellitus in a subsequent pregnancy
5. Type I diabetes
6. Impaired glucose tolerance
7. Cardiovascular health (as defined by trialists, including blood pressure (BP), hypertension, cardiovascular disease, metabolic syndrome)
8. Return to pre-pregnancy weight (not pre-specified)

Neonatal/infant

1. Stillbirth
2. Neonatal mortality
3. Gestational age at birth
4. Preterm birth (less than 37 weeks' gestation and less than 32 weeks' gestation)

5. Apgar score (less than seven at five minutes)
6. Macrosomia (birthweight greater than 4000 g and birthweight greater than 4500 g)
7. Small-for-gestational age
8. Birthweight and z score
9. Head circumference and z score
10. Length and z score
11. Ponderal index
12. Adiposity
13. Shoulder dystocia
14. Bone fracture
15. Nerve palsy
16. Respiratory distress syndrome
17. Hypoglycaemia
18. Hyperbilirubinaemia
19. Neonatal hypocalcaemia
20. Polycythaemia
21. Relevant biomarker changes associated with the intervention (e.g. cord c peptide, cord insulin)
22. Fetal anomaly

Later infant and childhood secondary outcomes

1. Weight and z scores
2. Height and z scores
3. Head circumference and z scores
4. Adiposity (e.g. as measured by BMI, skinfold thickness)
5. Blood pressure
6. Type 1 diabetes
7. Type 2 diabetes
8. Impaired glucose tolerance
9. Dyslipidaemia or metabolic syndrome
10. Educational achievement

Child as an adult secondary outcomes

1. Weight
2. Height
3. Adiposity (e.g. as measured by BMI, skinfold thickness)
4. Cardiovascular health (as defined by trialists, including BP, hypertension, cardiovascular disease, metabolic syndrome)
5. Type I diabetes
6. Type 2 diabetes
7. Impaired glucose tolerance
8. Dyslipidaemia or metabolic syndrome
9. Employment, education and social status/achievement

Health service use

1. Number of hospital or health professional visits (e.g. midwife, obstetrician, physician, dietitian, diabetic nurse)
2. Number of antenatal visits or admissions
3. Length of antenatal stay

4. Neonatal intensive care unit admission
5. Length of postnatal stay (mother)
6. Length of postnatal stay (baby)
7. Costs to families associated with the management provided
8. Costs associated with the intervention
9. Cost of maternal care
10. Cost of offspring care

Search methods for identification of studies

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

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting their Information Specialist (31 March 2016).

The Register is a database containing over 21,000 reports of controlled trials in the field of pregnancy and childbirth. For full search methods used to populate the Pregnancy and Childbirth Group's Trials Register including the detailed search strategies for CENTRAL, MEDLINE, Embase and CINAHL; the list of hand-searched 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 Group](#) in the Cochrane Library and select the '*Specialized Register*' section from the options on the left side of the screen.

Briefly, the Cochrane Pregnancy and Childbirth Group'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 Group 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](#); [Ongoing studies](#)).

Searching other resources

We searched the reference lists of retrieved studies.
We did not apply any language or date restrictions.

Data collection and analysis

For methods used in the previous version of this review, see [Farrar 2007](#).

For this update, we planned to use the following methods to assess the four reports that we identified as a result of the updated search. Unfortunately, no new studies were included in this update. The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Selection of studies

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

Data extraction and management

We designed a form to extract data. For eligible studies, two review authors planned to extract the data using the agreed form. We would have resolved discrepancies through discussion or, if required, consulted the third review author. We planned to enter data into Review Manager software ([RevMan 2014](#)) and to check for accuracy.

When information regarding any of the above was unclear, we planned to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors planned to assess independently the risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We would have resolved any disagreement by discussion.

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

For each included study we planned to describe the methods used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups. We would have assessed the methods as:

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

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

For each included study we planned to describe the method used to conceal the allocation sequence and determined whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We would have assessed the methods as:

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

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

We planned to describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received.

We would have 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 would have assessed blinding separately for different outcomes or classes of outcomes.

We would have assessed the methods as:

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

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

We planned to describe for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We would have assessed blinding separately for different outcomes or classes of outcomes.

We would have 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 trial and for each outcome or class of outcomes, we planned to describe the completeness of data including attrition and exclusions from the analysis. We would have stated whether attrition and exclusions were reported, 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. We would have assessed the 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 carried out with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We planned to describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We would have assessed the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

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

For each included trial we planned to describe any important concerns we had about other possible sources of bias.

We would have assessed whether each trial 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 intended to make explicit judgements about whether trials were at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we planned to assess the likely magnitude and direction of the bias and whether we considered it likely to impact on the findings. We intended to explore the impact of the level of bias through undertaking sensitivity analyses - see [Sensitivity analysis](#) but there were insufficient data to do so.

Assessment of the quality of the evidence using the GRADE approach

For this update, we assessed the quality of the evidence using the GRADE approach as outlined in the [GRADE handbook](#) in order to assess the quality of the body of evidence relating to the following outcomes for the main comparison. We used the Cochrane Pregnancy and Childbirth GRADE core outcome set for reviews of diabetes in pregnancy.

Mother

1. Hypertensive disorders
2. Caesarean section
3. Development of type 2 diabetes
4. Perineal trauma
5. Return to pre-pregnancy weight
6. Postnatal depression
7. Induction of labour

Infant

1. Large-for-gestational age
2. Stillbirth and neonatal mortality
3. Mortality or morbidity composite
4. Neonatal hypoglycaemia
5. Adiposity
6. Type 1 and type 2 diabetes
7. Neurosensory disability

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

Measures of treatment effect

Dichotomous data

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

Continuous data

We used the mean difference where outcomes were measured in the same way between trials. We planned to use the standardised mean difference to combine trials that measured the same outcome, but used different methods.

Unit of analysis issues

Cluster-randomised trials

No cluster-randomised trials were included in this update. In future updates if eligible and included, we will include cluster-randomised trials in the analyses along with individually-randomised trials. We will adjust their standard errors using the methods described in the *Handbook* [Section 16.3.4 or 16.3.6] using an estimate of the intracluster 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 plan to 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 the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Cross-over trials

Cross-over trials are not eligible for inclusion.

Other unit of analysis issues

Multiple pregnancy

In future updates, if women are included in a trial randomised with a multiple pregnancy, we will present maternal data as per woman randomised and neonatal data as per infant.

Multiple-arm studies

In future updates, where a trial has multiple intervention arms we will avoid 'double counting' of participants by combining groups, if appropriate, to create a single pair-wise comparison. Where this is not possible, we will split the 'shared' group (often the 'control' group) into two or more groups with smaller sample size and include two or more (reasonably independent) comparisons.

Dealing with missing data

For included studies, we noted levels of attrition. In future updates, if more eligible studies are included, we will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, analyses were carried out, 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. 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 τ^2 , I^2 and χ^2 statistics. We regarded heterogeneity as substantial if an I^2 was greater than 30% and either a τ^2 was greater than zero, or there was a low P value (less than 0.10) in the χ^2

test for heterogeneity. Had we identified substantial heterogeneity (above 30%), we planned to explore it by pre-specified subgroup analysis.

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 assess funnel plot asymmetry visually. 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 software (RevMan 2014). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar.

If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, we planned to use random-effects meta-analysis 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 planned to discuss the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful, we 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 τ^2 and I^2 .

Subgroup analysis and investigation of heterogeneity

Had we had identified substantial heterogeneity, we planned to investigate it using subgroup analyses and sensitivity analyses and to consider whether an overall summary was meaningful, and if it was, to use the random-effects analysis to produce it.

We planned to carry out the following subgroup analyses.

1. Pre-existing versus gestational diabetes

We were unable to carry out subgroup analysis because of insufficient data. We will perform this subgroup analysis in future updates of this review if more data become available. We will use the primary outcomes in subgroup analysis.

We will assess subgroup differences by interaction tests available within RevMan (RevMan 2014) and report the results of subgroup analyses quoting the χ^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We planned to carry out the following sensitivity analyses to explore the effect of trial quality assessed by concealment of allocation, high attrition rates, or both, with poor quality studies being excluded from the analyses in order to assess whether this makes any difference to the overall result. However, there were insufficient data to allow us to carry out any sensitivity analyses.

1. Trial quality (if rated 'high risk of bias')
2. Treatment started before and during pregnancy

RESULTS

Description of studies

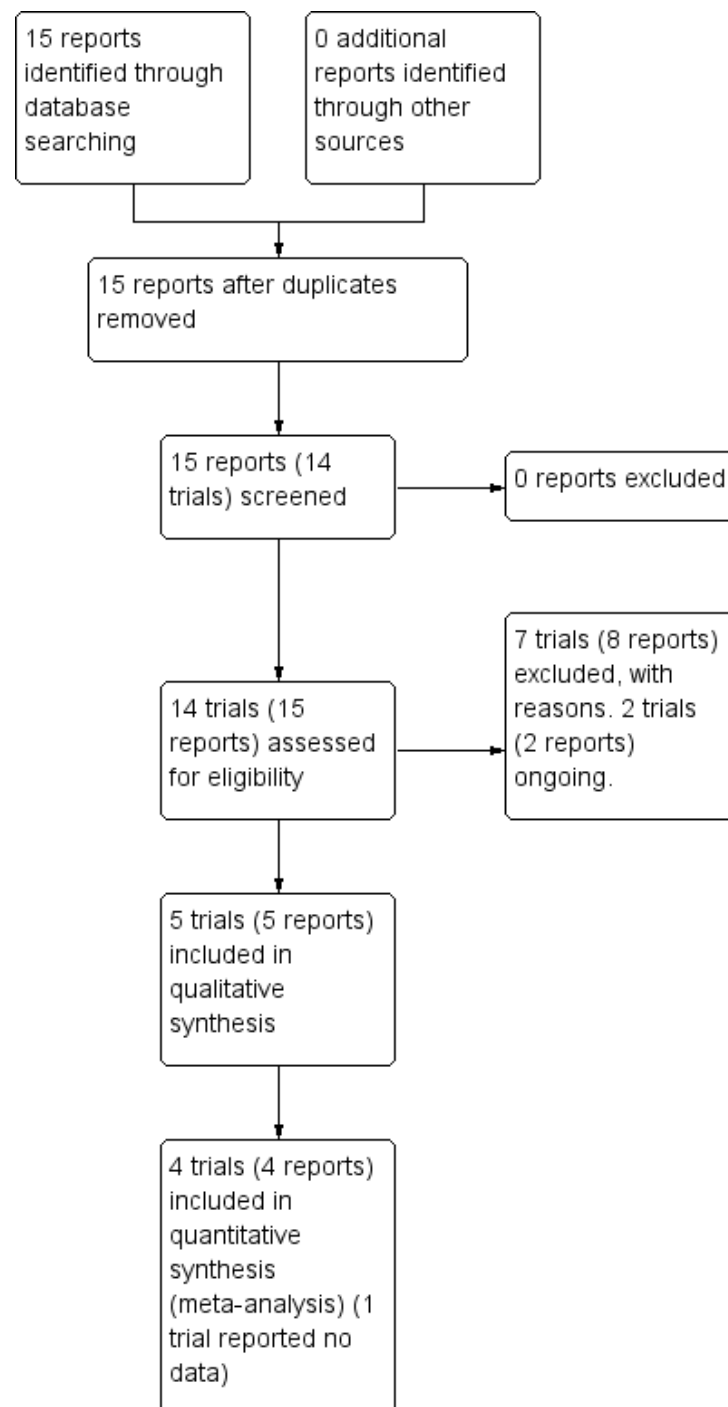
We included five trials with 153 women and 154 pregnancies. All five trials were carried out in single centres.

Results of the search

The updated search in March 2016 identified four new reports of three trials ([Murphy 2011](#); [Stewart 2014](#); [Thompson 2014](#)). [Murphy 2011](#) was excluded because it does not compare continuous subcutaneous insulin infusion pump (CSII) with multiple daily injections (MDI). [Stewart 2014](#) and [Thompson 2014](#) are currently ongoing.

This updated review is therefore comprised of five trials (involving 153 women and 154 pregnancies) ([Trossarelli 1984](#); [Botta 1986](#); [Carta 1986](#); [Nosari 1993](#); [Mello 2005](#)). A total of seven trials have been excluded, and two are ongoing. See [Figure 1](#).

Figure 1. Study flow diagram.



Included studies

[Botta 1986](#) conducted a single-centre trial in Italy. The paper was translated to English prior to inclusion. Ten participants were included and 'divided randomly' into two groups with no other information reported. Five participants were given 'optimised traditional insulin therapy' and five CSII using a micropump (Lilly CPI 9100). There were no losses to follow-up, which was carried out until birth. Outcomes were: gestational age at birth, caesarean section, weight gain during pregnancy, preterm birth, hyperbilirubinaemia, and maternal days hospitalised.

[Carta 1986](#) in a single-centre trial in Italy included 29 women, 15 women with type 1 diabetes (13 on conventional insulin therapy, two on continuous insulin therapy) and 14 women with type 2 diabetes (four were on oral hypoglycaemics, 10 were diet-controlled). Recruitment was undertaken in the first trimester, two women allocated to CSII had been using a CSII pump pre-conceptually. For women randomised to CSII, a Microject MC 20 portable syringe pump was used with porcine insulin (Actrapid MC 40 U/ml); adjustments were made to the dosage in order to obtain strict glycaemic control (fasting blood glucose (BG) < 80 + 10 mg/dL, postprandial BG < 120 mg/dL). Participants randomised to MDI, were given Actrapid MC split into four boluses. Outcomes were: maternal and neonatal mortality, large-for-gestational age, fetal anomaly and hypoglycaemia, weight gain during pregnancy, mean 24-hour BG, mean HbA1c, gestational age at delivery, preterm birth, birthweight and rate of instrumental delivery.

[Mello 2005](#) was a single-centre trial in Italy and included 71 women with type 1 diabetes. The women were randomised in their first trimester, although the trial fulfilled eligibility criteria for inclusion, data were described rather than reported as raw or mean results and therefore could not be included in the meta-analysis.

[Nosari 1993](#) conducted a single-centre trial in Italy, included 31 women with type 1 diabetes undergoing 32 pregnancies. Using sealed envelopes, the women were allocated to receive either CSII or MDI. Four women were recruited in the pre-conception period and 28 recruited during the first trimester. Participants were described by the authors as 'highly motivated'. Microject MC 20 and Daedi B.V. portable battery-powered syringe infusion pumps were used. Participants receiving MDI had four daily insulin injections (regular insulin at each meal and intermediate acting insulin

at night; type of insulin used was not reported). Outcomes were: maternal and neonatal mortality, large-for-gestational age, fetal anomaly and hypoglycaemia, mean 24-hour BG, mean HbA1c, gestational age at delivery, preterm birth, Apgar score less than seven at five minutes, respiratory distress syndrome, birthweight and rate of instrumental delivery.

[Trossarelli 1984](#) was a single-centre trial in Italy that included 12 women with type 1 diabetes recruited in their first trimester, no information was provided regarding the method of insulin administration other than that the trial compared CSII with MDI. Results were mainly reported descriptively. Outcomes were: perinatal mortality, large-for-gestational age, maternal weight gain during pregnancy, mean 24-hour BG in each trimester, and respiratory distress syndrome.

For details of included trials, see the tables of [Characteristics of included studies](#).

Excluded studies

We excluded seven trials ([Burkart 1988](#); [Collaborative 1993](#); [Coustan 1986](#); [Ignatova 2007](#), [Laatikainen 1987](#); [Murphy 2011](#); [Zoupas 1991](#)). [Burkart 1988](#) excluded participants from analysis if normoglycaemia was not achieved. [Collaborative 1993](#) compared conventional with intensive therapy, so was the wrong comparison. [Coustan 1986](#) did not report at what gestation the women recruited in pregnancy commenced therapy, and some women were recruited up to a year pre-conceptually making assessment of treatment effects difficult. [Ignatova 2007](#) is probably not a randomised trial as participants were 'divided' into two groups. [Laatikainen 1987](#) recruited 30 women, nine declined the allocated CSII intervention, no woman declined MDI. Only measures of retinopathy were reported. [Murphy 2011](#) did not evaluate CSII and MDI; they carried out a two-arm cross-over trial comparing closed-loop versus conventional CSII. [Zoupas 1991](#) is a trial registered on the Oxford Database of Perinatal Trials that remains unpublished, no information is available on trial methodology or outcomes and attempts to contact the author have been unsuccessful. For further details see [Characteristics of excluded studies](#).

Risk of bias in included studies

See [Figure 2](#) and [Figure 3](#).

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

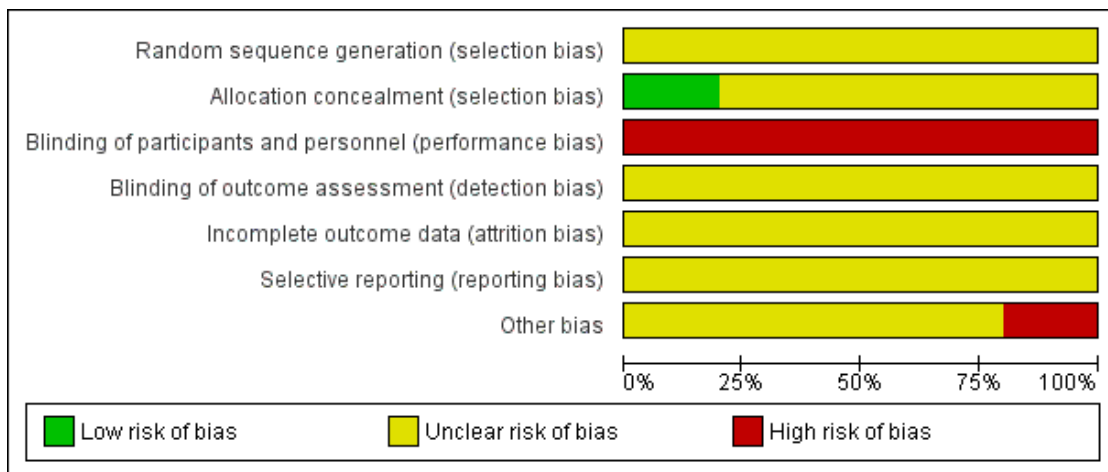


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Botta 1986	?	?	-	?	?	?	?
Carta 1986	?	?	-	?	?	?	?
Mello 2005	?	?	-	?	?	?	?
Nosari 1993	?	+	-	?	?	?	-
Trossarelli 1984	?	?	-	?	?	?	?

Allocation

Nosari 1993 used sealed envelopes to conceal allocation of their participants, a method at low risk of bias. However, the risk of bias for method of randomisation is unclear as this is not reported. All other trials had unclear risk of selection bias for both random sequence generation and allocation concealment. Botta 1986 reported only that their participants were “divided randomly”. Carta 1986 do not make clear their randomisation procedure, stating only that participants were randomly assigned to either CSII or MDI. They also included in their group two women who were receiving CSII preconceptually and prior to randomisation. Mello 2005 and Trossarelli 1984 are abstracts and therefore provide only short descriptions of the methods. Attempts to contact the authors for clarification of methods and results have been unsuccessful.

Blinding

Blinding of the type of intervention from clinician and participant for the trials is not possible because of the nature of the study, placing studies at high risk of bias. Outcome assessors could however be blinded to the intervention, though this was not reported by any of the trials, so the risk of bias is unclear.

Incomplete outcome data

All trials had unclear risk of attrition bias. The numbers of women included in analysis across pregnancy comparing maternal 24-hour mean glucose and mean HbA1c varied in Carta 1986 from 13 to 15 in the CSII group and from eight to 14 in the MDI group. Carta 1986 only report that 15 women with type 1 and 14 women with type 2 diabetes were included (plus 10 non-diabetic controls). Carta 1986 do not report any withdrawals or analysis exclusions. Similarly, Nosari 1993 only reported the number of women randomised (31 women who had 32 pregnancies during the study period). The number of women included in each table of results presented (16 MDI and 16 CSII) suggests no attrition, apart from for the maternal and fetal or neonatal complications table. Follow-up of study participants continued into the early postnatal period and there were no losses to follow-up. Insufficient information is provided by Mello 2005 and Trossarelli 1984 to draw conclusions regarding attrition. No information regarding attrition was reported by Botta 1986.

Selective reporting

Outcomes were not prespecified by any of the included trials, therefore it is possible that selective reporting could have taken place. Mello 2005 although eligible and therefore included in this review, does not report data in a format that can be used within the meta-

analysis.

Other potential sources of bias

All trials were small, with limited reporting of methods. Due to this, they were judged to be at unclear of high risk of bias. Additionally, Nosari 1993 describes the study population as highly motivated, and therefore arguably a biased sample and not a generalisable population. This was judged to introduce high risk of bias.

Effects of interventions

See: [Summary of findings for the main comparison CSII versus MDI: maternal outcomes](#); [Summary of findings 2 CSII versus MDI: infant outcomes](#)

Results from one trial, Carta 1986, were presented as type 1 and 2 diabetes. For most outcomes (excluding weight gain), we combined these results for analysis to ease comparison between the trials. Nosari 1993 and Trossarelli 1984 expressed their mean results with standard errors (SE); these were converted to standard deviations (SD) to enable analysis in Review Manager (RevMan 2014). For the purposes of the meta-analysis, CSII was classified as the intervention group and MDI as the control.

Primary outcomes

There were no differences between CSII and MDI in the primary outcomes reported in the included studies: **caesarean section** (risk ratio (RR) 1.09, 95% confidence interval (CI) 0.66 to 1.77; three trials, 71 women, [Analysis 1.2, evidence graded very low](#)), **large-for-gestational age** (RR 4.15, 95% CI 0.49 to 34.95; three trials, 73 infants; [Analysis 1.4; evidence graded very low](#)), and **perinatal mortality** (RR 2.33, 95% CI 0.38 to 14.32; four trials, 83 infants, [Analysis 1.5, evidence graded very low](#)).

Hypertensive disorders of pregnancy and **development of type 2 diabetes** were not reported for mothers in the included studies. A **composite outcome** of serious neonatal outcomes, and neurosensory disability were not reported for infants in the included studies.

Secondary outcomes

Maternal outcomes

There was no evidence of differences between CSII and MDI in the maternal secondary outcomes reported. This may reflect the few outcomes and participants included in the limited number of small trials we were able to include. No differences were found in:

maternal weight gain during pregnancy (mean difference (MD) 0.52, 95% CI -1.12 to 2.17; three trials, 51 women; [Analysis 1.10](#)), **24-hour mean BG** in each trimester (first trimester: MD 0.12, 95% CI -7.19 to 7.43; three trials, 67 women; [Analysis 1.11](#); second trimester: MD 1.77, 95% CI -5.02 to 8.56; three trials, 73 women; [Analysis 1.12](#); third trimester: MD 0.08, 95% CI -5.57 to 5.72; three trials, 69 women; [Analysis 1.13](#)), **mean maternal HbA1c** in each trimester (first trimester: MD -0.20, 95% CI -2.13 to 1.73; one trial, 32 women; [Analysis 1.14](#); second trimester: MD 0.70, 95% CI -2.29 to 3.69; one trial, 32 women; [Analysis 1.15](#); third trimester: MD 0.10, 95% CI -2.38 to 2.58; one trial, 32 women; [Analysis 1.16](#)), **maternal hypoglycaemia** (RR 3.00, 95% CI 0.35 to 25.87; two trials, 61 women; [Analysis 1.17](#)), and **maternal hyperglycaemia** (RR 7.00, 95% CI 0.39 to 125.44; two trials, 61 women; [Analysis 1.18](#)).

The included studies did not report several GRADE outcomes: **perineal trauma**, **return to pre-pregnancy weight**, **postnatal depression**, **induction of labour**. Many maternal secondary outcomes were also not reported: **placental abruption**, **postpartum haemorrhage**, **postpartum infection**, **adherence to the intervention**, **behaviour changes associated with the intervention**, **relevant biomarker changes associated with the intervention** (e.g. adiponectin, free fatty acids, triglycerides, high-density lipoproteins, low-density lipoproteins, insulin), **sense of well-being and quality of life**, **views of the intervention**, **breast-feeding** (e.g. at discharge, six weeks postpartum), **use of additional pharmacotherapy**, **maternal mortality**, **body mass index (BMI)**, **gestational diabetes mellitus in a subsequent pregnancy**, **type I diabetes**, **impaired glucose tolerance**, and **cardiovascular health**.

Infant outcomes

In two trials, with a total of 61 infants, CSII was associated with an increase in **mean birthweight** compared with MDI of borderline statistical significance (MD 220.56 g, 95% CI -2.09 g to 443.20 g; $P = 0.05$; [Analysis 1.27](#)), however, the large CI and the lack of a difference in **macrosomia** rate (RR 3.20, CI 0.14 to 72.62; two trials, 61 infants suggests uncertainty; [Analysis 1.25](#)). **Large-for-gestational age** (see primary outcomes) and **small-for-gestational age** (average RR 1.40, 95% CI 0.10 to 18.71; $I^2 = 31\%$; two trials, 61 infants; [Analysis 1.26](#)), suggests uncertainty of effect. No significant differences were found in: **gestation at delivery** (MD -1.18, 95% CI -2.92 to 0.57; three trials, 71 infants; [Analysis 1.21](#)), **preterm birth < 37 weeks' gestation** (RR 0.77, 95% CI 0.18 to 3.24; three trials, 71 infants; [Analysis 1.22](#)), **preterm birth < 32**

weeks' gestation (RR 0.33, 95% CI 0.01 to 7.62; three trials, 71 infants; [Analysis 1.23](#)), **neonatal hypoglycaemia** (RR 1.00, 95% CI 0.07 to 14.64; one trial, 32 infants; [Analysis 1.30](#); *evidence graded very low*), **respiratory distress syndrome** (RR 3.00, 95% CI 0.13 to 68.57; two studies, 44 infants; [Analysis 1.29](#)), **neonatal hyperbilirubinaemia** (RR 0.33, 95% CI 0.02 to 6.65; one study, 10 infants; [Analysis 1.31](#)), and **fetal anomaly** (RR 1.07, 95% CI 0.07 to 15.54; two trials, 61 infants; [Analysis 1.32](#)).

There were no data reported on many important infant outcomes. GRADE outcomes not reported were: **adiposity**, and **diabetes**. Other neonatal and infant secondary outcomes not reported were: **stillbirth**, **neonatal mortality**, **head circumference and z score**, **length and z score**, **ponderal index**, **shoulder dystocia**, **bone fracture nerve palsy**, **polycythaemia**, and **relevant biomarker changes associated with the intervention** (e.g. cord c peptide, cord insulin). Outcomes from later infant and childhood follow-up were not reported in any of the trials, thus the following outcomes were not reported: **weight and z scores**, **height and z scores**, **head circumference and z scores**, **adiposity** (e.g. as measured by BMI, skinfold thickness), **blood pressure**, **type I diabetes**, **type 2 diabetes**, **impaired glucose tolerance**, **dyslipidaemia or metabolic syndrome**, and **educational achievement**. Follow-up into adulthood was also not carried out, so the following outcomes were not reported: **weight**, **height**, **adiposity** (e.g. as measured by BMI, skinfold thickness), **cardiovascular health** (as defined by trialists, including BP, hypertension, cardiovascular disease, metabolic syndrome), **type I diabetes**, **type 2 diabetes**, **impaired glucose tolerance**, **dyslipidaemia or metabolic syndrome**, and **employment**, **education and social status/achievement**.

Health service use

The only outcome reported for use of healthcare resources was **length of postnatal stay**, which indicates no difference between groups including a small sample of women (MD 9.40, CI -6.04 to 24.84; one trial, 10 women; [Analysis 1.34](#)).

Other outcomes measuring health service use and cost not reported were: **number of hospital or health professional visits** (e.g. midwife, obstetrician, physician, dietitian, diabetic nurse), **number of antenatal visits or admissions**, **length of antenatal stay**, **neonatal intensive care unit admission**, **length of postnatal stay (baby)**, **costs to families associated with the management provided**, **costs associated with the intervention**, **cost of maternal care**, and **cost of offspring care**.

ADDITIONAL SUMMARY OF FINDINGS [\[Explanation\]](#)

Continuous subcutaneous insulin infusion (CSII) versus multiple daily injections (MDI) of insulin for pregnant women with diabetes					
Patient or population: infants of pregnant women with diabetes Setting: 4 studies in Italy Intervention: GRADE CSII Comparison: MDI					
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with MDI	Risk with GRADE CSII			
Large-for-gestational age	Study population		RR 4.15 (0.49 to 34.95)	73 (3 RCTs)	⊕○○○ VERY LOW ¹²
	0 per 1000	0 per 1000 (0 to 0)			
Perinatal mortality (stillbirth and neonatal mortality)	Study population		RR 2.33 (0.38 to 14.32)	83 (4 RCTs)	⊕○○○ VERY LOW ¹²
	24 per 1000	55 per 1000 (9 to 341)			
Mortality or morbidity composite				(0 studies)	outcome not reported
Neonatal hypoglycaemia	Study population		RR 1.00 (0.07 to 14.64)	32 (1 RCT)	⊕○○○ VERY LOW ²³
	63 per 1000	63 per 1000 (4 to 915)			
Adiposity (infant)				(0 studies)	outcome not reported
Type 1 and type 2 diabetes (infant)				(0 studies)	outcome not reported

Neurosensory disability	(0 studies)	outcome 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 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 All studies contributing data had design limitations.

² Wide confidence interval crossing the line of no effect, small sample size and few events.

³ One study with design limitations.

DISCUSSION

Conventionally, insulin has been administered subcutaneously in the form of a basal/bolus regimen, known as multiple daily injections (MDI). This method consists of pre-meal boluses of short-acting insulin and a later evening basal injection of long-acting insulin, usually given with pen injection devices. An alternative insulin administration method is the continuous subcutaneous insulin infusion pump (CSII). Modern pumps are small and lightweight, different basal rates can be preset and boluses given as required and a recent advance is the development of the tubing-free pump in which the reservoir and integrated infusion set adhere to the skin (patch pump). Potentially, CSII may reduce the risk of hypoglycaemia and ensure a more consistent blood glucose level, leading to a reduction in risk of adverse perinatal outcomes, however CSII was associated with a greater mean birthweight in the two trials reporting this outcome and although there was no significant difference in risk of macrosomia in one small trial, the point estimate suggests MDI may convey greater benefit.

At present, the insulin administration method used by most women is driven by their own and their medical teams' preferences and with what is available in a particular area of the country, rather than evidence of effectiveness. Given that funding for pump therapy may come from a variety of sources: personal, hospital or community, funding influences availability of CSII pumps for many women. Disappointingly none of the trials assessed the economic implications of CSII versus MDI use and only one reported any measure of health service resource use, therefore this is an area that requires investigation in the future.

Because theoretically CSII should result in less fluctuation in glucose level, some women may be offered CSII pumps as an alternative to MDI, particularly if their diabetes is difficult to control. The majority of women in many countries have no choice in how they administer insulin however, and this may be due to the lack of good quality evidence indicating superiority of one method of insulin administration over another. Large high-quality trials are therefore needed that evaluate the important outcomes indicated in this review, particularly the unexpected finding of increased mean birthweight with CSII use compared to MDI. The population included in future trials should include women with gestational diabetes mellitus (GDM), as well as pre-existing diabetes, those recruited should as far as possible reflect the general obstetric population of women with diabetes (rather than just motivated women or women with difficult to treat diabetes) and reporting of methods and findings should be comprehensive and transparent. As all the trials were single-centre and undertaken in Italy, generalisability of findings to other populations may be inappropriate, therefore multi-centre trials or trials in centres with multi-ethnic populations would be helpful.

Summary of main results

This review identified five small trials, with 153 women and 154 pregnancies. There were no clear differences found in any of the primary outcomes reported between CSII and MDI in the included trials: caesarean section, large-for-gestational age, and perinatal mortality. There were also no clear differences for the following secondary outcomes reported: maternal weight gain during pregnancy, maternal 24-hour mean blood glucose and mean HbA1c in each trimester, maternal hypoglycaemia and hyperglycaemia, gestational age at delivery, preterm birth < 37 weeks' gestation, preterm birth < 32 weeks' gestation, Apgar score less than seven at five minutes, macrosomia, small-for-gestational age, mean birthweight, respiratory distress syndrome, neonatal hypoglycaemia, neonatal hyperbilirubinaemia, and fetal anomaly.

In two trials, including a total of 61 infants, CSII was associated with an increase in mean birthweight compared with MDI. However, this result was not repeated for macrosomia rate or large-for-gestational age, suggesting uncertainty in effect.

Many important outcomes were not reported, including most GRADE outcomes: hypertensive disorders, maternal development of type 2 diabetes, induction of labour, perineal trauma, return to pre-pregnancy weight, postnatal depression, mortality or morbidity composite, adiposity, and subsequent offspring type 1 and type 2 diabetes. There was no longer-term follow-up of the infants in these studies. Information on health service use is also lacking, with length of postnatal stay reported in only one study of 10 women.

Overall completeness and applicability of evidence

The trials included are small and include few women. Three were undertaken in the 1980s, one in the 1990s and since this time pump technology has advanced. Therefore, adequately powered trials that report all outcomes suggested by this review to evaluate patch pumps compared with MDI and more conventional CSII with MDI or use a multi-factorial approach are required.

There were no trials of appropriate methodological quality that assessed the use of MDI versus CSII for women with GDM. Prevalence of GDM is increasing and these women may require insulin; this is a group of women who should be included in future trials.

Quality of the evidence

The trials included in this review were small, with few participants, the quality of reporting was poor and therefore generally risk of bias was unclear. It is not possible to blind participants or clinicians to intervention allocation in trials such as those in this review, however outcome assessors can be blinded and this was not reported. We do not know if the women who participated were representative of the general population of women with diabetes,

and therefore if the results can be generalised, one trial [Nosari 1993](#) reported that their participants were 'highly motivated'. Researchers should try to ensure by using appropriate methods that their trial population reflects the general obstetric population of women with diabetes as closely as possible.

Most GRADE outcomes were not reported. For the GRADE outcomes that were reported, our assessment was that the evidence is *very low quality* (**caesarean section, large-for-gestational age, perinatal mortality, and neonatal hypoglycaemia**). This was due to design limitations in the included trials, small sample sizes in those studies contributing data, wide confidence intervals crossing both the line of no effect and the line of appreciable benefit and/or harm, and often few events. These judgements are shown in [Summary of findings for the main comparison](#) and [Summary of findings 2](#). We are therefore uncertain whether CSII or MDI improves outcomes for pregnant women with diabetes and their infants.

Potential biases in the review process

The assessment of risk of bias involves subjective judgements. This potential limitation is minimised by following the procedures in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)), with two or more review authors independently assessing studies and resolving any disagreement through discussion, and if required involving a third assessor in the decision. We undertook a comprehensive, systematic search of databases to reduce the potential for publication bias, without language or publication status restrictions.

Agreements and disagreements with other studies or reviews

Our finding, that the limited and potentially low-quality evidence prevents the drawing of meaningful conclusions regarding the effectiveness of one method of insulin administration over another in pregnancy for women requiring insulin supports the findings of another review ([Mukhopadhyay 2007](#)). [Mukhopadhyay 2007](#) suggests their results do not demonstrate a clear-cut benefit of CSII over MDI and that large randomised trials are required comparing newer pumps which use rapid acting insulin analogues with MDI. Similar to our recommendations, the authors suggest cost-effectiveness analyses are undertaken.

AUTHORS' CONCLUSIONS

Implications for practice

At present there are insufficient data to draw conclusions in relation to the effectiveness of one method of insulin administration over another. Both methods appear to have advantages and disadvantages, though these are often not reported by trials. Decisions regarding the use of different administration methods in the context of pregnancy should therefore be made according to individual needs and available resources.

Implications for research

Large multi-centre randomised, adequately powered trials are needed to assess the effectiveness of continuous subcutaneous insulin infusion compared with multiple daily injections for women with diabetes (GDM and pre-existing) in pregnancy who require insulin. It would be beneficial if outcomes were consistent across trials and included women's preferences. Further trials to assess the effects of pumps on birthweight and macrosomia rates are needed. Future trials should undertake longer-term follow-up of participants (women and their infants) as well as assessment of associated costs.

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For this update, we used the Cochrane Pregnancy and Childbirth core outcome set for reviews of diabetes in pregnancy, developed by the Cochrane Pregnancy and Childbirth Australasian satellite.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Botta 1986

Methods	“Randomly divided”.
Participants	10 women recruited from 8 weeks to ‘term’.
Interventions	CSII versus MDI.
Outcomes	Gestational age at birth, caesarean section, weight gain during pregnancy, preterm birth, hyperbilirubinaemia, and maternal days hospitalised
Notes	Single-centre trial in Italy.

<i>Risk of bias</i>		<i>Risk of bias</i>
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of the type of intervention from clinician and participant for the trials was not possible because of the nature of the study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of assessors not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported.
Selective reporting (reporting bias)	Unclear risk	Pre-specified outcomes not reported.
Other bias	Unclear risk	Small trial group, limited reporting.

Carta 1986

Methods	“Randomly assigned” no other information reported.
Participants	15 women with type 1 diabetes (13 on conventional insulin therapy, 2 on continuous insulin therapy) and 14 women with type 2 diabetes (4 were on oral hypoglycaemics, 10 diet-controlled). Recruitment occurred in the first trimester, 2 women allocated to CSII had already been using a CSII pump pre-conceptually

Interventions	CSII versus MDI. Participants were hospitalised initially in order to achieve optimal glycaemic control, diet was prescribed according to individual needs. A Microject MC 20 portable syringe pump was used with porcine insulin (Actrapid MC) 40 U/mL, adjustments were made to the dosage in order to obtain strict glycaemic control (fasting BG < 80 + 10 mg/dL, postprandial BG < 120 mg/dL). Participants randomised to the MDI dose were given Actrapid MC split into 4 boluses
Outcomes	Maternal and neonatal mortality, large-for-gestational age, fetal anomaly and hypoglycaemia, weight gain during pregnancy, mean 24-hour BG, mean HbA1c, gestational age at delivery, preterm birth, birthweight and rate of instrumental delivery
Notes	Single-centre trial in Italy. Participants and their neonates were followed up at delivery and for the first 2 days postnatally

<i>Risk of bias</i>			<i>Risk of bias</i>
Bias	Authors' judgement	Support for judgement	
Random sequence generation (selection bias)	Unclear risk	Not reported.	
Allocation concealment (selection bias)	Unclear risk	Not reported.	
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of the type of intervention from clinician and participant for the trials was not possible because of the nature of the study	
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of assessors not reported.	
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The numbers of women included in analysis across pregnancy comparing maternal 24-hour mean glucose and mean HbA1c varied from 13 to 15 in the CSII group and from 8 to 14 in the MDI group	
Selective reporting (reporting bias)	Unclear risk	Pre-specified outcomes not reported.	
Other bias	Unclear risk	Small trial group, limited reporting of methods.	

Mello 2005

Methods	“Randomly assigned”.
Participants	71 women with type 1 diabetes.
Interventions	MDI versus CSII.
Outcomes	Daily glucose levels, 24-hour glycaemic profiles, infant abdominal fat deposition
Notes	Raw and mean data not reported, therefore could not be included in the analysis

Risk of bias***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of the type of intervention from clinician and participant for the trials was not possible because of the nature of the study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of assessors not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported.
Selective reporting (reporting bias)	Unclear risk	Pre-specified outcomes not reported.
Other bias	Unclear risk	Single-centre trial in Italy, small trial group, limited reporting of methods

Nosari 1993

Methods	“Randomly allocated”, using sealed envelopes.
Participants	31 women with type 1 insulin-dependent diabetes included undergoing 32 pregnancies, 1 woman included twice for separate pregnancies. 4 women were recruited in the pre-conception period, 28 women recruited during their first trimester. The women were described as highly motivated and referred to their centre for intensive therapy
Interventions	Allocated either CSII or MDI. Microject MC 20 and Daedi B.V. portable battery-powered syringe infusion pumps, participants receiving MDI had 4 daily insulin injections (regular insulin at each meal and intermediate acting insulin at night, type of insulin used was not stated)

Nosari 1993 (Continued)

Outcomes	Maternal and neonatal mortality, large-for-gestational age, fetal anomaly and hypoglycaemia, mean 24-hour BG, mean HbA1c, gestational age at delivery, preterm birth, Apgar score < 7 at 5 minutes, respiratory distress syndrome, birthweight and rate of instrumental delivery
Notes	No losses to follow-up.

<i>Risk of bias</i>			<i>Risk of bias</i>
Bias	Authors' judgement	Support for judgement	
Random sequence generation (selection bias)	Unclear risk	Not reported.	
Allocation concealment (selection bias)	Low risk	Used sealed envelopes to conceal allocation of their participants	
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of the type of intervention from clinician and participant for the trials was not possible because of the nature of the study	
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of assessors not reported.	
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided.	
Selective reporting (reporting bias)	Unclear risk	Pre-specified outcomes not reported.	
Other bias	High risk	Small trial group, described as "highly motivated". Single-centre trial in Italy, limited reporting of methods	

Trossarelli 1984

Methods	"Randomly assigned".
Participants	12 women with type 1 diabetes.
Interventions	MDI versus CSII.
Outcomes	Perinatal mortality, large-for-gestational age, maternal weight gain during pregnancy, mean 24-hour BG in each trimester, and respiratory distress syndrome
Notes	Several data outcomes described as comparable rather than reported as statistics

<i>Risk of bias</i>		<i>Risk of bias</i>
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of the type of intervention from clinician and participant for the trials was not possible because of the nature of the study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of assessors not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported.
Selective reporting (reporting bias)	Unclear risk	Pre-specified outcomes not reported.
Other bias	Unclear risk	Not reported.

BG: blood glucose

CSII: continuous subcutaneous insulin infusion

HbA1c: glycated haemoglobin

MDI: multiple daily injection

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Burkart 1988	Exclusion of MDI group participants from analysis if normoglycaemia not achieved (number not reported)
Collaborative 1993	Wrong intervention: conventional versus intensive therapy, rather than CSII versus MDI. Women using CSII and MDI therapy included in the intensive therapy group
Coustan 1986	21 women randomised antenatally (1 randomised twice for separate pregnancies), gestation at randomisation not stated, therefore length of treatment may be inconsistent. 7 women randomised in the pre-conceptual period, conceiving between 2 weeks and 1 year. The differences in time to conceive and treatment length is likely to lead to inconsistency of treatment effects

(Continued)

Ignatova 2007	Probably not a randomised study: 41 women were “divided” into 2 groups. Number of women included in the study and by study group inconsistently reported (41 women included and 21 in each of the 2 groups)
Laatikainen 1987	30 women randomised, 9 declined CSII, so did not receive the allocated intervention and were reported as a separate group, thus potentially confounding the results
Murphy 2011	Wrong intervention: 2-arm cross-over trial comparing closed-loop versus conventional CSII
Zoupas 1991	No methods or data provided by trial authors, therefore assessment of the trial is not possible

CSII: continuous subcutaneous insulin infusion

MDI: multiple daily injection

Characteristics of ongoing studies [ordered by study ID]

Stewart 2014

Trial name or title	CLIP-03.
Methods	2-arm cross-over trial comparing closed-loop CSII overnight with not closed-loop (continuous glucose monitor and insulin pump but not closed-loop) CSII overnight
Participants	Pregnant women with type 1 diabetes, 8-24 weeks GA. Setting: UK.
Interventions	Closed-loop CSII overnight versus continuous glucose monitor and insulin pump but not closed-loop
Outcomes	Overnight time spent in the target glucose range (3.5-7.8 mmol/L), number of episodes of nocturnal hypoglycaemia, duration and outcome of events. Frequency and duration of use of the closed-loop system, users' responses (lifestyle change and diabetes self-management). Overnight time above and below target range, metabolic control, trends in CGM data
Starting date	01/04/2014.
Contact information	Dr Zoe Stewart.
Notes	This study may not be eligible for inclusion, because it does not compare CSII with MDI

Thompson 2014

Trial name or title	
Methods	2-arm randomised trial, comparing insulin pump with multiple daily insulin injection. Single-blind (outcome assessor). The information indicates that allocation is “randomized”, there is no description of the method
Participants	Pregnant women with type 1 or type 2 diabetes prior to pregnancy. First trimester, singleton pregnancy, receiving intensive insulin therapy of less than 100 unit of insulin per day Setting: Canada.
Interventions	Insulin pump versus multiple daily insulin injections.
Outcomes	Composite obstetric/perinatal morbidity or mortality, mean maternal HbA1c during pregnancy, number of episodes of severe hypoglycaemia
Starting date	April 2014.
Contact information	Dr David Thompson david.thompson@vch.ca
Notes	

CGM: continuous glucose monitor

CSII: continuous subcutaneous insulin infusion

GA: gestational age

HbA1c: glycated haemoglobin

MDI: multiple daily injection

DATA AND ANALYSES

Comparison 1. Continuous subcutaneous insulin infusion versus multiple daily injections

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hypertensive disorders of pregnancy (including pre-eclampsia, pregnancy-induced hypertension, eclampsia)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Caesarean section	3	71	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.66, 1.77]
3 Development of type 2 diabetes	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Large-for-gestational age	3	73	Risk Ratio (M-H, Fixed, 95% CI)	4.15 [0.49, 34.95]
5 Perinatal mortality	4	83	Risk Ratio (M-H, Fixed, 95% CI)	2.33 [0.38, 14.32]
6 Mortality or morbidity composite	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Neurosensory disability	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Induction of labour	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Perineal trauma	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Weight gain during pregnancy	3	51	Mean Difference (IV, Fixed, 95% CI)	0.52 [-1.12, 2.17]
11 Maternal 24-hour mean blood glucose (mg/dL) first trimester	3	67	Mean Difference (IV, Fixed, 95% CI)	0.12 [-7.19, 7.43]
12 Maternal 24-hour mean blood glucose (mg/dL) second trimester	3	73	Mean Difference (IV, Fixed, 95% CI)	1.77 [-5.02, 8.56]
13 Maternal 24-hour mean blood glucose (mg/dL) third trimester	3	69	Mean Difference (IV, Fixed, 95% CI)	0.08 [-5.57, 5.72]
14 Mean HbA1c first trimester	1	32	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-2.13, 1.73]
15 Mean HbA1c second trimester	1	32	Mean Difference (IV, Fixed, 95% CI)	0.70 [-2.29, 3.69]
16 Mean HbA1c third trimester	1	32	Mean Difference (IV, Fixed, 95% CI)	0.10 [-2.38, 2.58]
17 Maternal hypoglycaemia	2	61	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.35, 25.87]
18 Maternal hyperglycaemia	2	61	Risk Ratio (M-H, Fixed, 95% CI)	7.0 [0.39, 125.44]
19 Postnatal depression	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
20 Postnatal weight retention or return to pre-pregnancy weight	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
21 Gestational age at birth	3	71	Mean Difference (IV, Fixed, 95% CI)	-1.18 [-2.92, 0.57]
22 Preterm birth < 37 weeks' gestation	3	71	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.18, 3.24]
23 Preterm birth < 32 weeks' gestation	3	71	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.62]
24 Apgar score < 7 at 5 minutes	1	32	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
25 Macrosomia	2	61	Risk Ratio (M-H, Fixed, 95% CI)	3.2 [0.14, 72.62]
26 Small-for-gestational age	2	61	Risk Ratio (M-H, Random, 95% CI)	1.40 [0.10, 18.71]
27 Mean birthweight grams	2	61	Mean Difference (IV, Fixed, 95% CI)	220.56 [-2.09, 443.20]
28 Adiposity (infant)	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
29 Respiratory distress syndrome	2	44	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 68.57]
30 Neonatal hypoglycaemia	1	32	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 14.64]
31 Neonatal hyperbilirubinaemia	1	10	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.02, 6.65]

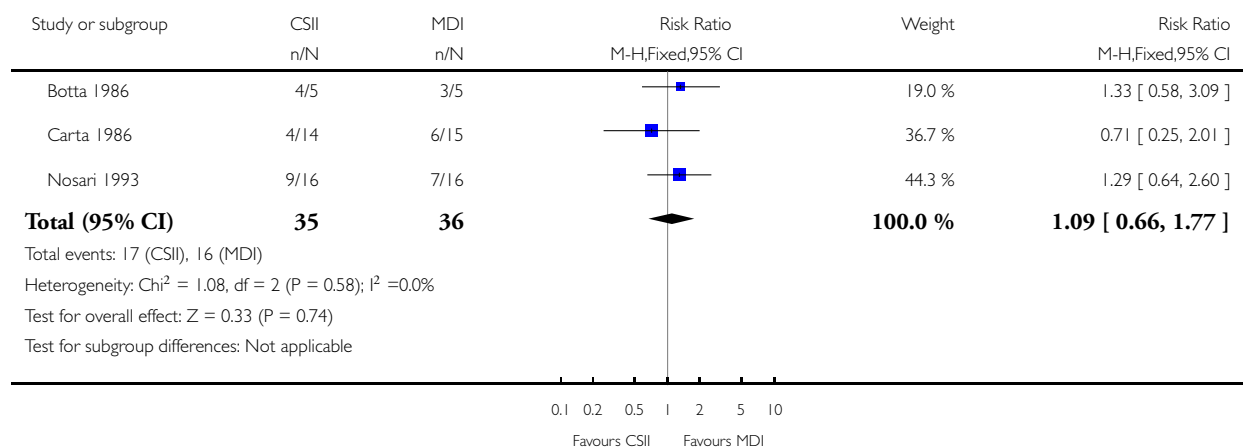
32 Fetal anomaly	2	61	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.07, 15.54]
33 Diabetes (infant)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
34 Length of postnatal stay (mother)	1	10	Mean Difference (IV, Fixed, 95% CI)	9.40 [-6.04, 24.84]

Analysis 1.2. Comparison 1 Continuous subcutaneous insulin infusion versus multiple daily injections, Outcome 2 Caesarean section.

Review: Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes

Comparison: 1 Continuous subcutaneous insulin infusion versus multiple daily injections

Outcome: 2 Caesarean section

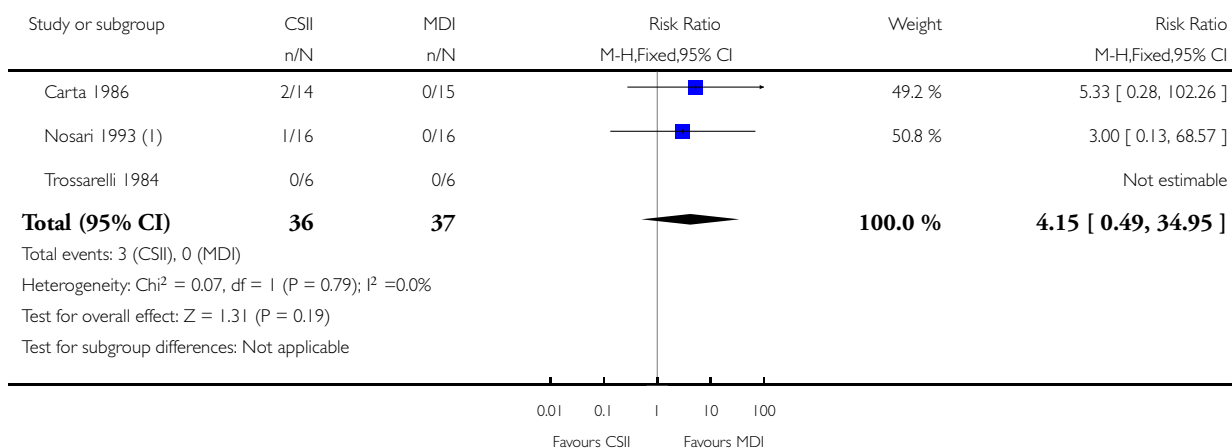


Analysis 1.4. Comparison 1 Continuous subcutaneous insulin infusion versus multiple daily injections, Outcome 4 Large-for-gestational age.

Review: Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes

Comparison: 1 Continuous subcutaneous insulin infusion versus multiple daily injections

Outcome: 4 Large-for-gestational age



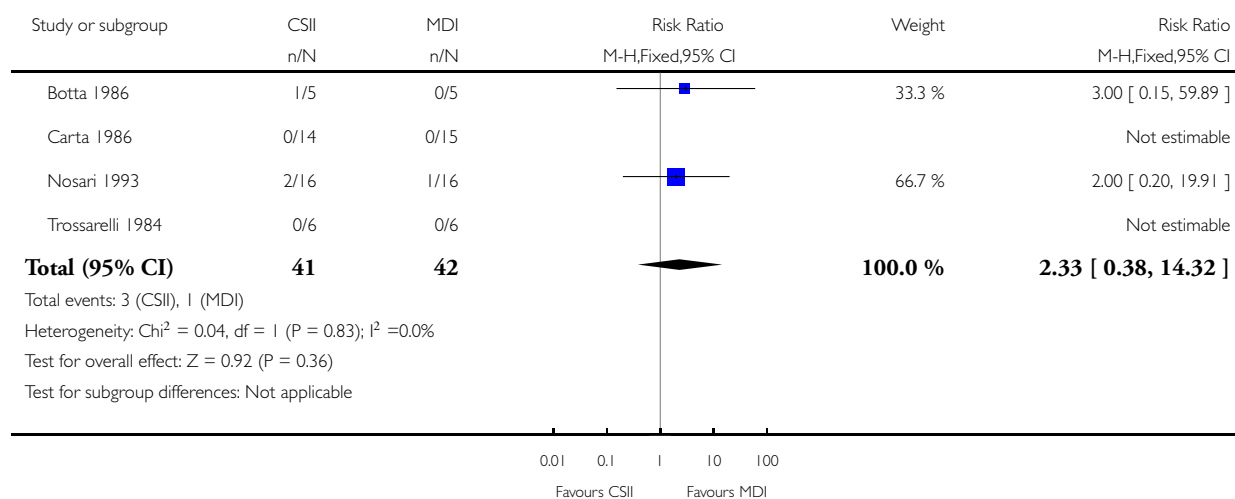
(1) birthweight above the 90th percentile

Analysis 1.5. Comparison 1 Continuous subcutaneous insulin infusion versus multiple daily injections, Outcome 5 Perinatal mortality.

Review: Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes

Comparison: 1 Continuous subcutaneous insulin infusion versus multiple daily injections

Outcome: 5 Perinatal mortality

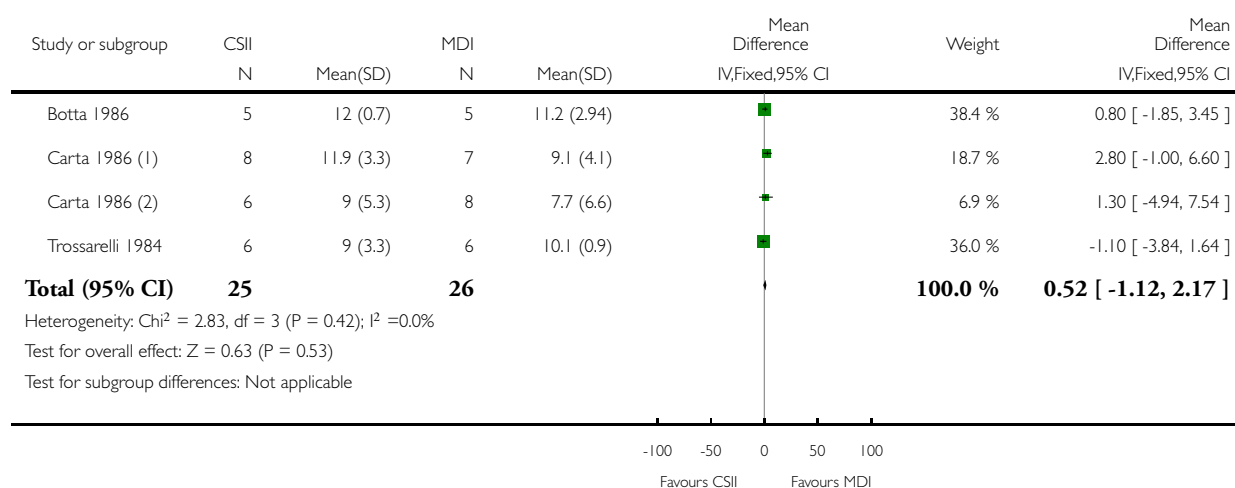


Analysis 1.10. Comparison 1 Continuous subcutaneous insulin infusion versus multiple daily injections, Outcome 10 Weight gain during pregnancy.

Review: Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes

Comparison: 1 Continuous subcutaneous insulin infusion versus multiple daily injections

Outcome: 10 Weight gain during pregnancy



(1) Type 1 diabetes

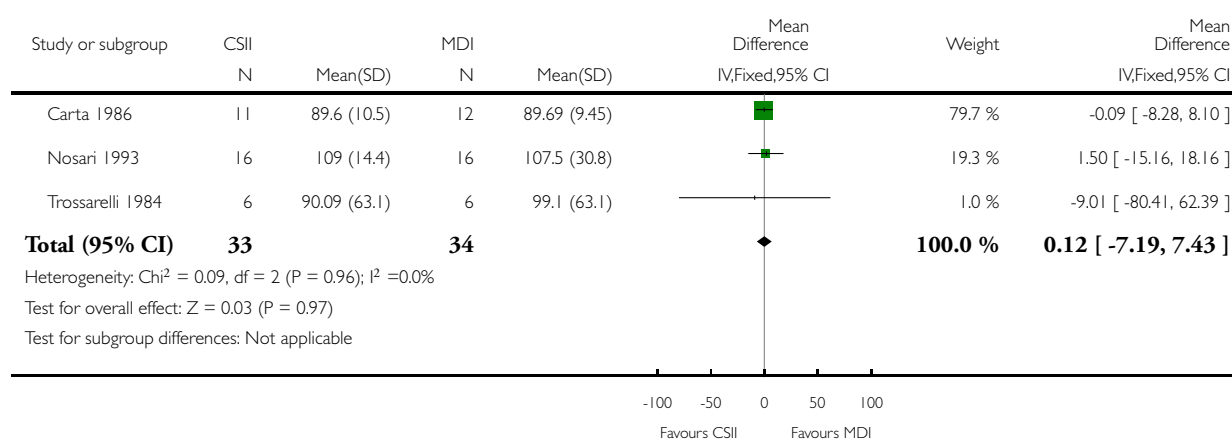
(2) Type 2 diabetes

Analysis 1.11. Comparison 1 Continuous subcutaneous insulin infusion versus multiple daily injections, Outcome 11 Maternal 24-hour mean blood glucose (mg/dL) first trimester.

Review: Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes

Comparison: 1 Continuous subcutaneous insulin infusion versus multiple daily injections

Outcome: 11 Maternal 24-hour mean blood glucose (mg/dL) first trimester

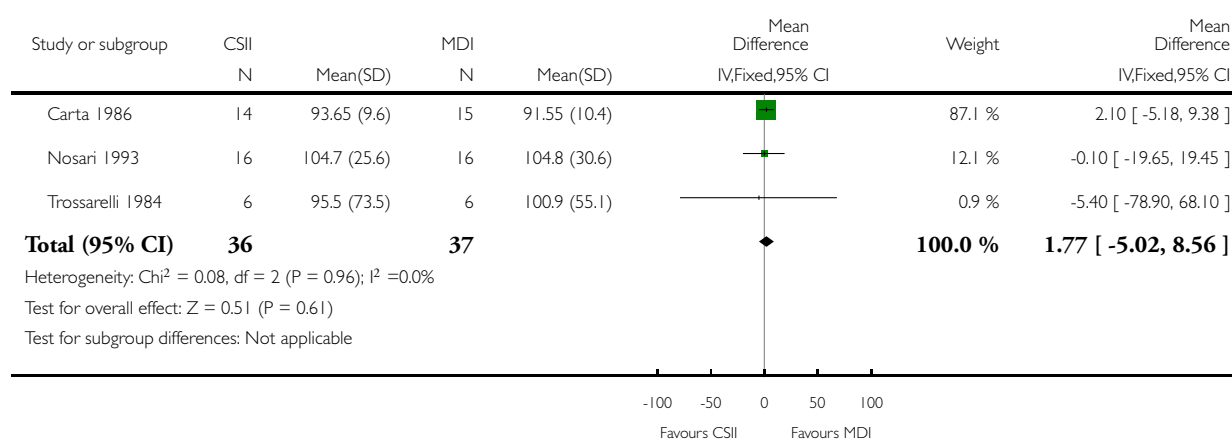


Analysis 1.12. Comparison 1 Continuous subcutaneous insulin infusion versus multiple daily injections, Outcome 12 Maternal 24-hour mean blood glucose (mg/dL) second trimester.

Review: Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes

Comparison: 1 Continuous subcutaneous insulin infusion versus multiple daily injections

Outcome: 12 Maternal 24-hour mean blood glucose (mg/dL) second trimester

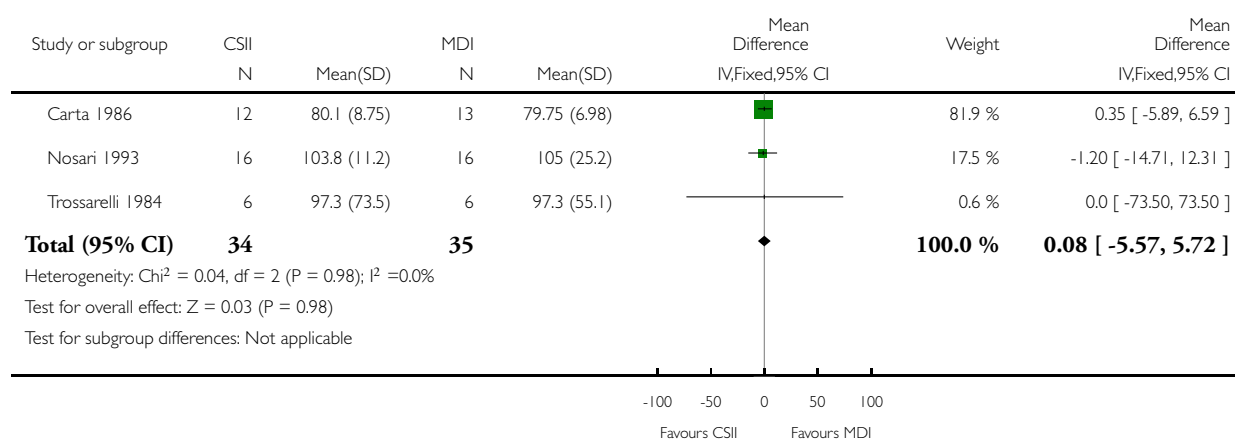


Analysis 1.13. Comparison 1 Continuous subcutaneous insulin infusion versus multiple daily injections, Outcome 13 Maternal 24-hour mean blood glucose (mg/dL) third trimester.

Review: Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes

Comparison: 1 Continuous subcutaneous insulin infusion versus multiple daily injections

Outcome: 13 Maternal 24-hour mean blood glucose (mg/dL) third trimester

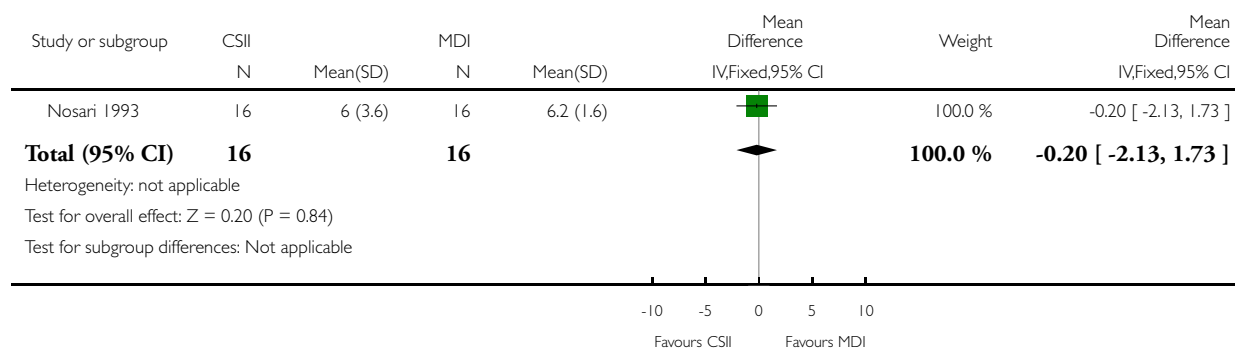


Analysis 1.14. Comparison 1 Continuous subcutaneous insulin infusion versus multiple daily injections, Outcome 14 Mean HbA1c first trimester.

Review: Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes

Comparison: 1 Continuous subcutaneous insulin infusion versus multiple daily injections

Outcome: 14 Mean HbA1c first trimester

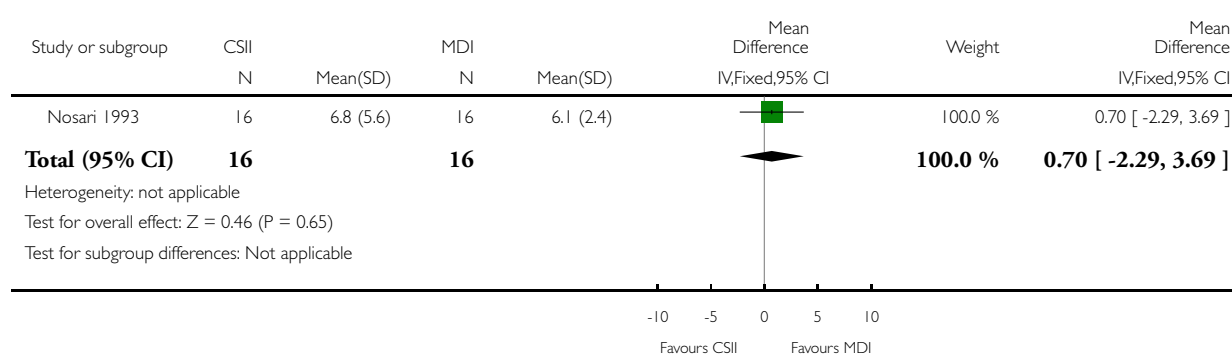


Analysis 1.15. Comparison 1 Continuous subcutaneous insulin infusion versus multiple daily injections, Outcome 15 Mean HbA1c second trimester.

Review: Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes

Comparison: 1 Continuous subcutaneous insulin infusion versus multiple daily injections

Outcome: 15 Mean HbA1c second trimester

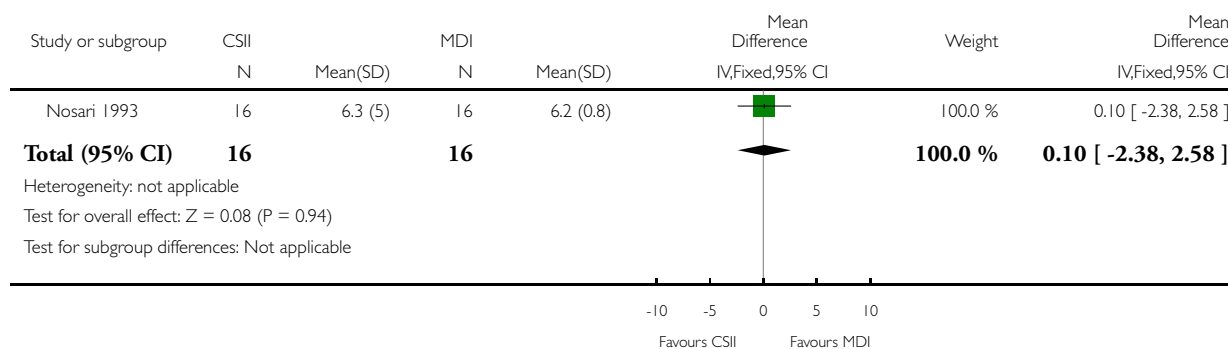


Analysis 1.16. Comparison 1 Continuous subcutaneous insulin infusion versus multiple daily injections, Outcome 16 Mean HbA1c third trimester.

Review: Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes

Comparison: 1 Continuous subcutaneous insulin infusion versus multiple daily injections

Outcome: 16 Mean HbA1c third trimester

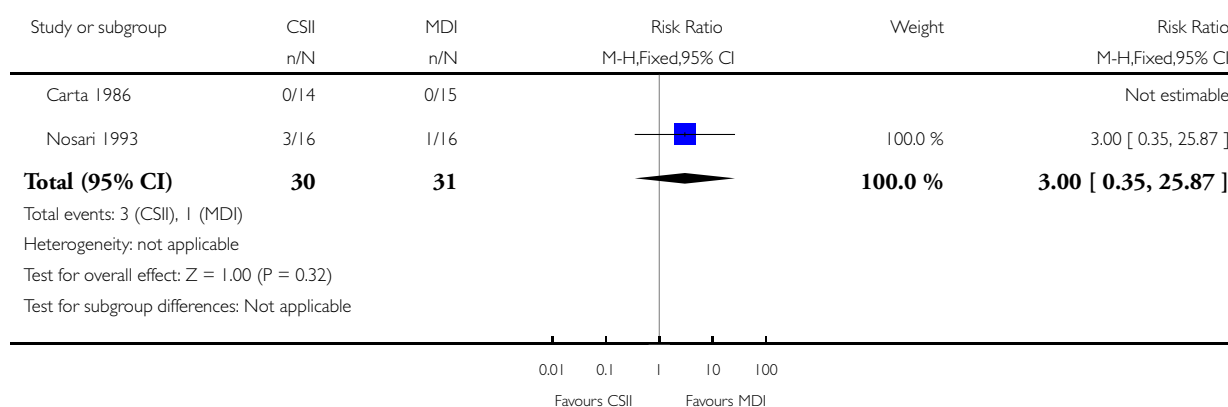


Analysis 1.17. Comparison 1 Continuous subcutaneous insulin infusion versus multiple daily injections, Outcome 17 Maternal hypoglycaemia.

Review: Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes

Comparison: 1 Continuous subcutaneous insulin infusion versus multiple daily injections

Outcome: 17 Maternal hypoglycaemia

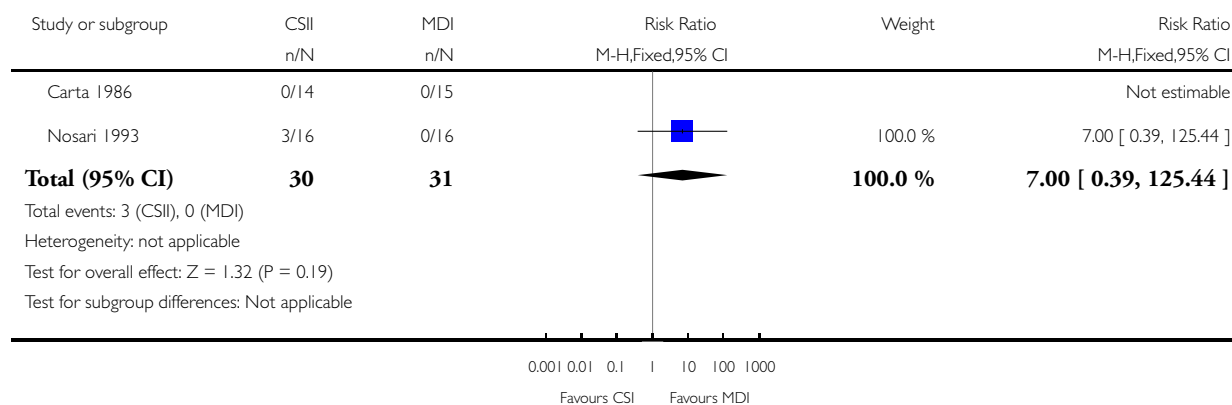


Analysis 1.18. Comparison 1 Continuous subcutaneous insulin infusion versus multiple daily injections, Outcome 18 Maternal hyperglycaemia.

Review: Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes

Comparison: 1 Continuous subcutaneous insulin infusion versus multiple daily injections

Outcome: 18 Maternal hyperglycaemia

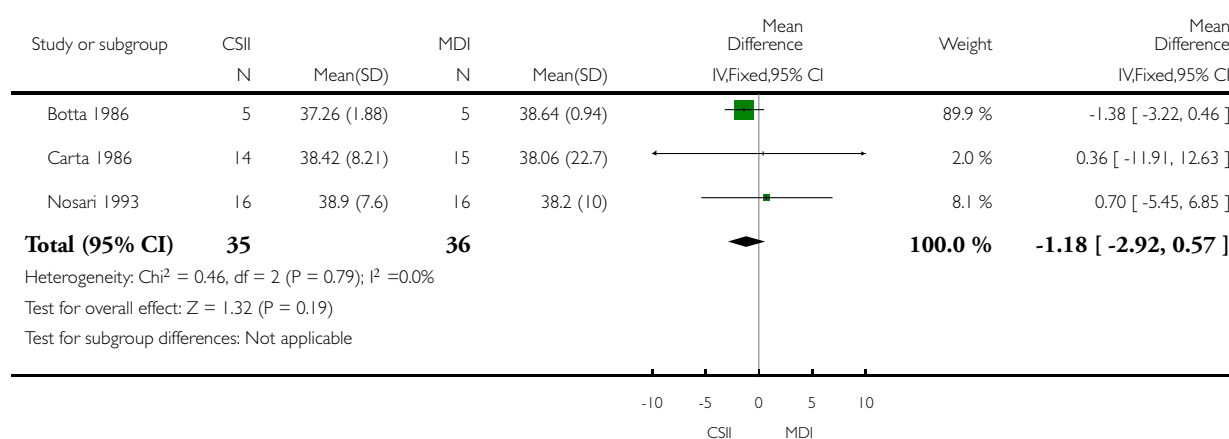


Analysis 1.21. Comparison 1 Continuous subcutaneous insulin infusion versus multiple daily injections, Outcome 21 Gestational age at birth.

Review: Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes

Comparison: 1 Continuous subcutaneous insulin infusion versus multiple daily injections

Outcome: 21 Gestational age at birth

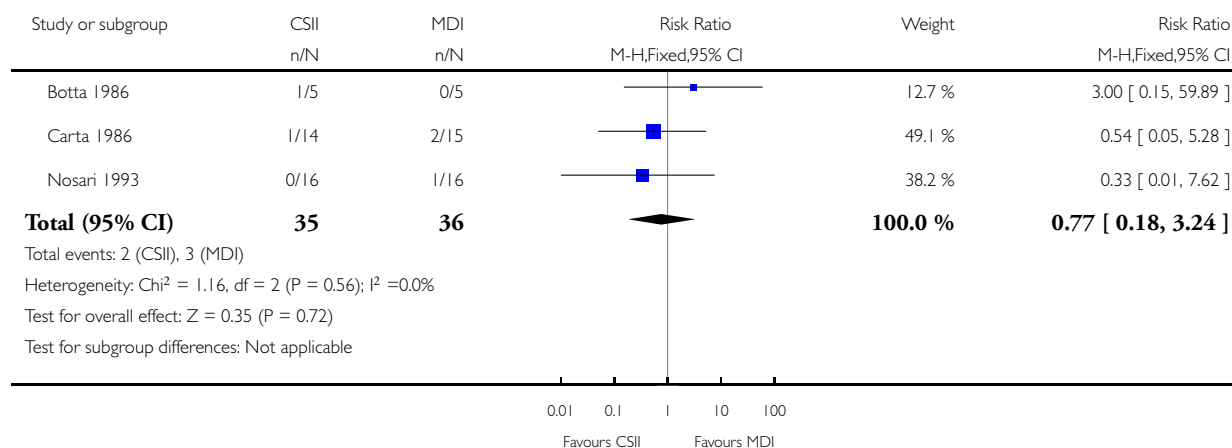


Analysis 1.22. Comparison 1 Continuous subcutaneous insulin infusion versus multiple daily injections, Outcome 22 Preterm birth < 37 weeks' gestation.

Review: Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes

Comparison: 1 Continuous subcutaneous insulin infusion versus multiple daily injections

Outcome: 22 Preterm birth < 37 weeks' gestation

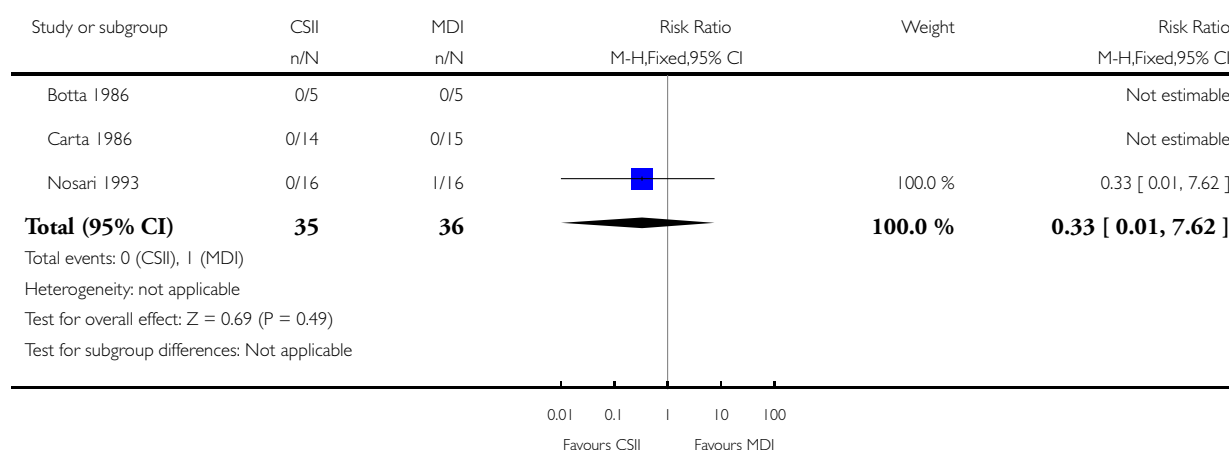


Analysis 1.23. Comparison 1 Continuous subcutaneous insulin infusion versus multiple daily injections, Outcome 23 Preterm birth < 32 weeks' gestation.

Review: Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes

Comparison: 1 Continuous subcutaneous insulin infusion versus multiple daily injections

Outcome: 23 Preterm birth < 32 weeks' gestation

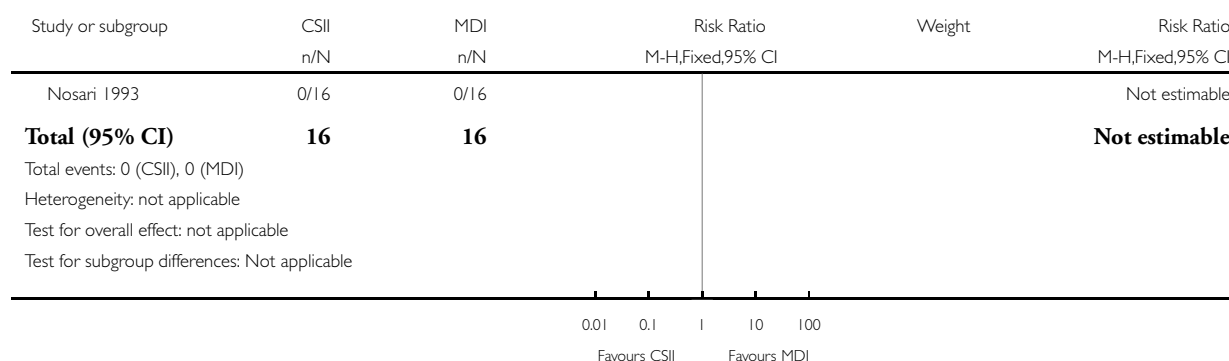


Analysis 1.24. Comparison 1 Continuous subcutaneous insulin infusion versus multiple daily injections, Outcome 24 Apgar score < 7 at 5 minutes.

Review: Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes

Comparison: 1 Continuous subcutaneous insulin infusion versus multiple daily injections

Outcome: 24 Apgar score < 7 at 5 minutes

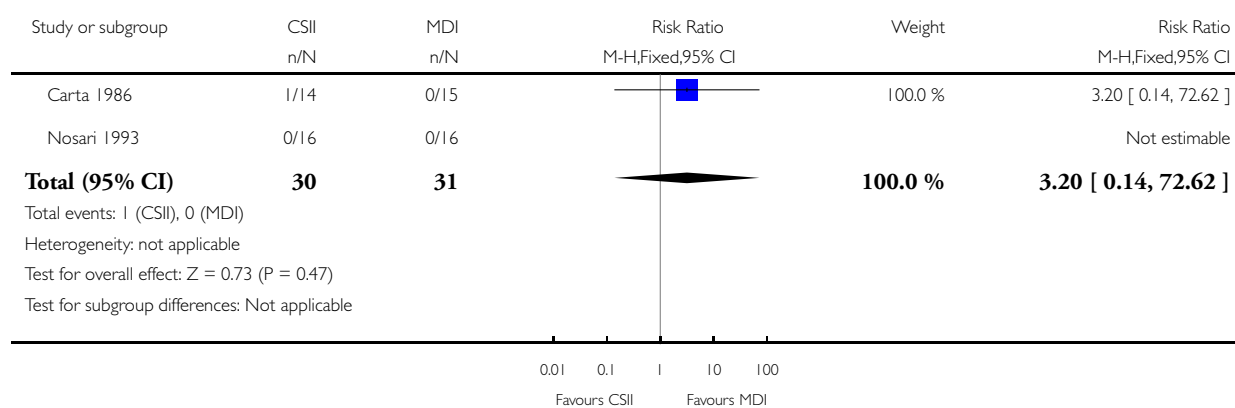


Analysis 1.25. Comparison 1 Continuous subcutaneous insulin infusion versus multiple daily injections, Outcome 25 Macrosomia.

Review: Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes

Comparison: 1 Continuous subcutaneous insulin infusion versus multiple daily injections

Outcome: 25 Macrosomia

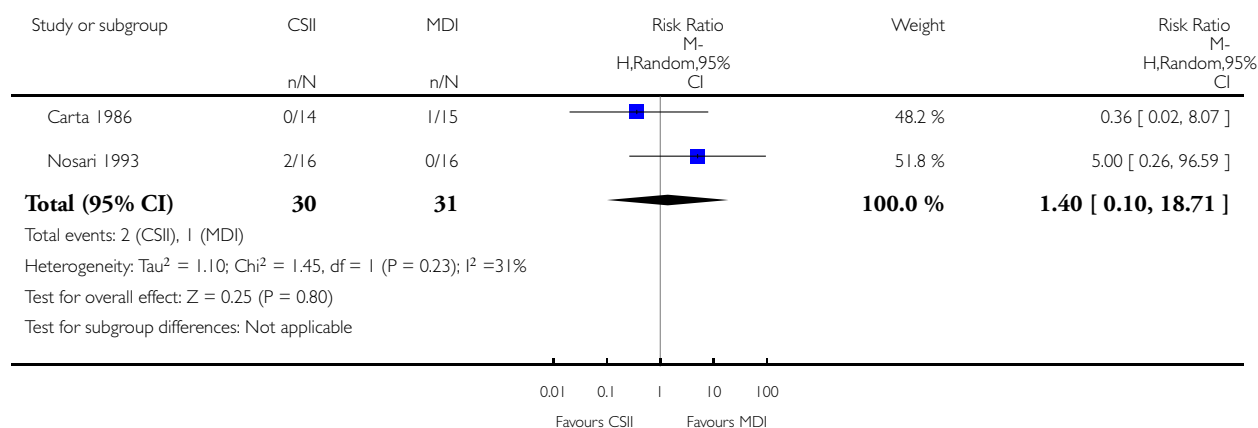


Analysis 1.26. Comparison 1 Continuous subcutaneous insulin infusion versus multiple daily injections, Outcome 26 Small-for-gestational age.

Review: Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes

Comparison: 1 Continuous subcutaneous insulin infusion versus multiple daily injections

Outcome: 26 Small-for-gestational age

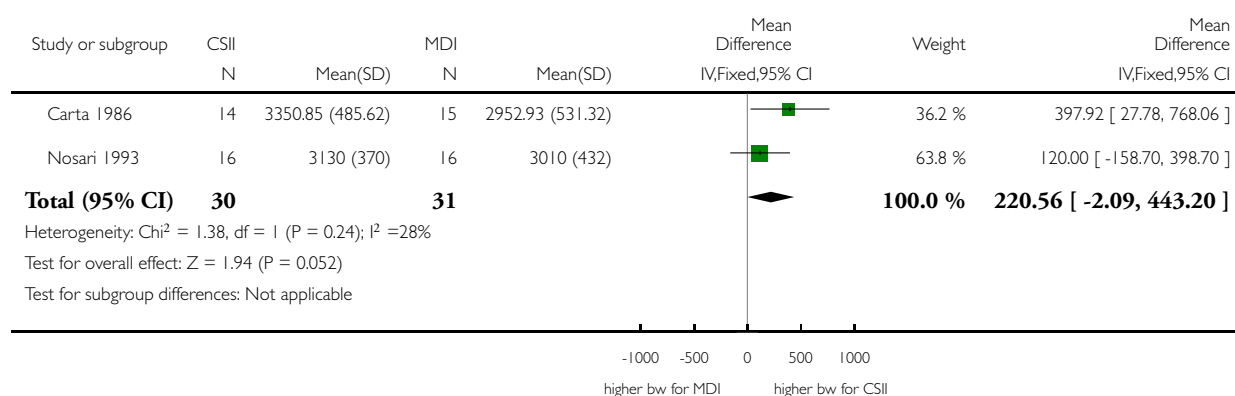


Analysis 1.27. Comparison 1 Continuous subcutaneous insulin infusion versus multiple daily injections, Outcome 27 Mean birthweight grams.

Review: Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes

Comparison: 1 Continuous subcutaneous insulin infusion versus multiple daily injections

Outcome: 27 Mean birthweight grams

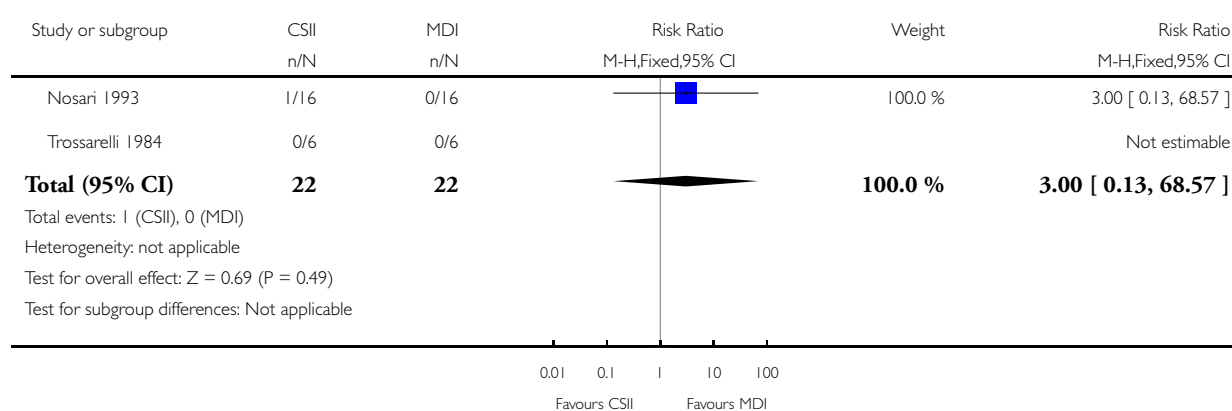


Analysis 1.29. Comparison 1 Continuous subcutaneous insulin infusion versus multiple daily injections, Outcome 29 Respiratory distress syndrome.

Review: Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes

Comparison: 1 Continuous subcutaneous insulin infusion versus multiple daily injections

Outcome: 29 Respiratory distress syndrome

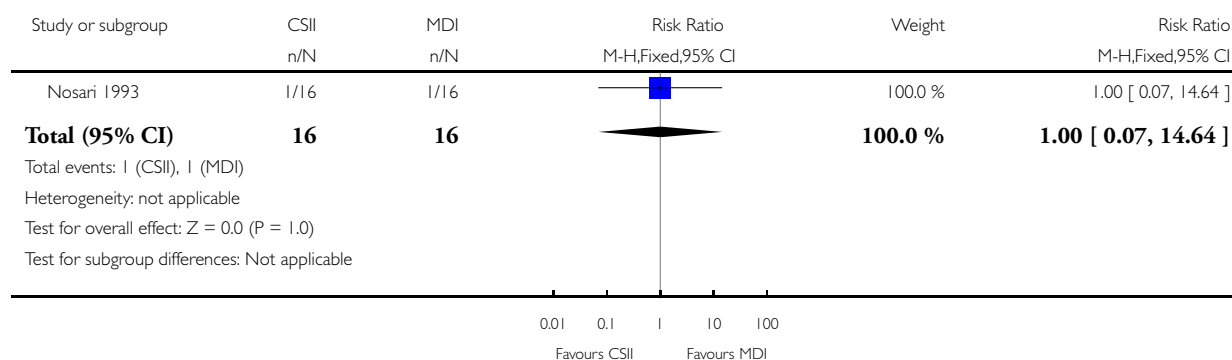


Analysis 1.30. Comparison 1 Continuous subcutaneous insulin infusion versus multiple daily injections, Outcome 30 Neonatal hypoglycaemia.

Review: Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes

Comparison: 1 Continuous subcutaneous insulin infusion versus multiple daily injections

Outcome: 30 Neonatal hypoglycaemia

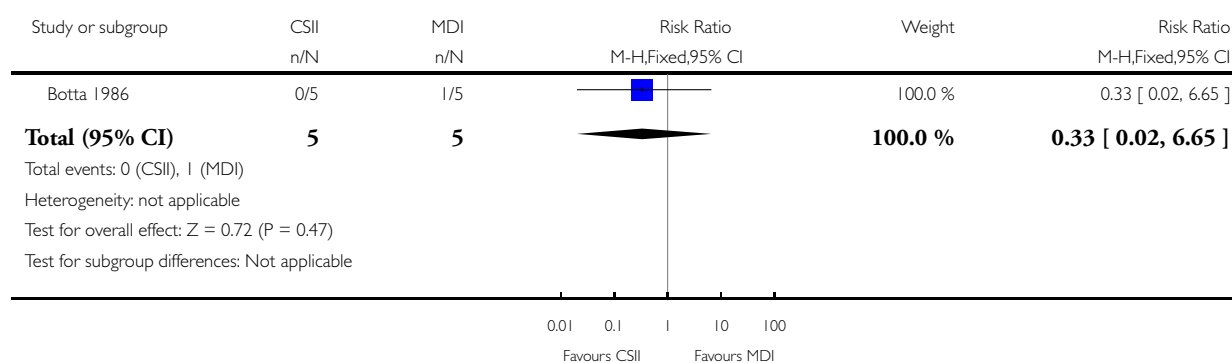


Analysis 1.31. Comparison 1 Continuous subcutaneous insulin infusion versus multiple daily injections, Outcome 31 Neonatal hyperbilirubinaemia.

Review: Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes

Comparison: 1 Continuous subcutaneous insulin infusion versus multiple daily injections

Outcome: 31 Neonatal hyperbilirubinaemia

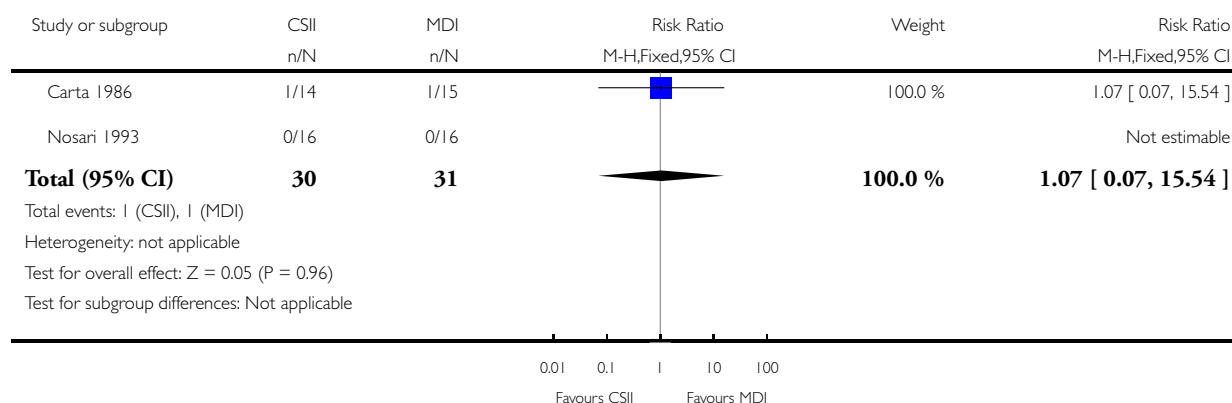


Analysis 1.32. Comparison 1 Continuous subcutaneous insulin infusion versus multiple daily injections, Outcome 32 Fetal anomaly.

Review: Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes

Comparison: 1 Continuous subcutaneous insulin infusion versus multiple daily injections

Outcome: 32 Fetal anomaly

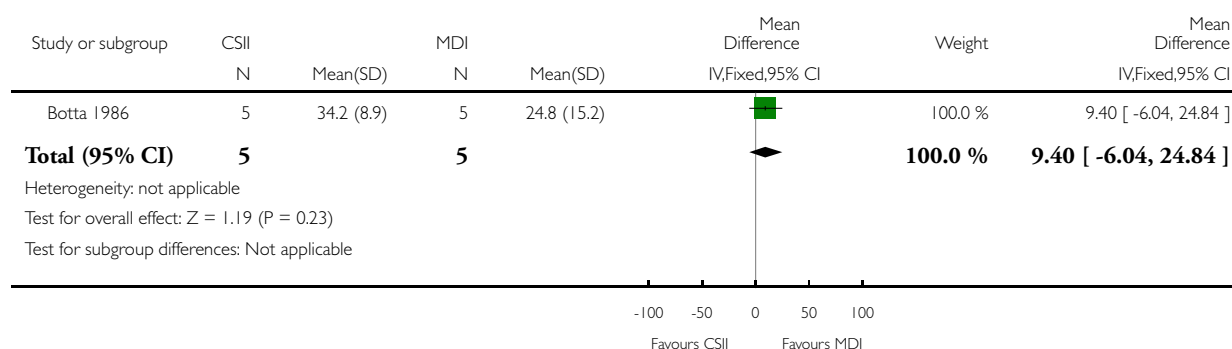


Analysis 1.34. Comparison 1 Continuous subcutaneous insulin infusion versus multiple daily injections, Outcome 34 Length of postnatal stay (mother).

Review: Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes

Comparison: 1 Continuous subcutaneous insulin infusion versus multiple daily injections

Outcome: 34 Length of postnatal stay (mother)



WHAT'S NEW

Last assessed as up-to-date: 31 March 2016.

Date	Event	Description
31 March 2016	New citation required but conclusions have not changed	No new studies included in this update.
31 March 2016	New search has been performed	Search updated and four new reports of three trials identified (Murphy 2011 ; Stewart 2014 ; Thompson 2014). One trial was excluded (Murphy 2011) and two are currently ongoing (Stewart 2014 ; Thompson 2014). Two 'Summary of findings' tables have been added in this update and the core outcome set for reviews of diabetes in pregnancy has been incorporated

HISTORY

Protocol first published: Issue 4, 2005

Review first published: Issue 3, 2007

Date	Event	Description
31 July 2011	New search has been performed	Search update. The updated search identified two new reports; Ignatova 2007 has been excluded, Trossarelli 1984 has been included. Two trials previously awaiting assessment (Botta 1986 ; Mello 2005) have been included. This updated review now includes five studies (involving 153 women and 154 pregnancies), the results and conclusions have not changed. Division and names of outcomes have been changed from main and additional, to primary and secondary. Primary outcomes are now macrosomia for the infant and operative birth for the mother. Economic evaluation has been added as a secondary outcome
1 September 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Diane Farrar drafted the review and update, assessed study quality, undertook data entry and analysis in Review Manager. Jane West assessed study quality and made comments and suggestions on drafts of the review and update. Derek Tuffnell assessed study quality and made comments and suggestions on drafts of the review and update. In the review update, Helen West assessed all trials for inclusion, prepared GRADE tables and commented on the draft.

DECLARATIONS OF INTEREST

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.

SOURCES OF SUPPORT

Internal sources

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

External sources

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

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For this update, we have used the Cochrane Pregnancy and Childbirth core outcome set for reviews of diabetes in pregnancy, developed by the Cochrane Pregnancy and Childbirth Australasian satellite.

We have added 'Summary of findings' tables and an assessment of the quality of the evidence using the GRADE approach.

'Return to pre-pregnancy weight' was added as a secondary outcome (long-term maternal outcomes) in the 2016 update.

INDEX TERMS

Medical Subject Headings (MeSH)

*Insulin Infusion Systems; *Pregnancy in Diabetics; Birth Weight; Diabetes Mellitus, Type 1 [*drug therapy]; Hypoglycemic Agents [*administration & dosage]; Injections, Subcutaneous; Insulin [*administration & dosage]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy