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Different intensities of glycaemic control for women with gestational diabetes mellitus (Review)

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Different intensities of glycaemic control for women with gestational diabetes mellitus

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A B S T R A C T

Background

Gestational diabetes mellitus (GDM) has major short- and long-term implications for both the mother and her baby. GDM is defined as a carbohydrate intolerance resulting in hyperglycaemia or any degree of glucose intolerance with onset or first recognition during pregnancy from 24 weeks' gestation onwards and which resolves following the birth of the baby. Rates for GDM can be as high as 25% depending on the population and diagnostic criteria used and rates are increasing globally. Risk factors associated with GDM include advanced maternal age, obesity, ethnicity, family history of diabetes, and a previous history of GDM, macrosomia or unexplained stillbirth. There is wide variation internationally in glycaemic treatment target recommendations for women with GDM that are based on consensus rather than high-quality trials.

Objectives

To assess the effect of different intensities of glycaemic control in pregnant women with GDM on maternal and infant health outcomes.

Search methods

We searched the Cochrane Pregancy and Childbirth Group's Trials Register (31 January 2016), ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP) (1 February 2016) and reference lists of the retrieved studies.

Selection criteria

We included one randomised controlled trial. Cluster-randomised and quasi-randomised controlled trials were eligible for inclusion.

Data collection and analysis

We used the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* for carrying out data collection, assessing study quality and analysing results. Two review authors independently assessed trial eligibility for inclusion, evaluated methodological quality and extracted data for the one included study. We sought additional information from one trial author but had no response. We assessed the quality of evidence for selected outcomes using the GRADE approach.

Main results

We included one Canadian trial of 180 women, recruited between 20 to 32 weeks' gestation, who had been diagnosed with GDM. Data from 171 of the 180 women were published as a conference abstract and no full report has been identified. The overall risk of bias of the single included study was judged to be unclear.

The included trial did not report on any of this review's primary outcomes. For the mother, these were **hypertension disorders of pregnancy** or **subsequent development of type 2 diabetes**. For the infant, our primary outcomes were (**perinatal (fetal and neonatal) mortality**; **large-for-gestational age**; **composite of death or severe morbidity** or later childhood **neurosensory disability**).

The trial did report data relating to some of this review's secondary outcomes. There was no clear difference in **caesarean section** rates for women assigned to using *strict* glycaemic targets (pre-prandial 5.0 mmol/L (90 mg/L) and at one-hour postprandial 6.7 mmol/L (120 mg/dL)) (28/85, 33%) when compared with women assigned to using *liberal* glycaemic targets (pre-prandial 5.8 mmol/L (103 mg/dL) and at one-hour postprandial 7.8 mmol/L (140 mg/dL)) (21/86, 24%) (risk ratio (RR) 1.35, 95% confidence interval (CI) 0.83 to 2.18, one trial, 171 women; *very low quality*). Using the GRADE approach, we found the quality of the evidence to be *very low* for **caesarean section** due to poor reporting of risk of bias, imprecision and publication bias. *Strict* glycaemic targets were associated with an increase in the **use of pharmacological therapy** (identified as the use of insulin in this study) (33/85; 39%) compared with *liberal* glycaemic targets (18/86; 21%) (RR 1.85, 95% CI 1.14 to 3.03; one trial, 171 women). CIs are wide suggesting imprecision and caution is required when interpreting the data. No other secondary maternal outcome data relevant to this review were reported. For the infant, there were no clear differences between the groups of women receiving *strict* and *liberal* glycaemic targets for **macrosomia** (birthweight greater than 4000 g) (RR 1.35, 95% CI 0.31 to 5.85, one trial, 171 babies); **small-for-gestational age** (RR 1.12, 95% CI 0.48 to 2.63, one trial, 171 babies); **birthweight** (mean difference (MD) -92.00 g, 95% CI -241.97 to 57.97, one trial, 171 babies) or **gestational age** (MD -0.30 weeks, 95% CI -0.73 to 0.13, one trial, 171 babies). **Adverse effects** data were not reported. No other secondary neonatal outcomes relevant to this review were reported.

Authors' conclusions

This review is based on a single study (involving 180 women) with an unclear risk of bias. The trial (which was only reported in a conference abstract) did not provide data for any of this review's primary outcomes but did provide data for a limited number of our secondary outcomes. There is insufficient evidence to guide clinical practice for targets for glycaemic control for women with GDM to minimise adverse effects on maternal and fetal health. Glycaemic target recommendations from international professional organisations for maternal glycaemic control vary widely and are reliant on consensus given the lack of high-quality evidence.

Further high-quality trials are needed, and these should compare different glycaemic targets for guiding treatment of women with GDM, assess both short-term and long-term health outcomes for women and their babies, include women's experiences and assess health services costs. Four studies are ongoing.

P L A I N   L A N G U A G E   S U M M A R Y

What is the most effective blood sugar range to guide treatment for women who develop gestational diabetes mellitus (GMD) in their pregnancy?

What is the issue?

Up to a quarter of pregnant women develop gestational diabetes mellitus (GDM) depending on their ethnicity and the diagnostic criteria used. GDM is evident as high blood sugar levels (hyperglycaemia) during pregnancy and is associated with an increased risk of developing high blood pressure (hypertension) and protein in the urine during pregnancy (pre-eclampsia). These women are more likely to have a caesarean birth, develop type 2 diabetes, postnatal depression, and cardiovascular disease later on in life. The high blood sugar levels that are associated with GDM often return to normal as soon as the baby is born, but women with GDM are at risk of again developing GDM in future pregnancies. Babies whose mothers have been diagnosed with GDM are at an increased risk of having a birthweight greater than 4000 g, increased risk of birth trauma because of their size and developing breathing difficulties after birth. The babies are also at risk of future obesity and type 2 diabetes.

Why is this important?

Women with GDM are treated with the aims of controlling high maternal blood sugar levels and reducing the risks of GDM for the mother and the baby. Blood sugar control is monitored by measuring blood sugar concentrations to ensure they are maintained within

a pre-defined level or range. The blood sugar results are usually obtained by the mother using a finger prick to collect a drop of her blood on a test strip, which is inserted into a small machine (a glucometer) that reads the sugar level of the blood on the test strip. The glucometer reading alerts the pregnant woman to her current blood sugar level and is used to guide her treatment. For example, how many units of insulin she requires before eating. However, it is currently unclear how to advise pregnant women with newly diagnosed GDM what is the most effective blood sugar range to aim for and guide treatment.

What evidence did we find?

We searched for evidence on 31 January 2016 and found one small randomised controlled trial (abstract only) that was of poor quality and involved 180 women from Canada.The trial compared two blood sugar ranges, one strict the other more liberal, and reported a very few health outcomes for the pregnant woman and her baby.

The trial did not provide any data for this review's main outcomes. For the woman, these related to the development of high blood pressure and protein in the urine during pregnancy, developing type 2 diabetes. For the baby, these outcomes related to death of the baby, increased birthweight, increased risk of birth trauma because of their size, and disability.

More women were on insulin in the strictly controlled group (but this result is based on very low quality evidence). No clear differences were reported for caesarian section rates. No other secondary outcome data for women with GDM relevant to this review were reported. No differences were reported for the number of babies that had a birthweight greater than 4000 g or were small-for-gestational age. No other secondary outcomes for the babies relevant to this review were reported.The study did not report on adverse events.

What does this mean?

This review found that there is not yet enough evidence from randomised controlled trials to determine the best blood sugar range for improving health for pregnant women with GDM and their babies. Four studies are ongoing but not yet complete. More high-quality studies are needed that compare different targets for blood sugar levels and assess both short-term and long-term health outcomes for women and their babies to guide treatment. Studies should include women's experiences and assess health services costs.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Intensity of glycaemic control for women with gestational diabetes mellitus - *strict* glycaemic targets versus *liberal* glycaemic targets
(Maternal outcomes)

Patient or population: Women with GDM
Setting: Canada
Intervention: Strict intensity of glycaemic control: preprandial: 5.0 mmol/L (90 mg/dL) and at one-hour postprandial: 6.7 mmol/L (120 mg/dL)
Comparison: Less strict glycaemic control: preprandial 5.8 mmol/L (104 mg/dL) and at one-hour postprandial 7.8 mmol/L (140 mg/dL)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with less strict glycaemic control	Risk with strict glycaemic control				
Hypertensive disorders of pregnancy			not estimable	(0 studies)		No data reported for hypertensive disorders of pregnancy in the included study
Caesarean section	**244 per 1000**	**330 per 1000** (203 to 532)	**RR 1.35** (0.83 to 2.18)	171 (1 study)	⊕◯◯◯ **very low**[1,2,3]	
Supsequent development of type 2 diabetes			not estimable	(0 studies)		No data reported for subsequent development of type 2 diabetes in the included study
Perineal trauma			not estimable	(0 studies)		No data reported for perineal trauma in the included study.
Return to pre-pregnancy weight			not estimable	(0 studies)		No data reported for return to pre-pregnancy weight in the included study

Postnatal depression		not estimable	(0 studies)	No data reported for postnatal depression in the included study
Induction of labour		not estimable	(0 studies)	No data reported for induction of labour in the included study

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
__CI:__ Confidence interval; __RR:__ Risk ratio; __OR:__ Odds ratio;

GRADE Working Group grades of evidence
__High quality:__ Further research is very unlikely to change our confidence in the estimate of effect.
__Moderate quality:__ Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
__Low quality:__ Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
__Very low quality:__ We are very uncertain about the estimate.

[1] Lack of detail to make a judgement about random sequence generation, allocation concealment, attrition bias and reporting bias. Open label study and no details regarding blinding of outcome assessors was reported.
[2] Wide confidence intervals that cross the line of no effect.
[3] Evidence based on a single trial that was only published in conference abstract form.

B A C K G R O U N D

Description of the condition

Gestational diabetes mellitus (GDM) is a carbohydrate intolerance resulting in hyperglycaemia, or any degree of glucose intolerance with onset or first recognition during pregnancy from 24 weeks' gestation onwards and which resolves following the birth of the baby (NICE 2015; WHO 2013). The global prevalence of GDM is reported to be between 1% to 25.5%, depending on the diagnostic criteria used and women's ethnicity (ACOG 2013; Bottalico 2007; Cheung 2003; Ferrara 2007; NICE 2015; Sacks 2012), and rates are likely to increase with the reported global obesity epidemic (Athukorala 2010; Kim 2010; Rowlands 2010; Zhang 2010). Obesity has been identified as a significant risk factor for GDM (Boney 2005; Chu 2007; Mokdad 2003; Oteng-Ntim 2012; Rosenberg 2005; Torloni 2009).

During pregnancy, hormones released by the placenta cause an increase in maternal insulin resistance to ensure a constant supply of glucose and other nutrients to the growing fetus (McCance 2011; Wilcox 2005). The maternal pancreas compensates for the pregnancy-induced insulin resistance by secreting more insulin. GDM occurs when this compensatory mechanism fails and not enough insulin is available to metabolise glucose (McCurdy 2010; Wilcox 2005). The maternal blood glucose concentration then increases resulting in hyperglycaemia. Increased amounts of glucose cross the placenta, over-nourishing the fetus, with increased fetal insulin secretion in response (Evans 2009; Ragnarsdottir 2010; Suman Rao 2013). Increased fetal insulin may act as a growth stimulating factor (Pedersen 1954).

Recognised risk factors for developing GDM include obesity, advanced maternal age, weight gain in pregnancy, and a family history of type 2 diabetes (Athukorala 2010; Chu 2007; Kim 2010; Torloni 2009; Zhang 2010). Women of certain ethnicities, such as Asian, African American, Native American, Hispanic, and Pacific Island have an increased risk (Carolan 2012; Chamberlain 2013; Kim 2013; Schneider 2012).

GDM has major short- and long-term implications for both the mother and her baby. Women with GDM are at higher risk of developing gestational hypertension and pre-eclampsia, and are at increased risk of having a caesarean section (Crowther 2005; HAPO 2008; McCance 2011; NICE 2015). In the long-term, these women are at significantly increased risk of developing cardiovascular disease and over half will develop type 2 diabetes within five to 10 years (Bellamy 2009). Infants of women with GDM have a greater incidence of being born large-for-gestational age and macrosomic (variously defined as birthweight greater than 4000 g to 4500 g) (Young 2013), which increases the risk of shoulder dystocia and associated birth trauma such as bone fractures and nerve palsy (Athukorala 2006). Macrosomia has been associated with developmental delay in childhood (Ornoy 2005; Slining 2010). In the neonatal period, these infants are at higher risk of hypo-

glycaemia due to fetal hyperinsulinaemia and need to adjust to not having the high maternal glucose supply (Devlieger 2008). Neonatal hypoglycaemia is associated with developmental delay in childhood (Lucas 1988). There are life-long health risks to the infants of mothers with GDM such as higher rates of obesity and type 2 diabetes in childhood (Page 2014), and an increased risk of diabetes, hypertension, cardiovascular disease in later life (Ornoy 2011), and evidence from published cohort studies indicating an increased risk of postpartum depression (Kozhimannil 2009; Nicklas 2013). Observational neurodevelopmental studies of children of mothers with diabetes (including women with GDM), report a higher rate of neurosensory disability (including gross and fine motor abnormalities, attention deficit hyperactivity disorder (ADHD), learning difficulties, and possibly autism spectrum disorder (ASD)) (Gardener 2009; Krakowiak 2012; Nomura 2012; Ornoy 2015).

Screening and diagnosis of GDM remain controversial, with some countries recommending universal screening of all pregnant women between 24 to 28 weeks' gestation (Nankervis 2013), and others only recommending selective screening (NICE 2015). The amount of glucose recommended for the diagnostic oral glucose tolerance test (OGTT) differs between countries (75 g and 100 g) and there is significant variation in the fasting, one-, two- and three-hour postprandial plasma glucose concentrations above which GDM is diagnosed (ACOG 2013; Nankervis 2013; New Zealand Ministry of Health 2014; NICE 2015; SIGN 2014; Thompson 2013; WHO 2013).

Similarly, there is wide variation internationally in glycaemic treatment targets recommended for optimal outcomes for women with GDM and their babies(see Table 1). As evidence emerges that current target thresholds may need to be lower than previously thought to reduce morbidity (Hernandez 2011; Hernandez 2015; Metzger 2008), professional organisations are increasingly advocating lower treatment targets that are closer to observed blood glucose concentrations in pregnant women without GDM (HSE 2010; Nankervis 2013). However, concerns have been raised that lower glycaemic targets may be associated with an increased risk of infants being born small-for-gestational age (Garner 1997; Langer 1989; Langer 1994), and a potential increased risk of hypoglycaemia in the mother (DCCT 1996), and therefore in, the fetus.

Description of the intervention

Treatment of GDM aims to reduce the associated risks of gestational diabetes for the mother and baby by controlling the high maternal blood glucose concentrations (Alwan 2009). Glycaemic control is usually measured by monitoring capillary blood glucose concentrations to ensure blood glucose concentrations are maintained within a pre-defined threshold (Metzger 2008). This may be achieved through the use of diet and lifestyle modifications (ADA 2001; New Zealand Ministry of Health 2014; NICE 2015; SIGN 2014), or with the addition, if necessary, of phar-

macological interventions such as oral hypoglycaemic medications or subcutaneous insulin (ACOG 2013; New Zealand Ministry of Health 2014; NICE 2015; SIGN 2014). Trials of interventions for GDM usually compare different treatment strategies with glycaemic control as an outcome, not an intervention (Middleton 2012). The focus of this review is comparing different treatment targets of glycaemic control in women with GDM and the impact on maternal and fetal health.

How the intervention might work

There is a continuous relationship between increasing maternal blood glucose concentrations and detrimental maternal and fetal outcomes (Langer 1994; Metzger 2008). Treatment of GDM aims to maintain maternal blood glucose concentrations within certain glycaemic target thresholds, reducing the physiological response of the fetus to elevated maternal blood glucose concentrations and has been shown to be beneficial in reducing perinatal morbidity (Crowther 2005; Landon 2009). The Maternal-Fetal Medicine Units Network (MFMU) trial (Landon 2009) and the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) trial (Crowther 2005), both compared treatment of GDM with no treatment. The MFMU Network trial had tighter glycaemic control targets (fasting plasma glucose < 5.3 mmol/L (95 mg/ dL) and two-hour postprandial < 6.7 mmol/L (120 mg/dL)) than the ACHOIS trial (fasting plasma glucose < 5.5 mmol/L (99 mg/ dL) and two-hour postprandial < 7.0 mmol/L (126 mg/dL)), and demonstrated a reduction in the risk of caesarean section (risk ratio (RR) 0.79, 97% confidence interval (CI) 0.64 to 0.99) not shown in the ACHOIS trial (RR 0.97, 95% CI 0.81 to 1.16), although both trials demonstrated reductions in birthweight and large-for-gestational-age infants in women with GDM who received treatment compared with women who were not treated (Crowther 2005; Landon 2009; Ornoy 2015). Such evidence suggests lower glycaemic targets may be of benefit.

Why it is important to do this review

The evidence for optimal glycaemic targets for women with GDM is limited and of varying quality (Hernandez 2015). It appears that women who have better controlled blood glucose concentrations in pregnancy have a lower incidence of pre-eclampsia and large-for-gestational-age babies (Crowther 2005; Landon 2009). The infants of these women have a reduced incidence of neonatal hypoglycaemia and perinatal mortality (Landon 2009). Target recommendations from international professional organisations for maternal glycaemic control vary widely, all relying on consensus as there is a lack of high quality evidence (ADA 2013; Metzger 2007; Nankervis 2013; New Zealand Ministry of Health 2014; NICE 2015; SIGN 2014; Thompson 2013).

In assessing evidence related to determining the optimal degree of glycaemic targets, this review will contribute to knowledge that can be used to minimise the risk of adverse birth outcomes and diabetic complications for pregnant women and their babies.

O B J E C T I V E S

The purpose of this review is to assess the effect of different intensities of glycaemic control in pregnant women with GDM on maternal and infant health outcomes.

M E T H O D S

Criteria for considering studies for this review

Types of studies

All published and unpublished randomised controlled trials, cluster-randomised and quasi-randomised controlled trials, including conference abstracts assessing different intensities of glycaemic control for women with GDM, were eligible for inclusion (Higgins 2011). Cross-over trials were not eligible for inclusion, as changes in insulin sensitivity throughout pregnancy make cross-over trials an inappropriate methodology for this review and women with GDM are usually advised of only one glycaemic target range to guide their treatment in their pregnancy.

Types of participants

All pregnant women diagnosed with GDM. Due to varying diagnostic methods and criteria used internationally, we defined screening and subsequent diagnosis and diagnostic criteria as identified in the individual trials. Women with known pre-existing type 1 or type 2 diabetes were excluded.

Types of interventions

The type of intervention includes any glycaemic treatment targets (blood glucose concentration) used for glycaemic control for women with GDM to guide treatment. For further clarity, we converted blood glucose values into both mmol/L and mg/dL as different countries express glucose values in either mmol/L or mg/dL. For example, most Europe, New Zealand, Australia and North America generally use mmol/L and America, China and Germany generally use mg/dL. Trials often express their interventions additionally in non-numerical terms for example: 'loose', 'standard care', 'low(er)', 'less tight', 'moderate', 'tight', 'very tight', 'strict(er)', 'intensive therapy' and 'liberal'. We will use the trial

definitions to assist with clarity when discussing the results instead of using the numerical ranges repeatedly.

Types of outcome measures

The primary and secondary maternal and infant outcome measures are based on consensus between the review authors and all other review authors of Cochrane systematic reviews for treatment of GDM.

Primary outcomes

Maternal

1. Hypertensive disorders of pregnancy (including pre-eclampsia, pregnancy-induced hypertension, eclampsia).
2. Subsequent development of type 2 diabetes.

Infant

1. Perinatal (fetal and neonatal) mortality.
2. Large-for-gestational age (birthweight greater than the 90th centile; or as defined by individual trial).
3. Composite of mortality or serious morbidity (variously defined by trials, e.g. infant death, shoulder dystocia, bone fracture or nerve palsy).
4. Neurosensory disability (variously defined by individual trials).

Secondary outcomes

Maternal

1. Caesarean section.
2. Maternal mortality.
3. Weight gain during pregnancy.
4. Placental abruption.
5. Induction of labour.
6. Perineal trauma.
7. Postpartum haemorrhage.
8. Postpartum infection requiring use of antibiotics (variously defined).
9. Maternal hypoglycaemia.
10. Glycaemic control during/end of intervention (as defined by trialists).
11. Use of pharmacological treatment (insulin, oral hypoglycaemics).
12. Relevant biomarker changes associated with the intervention (including adiponectin, free fatty acids, triglycerides, high density lipoproteins, low density lipoproteins, insulin).
13. Breastfeeding.

14. Adherence with treatment/management.
15. Sense of wellbeing and quality of life.
16. Views of the intervention.
17. Behaviour change associated with the intervention.

Long-term maternal outcomes

1. Postnatal depression.
2. Postnatal weight retention or return to pre-pregnancy weight.
3. Body mass index (BMI).
4. GDM in a subsequent pregnancy.
5. Type 1 diabetes mellitus.
6. Impaired glucose tolerance.
7. Cardiovascular health (as defined by trialists, including blood pressure, hypertension, cardiovascular disease, metabolic syndrome).

Infant

1. Stillbirth.
2. Neonatal death.
3. Macrosomia (birthweight $\geq$ 4000 g, or as defined by individual trial).
4. Small-for-gestational age (birthweight less than the 10th centile, or as defined by individual trial).
5. Shoulder dystocia.
6. Bone fracture.
7. Nerve palsy.
8. Preterm birth (< 37 weeks' gestation; < 32 weeks' gestation).
9. Gestational age at birth.
10. Birthweight and z score.
11. Head circumference and z score.
12. Length and z score.
13. Ponderal index.
14. Hypoglycaemia (variously defined).
15. Respiratory distress syndrome.
16. Neonatal jaundice (hyperbilirubinaemia).
17. Hypocalcaemia.
18. Adiposity (variously defined by trials, e.g. skinfold thickness, fat mass).
19. Polycythaemia.
20. Apgar score < seven at five minutes.
21. Relevant biomarker changes associated with the intervention (including cord c peptide, cord insulin).

Later childhood

1. Weight and z score.
2. Height and z score.
3. Head circumference and z score.
4. Adiposity (including BMI, skinfold thickness).
5. Blood pressure.

6. Type 1 diabetes mellitus.
7. Type 2 diabetes mellitus.
8. Impaired glucose tolerance.
9. Dyslipidaemia or metabolic syndrome.
10. Educational achievement.

Adulthood outcomes

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

Health services

1. Number of antenatal visits or admissions.
2. Number of hospital or health professional visits (including midwife, obstetrician, physician, dietician, diabetic nurse).
3. Admission to neonatal intensive care unit/nursery.
4. Length of antenatal stay.
5. Length of postnatal stay (maternal).
6. Length of postnatal stay (baby).
7. Cost of maternal care.
8. Cost of offspring care.
9. Costs associated with the intervention.
10. Costs to families associated with the management provided.

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 the Trials Search Co-ordinator (31 January 2016).

The Register is a database containing over 20,000 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 handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service, please follow this link to the editorial information about the Cochrane Pregnancy and Childbirth 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 the Trials Search Co-ordinator 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 Trials Search Co-ordinator 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, Excluded, Awaiting Classification or Ongoing studies). In addition, we searched ClinicalTrials.gov, and the WHO International Clinical Trials Registry Platform (ICTRP) (1 February 2016) for unpublished, planned and ongoing trial reports (see Appendix 1 for search terms we used).

Searching other resources

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

Data collection and analysis

The following methods were used for assessing the eight reports that were identified as a result of the search.

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 we identified as a result of the search strategy. We had no disagreement, hence did not require to consult with a third author.

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

Figure 1. Study flow diagram
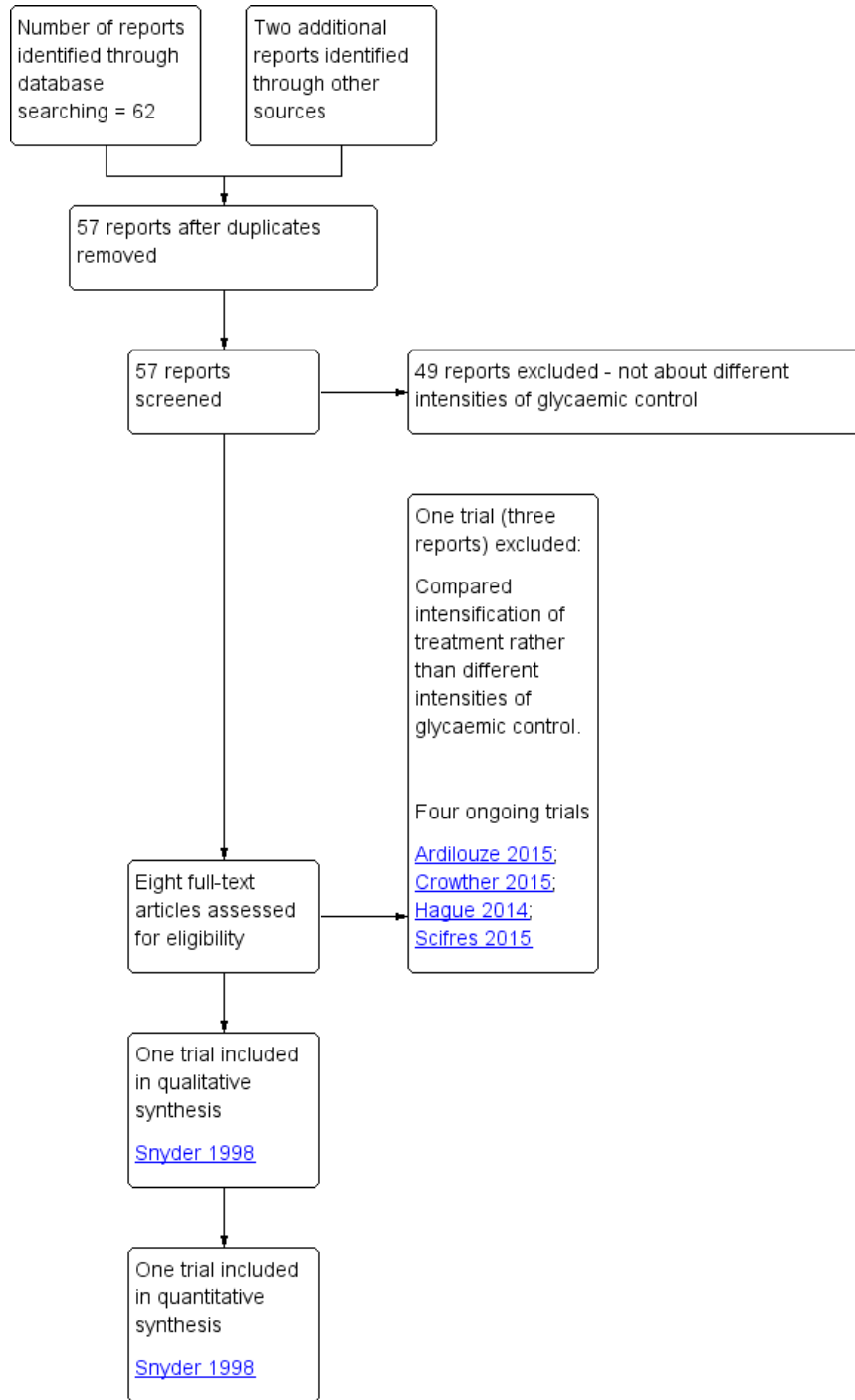
Data extraction and management

We used the Cochrane Pregnancy and Childbirth Group data extraction form. Two review authors (RM and JB) extracted data from the one identified study using the agreed form. We entered the data into Review Manager software (RevMan 2014) and checked for accuracy.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for the one included study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreement by discussion or by involving a third author. Seeking statistical advice for calculating intra cluster correlations from cluster-randomised trials as outlined in our published protocol, was not required.

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

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

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

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

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

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

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

We described for the included study the methods used, if any, to blind study participants and personnel from knowledge of which

intervention a participant received. We considered that studies are at low risk of bias if they were blinded, or if we judged that the lack of blinding would be unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes. We assessed the methods as:

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

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

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

- low, high or unclear risk of bias.

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

We described for the included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. We attempted to contact the trial authors for further information and planned to include any relevant missing data in the analyses which we undertook.
We assessed methods as:

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

(5) Selective reporting (checking for reporting bias)

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

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);

- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest 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)

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

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

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

(7) Overall risk of bias

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

Assessment of the quality of the evidence using the GRADE approach

We assessed the quality of the evidence of the included trial using the GRADE approach as outlined in the GRADE Handbook Chapter 5 (Schünemann 2013) with the software GRADEpro GDT (GRADEpro GDT 2015) producing two 'Summary of findings' tables. A summary of the intervention effect and a measure of quality for each of the following outcomes was produced using the GRADE approach. GRADEpro five criteria (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. We chose seven maternal and seven child (as neonate, child, adult) outcomes (seven are the maximum of outcomes permitted with this software), as listed below. These are based on consensus between the review authors and all other review authors of Cochrane systematic reviews for treatment of GDM. For the included trial the only outcome (maternal) able to be assessed for quality was caesarian section, no other data were available for the other listed outcomes. See (Summary of findings for the main comparison) and (Summary of findings 2).

Maternal

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

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

Child (as neonate, child, adult)

1. Large-for-gestational age.
2. Perinatal mortality.
3. Composite of mortality and serious morbidity.
4. Neonatal hypoglycaemia.
5. Adiposity.
6. Diabetes.
7. Neurosensory disability.

Measures of treatment effect

Dichotomous data

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

Continuous data

For continuous data, we used the mean difference (MD). In future updates, if appropriate, we will use the standardised mean difference (SMD) to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomised trials

No cluster-randomised trials were identified. If cluster-randomised trials are identified in future updates of this review we will make adjustments to the standard errors using the methods described in the *Handbook* [Section 16.3.6] using an estimate of the intra cluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. We will consider it reasonable to combine the results from both cluster-randomised trials and individually-randomised trials if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

Multiple pregnancy

The included trial did not report on multiple pregnancy. If in the future updates of this review, trials do report on multiple pregnancy, we will present maternal data as per woman randomised and neonatal data per infant.

Multiple-arm studies

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

Dealing with missing data

For the included study, we noted the levels of attrition did not exceed 20%. In future updates of the review, we will explore the impact of including studies with high levels of missing data (> 20%) in the overall assessment of treatment effect by using sensitivity analysis.

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

Assessment of heterogeneity

We planned to assess statistical heterogeneity in each meta-analysis using the Tau², I² and Chi² statistics, but identified only one trial. If future updates include further trials then we will regard heterogeneity as substantial if an I² is greater than 30% and either a Tau² is greater than zero, or there is a low P value (less than 0.10) in the Chi² test for heterogeneity (Higgins 2011).

Assessment of reporting biases

A single trial is included in this review. 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). Only one trial was included so there are no data combined in meta-analysis. In future updates, we will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. In future updates, if more trials are included and there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials is considered clinically meaningful. The random-effects summary will be treated as the average of the range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful, we will not combine trials.

If we use random-effects analyses, the results will be presented as the average treatment effect with 95% confidence intervals, and the estimates of Tau² and I².

Subgroup analysis and investigation of heterogeneity

As there is currently only a single trial included in the review, we have not explored heterogeneity or subgroup analyses. If, in future updates, we identify substantial heterogeneity, we will investigate it using subgroup analyses and sensitivity analyses. We will consider whether an overall summary is meaningful, and if it is, use a random-effects model.

We will not combine trials based on the individual trial definition of intensity of glycaemic control. We will use the mmol/L (mg/dL) thresholds used in the trials and subgroups based on these if there is significant heterogeneity.

1. Types of strategies used to target or achieve glycaemic control, or both

i) Diet and lifestyle changes alone versus

ii) Oral hypoglycaemics +\- diet and lifestyle changes versus

iii) Insulin therapy +\- diet and lifestyle changes.

2. Criteria used for diagnosis of GDM

i) International Association of Diabetes in Pregnancy Study Group (IADPSG 2010), Australasian Diabetes in Pregnancy Society (Nankervis 2013); World Health Organization (WHO 2013); American Diabetes Association (ADA 2013); Scottish Intercollegiate Guidelines Network (SIGN 2014) versus

ii) New Zealand Ministry of Health (New Zealand Ministry of Health 2014) versus

iii) National Institute of Health and Clinical Excellence (NICE 2015) versus

iv) Canadian Diabetes Association (Thompson 2013) versus

v) American College of Obstetricians and Gynecologists (ACOG 2013) versus

vi) Carpenter et al (Carpenter 1982) versus

vii) National Diabetes Data Group (National Data Group 1979) versus

viii) Hoffmann et al (ADIPS) (Hoffman 1998), NICE (NICE 2008), WHO (WHO 1999) versus

ix) Any others identified by individual trial.

3. Gestational age at diagnosis

i) < 24 weeks versus.

ii) 24 to < 28 weeks versus.

iii) ≥ 28 weeks.

4. Woman's ethnicity as identified from the trials

5. Women who are primiparas versus multiparas

6. Twin pregnancies versus singleton pregnancies

The following outcomes would be used in any subgroup analyses.

Maternal

1. Hypertensive disorders of pregnancy.
2. Subsequent development of type 2 diabetes.

Infant

1. Perinatal (fetal and neonatal) mortality.
2. Large-for-gestational age (birthweight greater than the 90th centile; or as defined by individual trial).
3. Composite of mortality or serious morbidity.

In future updates if further trials are identified for inclusion, we will assess subgroup differences by interaction tests available within RevMan (RevMan 2014) and report the results of subgroup analyses quoting the Chi² statistic and P value, and the interaction test I² value.

Sensitivity analysis

Planned sensitivity analyses were not needed. In future updates will carry out sensitivity analysis, if required, to investigate the effect of the randomisation unit where we include cluster-randomised trials along with individually-randomised trials. We will also carry out sensitivity analysis to explore the impact of including studies assessed as high risk of bias due to randomisation method (e.g. quasi-randomisation versus true randomisation), and allocation concealment on the primary outcomes in order to assess whether this makes any difference to the overall results. In addition, we will perform sensitivity analysis by excluding trials assessed as high risk of bias due to missing data.

R E S U L T S

Description of studies

Results of the search

We identified eight reports of six trials. Two trials (Garner 1997; Snyder 1998) are published (four reports) and four (Ardilouze 2015; Crowther 2015; Hague 2014; Scifres 2015) are ongoing studies Ongoing studies (see: Figure 1).

Included studies

We included one study (Snyder 1998) in this review. The publication, from Canada, was in abstract form only. No full-text publication has been identified. RM emailed co-author (Meltzer) for further information, as Meltzer was the only author with a contact email address found via the Internet. Synder, the main author and co-authors Morin and Nadeau were not contactable. No response from Meltzer was received at time of submission.

Snyder 1998, was conducted in Canada and involved 180 women. The women were diagnosed with GDM between 20 to 32 weeks' gestation, and were recruited over a 12-month period (1996 to 1997). The study compared *strict* versus *liberal* glycaemic targets for glycaemic control for women treated with insulin. *Strict* glycaemic targets for insulin treatment were defined as (preprandial: 5.0 mmol/L (90 mg/dL) and at one-hour postprandial: 6.7 mmol/L (120 mg/dL)) and *liberal* glycaemic targets were defined as (preprandial: 5.8 mmol/L (104 mg/dL) and at one-hour postprandial: 7.8 mmol/L (140 mg/dL)). No other inclusion criteria were detailed. Data for other characteristics (pre-pregnancy body mass index (BMI), maternal age, gestational age at diagnosis and length of treatment) and the criteria used to diagnose GDM were not reported. No funding sources were identified.

Excluded studies

We excluded on study (Garner 1997) as it was a study of intensification of treatment, not of comparing different intensities of glycaemic control targets in women diagnosed with GDM. See Characteristics of excluded studies.

Risk of bias in included studies

The overall quality of the included study was judged to be unclear as it was only published as a conference abstract and provided limited information about the methods used.

The 'Risk of bias' summaries (Figure 2 and Figure 3) present the review authors' judgements about each 'Risk of bias' item from the included study.

Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item from the included study.

Figure 3. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages from the included study.
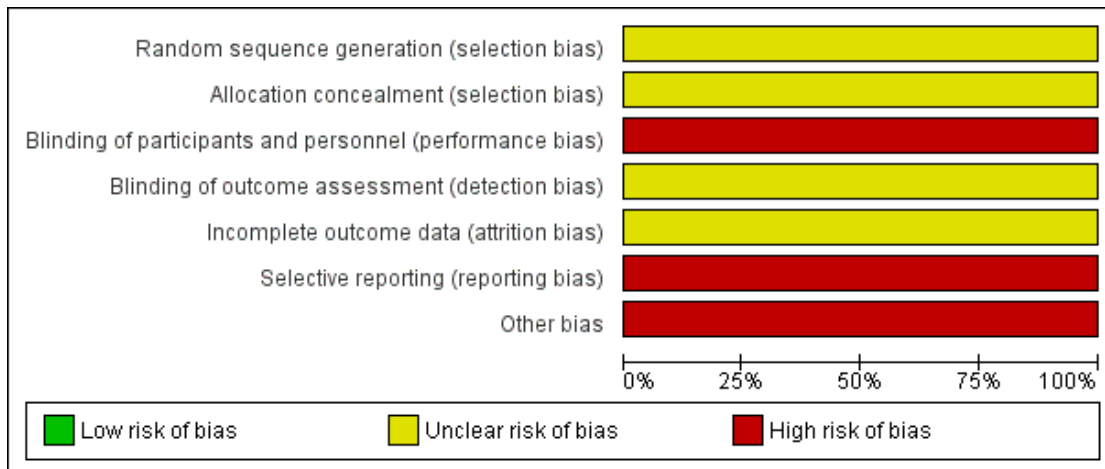
Allocation

The method of random sequence generation was not described in detail. Allocation concealment was not described.

Blinding

In this study the blinding of women, their clinical carers and the researcher to group allocation was most likely not feasible. A lack of blinding may have influenced the study outcomes. No details were provided as to whether or not there was blinding of outcome assessors.

Incomplete outcome data

Data are reported for 171 of 180 women who were recruited to the study (Snyder 1998). No data for the missing nine women were provided. Intention-to-treat analysis is not reported.

Selective reporting

As the included study was only published in abstract form it is unclear if the data reported represent all of the pre-specified outcomes for the study or if only selected outcomes are reported.

Other potential sources of bias

It was not possible to judge if there were other sources of bias as little information is provided in the conference abstract. The statement "the groups were comparable for pre-pregnancy body mass, maternal age, gestational age at diagnosis and length of treatment" is not substantiated with any data.

Effects of interventions

See: **Summary of findings for the main comparison** Intensity of glycaemic control for women with gestational diabetes mellitus - *strict* glycaemic targets versus *liberal* glycaemic targets (Maternal outcomes); **Summary of findings 2** Intensity of glycaemic control for women with gestational diabetes mellitus - *strict* glycaemic targets versus *liberal* glycaemic targets (Child (as neonate, child, adult) outcomes)

See: Summary of findings for the main comparison: Intensity of glycaemic control for women with GDM and Summary of findings 2: and for their children.

Primary outcomes

Maternal outcomes

No data were reported for **hypertension disorders of pregnancy** or **subsequent development of type 2 diabetes**.

Infant outcomes

No data were reported for any of the neonatal primary outcomes for this review (**perinatal (fetal and neonatal) mortality**; **large-for-gestational age**; **composite of death or severe morbidity** or later childhood **neurosensory disability**).

Secondary outcomes

Maternal outcomes

Twenty-eight of 85 (33%) women in the *strict* group had a caesarean section compared with 21 of 86 women (24%) in the *liberal* group. There was no difference in risk of birth by **caesarean section** (risk ratio (RR) 1.35, 95% confidence interval (CI) 0.83 to 2.18, one trial, 171 women), Analysis 1.1. Caesarean section was the only pre-specified outcome with available data for GRADE assessment. The quality of the evidence for caesarean section was judged to be *very low* due to lack of details for the individual components of risk of bias, evidence of imprecision and publication bias. The chance of birth by caesarean section in the *liberal* glycaemic target group was 24%; for women in the *strict* glycaemic control group the chance of birth by caesarean section ranged from 20% to 53%.

Strict glycaemic targets were associated with an increase in the **use of pharmacological therapy** (identified as the use of insulin in this study) (33/85; 39%) compared with *liberal* glycaemic targets (18/86; 21%) (RR 1.85, 95% CI 1.14 to 3.03; one trial, 171 women), Analysis 1.2. CIs are wide suggesting imprecision and caution is required when interpreting the data.

No data were reported for any of the other maternal secondary outcomes for this review (maternal mortality; weight gain during pregnancy; placental abruption; induction of labour; perineal trauma; postpartum haemorrhage; postpartum infection requiring use of antibiotics (variously defined); maternal hypoglycaemia; glycaemic control during/end of intervention (as defined by trialists); use of pharmacological treatment (oral hypoglycaemic); relevant biomarker changes associated with the intervention (including adiponectin, free fatty acids, triglycerides, high density lipoproteins, low density lipoproteins, insulin); breastfeeding; adherence with treatment/management; sense of wellbeing and quality of life; views of the intervention; behaviour change associated with the intervention).

Long-term maternal outcomes

No data were reported for any of the long-term maternal outcomes for this review (postnatal depression; postnatal weight retention or return to pre-pregnancy weight; BMI; GDM in a subsequent pregnancy; type 1 diabetes mellitus; impaired glucose tolerance; cardiovascular health (as defined by trialists, including blood pressure, hypertension, cardiovascular disease, metabolic syndrome)).

Infant outcomes

There were no clear differences for babies born to women receiving *strict* glycaemic targets for insulin treatment when compared to babies born to women receiving *liberal* glycaemic targets for insulin treatment for:

- **macrosomia** (birthweight > 4000 g) RR 1.35, 95% CI 0.31 to 5.85; one trial, 171 babies, Analysis 1.3;
- **small-for-gestational age** RR 1.12, 95% CI 0.48 to 2.63; one trial, 171 babies, Analysis 1.4;
- **gestational age at birth mean difference** (MD) -0.30 weeks, 95% CI -0.73 to 0.13; one trial, 171 babies, Analysis 1.5;
- **birthweight** MD -92.00 g, 95% CI -241.97 to 57.97; one trial, 171 babies, Analysis 1.6.

No data were reported for any of the other neonatal outcomes for this review (stillbirth; neonatal death; shoulder dystocia; bone fracture; nerve palsy; preterm birth (< 37 weeks' gestation; < 32 weeks' gestation); birthweight z score; head circumference and z score; length and z score; ponderal index; hypoglycaemia; respiratory distress syndrome; hyperbilirubinaemia; hypocalcaemia; adiposity; polycythaemia; Apgar score < seven at five minutes; relevant biomarker changes associated with the intervention).

Later childhood outcomes

No data were reported for any of the childhood outcomes for this review (weight and z score; height and z score; head circumference and z score; adiposity (including BMI, skinfold thickness); blood pressure; type 1 diabetes mellitus; type 2 diabetes mellitus; impaired glucose tolerance; dyslipidaemia or metabolic syndrome; educational achievement).

Adulthood outcomes

No data were reported for any of the adulthood outcomes for this review (weight; height; adiposity (including skinfold thickness, fat mass); cardiovascular health (as defined by trialists, including blood pressure, hypertension, cardiovascular disease, metabolic syndrome); type 1 diabetes mellitus; type 2 diabetes mellitus; impaired glucose tolerance; dyslipidaemia or metabolic syndrome; employment, education and social status/achievement).

Health services outcomes

No data were reported for any of the health service outcomes for this review (number of antenatal visits or admissions; number of hospital or health professional visits (including midwife, obstetrician, physician, dietician, diabetic nurse); admission to neonatal intensive care unit/nursery; length of antenatal stay; length of postnatal stay (maternal); length of postnatal stay (baby); cost of maternal care; cost of offspring care; costs associated with the intervention; costs to families associated with the management provided).

Intensity of glycaemic control for women with gestational diabetes mellitus - *strict* **glycaemic targets versus** *liberal* **glycaemic targets (Child (as neonate, child, adult) outcomes)**

Patient or population: Children (as neonate, child, adult) of women with GDM
Setting: Canada
Intervention: Strict intensity of maternal glycaemic control: preprandial: 5.0 mmol/L (90 mg/dL) and at one-hour postprandial: 6.7 mmol/L (120 mg/dL)
Comparison: Less strict maternal glycaemic control: preprandial 5.8 mmol/L (104 mg/dL) and at one-hour postprandial 7.8 mmol/L (140 mg/dL)

Outcomes	Anticipated absolute effects*(95%CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with less strict glycaemic control	Risk with strict glycaemic control				
Large-for-gestational age - not reported	see comment	see comment	not estimable	(0 studies)	-	No data reported for large-for-gestational age in the included study
Perinatal mortality - not reported	see comment	see comment	not estimable	(0 studies)	-	No data reported for perinatal mortality in the included study
Composite of mortality and serious morbidity - not reported	see comment	see comment	not estimable	(0 studies)	-	No data reported for composite of mortality and serious morbidity in the included study
Neonatal hypoglycaemia - not reported	see comment	see comment	not estimable	(0 studies)	-	No data reported for neonatal hypoglycaemia in the included study

Adiposity - not reported	see comment	see comment	not estimable	(0 studies)	-	No data reported for adiposity in the included study.
Diabetes - not reported	see comment	see comment	not estimable	(0 studies)	-	No data reported for diabetes in the included study.
Neurosensory disability - not reported	see comment	see comment	not estimable	(0 studies)	-	No data reported for neurosensory disability in the included study

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

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

D I S C U S S I O N

Summary of main results

The effect of different intensities of glycaemic control in pregnant women with GDM for improving maternal and infant outcomes was assessed in this review. Only one study (involving 180 women) was identified that met the inclusion criteria for this systematic review (Snyder 1998). In the trial, the capillary glycaemic targets compared were: preprandial: 5.0 mmol/L (90 mg/dL) and at one-hour postprandial: 6.7 mmol/L (120 mg/dL) for the *strict* group and for the *liberal* glycaemic group: preprandial 5.8 mmol/L (104 mg/dL) and at one-hour postprandial 7.8 mmol/L (140 mg/dL). The *strict* glycaemic targets were associated with an increase in the use of insulin requirements. No clear differences were seen for any of the secondary outcomes for this systematic review. Based on the current limited data it remains unclear which glycaemic targets should be recommended for women with GDM for improving their health and the health of their babies.

Overall completeness and applicability of evidence

There is currently very limited evidence on the effectiveness of different intensities of glycaemic control in women with GDM. The available data are from one small (n = 180 women) Canadian study that has only been published as a conference abstract (Snyder 1998). The study reported no data for this reviews' primary maternal or infant outcomes. No data were available for maternal and child long-term outcomes or health service outcomes. Limited secondary outcomes for this review were reported.

Although an increased use of insulin treatment was associated with women randomised to the *strict* glycaemic control group, there are no data reported in adverse effects such as maternal hypoglycaemia. The study recruited "women between 20-37 gestation referred for GDM who were then randomised to receive insulin at either the recommended *liberal* or *strict* criteria". It did not include other treatments for example, oral hypoglycaemic agents or diet and lifestyle interventions.

Due to one included study with small numbers of participants, receiving insulin as the only treatment option when treatment was needed and overall unclear risk of bias, the generalisability of the current evidence is very limited.

Four ongoing trials were identified and data from these studies, when published, will be included in future updates of this systematic review (see Ongoing studies).

Quality of the evidence

For the one included study, random sequence generation and allocation concealment were judged to be unclear due to lack of detail. Performance bias was judged to be of high risk as the study was unlikely to have been blinded. There was insufficient detail to make a judgement about detection bias. Attrition bias was judged to be unclear as of the 180 women recruited, outcome data were available for 171 women and babies. The reasons for the missing participants were not explained. Selective reporting was judged to be of high risk as the conference abstract is likely to have reported on a selection of outcomes from the study rather than the pre-specified study outcomes. The study was only reported as a conference abstract and no full publication was found.

We graded the quality of the evidence for caesarean section as *very low* due to poor reporting of risk of bias, imprecision and publication bias. Data for the other selected outcomes for GRADE were not reported in the included study. See Summary of findings for the main comparison; Summary of findings 2.

Potential biases in the review process

Systematic searches of all potential eligible trials were carried out by the Trials Search Co-ordinator for the Cochrane Pregnancy and Childbirth Group and the authors of this review. We also searched the Cochrane Pregancy and Childbirth Group's Trials Register, ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP) and the reference lists of the identified trials. One author was contacted for the included study via email for additional data but no response was received. No evidence of potential bias was identified through these systematic searches for published and unpublished studies. If we identify any studies in future searches, we will assess them for potential inclusion in this review. As the quality of the included trial is unclear and outcome data are missing, a potential for bias is present. Therefore, the study results should be interpreted with caution.

Agreements and disagreements with other studies or reviews

In this review we did not find sufficient evidence to fully evaluate which intensity of glycaemic control for women with GDM was most effective for improving the health outcomes for women and their babies. Results from only one published study (Snyder 1998) are available, but the overall risk of bias from this small trial is unclear (Figure 2 and Figure 3).

There is limited evidence to guide clinical practice for targets for glycaemic control for women with GDM to minimise adverse effects on maternal and fetal health. Glycaemic target recommendations from international professional organisations for maternal glycaemic control vary widely and are reliant on consensus given the lack of high-quality evidence (ADA 2013; Metzger 2007; Nankervis 2013; New Zealand Ministry of Health 2014; NICE 2015; SIGN 2014;Thompson 2013) (Table 1). The evidence on

which these recommendations have been made is generally unclear.

Prutsky and colleagues published a systematic review that included 34 observational studies, involving 9433 women (Prutsky 2013), summarising the evidence for glycaemic targets in pregnant women with GDM, type 1 diabetes and type 2 diabetes. No relevant randomised controlled trials were identified. Twenty-six of the 34 observational studies included women with GDM. Overall, the quality of the evidence of the observational studies included was judged to be low, with the literature limited and heterogeneity amongst the studies high. The results of Prutsky's systematic review showed that a fasting glucose target of < 5.0mmol/L was associated with a significant reduction in macrosomia (P < 0.01), large-for-gestational-age infants (P = 0.01), neonatal hypoglycaemia (P = 0.01), and neonatal jaundice (P = 0.01). For the mother, there was a significant reduction in pre-eclampsia during the third trimester of pregnancy (P = 0.01) (Prutsky 2013). Based on the results from these observational studies, the authors concluded that it remains unclear whether glucose targets above or below a fasting glucose threshold of < 5.0 mmol/L offer a better balance of benefits and risks. There was insufficient evidence on postprandial measures to assess different cut-off points and health outcomes. The review authors highlighted that there have been no well-conducted large randomised controlled trials comparing any two glycaemic thresholds that report on benefits and harms for the mother and her baby. In the light of the current evidence assessed in our review, we have reached the same conclusion.

AUTHORS' CONCLUSIONS

Implications for practice

The overall risk of bias of the single included study was judged to be unclear as it has only been reported as an abstract and provided very little information about the study method used. Women using *stricter* glycaemic targets in the included study used more insulin therapy, which would be expected, but no data were provided for adverse effects such as maternal hypoglycaemia. There was no difference in the risk of being born small-for-gestational age. It is important to note that these findings are based on limited data from one small randomised trial with evidence of imprecision for the few published outcomes. There is currently insufficient evidence to support *strict* over more *liberal* glycaemic treatment targets for women with GDM. It will also be important to evaluate women's views of adhering to different glycaemic intensities and how this affected their daily life to understand and overcome impractical-

ities and inconveniences such as hospital clinic attendances and the effect of blood glucose monitoring.

Implications for research

Further larger high-quality trials are needed that compare different intensities of glycaemic control targets to guide the treatment of women with GDM. High-quality trials should evaluate different blood glycaemic targets to guide treatment, assess both short-term and long-term health outcomes for women and their babies, include women's experiences and assess health services costs. Four ongoing randomised controlled trials were identified and data from these studies, if published, (Ardilouze 2015; Crowther 2015; Hague 2014; Scifres 2015) see also Characteristics of ongoing studies will be included in future updates of this review. These trials are of varying sizes, with Ardilouze 2015, Hague 2014 and Scifres 2015 involving 30, 40 and 60 women with GDM, respectively and Crowther 2015 involving 1080 women. All trials are comparing glycaemic control targets for women with GDM. Crowther 2015, Hague 2014 and Scifres 2015 are using the same glycaemic targets for their intervention group (5.0 mmol/L (90 mg/dL) pre-prandial and at two hours postprandial 6.7 mmol/L (120 mg/dL)). Non-numerical terms used to describe the intervention range from 'normal', 'standard care', 'low', 'less tight', 'tight' to 'very tight' and 'intensive therapy'.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Snyder 1998

Methods	Randomised controlled trial.
Participants	180 women. Inclusion criteria: pregnant women, 20 to 37 weeks' gestation, referred for GDM (no details of diagnostic criteria) Exclusion criteria: no details. Setting: Royal Victoria Hospital, McGill Univeristy, Montreal, Canada Timing: 1996 to 1997.
Interventions	*Liberal* glycaemic control criteria: before meal 5.8 mmol/L (104 mg/dL) and 1-hour postprandial 7.8 mmol/L (140 mg/dL). Monitored weekly and twice a week after 32 weeks'. Birth planned before 40 weeks' gestation (n = 86). Treated with Insulin if outside *liberal* glycaemic targets. *Strict* glycaemic control criteria: before meal 5.0 mmol/L (90 mg/dL) and 1-hour postprandial 6.7 mmol/L (120 mg/dL). Monitored weekly and twice a week after 32 weeks'. Birth planned before 40 weeks' gestation (n = 85). Treated with Insulin if outside *strict* glycaemic targets.
Outcomes	Insulin therapy, caesarean section, gestational age at birth, birthweight, birthweight > 4 kg, small-for-gestational age, induction of labour, neonatal birth trauma, neonatal metabolic disturbances
Notes	Sample size calculation - not reported. ITT analysis - not clear, data reported for 171/180 women. Conference abstract only. One of the authors, Sara Meltzer, was contacted via email to request further information, e.g. study protocol or any further unpublished papers. No response was received at time of submission

Risk of bias

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

Snyder 1998 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details as to whether outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data reported on 171 of 180 women enrolled. No details on loss to follow-up
Selective reporting (reporting bias)	High risk	Conference abstract only. Data not reported for all outcomes, only stated that no differences
Other bias	High risk	Authors state that there was no difference between groups at baseline but no data provided. No protocol has been identified for this trial and no full publication has been identified

GDM: gestational diabetes mellitus
ITT: intention to treat

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

Study	Reason for exclusion
Garner 1997	In this Canadan study, 300 women diagnosed with GDM were randomised to either receive 'intensive' follow-up care or 'routine care'. 'Intensive' follow-up care took place with an obstetrician and an endocrinologist in a tertiary setting and after receiving dietary counselling women were placed on a calorie-restricted diet. Daily blood glucose estimations were obtained, women were seen bi-weekly at the hospital where biophysical profiles were performed at each visit and ultrasonographic assessments for fetal growth, amniotic fluid volume and cardiac size performed. In the 'routine care' group, women were not seen by a dietician, advised stay on an unrestricted healthy diet, performed only 2 glucose levels weekly at home and returned for follow-up care to their primary obstetric care provider in the community. No high-risk monitoring of the fetus unless there was an indication All women in the trial were recommended to maintain their fasting glucose level < 4.4 mmol/L (79 mg/dL) and 1-hour postprandial < 7.8 mmol/L (140 mg/dL). The intensification of the treatment was compared between the 2 groups, not different intensities of glycaemic control

GDM: gestational diabetes mellitus

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

Ardilouze 2015

Trial name or title	Glycemic objectives of women with GDM.
Methods	Randomised controlled trial. Unblinded. Canada.
Participants	30 women, 15-32 weeks' gestation. Excluded: known type 1 or type 2 diabetes, treatment interfering with glucose metabolism
Interventions	*Normal* glycaemic control target: fasting: 5.3 mmol/L (95 mg/dL) and 2-hour after meals: 6.7 mmol/L (120 mg/dL). Using diet, physical exercise or insulin to reach normal glycaemic control *Low* glycaemic control target: fasting: 4.8 mmol/L (86 mg/dL) and 2-hour after meals: 5.9 mmol/L (106 mg/dL). Using diet, physical exercise or insulin to reach low glycaemic control
Outcomes	Primary outcome: fetal glycated haemoglobin at delivery. Secondary outcome: treatment satisfaction.
Starting date	March 2015.
Contact information	Jean-Luc Ardilouze: Jean-Luc.Ardilouze@USherbrooke.ca Julie Menard: jumenard.chus@ssss.gouv.qc.ca
Notes	Clinical Trial Identifier: NCT02478762.

Crowther 2015

Trial name or title	Optimal glycaemic targets for women with gestational diabetes: the randomised trial - TARGET
Methods	Multi-centre, stepped wedge, cluster-randomised controlled trial Funding: Health Research Council of New Zealand.
Participants	A total sample size of 1080 participants from 10 hospitals in New Zealand providing care for women newly diagnosed with GDM Inclusion criteria: pregnant women newly diagnosed with GDM between 24-34 weeks' gestation and receiving treatment for GDM Exclusion criteria: pregnant women with GDM where the fetus has a major anomaly.
Interventions	*Less tight* glycaemic targets for glycaemic control in women newly diagnosed with GDM - fasting plasma glucose < 5.5 mmol/L (99 mg/dL); 1-hour postprandial < 8.0 mmol/L (144 mg/dL); 2-hour postprandial < 7.0 mmol/L (126 mg/dL). These targets will be used by the responsible clinician for glycaemic control following diagnosis of GDM until the birth of the baby until stepped wedged cluster-randomisation occurs for the intervention to: *tight* glycaemic targets for glycaemic control in women newly diagnosed with GDM fasting plasma glucose ≤ 5.0 mmol/L (90 mg/dL); 1-hour postprandial ≤ 7.4 mmol/L 133mg/dL); 2-hour postprandial ≤ 6.7 mmol/L (120 mg/dL). These targets will be used by the responsible clinician for glycaemic control following diagnosis of GDM until the birth of the baby

Crowther 2015 *(Continued)*

Outcomes	Primary outcome: large-for-gestational-age infant (birthweight >90th centile using customised charts). Secondary outcomes: up to the time of hospital discharge after birth: for the woman: pre-eclampsia, induction of labour, mode of birth, gestational weight gain, maternal hypoglycaemia, mean daily fasting and postprandial capillary glucose concentration during treatment, proportion of glucose values within target, diet quality, physical activity, length of postnatal stay, health status, anxiety, depression and breastfeeding at discharge, resource utilisation for the baby: perinatal death, birth trauma, nerve palsy, bone fracture, shoulder dystocia; gestational age at birth, birthweight, macrosomia, small-for-gestational age, length, head circumference, fat mass, respiratory support, hypoglycaemia, hyperbilirubinaemia, lipid and inflammatory markers from cord blood, neonatal intensive care unit admission, length of postnatal stay, resource utilisation
Starting date	29.05.2015.
Contact information	Professor Caroline Crowther, The Liggins Institute, The University of Auckland 85 Park Road, Grafton, Auckland 1023, New Zealand. Ph.+64 9 923 6011; c.crowther@auckland.ac.nz
Notes	Clinical Trial Identifier: ACTRN12615000282583.

Hague 2014

Trial name or title	An evaluation of the safety of very tight glycaemic control versus tight glycaemic control in women with gestational diabetes - GluT pilot
Methods	Randomised controlled trial. Funding: Women's and Children's Hospital, Adelaide, SA, Australia; Robinson Research Institute University of Adelaide, SA, Australia; Novo Nordisk Regional Support Scheme for 2013, Baulkham Hills, NSW, Australia
Participants	40 women with GDM diagnosed on 75 g OGTT: fasting glucose ≥ 5.5 mmol/L (99 mg/dL) and 2 hours glucose ≥ 8.5 mmol/L (153 mg/dL), between 12 and 30 weeks' gestation, with a singleton or twin pregnancy, not previously diagnosed as diabetic, attending antenatal care at collaborating hospitals, and giving informed written consent. Minimum age 18 years Exclusion criteria > 30 + 0 weeks' gestation, or with triplets or higher order gravidity, or with major active medical disorders (including psychiatric disease requiring antipsychotic medication and inflammatory disorders requiring corticosteroid therapy, but not including chronic hypertension)
Interventions	*Very tight* glycaemic control as monitored by self-monitoring of blood glucose with a memory glucometer, aiming to keep fasting capillary blood glucose < 5.0 mmol/L (90 mg/dL) and 2-hour postprandial capillary blood glucose < 6.7 mmol/L (120 mg/dL) until birth, using diet, exercise, insulin, other drugs, as necessary, and at appropriate doses to maintain the control, under the supervision of an obstetric physician and a diabetes nurse educator and *tight* glycaemic* control as monitored by self-monitoring blood glucose with a memory glucometer, aiming to keep fasting capillary blood glucose < 5.5 mmol/L (99 mg/dL) and 2-hour postprandial < 7.0 mmol/L (126 mg/dL) until birth, using diet, exercise, insulin, other drugs, as necessary, and at appropriate doses to maintain the control, under the supervision of an obstetric physician and a diabetes nurse educator *email correspondence confirmed the tight glycaemic targets as stated above. On the ANZCTR very tight and tight glycaemic targets are listed as the same glycaemic targets, which according to Hague is a typo and will be rectified soon. At time of submission of this review it had not been corrected

Outcomes	Primary outcomes: maternal hypoglycaemia: self-monitoring capillary blood glucose < 3.0 mmol/L (54 mg/dL) - number of episodes, symptomatic or not and severe maternal hypoglycaemia: self monitoring capillary blood glucose < 2.5 mmol/L (45 mg/dL) - number of episodes Secondary outcomes: birthweight; neonatal hypoglycaemia in whole blood from heel prick < 2.6 mmol/L (47 mg/dL); severe neonatal hypoglycaemia in whole blood from heel prick < 2.0 mmol/L (36 mg/dL)
Starting date	23.12.2014.
Contact information	Professor William "Bill" Hague, Women's and Children's Hospital, 72 King William Road, North Adelaide, SA 5006, Australia, Ph. +61 4 11114575; bill.hague@adelaide.edu.au
Notes	Clinical Trial Identifier: ACTRN12614001250628.

Scifres 2015

Trial name or title	Randomised controlled clinical pilot trial of intensive management for gestational diabetes (GDM-MOMS)
Methods	Randomised clinical pilot trial designed to assess the feasibility of randomising obese women with GDM to lower glycaemic thresholds compared to standard care Neither patients nor their providers will be blinded to patient study group. All women will receive standard nutritional counselling at the time of diagnosis, and they will also be treated with either glyburide or insulin as dictated by standard care
Participants	60 obese women with a new diagnosis of GDM using the Carpenter-Coustan criteria, singleton gestation, between 20-30 weeks of gestation
Interventions	Active comparator "*Standard care*": target fasting blood glucose values < 95 mg/dL (5.3 mmol/L) and 1-hour postprandial values < 140 mg/dL (7.8 mmol/L) Experimental "*Intensive therapy*": target fasting blood glucose values < 90 mg/dL (5.0 mmol/L) and 1-hour postprandial values < 120 mg/dL (6.7 mmol/L)
Outcomes	Primary outcome: change in baseline maternal glycaemia at 32-36 weeks' gestation. Secondary outcomes: neonatal body composition, cytokine measurements, physical activity, sleep assessments, patient questionnaires, lipid measurements, glucose measurements
Starting date	June 2015 (estimated study completion date: September 2018, estimated primary outcome measure completion date: September 2017)
Contact information	Christina Scifres, MD, University of Oklahoma christy-zornes@ouhsc.edu stephanie-boothroyd@ouhsc.edu
Notes	Clinical Trial Identifier: NCT02530866.

GDM: gestational diabetes mellitus
OGTT: oral glucose tolerance test

DATA AND ANALYSES

Comparison 1.   Intensity of glycaemic control - *strict* **glycaemic targets versus** *liberal* **glycaemic targets**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Caesarean section	1	171	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.83, 2.18]
2 Use of pharmacological therapy	1	171	Risk Ratio (M-H, Fixed, 95% CI)	1.85 [1.14, 3.03]
3 Macrosomia	1	171	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.31, 5.85]
4 Small-for-gestational age	1	171	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.48, 2.63]
5 Gestational age at birth (weeks)	1	171	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-0.73, 0.13]
6 Birthweight	1	171	Mean Difference (IV, Fixed, 95% CI)	-92.0 [-241.97, 57.97]

Analysis 1.1.   Comparison 1 Intensity of glycaemic control - strict glycaemic targets versus liberal glycaemic targets, Outcome 1 Caesarean section.

Review: Different intensities of glycaemic control for women with gestational diabetes mellitus

Comparison: 1 Intensity of glycaemic control - *strict* glycaemic targets versus *liberal* glycaemic targets

Outcome: 1 Caesarean section

Study or subgroup	Stricter target n/N	Liberal target n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Snyder 1998	28/85	21/86		100.0 %	1.35 [0.83, 2.18]
Total (95% CI)	**85**	**86**		**100.0 %**	**1.35 [0.83, 2.18]**
Total events: 28 (Stricter target), 21 (Liberal target)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.22 (P = 0.22)					
Test for subgroup differences: Not applicable					

0.1 0.2 0.5 1 2 5 10

Favours stricter target   Favours liberal target

Analysis 1.2. Comparison 1 Intensity of glycaemic control - strict glycaemic targets versus liberal glycaemic targets, Outcome 2 Use of pharmacological therapy.

Review: Different intensities of glycaemic control for women with gestational diabetes mellitus

Comparison: 1 Intensity of glycaemic control - *strict* glycaemic targets versus *liberal* glycaemic targets

Outcome: 2 Use of pharmacological therapy

Study or subgroup	Stricter target	Liberal target	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
Snyder 1998	33/85	18/86		100.0 %	1.85 [1.14, 3.03]
Total (95% CI)	**85**	**86**		**100.0 %**	**1.85 [1.14, 3.03]**

Total events: 33 (Stricter target), 18 (Liberal target)

Heterogeneity: not applicable

Test for overall effect: Z = 2.47 (P = 0.013)

Test for subgroup differences: Not applicable

0.01   0.1   1   10   100

Favours stricter target   Favours liberal target

Analysis 1.3. Comparison 1 Intensity of glycaemic control - strict glycaemic targets versus liberal glycaemic targets, Outcome 3 Macrosomia.

Review: Different intensities of glycaemic control for women with gestational diabetes mellitus

Comparison: 1 Intensity of glycaemic control - *strict* glycaemic targets versus *liberal* glycaemic targets

Outcome: 3 Macrosomia
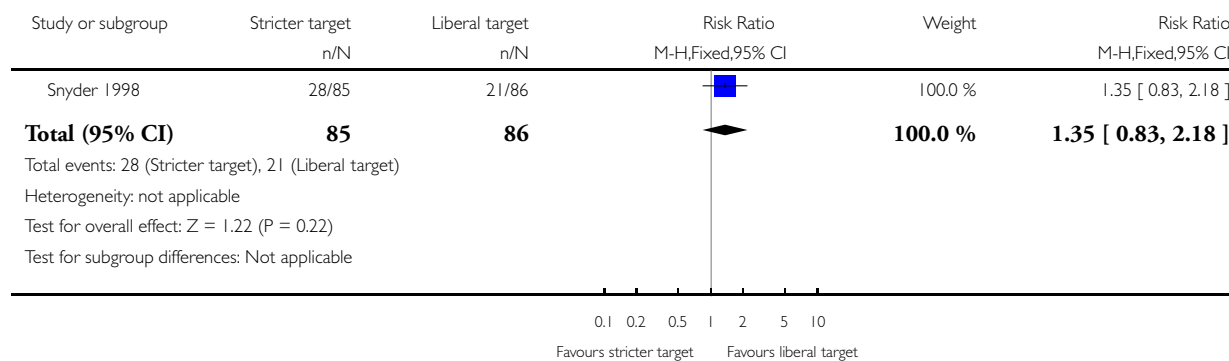
Study or subgroup	Stricter target	Liberal target	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
Snyder 1998	4/85	3/86		100.0 %	1.35 [0.31, 5.85]
Total (95% CI)	**85**	**86**		**100.0 %**	**1.35 [0.31, 5.85]**

Total events: 4 (Stricter target), 3 (Liberal target)

Heterogeneity: not applicable

Test for overall effect: Z = 0.40 (P = 0.69)

Test for subgroup differences: Not applicable

0.01   0.1   1   10   100

Favours stricter targets   Favours liberal targets

Analysis 1.4. Comparison I Intensity of glycaemic control - strict glycaemic targets versus liberal glycaemic targets, Outcome 4 Small-for-gestational age.

Review: Different intensities of glycaemic control for women with gestational diabetes mellitus

Comparison: 1 Intensity of glycaemic control - *strict* glycaemic targets versus *liberal* glycaemic targets
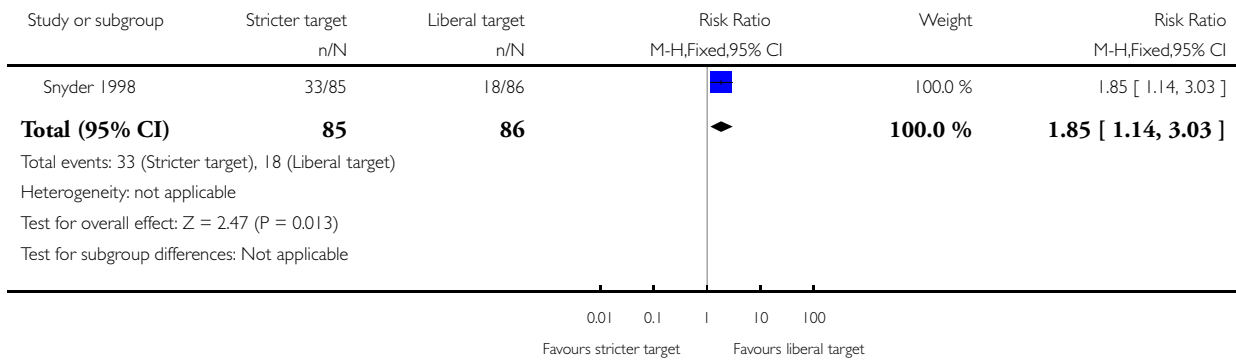
Outcome: 4 Small-for-gestational age

Study or subgroup	Stricter target	Liberal target	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
Snyder 1998	10/85	9/86		100.0 %	1.12 [0.48, 2.63]
Total (95% CI)	**85**	**86**		**100.0 %**	**1.12 [0.48, 2.63]**

Total events: 10 (Stricter target), 9 (Liberal target)

Heterogeneity: not applicable

Test for overall effect: Z = 0.27 (P = 0.79)

Test for subgroup differences: Not applicable

```
         0.01   0.1    I    10    100
```
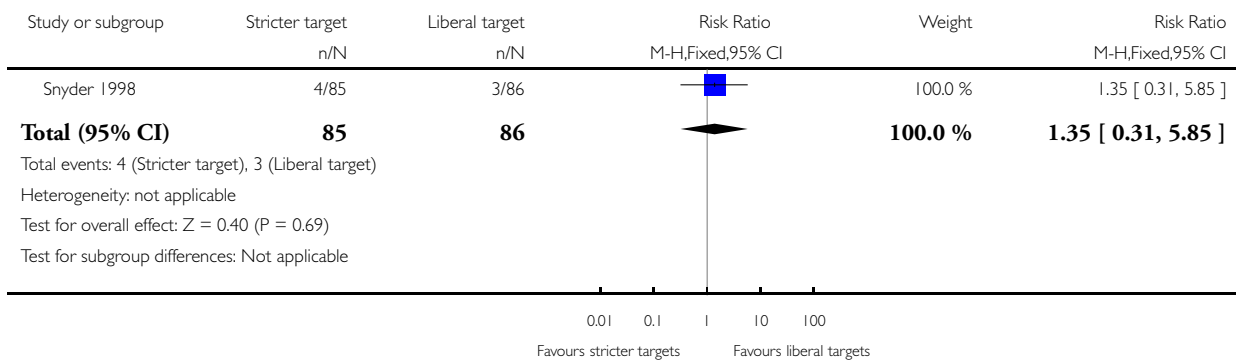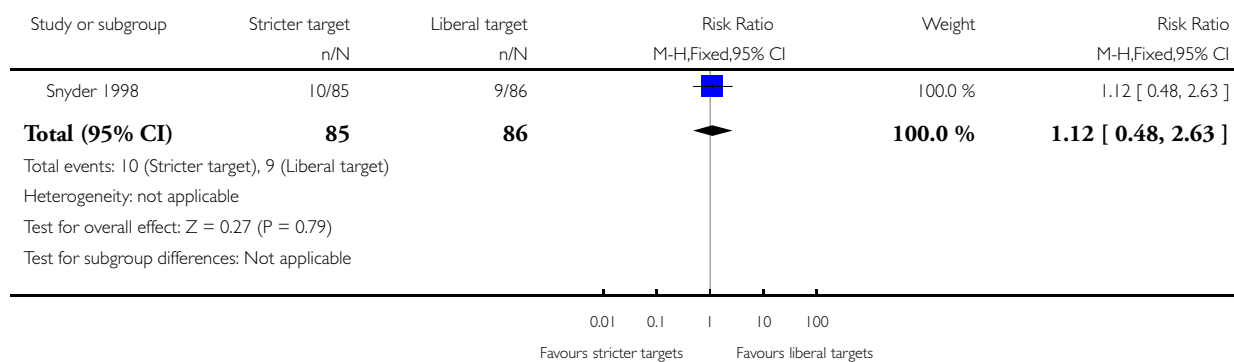Favours stricter targets   Favours liberal targets

Analysis 1.5. Comparison I Intensity of glycaemic control - strict glycaemic targets versus liberal glycaemic targets, Outcome 5 Gestational age at birth (weeks).

Review: Different intensities of glycaemic control for women with gestational diabetes mellitus

Comparison: 1 Intensity of glycaemic control - *strict* glycaemic targets versus *liberal* glycaemic targets

Outcome: 5 Gestational age at birth (weeks)

Study or subgroup	Stricter target		Liberal target		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Snyder 1998	85	38.6 (1.7)	86	38.9 (1.1)		100.0 %	-0.30 [-0.73, 0.13]
Total (95% CI)	**85**		**86**			**100.0 %**	**-0.30 [-0.73, 0.13]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.37 (P = 0.17)

Test for subgroup differences: Not applicable

```
        -4    -2    0    2    4
```
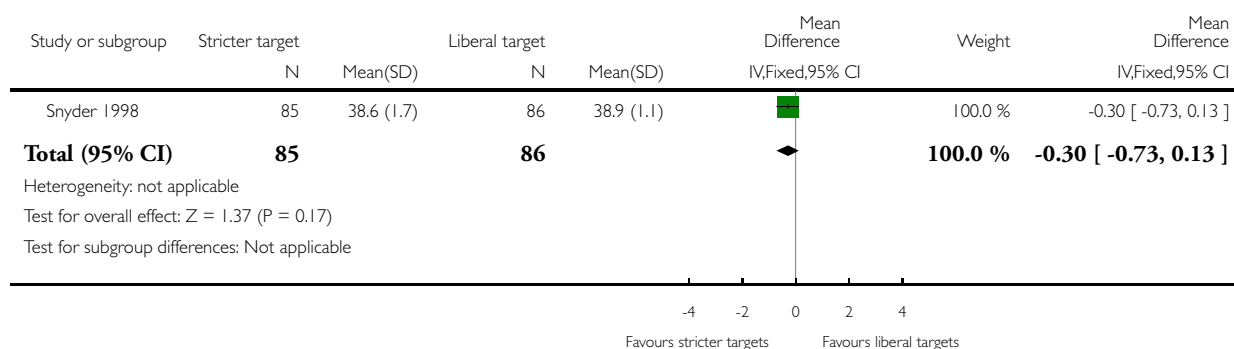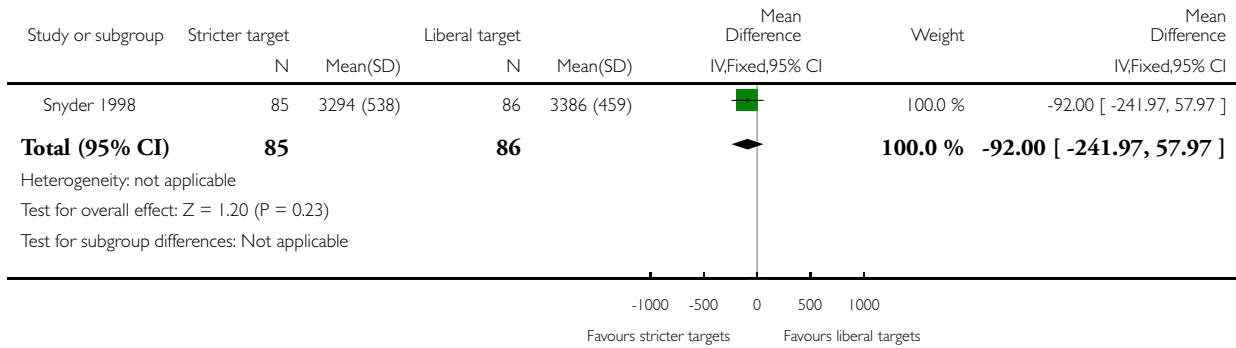Favours stricter targets   Favours liberal targets

Analysis 1.6. Comparison 1 Intensity of glycaemic control - strict glycaemic targets versus liberal glycaemic targets, Outcome 6 Birthweight.

Review: Different intensities of glycaemic control for women with gestational diabetes mellitus

Comparison: 1 Intensity of glycaemic control - *strict* glycaemic targets versus *liberal* glycaemic targets

Outcome: 6 Birthweight

Study or subgroup	Stricter target N	Mean(SD)	Liberal target N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Snyder 1998	85	3294 (538)	86	3386 (459)		100.0 %	-92.00 [-241.97, 57.97]
Total (95% CI)	**85**		**86**			**100.0 %**	**-92.00 [-241.97, 57.97]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.20 (P = 0.23)

Test for subgroup differences: Not applicable

-1000 -500 0 500 1000

Favours stricter targets   Favours liberal targets

ADDITIONAL TABLES

Table 1. GDM treatment targets for glycaemic control from Clinical Practice Guidelines

	Fasting plasma glucose mmol/L (mg/dL)[1]	1-hour postprandial mmol/L (mg/dL)[1]	2-hours postprandial mmol/L (mg/dL)[1]
Australasian Diabetes in Pregnancy Society (ADIPS) Nankervis 2013 (p. 5) and New Zealand Ministry of Health (NZMOH) New Zealand Ministry of Health 2014 (p. 32)	≤ 5.0 (90)	≤ 7.4 (133)	≤ 6.7 (120)
American Diabetes Association (ADA) ADA 2013 (S21) Canadian Diabetes Association (CDA) Thompson 2013 (S178)	≤ 5.3 (95)	≤ 7.8 (140)	≤ 6.7 (120)
National Institute of Health and Clinical Excellence (NICE) NICE 2015 (p. 21)	< 5.3 (95)	< 7.8 (140)	< 6.4 (115)

Table 1. GDM treatment targets for glycaemic control from Clinical Practice Guidelines *(Continued)*

5th International Workshop on GDM Metzger 2007 (S254)	5.0 (90) to 5.5 (99)	< 7.8 (140)	< 6.7 (120) to 7.1 (127)
Scottish Intercollegiate Guidelines Network SIGN 2014 (p. 59)	4.0 (72) to 6.0 (108)	< 8.0 (144)	< 7.0 (126)
German Diabetes Asociation (DDA) Kleinwechter 2014 (p. 404)	3.6 (65) to 5.3 (95)	< 7.8 (140)	< 6.7 (120)

[1]RM converted all published glycaemic values for GDM treatment into both mmol/L or mg/dL

APPENDICES

Appendix 1. Search terms

ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP).
glycemic control AND pregnancy
glycemic control AND pregnant
glycaemic control AND pregnancy
glycaemic control AND pregnant
glycemic control AND gestational
glycemic control AND gestational
gestational diabetes mellitus AND treatment thresholds
gestational diabetes mellitus AND treatment targets

CONTRIBUTIONS OF AUTHORS

Tineke Crawford (TC) and Julie Brown (JB) were both involved in conceiving the review. TC was responsible for preparing the initial draft of the protocol, and designing the search strategies. JB and Caroline Crowther (CC) assisted in the preparation of the protocol. Jane Alsweiler (JA) and Ruth Martis (RM) provided additional comments and feedback.

RM and JB were responsible for the preparation of the review. JA, TC and CC provided feedback and comments throughout the preparation of the review.

DECLARATIONS OF INTEREST

Caroline Crowther, Julie Brown and Jane Alsweiler are principal investigators, and Ruth Martis is a doctoral student on the TARGET randomised controlled trial examining optimal glycaemic targets for GDM which is currently ongoing. None of the authors associated with the TARGET randomised controlled trial will be involved in data extraction or assessment of risk of bias. Tineke Crawford will lead the data extraction for TARGET and we will seek assistance from another researcher not associated with the trial.

SOURCES OF SUPPORT

Internal sources

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Institutional support

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Institutional support

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- National Health and Medical Research Council, Australia Funding for the PCG Australian and New Zealand Satellite, Australia.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The published protocol listed seven maternal and child outcomes together to be assessed for quality using the GRADEpro approach. This has now changed for this review to seven outcomes each, maternal and child (as neonate, child, adult). The authors identified that mother and child outcomes needed to be assessed for quality separately.

We have modified some of the outcomes for this review based on consensus between the review authors and other review authors of Cochrane reviews for treatment of GDM. The outcomes are now in line with the updated outcomes across GDM reviews.

Primary outcomes

For the mother - caesarean section was amended from being a primary outcome to a secondary outcome. Pre-eclampsia was amended to hypertensive disorders of pregnancy (including pre-eclampsia, pregnancy-induced hypertension and eclampsia). Subsequent development of type 2 diabetes was moved from a long-term maternal outcome to a primary outcome.

For the infant - death or severe morbidity (variously defined by trials, e.g. infant death, shoulder dystocia, bone fracture or nerve palsy) was amended from a secondary outcome to a primary outcome.

Secondary outcomes

Deleted outcomes

The following maternal secondary outcomes were deleted: mode of birth (normal vaginal birth, operative vaginal birth, caesarean section); hyperglycaemia requiring changes in management during pregnancy; diabetic ketoacidosis; anxiety.

The following long-term maternal outcomes were deleted: postnatal glucose tolerance; development of type 2 diabetes mellitus; hypertension; blood lipids.

The following neonatal secondary outcomes were deleted: death in infancy or childhood; congenital fetal anomaly; Z scores of birthweight, head circumference, length; neonatal infection; neonatal hyperglycaemia.

The following later childhood outcomes were deleted: appropriate weight for age; anthropometry (weight, height, head circumference, adiposity, skinfold thickness, fat mass); developmental delay (variously defined by individual trials).

The following health service outcome was deleted: length of stay in neonatal intensive care unit/nursery.

Amended outcomes

The following maternal secondary outcomes were amended: hypoglycaemia requiring treatment during pregnancy amended to maternal hypoglycaemia. Glycaemic control achieved (e.g. blood glucose or HbA1c concentrations) (proportion of blood glucose concentrations within target) amended to glycaemic control during/end of intervention (as defined by trialists). Satisfaction with treatment/management amended to views of the intervention; postnatal weight retention amended to postnatal weight retention or return to pre-pregnancy weight. Postnatal depression was moved to long-term maternal outcomes.

The following neonatal secondary outcomes were amended: preterm birth amended to preterm birth (< 37 weeks' gestation; < 32 weeks' gestation); birthweight, head circumference and length amended to birthweight and z score; head circumference and z score and length and z score. Fetal adiposity amended to adiposity; neonatal hypoglycaemia amended to hypoglycaemia (variously defined).

The following adulthood outcomes were amended: metabolic syndrome was amended to dyslipidaemia or metabolic syndrome; glucose tolerance/type 2 diabetes mellitus was amended to type 1 diabetes, type 2 diabetes, Impaired glucose tolerance. Blood pressure and blood lipids were amended to cardiovascular health (as defined by trialists, including blood pressure, hypertension, cardiovascular disease, metabolic syndrome).

The following health service outcomes were amended: maternal antenatal admission amended to length of antenatal stay; additional requirements for families (such as change of diet, exercise, extra antenatal visits, glucose monitoring and strips) amended to costs to families associated with the management provided. Use of healthcare services in pregnancy (consultations, blood glucose monitoring, length and number of antenatal visits, and to whom - midwife/obstetrician/physician) amended to number of antenatal visits or admissions and number of hospital or health professional visits (including midwife, obstetrician, physician, dietician, diabetic nurse).

Additional outcomes

The following maternal secondary outcomes were added: behaviour change associated with the intervention; relevant biomarker changes associated with the intervention (including adiponectin, free fatty acids, triglycerides, high density lipoproteins, low density lipoproteins, insulin); sense of wellbeing and quality of life.

The following long-term maternal outcomes were added: GDM in a subsequent pregnancy; type 1 diabetes mellitus; impaired glucose tolerance; cardiovascular health (as defined by trialists, including blood pressure, hypertension, cardiovascular disease, metabolic syndrome).

The following neonatal secondary outcomes were added: Apgar score < seven at five minutes; polycythaemia; relevant biomarker changes associated with the intervention (including cord c peptide, cord insulin). The following later childhood outcomes were added: weight and z score; height and z score; head circumference and z score; adiposity (including body mass index (BMI), skinfold thickness); blood pressure; type 1 diabetes mellitus; type 2 diabetes mellitus; impaired glucose tolerance; dyslipidaemia or metabolic syndrome; educational achievement.

The following adulthood outcomes were added: weight, height, adiposity (including BMI, skinfold thickness); employment, education and social status/achievement.

The following health service outcomes were added: costs associated with the intervention; length of postnatal stay (baby)

Subgroup analysis and investigation of heterogeneity

Within the methods for subgroup analysis, the following subgroup has been added.

4. Woman's ethnicity as identified from the trials.