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Preconception care for diabetic women for improving maternal and infant health (Review)

Tieu J, Middleton P, Crowther CA, Shepherd E

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[Intervention Review]

Preconception care for diabetic women for improving maternal and infant health

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ABSTRACT

Background

Infants born to mothers with pre-existing type 1 or type 2 diabetes mellitus are at greater risk of congenital anomalies, perinatal mortality and significant morbidity in the short and long term. Pregnant women with pre-existing diabetes are at greater risk of perinatal morbidity and diabetic complications. The relationship between glycaemic control and health outcomes for both mothers and infants indicates the potential for preconception care for these women to be of benefit. This is an update of the original review, which was first published in 2010.

Objectives

To assess the effects of preconception care in women with diabetes on health outcomes for mothers and their infants.

Search methods

We searched Cochrane Pregnancy and Childbirth's Trials Register (31 January 2017) and reference lists of retrieved articles.

Selection criteria

Randomised controlled trials (RCTs) assessing the effects of preconception care for diabetic women. Cluster-RCTs and quasi-RCTs were eligible for inclusion but none were identified.

Data collection and analysis

Two reviewers independently assessed study eligibility, extracted data and assessed the risk of bias of the included studies. We checked data for accuracy and assessed the quality of the evidence using the GRADE approach.

Main results

We included three trials involving 254 adolescent girls with type 1 or type 2 diabetes, with an overall unclear to high risk of bias. The three trials were conducted at diabetes clinics in the USA, and assessed the READY-Girls (Reproductive-health Education and Awareness of Diabetes in Youth for Girls) programme versus standard care.

Considering primary outcomes, one trial reported no pregnancies in the trial period (12 months) (very low-quality evidence, with downgrading based on study limitations (risk of bias) and imprecision); in the other two trials, pregnancy was an exclusion criterion, or was not clearly reported on. None of the trials reported on the other primary maternal outcomes, hypertensive disorders of pregnancy and

caesarean section; or primary infant outcomes, large-for-gestational age, perinatal mortality, death or morbidity composite, or congenital malformations. Similarly, none of the trials reported on the secondary outcomes, for which we had planned to assess the quality of the evidence using the GRADE approach (maternal: induction of labour; perineal trauma; gestational weight gain; long-term cardiovascular health; infant: adiposity; type 1 or 2 diabetes; neurosensory disability).

The majority of secondary maternal and infant outcomes, and outcomes relating to the use and costs of health services were not reported by the three included trials. Regarding behaviour changes associated with the intervention, in one trial, participants in the preconception care group had a slightly higher score for the actual initiation of discussion regarding preconception care with healthcare providers at follow-up (nine months), compared with those in the standard care group (mean difference 0.40, 95% confidence interval -0.02 to 0.82 (on a scale of 0 to 4 points); participants = 87) (a summation of four dichotomous items; possible range 0 to 4, with 0 being no discussion).

Authors' conclusions

There are insufficient RCT data available to assess the effects of preconception care for diabetic women on health outcomes for mothers and their infants.

More high-quality evidence is needed to determine the effects of different protocols of preconception care for diabetic women. Future trials should be powered to evaluate effects on short- and long-term maternal and infant outcomes, and outcomes relating to the use and costs of health services. We have identified three ongoing studies that we will consider in the next review update.

PLAIN LANGUAGE SUMMARY

Preconception care for women with diabetes to improve maternal and infant health

What is the issue?

The aim of this Cochrane review was to find out if giving women with diabetes specialised care before they become pregnant has an impact on their health, and on the health of their future babies. We collected and analysed all relevant studies to answer this question (date of search: January 2017).

Why is this important?

If a woman has type 1 or type 2 diabetes, and she becomes pregnant, she is at a greater risk of high blood pressure, and her baby has a greater risk of being born early (preterm - before 37 weeks). In addition, her pregnancy makes it more likely she will develop one or more of the known complications of diabetes, such as heart disease, problems with the nervous system and eyesight problems. Babies born to mothers with type 1 or type 2 diabetes may be larger, and they have a higher risk of death and abnormality of the spinal column or brain. They are also at risk of developing type 2 diabetes in the long term.

Effective control of blood sugar level (glycaemic control) is part of diabetes care. The relationship between glycaemic control and better health outcomes for mothers and their babies indicates that specialist care before pregnancy (preconception care) could be of benefit. This involves education and support, and help with self-monitoring of blood sugar levels, and self-care.

We searched for studies which looked at preconception care in diabetes clinics.

What evidence did we find?

We found three randomised controlled trials, conducted at diabetes clinics in the USA. The total number of participants in the studies was 254. The participants were all adolescent girls involved in the programme READY-Girls (Reproductive-health Education and Awareness of Diabetes in Youth for Girls). Their care was compared with standard care.

None of these three trials gave us the information on the health outcomes we needed. In one trial, there were no pregnancies among the participants during the period of the study, and the other two trials' reporting of pregnancy was not sufficient. There were no data about short and long term outcomes for the mothers and their babies, or about the use of the health service and related costs.

What does this mean?

Because the information is lacking, we have no evidence from this Cochrane review to guide practice on this topic. Further large, well-designed, randomised controlled trials are required. Three trials are ongoing and will be considered in the next update of this review.

Summary of findings for the main comparison. Preconception care versus standard care for diabetic women: outcomes for the woman

Preconception care versus standard care for diabetic women for improving maternal and infant health: women's outcomes

Patient or population: adolescent girls with type 1 or type 2 diabetes
Setting: USA
Intervention: preconception care
Comparison: standard care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with standard care	Risk with preconception care				
Pregnancy	Study population		not estimable	109 (1 RCT)	⊕⊖⊖⊖ Very low[1,2]	No pregnancies reported in 1 RCT In 2 additional RCTs pregnancy was an exclusion criterion or was not clearly reported
	0 per 1000	0 per 1000 (0 to 0)				
Hypertensive disorders of pregnancy	Study population		not estimable	(0 studies)	-	
	0 per 1000	0 per 1000 (0 to 0)				
Caesarean section	Study population		not estimable	(0 studies)	-	
	0 per 1000	0 per 1000 (0 to 0)				
Perineal trauma	Study population		not estimable	(0 studies)	-	
	0 per 1000	0 per 1000 (0 to 0)				
Gestational weight gain	Study population		not estimable	(0 studies)	-	
	0 per 1000	0 per 1000 (0 to 0)				

Cardiovascular health	Study population		not estimable	(0 studies)	-
	0 per 1000	0 per 1000 (0 to 0)			
Induction of labour	Study population		not estimable	(0 studies)	-
	0 per 1000	0 per 1000 (0 to 0)			

*__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; **RCT**: randomised controlled trial; **RR:** Risk ratio

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

[1]The study had design limitations (-1).
[2]No events and small sample size (-2).

Summary of findings 2. Preconception care versus standard care for diabetic women: outcomes for the child

Preconception care versus standard care for diabetic women for improving maternal and infant health: child outcomes

Patient or population: adolescent girls with type 1 or 2 diabetes
Setting: USA
Intervention: preconception care
Comparison: standard care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with standard care	Risk with preconception care				
Large-for-gestational age	Study population		not estimable	(0 studies)	-	
	0 per 1000	0 per 1000 (0 to 0)				

Perinatal mortality	Study population		not estimable	(0 studies)	-
	0 per 1000	0 per 1000 (0 to 0)			
Death or morbidity composite	Study population		not estimable	(0 studies)	-
	0 per 1000	0 per 1000 (0 to 0)			
Congenital malformations	Study population		not estimable	(0 studies)	-
	0 per 1000	0 per 1000 (0 to 0)			
Adiposity	Study population		not estimable	(0 studies)	-
	0 per 1000	0 per 1000 (0 to 0)			
Type 1 or 2 diabetes	Study population		not estimable	(0 studies)	-
	0 per 1000	0 per 1000 (0 to 0)			
Neurosensory disability	Study population		not estimable	(0 studies)	-
	0 per 1000	0 per 1000 (0 to 0)			

*__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

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

BACKGROUND

Description of the condition

The system of glucose control by insulin can be disrupted in two ways. A problem with insulin release can occur, such as in type 1 diabetes mellitus. Alternatively, insulin may not act as effectively in promoting glucose uptake. This is known as insulin resistance, and is seen in type 2 diabetes mellitus and gestational diabetes mellitus. Pre-existing diabetes refers to pregnant women who have previously been diagnosed with type 1 or type 2 diabetes mellitus, or other rare types of diabetes mellitus. Interconception care for women who have a history of gestational diabetes mellitus in a previous pregnancy is the topic of another Cochrane Review (Tieu 2013). Routine preconception care is evaluated in the Whitworth 2009 Cochrane Review.

Infant effects

It is widely acknowledged that pre-existing diabetes in pregnant women is associated with increased risk of stillbirth, neonatal mortality and congenital anomalies (Abell 2016; Negrato 2012; Ornoy 2015). Major congenital malformations among infants born to women with pre-existing diabetes may be found in the following systems: cardiovascular (e.g. cardiac transportation of the great arteries; ventricular septal defects), central nervous (e.g. neural tube defects), gastrointestinal (e.g. duodenal atresia), musculoskeletal (e.g. arthrogryposis), urinary tract (e.g. hydronephrosis), as well as caudal regression syndrome, cleft lips and palate anomalies (Negrato 2012).

Fetal hyperinsulinaemia associated with pre-existing diabetes can contribute to neonatal morbidity in a similar way to its effect in gestational diabetes. As well as an increased risk of perinatal mortality, pre-existing diabetes has been associated with adverse outcomes including macrosomia, large-for-gestational age, shoulder dystocia, neonatal hypoglycaemia, preterm birth, hyperbilirubinaemia, hypocalcaemia and neonatal intensive care unit admission (Abell 2016; Abell 2017; Negrato 2012).

Infants born to women with pre-existing diabetes are also at an increased risk of developing obesity, type 2 diabetes and cardiovascular disease in the long term (Abell 2016; Negrato 2012). This effect is attributed to the intrauterine environment and genetic predisposition (Abell 2016; Negrato 2012). Infants born to diabetic women may also have an increased risk of long term adverse neurodevelopmental outcomes, such as gross and fine motor abnormalities, attention deficit hyperactivity disorder, learning difficulties, and possibly autism spectrum disorder (Ornoy 2015).

Maternal effects

Pre-existing diabetes has been associated with adverse outcomes for women including caesarean section, pregnancy-induced hypertension and pre-eclampsia (Abell 2016; Negrato 2012; Ornoy 2015). Pregnancy may also accelerate the effects of diabetes on renal function in women with moderate to severe renal insufficiency and uncontrolled hypertension (Negrato 2012; Ornoy 2015). Pregnancy is also a risk factor for progression of diabetic retinopathy (Negrato 2012). Additionally, diabetes-induced heart disease may worsen in women with pre-existing diabetes during pregnancy (Ornoy 2015).

Description of the intervention

Education

Clinical guidelines have placed a strong emphasis on patient education on the risks of diabetes and pregnancy (ADA 2017; ADIPS 2005; NICE 2015; Thompson 2013). They explain the risks to both mother and infant, and the potential for these risks to be reduced through adequate glycaemic control, and they stress that women should continue contraception until target glycaemic control has been reached (ADA 2017; ADIPS 2005; NICE 2015; Thompson 2013).

Management of diabetes

Because of the strong association between glycaemic control, as measured by glycated haemoglobin (HbA1c), and congenital anomalies, glycaemic targets are central to preconception care. Glucose and HbA1c levels are achieved through adequate nutritional therapy, (short-acting) insulin therapy and self-monitoring of blood glucose concentrations (ADA 2017; ADIPS 2005; NICE 2015). Insulin is preferred for diabetes management due to limited evidence on the safety and efficacy of oral anti-diabetic agents (ADA 2017; ADIPS 2005; NICE 2015). The use of an oral agent (e.g. metformin) may be suggested as an alternative to insulin therapy (NICE 2015). While aiming to achieve glycaemic targets, women are also warned to avoid hypoglycaemia.

Diabetes complication assessments

An assessment of diabetes-related complications is commonly recommended as part of determining the progression of diabetes (ADA 2017; ADIPS 2005; NICE 2015). This includes investigations and examinations for retinal, renal and vascular complications (ADA 2017; ADIPS 2005; NICE 2015; Thompson 2013). These assessments may also provide an indication of how pregnancy may affect the progression of diabetes in the mother.

Multidisciplinary approach

While there is a strong focus on glycaemic control, preconception care is multidisciplinary. The healthcare team may include an obstetrician, endocrinologist or other physician with experience of diabetes in pregnancy, dietitian, diabetes educator and other health professionals as required (ADA 2017; ADIPS 2005). This approach is suggested to ensure adequate support from preconception through to the postnatal period in terms of diabetes and pregnancy complications but also to provide psychosocial support (ADA 2017).

Cost effectiveness

A recent study (estimating the preconception care-preventable health and cost burden of adverse birth outcomes associated with diagnosed and undiagnosed diabetes preconception in the United States), suggested a substantial health and cost burden that could be prevented by universal preconception care, thus offsetting the cost of providing such care (Peterson 2015).

How the intervention might work

The exact pathogenesis of diabetes-related pregnancy complications is believed to be multifactorial. While the risk of congenital malformations has been strongly associated with glycaemic control (with high glucose concentrations during critical periods of development believed to be the major teratogen in diabetic pregnancies), the precise mechanisms by which

malformations occur have not been conclusively determined (Negrato 2012; Ornoy 2015). In addition to hyperglycaemia itself, hyperketonaemia, and disordered metabolism of arachidonic acid, myo-inositol and prostaglandin, as well as increased oxidative stress, have all been associated with changes in embryonic development in the pregnancies of diabetic women (Negrato 2012; Ornoy 2015).

Glycaemic control in pregnancy

Glycaemic control can be measured in several ways, but is most commonly reflected by blood glucose concentrations or HbA1c levels. Blood glucose, while easy to measure, is highly variable and dependent on many factors. HbA1c, however, provides a picture of glycaemic control over a prolonged period of several weeks or months prior to the test and is, therefore, commonly considered a better indicator of overall glycaemic control. Both have been used in the preconception care of diabetic women, and a strong focus is often placed on achieving target HbA1c levels (ADA 2017; ADIPS 2005; NICE 2015; Thompson 2013).

In women with pre-existing diabetes, pregnancy planning, and improved glycaemic control prior to and during pregnancy, have been associated with reductions in adverse outcomes, including pregnancy loss and congenital malformations (Kekäläinen 2016; Kitzmiller 2010; Pearson 2007). A systematic review and meta-analysis of observational evidence supported an association between preconception care for diabetic women and improved glycaemic control (lower HbA1c in the first trimester of pregnancy), as well as reductions in congential malformations, preterm birth and perinatal mortality (Wahabi 2010). Thus, achieving and maintaining adequate glycaemic control is likely to be an important component of preconception care for diabetic women.

Why it is important to do this review

Type 1 and type 2 diabetes are becoming increasingly prevalent worldwide. With the potential adverse effects of diabetes on mothers and their infants, there is an urgent need for adequate management of diabetic women in the preconceptual period. This is an update of the original review, which was first published in 2010 (Tieu 2010).

OBJECTIVES

To assess the effects of preconception care in women with diabetes on health outcomes for mothers and their infants.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials, quasi-randomised controlled trials and cluster-randomised trials were eligible for inclusion. Due to the nature of the topic being considered, cross-over trials were not eligible for inclusion.

Types of participants

Women of reproductive age with diabetes mellitus (type 1 or type 2) who were not pregnant.

Types of interventions

Any protocol for preconception care of diabetic women compared with no preconception care, or one protocol of preconception care compared with another protocol of preconception care.

Types of outcome measures

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

Primary outcomes

For the woman

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

For the child

- Large-for-gestational age
- Perinatal mortality (stillbirth and neonatal mortality)
- Death or morbidity composite (variously defined by trials, e.g. infant death, shoulder dystocia, bone fracture or nerve palsy)
- Congenital malformations (e.g. neural tube defects including anencephaly, spina bifida)

Secondary outcomes

For the woman

All women (preconception - before and after intervention commenced, antenatal, postnatal)

- Adherence to the intervention
- Behaviour changes associated with the intervention
- Sense of well-being and quality of life
- Views of the intervention
- Use of pharmacotherapy (insulin use; oral anti-diabetic agent use)
- Glycaemic control during/end of intervention (HbA1c or blood glucose)
- Hypoglycaemia
- Mortality
- Diabetic complications (e.g. retinopathy, nephropathy, neuropathy, ischaemic heart disease, cerebrovascular disease, peripheral vascular disease)
- Body mass index

If pregnant during trial period

- Operative vaginal birth
- Induction of labour
- Perineal trauma
- Placental abruption
- Postpartum haemorrhage
- Postpartum infection
- Gestational weight gain
- Breastfeeding (e.g. at discharge, six weeks postpartum)

Long-term

- Postnatal depression
- Postnatal weight retention or return to pre-pregnancy weight
- Cardiovascular health (e.g. blood pressure, hypertension, cardiovascular disease, metabolic syndrome)

For the child

Neonatal/infant

- Abortion (spontaneous or therapeutic)/miscarriage
- Stillbirth
- Neonatal mortality
- Postneonatal mortality
- Gestational age at birth
- Preterm birth (less than 37 weeks' gestation and less than 32 weeks' gestation)
- Apgar score (less than seven at five minutes)
- Macrosomia
- Small-for-gestational age
- Birthweight and z score
- Length and z score
- Head circumference and z score
- Ponderal index
- Adiposity
- Shoulder dystocia
- Bone fracture
- Nerve palsy
- Respiratory distress syndrome
- Hypoglycaemia
- Hyperbilirubinaemia
- Hypocalcaemia
- Polycythaemia

Later infant, childhood/adulthood

- Weight and z scores
- Height and z scores
- Head circumference and z scores
- Adiposity
- Type 1 diabetes
- Type 2 diabetes
- Impaired glucose tolerance
- Cardiovascular health (e.g. blood pressure, hypertension, cardiovascular disease, dyslipidaemia, metabolic syndrome)
- Employment, education and social status/achievement
- Neurosensory disability

Health service use

- Number of hospital or health professional visits (e.g. midwife, obstetrician, physician, dietitian, diabetic nurse)
- Number of antenatal visits or admissions
- Length of antenatal stay
- Neonatal intensive care unit admission
- Length of postnatal stay (mother)
- Length of postnatal stay (baby)
- Costs to families associated with the management provided
- Costs associated with the intervention
- Cost of maternal care
- Cost of offspring care

Search methods for identification of studies

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

Electronic searches

We searched Cochrane Pregnancy and Childbirth's Trials Register by contacting their Information Specialist (31 January 2017).

The Register is a database containing over 23,000 reports of controlled trials in the field of pregnancy and childbirth. For full search methods used to populate Cochrane Pregnancy and Childbirth's Trials Register including the detailed search strategies for CENTRAL, MEDLINE, Embase and CINAHL; the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service, please follow this link to the editorial information about Cochrane Pregnancy and Childbirth in the Cochrane Library and select the '***Specialized Register***' section from the options on the left side of the screen.

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

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. monthly searches of CINAHL (EBSCO);
5. handsearches of 30 journals and the proceedings of major conferences;
6. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.
7. scoping searches of ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP).

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

Searching other resources

We searched the reference lists of retrieved studies.

We did not apply any language or date restrictions.

Data collection and analysis

For methods used in the previous version of this review, see Tieu 2010.

For this update, we used the following methods for assessing the 12 reports that were identified as a result of the updated search.

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

Selection of studies

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

Data extraction and management

We designed a form to extract data. For eligible studies, two reviewers extracted the data using the agreed form. We resolved discrepancies through discussion or, if required, we consulted a third reviewer. We entered data into Review Manager 5 (RevMan 5) software (RevMan 2014) and checked them for accuracy.

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

Assessment of risk of bias in included studies

Two reviewers independently assessed risk of bias for each trial using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreement was resolved by discussion or by involving a third reviewer.

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

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

We assessed the method as:

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

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

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

We assessed the methods as:

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

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

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

We assessed the methods as:

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

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

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

We assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

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

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

We assessed methods as:

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

(5) Selective reporting (checking for reporting bias)

We described for each included trial 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 trial's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the trial's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest were reported

incompletely and so could not be used; trial failed to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

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

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

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the*Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). With reference to (1) to (6) above, we planned to assess the likely magnitude and direction of the bias and whether we considered it was likely to impact on the findings. In future updates, we will 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

For this update we planned to use the GRADE approach as outlined in the GRADE handbook in order to assess the quality of the body of evidence relating to the following outcomes for the main comparison. The following outcomes are taken from the GRADE standard outcome set agreed by consensus between review authors of Cochrane Pregnancy and Childbirth systematic reviews for prevention and treatment of gestational diabetes mellitus (GDM) and pre-existing diabetes.

For the woman

- Pregnancy
- Hypertensive disorders of pregnancy
- Caesarean section
- Perineal trauma
- Induction of labour
- Gestational weight gain
- Cardiovascular health

For the child

- Large-for-gestational age
- Perinatal mortality
- Death or morbidity composite
- Congenital malformations
- Adiposity
- Type 1 or 2 diabetes
- Neurosensory disability

We used GRADEpro Guideline Development Tool (GRADEproGDT) to import data from RevMan 5 (RevMan 2014) in order to create 'Summary of findings' tables. We produced a summary of the intervention effect and a measure of quality for each of the above outcomes using the GRADE approach, which uses five considerations (trial limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

Measures of treatment effect

Dichotomous data

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

Continuous data

For continuous data, we used the mean difference. We planned to use the standardised mean difference to combine trials that measured the same outcome, but used different methods.

Unit of analysis issues

Cluster-randomised trials

We planned to include cluster-randomised trials in the analyses along with individually randomised trials. In future updates of this review, if we include cluster-randomised trials, we will adjust their sample sizes using the methods described in the *Cochrane Handbook of Systematic Reviews of Interventions,* using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from another source. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the effect of variation in the ICC. If we identify both cluster-randomised trials and individually randomised trials, we will synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the trial designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

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

Cross-over trials

We planned to exclude any cross-over trials due to the nature of the outcomes we are considering.

Dealing with missing data

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

For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis, that is, we attempted to include all participants randomised to each group in the analyses. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We planned to assess statistical heterogeneity in each meta-analysis using the Tau^2, I^2 (Higgins 2003) and Chi^2 statistics. We planned to regard heterogeneity as substantial if I^2 was greater than 30% and either Tau^2 was greater than zero, or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity. If we had

identified substantial heterogeneity (above 30%), we planned to explore it by pre-specified subgroup analysis (Deeks 2011).

Assessment of reporting biases

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

Data synthesis

We carried out statistical analysis using RevMan 5 software (RevMan 2014). We planned to use fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: that is, where trials were examining the same intervention, and we judged the trials' populations and methods to be sufficiently similar.

If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, we planned to use random-effects meta-analysis to produce an overall summary if an average treatment effect across trials was considered clinically meaningful. We planned to treat the random-effects summary as the average range of possible treatment effects and we planned to discuss the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful, we planned to not combine trials. If we had used random-effects analyses, the results would have been presented as the average treatment effect with 95% confidence intervals, and the estimates of Tau^2 and I^2.

Subgroup analysis and investigation of heterogeneity

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

We planned to carry out the following subgroup analyses.

- Intensity of intervention programme (how often, how long, type of health professional(s) - trials would be characterised as reported and categorised where there was sufficient information)
- Type of intervention programme (variations include supports - individual or group intervention and partner support, mode - verbal or written, content - glycaemic control targets, dietary and lifestyle advice, etc)

We planned to use primary outcomes in subgroup analyses.

We planned to assess subgroup differences by interaction tests available within RevMan 5 (RevMan 2014). We planned to report the results of subgroup analyses quoting the Chi^2 statistic and P value, and the interaction test I^2 statistic value.

Sensitivity analysis

We planned to carry out sensitivity analyses to explore the effect of trial quality assessed by concealment of allocation, high attrition rates, or both, with poor-quality studies being excluded from the analyses in order to assess whether this made any difference to the overall result.

RESULTS

Description of studies

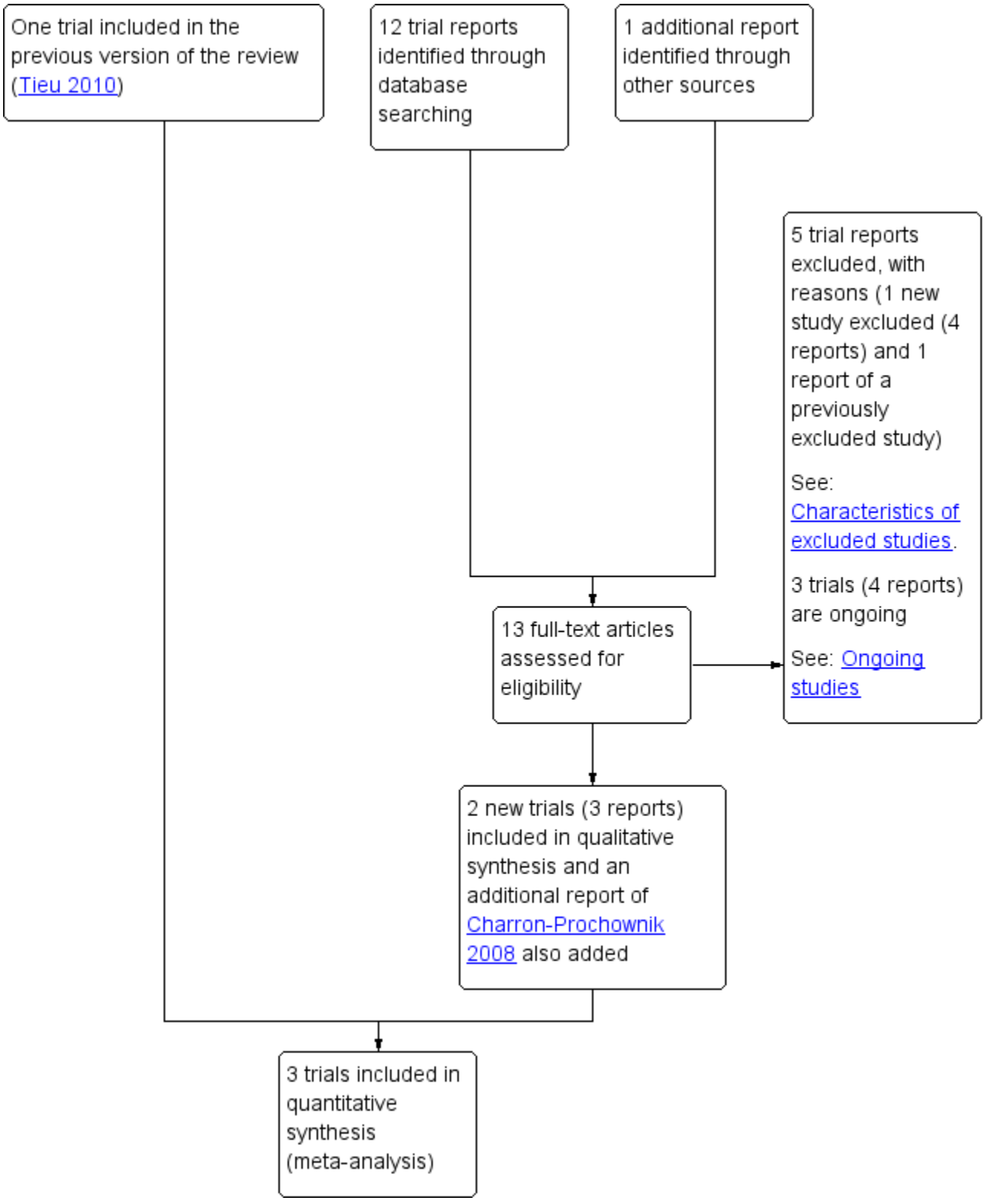
Results of the search

The updated searches identified 13 new trial reports. Following the application of the eligibility criteria, we included two new trials (Charron-Prochownik 2013; Fischl 2010), excluded one new trial (Mathiesen 2012), and identified three new ongoing trials (NCT01788527; NTR2742; NCT02508779).

Previously, we had included one trial (Charron-Prochownik 2008) and excluded two trials (DCCT 1996; Mathiesen 2007).

See: Figure 1.

Figure 1. Study flow diagram



Included studies

The three included studies were randomised controlled trials (Charron-Prochownik 2008; Charron-Prochownik 2013; Fischl 2010).

Settings

All three trials were conducted at diabetes clinics in the USA, with dates of recruitment not reported (Charron-Prochownik 2008; Charron-Prochownik 2013; Fischl 2010).

Participants

In total 254 participants were randomised in the three trials (Charron-Prochownik 2008; Charron-Prochownik 2013; Fischl 2010). All trials recruited adolescent girls, between 13 and 19.9 years (Fischl 2010), 16 and 19.9 years (Charron-Prochownik 2008) and 13 to less than 20 years (Charron-Prochownik 2013), with either type 1 (Charron-Prochownik 2008; Fischl 2010) or type 1 or 2 diabetes (Charron-Prochownik 2013). Two trials did not report any exclusion criteria (Charron-Prochownik 2013; Fischl 2010). Charron-Prochownik 2008 excluded girls with pregnancies during the trial period.

Interventions

All three trials assessed the READY-Girls (Reproductive-health Education and Awareness of Diabetes in Youth for Girls) programme, which was modified over the course of the studies. First, Charron-Prochownik 2008 assessed a CD-ROM and book in two intervention groups, whereby participants received either a self-instructional, developmentally appropriate, evidence-based CD-ROM or a book, as well as one comprehensive counselling session before a routine diabetes clinic visit, with three-month follow-up. Fischl 2010 then assessed the effects of a multiple session intervention of the READY-Girls programme, with the intervention group viewing two CD-ROMs (sessions one and two), reading a book version (session three), and having a brief counselling session with a research nurse during three consecutive diabetes clinic visits over a nine-month period. In Charron-Prochownik 2013, the programme was further modified, with the intervention group viewing two DVDs (sessions one and two), reading a book version (session three), with 12-month follow-up.

Outcomes

The three trials focused on similar outcomes related to reproductive health and preconception care knowledge, attitudes and beliefs, intentions and actual behaviours regarding initiating preconception counselling discussions, and preventing unplanned pregnancies (Charron-Prochownik 2008; Charron-Prochownik 2013; Fischl 2010), though variably reported on additional outcomes, such as metabolic control (HbA1c). An additional report (Thurheimer 2016) presented pooled data from two of the trials (Charron-Prochownik 2008; Fischl 2010) on general risk-taking behaviours, condom use, and sexually transmitted infections. Outcomes were assessed at three- (Charron-Prochownik 2008), nine- (Fischl 2010) and 12-month follow-up (Charron-Prochownik 2013).

Funding and declarations of interest

All three trials reported funding support including from the American Diabetes Association (Charron-Prochownik 2008; Fischl 2010), the General Clinical Research Center of the Children's Hospital of Pittsburgh (Charron-Prochownik 2008; Charron-Prochownik 2013; Fischl 2010), the National Institutes of Health/National Institute of Nursing Research/Center for Research in Chronic Disorders (Charron-Prochownik 2008; Charron-Prochownik 2013; Fischl 2010), and the Pediatric Clinical and Translational Research Center (Charron-Prochownik 2013; Fischl 2010).

Charron-Prochownik 2008 did not report on declarations of interest, and both Fischl 2010and Charron-Prochownik 2013 reported that the authors had no conflicts of interest to declare.

Excluded studies

We excluded three trials (DCCT 1996; Mathiesen 2007; Mathiesen 2012), published as 12 reports, from this review. We excluded the Diabetes Complications and Control Trial (DCCT 1996), since all women planning pregnancy or who became pregnant received the same preconception care. Both Mathiesen 2007 and Mathiesen 2012 evaluated different types of insulin rather than preconception care.

Risk of bias in included studies

Allocation

We judged all three trials to be at unclear risk of selection bias overall. Both Charron-Prochownik 2008 and Fischl 2010 did not report on methods for sequence generation or allocation concealment. Charron-Prochownik 2013 reported that they used a 'minimisation algorithm' to generate the random sequence, but provided no further detail regarding how they had concealed allocation.

Blinding

As it was not feasible to blind participants or trial personnel (due to the nature of the interventions), we judged all three trials to be at high risk of performance bias (Charron-Prochownik 2008; Charron-Prochownik 2013; Fischl 2010). We judged the three trials to be at unclear risk of detection bias, as they did not discuss whether it was possible to blind any of the outcome assessments (and/or the impact of lack of blinding of outcome assessments) (Charron-Prochownik 2008; Charron-Prochownik 2013; Fischl 2010).

Incomplete outcome data

We judged one trial to be at low risk of attrition bias, with only one out of 88 of the participants (from the intervention group) dropping out over the course of the trial (Fischl 2010). We judged one trial to be at high risk of attrition bias, with data not reported for one out of 17 and five out of 20 participants in the intervention and control groups respectively (Charron-Prochownik 2008). The third trial we judged to be at unclear risk of attrition bias, as, while complete data were provided for 109 out of 113 of the participants, the number randomised and lost from each group, and reasons for incomplete data, were not reported (Charron-Prochownik 2013).

Selective reporting

We judged all three trials to be at unclear risk of selective reporting, with none of the trials providing access to a trial registration or published trial protocol to assess reporting bias (Charron-Prochownik 2008; Charron-Prochownik 2013; Fischl 2010). None of the included trials provided the majority of data in a way that allowed us to extract them for inclusion in meta-analyses (that is, mean values reported in figures, with no measures of variance).

Other potential sources of bias

Two of the trials did not provide baseline characteristics by group (Charron-Prochownik 2008; Fischl 2010), while Charron-Prochownik 2013 did report on some limited baseline characteristics, it was difficult to judge comparability, with small

numbers in each group (for example, for the characteristic '≥ 1 episode unprotected sex', this was reported for 64% of intervention group participants versus 36% of control group participants).

Overall risk of bias

In general, assessment of the included trials (Charron-Prochownik 2008; Charron-Prochownik 2013; Fischl 2010) for methodological quality revealed an unclear to high risk of bias (Figure 2; Figure 3). Allocation concealment, blinding and selective reporting biases were unclear.

Figure 2. Methodological quality graph: reviewers' judgements about each methodological quality item presented as percentages across all included studies

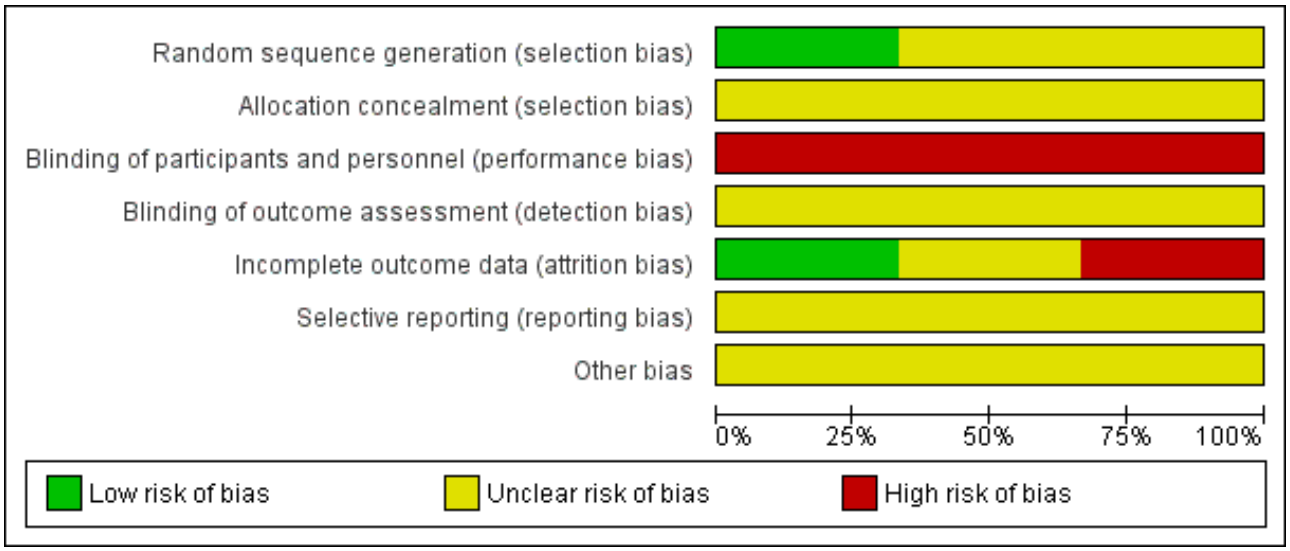
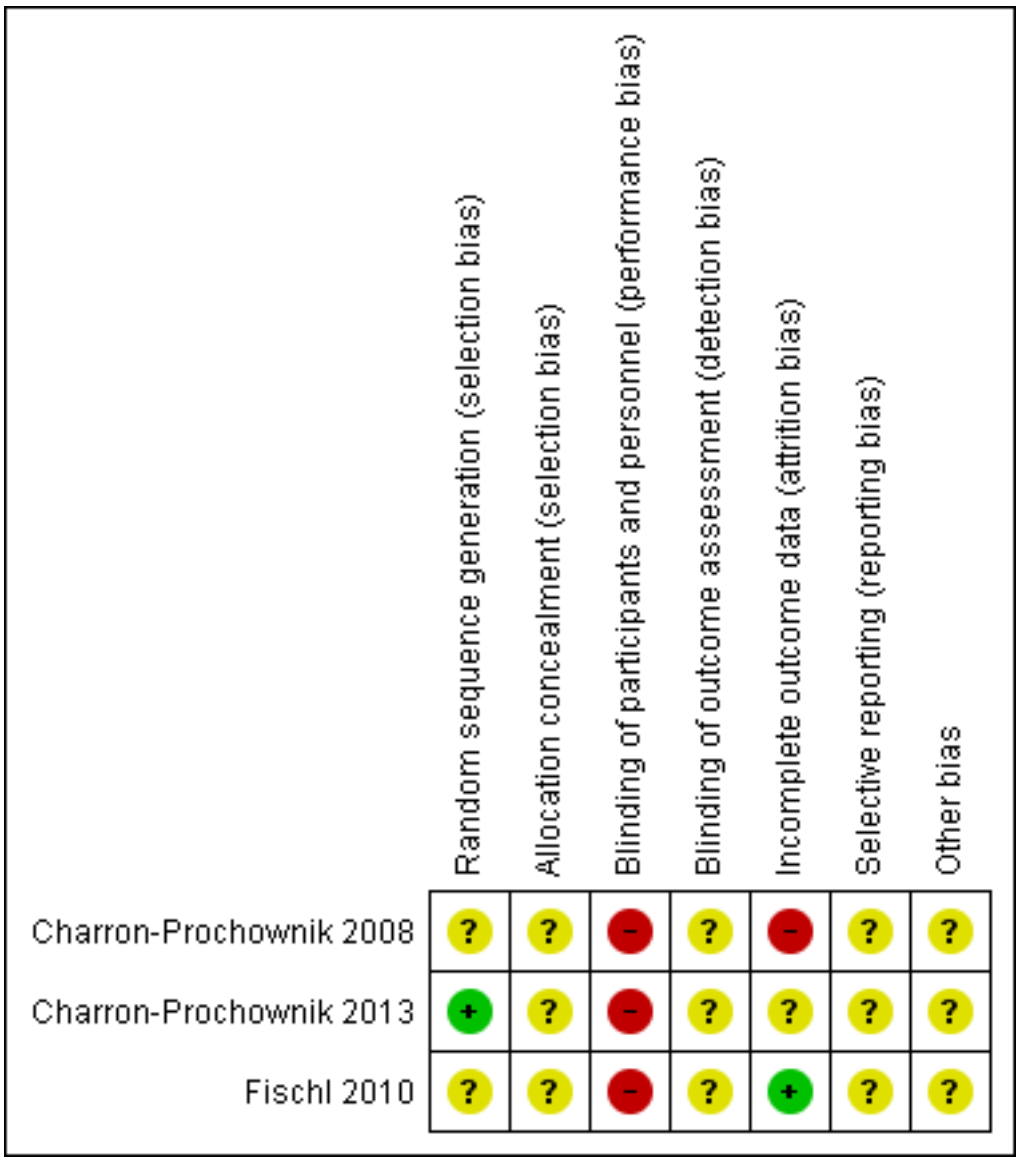


Figure 3. Methodological quality summary: reviewers' judgements about each methodological quality item for each included study



Effects of interventions

See: **Summary of findings for the main comparison** Preconception care versus standard care for diabetic women: outcomes for the woman; **Summary of findings 2** Preconception care versus standard care for diabetic women: outcomes for the child

Preconception care versus standard care for diabetic women

Primary outcomes

For the woman

Pregnancy

Charron-Prochownik 2008 excluded participants with pregnancies during the trial period. Fischl 2010 detailed that "Two participants reported a pregnancy," however it was not reported whether these were previous pregnancies, or pregnancies during the trial period, and from which trial group(s) the adolescent girls with pregnancies came. Charron-Prochownik 2013 reported that there were no pregnancies among the adolescent girls throughout the trial period (12 months) (Analysis 1.1) (very low-quality evidence).

As the three trials (Charron-Prochownik 2008; Charron-Prochownik 2013; Fischl 2010) did not report on any pregnancies among their participants in the trial periods, there were no data available to report on the remaining review outcomes related to pregnancy, for women or their children.

Hypertensive disorders of pregnancy

None of the included trials reported on this outcome.

Caesarean section

None of the included trials reported on this outcome.

For the child

Large-for-gestational age

None of the included trials reported on this outcome.

Perinatal mortality

None of the included trials reported on this outcome.

Death or morbidity composite

None of the included trials reported on this outcome.

Congenital malformations

None of the included trials reported on this outcome.

Secondary outcomes

For the woman

Behaviour changes associated with the intervention

Fischl 2010 reported on the actual initiation of discussion with healthcare provider (a summation of four dichotomous items; possible range 0 to 4, with 0 being no discussion). Adolescent girls in the preconception care group had a higher score for the actual initiation of discussion at nine months, compared with girls in the standard care group (mean difference 0.40, 95% confidence interval -0.02 to 0.82; participants = 87; studies = 1; P = 0.06) (Analysis 1.2). In the text, it was reported that "Only the [intervention group] significantly increased over time with... actual initiation of discussion about (P 0.001) preconception counselling and reproductive health with their diabetes health care team... [intervention group] teens showed only a marginal effect in their consistency to use highly effective birth control methods over time compared with the [standard care] teens (P 0.10)".

Charron-Prochownik 2008 detailed in text that "Actual behaviours (seeking [preconception counselling] and using effective family planning) had no significant group-by-time effect".

An additional report (Thurheimer 2016) detailed a secondary analysis of pooled data from Charron-Prochownik 2008 and Fischl 2010 relating to general risk-taking behaviours, condom use, and sexually transmitted infections (STIs) at three-month follow-up. While it was stated that 136 of the 141 participants from the two trials were included, it was also noted that "Attrition of 28 subjects (21%) occurred for the 3-month follow-up". It was not clear how many girls were in each group at follow-up, and thus we could not include these data in meta-analyses: "When the groups were compared over time, there were no significant interactions or main effects between them on sexual or other risk-taking behaviors" ("ever" unprotected sex, P = 0.498; > 1 sex partner, P = 0.604; "ever" smoked cigarettes, P = 0.883; "ever" used alcohol, P = 0.572; "ever" used illicit drugs, P = 0.502); "When the groups were compared over time, there were no significant differences between them on most frequent birth control use" ("ever" used condoms, P = 0.179); "At 3 months, an additional subject in the RG-C reported an STI... Therefore, there were no significant interactions or main effects between groups" ("ever" diagnosed with STI, P = 0.775).

Charron-Prochownik 2013 reported on behaviour changes at 12 months, however it was not clear how many girls were in each group at follow-up; thus we could not include these data in meta-analyses: "[intervention group] participants, compared with [control group], showed a trend towards lower rates of overall sexual activity; less sexual debut (35 vs. 41%)… and increased abstinence (44 vs. 32%). Although not significant, these patterns were consistent. As expected over time, both groups showed an increase in becoming sexually active (X2 [3] = 18.36, P = 0.0004). There were no significant group, time, or group-by-time effects for abstinence. With regards to risk taking behaviors, there were no significant group-by-time effects of group or time differences at 12 months on the number of partners, unprotected sexual intercourse, or condom use; although fewer IG participants tended to engage in these risky behaviors at the 12-month follow-up visit (for example, 11% [n = 4] of CG vs. 0% of IG had multiple partners at 12 months)...none of the teens reported any actual [preconception counselling] seeking behavior to plan a pregnancy".

Views of the intervention

Charron-Prochownik 2008 reported in text that "Both [the CD and the book] were rated (94-100%) as having helpful, easy-to-understand information".

Glycaemic control during/end of intervention (HbA1c or blood glucose)

Charron-Prochownik 2008 reported on mean percentage change in HbA1C from baseline to three months, however did not provide measures of variance, and thus we could not include these data in the review; the manuscript reports: "A1C had no significant group differences from baseline to 3-month follow-up (P = 0.134). However, those who received the CD had an average decrease of -1% compared with those who received the book (average increase 2%) and control subjects (average increase 8%)".

Outcomes not reported by included trials

None of the included trials reported on any of the other secondary outcomes for the woman pre-specified in this review, including: adherence to the intervention; sense of well-being and quality of life; use of pharmacotherapy; hypoglycaemia; mortality; diabetic complications; body mass index; operative vaginal birth; induction of labour; perineal trauma; placental abruption; postpartum haemorrhage; postpartum infection; weight gain during pregnancy; breastfeeding; postnatal depression; postnatal weight retention or return to pre-pregnancy weight; cardiovascular health

For the child

Outcomes not reported by included trials

None of the included trials reported on any of the secondary outcomes for the child pre-specified in this review, including: abortion/miscarriage; stillbirth; neonatal mortality; postneonatal mortality; gestational age at birth; preterm birth; Apgar score; macrosomia; small-for-gestational age; birthweight; length; head circumference; ponderal index; adiposity; shoulder dystocia; bone fracture; nerve palsy; respiratory distress syndrome; hypoglycaemia; hyperbilirubinaemia; hypocalcaemia; polycythaemia; childhood/adulthood weight; height; head circumference; adiposity; type 1 diabetes; type 2 diabetes; impaired glucose tolerance; cardiovascular health; employment, education and social status/achievement; neurosensory disability.

Health service use

Costs associated with the intervention

Fischl 2010 reported that "the READY-Girls intervention cost [USD] $18 per participant. Thus, it would cost approximately $1,800 to deliver the program to 100 teens… one unplanned pregnancy for a teen in the U.S. would cost approximately $2,800… Thus, if pregnancy were prevented in 1 year for 100 teens, the program costs would be offset. If > 0.6 pregnancies were prevented in 1 year, the program would be cost-saving".

Charron-Prochownik 2013 detailed that "To determine cost-effectiveness, we computed program delivery costs and compared the [intervention group] to [control group] on the probability of becoming pregnant. Self-reported outcome measures included a weighted probability of becoming pregnant calculated for each subject at each time point using an algorithm on the effectiveness and frequency of their [birth control] methods used in the past 3 months. There appeared to be a trend in the direction of decreasing the probability of becoming pregnant for the [intervention group] teens and increasing for the [control group] teens (t = 1.715, P = 0.09)".

Outcomes not reported by included trials

None of the included trials reported on any of the other secondary outcomes relating to the use of health services pre-specified in this review, including: number of hospital or health professional visits; number of antenatal visits or admissions; length of antenatal stay; neonatal intensive care unit admission; length of postnatal stay; costs to families associated with the management provided; cost of maternal care; cost of offspring care.

DISCUSSION

Summary of main results

The effect of pre-existing diabetes on health outcomes for mothers and their infants combined with observational evidence of the benefits of preconception care have prompted the implementation of preconceptual care for women with diabetes (ADA 2017; ADIPS 2005; NICE 2015; Thompson 2013). Various guidelines agree on the need for multidisciplinary care in the management of glycaemic control and diabetic complications. However, there is a lack of high-quality, randomised evidence to support providing preconception care over standard care, or what type of care should be offered.

This review included three small randomised controlled trials, involving 254 adolescent girls with type 1 or type 2 diabetes.

Only one trial (Charron-Prochownik 2013) reported on the maternal primary outcome of 'pregnancy', and reported no pregnancies in the preconception care or standard care groups across the 12-month duration of the trial. One trial (Charron-Prochownik 2008) excluded girls with pregnancies during the trial period, and one (Fischl 2010) did not clearly report on the outcome, pregnancy. Thus, none of the other maternal or child primary outcomes for this review were reported by the included trials. Regarding behaviour changes associated with the intervention, one trial (Fischl 2010) reported a higher score for the actual initiation of discussion at nine months for adolescent girls in the preconception care group, compared with those in the standard care group.

As it was not possible to extract outcome data in a format suitable for input into meta-analyses, we took additional narrative results from the three included trials relating to the review outcomes, behaviour changes associated with the intervention, views of the intervention, glycaemic control, and costs associated with the intervention.

Regarding behaviour changes: Charron-Prochownik 2008, reported no clear differences between groups for seeking preconception counselling and using effective family planning; in Fischl 2010, there was no clear difference for consistency to use highly effective birth control methods over time between groups; and Charron-Prochownik 2013 showed no clear differences between groups for overall sexual activity, sexual debut and abstinence, nor for risk-taking behaviours (number of partners, unprotected sexual intercourse, condom use). Considering views of the intervention, the adolescent girls receiving preconception care in Charron-Prochownik 2008 considered both the CD and book resources to be helpful and easy to understand. In regards to glycaemic control, Charron-Prochownik 2008 reported no clear difference between groups in HbA1c over time. Finally, considering costs associated with the intervention, Fischl 2010 reported that the intervention would be 'cost-saving' if at least 0.6 pregnancies were prevented in one year (based on the intervention costing USD 18 per participant, and one unplanned pregnancy costing approximately USD 2800 in the USA); and in relation to cost-effectiveness Charron-Prochownik 2013 detailed a 'trend' in the direction of decreasing the probability of becoming pregnant for the preconception care group, and increasing the probability for the standard care group.

Overall completeness and applicability of evidence

The evidence is limited in terms of the number of trials available, and in the lack of data reported for the majority of outcomes pre-specified for this review. The trials were all conducted at diabetes clinics in the USA with adolescent girls with type 1 or type 2 diabetes, and assessed the READY-Girls (Reproductive-health Education and Awareness of Diabetes in Youth for Girls) programme (Charron-Prochownik 2008; Charron-Prochownik 2013; Fischl 2010). Thus, the results are unlikely to be applicable to all settings or countries worldwide.

Trials involving preconception care are difficult to design and implement. For example, it is important to consider that outcomes applicable for women receiving preconception care vary significantly depending on whether or not they become pregnant and consequently outcomes for their infants. Future research should not only aim to include health outcomes for mothers and their infants during and after pregnancy, but also collect data on long-term outcomes for both. Outcomes should also include the views of women on the preconception care and the cost-effectiveness of the intervention. The outcomes important to measure in mothers with pre-existing diabetes in pregnancy can have very small prevalence rates, requiring trials to have very large numbers of women. Furthermore, the intensity of care required in multidisciplinary preconception care and long-term follow-up present further hurdles in trial design.

Given the recommendation for preconception care from various guidelines and the existing observational evidence, it may be inappropriate for sites with a preconception care programme as standard to offer a no preconception care arm. It may still be possible, however, to evaluate the provision of preconception

care compared with standard care where no preconception care programme exists. Future trials should also consider comparing different protocols of preconception care, which would be appropriate for sites where preconception care is provided as standard care.

Quality of the evidence

Overall, we judged the risk of bias of the included studies to be unclear to high due to lack of key methodological information.

We assessed the quality of the evidence for one outcome only, pregnancy, and we judged it to be very low. Downgrading was due to trial limitations (risk of bias) and imprecision (Summary of findings for the main comparison). None of the other outcomes selected for judgement using GRADE had reported data.

Potential biases in the review process

A detailed, systematic search was conducted by Cochrane Pregnancy and Childbirth's Information Specialist, without language or publication status restrictions. It is possible that additional trials assessing preconception care for diabetic women have been published but not identified; or that further trials have been conducted but are not yet published. Should any such studies be identified, we will include them in future updates of this review.

In order to minimise bias throughout the review process, two reviewers independently assessed eligibility for inclusion, extracted data and assessed risk of bias.

Agreements and disagreements with other studies or reviews

We identified one additional systematic review of preconception care for diabetic women for improving maternal and fetal outcomes (Wahabi 2010). This systematic review included one controlled trial (DCCT 1996, which we excluded from our review), 11 prospective cohort studies, seven retrospective cohort studies, and one case control study (Wahabi 2010). Meta-analyses of the included observational studies suggested reductions in HbA1c in the first trimester of pregnancy, congenital malformations, preterm birth and perinatal mortality with preconception care.

We also identified a review of the quality and content of clinical guidelines concerned with preconception care of women with diabetes (Mahmud 2010). This review included five guidelines (all judged to be high quality), and determined these to be consistent in their recommendations, including about the risks of congential malformation related to uncontrolled glucose preconceptually, use of contraception prior to achieving adequate glycaemic control, the use of HbA1c to monitor glycaemic control, and when to commence insulin (Mahmud 2010). Differences in recommendations related to optimal targets for metabolic control, and the use of metformin preconceptually and during pregnancy (Mahmud 2010).

AUTHORS' CONCLUSIONS

Implications for practice

At present there is support to provide preconception care for women with diabetes where possible according to various guidelines. There are currently, however, insufficient randomised controlled trial data available to assess the effects of preconception care in women with diabetes on health outcomes for mothers and their infants, or to support any particular protocol of preconception care over another.

Implications for research

In light of the limitations associated with the current evidence, further randomised controlled trials are warranted to determine the effects of preconception care for diabetic women. Future trials must be sufficiently powered, and well-designed to assess women's adherence and views, and to allow important differences in relevant clinical outcomes for mothers and their infants to be detected, including longer-term maternal, infant, child or adult outcomes, or both, and those related to the use and costs of health services.

We have identified three additional trials as being planned or underway. These trials are assessing interventions for achieving optimal glycaemic control preconception (such as through the use of continuous glucose monitoring systems) and we will consider them for inclusion in the next update of this review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Charron-Prochownik 2008

Methods	Randomised controlled trial
Participants	53 girls were randomised **Setting:** diabetes clinic, Pennsylvania, USA; recruitment dates not clear **Inclusion criteria:** adolescent girls aged 16-19.9 years of age, with type 1 diabetes **Exclusion criteria:** pregnancy during trial period (additional information provided by trial authors)
Interventions	**Intervention groups** READY-Girls **CD-ROM group (n = 17):** received a self-instructional, developmentally appropriate, evidence-based CD-ROM and 1 comprehensive session before a routine diabetes clinic visit **Book group (n = 16):** received a self-instructional, developmentally appropriate, evidence-based book and 1 comprehensive session before a routine diabetes clinic visit **Control group (n = 20):** received standard care. Women were seen at routine diabetes clinic visits only
Outcomes	Process evaluation: timing, effort, ease of use, satisfaction Outcome measures: reproductive health and preconception care knowledge, beliefs, intention and behaviours, and metabolic control Outcomes assessed at baseline, post-intervention and 3-month follow-up by questionnaires Note: Thurheimer 2016 pooled data from Charron-Prochownik 2008 and Fischl 2010, and reported on general risk-taking behaviours, condom use, and sexually transmitted infections
Notes	**Funding:** American Diabetes Association Clinical Research Award (1999 –2003), the General Clinical Research Center of Children's Hospital of Pittsburgh (grant M01 RR00084), and the National Institutes of Health/National Institute of Nursing Research/Center for Research in Chronic Disorders (grant P30 NR03924) **Declarations of interest:** not reported
Risk of bias	

Charron-Prochownik 2008 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomized, controlled, repeated-measures feasibility study."
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and personnel not feasible
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors not specified. Data collection for some outcomes used self-administered questionnaires. It was not clear how lack of blinding would affect the outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	High risk	Data not reported for 1 participant from the CD-ROM group and 5 participants from the control group for HbA1c at 3 months (differential proportion of missing data in already small cohort). Note: Thurheimer 2016 presented pooled data from Charron-Prochownik 2008 and Fischl 2010, and reported on outcomes at 3 months for 136/141 (96%) participants across the 2 trials; Thurheimer 2016 reported that attrition of 28/136 (21%) participants occurred for 3-month follow-up; it is not clear how many participants were lost from each group, and how missing data were handled: "It was assumed that the data were missing at random as related to the developmental age of the subjects and not to the outcome variables being studied... Because the goal of the study was to examine the risk-taking behaviors of these particular subjects rather than all adolescents in general, missingness is considered ignorable and therefore missing at random. This allowed for a more unbiased estimation to be made through observed data within each group... It was expected that the subjects would be independent from one study to the next, and since analysis of the same subjects was being tested longitudinally, the data were highly correlated."
Selective reporting (reporting bias)	Unclear risk	Insufficient information to assess, with no access to trial protocol. Results reported in figures (with no measures of variance), including HbA1c reported only as mean % change, with no measure of variance
Other bias	Unclear risk	Baseline characteristics not reported by group

Charron-Prochownik 2013

Methods	Randomised controlled trial
Participants	113 girls were randomised **Setting:** diabetes clinics at 2 university hospitals, USA; dates of recruitment not clear **Inclusion criteria:** adolescent girls between 13 and < 20 years with type 1 or type 2 diabetes for > 1 year **Exclusion criteria:** not described
Interventions	**Intervention group (n = 51 had complete data):** READY-Girls In addition to routine care in the diabetes clinic, girls received the READY-Girls programme over 3 consecutive visits attached to their routine visits. A trained research nurse/research associate prepared the

Charron-Prochownik 2013 *(Continued)*

	computer in a private room for data collection and DVD programme viewing. At baseline, girls were given DVD-1; they received boosters at 3 (DVD-2) and 6 months (book). The first DVD sessions provided evidence-based information (viewing time mean: 36.3 (6.2) minutes); the second DVD included exercises to apply information about preconception counselling from DVD-1 (viewing time of 25.4 (7.4) minutes); in the third session the girls read a book that reinforced the information in DVD-1 (reading time of 20.4 (4.0) minutes). **Control group (n = 58 had complete data):** girls received routine care in the diabetes clinic, including general preconception counselling March of Dimes pamphlets
Outcomes	Diabetes and reproductive health knowledge; attitudes/beliefs, behaviours related to family planning; initiation of preconception care and discussions with healthcare practitioners Data were collected by validated questionnaires at baseline, and each booster session (3 and 6 months) and 12-month follow-up
Notes	**Funding:** Supported by Grant R01-HD-044097 from the National Institutes of Health/Eunice Kennedy Shriver National Institute of Child Health and Human Development, the General Clinical Research Center of the Children's Hospital of Pittsburgh (M01-RR-0084), the Pediatric Clinical and Translational Research Center (National Institutes of Health/National Center for Research Resources/Clinical and Translational Science Award UL1-RR-024153), and the National Institutes of Health/National Institute of Nursing Research/Center for Research in Chronic Disorders (P30-NR-03924) **Declarations of interest:** "No potential conflicts of interest relevant to this article were reported."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomized using a minimization algorithm."
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and personnel not feasible
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors not specified. Data collection for some outcomes used self-administered computer programme. It was not clear how lack of blinding would affect the outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	109/113 girls recruited had complete data; numbers randomised to each group not reported, nor the reasons for incomplete data. Attrition at 12 months was 16% (18/113)
Selective reporting (reporting bias)	Unclear risk	Data presented in text and in figures (e.g. means with no measure of variance). No access to trial registration/protocol to further assess whether all pre-specified outcomes were reported as planned
Other bias	Unclear risk	Manuscript reports "no significant demographic differences between groups at baseline" (relatively small sample; difficult to determine group differences, i.e. ≥ 1 episode unprotected sex: 64% intervention group vs 36% control group)

Fischl 2010

Methods	Randomised controlled trial
Participants	88 girls were randomised **Setting:** 2 university-based diabetes clinics in the northeast section of the USA; dates of recruitment not clear **Inclusion criteria:** adolescent girls, aged 13-19.9 years, with type 1 diabetes **Exclusion criteria:** not described
Interventions	**Intervention group (n = 43):** READY-Girls Standard care plus evidence-based, theory-driven preconception counselling programme tailored for teens with diabetes. The intervention raised awareness; provided information about the effects of diabetes on reproductive health, puberty, sexuality and pregnancy; focused on the benefits of preconception counselling in preventing unplanned pregnancies; enhanced communication skills. Adolescent girls viewed 2 CD-ROMs, read a book version, and had a brief research nurse counselling session during 3 consecutive diabetes clinic visits over a 9-month period. The first CD session provided information on reproductive health and preconception care; the second included exercises to develop communication and decision-making skills concerning pre-conception counselling; in the third, the teens read a book with information that reinforced the information in the CDs; after sessions 2 and 3 the teens had a brief 1-on-1, face-to-face counselling session with research nurses to answer questions about reproductive health and preconception care. **Control group (n = 45):** teens received usual care provided in the paediatric diabetes clinics, involving quarterly (every 3 months) clinic visits **All adolescent girls:** during the first sessions, all teens read a March of Dimes brochure on preconception care
Outcomes	Cognitive, psychosocial and behaviour outcomes based on the Expanded Health Belief Model: reproductive health and preconception counselling knowledge and attitudes; intentions and actual behaviours regarding initiating preconception counselling discussion with the healthcare team and preventing unplanned pregnancies; resource utilisation and cost of the intervention; short-term clinical outcomes and likely long-term clinical outcomes Outcomes were assessed at 4 sessions with self-administered questionnaires (baseline, 3 months, 6 months and 9 months) Note: Thurheimer 2016 pooled data from Charron-Prochownik 2008 and Fischl 2010, and reported on: general risk-taking behaviours, condom use, and sexually transmitted infections
Notes	**Funding:** supported by the American Diabetes Association Clinical Research Award (7-02-CR-06), the General Clinical Research Center of Children's Hospital of Pittsburgh (M01 RR0084), the Pediatric Clinical and Translational Research Center (NIH/NCRR/CTSA UL1 RR024153), and the National Institutes of Health/National Institute of Nursing Research/Center for Research in Chronic Disorders (P30NR03924) **Declarations of interest:** "No potential conflicts of interest relevant to this article were reported."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomized-controlled repeated measures design" "were randomized."
Allocation concealment (selection bias)	Unclear risk	Not described

Fischl 2010 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and personnel not feasible
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors not specified. Data collection for some outcomes used self-administered questionnaires. It was not clear how lack of blinding would affect the outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	1/88 of the teens dropped out of the intervention group. Note: Thurheimer 2016 presented pooled data from Charron-Prochownik 2008 and Fischl 2010, and reported on outcomes at 3 months for 136/141 (96%) participants across the 2 trials; Thurheimer 2016 reported that attrition of 28/136 (21%) participants occurred for 3-month follow-up; it is not clear how many participants were lost from each group, and how missing data were handled: "It was assumed that the data were missing at random as related to the developmental age of the subjects and not to the outcome variables being studied... Because the goal of the study was to examine the risk-taking behaviors of these particular subjects rather than all adolescents in general, missingness is considered ignorable and therefore missing at random. This allowed for a more unbiased estimation to be made through observed data within each group... It was expected that the subjects would be independent from one study to the next, and since analysis of the same subjects was being tested longitudinally, the data were highly correlated."
Selective reporting (reporting bias)	Unclear risk	Not possible to confidently assess with no access to trial protocol, though data not fully reported in a way that allows them to be included in meta-analyses
Other bias	Unclear risk	Baseline characteristics were not presented (only some summary characteristics across the total population); "There were no significant differences in demographic variables between the two group"

Abbreviations: HbA1c: glycated haemoglobin; READY-Girls: Reproductive-health Education and Awareness of Diabetes in Youth for Girls

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

Study	Reason for exclusion
DCCT 1996	All women planning pregnancy or who become pregnant received the same preconception care
Mathiesen 2007	Trial evaluated different types of insulin rather than preconception care
Mathiesen 2012	Trial evaluated different types of insulin rather than preconception care

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

NCT01788527

Trial name or title	Continuous glucose monitoring in women with type 1 diabetes in pregnancy trial (CONCEPTT)
Methods	Randomised controlled trial
Participants	**Inclusion criteria:** clinical diagnosis of type 1 diabetes and using daily insulin therapy for ≥ 1 year; age 18-40 years; insulin regimen involving either the use of an insulin pump or multiple daily injec-

NCT01788527 *(Continued)*

	tions of insulin (≥ 3 shots/d) (women using premixed fixed doses of insulin at the time of enrolment not eligible); insulin regimen must be stable for ≥ 4 weeks (i.e. on multiple insulin injections or on insulin pump) prior to randomisation; no plan to be moving out of the area of the clinical centre during the next year, unless the move will be to an area served by another study centre; informed signed consent **Specific inclusion criteria to the respective groups** **Pre-pregnancy:** women who are planning pregnancy and wish to optimise glycaemic control before conception **Pregnancy:** ≤ 13 weeks' and 6 days' gestation at time of randomisation: live singleton fetus; dating ultrasound done to confirm gestational age, viability and rule out multiples **Exclusion criteria:** type 2 diabetes; GDM; previous participation in the study; estimated GFR < 60 mL/min/1.73; presence of a significant medical disorder or use of a medication such as oral glucocorticoids that in the judgment of the investigator will affect the wearing of the sensors or the completion of any aspect of the protocol; inpatient psychiatric treatment in the past 6 months; subjects using premixed fixed doses of insulin at the time of enrolment **Specific exclusion criteria to the respective groups** **Pre-pregnancy:** HbA1c < 7.0% or > 10.0% **Pregnancy:** HbA1c < 6.5% or > 10.0%; known current higher order pregnancies; known potentially major fetal anomaly
Interventions	**Intervention:** CGM with device **Control:** no intervention, standard of care, home glucose monitoring
Outcomes	**Primary outcomes:** glycaemic control in pre-pregnant group (glycaemic control as measured by HbA1c at 24 weeks or at conception. If the woman becomes pregnant, HbA1c will be measured post-confirmation of a positive pregnancy test and will contribute to the primary outcome); glycaemic control in pregnant group (glycaemic control as measured by HbA1c at 34 weeks' gestation. In women who do not progress to 34 weeks' gestation, the latest measured HbA1c will be used to contribute to the primary outcome) **Secondary outcomes:** time in target in pre-pregnant group; time in target and HbA1c in pregnant group; hypertension; caesarean section; weight gain; area under the curve for blood sugars; severe, moderate, mild hypoglycaemia; glucose variability; length of hospital stay; infant birthweight > 90th centile; pregnancy loss; preterm birth; birth injury; shoulder dystocia; neonatal hypoglycaemia; hyperbilirubinaemia; respiratory distress syndrome; NICU admission; cord blood gas pH < 7.0; hyperinsulinaemia; composite fetal outcome; sum of skin folds > 90th centile; other anthropometric measures
Starting date	Study start date: March 2013 Estimated completion date: July 2017
Contact information	Denice Feig, Mount Sinai Hospital, New York
Notes	Estimated enrolment: 325

NCT02508779

Trial name or title	BGAT (Blood Glucose Awareness Training) for users who might become pregnant (Bump2Be)
Methods	Randomised controlled trial
Participants	**Inclusion criteria:** diagnosed with type 1 diabetes mellitus for ≥ 1 year; either actively trying to get pregnant or planning to become pregnant in the 12 months following enrolment in this study: own and routinely use a blood glucose memory meter; measure blood glucose > 2 times/d; able to download personal blood glucose meter onto a computer; able to read and speak English; able to

NCT02508779 *(Continued)*

	provide informed consent; have regular access to a computer and the internet, be able to view the website content independently; reside in the USA **Exclusion criteria:** residents of another country; unable to travel for blood work
Interventions	**Intervention:** Bump2Be blood glucose awareness training for pregnancy or preconception **Control:** routine care provided by woman's medical team
Outcomes	**Primary outcomes:** reduced frequency of extreme blood glucose (as defined by the low and high blood glucose index); reduced consequences of extreme blood glucose (e.g. diabetic ketoacidosis) **Seondary outcomes:** improved estimation of blood glucose; improved detection of low and high blood glucose; reduced fear of hypoglycaemia; reduced extreme avoidance of hyperglycaemia; improved well-being; improved internal locus of control
Starting date	Study start date: July 2015 Estimated study completion date: October 2016
Contact information	Lee M Ritterband, University of Virginia Behavioral Health and Technology Laboratory, USA
Notes	Estimated enrolment: 58

NTR2742

Trial name or title	Improving preconceptional sub-optimal glycaemic control in type 1 diabetes using RealTime Continuous Glucose Monitoring (RT-CGMS): a randomised clinical trial
Methods	Randomised controlled trial
Participants	**Inclusion criteria:** diagnosed with diabetes mellitus 1 for ≥ 1 year (diagnosis < 30 years of age and anti-GAD antibodies and/or experienced ketoacidosis); insulin pump (connectable with or changeable in a RT-CGMS device of Medtronic) for at least 3 months; reliable performance of SMBG at least 5 times/d for at least 5 d/week; child wish; stable HbA1c 7.0-7.7 (53-61 mmol/mol): if consecutive values (2 months) show a decrease, this decrease is accepted up to (including) 0.5% (5 mmol/mol); age 18-41 years; willing to (woman herself) and capable of (as estimated by treating doctor) using RT-CGMS; able to read and speak Dutch; written informed consent; internet access (uploading results sensor) **Exclusion criteria:** co-existent medical problems that would interfere with study participation; use of medication that could influence glycaemic control (for example corticosteroids) in last 3 months; ≥ 2 severe hypoglycaemia in the last 6 months (defined as an episode of hypoglycaemia resulting in seizure or coma or the use of glucagon or intravenous glucose for recovery)
Interventions	**Intervention:** RT-CGM system every other week for 4 months (intervention group) **Control:** standard extensive care with 2 times a blind CGM system measurement of 48 h (control group)
Outcomes	**Primary outcome:** absolute reduction in HbA1c (HbA1c at the end of study versus HbA1c at inclusion) **Secondary outcomes:** severe hypoglycaemia; women with a fall in HbA1c of ≥ 0.4% (≥ 5 mmol/mol); women that reach target HbA1c (< 7.0% or < 53 mmol/mol); time to reach target HbA1c (< 7.0% or < 53 mmol/mol); numbers of consultations (at the clinic, by telephone, by email); change in glycaemic variability; composite end point: reduction of HbA1 ≥ 0.4% (≥ 5 mmol/mol) without an episode of severe hypoglycaemia; frequency of use RT-CGMS; fear of hypoglycaemia; quality-of-life; satisfaction with the device

NTR2742 *(Continued)*

Starting date	Planned start date: 1 March 2011 Panned completion date: 1 September 2012
Contact information	Dr LBEA Hoeks, University Medical Centre, Utrecht
Notes	Estimated enrolment: 20

Abbreviations: CGM: continuous glucose monitoring; GAD: glutamic acid decarboxylase; GDM: gestational diabetes mellitus; GFR: glomerular filtration rate; HbA1c: glycated haemoglobin; NICU: neonatal intensive care unit; RT-CGMS: real-time continuous glucose monitoring system; SMBG: self-monitoring of blood glucose

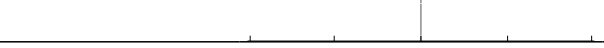
DATA AND ANALYSES

Comparison 1. Preconception care versus standard care for diabetic women

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pregnancy	1	109	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Behaviour changes associated with the intervention	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Initiating discussions about preconception counselling and reproductive health with diabetes healthcare team: 9-month follow-up	1	87	Mean Difference (IV, Fixed, 95% CI)	0.40 [-0.02, 0.82]

Analysis 1.1. Comparison 1 Preconception care versus standard care for diabetic women, Outcome 1 Pregnancy.

Study or subgroup	Preconception care n/N	Standard care n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Charron-Prochownik 2013	0/51	0/58			Not estimable
Total (95% CI)	**51**	**58**			**Not estimable**
Total events: 0 (Preconception care), 0 (Standard care)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



Analysis 1.2. Comparison 1 Preconception care versus standard care for diabetic women, Outcome 2 Behaviour changes associated with the intervention.

Study or subgroup	Preconception care N	Mean(SD)	Standard care N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.2.1 Initiating discussions about preconception counselling and reproductive health with diabetes healthcare team: 9-month follow-up							
Fischl 2010	42	1.4 (1)	45	1 (1)		100%	0.4[-0.02,0.82]
Subtotal ***	**42**		**45**			**100%**	**0.4[-0.02,0.82]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.89(P=0.06)							

WHAT'S NEW

Date	Event	Description
31 January 2017	New search has been performed	Searched updated. Methods updated, including two 'Summary of findings' tables. One new author (Emily Shepherd) was involved in this update. We have updated our primary and secondary review outcomes to be in line with those standard outcomes that are/will be used in other Cochrane Pregnancy and Chilbirth diabetes in pregnancy reviews (which we have adapted, as appropriate).
31 January 2017	New citation required and conclusions have changed	Two new trials included (Charron-Prochownik 2013; Fischl 2010). Additional outcome data (predominately narrative) for: pregnancy; behaviour changes associated with the intervention; women's views of the intervention; glycaemic control; costs associated with the intervention.

HISTORY

Protocol first published: Issue 2, 2009
Review first published: Issue 12, 2010

Date	Event	Description
10 January 2011	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

In this update of the review Emily Shepherd, assessed studies for eligibility and extracted data. Emily Shepherd drafted the first version of the update and all review authors made comments on subsequent drafts and contributed to the final version.

In the previous version of this review Joanna Tieu and Philippa Middleton assessed studies for inclusion and extracted data. Caroline Crowther also consulted on study inclusion and data extraction. The review was written by Joanna Tieu with help and regular feedback from Caroline Crowther and Philippa Middleton.

Joanna Tieu researched and wrote the protocol with aid and regular feedback from Professor Caroline Crowther and Philippa Middleton.

DECLARATIONS OF INTEREST

Joanna Tieu: is supported by an NHMRC postgraduate scholarship and Arthritis Australia Ken Muirden fellowship (jointly funded by the Australian Rheumatology Association and Roche).

Philippa Middleton: none known.

Caroline A Crowther: none known.

Emily Shepherd: none known.

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Internal sources

- ARCH: Australian Research Centre for Health of Women and Babies, Robinson Research Institute, The University of Adelaide, Australia.

External sources

- NHMRC: National Health and Medical Research Council, Australia.

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- NIHR: National Institute for Health Research, UK.

  NIHR Cochrane Programme Grant Project: 13/89/05 – Pregnancy and childbirth systematic reviews to support clinical guidelines

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In this update of the review:

- we have updated our primary and secondary review outcomes to be in line with those standard outcomes that are/will be used in other Cochrane Pregnancy and Chilbirth diabetes in pregnancy reviews (which we have adapted, as appropriate);
- we have updated the methods in line with those in the standard template used by Cochrane Pregnancy and Childbirth;
- we have used the GRADE approach to assess the quality of the body of evidence and we have included 'Summary of findings' tables.

INDEX TERMS

Medical Subject Headings (MeSH)

*CD-ROM; Diabetes Mellitus, Type 1 [blood] [*therapy]; Diabetes Mellitus, Type 2 [blood] [*therapy]; Glycated Hemoglobin A [metabolism]; Intention to Treat Analysis; Patient Education as Topic [methods]; Preconception Care [*methods]; Randomized Controlled Trials as Topic

MeSH check words

Adolescent; Female; Humans; Pregnancy; Young Adult