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Author(s)	Biesty, Linda M.; Egan, Aoife M.; Dunne, Fidelma P.; Smith, Valerie; Meskell, Pauline; Dempsey, Eugene M.; Ni Bhuinneain, G. Meabh; Devane, Declan
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Planned birth at or near term for improving health outcomes for pregnant women with pre-existing diabetes and their infants (Review)

Biesty LM, Egan AM, Dunne F, Smith V, Meskell P, Dempsey E, Ni Bhuinneain GM, Devane D

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T A B L E   O F   C O N T E N T S

Planned birth at or near term for improving health outcomes for pregnant women with pre-existing diabetes and their infants

Linda M Biesty[1], Aoife M Egan[2], Fidelma Dunne[3], Valerie Smith[4], Pauline Meskell[5], Eugene Dempsey[6], G Meabh Ni Bhuinneain[7], Declan Devane[1]

[1]School of Nursing and Midwifery, National University of Ireland Galway, Galway, Ireland. [2]Galway Diabetes Research Centre, National University of Ireland Galway/University Hospital Galway, Galway, Ireland. [3]National University of Ireland Galway, Galway, Ireland. [4]School of Nursing and Midwifery, Trinity College Dublin, Dublin, Ireland. [5]Department of Nursing and Midwifery, University of Limerick, Limerick, Ireland. [6]Neonatology, Cork University Maternity Hospital, Wilton, Ireland. [7]Department of Obstetrics and Gynaecology, Mayo University Hospital, Saolta, Castlebar, Ireland

Contact address: Linda M Biesty, School of Nursing and Midwifery, National University of Ireland Galway, Aras Moyola, Galway, Ireland. linda.biesty@nuigalway.ie.

A B S T R A C T

Background

Pregnant women with pre-existing diabetes (Type 1 or Type 2) have increased rates of adverse maternal and neonatal outcomes. Current clinical guidelines support elective birth, at or near term, because of increased perinatal mortality during the third trimester of pregnancy.

This review replaces a review previously published in 2001 that included "diabetic pregnant women", which has now been split into two reviews. This current review focuses on pregnant women with pre-existing diabetes (Type 1 or Type 2) and a sister review focuses on women with gestational diabetes.

Objectives

To assess the effect of planned birth (either by induction of labour or caesarean birth) at or near term gestation (37 to 40 weeks' gestation) compared with an expectant approach, for improving health outcomes for pregnant women with pre-existing diabetes and their infants. The primary outcomes relate to maternal and perinatal mortality and morbidity.

Search methods

We searched Cochrane Pregnancy and Childbirth's Trials Register, ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP) (15 August 2017), and reference lists of retrieved studies.

Selection criteria

We planned to include randomised trials (including those using a cluster-randomised design) and non-randomised trials (e.g. quasi-randomised trials using alternate allocation) which compared planned birth, at or near term, with an expectant approach for pregnant women with pre-existing diabetes.

Data collection and analysis

Two of the review authors independently assessed study eligibility. In future updates of this review, at least two of the review authors will extract data and assess the risk of bias in included studies. We will also assess the quality of the evidence using the GRADE approach.

Main results

We identified no eligible published trials for inclusion in this review.

We did identify one randomised trial which examined whether expectant management reduced the incidence of caesarean birth in uncomplicated pregnancies of women with gestational diabetes (requiring insulin) and with pre-existing diabetes. However, published data from this trial does not differentiate between pre-existing and gestational diabetes, and therefore we excluded this trial.

Authors' conclusions

In the absence of evidence, we are unable to reach any conclusions about the health outcomes associated with planned birth, at or near term, compared with an expectant approach for pregnant women with pre-existing diabetes.

This review demonstrates the urgent need for high-quality trials evaluating the effectiveness of planned birth at or near term gestation for pregnant women with pre-existing (Type 1 or Type 2) diabetes compared with an expectant approach.

PLAIN LANGUAGE SUMMARY

Planned birth at or near term for improving health outcomes for pregnant women with pre-existing diabetes and their infants

What is the issue?

The aim of this Cochrane review was to find out if planning an elective birth at or near the term of pregnancy, compared to waiting for labour to start spontaneously, has an impact on the health of women with diabetes and the health of their babies. This review focuses on women who have diabetes before becoming pregnant (pre-existing diabetes). Elective birth is carried out either by induction of labour or caesarean section, and 'at or near term' means 37 to 40 weeks' gestation.

To answer this question, we searched for all relevant studies (date of search: 15 August 2017), with the aim of collecting and analysing them together.

Why is this important?

When women with diabetes (Type 1 or Type 2) become pregnant they are at higher risk of complications than women who do not have diabetes. For example, their babies may be larger and have a higher risk of death in the later weeks of pregnancy. Because of these risks, many clinicians have recommended that women with diabetes have an elective birth (usually by induction) at or near term (37 to 40 weeks' gestation), rather than waiting for labour to start spontaneously or until 41 weeks' gestation if all is well. Induction has the disadvantage of increasing the incidence of forceps or ventouse births, and women often find it difficult to cope with an induced labour. Caesarean section is a major operation which can lead to blood loss, infections and increased chance of problems with subsequence births. Early birth can increase the chance of breathing problems for babies. It is important to know which approach to birth has a better impact on the health outcomes of women with pre-existing diabetes and their babies.

What evidence did we find?

We found no studies that addressed our specific question.

What does this mean?

In the absence of randomised studies, we are unable to say if women with pre-existing diabetes and their babies experience better health outcomes if they have a planned birth (by induction of labour or caesarean section at 37 to 40 weeks' gestation) compared to waiting for labour to begin spontaneously or until 41 weeks' gestation if all is well. More research is needed to answer this question.

BACKGROUND

There are several clinical situations where planned birth has been advocated with the aim of reducing adverse outcomes for both mother and baby (Dodd 2014). These include: an otherwise low-risk singleton pregnancy after 41 weeks (Gulmezoglu 2012); for women with an uncomplicated twin pregnancy at 37 weeks' gestation (Dodd 2014); and for women at 37 to 40 weeks' gestation where a clinical suspicion of macrosomia exists (Boulvain 2016). Systematic reviews of these three scenarios reveal that induction of labour after 41 weeks is the only intervention associated with a reduction in perinatal mortality (Gulmezoglu 2012). A previously published Cochrane review concluded that elective birth at term in pregnant women with insulin-requiring diabetes reduces the risk of macrosomia but does not impact on maternal or neonatal morbidity (Boulvain 2001).

The original review 'Elective delivery in diabetic pregnant women' (Boulvain 2001) has now been split into the following two reviews.

1. Planned birth at or near term for improving health outcomes for pregnant women with pre-existing diabetes and their infants (this review)

2. Planned birth at or near term for improving health outcomes for pregnant women with gestational diabetes and their infants (Biesty 2018)

As gestational diabetes is typically a transient glucose abnormality occurring late in the second trimester of pregnancy, whilst pre-existing diabetes exists throughout the entire pregnancy, it is important to clearly differentiate between these different conditions when approaching the issue of planned birth. It is acknowledged that there are similarities in the background, methods and outcomes between these two systematic reviews.

Description of the condition

Pre-existing diabetes refers to maternal diabetes that existed prior to the pregnancy. This typically refers to Type 1 and Type 2 diabetes, however the term also encompasses rarer forms of diabetes, e.g. Maturity Onset Diabetes of the Young (MODY). Type 1 diabetes is characterised by autoimmune destruction of beta cells, usually leading to absolute insulin deficiency; Type 2 diabetes occurs due to a progressive loss of insulin secretion on a background of insulin resistance, and is likely to be the result of interactions between genetic, environmental and immunological factors (ADA 2016; Zaccardi 2016). Although estimates vary, it is believed that 0.5% to 0.9% of pregnancies are complicated by pre-existing diabetes (Correa 2015; NICE 2015). While the prevalence of both Type 1 and Type 2 diabetes has increased in recent years (NICE 2015), the rate of Type 2 diabetes in pregnant women in the USA more than quadrupled in the period from 1994 to 2004, overtaking the rates of pre-existing Type 1 diabetes (Albrecht 2010). This increase in prevalence of Type 2 diabetes is in line with the worldwide rise in obesity rates and advancing maternal age (ACOG 2005; Egan 2015; Zhu 2016).

In the setting of pre-existing diabetes, pregnancy is considered to be high risk and is associated with increased rates of adverse maternal and neonatal outcomes. Studies from the United Kingdom and Ireland reveal a congenital malformation rate twice that of the background population (24/1000), a five-fold increased risk of stillbirth (25/1000), and a three-fold increased risk of perinatal mortality and caesarean birth (25/1000) (Macintosh 2006; Dunne 2009; Egan 2015). During the third trimester, issues of significant concern are: late fetal death; complications necessitating premature birth; and the potential for birth trauma associated with fetal macrosomia (Cousins 1987; Hanson 1993; Dunne 2009). Although recent research has noted a higher risk of adverse neonatal outcomes including stillbirths and congenital abnormalities in offspring of women with Type 1 compared to Type 2 diabetes (Owens 2015), an earlier systematic review found perinatal mortality to be higher for women with Type 2 compared with Type 1 diabetes (Balsells 2009). It should be noted that women with Type 2 diabetes are more commonly from ethnic minorities and are often cared for in community settings with minimal access to specialist care (Murphy 2010). This makes them an especially vulnerable group.

The hyperglycaemia-hyperinsulinaemia hypothesis, also known as the Pederson Hypothesis, aims to explain the underlying pathology that leads to the disordered fetal growth associated with the diabetic pregnancy. It states that "maternal hyperglycaemia results in fetal hyperglycaemia and, hence, in hypertrophy of fetal islet tissue with insulin-hypersecretion. This again means a greater fetal utilisation of glucose" (Pedersen 1952; Pedersen 1967). More recently, it has been suggested that additional factors such as alterations in lipid metabolism and inflammatory change may contribute to the abnormal metabolic environment associated with diabetic pregnancies, particularly when obesity co-exists (Catalano 2011). Such metabolic disruptions can affect organogenesis in early pregnancy, and cardiac malformations in particular are more common in infants of women with diabetes (Inkster 2006). As the pregnancy progresses, this abnormal intrauterine environment may result in the aforementioned neonatal morbidity, including being large-for-gestational age; having neonatal hypoglycaemia, hyperbilirubinaemia, hypocalcaemia; and increased need for admission to an intensive care unit (Macintosh 2006; Dunne 2009; Middleton 2016). It is becoming increasingly evident that exposure to maternal diabetes in utero may also have a longer-term negative impact on the offspring, with one recent study noting that adolescent offspring of women with Type 1 diabetes have lower cognitive function compared with a control group even after adjusting for

confounders (Bytoft 2016). In addition, long-term follow up of offspring of women with diabetes reveal that they have elevated rates of obesity and Type 2 diabetes later in life (Dabelea 2000). Due to the association between hyperglycaemia and poor pregnancy outcomes, pregnant women with diabetes are advised to keep blood glucose levels as close to normal as possible. Frequent capillary blood-glucose monitoring and tight targets such as fasting glucose of less than 5.3 mmol/L (96 mg/dL) and one-hour post prandial of less than 7.8 mmol/L (140 mg/dL) are typically recommended (NICE 2015). While HbA1c is not entirely reliable in pregnancy, higher levels (HbA1c more than 6.0% to 6.5% or more than 42 to 48 mmol/mol) may still be used as a marker of poor glycaemic control and a higher risk pregnancy (Egan 2015; Maresh 2015). In early pregnancy, there is increased insulin sensitivity, lower glucose levels and lower insulin requirements in women with Type 1 diabetes (ADA 2016). During the second and early third trimesters, physiological insulin resistance increases to facilitate the transfer of glucose across the placenta to the fetus and ensure adequate growth and development (Farrar 2016). This creates a significant challenge for women with diabetes who must adjust their treatments regularly to match these increasing insulin requirements and achieve their therapeutic goals. Typically, care of these women involves significant input from a multidisciplinary team of specialists, with intensive monitoring throughout the pregnancy, including frequent ultrasound surveillance of fetal growth (NICE 2015). Unfortunately, the prevalence of large-for-gestational age or macrosomia (or both) remains high in infants of women with diabetes, even in pregnancies that are considered 'well-controlled' (Evers 2002). In the past, some authors have proposed to perform birth before full term in women with pre-existing diabetes, because of increased perinatal mortality during the third trimester (Hunter 1989). This viewpoint is also reflected in current clinical guidelines (NICE 2015).

Description of the intervention

A woman's pregnancy is considered to be 'at term' when her pregnancy duration reaches 37 weeks (Gulmezoglu 2012). Planned birth involves the early birth of the infant either by induction of labour or caesarean section. This typically takes place between 37 and 40 weeks' gestation. Methods of induction vary according to local protocols and typically depend on cervical status. The process generally involves cervical ripening with misoprostol or prostaglandin E2 (PGE2) followed by amniotomy and oxytocin infusion if labour has not started (Boulvain 2016). An alternative is the expectant approach to the management of birth, which refers to waiting for the spontaneous onset of labour in the absence of any maternal or fetal issues that may necessitate birth (Bond 2017).

How the intervention might work

In pregnant women with pre-existing diabetes, the rationale for performing an elective birth includes a possible reduction in perinatal morbidity and mortality, particularly in relation to complications associated with macrosomia (Brudenell 1989). Macrosomia is typically defined as a birthweight of more than 4000 g (Feig 2015). It is associated with an increased chance of prolonged labour, maternal trauma, emergency caesarean birth, and birth injuries for the infant, including clavicle fracture and brachial plexus injury (Perlow 1996; Ju 2009). This has resulted in certain clinical practice guidelines recommending that pregnant women with diabetes be offered planned birth through induction of labour or by elective caesarean section (if indicated) between 37 weeks plus 0 days, and 38 weeks plus 6 days, of pregnancy (NICE 2015). A recent Cochrane review of induction of labour at or near term for suspected fetal macrosomia (Boulvain 2016) concluded that further trials are necessary to clarify if the benefits - including lower mean birthweight and fewer instances of birth fracture and shoulder dystocia - outweigh the risks, which include increased perineal damage.

Why it is important to do this review

In 1989, the St Vincent declaration called on governments and healthcare services to implement effective measures to achieve pregnancy outcomes in women with diabetes that approximate those of women without diabetes within five years (St Vincent Declaration 1990). While this goal was not achieved, it is important that we strive to identify any measures that may assist in meeting this target in our care for women with diabetes. Planned birth may have potential benefits, possibly reducing the risks of prolonged labour and elevated rates of caesarean section following induction of labour (Macer 1992). Birth by caesarean section, including elective caesarean, may increase the risk of maternal morbidity including postpartum infections, haemorrhage or uterine rupture during subsequent labour (Irion 1998). Induction of labour may lead to increased interventions during labour and birth and an increase in maternal morbidity (Khireddine 2013). Furthermore, early-term birth is associated with an increased risk of multiple neonatal morbidities including respiratory distress syndrome and the need for mechanical ventilation and admission to a neonatal intensive care unit (ACOG 2013). Women's views on elective birth versus continued antenatal surveillance should also be considered (Dodd 2014). The existing Cochrane review on this topic, 'Elective delivery in diabetic pregnant women'(Boulvain 2001), does not make the distinction between women with established, pre-existing diabetes and those with gestational diabetes (a condition associated with carbohydrate intolerance resulting in hyperglycaemia of variable severity with onset or first recognition during pregnancy) (WHO 2014). Finally, this review was published in 2001 and it is possible that additional evidence on this

subject is now available for analysis.

Based on the above, it is now important to assess the effect of planned birth compared with an expectant approach for pregnant women with pre-existing diabetes on maternal and perinatal mortality and morbidity. Women and healthcare professionals need unbiased information on this subject and this is best provided by meta-analysis of high-quality randomised controlled trials.

O B J E C T I V E S

To assess the effect of planned birth (either by induction of labour or caesarean birth) at or near term gestation (37 to 40 weeks' gestation) compared with an expectant approach, for improving health outcomes for pregnant women with pre-existing diabetes and their infants. The primary outcomes relate to maternal and perinatal mortality and morbidity.

M E T H O D S

Criteria for considering studies for this review

Types of studies

We planned to include all published randomised trials (including those using a cluster-randomised design) and non-randomised trials which compared planned birth at or near term gestation, with an expectant approach for pregnant women with pre-existing diabetes. Non-randomised trials are trials in which participants are allocated to treatment groups using non-random methods (e.g. alternate) (EPOC 2016).

Cross-over studies were not eligible for inclusion as this design is not appropriate for this intervention.

Studies published in abstract form only were eligible for inclusion where information on risk of bias and primary or secondary outcomes could be obtained.

Types of participants

Pregnant women, at or near term gestation (37 to 40 weeks' gestation), with pre-existing diabetes (Type 1 or Type 2) as diagnosed according to each included study.

Women with gestational diabetes are included in a different Cochrane review, 'Planned birth at or near term for improving health outcomes for pregnant women with gestational diabetes and their infants' (Biesty 2018)

We planned to exclude trials that included women both with gestational diabetes and pre-existing diabetes, where data could not be separated.

Types of interventions

Planned birth (induction of labour or caesarean section) at or near term gestation (37 to 40 weeks' gestation).

Induction of labour was defined by trial authors and may include the use of prostaglandins, misoprostol, oxytocin, amniotomy or a combination of these.

Comparisons

1. Planned birth (induction of labour/caesarean section), at or near term gestation versus an expectant approach

An expectant approach to the management of birth refers to waiting for the spontaneous onset of labour in the absence of any maternal of fetal issues that may necessitate birth (Bond 2017) (or until 41 weeks' gestation or more, when induction of labour may be offered).

Types of outcome measures

For this review, we adapted the core outcome set agreed by consensus between review authors of the Cochrane Pregnancy and Childbirth systematic reviews for prevention and treatment of gestational diabetes mellitus and pre-existing diabetes. The core outcome set was adapted to ensure that the outcome measures included were appropriate for this research question.

Primary outcomes

Maternal

1. Maternal mortality or serious maternal morbidity (e.g. cardiac arrest, respiratory arrest, admission to intensive care unit (ICU))
2. Caesarean section
3. Instrumental vaginal birth (forceps or vacuum)

Neonatal

1. Perinatal mortality rate (corrected, i.e. stillbirth and early neonatal deaths excluding lethal congenital anomalies)
2. Shoulder dystocia
3. Large-for-gestational age (birthweight greater than the 90th centile or as defined by the trial authors)
4. Acidaemia (as evident by a pH of less than 7.0 or a base deficit greater than 12 mmol/L in umbilical arterial cord blood or neonatal blood sample within the first hour of life, or both)

We planned to include all primary outcomes in a 'Summary of findings' table.

Secondary outcomes

Maternal

1. Maternal death
2. Cardiac arrest
3. Respiratory arrest
4. Admission to ICU
5. Intact perineum
6. Uterine rupture
7. Postpartum haemorrhage (defined as 1000 mL or more)
8. Postnatal depression (as measured by either the Edinburgh Postnatal Depression Scale, the Postpartum Depression Screening Scale, the Beck Depression Inventory or other validated scales)
9. Maternal satisfaction (as measured by trial authors)
10. Intact perineum

Neonatal

1. Brachial plexus injury
2. Bone fracture at birth
3. Intracranial haemorrhage (all grades)
4. Hypoxic ischaemic encephalopathy
5. Respiratory distress syndrome
6. Neonatal hypoglycaemia (blood glucose concentrations below the normal range, investigator defined)
7. Neonatal hyperbilirubinaemia (blood bilirubin concentrations above the normal range, investigator defined)
8. Small-for-gestational age (birthweight below the third centile or as defined by the trial authors)
9. Admission to neonatal ICU
10. Neurosensory disability (defined by a standardised assessment tool at approximately two years of age)

Health service outcomes

1. Length of postnatal stay (mother)
2. Length of postnatal stay (baby)
3. Cost

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 (15 August 2017). The Register is a database containing over 24,000 reports of controlled trials in the field of pregnancy and childbirth. For full search

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

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

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

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 (Excluded studies; Studies awaiting classification).

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

Searching other resources

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

Data collection and analysis

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

Selection of studies

Two review authors (LB, DD) independently assessed for inclusion all potential eligible studies identified by our search strategy. We planned to resolve any disagreement through discussion or, if required, we planned to consult a third person.

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

There were no studies identified as eligible for inclusion in this review. In future updates, if there are any eligible studies identified for inclusion, we will use the following methods.

Data extraction and management

We will design a form to extract data. For eligible studies, two review authors will extract the data independently using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult a third person. We will pilot test the data extraction tool on two papers prior to the conduct of the full review and amend as necessary. One review author will enter all data into Review Manager 5 (RevMan 2014) software which will be checked for accuracy against the data extraction sheets by a second review author. Where additional information is needed, we will try to contact authors of the original reports to provide further details. When information regarding any of the above is unclear, we will attempt to contact authors of the original reports to provide further details and will note this contact in the 'Characteristics of included studies' tables.

Assessment of risk of bias in included studies

Two review authors will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreement by discussion or by involving a third assessor. The following sections refer to individually randomised trials. If cluster-randomised trials are included we will use appropriate methods for assessing bias in these designs, as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Where information on risk of bias relates to unpublished data or correspondence with trialists, this will be noted in the 'Risk of bias' table.

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

We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.
We will assess the method as being at:
- 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. alternate, odd or even date of birth; hospital or clinic record number);
- unclear risk of bias (insufficient information to allow a judgement).

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

We will describe for each included study the method used to conceal allocation to interventions prior to assignment and will assess whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.
We will assess the methods as being at:
- 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 will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will consider that studies are at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. We will assess risk of detection bias for self-reported and objective outcome measurement. We will assess the methods as being at:
- 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 will describe for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We will consider blinding separately for different outcomes where appropriate (for example, blinding may have the potential to differently affect subjective versus objective outcome measures).
We will assess methods used to blind outcome assessment as being at 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 will describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised women), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we will re-include missing data in the analyses which we undertake. We will assess risk of attrition bias for self-reported and objective outcome measurement.

We will assess methods as being at:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups, the proportion of missing data were less than the effect size, i.e. unlikely to overturn the results);
- high risk of bias (For self-reporting outcomes of maternal depression and satisfaction we will judge attrition of > 20% as high risk of bias. For other outcomes, we will explore if numbers or reasons for missing data imbalance across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation and judge based on these findings);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found.
· We will assess the methods as being at:

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

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

We will describe for each included study any important concerns we have about other possible sources of bias.
We will assess whether each study was free of other problems that could put it at risk of bias:

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

(7) Overall risk of bias

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. 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

We will assess the quality of the evidence using the GRADE approach as outlined in the GRADE handbook in order to assess the quality of the body of evidence relating to the following outcomes for the comparisons of planned birth (induction of labour or caesarean section), at or near term gestation versus an expectation approach.

1. Maternal mortality or serious maternal morbidity (e.g. cardiac arrest, respiratory arrest, admission to ICU)
2. Caesarean section
3. Instrumental vaginal birth (forceps or vacuum)
4. Perinatal mortality rate (corrected, i.e. stillbirth and early neonatal deaths excluding lethal congenital anomalies)
5. Shoulder dystocia
6. Large-for-gestational age (birthweight greater than the 90th centile or as defined by the trial authors)
7. Acidaemia (as evident by a pH of less than 7.0 or a base deficit greater than 12 mmol/L in umbilical arterial cord blood or neonatal blood sample within the first hour of life, or both)

We will use the GRADEpro Guideline Development Tool to import data from Review Manager 5 (RevMan 2014) to create 'Summary of findings' tables. A summary of the intervention effect and a measure of quality for each of the above outcomes will be produced using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious limitations (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 will present results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we will use the mean difference if outcomes are measured in the same way between trials. We will use the standardised mean difference to combine trials that measure the same outcome, but use different methods. We will report mean and standardised mean differences with 95% confidence intervals.

Unit of analysis issues

Cluster-randomised trials

We will include cluster-randomised trials in the analyses along with individually randomised trials. We will adjust their sample sizes using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (section 16.3.4 or 16.3.6) (Higgins 2011) using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is unlikely.

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

Studies with multiple arms

For studies with multiple treatment arms, we will combine all relevant experimental intervention groups in the study (e.g. groups with different methods for induction of labour) into a single group and all comparable relevant control intervention groups into a single control group and perform a single pair-wise comparison, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (section 16.5.4) (Higgins 2011).

Dealing with missing data

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

For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomised to each group in the analyses, and all participants will be analysed in the group to which they were allocated, regardless of whether they received the allocated intervention. The denominator for each outcome in each trial will be the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

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

Assessment of reporting biases

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 will carry out statistical analysis using Review Manager 5 (RevMan 2014). We will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect, i.e. where trials are examining the same intervention, and the trials' populations and methods are judged to be sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary if an average treatment effect across trials is considered clinically meaningful. The random-effects summary will be treated as the average of the range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful we will not combine trials.

If we use random-effects analyses, the results will be presented as the average treatment effect with 95% confidence intervals, and the estimates of Tau^2 and I^2.

Subgroup analysis and investigation of heterogeneity

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

We plan to carry out the following subgroup analyses.

1. Women with Type I diabetes versus women with Type 2 diabetes
2. Parity: primiparous women versus multiparous women
3. Birth by planned caesarean section versus planned elective induction of labour

The following outcomes will be used in subgroup analysis.

Maternal

1. Maternal mortality or serious maternal morbidity (e.g. cardiac arrest, respiratory arrest, admission to ICU)
2. Caesarean section
3. Instrumental vaginal birth (forceps or vacuum)

Neonatal

    1. Corrected perinatal mortality rate (stillbirths and early neonatal deaths, excluding lethal congenital anomalies)

    2. Shoulder dystocia

    3. Large-for-gestational age (birthweight greater than the 90th centile or as defined by the trial authors)

    4. Acidaemia (as evident by a pH of less than 7.0 or a base deficit greater than 12 mmol/L in umbilical arterial cord blood or neonatal blood sample within the first hour of life, or both

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

Sensitivity analysis

We will conduct a sensitivity analysis based on risk of bias in trials. We will exclude all studies at high or unclear risk of bias for either sequence generation or allocation concealment to see if this makes any difference to the overall results. This is based on growing empirical evidence that these factors are a particularly important potential source of bias (Higgins 2011). We will limit sensitivity analyses to primary outcomes.
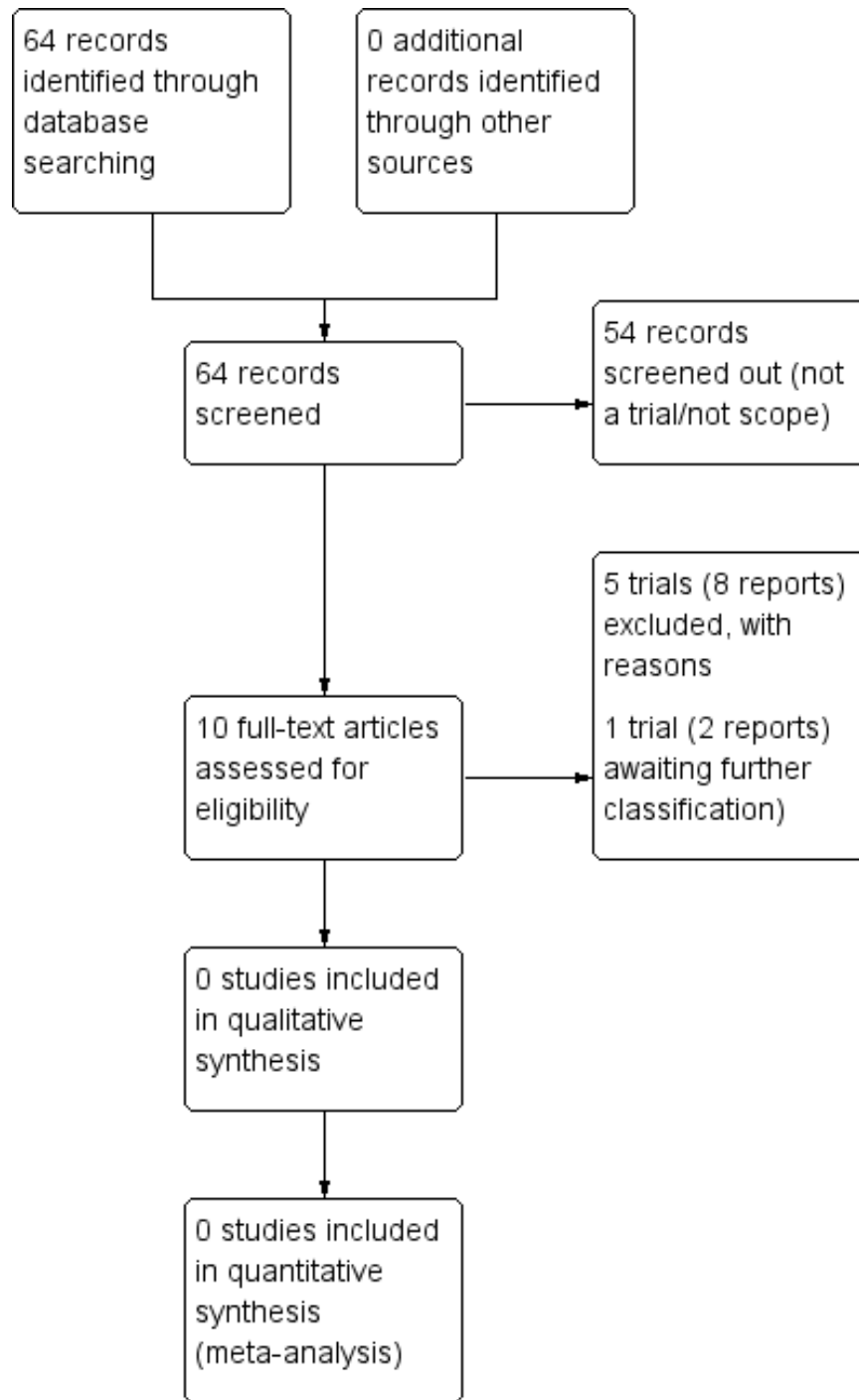
R E S U L T S

Description of studies

No studies were eligible for inclusion in this review (see Characteristics of excluded studies and Characteristics of studies awaiting classification).

Results of the search

See: Figure 1.

Figure 1. Study flow diagram.

We identified 64 citations through our searches. After screening, we retrieved 10 reports of six trials for potential inclusion in the review.

Included studies

No studies were eligible for inclusion.

Excluded studies

We excluded five studies (Alberico 2017; Dhaneshwor 2011; Ghosh 1979; Khojandi 1974; Worda 2017) (see Characteristics of excluded studies). We excluded four studies (Alberico 2017; Dhaneshwor 2011; Khojandi 1974; Worda 2017) because the participants were women with gestational diabetes. We excluded the remaining study (Ghosh 1979) as no further details or publications have been made available in relation to this study since the publication of the conference abstract 38 years ago.

We sent communications to the named contact author of one trial (Henry 1992) to obtain data that related specifically to the women with Type 1 or Type 2 diabetes in their trial. We are awaiting a reply (See Characteristics of studies awaiting classification).

Risk of bias in included studies

As no studies were included in this review, we could not assess risk of bias.

Allocation

No studies were included in this review, therefore we could not assess the risk of selection bias.

Blinding

No studies were included in this review, therefore we could not assess the risk of performance bias and detection bias.

Incomplete outcome data

No studies were included in this review, therefore we could not assess the risk of attrition bias.

Selective reporting

No studies were included in this review, therefore we could not assess the risk of reporting bias.

Other potential sources of bias

No studies were included in this review, therefore we could not assess the risk of other potential sources of bias.

Effects of interventions

As there were no studies included in this review, we could not assess the effects of interventions.

DISCUSSION

We identified one completed trial (Henry 1992) which is awaiting assessment. This trial was designed to compare elective induction of labour with expectant management for reducing the incidence of caesarean birth in pregnant women with insulin-requiring gestational diabetes or pre-existing diabetes. However, to date, published results do not separate the data of pregnant women with pre-existing diabetes and women with gestational diabetes.

The risks for women with pre-existing diabetes and their neonates during pregnancy have been explored in the earlier sections of this review. The risks of having a baby diagnosed with macrosomia or large-for-gestational age (or both) remains high for these women, even for those considered to have "well controlled diabetes" (Evers 2002). The association between macrosomia and late fetal death, and the potential for birth trauma, remain as concerns (Dunne 2009). These concerns are reflected in clinical guidelines (e.g. NICE 2015) which propose planned birth before term for pregnant women with pre-existing diabetes. Yet, to date, no results from randomised trials have been published relating to the effect of planned birth at or near term gestation, compared with an expectant approach, for improving health outcomes for pregnant women with pre-existing diabetes and their babies. This review demonstrates the urgent need for such trials.

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence from randomised trials to inform implications for practice. It is beyond the scope of this review to identify other sources of evidence, as they have not been considered for inclusion.

Implications for research

This review demonstrates the urgent need for high-quality trials evaluating the effectiveness of planned birth at or near term gestation for women with Type 1 or Type 2 diabetes, compared with an

expect approach. However, the equipoise on optimal approach must be considered when planning such trials and attention must be given to strategies to optimise the recruitment of women to such studies.

ACKNOWLEDGEMENTS

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CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Alberico 2017	This study explores immediate birth versus expectant management for women with gestational diabetes at term
Dhaneshwor 2011	This study compares expectant management versus induction of labour for women with gestational diabetes
Ghosh 1979	No further details or publication in the intervening period (38 years)
Khojandi 1974	The focus of this study was women with gestational diabetes.
Worda 2017	This study evaluates the impact of induction of labour on maternal and fetal outcomes in women with insulin-dependent gestational diabetes

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

Henry 1992

Methods	**Study Design:** "randomised trial" **Duration of the study:** 3.5 years
Participants	**Setting:** Women's Hospital, Los Angeles County- University of Southern California Medical Center **Inclusion criteria:** "women diagnosed before pregnancy with insulin-dependent diabetes mellitus or non-insulin-dependent diabetes mellitus without vascular complications or with gestational diabetes requiring insulin treatment during pregnancy, and with good metabolic control of blood glucose levels ... 38 completed weeks gestation (266 days), good compliance with clinical appointments and home blood glucose monitoring, no abnormalities in the twice weekly antepartum assessment with nonstress testing and amniotic fluid volume measurement performed from 34 weeks onward, singleton gestation and cephalic presentation, clinical and ultrasonographic estimation of fetal weight <3800gm at 38 completed weeks with no evidence of intrauterine growth retardation, no other medical or obstetric complications, a candidate for trial of vaginal delivery (no more than 2 previous C-sections)"
Interventions	**Planned birth:** N = 100 women, "labour was induced with iv oxytocin .... in women with favourable Bishops Score (<4), unscarred uteri and normal amniotic fluid indexes (>5.0cms), up to 3 applications of vaginal prostaglandin (3 mg) were used for cervical ripening before oxytocin treatment" **Expectant approach:** N = 100 women, "expectant management consisted of daily split dose insulin therapy and home blood glucose monitoring, weekly antenatal clinic visits, and twice-weekly antepartum testing". Induction of labour indicated by: "suspected fetal distress .... preeclampsia, maternal hyperglycaemia, estimated fetal weight > 4200gm, 42 weeks gestation"

Henry 1992 *(Continued)*

Outcomes	**Outcomes considered relevant to this review:** mode of delivery - vaginal delivery, caesarean delivery; infant birth-weight - macrosomia, large-for-gestational age; infant outcome - shoulder dystocia, birth trauma (bone fracture, Erbs palsy), hypoglycaemia, mortality
Notes	**Funding:** not known **Trial authors declaration of Interest:** none declared **The authors were contacted on:** 10th Jan 2017, to obtain data specifically related to pregnant women with pre-existing diabetes in both the experimental and control groups

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. Search terms for ICTRP and ClinicalTrials.gov

WHO International Clinical Trials Registry Platform (ICTRP)
(we ran each line and alternative spelling separately and then de-duplicated)
GDM AND c(a)esarean
diabetes AND c(a)esarean
diabetic AND c(a)esarean
planned AND birth AND GDM
planned AND birth AND diabetes
planned AND birth AND diabetic
elective AND birth AND GDM
elective AND birth AND diabetes
elective AND birth AND diabetic
induction AND labo(u)r AND diabetes
induction AND labo(u)r AND GDM
Induction AND labo(u)r AND diabetic
expectant AND birth AND GDM
expectant AND birth AND diabetic
expectant AND birth AND diabetes
ClinicalTrials.gov
(we ran each search separately and then de-duplicated)
Advanced search
1.
diabetes OR diabetic OR GDM - Condition
cesarean OR caesarean - Intervention
2.
diabetic OR diabetes OR GDM - Condition
(planned OR elective OR expectant) AND (birth OR delivery) - Intervention
3.
diabetes OR diabetic OR GDM - Condition
induction AND (labour OR labor)

CONTRIBUTIONS OF AUTHORS

Aoife Egan (AE) and Fidelma Dunne (FD) drafted the background section. All other authors contributed to editing the background text. All authors contributed to drafting the inclusion criteria for the review. Linda Biesty (LB) and Declan Devane (DD) drafted the methodology and all authors read and commented on this. LB wrote the discussion and conclusions sections with input from all authors. LB is the guarantor of this review.

DECLARATIONS OF INTEREST

Linda M Biesty: none known.

Aoife M Egan: none known.

Fidelma Dunne: none known.

Valerie Smith: none known.

Pauline Meskell: none known.

Eugene Dempsey: none known.

Méabh Ní Bhuinneáin: none known.

Declan Devane: none known.

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Internal sources

- No sources of support supplied

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The title has changed from 'Planned elective birth at or near term for improving health outcomes for pregnant women with pre-gestational diabetes (Type 1 or Type 2)' to 'Planned birth at or near term for improving health outcomes for pregnant women with pre-existing diabetes and their infants'.

The protocol for this Cochrane review was published in PROSPERO on 26 September 2017 - see http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017072506. The protocol was not published in the Cochrane Library.

NOTES

The original review 'Elective delivery in diabetic pregnant women' (Boulvain 2001) has now been split into two reviews.

- Planned birth at or near term for improving health outcomes for pregnant women with gestational diabetes and their infants (Biesty 2018).

- Planned birth at or near term for improving health outcomes for pregnant women with pre-existing diabetes and their infants (this review).