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[Intervention Review]

Antenatal breast milk expression by women with diabetes for improving infant outcomes

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ABSTRACT

Background

Some women with diabetes in pregnancy are encouraged to express and store colostrum prior to birthing. Following birth, the breastfed infant may be given the stored colostrum to minimise the use of artificial formula or intravenous dextrose administration if correction of hypoglycaemia is required. However, findings from observational studies suggest that antenatal breast milk expression may stimulate labour earlier than expected and increase admissions to special care nurseries for correction of neonatal hypoglycaemia.

Objectives

To evaluate the benefits and harms of the expression and storage of breast milk during late pregnancy by women with diabetes.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 June 2014).

Selection criteria

All published and unpublished randomised controlled trials comparing antenatal breast milk expressing with not expressing, by pregnant women with diabetes (pre-existing or gestational) and a singleton pregnancy.

Data collection and analysis

Two review authors independently evaluated reports identified by the search strategy.

Main results

There were no published or unpublished randomised controlled trials comparing antenatal expressing with not expressing. One randomised trial is currently underway.

Authors' conclusions

There is no high level systematic evidence to inform the safety and efficacy of the practice of expressing and storing breast milk during pregnancy.

PLAIN LANGUAGE SUMMARY

Breast milk expression during pregnancy by women with diabetes for improving infant outcomes

Babies born to women who have diabetes during pregnancy, either already existing or gestational, are at increased risk of low blood sugars after birth. This is because the babies have been exposed to higher than usual blood sugar (glucose) levels during the pregnancy and so have been producing relatively high levels of insulin. Some of these babies require additional breast milk, formula feeds or transfer to a special care nursery for intravenous fluids to correct the low blood sugar levels.

Some maternity care providers and women propose that expressing and storing colostrum, the initial nutrient-rich breast milk, during pregnancy, can be given to the baby if they develop low blood sugars after birth. This may help avoid the need for formula feeds if breastfeeding, intravenous fluids and separation from the mother if the baby has to go to the special care nursery. Although this process seems logical and is sometimes recommended, two small observational studies have shown that mothers who expressed breast milk during pregnancy were more likely to have their babies early and more of the babies were cared for in the special care nursery compared with those whose mothers did not express.

This systematic review sought to identify randomised controlled trials comparing outcomes for women with diabetes who were advised to express with women not advised to express and store breast milk during pregnancy. The search did not find any completed trials, although one trial is currently underway.

There is no high level evidence about the potential benefits and harms of the expression and storage of breast milk during pregnancy by women with diabetes.

BACKGROUND

Description of the condition

Infants born to mothers who have diabetes in pregnancy (gestational or pre-existing) are at increased risk of neonatal hypoglycaemia (low blood sugar) compared to other infants (Hanson 1993). This can be explained by their exposure to higher glucose levels in utero than usual, with subsequent increased insulin secretion. These infants may then need to adjust their insulin secretion to deal with postnatal glucose intake levels. It is for this reason that, in the first few days of life, many of these infants become hypoglycaemic and will require additional glucose, provided by intake from breastfeeding or breast milk expressed after birth, from donor human milk, artificial formula or via an intravenous infusion.

To avoid this condition developing in infants born to mothers who have diabetes in pregnancy, a readily available supply of breast milk from birth would seem to be an attractive option. This is particularly so in view of the World Health Organization's (WHO) recommendation that infants be exclusively breastfed, whether directly from the breast or as expressed breast milk, for the first six months, that is, without any supplements, artificial formula or solid food (WHO 2011).

However, a number of barriers may be identified to successful initiation of breastfeeding in this group of mothers and their babies. Colostrum from early breastfeeds in the first hours after birth would normally provide all the necessary nutrients for infants born to women without diabetes (WHO 2011). The additional nutritive needs of infants born to women with diabetes may not be sufficiently met by colostrum from early breastfeeds (Hanson 1993). Additionally, because euglycaemia (normal levels of glucose in the blood) appears to be an important influence on the onset of lactogenesis II (the copious flow of milk within a few days of giving birth), women with diabetes in pregnancy with hypoglycaemia or hyperglycaemia may be at increased risk of delaying this progression (Arthur 1994; Neubauer 1993). Thus, the infant who is already at increased risk of morbidity related to his/her mother's

diabetes, may also be exposed to artificial formula and separation from the mother if transferred to a nursery facility for intravenous fluid administration and glucose monitoring.

Further, avoidance of dietary exposure to some proteins found in cow's milk and the potential for a stronger immune system in exclusively breastfed infants may decrease the likelihood of these children subsequently developing B-cell autoimmunity and Type 1 diabetes (Ip 2007; Newburg 2005; Silverman 1995).

Description of the intervention

Antenatal breast milk expression in women with diabetes has been proposed as an intervention for building up a supply of colostrum expressed during pregnancy that can be used if needed after the birth.

Historically, antenatal breast preparation, including milk expression, was proposed as a means of minimising breastfeeding problems in the postnatal period. Chapman 2013a reviewed the evolution of antenatal breast preparation and described three epochs of trends. Epoch I: antenatal breast preparation, with publications from 1946 to 1983, described antenatal expressing and discarding colostrum. The studies by Waller 1946 and Blaikley 1953 involved having women express and discard colostrum from 20 or 28 weeks of pregnancy respectively. Overall findings included improved milk flow postnatally, less breast engorgement, less cracked nipples and improved exclusivity of breastfeeding to six months for infants of women who had expressed, compared with those who had not. These findings contrasted with those of Ingleman-Sundberg 1958, who compared outcomes in 656 women who did or did not express from 20 weeks of pregnancy and reported no difference in breastfeeding rates and a trend toward increase mastitis in women who had expressed during pregnancy. Similarly, Brown 1975 reported no differences in nipple trauma or sensitivity for either breast in three groups of women (total n = 57) who had used nipple rolling, creams or expressing during pregnancy on one breast and not the other.

Epoch 2 of the review by Chapman 2013a included publications from 1986 to 1993 of nipple stimulation, that reported on the contraction stress test and as a means of ripening the cervix and augmenting labour (Kavanagh 2005; Langrew 1995). The contraction stress test involved nipple stimulation during electronic fetal heart rate monitoring to determine the fetal response to the stress of an increase in circulating oxytocin that may lead to uterine contractions (Langrew 1995). Both the release of oxytocin during breast or nipple stimulation and the potential for this intervention to influence labour are discussed below under The safety, effectiveness and acceptability by women of antenatal colostrum expression.

Chapman 2013a outlined Epoch 3 (2008 to the present) as the emergence of antenatal breast milk expression for building up a store of colostrum (although some publications pre-date this epoch, for example, Clay 2005; Oscroft 2001). This involves teaching women to hand express colostrum, for example, once or twice a day for several minutes and collect this in a syringe or cup. Expressed colostrum can be labelled with the mother's name and date of birth, then stored by placing the syringe into a sealed plastic bag and placing it in the freezer. The woman can then bring the frozen colostrum with her to the hospital in a cold container when she is admitted for the birth. Varying amounts of colostrum are able to be expressed at each episode, for example, Forster 2011a reported a median of 1.67 mL (range 0.21 to 14.1mL) from 26 women. These women expressed a median of 39.6 mL (range 5 to 310 mL) in total over a period of 14 days (range 4 to 30 days). Rietveld 2011 reported findings for 10 women with diabetes in pregnancy, who had been instructed to express twice daily from 34 weeks' gestation until the birth of the baby. The purpose of the study was to consider issues of the feasibility of antenatal expressing, storage and provision of stored colostrum to the infants if they became hypoglycaemic after birth. Women averaged 53 episodes of expression (range 19 to 80), which they conducted once or twice daily. The total volume of expressed colostrum averaged 88.5 mL (range 2.8 to 322 mL). The women gave birth at an average of 38 weeks and five days, with all infants being born after 37 weeks. One baby had a blood glucose level of 1.7 mmol/L (i.e. hypoglycaemia, although not confirmed by a true blood glucose (TBG) measurement) and was supplemented with cows' milk formula, even though banked colostrum was available. The hypoglycaemia persisted to the next test prior to feeding (2.4 mmol/L) and the baby received some banked colostrum following the breast feed. Women reported being satisfied with the process of expressing and storing colostrum and agreed that this was helpful with breastfeeding.

A randomised controlled trial of pregnant women (without diabetes) antenatal expressing and then discarding the colostrum was reported by Singh 2009, who tested the hypothesis that this practice would reduce breastfeeding failures following birth. They noted that 2% of the 71 participants in the non-expressing group took over 72 hours from the birth to achieve "full lactation" (undefined), compared with none in the expressing group ($P < 0.01$). The proposed advantage of antenatal expression and storage of colostrum is that, following birth, should additional nutrition be required, this can be given instead of artificial formula (Cox 2006). A survey of lactation consultants in Australia reported a growing awareness of antenatal breast milk expression, even when the practice was not promoted by the individual lactation consultants who responded to the survey (Chapman 2013b).

The safety, effectiveness and acceptability by women of antenatal colostrum expression

Women in some parts of the world continue breastfeeding their child during a subsequent pregnancy, with some evidence of the safety and effectiveness of this practice for the pregnancy (not increasing the risk of miscarriage), intrauterine fetal growth or

concerns about infant growth and morbidity (Avrim 2014; Isihi 2009; Marquis 2003; Merchant 1990; Moscone 1993; Pareja 2012).

Breast or nipple stimulation, including through sexual activity, in preparation for breastfeeding, to stimulate cervical preparation for labour, expression of breast milk, or through suckling by the baby, results in the release of the hormone, oxytocin, which may lead to uterine contractions (Amico 1986; Bealer 2010; Christensson 1989). This raises the issue of the potential for antenatal colostrum expression to unintentionally influence the timing of the birth. Specifically, breast or nipple stimulation may be utilised as a means of inducing labour, as reported in a systematic review of six trials (719 women) comparing stimulation with no intervention in women from 37 weeks of gestation (Kavanagh 2005). The review reported a significant reduction in the proportion of women not in labour within 72 hours (62.7% versus 93.6%, risk ratio (RR) 0.67, 95% confidence interval (CI) 0.60 to 0.74). Although these findings were only significant in women who entered the study with a favourable cervix (that is, ready for labour), some older randomised trials have demonstrated an improvement in the Bishop's score, which gauges cervical preparedness for labour (Damania 1992; Di Lieto 1989; Salmon 1986).

To explore whether expressing colostrum during pregnancy influenced the timing of labour onset, Soltani 2012 reported outcomes from a retrospective cohort study of 94 women with diabetes who expressed or did not express antenatally. There was a trend for infants of mothers who had expressed antenatally to be more likely to be born a week earlier (mean gestation 37.1 weeks, standard deviation (SD) 2.6) than infants whose mothers had not undertaken antenatal breast milk expression (mean 38.2 weeks, SD 2.2), although this did not reach statistical significance (P = 0.06). The clinical, if not the statistical, importance of birthing a week earlier, albeit still "at term", or "near term" given the range of gestation indicated by the standard deviation, warrants consideration when noting the trend for more babies whose mothers had expressed colostrum antenatally to be admitted to the neonatal nursery (33% versus 12% in the non-expressing group, P = 0.06) (Soltani 2012). This concern was supported by findings from the study by Forster 2011a, which enrolled 43 women with diabetes in a prospective non-randomised study of antenatal breast milk expression twice a day for 10 minutes from 36 weeks' gestation. Outcomes for this group were compared with those from a retrospective audit of 89 women with diabetes who had not expressed during pregnancy. Forster 2011a reported increased rates of admission to the special care nursery in the expressing group (RR 1.79, 95% CI 0.94 to 3.33). The wide CI suggests that more participants would be required to confirm or refute this concern. The proportion of these nursery admissions attributed to neonatal hypoglycaemia was 64%, compared to 54% in the non-expressing group. The study by Forster 2011a also reported that five women experienced uterine tightening or Braxton Hicks contractions after expressing and did not continue this activity. Forty per cent of infants of women who had expressed milk received artificial formula within 24 hours of birth compared with 56% of the comparison group (RR 0.72, 95% CI 0.48 to 1.09).

Forster 2011a, asked women to record their blood glucose levels after the first three episodes of expressing. The group median blood glucose levels were normal, although two women reported a blood glucose of < 3.5 mmol/L after their first episode of expressing. This potential for hypoglycaemia warrants further consideration in this group of women.

Women have identified positive aspects of their experiences with antenatal expressing. For example, in the study by Forster 2011a, 30% of the women who had expressed antenatally noted that they had increased confidence and felt more prepared for postnatal breastfeeding. Women also noted their positive feelings about having a ready supply of colostrum and learning to express. Some women found antenatal expressing difficult (31%) and reported sore breasts/nipples (19%).

How the intervention might work

The storage of expressed colostrum to be given (if required) in addition to breast milk obtained directly from the breast or expressed after birth, may avert the need for artificial formula or intravenous fluid administration if correction of hypoglycaemia is required. Some clinical guidelines (e.g. NICE 2008) recommend close monitoring of the baby's blood sugar level in the postnatal period, with the mother and baby remaining together for care. Should the infant become hypoglycaemic (often defined as a true blood glucose (TBG) of less than 2.6 mmol/L), a prescribed series of escalating interventions is followed, which may include separation of the baby from the mother through admission to a special or intensive care nursery if an additional feed of breast milk or formula does not result in euglycaemia within an hour, or by the time of the next feed (NETS 2009). Consequently, there are substantial economic and social costs attributable to such admissions and to separation of the mother and her baby (Argus 2009; Figueiredo 2009). The limited expenses involved in educating women to express and the provision of sterile containers and freezer storage would be likely to be considerably less than the costs of specialised nursery admission and treatment.

Why it is important to do this review

As with any intervention, the best intent is not the same as high-quality evidence when considering the safety and effectiveness of that intervention. We are faced here with an emerging practice of antenatal breast milk expression and storage in guidelines that do not cite evidence from a systematic review of randomised controlled trials (for example, Ballarat Health Services 2010; Capital & Coast District Health Board 2012; Cox 2010; LaLeche League Great Britain 2008; LaLeche League Great Britain

2010; Ramsay Health Care 2011; Sandwell & West Birmingham Hospitals 2012). The theoretical potential for benefit to the infant and the possibility of concerns about timing of onset of labour and of nursery admission for neonatal hypoglycaemia (as noted in small observational studies), mandate the need for rigorous evaluation of the evidence of the safety and efficacy of antenatal breast milk expression by women with diabetes in pregnancy to improve the outcomes for their infants. The findings of this systematic review will also have the potential to impact upon successful breastfeeding, that may reduce the risk for the mother (if she experienced gestational diabetes in the index pregnancy) and the infant, of developing diabetes later in life.

OBJECTIVES

To evaluate the benefits and harms of the expression and storage of breast milk during late pregnancy by women with diabetes.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials, quasi-randomised trials and cluster-randomised trials that compare antenatal breast milk expressing compared with not expressing. Cross-over trials are unlikely to be appropriate for this research question and will therefore be excluded. We also plan to exclude studies that are only reported in abstract form, if they are identified in future updates of this review.

Types of participants

Pregnant women with diabetes (pre-existing or gestational) with a singleton pregnancy and their infants.

Types of interventions

Antenatal breast milk expressing, with or without storage of colostrum for later use, compared with not expressing.

Types of outcome measures

Primary outcomes

1. Spontaneous onset of established labour prior to 37 weeks' gestation.
2. Exclusive feeding with breast milk during the period of hospital-based care following birth.
3. Number of episodes of low blood glucose.
4. Admission to special care nursery or neonatal intensive care nursery.

Secondary outcomes

Maternal

1. Breast/nipple discomfort in late pregnancy.
2. Commenced breastfeeding or milk expression following birth.
3. Women's satisfaction with breastfeeding.

Infant

1. Gestational age at birth.
2. Duration of low blood glucose episode(s). Administration of intravenous dextrose.
3. Exclusive feeding with breast milk within 24 hours of discharge from hospital-based care.
4. Any feeding with breast milk within 24 hours of discharge from hospital-based care.
5. Exclusive feeding with breast milk at three and six months.
6. Any feeding with breast milk at three and six months.
7. Economic costs (as defined by trial author).

Other outcomes/considerations

We will also consider the following in the expressing group.

1. Women's views about antenatal breast milk expression.
2. Uterine contractions during or after antenatal breast milk expression.
3. Maternal hypoglycaemia following antenatal breast milk expression.

Search methods for identification of studies

Electronic searches

We contacted the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register (30 June 2014).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

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

Details of the search strategies for CENTRAL, MEDLINE and Embase, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

We did not apply any language restrictions.

Data collection and analysis

Selection of studies

Two review authors (C East and W Dolan) independently assessed for inclusion all the potential studies we identified as a result of the search strategy. We planned to resolve any disagreement through discussion or, if required, consult a third person.

We did not identify any studies for inclusion. Methods of data collection and analysis to be used in future updates of this review are provided in Appendix 1.

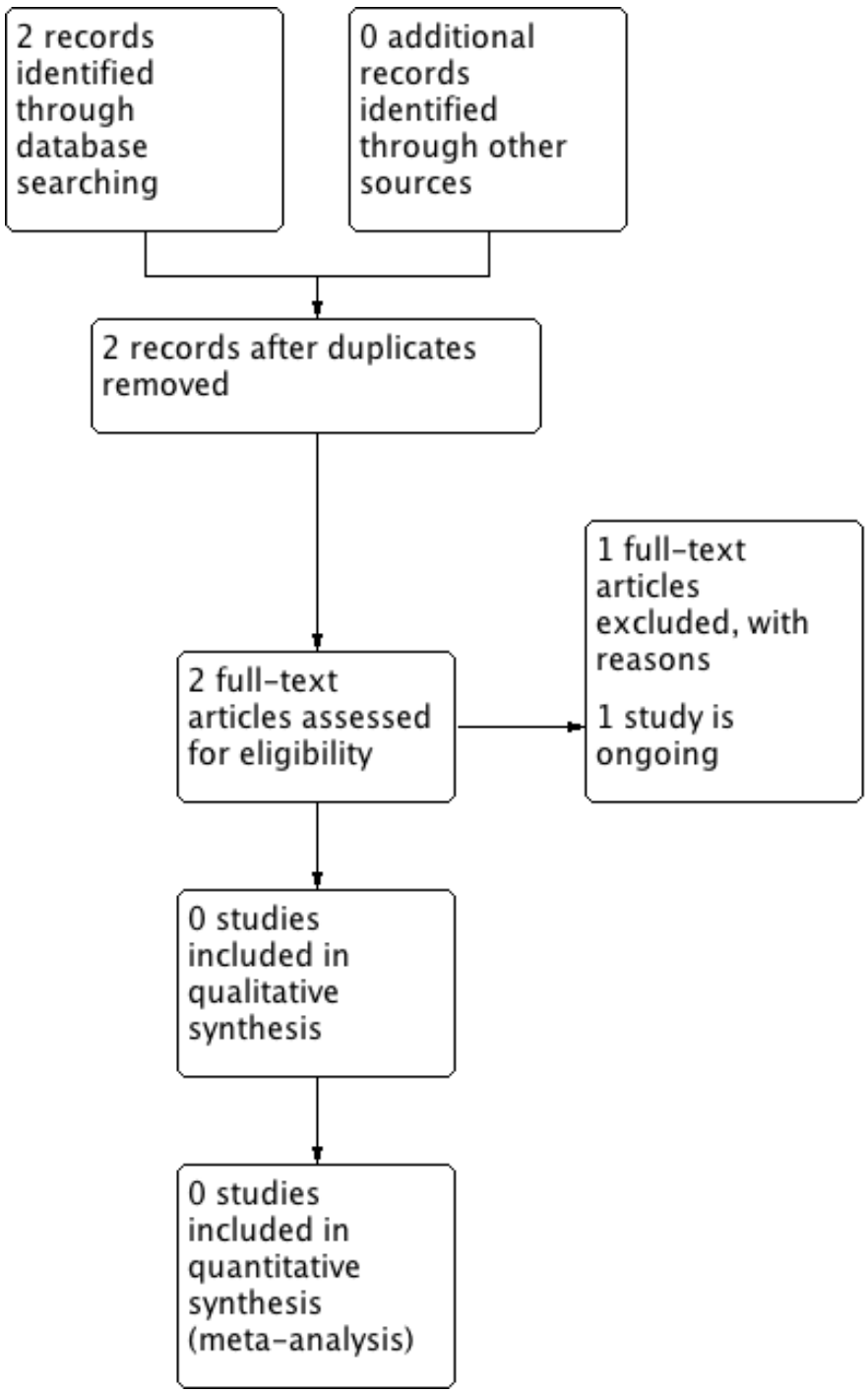
RESULTS

Description of studies

Results of the search

The search of the Cochrane Pregnancy and Childbirth Group's Trials Register retrieved two reports. One described observational data collected by Forster 2011a, that informed the design of the second report, Forster 2011b The DAME Study, which is the clinical trial registration of an ongoing randomised controlled trial in Australia (see Figure 1 and Characteristics of ongoing studies).

Figure 1. Study flow diagram.



Included studies

No studies were included.

Excluded studies

One study addressed a number of the outcomes of interest, but was an observational study (Forster 2011a). See Characteristics of excluded studies.

Risk of bias in included studies

No studies met the eligibility criteria for inclusion in this review.

Effects of interventions

There are no included studies in this review.

DISCUSSION

Summary of main results

The search strategy yielded no published studies that met the inclusion criteria. One study is currently underway (Forster 2011b). Some details of this study design are provided in Characteristics of ongoing studies.

The historical practices of preparation of the breasts, including nipple rolling and expressing colostrum during pregnancy, with the aim of improving breastfeeding success and minimising postnatal trauma and engorgement have, in the main, been discontinued, following no evidence of effect and recommendations not to teach this practice, as discussed in the comprehensive literature review of these practices by Chapman 2013b. The emergence of the concept of expressing colostrum antenatally and storing (freezing) this for postnatal use, seems a logical progression of the use of nature (colostrum) and science/technology (storage, in countries were this is available). This option may seem to be particularly useful for those babies who are susceptible to neonatal hypoglycaemia, such as those born to women with diabetes (Clay 2005; Cox 2010). As for any new concepts, the practice of antenatal breast milk expression for this purpose requires rigorous evaluation prior to widespread introduction. The one study that is currently in progress (Forster 2011b) may contribute data to that end.

Overall completeness and applicability of evidence

The comprehensive search strategy identified a range of published and unpublished material, with evidence of only the one ongoing study.

Potential biases in the review process

No evidence of bias was identified in the systematic searches for published and unpublished studies.

AUTHORS' CONCLUSIONS

Implications for practice

Antenatal breast milk expression and storage practices, evident in online consumer resources and some hospital guidelines, would appear to be a logical flow-on from the known benefits of preventing neonatal hypoglycaemia through early breastfeeding of babies born to women with diabetes in pregnancy, as well as improving breastfeeding success. However, they also need to be viewed by childbearing women and their carers in the context of the lack of high-quality evidence of their safety and efficacy, particularly in terms of the as yet unconfirmed potential for earlier birth and nursery admission at or after 36 weeks' of pregnancy.

Implications for research

The theoretical potential for benefit to the infant and the possibility of concerns about timing of onset of labour and of nursery admission for neonatal hypoglycaemia, albeit beyond 36 weeks' completed weeks of gestation (as noted in small observational studies), mandate the need for a rigorous evaluation of the evidence of the safety and efficacy of antenatal breast milk expression in women with diabetes in pregnancy. This would take the form of one or more randomised trials addressing the safety and effectiveness of antenatal breast milk expression by women with diabetes that aim to improve infant outcomes. Outcomes of interest may include those considered in this review.

ACKNOWLEDGEMENTS

As part of the pre-publication editorial process, this review has been commented on by three peers (an editor and two referees who are external to the editorial team), a member of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Forster 2011a	This observational study was conducted to determine the feasibility of a planned randomised controlled trial. Women with pre-existing or gestational diabetes (requiring insulin) who planned to breastfeed were enrolled. The women were encouraged to express and store colostrum from 36 weeks' gestation. Fetal heart rate monitoring was undertaken after expressing for the first time. There was no evidence of fetal compromise. The median volume of colostrum obtained as 39.6 mL. Outcomes for this group were compared with those from a retrospective audit of 89 women with diabetes who had not expressed during pregnancy

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

Forster 2011b

Trial name or title	Diabetes and antenatal milk expressing (DAME): a randomised controlled trial
Methods	Randomised controlled trial.
Participants	Women with diabetes in pregnancy who are intending to breastfeed
Interventions	Intervention: women with diabetes in pregnancy who are intending to breastfeed will commence twice daily antenatal milk expressing (and milk storage) from 36 weeks' gestation until birth Standard care: women with diabetes in pregnancy who are intending to breastfeed will receive usual care. In usual care, women are not advised to commence expressing breast milk antenatally
Outcomes	The proportion of infants: • requiring admission to the special or intensive care nursery; • receiving exclusive breast milk at three months of age; • receiving exclusive breast milk during the hospital stay after birth. The mean gestation at birth.
Starting date	1 May 2011.
Contact information	anita.moorhead@latrobe.edu.au
Notes	Two authors of the Cochrane Review, Della Forster and Christine East, are also investigators on the DAME trial. (See Declarations of interest)

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. Methods of data collection and analysis to be used in future updates of this review

Data collection and analysis

Selection of studies

At least two review authors (C East and W Dolan or D Forster) will independently assess for inclusion all the potential studies we identify as a result of the search strategy. A fourth co-author (to be appointed) will assist W Dolan in assessing for inclusion the Forster 2011b when it is considered in future updates of this review (see Declarations of interest).
We will resolve any disagreement through discussion or, if required, we will consult a third person.

Data extraction and management

We will design a form to extract data. For eligible studies, at least two review authors (CE and WD, or DF) will extract the data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult a third person. We will enter data into Review Manager software (RevMan 2014) and check for accuracy.
When information regarding any of the above is unclear, we will attempt to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors (CE and WD or DF) 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.

(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:

- 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 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:

- 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 blinding separately for different outcomes or classes of outcomes.
We will assess 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 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 assess blinding separately for different outcomes or classes of outcomes.
We will assess 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 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 participants), 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 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 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:

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

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

We 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.

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.

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 *Handbook* using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

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

Cross-over trials

As it unlikely that cross-over designs will be appropriate for this research question, we will exclude them.

Other unit of analysis issues

We will exclude multiple pregnancies in order to avoid the related issues with the unit of analysis.

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 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 or not 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 T^2, I^2 and Chi^2 statistics. We will regard heterogeneity as substantial if the I^2 is greater than 30% and either the T^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 the Review Manager software (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 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 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 T^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 analysis.

- Type of diabetes: gestational versus Type 1 versus Type 2.

The following outcome will be used in subgroup analysis.

- Exclusive breastfeeding during the period of hospital-based care following birth.

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

Sensitivity analysis

We will carry out sensitivity analysis to explore the effects of trial quality assessed by allocation concealment and other risk of bias components, by omitting studies rated as 'high risk of bias' for these components. This will be restricted to the primary outcomes.

CONTRIBUTIONS OF AUTHORS

Christine East compiled the protocol and review and is the guarantor for the review.

Willie Dolan and Della Forster contributed to the protocol and review content and reviewed them prior to submission.

DECLARATIONS OF INTEREST

Willie J Dolan: none known.

Della Forster is the Principal Investigator and Christine East is a co-investigator on a study that directly addresses this issue and that, when completed, would be included in this systematic review (Forster 2011b). All decisions relating to inclusion of that trial (assessment for inclusion, trial quality and data extraction) will be carried out by Willie Dolan and by an additional co-author (yet to be named) of this review who are not directly involved in the trial.

SOURCES OF SUPPORT

Internal sources

- Monash Health, Australia.

Women's and Children's Program

- Monash University, Australia.

School of Nursing and Midwifery

- Royal Women's Hospital, Australia.
- La Trobe University, Australia.

Mother and Child Health Research

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

A number of changes have been made in this review, compared to protocol, on the basis of greater clarity for the reader and on the recommendations of reviewers.

The Background has been extensively expanded in the review.

The following Types of outcome measures are those that were edited or added either following further discussions between the authorship about the importance and implications of outcomes, or at the suggestion of the reviewers.

Primary outcomes

#1 *Spontaneous onset of established labour prior to 37 weeks' gestation.*

- This was a secondary outcome in the protocol. The authors have had further discussions and consider that if antenatal breast milk expression contributes in any way to earlier than expected birth, albeit close to the time of being term, then this may not serve the babies well, as near-term babies require more care than their term counterparts.

#2 *Exclusive feeding with breast milk during the period of hospital-based care following birth*.

- This was edited to capture infant feeding with expressed breast milk, rather than potentially interpreting the outcomes as only feeding from the breast directly. Several of the secondary outcomes have also been edited to reflect this.

#3 & #4 in the protocol, *Duration of low blood glucose episode(s) and Administration of intravenous dextrose.*

- The authors have discussed the priorities of the limited number of primary outcomes (3 or 4) in Cochrane systematic reviews. These two outcomes have now been made secondary outcomes. Given that the main goal of antenatal breast milk expression is to improve infant outcomes, this can be better reflected in the need to care for these babies in the special care nursery or intensive care

nursery, where the duration of low blood glucose episodes will influence the need for intravenous dextrose. Hence, the revised outcome #4 is as follows:

Revised #4 *Admission to special care nursery or neonatal intensive care nursery.*

Secondary outcomes

Maternal

#1 in the protocol, *Uterine contractions during or after antenatal breast milk expression*, has been moved to "Other outcomes/considerations", as this will only apply to the group of women who are expressing.
#1 in the review is now, *Breast/nipple discomfort in late pregnancy*.

- This has been added at the suggestion of the reviewers.

#5 Commenced breastfeeding or milk expression following birth.

- This has been added at the suggestion of the reviewers.

Infant

- These changes are described under "Primary outcomes", above.

Other outcomes/considerations

This has now been edited to reflect that certain outcomes may only be noted in the group of women who are expressing antenatally. We will also consider the following in the expressing group.
#2 Uterine contractions during or after antenatal breast milk expression.

- as described above

#3 Maternal hypoglycaemia following antenatal breast milk expression.

- The authors have added this as an important consideration for the mother in this group.

The Types of participants and Types of interventions have undergone minor wording changes to clarify the intent of the protocol wording.

INDEX TERMS

Medical Subject Headings (MeSH)

*Colostrum; *Diabetes Mellitus; *Pregnancy in Diabetics; Breast Milk Expression [*adverse effects]; Hypoglycemia [*therapy]; Infant, Newborn, Diseases [*therapy]

MeSH check words

Female; Humans; Infant, Newborn; Pregnancy