Advising women with diabetes in pregnancy to express breastmilk in late pregnancy (Diabetes and Antenatal Milk Expressing [DAME]): a multicentre, unblinded, randomised controlled trial

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Summary

Background **Infants of women with diabetes in pregnancy are at increased risk of hypoglycaemia, admission to a neonatal intensive care unit (NICU), and not being exclusively breastfed. Many clinicians encourage women with diabetes in pregnancy to express and store breastmilk in late pregnancy, yet no evidence exists for this practice. We aimed to determine the safety and efficacy of antenatal expressing in women with diabetes in pregnancy.**

Methods **We did a multicentre, two-group, unblinded, randomised controlled trial in six hospitals in Victoria, Australia. We recruited women with pre-existing or gestational diabetes in a singleton pregnancy from 34 to 37 weeks' gestation and randomly assigned them (1:1) to either expressing breastmilk twice per day from 36 weeks' gestation (antenatal expressing) or standard care (usual midwifery and obstetric care, supplemented by support from a diabetes educator). Randomisation was done with a computerised random number generator in blocks of size two and four, and was stratified by site, parity, and diabetes type. Investigators were masked to block size but masking of caregivers was not possible. The primary outcome was the proportion of infants admitted to the NICU. We did the analyses by intention to treat; the data were obtained and analysed masked to group allocation. This trial is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12611000217909.**

Findings **Between June 6, 2011, and Oct 29, 2015, we recruited and randomly assigned 635 women: 319 to antenatal expressing and 316 to standard care. Three were not included in the primary analysis (one withdrawal from the standard care group, and one post-randomisation exclusion and one withdrawal from the antenatal expressing group). The proportion of infants admitted to the NICU did not differ between groups (46 [15%] of 317 assigned to antenatal expressing *vs* 44 [14%] of 315 assigned to standard care; adjusted relative risk 1·06, 95% CI 0·66 to 1·46). In the antenatal expressing group, the most common serious adverse event for infants was admission to the NICU for respiratory support (for three [<1%] of 317. In the standard care group, the most common serious adverse event for infants was moderate to severe encephalopathy with or without seizures (for three [<1%] of 315).**

Interpretation **There is no harm in advising women with diabetes in pregnancy at low risk of complications to express breastmilk from 36 weeks' gestation.**

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Introduction

Although breastfeeding is recognised as a public health priority for women, children, and the community, it has been somewhat neglected in high-income countries.[1] Effective interventions to improve breastfeeding rates are needed,[2] particularly in the context of complications in pregnancy, such as diabetes. Diabetes is the second-highest contributor to loss of health in Australia[3] and type 2 diabetes and gestational diabetes are increasing globally. Gestational diabetes occurs, on average, in 7% of pregnancies (range 1–14% depending on the population characteristics and diagnostic tests used),[4] and is the strongest single population predictor of type 2 diabetes.[5] An additional 1% of women younger than 44 years have pre-existing diabetes (types 1 or 2),[6] with type 2 diabetes increasing in women of childbearing age.[7] Since 2009, women who have glucose intolerance at the first pregnancy visit are diagnosed as having type 2 diabetes, not gestational diabetes.[4] The proportion of women being diagnosed with diabetes is increasing because of the lowering of diagnostic thresholds and increasing numbers of women of reproductive age who are overweight and obese.[8] Pregnancies affected by diabetes are at higher risk of perinatal complications.[9] Antenatal expressing—the practice of expressing breastmilk (colostrum) during pregnancy—is an increasingly widespread phenomenon, especially encouraged in women with diabetes in pregnancy but without evidence underpinning the practice.[10–14]

There are many reasons for expressing breastmilk during pregnancy. Infants of women with diabetes in pregnancy are at risk of developing hypoglycaemia and other morbidities in the neonatal period. They also have

Research in context

Evidence before this study

We previously undertook and published a Cochrane systematic review that included a comprehensive search for randomised controlled trials, quasirandomised trials, and cluster-randomised trials that compared antenatal breastmilk expressing with not expressing in pregnant women with diabetes. We did an updated search of the Cochrane Pregnancy and Childbirth Group's Trials Register, in accordance with the standard methods of the Cochrane Pregnancy and Childbirth Group on June 30, 2014, and without language restrictions. No new trials were identified. Only two non-randomised pilot studies of the increasingly widespread practice of antenatal expressing in women with diabetes in pregnancy have been published; both showed increased admissions to the neonatal intensive care unit for infants whose mothers had expressed, and one also showed that births occurred a week earlier on average. Safety and efficacy have not been assessed in randomised trials, and we have not identified any relevant studies in the intervening period.

Added value of this study

Despite the growing emergence of information for women about antenatal expression of breastmilk, we report here the first trial to provide evidence of the safety and efficacy of this practice. The DAME study enrolled women with pre-existing or gestational diabetes in a singleton pregnancy, reflecting the lower end of risk for complications of diabetes in pregnancy overall. Our results suggest there is no harm in advising these low-risk women with diabetes in pregnancy to express breastmilk from 36 weeks' gestation, in terms of the concerns highlighted in the reported observational studies—ie, increased risk of admission to a neonatal intensive care unit or earlier birth. Our study also showed some evidence of benefit as measured by the greater proportion of infants receiving breastmilk exclusively in the first 24 h of life and during the initial hospital stay. These findings support a practice that contributes to fulfilling WHO's mandate that infants be exclusively breastfed, in this case at least for the first days following birth, and contribute to the wider body of knowledge about practices that support breastfeeding.

Implications of all the available evidence

Women with diabetes in pregnancy who are otherwise considered at low risk of complications can be encouraged to hand-express breastmilk twice a day in late pregnancy to improve their chance of providing exclusive breastmilk for their infant. We caution, however, that further evidence is needed before extending this practice to higher-risk women.

For the **Cochrane Pregnancy and Childbirth Group** see http://onlinelibrary.wiley.com/o/cochrane/clabout/articles/PREG/frame.html

an increased risk of developing diabetes themselves,[9,15] and of being overweight later in life.[9] To manage hypoglycaemia, infant formula milk is more likely to be given to these babies and they are more likely than other infants to be separated from their mothers when admitted to the neonatal intensive-care unit (NICU) for intravenous glucose.[16] Colostrum stabilises infant glucose concentrations more effectively than infant formula milk,[17] and ensures infants maintain exclusive breastfeeding to enable optimum health outcomes.[1]

Lactation has an important role in helping women to return to a healthy metabolism after birth and reducing the long-term risk of developing type 2 diabetes for women with gestational diabetes.[18] However, women with diabetes in pregnancy tend to experience breastfeeding difficulties, leading to their infants not being exclusively breastfed,[19] and being more likely to be breastfed for a shorter duration.[20] Women with diabetes are also at risk of other comorbidities, most commonly obesity.[21] Separation of mother and infant after a caesarean birth (which is also more likely in women with diabetes in pregnancy), or infant admission to the NICU further decreases the likelihood of successfully establishing breastfeeding.[22] Impaired glucose tolerance is thought to hinder several stages of lactation,[23] manifested in a delayed onset of lactogenesis, whereby women with diabetes may have a 24 h delay compared with other women.[24]

This combination of factors has led to increasing numbers of maternity providers encouraging women with diabetes in pregnancy to express breastmilk in the weeks before birth, in an effort to have an adequate volume of breastmilk available for supplementary feeding should it be required to treat neonatal hypoglycaemia. However, current evidence for this practice is limited to two small pilot studies.[25,26] Findings from our previous study suggested an increased risk of NICU admissions in infants whose mothers had been advised to express antenatally,[25] as did the results from a small retrospective UK cohort study.[26] The findings from the UK study also suggested that birth occurred 1 week earlier in pregnancies when women were advised to express.[26] Additionally, the authors of a Cochrane review[10] concluded that more high-quality evidence is required before antenatal expressing is recommended to women with diabetes in pregnancy.

We undertook the DAME (Diabetes and Antenatal Milk Expressing) trial to explore the safety and efficacy of this practice for mother, fetus, and newborn infant.[12] Our primary hypothesis was that infants of women with diabetes in pregnancy (pre-existing or gestational) who start antenatal expression of breastmilk from 36 weeks' gestation are more likely to be admitted to the NICU after birth than those whose mothers receive standard care.[12]

Methods

Study design and participants

For the **protocol** see http://bmjopen.bmj.com/content/4/10/e006571.full

We did a multicentre, two-group, unblinded, randomised controlled trial at six hospitals in Victoria, Australia. Ethics approval was obtained from the following human research ethics committees (reference number in brackets): the Royal Women's Hospital (11/07 for Parkville and Sandringham campuses), Mercy Hospital for Women (11/06), La Trobe University (11-004), Monash Medical Centre (12181-B), Barwon Health (13/06), and Peninsula Health (14/PH/21).[12]

Eligible women had pre-existing or gestational diabetes, were between 34 and 37 weeks' gestation with a singleton pregnancy in a cephalic presentation, attending a study site for pregnancy care, planning to breastfeed, and had adequate English-speaking ability. Exclusion criteria were any history of antepartum haemorrhage or placenta praevia (even in the absence of any antenatal bleeding); an unknown or classic caesarean scar or more than one lower-segment caesarean scar; any suspicion of fetal compromise including known or suspected fetal growth restriction, documented macrosomia (estimated fetal weight ≥95th percentile with abdominal circumference >97th centile), polyhydramnios, or any abnormal tests of fetal wellbeing (whether clinical, ultrasound, or cardiotocography based); a known fetal anomaly; hypertension and proteinuria leading to concerns about fetal wellbeing; or if there was serious maternal mental health issues, or other severe maternal obstetric or medical issues. More details are in the published protocol.[12]

All eligible women booking for maternity care at the study sites during the recruitment period were offered trial participation by a study midwife from 34 to 37 weeks' gestation. Interested women provided written informed consent and completed a questionnaire regarding demographic details and breastfeeding intentions before randomisation took place.

Randomisation and masking

We randomly assigned eligible women (1:1) to either expressing breastmilk twice per day from 36 weeks' gestation (antenatal expressing) or standard care (usual midwifery and obstetric care, supplemented by support from a diabetes educator). Randomisation was done by a computerised random number generator in blocks sizes two and four, and was stratified by site, parity (first baby or not), and diabetes type (ie, pre-existing [types 1 or 2], gestational requiring insulin, or gestational not requiring insulin). The allocation sequence was generated and administered by the Clinical Epidemiology and Biostatistics Unit at the Murdoch Childrens Research Institute (VIC, Australia). Research midwives accessed the program via the internet to ascertain women's allocation when the women reached between 36 and 37 weeks' gestation and informed the women of group allocation immediately.

Investigators were masked to block size and group allocation, but masking of caregivers was not possible. Postnatal ward and NICU staff had to access expressed breastmilk in the freezer if it was available; they also had to be aware of all trial infants to undertake point-of-care true blood glucose (TBG) measurements (this was not a routine procedure at most of the sites). Outcome assessment by abstraction of medical record data was done masked to group allocation. Data were presented to a data monitoring committee on Nov 20, 2014, for an interim analysis in unlabelled study groups; the research team remained masked to group allocation at all stages until completion of the primary data analysis. Trial groups were relabelled for the analysis by an independent statistician such that those undertaking the analysis did not know which group was which.

Procedures

Any woman could discuss breastfeeding with midwives during pregnancy and could ask to see a lactation consultant in the antenatal period. No site participating in the trial recommended that women express breastmilk in the antenatal period outside the trial.

Women allocated to antenatal expressing received all standard advice and care as per existing hospital protocols, as well as instructions on hand-expressing breastmilk. They were encouraged to hand express twice per day for no more than 10 min until admission to hospital to give birth, unless any concerns arose that indicated that the intervention should cease (detailed more fully in the protocol).[12] Women were provided with written and verbal instructions on hand expressing, and on safe storage and transportation of breastmilk.[12] They labelled the expressed breastmilk with their hospital medical record number and kept it in syringes in their home freezer, then transported the frozen breastmilk in a cold storage box to a dedicated hospital freezer when they were admitted for the birth.

Demographic data (including maternal age, education, marital status, ethnic background, and smoking status) were obtained by questionnaire at recruitment before randomisation, and obstetric and neonatal medical outcomes were abstracted from the medical record after the birth.

Other outcome data were obtained by telephone-administered questionnaires at 2 weeks and 12 weeks post partum, with the questionnaire administrator masked to group. Women in the antenatal expressing group received diaries to document each episode of expressing. Data for an economic assessment were obtained at all data collection points.[12]

Existing guidelines for management of newborn infants at risk of hypoglycaemia were followed at each site, regardless of group allocation. Neonatal hypoglycaemia was defined as a TBG of less than 2·6 mmol/L, measured before feeds using the glucose oxidase method on a blood gas analyser in the NICU (or on a portable point of care TBG analyser, or in the laboratory) to facilitate an accurate measurement.[27]

Outcomes

The primary outcome was the proportion of infants admitted to the NICU, hand abstracted by research midwives masked to group assignment and verified by the trial coordinator. This outcome was to establish whether antenatal expressing of breastmilk from 36 weeks' gestation for pregnant women with diabetes increased the proportion of infants who required admission to the NICU, compared with infants of similar women receiving standard care.

Secondary short-term outcomes were gestational age at birth and the proportion of infants receiving breastmilk exclusively during the initial hospital stay (both as recorded in the medical record). To ensure accuracy, this was measured as exclusive breastmilk feeding from birth to age 24 h, and exclusive breastmilk feeding from birth to discharge (or to age 7 days for those with a longer length of stay). Other secondary outcomes were the proportion of infants receiving breastmilk exclusively at age 3 months (self-report by telephone); cost of the intervention to hospitals and to women, and cost-effectiveness against breastfeeding outcomes (medical records and self-report); women's views and experiences (self-report); fetal wellbeing associated with expressing (assessed by cardiotocography by the attending clinician); the number of antenatal expressing episodes and volumes collected (antenatal expressing group only); and time from birth to the onset of copious milk supply (also known as milk coming in, lactogenesis II, or secretory activation[24]).

We also obtained the following explanatory variables directly from medical records: reasons for NICU admission, hypoglycaemia treatments in the postnatal ward or NICU, length of time until three consecutive infant TBG concentrations of at least 2·6 mmol/L, maternal blood glucose concentrations after the first three expressing episodes, and maternal morbidity that could be attributed to expressing—eg, premature labour.

Women allocated to antenatal expressing maintained a diary of expressing, noting the date and time that each expressing episode took place, the volume of breastmilk expressed, and any other observations—eg, uterine activity, flow of milk, feelings in the nipple or breast. We assessed intervention fidelity using the diaries completed by the women in the antenatal expressing group and from specific questions at the end of the 3-month survey. We also asked all women at the 2-week and 12-weeks interviews if they expressed antenatally to check for any crossover

We monitored both maternal and fetal wellbeing for any signs of harm arising from the antenatal expressing and had several strategies in place for ongoing monitoring. Before randomisation, all women had cardiotocography to ensure this was reassuring, as per standard clinical protocols, assessed by attending clinical staff. Women in the antenatal expressing group were taught how to express while having cardiotocography surveillance; they then expressed opportunistically at any other time they had cardiotocography monitoring. The cardiotocography had to be normal before starting expressing, with immediate discontinuation of expressing if signs of associated fetal compromise occurred.[12] Women were advised of

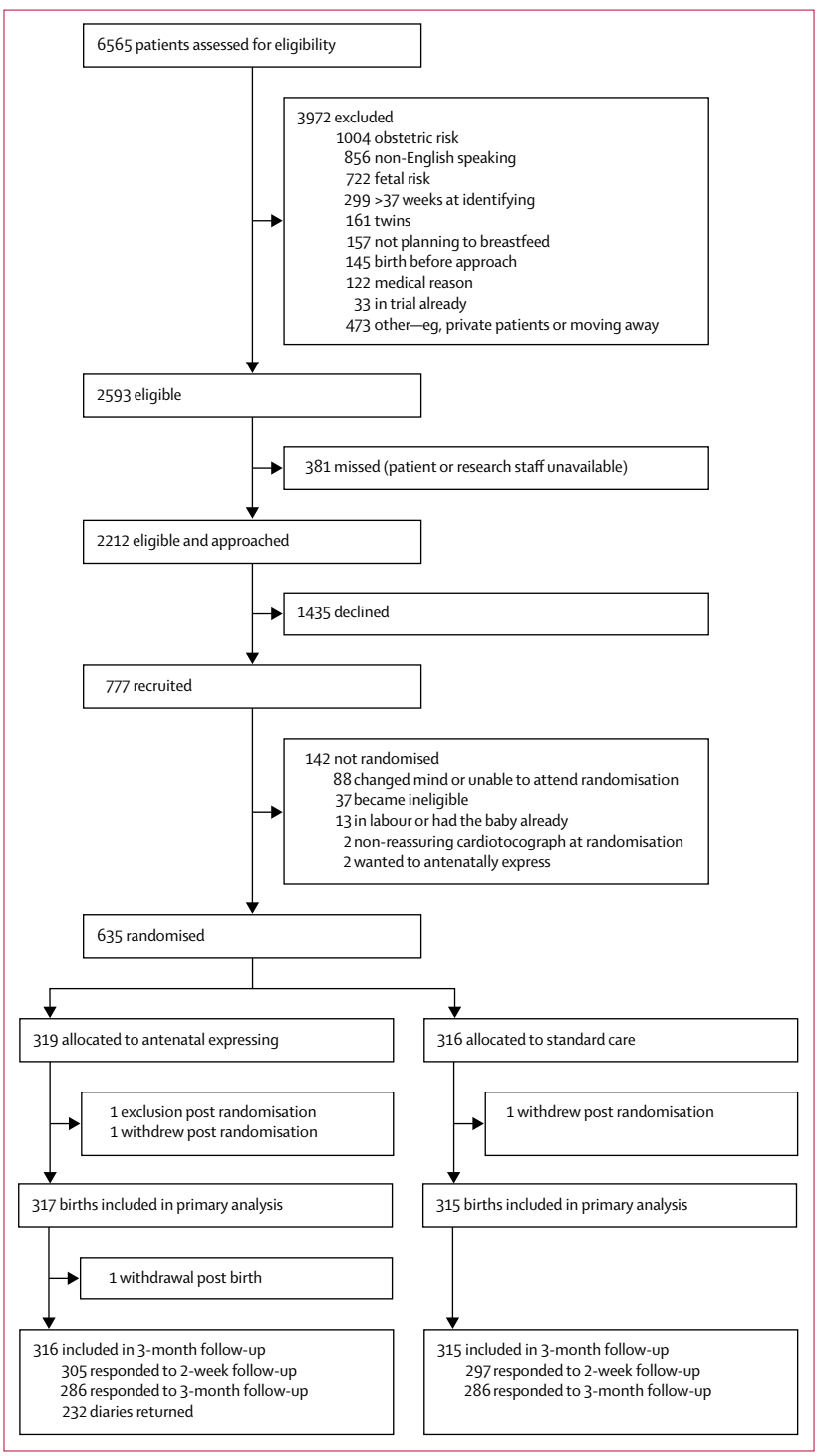

***Figure*: Trial profile**

precautions related to expressing in the antenatal period and informed of what actions to take if they had any concerns. Women in the antenatal expressing group were also asked to measure their blood glucose concentration after the first three episodes of expressing to assess any associated hypoglycaemia.[28] Serious adverse events for notification to a safety committee were prespecified and are in the study protocol.[12]

Statistical analysis

Our original trial protocol included only women with diabetes in pregnancy who required insulin, and our sample size calculation of 658 women was based on (estimates of the primary outcome in this group. Recruitment started in June, 2011. In May, 2012, we amended our inclusion criteria to include all low-risk women with diabetes in pregnancy because of lower than anticipated numbers of eligible women and based on independent expert advice recommending that external validity would be increased if the criteria were broadened. We revised our estimated baseline rate of admission to the NICU (our primary outcome) to 17%, rather than 20% as per our original calculation, following review of 2011 outcome data for all women with diabetes in pregnancy at one site (the Royal Women's Hospital, Parkville campus, VIC, Australia). Allowing for a 5% loss to follow-up, we required 658 women (329 per trial group) to detect an increase in the number of admissions to the NICU from 17% to 27% with a power of 85%; ie, we required 313 participants per group for the primary analysis. This sample size also ensured power to detect clinically important differences in the following secondary outcomes: exclusive breastfeeding at 3 months; mean duration of pregnancy; and breastfeeding exclusivity during the initial hospital stay.

Data were obtained in accordance with CONSORT guidelines for reporting of randomised trials,[29] including data for eligible non-participants. All analyses were by intention to treat, and done with Stata version 13. The primary outcome was calculated as event numbers and percentages by group allocation and compared using relative risks (RR) with 95% CIs, with standard care as the reference group. Breastfeeding outcomes were similarly calculated, as were other categorical variables. Comparisons of mean gestation were undertaken using a *t* test for all normally distributed continuous variables, or Mann-Whitney *U* tests to compare medians. Additional multivariate analyses were done to account for stratification variables (all analyses) and for additional documented factors that might affect an outcome based on the scientific literature (ie, education and maternal age for birth outcomes and NICU admission; and maternal age, education, and breastfeeding intention [the most significant predictor of infant-feeding outcomes] for breastfeeding outcomes; and education and age for gestation). Predicted probabilities of the outcomes were estimated using marginal standardisation after logistic regression (using the margins command). The predicted probabilities were then used to derive adjusted RR using the nlcom command in Stata 13. We present adjusted results for all primary and secondary outcomes. In addition to adjusting for parity in the primary analyses, we did an additional non-prespecified analysis of the primary and secondary outcomes by parity—ie, first baby or not. This trial is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12611000217909.

	Antenatal expressing (n=317)	Standard care (n=315)
Maternal age at recruitment (years)	33·1 (4·7; n=316)	32·2 (4·3)
Married or living with partner	303 (96%)	296 (94%)
Education level: graduate degree or higher	207 (65%)	175 (56%)
Household weekly income before tax ($AUD)		
<1400	126 (40%)	135 (43%)
≥1400	166 (52%)	151 (48%)
Declined to answer	25 (8%)	29 (9%)
Pension or benefit	19/315 (6%)	25/314 (8%)
Born in Australia	133 (42%)	149 (47%)
English as first language	187 (59%)	187/314 (60%)
Smoked pre-pregnancy	40 (13%)	39 (12%)
Maternal BMI pre-pregnancy (kg/m²)		
Underweight (<18·50)	10/304 (3%)	5/298 (2%)
Normal range (18·50–24·99)	155/304 (51%)	142/298 (48%)
Overweight (25·00–29·99)	71/304 (23%)	85/298 (29%)
Obese (≥30·00)	68/304 (22%)	66/298 (22%)
Type 1 diabetes	8 (3%)	12 (4%)
On insulin	8/8 (100%)	12/12 (100%)
Type 2 diabetes	14 (4%)	9 (3%)
On insulin	12/14 (86%)	8/9 (89%)
Gestational diabetes	295 (93%)	294 (93%)
On insulin	150/295 (51%)	149/294 (51%)
On metformin	2/295 (<1%)	2/294 (<1%)
Gestation at recruitment (weeks)	35·8 (1·0)	35·7 (0·9)
Gestation at randomisation (weeks)	36·9 (0·4)	36·9 (0·4)
Days from randomisation to birth	18·1 (7·0; n=314)	18·1 (6·7; n=315)
First baby	185 (58%)	178 (57%)
Characteristics specific to multiparous women only		
Number of previous children	1 (1–4, 1–1; n=132)	1 (1–5, 1–1; n=137)
Previously breastfed	129/132 (98%)	132/137 (96%)
Total previous breastfeeding (months)	14·7 (0–72, 4–19; n=129)	12·2 (0–64, 4–15; n=131)
Diabetes previous pregnancy	52/132 (39%)	56/136 (41%)
Previous antenatal expressing	5/132 (4%)	6/137 (4%)
Plan to breastfeed for ≥6 months	245 (77%)	237 (75%)

Data are mean (SD), n (%), n/N (%), or median (range, IQR; n). BMI=body-mass index.

***Table 1*: Characteristics of participants**

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author (DAF), SMD, LHA, and AMM had full access to all the data in the study and

DAF had final responsibility for the decision to submit for publication.

Results

Between June 6, 2011, and Oct 29, 2015, we recruited 777 women, of whom 635 were randomly assigned to treatment (most with a two-stage recruit and randomise strategy): 319 to antenatal expressing and 316 to standard care (figure 1). Reasons for non-randomisation included women becoming ineligible (eg, 37 [26%] of 142 not randomly assigned had a breech presentation) and deciding to not participate or being unable to attend for randomisation (88 [62%] of 142). Randomisation by site was as follows (number assigned to antenatal expressing/number assigned to standard care): Royal Women's Hospital Parkville 95/98; Sandringham 13/16; Mercy Hospital for Women 146/142; Monash Medical Centre 36/36; Barwon Health 20/16; and Frankston 9/8. One woman assigned to antenatal expressing was excluded after randomisation (the fetus was known to be breech pre-randomisation but trial staff were only notified of breech presentation after randomisation), and one withdrew from each group after randomisation, leaving 632 infants available for the primary analysis (317 in the antenatal expressing group and 315 in the standard care group). All these infants had the primary outcome ascertained . There was one further withdrawal after this point, in the antenatal expressing group, leaving 631 included in the denominator for the 3-month follow-up (316 in the antenatal expressing group and 315 in the standard care group).

Baseline characteristics for participants were similar between groups (table 1), including mean gestation at recruitment and mean weeks at randomisation. Most women in both groups had gestational diabetes, more than half were expecting their first baby, and half were either overweight or obese.

Of the women allocated to the antenatal expressing group, 44 (14%) of 316 either did not express at all after randomisation or expressed five times or fewer (table 2), but a substantial proportion expressed more than 20 times. 32 women allocated to standard care reported expressing in the antenatal period; the number of expressing episodes was not specifically ascertained, but two women stated they expressed only immediately before the birth. There were no between-group differences in any birth characteristics (eg, labour onset, type of birth, or blood loss; table 3).

The proportion of infants admitted to the NICU did not differ between groups (46 [15%] of 317 assigned to antenatal expressing *vs* 44 [14%] of 315 assigned to standard care; adjusted RR 1·06, 95% CI 0·66–1·46; table 3). Mean gestational age at birth also did not differ between groups. There was moderate evidence of association between allocation to maternal antenatal expressing and the proportion of infants receiving exclusive breastmilk during the first 24 h of life and during the initial hospital stay. There were no differences between the groups in other neonatal outcomes or breastmilk feeding outcomes (table 3). Costs, cost-effectiveness, women's views, and time to lactogenesis II) will be reported elsewhere.

The reasons for admission to NICU were similar in each group; the three most common reasons were hypoglycaemia, suspected infection, and respiratory distress (table 3). Fewer than half of all infants in each group were reported as having hypoglycaemia (132 [42%] of 315 in the antenatal expressing group, 22 of whom were admitted to the NICU; and 143 [46%] of 315 in the standard care group, 28 of whom were admitted to the NICU). More infants of mothers allocated to antenatal expressing received an extra breastfeed for management of hypoglycaemia compared with infants of mothers in standard care, and fewer received infant formula (table 3).

Maternal hypoglycaemia was not evident from data provided by the women of their first three blood glucose concentrations after expressing: mean 5·6 mmol/L (SD 1·04, range 3·8–13·6; n=199). 8% of women in both groups had an antenatal admission (26 assigned to antenatal expressing 26 assigned to standard care). There were no important differences in occurrences of individual symptoms leading to antenatal admission (abdominal pain or contractions unrelated to birth admission: four in antenatal expressing, seven in standard care; decreased fetal movements: 13 in antenatal expressing, eight in standard care; vaginal bleeding: one in each group).

Routine pre-randomisation cardiotocography was normal in all but two women, who were therefore not randomly assigned to treatment. In subsequent episodes of expressing done under cardiotocography surveillance, there was a transient increase in uterine activity for some

	Antenatal expressing group only (n=316)
Frequency of expressing	
Never expressed after randomisation	19 (6%)
2–5 times	25 (8%)
6–19 times	80 (25%)
≥20 times	134 (42%)
Expressed, but number of times unknown*	49 (16%)
Unknown	9 (3%)
Expressing outcomes	
Expressing episodes‡	20·0 (1–59, 9–33)
Volume expressed (mL)§	5·5 (0–905, 0–22)
Maternal blood glucose concentration after expressing	
Mean blood sugar concentration of first three measurements† (mmol/L)	5·6 (1·0)

Data are n (%), median (range, IQR), or mean (SD). *Data from 3-month interview. †Only 196 women recorded all three measurements. ‡n=258. §n=241.

Table 2: **Outcomes of antenatal expressing**

	Antenatal expressing (n=317)	Standard care (n=315)	Relative risk or mean difference (95% CI)	Adjusted relative risk or adjusted mean difference (95% CI)
Primary outcome				
Admission to NICU	46 (15%)	44 (14%)	1·04 (0·71 to 1·52)	1·06* (0·66 to 1·46)
Secondary outcomes				
Gestational age at birth (weeks)	38·6 (1·03)	38·7 (0·98)	−0·05 (−0·21 to 0·10)	−0·05† (−0·21 to 0·10)
Breastmilk feeding exclusively for first 24 h	217 (69%)	189 (60%)	1·15 (1·03 to 1·30)	1·15‡ (1·02 to 1·28)
Breastmilk feeding exclusively from birth to discharge (or to 7 days if still inpatient at that timepoint)§	178 (57%)	154 (49%)	1·16 (1·00 to 1·34)	1·16‡ (0·99 to 1·33)
Breastmilk feeding exclusively at 3 months	169/284 (60%)	156/286 (55%)	1·10 (0·95 to 1·26)	1·08‡ (0·92 to 1·23)
Any breastmilk feeding at 3 months	235/284 (83%)	233/286 (82%)	1·02 (0·94 to 1·10)	0·99‡ (0·92 to 1·07)
Other neonatal outcomes				
Preterm birth	5 (2%)	1 (<1%)	5·02 (0·59 to 42·7)	4·61* (0·53 to 39·92)
Birthweight (g)	3325 (420)	3338 (421)	−12·71 (−78·43 to 53·01)	−1·12¶ (−63·03 to 64·76)
Birthweight <2500 g	7 (2%)	3 (1%)	2·34 (0·61 to 8·97)	2·13* (0·55 to 8·19)
Apgar score <7 at 5 min	7 (2%)	8 (3%)	0·87 (0·32 to 2·37)	0·92* (0·34 to 2·54)
Time until three consecutive blood sugar level measurements ≥ 2·6 mmol/L (h)‖	12·7 (5·2)	13·2 (6·5)	−0·49 (−1·48 to 0·51)	−0·57¶ (−1·57 to 0·42)
Length of hospital stay (h)	70·9 (56·4)	72·1 (54·9)	−1·19 (−9·99 to 7·51)	−1·51¶ (−10·07 to 7·00)
Reasons for admission to NICU**				
Hypoglycaemia	19/45 (42%)	16/44 (36%)	..	..
Suspected infection	19/45 (42%)	18/44 (41%)	..	..
Respiratory distress	12/45 (27%)	10/44 (23%)	..	..
Hypothermia	4/45 (9%)	5/44 (11%)	..	..
Depression at birth requiring admission	3/45 (7%)	6/44 (14%)	..	..
Jaundice	3/45 (7%)	0/44	..	..
Weight loss or poor feeding	1/45 (2%)	1/44 (2%)	..	..
Preterm	2/45 (4%)	0/44	..	..
Low birthweight or clinically wasted	2/45 (4%)	0/44	..	..
Macrosomia (> 90th centile)	0/45	2/44 (5%)	..	..
Poor maternal diabetes control	0/45	2/44 (5%)	..	..
Other	16/45 (36%)	16/44 (36%)	..	..
Hypoglycaemia management **				
Extra (top-up) breastfeed	48/132 (36%)	38/143 (27%)	..	..
Extra expressed breast milk	84/132 (64%)	73/143 (51%)	..	..
Extra infant formula	60/132 (46%)	84/143 (59%)	..	..
Intravenous glucose	14/132 (11%)	13/143 (9%)	..	..
Glucagon	0/132	5/143 (4%)	..	..
Hydrocortisone	0/132	0/143	..	..
Diazoxide	0/132	0/143	..	..
Maternal outcomes				
Onset of labour				
Spontaneous	84 (27%)	86 (27%)	..	..
Induced	189 (60%)	183 (58%)	..	..
No labour	44 (14%)	46 (15%)	..	..
Epidural or spinal analgesic for labour pain relief (only if laboured)	115 (42%)	103 (38%)	1·10 (0·90 to 1·36)	..
Caesarean birth	103 (33%)	93 (30%)	1·10 (0·87 to 1·39)	..
Blood loss (mL)	455·6 (339·5)	429·9 (381·2)	−25·68 (−82·67 to 30·89)	..

Data are n (%), mean (SD), or relative risk (RR; 95% CI). NICU=neonatal intensive care unit. ..=not applicable. *Adjusted for diabetes type (gestational or not), parity (first baby or not), education (degree or not), and age. †Adjusted for diabetes type (gestational or not), parity (first baby or not), education (degree or not), and age. ‡Adjusted for diabetes type (gestational or not), parity (first baby or not), education (degree or not), age, and breastfeeding intention (plan to breastfeed ≥6 months *vs* not). §Only 13 infants stayed >7 days. ¶Mean difference adjusted for diabetes type (gestational or not), parity (first baby or not), education (degree or not), and age. ‖Some infants did not have the time and date recorded for all blood glucose measurements, hence fewer numbers for this variable. **Could have more than one response, thus percentages can add up to more than 100.

Table 3: **Infant and maternal outcomes**

women, but no episodes of tachsystole or hyperstimulation. The safety committee was provided with a list of all serious adverse events in the first 300 births, and found no evidence that the intervention caused harm (table 4).

For women having a first baby, allocation to maternal antenatal expressing was not associated with increased admission to NICU (adjusted RR 0·83, 95% CI 0·45–1·21) or shorter mean gestation (adjusted mean difference –0·18 weeks, –0·39 to 0·37) compared with standard care. There was moderate evidence of association with infants receiving breastmilk exclusively in the first 24 h of life (adjusted RR 1·21, 1·03–1·40) and some evidence of association with exclusive breastmilk feeding during the initial hospital stay (adjusted RR 1·21, 0·96–1·47).

For women having a subsequent baby, allocation to maternal antenatal expressing was not associated with increased admission to NICU (adjusted RR 1·80, 95% CI 0·57–3·03), shorter mean gestation (adjusted mean difference 0·14, –0·09 to 0·12), or a difference in the proportion of infants receiving breastmilk exclusively in the first 24 h of life (adjusted RR 1·07, 0·89–1·25) or breastmilk feeding exclusively during the initial hospital stay (adjusted RR 1·11, 0·89–1·34). Since the study was not powered to detect differences as above for this analysis, these data should be interpreted accordingly.

	Antenatal expressing (n=317)	Standard care (n=315)
Perinatal or infant outcomes		
Fetal compromise associated with expressing*	3 (<1%)	..
Moderate to severe encephalopathy with or without seizures	0 (0%)	3 (<1%)
Admission to NICU for respiratory support	3 (<1%)	2 (<1%)
Perinatal death	0 (0%)	0 (0%)
Maternal outcomes		
Maternal hypoglycaemia within 30 min of expressing	17 (5%)	..
Abdominal pain after antenatal expression within 4 h	10 (3%)	..
Vaginal bleeding after antenatal expression within 4 h	0	..

Data are n (%). NICU=neonatal intensive care unit. ..=not applicable. *All three events were reviewed by a safety adverse events committee and there were no signs of compromise; decreased fetal movements occurred during or after expressing, necessitating presentation to hospital for fetal monitoring or cessation of the intervention.

Table 4: **Serious adverse events**

Discussion

We showed no evidence of harm from advising women with diabetes in pregnancy at low risk of complications to express breastmilk from 36 weeks' gestation—infants of women allocated to this group were no more likely to be admitted to a NICU than infants of women receiving standard care, and there was no difference in gestational duration between groups. Moreover, we showed evidence of a beneficial effect on exclusive breastmilk feeding from birth to age 24 h, and some evidence of continued effect from birth to discharge from hospital; however, this effect was not sustained to 3 months.

Our findings contrast with those from two previous pilot studies,[25,26] which suggested that antenatal expression might lead to increased admissions to NICU[25,26] and earlier delivery.[26] Our findings must be interpreted in the context of our stringent eligibility criteria: the women and infants in our trial were at very low risk of complications in the spectrum of women with diabetes in pregnancy.[25] Our results are the first evidence from a randomised trial and will inform the next Cochrane systematic review of antenatal expressing for women with diabetes in pregnancy, which currently includes no randomised trials.[10]

Our study strengths included the detailed collection of infant feeding outcomes, our ability to ensure all sites maintained a policy of not advising antenatal expressing outside the trial, thus limiting the chance of contamination, and our near-complete ascertainment of the primary and secondary outcomes—only three randomly assigned women and their infants were not included in the primary analysis. We had six study sites and included women with gestational diabetes as well as women with type 1 and type 2 diabetes, enhancing the external validity of the study. One study limitation was that given the type of intervention, we could not mask participants to group assignment. However, we aimed to mask other individuals connected with the trial at every stage possible—medical data were abstracted masked to trial group, telephone follow-up interviews were undertaken masked, and data cleaning and primary analysis were undertaken masked to group.

The study was controversial from its inception—we were challenged publicly on many occasions that this trial was unethical because the benefits of breastmilk are evident and that a practice such as this could not possibly cause harm,[13] and we responded in a published letter.[11] The controversy centred around the possible benefits and the absence of known harms (despite the evidence from the two pilot studies).[25,26] Internationally, the practice of expressing breastmilk in late pregnancy to provide a supply of mother's own milk for the immediate post-birth period when infants are at risk of hypoglycaemia and the mother's milk supply is not yet sufficient is growing.[14,30]

Our trial aimed to address concerns that antenatal breast stimulation might lead to oxytocin release and earlier onset of labour. Our findings have refuted this concern; although there were differences between groups in the number of infants born preterm (five in the antenatal expressing group versus one in the standard care group), the difference was not significant and these numbers do not provide evidence of an association with antenatal expressing. The mechanism for increased exclusive breastmilk feeding in hospital in women in the antenatal expressing group might have been the antenatal breast stimulation or the availability of milk expressed before birth. However, since many

women expressed small volumes (median 5 mL), we will further analyse the relationship between the amount of expressing and the volume expressed. Although the increase in the proportion of infants who were exclusively breastfed during their hospital stay was small, these infants were able to avoid infant formula milk in this important early period which might have long-term implications for future development of diabetes in these children.

Our findings must be interpreted in context—ie, the women recruited were a low-risk subset of the population of women who have diabetes in pregnancy. Given the results from the pilot studies had suggested reduced gestational age and increased NICU admission associated with antenatal expressing, women targeted for this study were those at the lowest risk of fetal compromise that might have been precipitated by increased uterine activity. We also excluded women for whom a caesarean birth was indicated, and increased uterine activity might plausibly have contributed to iatrogenic early birth. Given our positive findings, our main concern is that they will be inappropriately extrapolated to other groups (eg, women with threatened preterm birth). Future trials should therefore focus on groups who might benefit, but whose risk factors might be greater than the women included in our study.

DAME is the first trial to test the widespread practice of antenatal expressing. Our results suggest there is no harm in advising women with diabetes in pregnancy at low risk of complications to express breastmilk from 36 weeks' gestation, and some evidence of benefit. If clinicians choose to advise this group of women to express, this should be undertaken with clear guidelines and instructions for both women and health-care workers. This is not currently the case in Australia, where only 11 (37%) of 30 services advising women to express have guidelines in place.[11] The results of our study should not be extrapolated to high-risk groups with diabetes in pregnancy, or to other high-risk populations.

Contributors

DAF, AMM, and KMM conceived the project. DAF and AMM prepared the data and did the statistical analysis. LHA and AMM did the literature review. DAF and LHA wrote the first draft of the manuscript. All authors contributed to the study design, including data collection, tools, and study processes, data interpretation, and manuscript revision.

Declaration of interests

All authors except CE report a grant from the Australian National Health and Medical Research Council, for the conduct of the study. PGD reports other funds from Fisher and Paykel. CE declares no competing interests.

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