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Antenatal management of gestational diabetes mellitus can improve neonatal outcomes

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ABSTRACT

Objective: Pregnancies complicated with gestational diabetes mellitus (GDM) are at a higher risk for caesarean and instrumental deliveries as well as adverse neonatal outcomes such as fetal overgrowth, hypoglycaemia and neonatal intensive care admission. Our primary objective was to describe neonatal outcomes in a sample that included term infants of both GDM mothers and mothers with normal glucose tolerance (NGT).
Design and setting: this cross-sectional study included 599 term babies born between September and October 2010 at Royal Prince Alfred Hospital, Sydney, Australia. Maternal and neonatal data were collected from medical records and a questionnaire. Glycaemic control data was based on third trimester HbA1c levels and self-monitoring blood glucose levels (BGL). Univariate associations between GDM status and maternal demographic factors, as well as pregnancy outcomes, were estimated using χ^2 tests and *t*-tests, as appropriate.
Findings: of 599 babies, 67(11%) were born to GDM mothers. GDM mothers were more likely to be overweight/obese and of Asian ethnicity. Good glycaemic control was achieved in most GDM mothers. GDM babies were more likely to have been induced ($p=0.013$) and delivered earlier than non-GDM mothers ($p<0.001$), and they were also more likely to be breastfed within one hour of birth.
Conclusions and implications for practice: in this study, GDM infants were more likely to be induced and delivered earlier but otherwise they did not have significantly different neonatal outcomes compared to infants of NGT mothers. This can be attributed to the good GDM control by lifestyle modification and insulin if necessary. The role of labour induction in GDM pregnancies should be further investigated. Midwives have an important role in maternal education during pregnancy and in the postnatal period.

Introduction

Associated with the global epidemic of adult and childhood obesity, gestational diabetes mellitus (GDM) is also increasingly prevalent in both developed and developing countries (Ferrara, 2007). GDM, defined as carbohydrate intolerance with onset during pregnancy, affects fetal growth and development through the altered intrauterine environment and causes fetal overgrowth (Pederson et al., 1954).

The premise for GDM treatment is, in part, based on the assumption of a positive independent relationship between maternal glycaemia and neonatal adiposity (Catalano et al., 2003; Stuebe et al., 2012; Aris et al., 2014). The Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) study revealed strong, predominantly linear associations between maternal glycaemia and birthweight >90th percentile, per cent body fat (BF%) >90th

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percentile, pre-eclampsia, caesarean childbirth, shoulder dystocia and clinical neonatal hypoglycaemia (HAPO, 2008, 2009). Additionally, there is some evidence that with increasing levels of pregnancy glycaemia, the risk of spontaneous preterm birth is increased, independent of other perinatal complications (Hedderson et al., 2003). Two randomised clinical trials have shown that treatment of mild GDM reduces serious perinatal morbidity (Crowther et al., 2005; Landon et al., 2009).

The aim of this study was to describe neonatal outcomes in term infants of women with GDM compared to infants of mothers with normal glucose tolerance levels (NGT).

Methods

This was a cross-sectional study of all singleton, term infants (37–42 weeks gestation) born between September and October 2010 at Royal Prince Alfred Hospital (RPAH). RPAH is a major public teaching hospital in Sydney, Australia, with a predominantly inner urban, multicultural population and >5000 deliveries per year. This study was part of a larger body of work (Au et al., 2013, 2014, Carberry et al., 2013a). The sample size calculation was based on the main study question of estimating the number of neonates with low BF% which was our primary research outcome. For that question we estimated that we required a minimum sample of 384 neonates to provide a 95% confidence interval $\pm 3\%$. This was based on the assumption of 10% prevalence of neonates with low BF% giving 95% CI 7%, 13% (Carberry et al., 2013a, 2013b).

Patients

Eligible infants were singleton, term babies whose parents resided within the geographical catchment area of the RPAH. Infants with major congenital anomalies were excluded. For practical reasons, we were not able to conduct body composition measurements in the neonatal intensive care unit (NICU), and therefore we a-priori excluded babies who were admitted to NICU for more than two days.

Data collection

The data were collected from hospital records of the mother and newborn. Maternal data included age, ethnicity, parity, pre-pregnancy body mass index (BMI), gestational weight gain, alcohol and smoking history, diet, caffeine intake, education level, personal medical background, antenatal history and childbirth conditions. Paternal data included age, ethnicity, BMI and education. Neonatal data included gestational age, sex and neonatal outcomes.

Pregnancy measurements

Maternal pre-pregnancy weight was obtained from antenatal records. We used the World Health Organization (WHO) BMI classification as follows: underweight <18.50, normal range 18.50–24.99, overweight ≥ 25.00, obese ≥ 30.00 (Varner et al., 2000). Parity was defined as the number of viable previous pregnancies. Ethnicity was defined according to the Australian Standard Classification of Cultural and Ethnic Groups (Australian Bureau of Statistics, 2005).

Classification of disease was according to the WHO's International Classification of Diseases (ICD-10). Hypertension in pregnancy was defined as a systolic blood pressure ≥ 140 mmHg, and/or a diastolic blood pressure ≥ 90 mmHg.

Gestational age was calculated from the first day of last menstrual period using Naegele's rule. This date was adjusted to the first or second trimester ultrasound estimation of gestational age if the two estimates differed by $>$ seven days.

GDM diagnosis and management

The diagnosis of GDM was based on the Australian Diabetes In Pregnancy Society (ADIPS) criteria at the time of the study: universal screening for GDM at 26–28 weeks gestation using a 50 g or 75 g oral glucose challenge test (Hoffman et al., 1998). Confirmation of diagnosis was by a 75 g oral glucose tolerance test (OGTT). A venous plasma glucose ≥ 5.5 mmol/l fasting, and/or ≥ 8.0 mmol/l after two hours, was a positive result for GDM (Hoffman et al., 1998). Mothers with type 1 or type 2 diabetes were excluded.

Management of GDM, which included diet, exercise, self-monitoring of blood glucose levels (BGL) and insulin if needed, has been described previously (Au et al., 2013, Ross, 2006). Briefly, for each GDM mother, third trimester means of preprandial BGL for breakfast, as well as one-hour postprandial BGL for breakfast, lunch and dinner, were obtained by reviewing the patient's glucose logbooks. The minimum goals recommended at RPAH were pre-breakfast BGL <5.2 mmol/L and one hour postprandial BGL <7.5 mmol/L. These targets were considered to be good glycaemic control at RPAH and were lower than the minimum goals recommended by ADIPS at the time of the study, which were fasting BGL <5.5 mmol/L and one hour postprandial BGL <8.0 mmol/L (Hoffman et al., 1998). An upper, third trimester Haemoglobin A1c (HbA1c) limit of 5.6% in normal pregnancy was recommended (Nielson et al., 2004). Insulin therapy was commenced when glycaemic goals could not be met on dietary adjustment alone.

Pregnancy outcomes

Birth percentiles have been calculated based on population data (Beeby et al., 1996). Neonatal weight was classified as small for gestational age (SGA, birthweight <10th percentile), appropriate for gestational age (AGA, 10th–90th percentiles), or large for gestational age (LGA, >90th percentile) according to gestational age and sex.

Neonatal anthropometric measurements were made within 48 hours of birth. Neonatal body fat percentage (BF%) was assessed at birth by air displacement plethysmography using the PEA POD® (COSMED USA, Inc.) body composition system for infants from birth to six months of age. Measurement methodology has been described elsewhere (Au et al., 2013, 2014).

The type of labour was reported as spontaneous, induced or no labour. A definition of labour consisted of the latent and active phases of first stage, the second stage and the third stage. Spontaneous labour was defined as labour beginning and progressing without mechanical or pharmacologic stimulation, whereas induced labour was defined as the artificial stimulation of labour. The type of birth was reported as normal vaginal, emergency caesarean, elective caesarean (planned with or without medical indications) or instrumental (vaginal delivery using forceps or vacuum). Operative delivery included both caesarean and instrumental deliveries.

We developed a surrogate composite measure of neonatal morbidity associated with undernutrition (Carberry et al., 2013a). This included fetal distress, Apgar scores, hypothermia, length of stay and poor feeding (Appendix 1).

Breast feeding outcomes were optimised by prior staff education associated with implementation of the WHO and UNICEF Baby Friendly Hospital Initiative (BFHI) at RPAH several months before the study (World Health Organisation and UNICEF, 2009). Midwives were trained to incorporate the BFHI guidelines to the mother pair, encouraging safe, immediate post-birth, skin-to-skin contact with early breastfeeding. Early initiation of breast feeding was defined as $<$ one hour after birth and delayed as any time $>$ one hour.

Statistical methods

Descriptive statistics were calculated using the mean and standard deviation (SD) for continuous variables and number (per cent) of cases for categorical variables. Univariate associations between GDM status and maternal demographic factors, as well as pregnancy outcomes, were estimated using χ^2 tests and *t*-tests, as appropriate.

P-values <0.05 were considered statistically significant. All analyses were conducted in SPSS® (version 20.0.0, IBM®, New York, United States).

Ethics

The study was approved by the Human Research Ethics Committees of RPAH and the University of Sydney (HREC/09/RPAH645, SSA/09/RPAH646, University of Sydney Ref. no.12732). Informed written parental consent was obtained, and participation was voluntary.

Findings

Subjects

Eight hundred and fifteen mothers and their babies were approached for our study. Thirty-three were ineligible on the basis of more than two days of NICU admission, of which two were in the GDM group. A further 30 women refused participation and 150 were discharged early before enrolment. There were 602 mothers and their babies. Of these 532 mothers had a normal glucose tolerance (NGT) and 70 were identified as GDM. However, we further excluded three mothers who had pregestational diabetes, and thus our study population consisted of 532 with NGT and 67 diagnosed with GDM (Fig. 1).

Parental demographics

GDM mothers were more likely to be of Asian ethnicity. They were also more likely to be overweight/obese (Table 1). There was no significant difference in mean pre-pregnancy BMI between GDM women treated by lifestyle modification only (24.3 kg/m^2) compared to GDM women who required insulin (27.7 kg/m^2, $p=0.39$).

GDM control

The level of glycaemic control achieved in the GDM mothers has been described previously (Au et al., 2013). The minimum

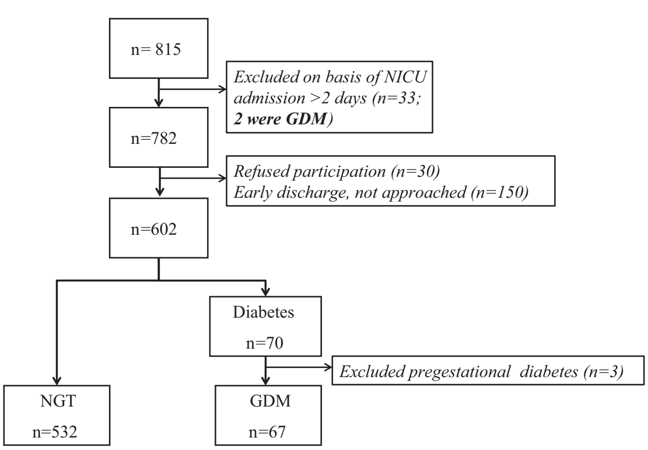

Fig. 1. Flowchart of subject selection.

Table 1
Comparison of maternal demographic, anthropometric and antenatal data between women with GDM compared to NGT women.

	GDM women (n=67) Mean ± SD or n (%)	Non-GDM women (n=532) Mean ± SD or n (%)	*p*
Age (years)	33.2 ± 4.7	32.5 ± 5.1	0.22
Pre-pregnancy Body mass index (kg/m^2)			
Underweight	5 (7%)	38 (7%)	0.011
Normal	32 (48%)	350 (66%)	
Overweight/Obese	24 (36%)	115 (22%)	
Missing data	6 (9%)	29 (5%)	
Weight gain (kg)	12.7 ± 7.1	13.1 ± 5.7	0.37
Parity			
1	31 (46%)	300 (56%)	0.098
> 1	36 (54%)	228 (43%)	
Missing data	0	4 (0.8%)	
Ethnicity			
Caucasian	27 (40%)	335 (63%)	0.001
Asian	36 (54%)	164 (31%)	
Other*	4 (6%)	33 (6%)	
Education			
< High school	2 (3%)	19 (4%)	0.57
High school completed	13 (19%)	135 (25%)	
Tertiary completed	48 (72%)	361 (68%)	
Missing data	4 (6%)	17 (3%)	
Smoking during pregnancy			
Yes	2 (3%)	23 (4%)	0.61
No	65 (97%)	509 (96%)	
Hypertension			
Gestational	7 (10%)	22 (4%)	0.15
Chronic pre-existing	0	5 (1%)	
Pre-eclampsia	0	8 (1.5%)	
Eclampsia	0	1 (0.1%)	

* Other ethnicities include African, Middle Eastern and Polynesian.

goals recommended at RPAH at the time of the study were pre-breakfast BGL <5.2 mmol/L and one hour postprandial BGL <7.5 mmol/L, which were lower than the ADIPS guidelines at the time of the study.

GDM treatment consisted of dietary modifications (low glycaemic index foods), exercise and insulin therapy if necessary. Good glycaemic control was achieved in most subjects, with 56 out of 62 (90%) women meeting both fasting and postprandial ADIPS targets at the time of study. Mean ± SD third trimester HbA1c was 5.4 ± 0.4 mmol/L. We obtained self-monitoring data for 46 women (mean of 132 readings per patient): mean ± SD BGLs were 4.8 ± 0.5 mmol/L fasting, 6.7 ± 1.1 mmol/L one-hour post-breakfast, 6.4 ± 0.7 mmol/L post-lunch, and 6.5 ± 0.7 mmol/L post-dinner. Thirty-eight (57%) women required diet and exercise therapy only, and 29 (43%) required both diet, exercise and insulin (range 4–152 U/day) in an attempt to maintain glucose values within the RPAH glycaemic targets.

Pregnancy outcomes

We previously reported that there were no significant differences in the body composition, birthweight or anthropometric measurements between the GDM and NGT infants after adjusting for gestational age, neonatal sex and maternal variables known to influence body composition (Au et al., 2013).

In this present study, we found that the GDM mothers were more likely to be induced compared to the NGT mothers (Table 2). When compared to NGT mothers, GDM mothers had earlier spontaneous labour (mean=38.9 weeks and 39.7 weeks respectively, $p=0.001$). GDM mothers were also induced earlier (39.1

Table 2
Comparison of pregnancy outcomes in the GDM and NGT group.

	GDM (n=67) Mean ± SD or n (%)	Non-diabetic (n=532) Mean ± SD or n (%)	p
Gestational age at childbirth	38.9 ± 1.2	39.6 ± 1.2	< 0.001
Birthweight			
Large-for-gestational age	5 (7%)	46 (9%)	0.75
Appropriate-for-gestational age	55 (82%)	426 (80%)	
Small-for-gestational age	7 (10%)	60 (11%)	
Type of labour			
Spontaneous	30 (45%)	328 (62%)	0.013
Induced	19 (28%)	121 (23%)	
No labour	18 (27%)	81 (15%)	
Fetal distress leading to operative childbirth	22 (33%)	164 (31%)	0.74
Type of birth			0.13
Normal vaginal birth	30 (45%)	294 (55%)	
Emergency caesarean	11 (16%)	81 (15%)	
Elective caesarean	16 (24%)	72 (14%)	
Instrumental birth	10(15%)	85 (16%)	
Apgar scores < 7			
One minute	11 (16%)	55 (10%)	0.11
Five minutes	3 (4%)	15 (3%)	
NICU admission > two days	2 (3.0%)	31 (5.8%)	0.35
Poor breastfeeding			
Poor frequency	11 (16%)	129 (24%)	0.40
Poor breastfeeding codes	16 (24%)	17 (24%)	
> 2 Expressed milk or artificial milk	23 (34%)	162 (30%)	
Time to first breastfeed < one hour	41 (61%)	221 (42%)	0.003
Neonatal hypoglycaemia	6 (9%)	57 (11%)	0.68

weeks and 39.9 weeks respectively, $p=0.009$) and had elective caesarean sections earlier (38.1 weeks and 38.7 weeks respectively, $p=0.02$) (Fig. 2). GDM was the sole indication for labour induction in 15 out of 19 (79%) cases. A higher proportion of GDM women (61%) initiated early breastfeeding within one hour after birth, compared to the NGT women (42%, $p=0.003$).

We also investigated whether there were differences between the babies born to GDM mothers who were predominantly diet-controlled versus those born to mothers treated with insulin (Table 3). GDM mothers who were treated with insulin were more likely to undergo induction of labour compared to GDM mothers who were predominantly diet-controlled (41% versus 18%, $p=0.03$).

Discussion

Our study shows that for women with well-controlled GDM, serious neonatal outcomes usually associated with GDM and fetal overgrowth were not significantly increased. These included fetal distress leading to operative childbirth, caesarean and instrumental deliveries, poor Apgar scores, large-for-gestational age (LGA) infants, neonatal hypoglycaemia and NICU admission. The overall good outcome can be attributed to the excellent control of hyperglycaemia predominantly by lifestyle modification and insulin if needed in the GDM mothers. However, we found a significantly higher rate of induction in the GDM group (28% versus 23%, $p=0.013$). Furthermore, GDM was the sole indication in 79% of the induction cases. There was also a higher rate of labour induction in the GDM group treated with insulin compared to GDM mothers who were predominantly diet-controlled only.

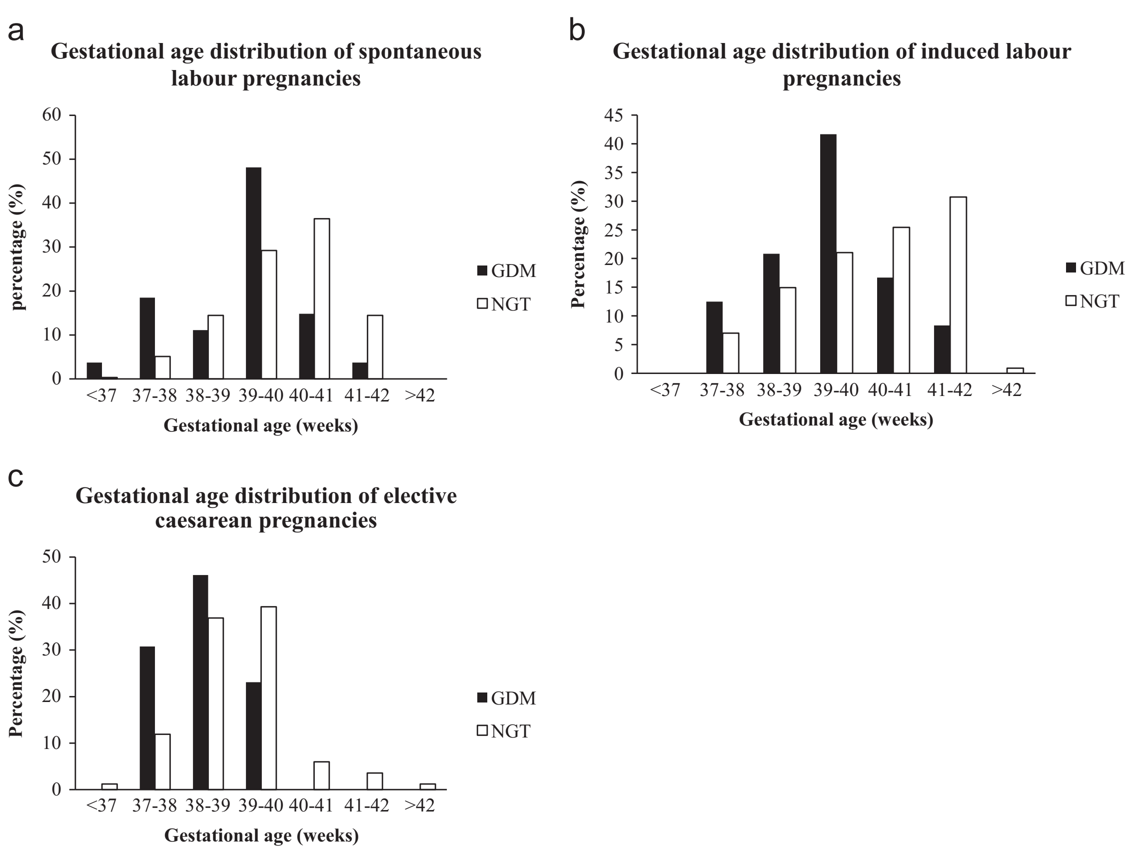

Fig. 2. Gestational age distribution at birth of GDM (solid bars) and NGT (open bars) infants with spontaneous labour pregnancies (a), induced labour pregnancies (b), and elective caesarean pregnancies (c). The proportion of pregnancies delivering early term is significantly higher in GDM infants compared to NGT infants.

Table 3
Comparison of neonatal outcomes between the GDM and the NGT groups.

	GDM diet ($n=38$) Mean ± SD or n (%)	GDM diet + insulin ($n=29$) Mean ± SD or n (%)	*p*
Gestational age at childbirth (weeks)	39.0 ± 1.3	38.8 ± 0.8	0.47
Birthweight			
Large-for-gestational age	2 (5%)	3 (10%)	0.51
Appropriate-for-gestational age	33 (87%)	22 (76%)	
Small-for-gestational age	3 (8%)	4 (14%)	
Abdominal circumference (cm)	29.7 ± 2.5	29.3 ± 2.2	0.57
Arm circumference (cm)	10.6 ± 0.9	10.5 ± 0.9	0.49
Type of labour			
Spontaneous	22 (58%)	8 (27%)	0.03
Induced	7 (18%)	12 (41%)	
No labour	9 (24%)	9 (31%)	
Fetal distress leading to operative childbirth	12 (32%)	10 (34%)	0.80
Type of birth			
Normal vaginal birth	18 (47%)	12 (41%)	0.95
Emergency caesarean	6 (16%)	5 (17%)	
Elective caesarean	9 (24%)	7 (24%)	
Instrumental birth	5 (13%)	5 (17%)	
Apgar scores < 7			
One minute	6 (16%)	5 (17%)	0.71
Five minutes	2 (5%)	1 (3%)	
NICU admission > two days	1 (2.6%)	1 (3.4%)	0.85
Poor breastfeeding			
Poor frequency	6 (16%)	5 (17%)	0.99
Poor breastfeeding codes	9 (24%)	7 (24%)	
> 2 Expressed milk or artificial milk	13 (34%)	10 (34%)	
Time to first breastfeed < one hour	23 (61%)	18 (62%)	0.94
Neonatal hypoglycaemia	5 (13%)	1 (3%)	0.19

Induction of labour is motivated by a variety of factors. For women with GDM, these may include: maternal preference to complete their pregnancy due to physical discomfort or concerns of complications such as shoulder dystocia or fetal demise (Rayburn and Zhang, 2002). Care providers may similarly be motivated to avoid the risk of complications, or they may have economic incentives to use elective induction (Rayburn and Zhang, 2002).

The GDM management guidelines from the Australasian Diabetes In Pregnancy Society (ADIPS), which is endorsed by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG), state that "childbirth before full term is not indicated unless there is evidence of macrosomia, polyhydramnios, poor metabolic control or other obstetric indications" (Rasmussen et al., 1992; Hoffman et al., 1998). Thus, induction of labour may be considered 'elective' (i.e. without other medical indications) if it is done merely for the diagnosis of GDM. In our study, insulin therapy was associated with a higher rate of labour induction in the GDM group.

To our knowledge, there has only been one randomized controlled trial that examined the timing of childbirth in women with diabetes (Kjos et al., 1993). This study found that compared to the group induced at 38 weeks, the expectant management group had an increase in LGA infants (23% versus 10%, $p=0.02$) but no significant difference in caesarean sections (Kjos et al., 1993). The authors concluded that childbirth should be contemplated at 38 weeks and if not careful assessment of fetal growth should be performed. In contrast, other studies reported no significant differences in birthweight, birthweight > 4000 g or shoulder dystocia in a GDM population treated with insulin and delivered at 38 weeks, compared to the expectantly managed diet-controlled GDM group with childbirth at 39 weeks (Rayburn et al., 2005).

Although childbirth at 38 weeks of gestation may be associated with a potential reduction in LGA infants, some evidence suggests that early term birth (< 39 weeks) is associated with increased risk of neonatal illness and mortality (Sengupta et al., 2013; Mally et al., 2015), as well as long-term morbidity including lower educational attainment (Marlow, 2012; Quigley et al., 2012). In our study, GDM mothers were induced earlier compared to the NGT mothers, and they also had elective caesarean sections earlier than their NGT counterparts. As good glycaemic control was achieved in most GDM women and their infants did not have increased birthweight, body fat per centage or anthropometric measurements (Hoffman et al., 1998; Au et al., 2013), early term childbirth by induction of labour or elective caesarean sections might not be indicated.

Postnatally, exclusive breast feeding for at least three months has been shown to reduce the risk of childhood obesity in the children of mothers with GDM, particularly in those born to obese GDM mothers (Grummer-Strawn and Mei, 2004; Schaefer-Graf et al., 2006). Early initiation of breastfeeding occurred in 61% of GDM infants which is significantly better than the 42% in infants of NGT mothers. This may be attributed to specific staff education targeting GDM mothers as part of the Baby Friendly Hospital Initiative at RPAH. Early initiation of breast feeding within the first hour after birth is associated with fewer feeding problems and longer duration of breast feeding which is important for long term outcomes for GDM infants (WHO and UNICEF, 2009; Carberry et al., 2013a, 2013b).

In conclusion, we suggest that the good glycaemic control achieved in this study can prevent the effects of maternal hyperglycaemia on poor neonatal outcomes. GDM treatment should consist of diet and exercise. Insulin should be used, however, if good glycaemic control cannot be achieved by lifestyle modifications alone. Midwives have a pivotal role in antenatal and postnatal care as they have frequent contact with pregnant women and new mothers. They can encourage GDM mothers to use healthy lifestyle modifications and to breastfeed their babies as early as possible after birth.

For uncomplicated GDM pregnancies, care should be taken to not cause iatrogenic morbidity by early term birth. However, in GDM women with poor glycaemic control or who do not adhere with management, there should be a thorough evaluation of risks and benefits of management and intervention. Future work includes longer-term follow-up of our cohort to evaluate the association between gestational glycaemic control and outcomes such as childhood obesity and diabetes. Additional research is also warranted on the timing of childbirth for mothers with well-controlled GDM with no evidence of maternal or fetal compromise. Importantly, there needs to be translation of this knowledge into obstetric and midwifery practice.

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Appendix 1

Outcomes used for the composite neonatal morbidity

1. Fetal distress leading to operative childbirth and/or thick meconium at birth,
2. Low Apgar scores (< 7 at five minutes) leading to resuscitation at birth,
3. Hypothermia (< 36.5 °C or 97.7 °F) at any time,
4. Longer length of hospital stay than standard clinical practice (> three days for normal vaginal childbirth and instrumental childbirth and > five days for caesarean section), and
5. Poor feeding based on three criteria with at least two of the following:

(1) frequency (< three first 24 hour, < six next 24 hour);
(2) poor breastfeeding (or bottle feeding) codes (< code 4 × 3) (codes ranged from one to six, where 1 was defined by "breast offered but does not attach" and six was defined as "long feed with good nutritive sucking");
(3) expressed breast milk or artificial (greater than twice) if breastfed.

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