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MATERNAL-FETAL MEDICINE

Perinatal outcome following induction of labor in patients with good glycemic controlled gestational diabetes: does timing matter?

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Abstract

Purpose To compare maternal and neonatal outcomes in women with good glycemic controlled gestational diabetes mellitus (GDM) undergoing induction of labor at early and late term.

Methods A retrospective cohort study of all women with singleton pregnancies and well-controlled GDM undergoing induction of labor for non-GDM indications in the early (37 + 0–38 + 6 gestational weeks) and late term (39 + 0–40 + 6 weeks), in a single university-affiliated medical center (2014–2016). Exclusion criteria included: pre-gestational diabetes, multiple gestations and elective cesarean delivery. Maternal and neonatal outcomes were compared between groups. Composite maternal outcome included: post-partum hemorrhage, blood products transfusion, and cesarean or instrumental delivery. Composite neonatal outcome included: neonatal intensive care unit admission, respiratory distress syndrome, hypoglycemia and jaundice.

Results Overall, 430 women met inclusion criteria. Amongst them, 193 (44.88%) were induced at early term and 237 (55.11%) were induced at late term. There were higher rates of hypertensive complications of any kind and pre-eclampsia, in women induced at early term (11.04% vs. 4.26%, $p = 0.021$, and 5.92% vs. 1.60%, $p = 0.04$, respectively). There were no differences in maternal and neonatal outcomes between groups. Rates of composite maternal outcome and composite neonatal outcome did not differ between groups (OR 0.92, 95% CI 0.59–1.44, $p = 0.73$ and OR 0.78, 95% CI 0.47–1.3, $p = 0.36$, respectively).

Conclusion Women with good glycemic controlled GDM may be safely induced at early term, when other indications exist, without an increased risk for adverse maternal or neonatal outcomes.

Keywords Induction of labor · Gestational diabetes · Term · Good glycemic control

Introduction

Women with gestational diabetes mellitus (GDM) have increased maternal and neonatal morbidity including pre-eclampsia, cesarean delivery (CD) [1, 2], neonatal macrosomia, neonatal hypoglycemia, shoulder dystocia, birth trauma and stillbirth, among others [3, 4]. There is a linear correlation between the rate of these complications and maternal glucose levels measured on the glucose tolerance test [5]. Furthermore, it has been demonstrated, that at any given gestational age, neonates to women with diabetes are at increased risk for respiratory complications, including respiratory distress syndrome (RDS) and transient tachypnea of the newborn (TTN).

It is common that women with uncomplicated good glycemic controlled GDM be managed expectantly until term [6, 7]. Various studies have yielded conflicting results regarding neonatal and maternal outcomes when comparing induction of labor to expectant management at term in these women. Whereas some showed no differences in CD rates or macrosomia with induction of labor at 38 weeks of gestation vs. expectant management [8, 9], others demonstrated lower rates of large for gestational age (LGA)

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neonates [10] and higher rates of hyperbilirubinemia in the induction group [8], with an increase in shoulder dystocia in the expectant management group [9]. The American College of Obstetricians and Gynecologists (ACOG) [3] states that the timing of delivery in women with GDM controlled by diet should not be before 39 weeks of gestation, unless otherwise indicated. In such women, expectant management up to 40 6/7 weeks of gestation in the setting of indicated antepartum testing is generally appropriate [3]. For women with medically controlled GDM, the ACOG recommends delivery from 39 0/7 weeks to 39 6/7 weeks of gestation. Notwithstanding the above, other indications for delivery may exist, requiring induction of labor earlier than planned.

The above-mentioned studies compared perinatal outcome in women with good glycemic controlled GDM undergoing induction of labor vs. expectant management. However, data are scarce regarding perinatal outcome following induction of labor due to non-GDM indications stratified by timing of delivery.

Hence, we aimed to examine the association between maternal and neonatal outcomes in women with well glycemic controlled GDM undergoing induction of labor at early vs. late term, due to non-GDM-related indications.

Methods

We conducted a retrospective cohort study of all women with GDM, carrying a singleton fetus, who delivered in a single, tertiary, university-affiliated medical center between January 2014 and December 2016. The study was approved by our local Institutional Review Board (RMC 17-0599). Informed consent was waived due to the retrospective design of the study.

We only included women with good glycemic controlled GDM who underwent induction of labor at term (37 + 0–40 + 6).

Exclusion criteria included: termination of pregnancy, major congenital malformations or chromosomal anomalies, elective CD, and women with a diagnosis of type I or type II diabetes mellitus.

Data were retrieved from the comprehensive computerized perinatal database of our center, and was cross tabulated using an individualized identification number per patient. Data from the neonatal unit and the neonatal intensive care unit (NICU) were integrated into the delivery room database using the unique admission number assigned to each woman and her offspring.

Collected data included demographic and obstetric parameters, labor and short-term maternal and neonatal outcome (up to discharge). Any hypertension was defined as including chronic hypertension, gestational hypertension and pre-eclampsia of any severity.

GDM was diagnosed by one of the following methods: a 100 g oral glucose tolerance test (OGTT) with at least one pathologic value or oral 50 g glucose challenge test (GCT) level of 200 mg/dl and above.

Women with GDM attended high-risk pregnancy outpatient clinics. Glucose levels were monitored by the patients six times a day. Normal fasting glucose levels were defined to be below 90 mg/dl and 2 h post-prandial defined as < 120 mg/dl. Initially, patients were counseled for life style modifications and began an appropriate dietary regimen. If glucose levels were sub-optimal (defined as > 20% high values), then oral anti-diabetics or insulin were initiated. Well glycemic controlled GDM was defined as > 80% normal glucose levels on self-monitoring, normal amniotic fluid volume and an estimated fetal weight appropriate for gestational age.

We compared maternal and neonatal outcome between women with good glycemic controlled GDM who underwent induction of labor at early term (37 + 0–38 + 6 weeks) and late term (39 + 0–40 + 6 weeks). Women with well glycemic controlled GDM and no other non-GDM indication for induction were routinely induced at our institution by 40–41 weeks of gestation unless spontaneous onset of labor had occurred by then. Non-GDM indications for early-term induction were variable and included any obstetric indication for early-term induction such as hypertension of any kind, reduced fetal movements, oligohydramnion, and non-reassuring fetal heart rate. Methods of induction were prostaglandin E2 (PGE2), extra-amniotic balloon, and oxytocin infusion, which were chosen according to the physician's discretion and local institutional practice.

Primary outcome was composite maternal outcome, which included: post-partum hemorrhage (PPH), blood products transfusion, and cesarean or instrumental delivery.

Secondary outcome was maternal and neonatal adverse outcome including: large for gestational age infant (LGA), which was defined as birthweight above the 90th percentile according to nationally accepted growth curves matched for gestational age at delivery and fetal sex [11], hypoglycemia, NICU admission, asphyxia, acidosis, jaundice requiring phototherapy, respiratory distress syndrome (RDS), and Erb's palsy.

Composite neonatal outcome included: NICU admission, RDS, hypoglycemia and jaundice.

Statistical analysis was generated using SAS Software, Version 9.4. Continuous variables were presented by median and range, categorical variables were presented by numbers and percentages. *t* test was used to compare the value of continuous variables between the two study groups, and Fisher's exact test was used to compare the value of categorical variables between the two study groups. Two-sided *p* value less than 0.05 was considered statistically significant.

Table 1 Baseline maternal characteristics

Variable	Early term ($N=193$)	Late term ($N=237$)	p Value
Age (years)	33 (22–44)	33 (21–46)	0.81
BMI (kg/m^2)	25.75 (18.13–42.97)	25.07 (17.30–48.5)	0.19
Parity	1 (0–6)	1 (0–10)	0.06
Previous cesarean delivery	1 (0.5)	5 (2.1)	0.23
Any hypertension[a]	17 (11.0)	8 (4.3)	0.02
Pre-eclampsia	9 (5.9)	3 (1.6)	0.04

Continuous variables are presented as median (range) and categorical numbers are presented as N (%)

BMI body mass index, *VBAC* vaginal birth after cesarean

[a]Any hypertension—including chronic hypertension, gestational hypertension and pre-eclampsia of any severity

Table 2 Maternal outcomes

Maternal outcomes	Early term ($N=193$)	Late term ($N=237$)	p Value
PPH	5 (3.3)	4 (2.2)	0.73
Maternal need for transfusion	1 (0.7)	1 (0.5)	1.0
Fever	3 (1.99)	3 (1.60)	1.0
Mode of delivery			
NVD	150 (77.72)	186 (78.48)	0.86
VE	25 (12.95)	27 (11.39)	
CD	18 (9.33)	24 (10.13)	

Continuous variables are presented as median (range) and categorical numbers are presented as n (%)

PPH post-partum hemorrhage, *NVD* normal vaginal delivery, *VE* vacuum extraction, *CD* cesarean delivery

Table 3 Neonatal outcomes

Neonatal outcomes	Early term ($N=193$)	Late term ($N=237$)	p Value
Birthweight (g)	3283 (2064–4372)	3320 (2460–4324)	0.06
5-min Apgar	10 (3–10)	10 (4–10)	0.70
Umbilical cord pH	7.34 (7.06–7.48)	7.34 (6.79–7.56)	0.38
NICU	7 (3.6)	6 (2.5)	0.57
LGA	3 (1.5)	1 (0.4)	0.33
Jaundice	31 (16.1)	30 (12.7)	0.33
TTN	2 (1.04)	1 (0.4)	0.59
RDS	0 (0)	0 (0)	
Fracture of clavicle	3 (1.6)	3(1.3)	1.0
Acidosis	0 (0)	1(0.4)	1.0
Hypoglycemia	1 (0.52)	0(0)	0.44

Continuous variables are presented as median (range) and categorical numbers are presented as N (%)

NICU neonatal intensive care unit, *SGA* small for gestational age neonate, *LGA* large for gestational age neonate, *TTN* transient tachypnea of the newborn, *RDS* respiratory distress syndrome

Results

Overall, 430 women met inclusion criteria. Amongst them, 193 (44.88%) were induced at early term and 237 (55.11%) were induced at late term. No differences were noted in maternal age and body mass index (BMI) (Table 1). There were significantly higher rates of hypertension of any kind and specifically pre-eclampsia, in women induced at early term (11.04% vs. 4.26%, $p=0.021$, and 5.92% vs. 1.60%, $p=0.04$, respectively). There were no differences in rates of vacuum-assisted instrumental delivery or CD between early and late term (12.9% vs. 11.4% and 9.3% vs. 10.1%, respectively, $p=0.86$). No differences in other maternal outcomes were noted (Table 2). Groups were comparable regarding neonatal outcome, including birth weight, Apgar score, cord blood pH, NICU admission, respiratory composite outcome and hypoglycemia (Table 3). Although rates of jaundice were higher in the early-term group (16.1% vs. 12.7%), this was not statistically significant. No case of Erb's palsy was documented in any of the study groups.

Rates of composite maternal outcome and composite neonatal outcome did not differ between groups (23.83% vs. 22.36%, OR 0.92, 95% CI 0.59–1.44, $p=0.73$, and 18.65% vs. 15.19%, OR 0.78, 95% CI 0.47–1.3, $p=0.36$, respectively).

Discussion

In this study, we compared maternal and neonatal outcomes in women with good glycemic controlled GDM undergoing induction of labor at early vs. late term. Our key finding was that there were no differences in maternal or neonatal adverse outcomes, including composite outcome, when comparing both groups.

Regarding basic maternal characteristics, it is of importance to note that women with good glycemic controlled GDM induced at early term had higher rates of hypertension of any kind (defined as: gestational hypertension, chronic hypertension or pre-eclampsia) and pre-eclampsia, as compared to women induced at late term. It is common practice that pregnant women with mild pre-eclampsia or gestational hypertension be induced at 37 weeks of gestation, due to improved maternal outcomes compared to expectant management [12]. This practice may explain the higher rates of hypertension of any kind and specifically pre-eclampsia in the group induced at early term, with hypertension tipping the scale to early-term induction even in the context of good glycemic controlled GDM.

We found that induction of labor at early vs. late term resulted in comparable maternal outcomes, such as CD rates, PPH and need for blood transfusion. A previous study by Feghali et al. [13] demonstrated that induction of labor in women with GDM results in similar risk for CD as expectant management at each gestational age between 37 and 39 weeks of gestation. However, their study did not compare induction of labor between early and late term, nor did it differentiate between good glycemic controlled GDM and non-optimally controlled GDM. A possible explanation for our finding of similar maternal outcomes, especially CD rates, between early- and late-term induction, may be the comparable newborn median birthweight between groups, acknowledging the known association between macrosomia and an increased risk for CD [14–17]. Likewise, our finding of comparable rates of PPH and need for blood transfusion may be attributed to similar rates of LGA neonates and vacuum extraction delivery, both known risk factors for PPH [18].

Our results also demonstrate that induction of labor at early vs. late term resulted in comparable neonatal outcomes. It is debated whether neonates to women with diabetes (both pre-gestational and gestational) are at increased risk for respiratory complications, other morbidities and mortality when compared to neonates of non-diabetic mothers, and whether this is true for any gestational age or just for preterm neonates [19]. These complications presumably occur due to delayed surfactant synthesis, a result of maternal hyperglycemia [20–21], and reduced fluid clearance in the fetal lungs, augmented by increased CD rates [22–24]. Our finding is, therefore, reassuring in that earlier induction at term, when other indications for delivery exist, did not result in poorer neonatal outcomes, including RDS and TTN. It seems reasonable to presume that induction at term, be it early or late, among women with good glycemic control, does not result in higher rates of neonatal respiratory complications. Likewise, when no indication for early induction exists, our findings suggest there is no harm in waiting for induction until 41 weeks of gestation, with no difference in median birthweight for infants induced at early or late term, and no significant difference in LGA neonates.

The relationship between maternal hyperglycemia and fetal macrosomia has been well demonstrated, along with other related adverse outcomes, such as neonatal hypoglycemia, hyperbilirubinemia and operative delivery [5]. Our study did not show a significant difference in birthweight or LGA neonates between induction at early and late term. This finding is reasonable since all the women included in our study had well-controlled glucose values. Our finding is reassuring given the association in various studies between macrosomia and an increased risk for CD [14–17] as stated previously, an increased risk that is almost entirely attributable to labor abnormalities [14, 25].

Our study had several limitations. First, due to its retrospective nature, it required necessitating future validation in large prospective studies. Second, some data were missing such as indication for induction and treatment modality for GDM, as well as rates of shoulder dystocia in each group. We did not differentiate between women with diet-controlled or medication-controlled GDM. A difference may exist between these subgroups regarding maternal characteristics and maternal and neonatal outcomes, although the prerequisite of glucose control is likely to minimize any difference, if such exists. Be that as it may, the strength of our study is in the inclusion of a large number of deliveries in a single university-affiliated medical center. To the best of our knowledge, this is the first study to compare induction at early term vs. late term in the pre-specified population of women with good glycemic controlled GDM.

We assume that glycemic control is the main factor affecting adverse perinatal outcomes in GDM, regardless of timing of delivery, when performing induction of labor at term. When good glycemic control is achieved, timing of induction has minor effect on outcome**.**

In conclusion, our results suggest that women with well glycemic controlled GDM may be safely induced at early term, when other indications exist, without a rise in adverse maternal or neonatal outcomes.

Author contributions AH: project development, data collection, data analysis, and manuscript writing. AP: data collection and data analysis. GO: project development and manuscript editing. EK: data collection and data analysis. UA: project development and manuscript editing. AW: project development and manuscript editing. EH: project development and manuscript writing. LS: project development, data collection, data analysis and manuscript writing.

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Compliance with ethical standards

Conflict of interest The authors report no conflicts of interest.

Informed consent All the procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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