

Antepartum fetal surveillance and neonatal acid-base status in pregnancies complicated by gestational and pregestational diabetes: a prospective observational study

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Abstract

Objective: To compare antepartum fetal well-being parameters and perinatal outcomes in pregnancies complicated by gestational diabetes mellitus (GDM) or pregestational diabetes mellitus (PGDM) with healthy pregnancies, and to assess the relationship between antenatal monitoring and neonatal acid–base status at birth.

Study Design: This prospective observational study included 152 pregnant women: 61 with GDM, 25 with PGDM, and 66 controls. Antepartum evaluation included fetal biometry, amniotic fluid assessment, umbilical artery and middle cerebral artery Doppler indices, and computerized cardiotocography. Delivery mode and neonatal outcomes, including umbilical cord blood gas analysis, were compared among groups.

Results: GDM and PGDM pregnancies showed lower umbilical artery pulsatility index values than controls ($p < 0.001$). Middle cerebral artery pulsatility index was slightly lower in GDM ($p = 0.028$). Some computerized cardiotocography parameters differed modestly among groups. Umbilical cord blood gas values showed clearer differences, especially in PGDM pregnancies. Cord pH was lower in PGDM and after vaginal delivery. pO_2 progressively decreased from controls to GDM and PGDM, whereas pCO_2 increased. Lactate levels were higher in PGDM pregnancies and vaginal deliveries.

Conclusions: Conventional antepartum monitoring showed limited differences between diabetic and healthy pregnancies, while neonatal acid–base status differed more clearly. A multimodal approach may improve fetal assessment and risk stratification.

Highlights

- Diabetic pregnancies showed altered neonatal acid-base status at birth
- Conventional antepartum monitoring showed limited discrimination ability
- PGDM pregnancies had the most pronounced cord blood gas abnormalities
- Advanced cCTG parameters showed subtle differences in diabetic pregnancies
- Multiparametric assessment may improve fetal surveillance in diabetes

Key message

In pregnancies complicated by maternal diabetes, conventional antepartum surveillance methods show only limited differences compared with healthy pregnancies, whereas neonatal acid-base status reveals more evident alterations, particularly in pregestational diabetes. These findings support the need for integrated multiparametric approaches to improve fetal risk assessment.

1. Introduction

Gestational diabetes mellitus (GDM) is one of the most common complications of pregnancy worldwide [1]. It is associated with several obstetric complications, including macrosomia and metabolic and cardiovascular abnormalities [1–3]. However, management and surveillance of diabetic pregnancies remain heterogeneous. Even though GDM is primarily a maternal disease [4], there may be significant repercussions on fetal health because of the altered maternal metabolic conditions [5]. In addition, this condition can be difficult to monitor with the most commonly used methodologies for antepartum fetal surveillance [6, 7]. Currently, obstetricians generally use three major fetal surveillance tests: i) Fetal biometry and amniotic fluid evaluation [8]; ii) Doppler velocimetry of the Umbilical Artery (UA) and Middle Cerebral Artery (MCA) [9, 10]; iii) Cardiotocography (CTG) [11–13]. Additionally, international guidelines recommend the use of Doppler velocimetry of the UA in the monitoring of diabetic pregnancies only if there is a known risk of intrauterine growth restriction (IUGR) [7, 14]. Moreover, antepartum CTG is recommended for monitoring pregnancies of women with pregestational diabetes mellitus (PGDM) [7]; it is considered beneficial for women with gestational diabetes mellitus (GDM) with poor glycemic control or treated with insulin or oral agents [6, 15, 16]. Nevertheless, the optimal timing and frequency of fetal monitoring in pregnancies complicated by diabetes has not been established [7], and it is unclear which method best predicts adverse perinatal outcomes. The aim of this study is to evaluate a comprehensive set of antepartum measurements and delivery outcomes in pregnancies complicated by maternal diabetes compared with healthy controls.

2. Material and methods

2.1 Study design and population

This prospective observational study was carried out on a population of pregnant women monitored by means of fetal biometry, amniotic fluid evaluation, Doppler velocimetry of the UA and MCA, and cardiotocography. Data were collected at the Department of Mother and Child at the University Hospital of Naples Federico II, in collaboration with the Polytechnic of Milan and the University of Pavia. The population consisted of a total of 152 pregnant women: 25 had a diagnosis of pregestational diabetes mellitus (PGDM), i.e. diabetes of Type 1 or Type 2; 61 were diagnosed with gestational diabetes mellitus (GDM), and 66 were controls. The distinction among diabetic groups (gestational and pregestational) was made according to ACOG guidelines [6, 7]. The study was conducted in accordance with the Declaration of Helsinki and approved by the local Ethics Committee (CAMPANIA 3, “Ethics Committee A.O.U. Federico II – A.O.R.N. Cardarelli”, study protocol number 2017RR5EW3, accepted on February 26, 2021). All participants provided written informed consent prior to enrollment. Inclusion criteria for the entire population were defined as follows: i) singleton pregnancy; ii) certain determination of pregnancy dating calculated from the first day of the last menstrual period and confirmed by ultrasound measurements according to the population nomograms [17]; iii) gestational age at or beyond 26 weeks of gestation; iv) no comorbidities unrelated to diabetes. Patients in the case group were identified based on OGTT results at 24–28 weeks of gestation [18]. PGDM includes diabetes of Type 1 and Type 2 and

was in most cases a known condition that preceded pregnancy [19]. Healthy controls were selected among those who matched the previous three inclusion criteria by adding the condition that they were defined as euglycemic during the screening examinations, i.e., OGTT, and had normal fasting blood glucose levels for all three pregnancy trimesters. Fasting glucose levels at the first and second trimester and pre-pregnancy BMI were retrospectively obtained from hospital records.

2.2 Fetal assessment

Fetal monitoring included fetal biometry and amniotic fluid evaluation, Doppler velocimetry of the UA and MCA and antepartum cCTG monitoring. Moreover, to assess maternal glycemic control, fasting blood glucose levels were measured during the third trimester of pregnancy in all groups.

2.2.1 Amniotic fluid assessment

Concerning amniotic fluid evaluation, the deepest vertical amniotic fluid pocket (DVP) was calculated in all pregnancies through the identification and measurement of the largest vertical diameter within an amniotic fluid pocket. Values lower than 2 cm identify oligohydramnios, while values over 8 cm are considered polyhydramnios [20].

2.2.2 Doppler velocimetry

The antepartum Doppler velocimetry was performed using a Voluson E8 (General Electric Healthcare Technologies, Milwaukee, WI, USA) ultrasound machine equipped with a 2–8MHz transabdominal transducer and color Doppler imaging was used to identify the UA and MCA vessels. Doppler flow spectra were obtained from the UA at the midsection of the umbilical cord and the middle portion of the MCA [21]. The indices considered for the analyses were UA and MCA pulsatility indices (UA-PI, MCA-PI) and the analysis was performed at the 26th, 32nd, and 36th weeks of gestation.

2.2.3 Antepartum computerized cardiotocography

The antepartum computerized CTG (cCTG) monitoring was performed in a controlled clinical environment with the patient lying on an armchair. The cCTG records were obtained using Philips Avalon FM30, which is equipped with an ultrasound transducer and a transabdominal tocodynamometer. Recordings lasted at least 40 minutes [22][22–24].

The parameters evaluated included baseline FHR, accelerations, STV, and spectral analysis parameters [25–30].

Moreover, the distribution of power in LF (0.03–0.15 Hz), MF (0.15–0.5 Hz), and HF (0.5–1 Hz) was calculated and expressed as the percentage of the total signal power [15].

2.3 Pregnancy outcomes

Neonatal data were collected for all newborns. They included gestational age and mode of delivery, birthweight, Apgar score at 1 and 5 minutes, UA blood gas values at birth, and access to the neonatal

intensive care unit (NICU). UA blood gas values collected are: pH, O₂ and CO₂ partial pressure (pO₂, pCO₂), cord arterial base excess (BECF), lactates and bicarbonate (HCO₃).

2.4 Statistical analysis

UA-PI and MCA-PI, which were assessed at three different time points during the last trimester, were compared among groups using repeated-measures ANOVA. Concerning the occurrence of oligohydramnios and polyhydramnios, differences between groups were evaluated using Fisher's exact test. The comparison of cCTG parameters between the three groups was made through the non-parametric Kruskal-Wallis test since normality was not respected for several of the analyzed features. The prevalence of Apgar scores less than 7, neonatal intensive care admission, small for gestational age and large for gestational age were compared across groups using Fisher's exact test. Correlations between the fasting glycemic values at the third trimester and neonatal outcomes (i.e., weight at birth and UA blood gas values at birth) were assessed by means of multiple linear regression models. When assessing the correlation with weight, type of diabetes and gestational week at birth were included to adjust for confounders. A p-value < 0.05 was considered statistically significant.

3. Results

3.1 Maternal characteristics

A total of 152 pregnant women were included in the study: 66 healthy controls, 61 with gestational diabetes mellitus (GDM), and 25 with pregestational diabetes mellitus (PGDM). Insulin therapy was used in all PGDM patients and in a minority of GDM patients, while insulin pump therapy was adopted in a subset of PGDM cases (Table 1.A). Maternal characteristics are summarized in Table 1.A. Women with GDM had a higher pre-pregnancy body mass index compared to controls, while PGDM patients showed intermediate values. Fasting glucose levels progressively increased from controls to GDM and PGDM across all trimesters. In accordance with current guidelines, HbA_{1c} was assessed only in the PGDM group (Table 1.B).

3.2 Amniotic fluid abnormalities

As shown in Table 2, almost all alterations in amniotic fluid values were identified in the diabetic populations. In particular, a substantial increase in the prevalence of polyhydramnios was observed.

3.3 Doppler indices

UA-PI and MCA-PI values are depicted in Figure 1. Both the GDM and PGDM groups showed significantly lower UA-PI values compared to controls ($p < 0.001$), while no significant differences were observed between GDM and PGDM across the examined gestational weeks. Regarding MCA-PI, a slight difference between groups was observed ($p = 0.027$), with lower values in GDM compared to controls ($p = 0.028$). MCA-PI is typically reported to increase with gestational age up to 32–34 weeks [31]; however, in our data, a significant decrease over time was observed from week 26 to 36 ($p < 0.001$). No significant

differences in temporal trends were found between groups ($p=0.338$). For completeness, 7 participants (3 GDM and 4 PGDM) delivered before 36 weeks of gestation and were therefore excluded from the repeated-measures analyses.

3.4 Computerized cardiotocography findings

CTG parameters at weeks 31 to 34+6, 35 to 36+6 and from 37 to delivery are reported in Table 3. When multiple recordings were available for the same subject in the same group of weeks, the average was considered. Among CTG parameters, statistically significant differences between diabetic groups and controls were identified only for MFprsa, LZ3, and STV. In particular, MFprsa significantly increased in GDM at weeks 35–36 ($p=0.03$). Similarly, MF% showed a non-significant trend toward higher values in GDM and PGDM at the same gestational age ($p=0.06$). Both diabetic groups showed significantly higher LZ3 at weeks 35–36 ($p=0.008$ and $p=0.006$ for GDM and PGDM, respectively) and at weeks 37+ ($p=0.005$ and $p=0.011$). A borderline significant reduction in STV ($p=0.049$) was identified at weeks 37+ for PGDM. GDM and PGDM were associated with significantly higher MFprsa and LZ3 values. LME models also identified a significant reduction in STV for both diabetic groups. No significant differences in CTG parameters were identified between the two diabetic groups.

3.5 Delivery and neonatal outcomes

We did not identify significant differences among groups concerning the increase in maternal BMI (ANOVA test, $p=0.069$), which was on average 3.52 ± 2.12 kg/m². As reported in Table 4 and shown in Figure 2, the overall incidence of caesarean section in both diabetic groups was more than double compared to controls. No operative vaginal deliveries were performed during the study. In 24% of PGDM and 6.5% of GDM pregnancies, delivery occurred prematurely (before 37 weeks) due to maternal or fetal complications, such as maternal hyperglycemia or IUGR. Substantial differences among groups in umbilical cord blood gas analysis were identified and are reported in Table 5. Cord pH was lower in PGDM compared to both GDM and controls, and vaginal deliveries were associated with lower pH values. pO_2 progressively decreased from controls to GDM and PGDM and was not significantly affected by mode of delivery, while pCO_2 showed the opposite trend. Lactate levels were higher in PGDM compared to both other groups and were lower in caesarean sections compared to vaginal deliveries. PGDM pregnancies were associated with higher birth weight compared to both GDM and control groups. In particular, in the PGDM group, 28% of neonates had a birth weight above the 95th percentile [32]. Despite most Apgar scores at one minute being reassuring, both GDM and PGDM were associated with lower Apgar1 values. An Apgar1 score <7 was assigned to 1 newborn in the control group, 5 in GDM and 2 in PGDM. At 5 minutes, only one newborn in the PGDM group had an Apgar score <7. The proportion of PGDM neonates requiring NICU admission was approximately double that observed in GDM and was higher in vaginal deliveries. More pregnancies complicated by polyhydramnios were delivered by caesarean section, both in PGDM (92.3%) and GDM (66.7%). Among these cases, 3 newborns showed a pH <7.05, both after caesarean and vaginal delivery. Among pregnancies complicated by oligohydramnios, 3 cases were associated with IUGR (birth weight <3rd percentile) and were delivered by

caesarean section. Two newborns required NICU admission, one of whom had a birth pH <7. After adjustment for confounders, few correlations were found between fasting glycemic levels and neonatal outcomes. Glycemia was significantly associated only with lactate levels (coefficient=0.256, p=0.026) and birth weight (coefficient=0.258, p=0.014). Stratification according to mode of delivery showed that vaginal delivery was consistently associated with lower cord pH and higher lactate levels across all groups. However, pregnancies complicated by PGDM continued to show less favorable acid-base values even among cesarean deliveries, particularly regarding pCO₂ and pO₂ levels.

4. Discussion

The main goal of this work was to compare antepartum measurements including amniotic fluid alterations, fetal Doppler indices, cCTG parameters, and outcome data between diabetic pregnancies and healthy controls.

4.1 Amniotic fluid abnormalities

PGDM and GDM are the most frequent etiological causes of polyhydramnios with a variable prevalence [33]. In our study, virtually all cases of polyhydramnios occurred in the diabetic group. In particular, we observed more than a twofold increase in the incidence of polyhydramnios in PGDMs compared to GDMs at the 32nd and 36th week of gestation. Polyhydramnios was associated with worse maternal and fetal outcomes, in particular, a higher percentage of caesarean sections and fetal pH lower than 7.05 at birth. However, the significance of polyhydramnios in diabetic pregnancies remains unclear [34–36]. In this study, we observed a very low incidence of oligohydramnios, which was nonetheless associated with an increased incidence of IUGR, need for caesarean section, and admission to NICU. In the literature, oligohydramnios has been also related to increased risk of low Apgar score and respiratory distress syndrome [37]. However, previous studies examining diabetes and oligohydramnios have come to inconsistent conclusions.

4.2 Doppler findings

Doppler evaluation showed a reduction in the UA-PI and MCA-PI values in both the diabetic populations compared to controls, especially regarding UA-PI. These results suggest the existence of a similar pathophysiological mechanism in GDM and PGDM, that induces a decreased impedance to flow in UA and MCA. This may be explained by changes in the placental structure and vascularization [38]. In previous studies [14, 39] it was found that the umbilical cord was significantly larger in fetuses of women with GDM compared to the normal population and UA diameter is much larger in the case of fetal macrosomia [40]. This explains why classical reference ranges of UA-PI and MCA-PI do not show adequate efficacy to predict adverse neonatal outcomes in pregnancies complicated by PGDM and GDM. Our findings suggest a limited discriminatory capacity of conventional UA Doppler indices for identifying altered neonatal acid-base status in pregnancies complicated by diabetes [6, 7, 41]. Although lower UA-PI and MCA-PI values are generally associated with better neonatal outcomes in the general population, our results suggest that in the diabetic population it might be useful to introduce a cut-off for

lower values of UA-PI and MCA-PI to identify fetuses at higher risk of adverse neonatal outcome. This hypothesis warrants further investigation. Fetuses of women with GDM and PGDM could be normoxic [42], and so might not show any anomalies in MCA-PI. On the other hand, fetal tissue may not receive sufficient oxygen, even if oxygen is at normal levels in the circulation with normal MCA-PI values [43]. Therefore, as also shown in [6, 7, 41, 44–46] MCA-PI values routinely used for monitoring high-risk pregnancies are not able to predict fetal well-being among women with GDM and PGDM. Indeed, in our study despite all the values of MCA-PI were reassuring, some babies were born with $\text{pH} < 7.05$.

4.3 cCTG findings

With regard to cCTG parameters, our results did not show differences in the FHR baseline values but identified a small reduction in STV values in the PGDM group compared to controls at term of pregnancy, potentially related to maternal hyperglycemia. This is in agreement with previous studies [47, 48], where findings were linked with a delay in the physiological maturation of the autonomic nervous system (ANS).

Moreover, in this study we also investigated a comprehensive set of non-standard cCTG parameters and found some associations with LZC and MFprsa. Concerning the potential application of LZC to FHR monitoring, both diabetic groups showed higher LZ3 values compared to controls from the 35th week of gestation. To the best of our knowledge, the only study evaluating LZC values in fetuses from diabetic pregnancies is Steyde et al. [47]. The results obtained in this study are consistent with those already reported, i.e., an increase in LZ3 in GDMs. Moreover, we also identified an increase in LZ3 in PGDMs. Previous studies applied LZC to monitor IUGR fetuses [48] and showed that they were characterized by higher values, very close to 1, supporting the hypothesis that the FHR belonging to the severe IUGRs is less regular than in healthy fetuses.

Among frequency parameters, MFprsa and MF have shown some discriminative capacity between GDMs and controls, in agreement with [47]. The physiological meaning of this finding and possible clinical implications remain unclear. However, this frequency band has been associated with fetal movements, which may suggest a state of hyperactivity in GDMs.

Overall, these findings suggest that the interpretation of cCTG parameters in diabetic pregnancies may be more complex than in uncomplicated pregnancies, as acute maternal metabolic alterations may potentially influence fetal acid-base status over relatively short time intervals, thereby limiting the temporal reliability of antepartum monitoring findings.

4.4 Delivery and neonatal outcomes

Umbilical cord blood gas analysis has increasingly been recognized as the most reliable indication of fetal oxygenation and acid-base condition at birth [49]. However, few studies analyzed umbilical cord blood gas values in neonates of diabetic mothers stratified by mode of delivery. In this study, we detected a significant decrease in pH and pO₂ and an increase in pCO₂ values in neonates of diabetic mothers. Moreover, values in PGDMs deviated more than GDMs compared to healthy pregnancies. The

observed differences in neonatal acid-base parameters may reflect a combination of metabolic alterations associated with maternal diabetes and delivery-related physiological stress. Given the known influence of labor and mode of delivery on umbilical cord blood gas values, these findings should be interpreted cautiously [2]. Nevertheless, the persistence of altered $p\text{CO}_2$ and $p\text{O}_2$ values among cesarean deliveries suggests that labor exposure alone may not entirely account for the observed findings, particularly in PGDM pregnancies. We found reduced oxygen levels and increased lactate levels at birth also in GDMs with normal maternal glucose levels and in PGDMs with good glycemic control, in agreement with [1, 2, 50]. We found very low correlations between glycemic levels and fetal neonatal outcomes. In particular, the only significant correlations after adjustment for confounders were between glycemic levels and neonatal weight ($r = 0.258$) and between glycemic levels and lactates ($r = 0.256$). The limited correlations observed may reflect the relatively good glycemic control in the study population, which reduced variability in glycemic exposure.

4.5 Limitations

The present study has several limitations. First, the relatively small sample size, particularly in the PGDM subgroup, may have reduced the statistical power to detect subtle differences among groups and limited the generalizability of the findings. Second, although umbilical cord blood gas values were stratified according to mode of delivery, the absence of patient-level multivariable analyses limits the possibility of fully disentangling the independent contribution of maternal diabetes from delivery-related confounding factors. In particular, labor exposure is known to substantially influence neonatal acid-base parameters and may have partially contributed to the observed differences. Moreover, GDM pregnancies were analyzed as a single group, without separate stratification according to insulin treatment, potentially masking differences related to disease severity and metabolic control. Finally, the lack of stratification between type 1 and type 2 PGDM further limits the interpretation of subgroup-specific pathophysiological mechanisms.

5. Conclusions

The present study evaluated multiple antepartum fetal monitoring techniques in pregnancies complicated by maternal diabetes and compared them with neonatal outcomes. Conventional antepartum surveillance methods showed only limited discriminatory capacity between diabetic and healthy pregnancies, whereas neonatal acid-base parameters differed more clearly, particularly in PGDM pregnancies. These findings support the potential value of integrated multiparametric approaches for fetal assessment in diabetic pregnancies while highlighting the importance of considering delivery-related factors when interpreting neonatal acid-base status. Non-conventional cCTG parameters showed some potential discriminative ability, suggesting that standard analysis methods may not fully capture the complexity of fetal heart rate dynamics. Further studies including larger populations and more comprehensive adjustment for confounding factors are needed to validate these findings.

Abbreviations

Umbilical Artery (UA); Middle Cerebral Artery (MCA); Cardiotocography (CTG); intrauterine growth restriction (IUGR); pregestational diabetes mellitus (PGDM); gestational diabetes mellitus (GDM); fetal heart rate (FHR); oral glucose tolerance test (OGTT); hemoglobin A1C (HbA1C); fetal movements series (FM); neonatal intensive care unit (NICU); computerized CTG (cCTG); average of the FHR baseline (MeanFHR); number of accelerations per hour (#Acc); Short Time Variation (STV); Sample Entropy (SampEn); ternary Lempel-Ziv complexity (LZ3); Phase Rectified Signal Averaging (PRSA); Deceleration Capacity (DC); Deceleration Reserve (DR); fetal movements (MovF%); UA pulsatility Index (UA-PI); MCA pulsatility Index (MCA-PI); Linear Mixed Effect models (LME); cord arterial base excess (BECF); autonomic nervous system (ANS).

Declarations

Funding: No specific funding was received for this study.

Conflicts of Interest: The authors declare that they have no conflicts of interest.

Data Availability: The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval: This research involving human data was performed in accordance with the Declaration of Helsinki. All patients/participants provided their written informed consent to participate in this study. The dataset was completely anonymized before data analysis. The study was reviewed and approved by the ethics committee CAMPANIA 3, which comprises “Ethics Committee A.O.U. Federico II – A.O.R.N. Cardarelli”, study protocol number 2017RR5EW3, accepted on February 26, 2021.

Consent to participate: Written informed consent was obtained from all participants prior to participation in the study.

Consent to publish: Not applicable, as no individual-level or identifiable data are included in this manuscript.

Author contribution: **Salvatore Tagliaferri:** Investigation, Writing – original draft, Supervision. **Dario Colacurci:** Methodology, Data curation, Writing – original draft. **Giulio Steyde:** Conceptualization, Investigation, Writing – original draft. **Laura Sarno:** Conceptualization, Data curation, Investigation, Methodology. **Maria Rosaria Motta:** Data curation, Investigation, Methodology. **Chiara Murolo:** Data curation, Investigation, Methodology. **Maria Giuseppina Trinchillo:** Data curation, Investigation, Methodology. **Marta Campanile:** Conceptualization, Methodology, Writing – original draft. **Edoardo Spairani:** Data curation, Investigation, Writing – original draft. **Giovanni Magenes:** Conceptualization, Methodology, Writing – original draft, Supervision. **Giuseppe Bifulco:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Giuseppe Maria Maruotti:** Conceptualization, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Maria Gabriella Signorini:**

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Tables

Tables 1 to 5 are available in the Supplementary Files section.

Figures

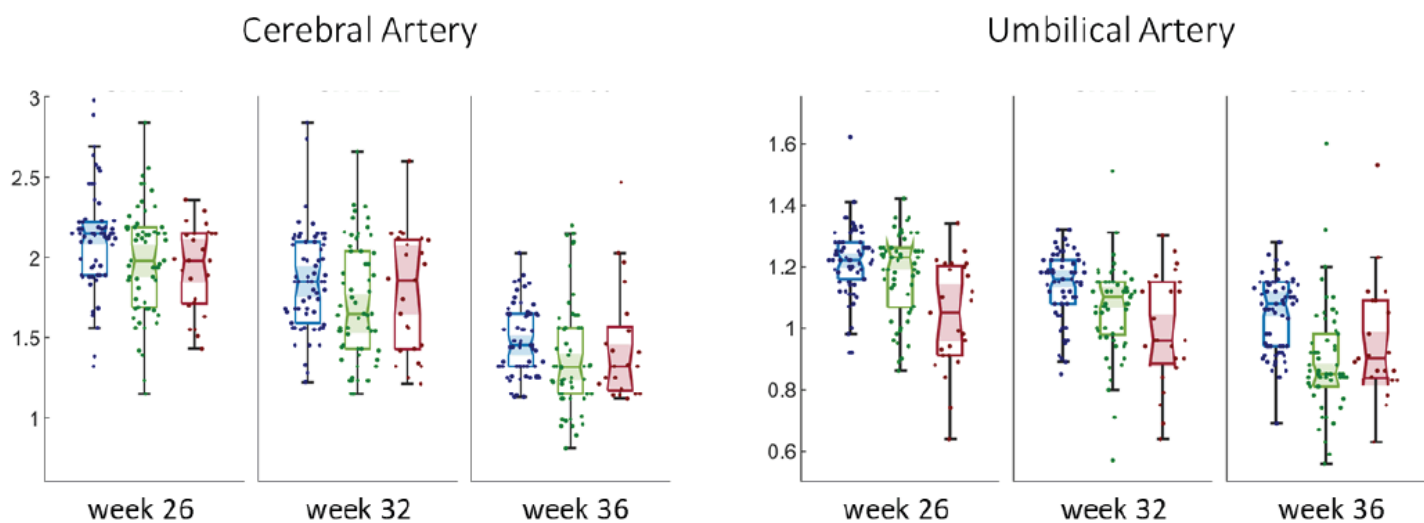


Figure 1

Comparison of umbilical artery (UA) and middle cerebral artery (MCA) pulsatility index values.

Groups are controls (blue), gestational diabetes mellitus (GDM, green), and pregestational diabetes mellitus (PGDM, red).

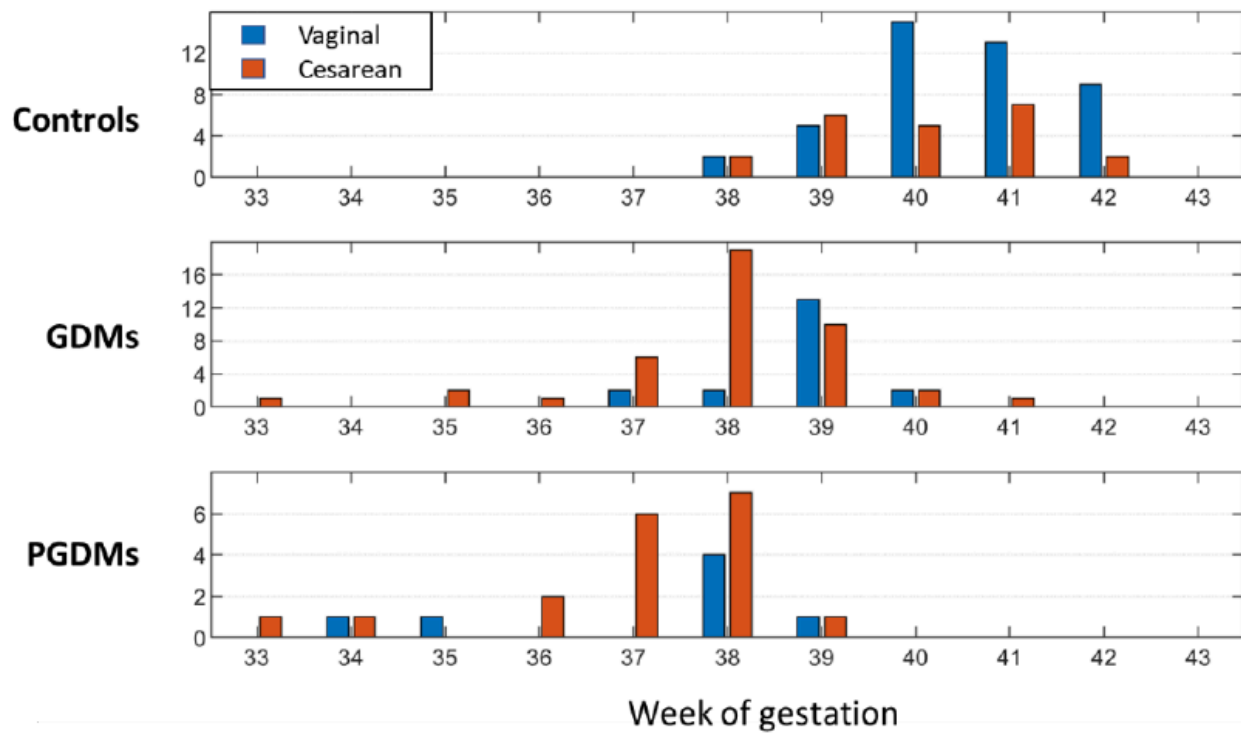


Figure 2

Distribution of mode of delivery by gestational age across study groups.

Supplementary Files

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