The fetal cerebroplacental ratio in pregnancies complicated by gestational diabetes mellitus

Anthea Gibbons[1,2], Christopher Flatley[1], Sailesh Kumar[1,2]

[1]Mater Research Institute - University of Queensland, Level 3 Aubigny Place, Raymond Terrace, South Brisbane, Queensland, Australia, QLD 4101, [2]School of Medicine, The University of Queensland, Brisbane, Australia.

Short title: Fetal cerebroplacental ratio and gestational diabetes mellitus.

Key words: cerebroplacental ratio, gestational diabetes mellitus, caesarean section, adverse perinatal outcome, fetal hypoxia

Corresponding author and individual responsible for reprint requests:

Professor Sailesh Kumar
Mater Research Institute/University of Queensland
Level 3, Aubigny Place
Raymond Terrace
South Brisbane
Queensland 4101
Australia
Tel: +617 31638844
Email: sailesh.kumar@mater.uq.edu.au

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/uog.17242

Abstract

Objective

This study aimed to assess the relationship between the cerebroplacental ratio (CPR) and intrapartum and perinatal outcomes in pregnancies complicated by gestational diabetes mellitus.

Methods

This was a retrospective cohort study of women diagnosed with gestational diabetes mellitus (GDM) birthing at the Mater Mothers' Hospital in Brisbane between 2007 and 2015. The CPR in 1089 non-anomalous singleton fetuses measured between 34+0 and 36+6 weeks gestation was compared between types of GDM treatment groups and correlated with intrapartum and perinatal outcomes.

Results

No difference in the CPR was observed between treatment groups. Fetuses with a CPR <10th centile were significantly more likely to have an adverse composite perinatal outcome (OR 2.93, 95% CI: 1.95-4.40, p<0.0001) and had higher rates of delivery with low birth weight and at an earlier gestation. This association was present regardless of type of diabetes treatment. Fetuses of women with insulin-controlled GDM had poorer neonatal outcomes than infants of women treated with oral hypoglycaemic agents or diet-control alone. The odds of having an adverse outcome were significantly increased in the insulin-treated group, (OR 1.75, 95%CI: 1.34-2.28, p<0.0001). This cohort also had higher rates of preterm birth and higher birth weights.

Conclusions

Regardless of the type of treatment, a low CPR was associated with increased rates of emergency operative birth and poorer neonatal outcomes in women with gestational diabetes mellitus.

Introduction

Although the prevalence of gestational diabetes mellitus (GDM) is approximately 7% in Australia, it accounts for almost 85% of all cases of diabetes[1] in pregnancy. There is a clear causal link between maternal hyperglycaemia and poor perinatal outcomes[2,3], with significantly increased rates of intrapartum fetal compromise, Caesarean Section (CS), macrosomia, low Apgar scores, Neonatal Intensive Care Unit (NICU) admission, surfactant use, sepsis and birth injury in diabetic women relative to non-diabetic controls. [4] Although the increased risks of adverse perinatal outcomes are multifactorial in nature, and in part, attributable to the increased risk of congenital malformations and preterm birth, there is considerable evidence that macro- and microscopic aberrations in placental and cord angio-architecture, as well as perturbations in immune and endothelial function, exist in diabetic pregnancies and also contribute to adverse outcomes in these women. [5,6] Whilst GDM is sometimes considered to be a milder form of metabolic disturbance than pre-gestational diabetes mellitus (PGDM), placental changes specific to GDM have also been described. These changes reflect a hypervascularised, hyperproliferative and pro-inflammatory cellular environment[5,7] and are believed to be secondary to maternal hyperglycaemia and fetal hyperinsulinemia with consequent imbalance between decreased placental oxygen supply and increased fetal oxygen demand. [5] As these placental abnormalities contribute to the risk of complications, identifying pregnancies with an abnormal maternal-placental-fetal compartment most likely to experience adverse clinical outcomes is important.

Given the increased risk of late pregnancy complications, particularly stillbirth, some international guidelines[8] now recommend planned delivery by 39+0 weeks gestation for women with PGDM and no later than 41+0 weeks for those with GDM. These guidelines also recommend assessment of fetal wellbeing late in pregnancy although the type of monitoring is often not specified.

The cerebroplacental ratio (CPR) is the ratio of the Middle Cerebral Artery Pulsatility Index (MCA PI) to the Umbilical Artery Pulsatility Index (UA PI).#A low CPR is associated with a myriad of adverse obstetric and perinatal outcomes[9], and may be considered a surrogate marker of suboptimal fetal growth or placental function. [10] However, there is limited data regarding the utility of the CPR in a diabetic cohort. The objective of this study thus, was to assess the relationship between the CPR and obstetric and perinatal outcomes in pregnancies complicated by GDM stratified according to type of diabetes control and to determine whether the CPR measured at 34+0-36+6 weeks gestation is predictive of adverse outcomes. To our knowledge, there have been no studies specifically assessing the value of the CPR in a GDM cohort although Fadda *et al.*'s 2001 study did suggest that abnormal UA and MCA Doppler indices in GDM pregnancies were associated with adverse perinatal outcomes. [11]

Methods

This was a retrospective cohort study of women with pregnancies complicated by GDM who birthed at the Mater Mothers' Hospital in Brisbane, Australia between January 2007 and December 2015. The Mater Mothers' Hospital is a major tertiary centre in the state of Queensland and the largest maternity hospital in Australia with a birth rate of approximately 10,000 per annum. Previous prospectively collected maternal demographic data was cross-referenced against the institution's ultrasound and neonatal databases to correlate outcomes. The study protocol was assessed and approved by the hospital's Human Research Ethics Committee (Reference number HREC/14/MHS/37).

All women with a non-anomalous singleton fetus and a diagnosis of GDM (regardless of treatment) who underwent an ultrasound scan between 34+0–36+6 weeks gestation with

recorded data for **both** the MCA PI and UA PI (to enable calculation of the CPR) were eligible for inclusion in this study. At the Mater Mothers' Hospital all women with diabetes in pregnancy receive serial scans for growth and wellbeing with the final scan before delivery generally taking place between 34+0 and 36+6 weeks gestation. Gestational diabetes mellitus was defined as a diagnosis of diabetes mellitus made on the basis of an abnormal glucose tolerance test using the criteria set out by the Australian Diabetes in Pregnancy Society.

Demographic data collected included maternal age, parity, body mass index (BMI), ethnicity (Caucasian, Asian, Indigenous, Indian or other), smoking status, maternal disease (thyroid disease, hypertension) and mode of conception. Indigenous ethnicity refers to patients identifying as being of Aboriginal or Torres Strait Islander origin. Gestational age was calculated using the last menstrual period or earliest ultrasound examination or by correlation with both. Doppler parameters were recorded in the absence of fetal breathing movements. An automated tracing method incorporating at least three waveforms was employed and repeated three times to obtain the mean PI. The angle of insonation was maintained at <30°. The MCA, either right or left, depending on waveform quality, was imaged using colour Doppler and its waveform recorded from the proximal third of the vessel distal to its origin at the circle of Willis. The UA Doppler waveforms were recorded from a free loop of cord. The CPR was calculated by dividing the MCA PI by the UA PI.

Outcomes analysed included mode of, and indication for, delivery, birth weight, birth weight centile (<10^{th} or >90^{th} centile), preterm birth (<37 weeks gestation) and adverse perinatal outcome. Adverse perinatal outcome was defined as a composite measure of ***any*** of perinatal death (fetal or neonatal) or Neonatal Critical Care Unit (NCCU) admission or severe respiratory distress or Apgar score <7 at 5 minutes or significant hypoglycaemia requiring

treatment or acidosis at birth (pH ≤ 7.0 or lactate ≥ 6 mmol/L). NCCU admission included admission to the special care nursery (SCN), intensive care nursery (ICN) and intensive care unit (ICU). Outcomes were stratified according to the type of GDM treatment (diet, oral hypoglycemic agents (OHA) and insulin) as well as to CPR centiles (<10^{th}, 10^{th}-90^{th}, >90^{th}).

Given the retrospective nature of this study and the difficulty in applying a rigorous definition to the diagnosis of fetal compromise we chose to adopt a pragmatic approach and used the primary indication for delivery/intervention as recorded in the perinatal database and cross-referenced this with the operative notes. We considered this definition reasonable, as the diagnosis of fetal compromise would generally have been made on the basis of an abnormal fetal heart pattern, fetal scalp pH or lactate, fully accepting the limitations of this methodology in our analysis.

Kruskal-Wallis tests were used for comparisons of medians where data showed a skewed distribution and ANOVA was used for comparisons of means between groups where the data was normally distributed. Proportions were compared using Chi-square test or Fisher's exact test where expected frequencies were <5. Statistics are reported as mean (Standard Deviation (SD)) or median (Inter-quartile Range (IQR)) for normally and non-normally distributed variables respectively or as the number of observations with the percentage of total. Univariate analysis was performed by logistic regression and odds ratio (OR) reported with 95% confidence intervals for insulin-controlled diabetes or CPR <10^{th} centile compared to the other treatment groups when stratifying by treatment and CPR respectively. Data were analyzed using R Commander (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at $p<0.05$. No adjustment was made for multiple comparisons.

Results

Over the study period, there were 1089 women with GDM who met all the inclusion criteria. Of these, 563 (51.7%) had diet-controlled GDM, 211 (19.4%) were on OHAs, and 315 (28.9%) required insulin. Table 1 details the maternal demographics, intrapartum outcomes and ultrasound characteristics of the three cohorts. Women who required insulin were older and had higher BMI than the other two groups. They were also more likely to be of Caucasian or Indigenous ethnicity. In contrast, Asian women were more likely to require only diet modification for adequate glycemic control compared to women of other ethnicities. There was no difference in parity, mode of conception, hypertension, thyroid disease or smoking rates between the groups. There was also no difference in the median total length of labor between the groups. Furthermore, there were no significant differences between treatment groups when comparing overall emergency CS rates, CS rates for non-reassuring fetal status (NRFS, intrapartum fetal compromise) or emergency CS rates for other indications. Elective CS rates were however higher in the insulin treated cohort. There were also no significant differences in any of the Doppler indices nor the CPR between the three groups.

Perinatal outcomes are detailed in Table 2. The mean gestation at delivery was significantly different between the three groups with women in the diet-controlled cohort delivering at a later gestation compared to the other two groups. Insulin treated women had the highest proportion of premature births (36.8%, 116/315). There was no difference in the mean birth weight or prevalence of neonates with birth weights <10^{th} centile. There was, however, an increased odds of neonates with birth weights >90^{th} centile in the insulin-treated group of women compared to the other groups (OR: 1.55, 95%CI: 1.03-2.34, p=0.036). Neonatal outcomes were also poorer in the insulin treated cohort, with higher rates of NCCU admission, respiratory distress, hypoglycaemia and death. The insulin treated group also had a significantly increased odds of having the adverse composite neonatal outcome (OR 1.75, 95%CI: 1.34-2.28, p<0.001).

Table 3 details the intrapartum and perinatal outcomes according to CPR centile categories. There was no difference in mode of delivery between the CPR groups. Although the CPR <10th centile cohort had the highest proportion of emergency CS for NRFS, this did not reach statistical significance. The mean gestation at delivery was lowest in the <10th centile and highest in the >90th centile cohorts (37.2 weeks vs. 38.2 weeks, p<0.001), with fetuses with a CPR <10th centile having a 3.32 (2.22 – 4.99, p<0.001) increased odds of being born preterm (<37weeks). The mean birth weight was also significantly lower in the <10th centile group compared to the >90th centile cohort (2733.5 g vs. 3507.7 g, p<0.001). A CPR <10th centile conferred an 8-fold (OR 8.22 95%CI: 5.19-13.02, p<0.001) increase in the odds of having a birth weight <10th centile. A CPR <10th centile was associated with an OR of 2.93 (95%CI: 1.95-4.40, p<0.001) of having an adverse composite neonatal outcome.

Table 4a shows outcomes stratified by CPR centile category then sub-grouped by diabetes treatment. There was no significant difference in birth weight by treatment within the CPR categories. There was however, a significant difference in gestational age at delivery with the gestational age significantly lower in the CPR <10th centile cohort compared to the CPR 10-90th centile and CPR >90th centile groups (both comparisons p<0.001). There was no difference in the composite outcome between treatment groups in the CPR <10th centile and >90th centile cohorts, however there were significantly different rates of the composite outcome between the three treatments cohorts in the CPR 10th-90th centile group. Several differences in method of birth were observed between treatments groups within the CPR 10th-90th centile and <10th centile cohorts. Significantly different rates of elective CS were observed in the <10th centile group, with a trend towards higher rates in the insulin-treated group. Likewise, in the 10th-90th centile group, there were significantly different SVD, overall

CS and elective CS rates, with the highest SVD rates seen in the diet-controlled group and higher overall CS and elective CS rates present in the insulin-treated group.

Table 4b details outcomes stratified by diabetes treatment and sub-grouped according to the CPR. No difference in method of birth was observed in any of the treatment categories between CPR centile groups except higher rates of emergency CS for NRFS observed in women requiring OHAs and with a CPR <10th centile. The mean gestation at delivery and birth weight were significantly different between CPR categories across all GDM treatment groups with earlier delivery and lower birth weight in the CPR <10th centile categories of each treatment group and increased gestational age and birth weight with increasing CPR. Across all treatment groups, there was also a significant difference in the proportion of composite adverse outcomes between CPR categories, with highest rates consistently seen in the CPR <10th centile cohort compared to any other group (OR 3.1, 95%CI: 1.76-5.30, p<0.001 for diet-controlled GDM, OR 3.3, 95%CI: 1.23-8.98, p=0.018 for OHA-treated GDM and OR 2.7, 95%CI: 1.23-5.96, p=0.013 for insulin-controlled GDM).

Discussion

The results from this large study demonstrate an association between a low CPR (<10th centile) measured between 34+0-36+6 weeks gestation in GDM pregnancies and lower birth weight, higher prevalence of birth weight <10th centile and worse perinatal outcomes in all treatment groups. Low CPR was associated with high rates of emergency CS for NRFS in OHA-treated pregnancies and our results also suggest that low CPR increases the risk of delivery <37 weeks for all GDM treatment categories with the highest risk seen in the OHA cohort.

There is now good data, both from prospective[12,13] and retrospective studies[14,15] linking a low CPR with suboptimal growth at term, increased rates of intrapartum compromise and emergency CS, poor condition at birth and increased neonatal unit admission. In addition, a low fetal CPR may reflect failure to reach its genetic growth potential at term,[10,16] despite normal birth weight. Fetuses with reduced feto-placental reserves prior to labour have decreased ability to tolerate the progressive hypoxic stress caused by intrapartum uterine contractions which reduce uterine blood flow by up to 60%.[17] The CPR reflects suboptimal placental function and subsequent fetal cardiovascular compensation and thus appears a better predictor of outcome than the UA PI or MCA PI individually.[9] Hence, it is likely a good modality for assessment of fetal wellbeing given the described specific placental abnormalities in diabetic pregnancies.

The increasing global prevalence of GDM and associated complications is a challenge for obstetric healthcare providers. There is good evidence that tight glycemic control[18] combined with planned delivery reduces both obstetric and perinatal complications. Improved perinatal mortality rates are partly attributable to enhanced prenatal care, including implementing rigorous blood glucose monitoring, antenatal fetal wellbeing assessment protocols and timely delivery. Nevertheless, stillbirth of non-anomalous fetuses in DM-complicated pregnancies is unpredictable and not consistently correlated with the degree of maternal hyperglycemia, suggesting a multifactorial etiology. This complexity in causation presents challenges in determining the most appropriate method of antenatal monitoring. Currently there is no single preferred method of fetal surveillance in diabetic pregnancies. The evidence regarding the use of feto-placental Dopplers in monitoring GDM pregnancies is conflicting, with several small, retrospective studies reporting no significant difference in UA PI in GDM patients compared to non-diabetic controls.[19,20] In addition, there is data suggesting the fetal MCA PI in GDM pregnancies is higher than in non-diabetic

pregnancies.[21] Despite this uncertainty, abnormal fetal Dopplers have been associated with increased incidence of perinatal complications, including CS for fetal compromise.[11] Indeed, a recent review proposed CPR evaluation in specific clinical conditions to assess its utility in predicting adverse outcome.[9] Given that a GDM diagnosis may include women with unrecognised diabetes antedating pregnancy and those who develop insulin resistance late in pregnancy, any placental compromise is likely to be variable depending on when metabolic dysregulation begins. In our view, given such variation in placental abnormalities and associated risk of fetal growth perturbations, the CPR would be a particularly useful adjunct in assessing fetal wellbeing in a diabetic cohort, as in the general population.

Although there was higher prevalence of emergency CS for NRFS in the CPR <10th centile cohort compared to the 10th-90th and the >90th centile groups (OR 1.50, 95%CI: 0.62-3.64, p=0.369), consistent with data from unselected populations[12,15], this difference was not statistically significant. One explanation may be the confounding effect of gestation, as almost all women with GDM are induced. Indeed, the mean gestation at delivery for women in the diet-, OHA- and insulin-controlled groups was <39 weeks (38.2, 38.0, and 37.6 weeks respectively). This slightly earlier delivery may explain why, even in the CPR <10th centile cohort, intrapartum fetal compromise was observed less frequently than in previous publications,[15,12] where the gestation at birth was later.

The mean Doppler indices in our three treatment groups correlated with those reported in previous publications,[14,19-21] supporting the observation of comparable CPR between GDM and non-GDM patients. We found the highest mean CPRs in the insulin-treated group, an observation noted by other investigators.[22] Our results are also in agreement with Fadda *et al.*'s smaller study showing that abnormal UA and MCA Doppler indices and a low CPR in GDM pregnancies were associated with adverse perinatal outcomes.[11] Here, within each

treatment group, women in the CPR <10th centile cohort had the lowest birth weight and gestational age at delivery and higher rates of the composite neonatal outcome measure.

The strengths of our study include the large number of cases from a tertiary centre and the inclusion of clinically relevant outcomes. The limitations were intrinsic to the retrospective nature of the study. Spanning nine years, the long study period saw evolution in hospital policy and practice, importantly including changing diagnostic criteria for GDM, potentially affecting the relationship between diabetes status, Dopplers and outcomes. In addition, inter- and intra-sonographer variability was unknown and not all outcomes of interest were reliably recorded. We were unable to confirm treatment adequacy and glycaemic control, gestation at GDM diagnosis or duration of treatment, all potentially confounding factors. Whilst it is possible that estimated fetal weight may have been considered in mode of delivery decisions, the CPR itself was unlikely to influence such decisions as this parameter was not included in the ultrasound report. Further, all cases had positive end diastolic flow in the UA, and thus would not have been considered abnormal by the treating obstetrician.

Despite these limitations, we have demonstrated that a low CPR in a GDM cohort is associated with low birth weight, preterm birth and increased risk of adverse perinatal outcomes. We have also shown no difference in the mean CPR between different GDM treatment groups. To our knowledge this is the first study assessing the utility of the CPR, stratified by type of GDM treatment for the prediction of intrapartum and perinatal outcomes. Our findings add to the increasing data on the utility of the CPR in risk stratification of late gestation pregnancies and may assist in clinical management. Further prospective studies are clearly necessary to establish the role of CPR in specific medical conditions including DM.

References

1. Hilder L, Zhichao Z, Parker M, Jahan S, Chambers G. Australia's Mothers and babies 2012. In: Welfare AIoHa, editor. Canberra: AIHW; 2014.
2. Langer O, Yogev Y, Most O, Xenakis EM. Gestational diabetes: the consequences of not treating. Am J Obstet Gynecol 2005; 192(4): 989-97.
3. Biri A, Korucuoglu U, Ozcan P, Aksakal N, Turan O, Himmetoglu O. Effect of different degrees of glucose intolerance on maternal and perinatal outcomes. J Matern Fetal Neonatal Med 2009; 22(6): 473-8.
4. Vilchez G, Dai J, Hoyos L, Gill N, Bahado-Singh R, Soko R. Labor and neonatal outcomes after term induction of labor in gestational diabetes. J Perinatol 2015; 35: 924-9.
5. Vambergue A, Fajardy I. Consequences of gestational and pregestational diabetes on placental function and birth weight. World J Diabetes 2011; 2(11): 196-203.
6. Leach L. Placental Vascular Dysfunction in Diabetic Pregnancies: Intimations of Fetal Cardiovascular Disease? Microcirculation 2011; 18(4): 263-9.
7. Dubova E, Pavlov K, Yesayan R, et al. Morphometric characteristics of placental villi in pregnant women with diabetes. Bull Exp Biol Med 2011; 151(5): 589-93.
8. National Institute for Health and Care Excellence. Diabetes in pregnancy: management from preconception to the postnatal period (NG3). London (UK): National Institute for Health and Care Excellence; 2015.
9. DeVore GR. The importance of the cerebroplacental ratio in the evaluation of fetal well-being in SGA and AGA fetuses. Am J Obstet Gynecol 2015; 213(1): 5-15.
10. Morales-Roselló J, Khalil A. Fetal cerebral redistribution: a marker of compromise regardless of fetal size. Ultrasound Obstet Gynecol 2015; 46(4): 385-8.
11. Fadda GM, D'Antona D, Ambrosini G, Cherchi P, Nardelli G, Capobianco G, Dessole S. Placental and fetal pulsatility indices in gestational diabetes mellitus. J Reprod Med 2001; 46(4): 365-70.
12. Prior T, Mullins E, Bennett P, Kumar S. Prediction of intrapartum fetal compromise using the cerebroumbilical ratio: a prospective observational study. Am J Obstet Gynecol 2013; 208(2): 124.e1-.e6.
13. Prior T, Mullins E, Bennett P, Kumar S. Prediction of fetal compromise in labor. Obstet Gynecol 2014; 123(6): 1263-71.
14. Sabdia S, Greer RM, Prior T, Kumar S. Predicting intrapartum fetal compromise using the fetal cerebro-umbilical ratio. Placenta 2015; 36(5): 594-8.
15. Khalil A, Morales-Rosello J, Elsaddig M, Khan N, Papageorghiou A, Bhide A, Thilaganathan B. The association between fetal Doppler and admission to neonatal unit at term. Am J Obstet Gynecol 2015; 213(1): 57.e1-.e7.
16. Prior T, Paramasivam G, Bennett P, Kumar S. Are fetuses that fail to achieve their growth potential at increased risk of intrapartum compromise? Ultrasound Obstet Gynecol 2015; 46(4): 460-4.
17. Low J, Pickersgill H, Killen H, Derrick E. The prediction and prevention of intrapartum fetal asphyxia in term pregnancies. Am J Obstet Gynecol 2001; 184(4): 724-30.
18. Metzger B, Lowe L, Dyer A, Trimble R, Chaovarindr U, Coustan D, Hadden D, McCance D, Hod M, McIntyre H, Oats J, Persson B, Rogers M, Sacks D. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 2008; 358(19): 1991-2002.
19. Santolaya-Forgas J, Otero J, Martinez-Arraras J. P15.10: Umbilical, fetal middle cerebral and uterine arteries resistance and pulsatility indices in well controlled insulin dependent gestational diabetes. Ultrasound Obstet Gynecol 2005; 26(4): 464-.

20. To W, Mok C. Fetal umbilical arterial and venous Doppler measurements in gestational diabetic and nondiabetic pregnancies near term. J Matern Fetal Neonatal Med 2009; 22(12): 1176-82.
21. Zanjani M, Nasirzadeh R, Fereshtehnejad S-M, Yoonesi Asl L, Alemzadeh S-AP, Askari S. Fetal cerebral hemodynamic in gestational diabetic versus normal pregnancies: a Doppler velocimetry of middle cerebral and umbilical arteries. Acta Neurol Belg 2013; 114(1): 15-23.
22. Maruotti G, Rizzo G, Sirico A, Sarno L, Cirigliano L, Arduini D, Martinelli P. Are there any relationships between umbilical artery pulsatility index and macrosomia in fetuses of type I diabetic mothers? J Matern Fetal Neonatal Med 2014; 27(17): 1776-81.

Table 1: Maternal demographics, intrapartum outcomes and ultrasound characteristics of study cohort stratified by GDM treatment

	Diet (n=563)	OHA (n=211)	Insulin (n=315)	p-value
Maternal age (years) §	32.2 [5.3]	32.5 [5.1]	33.2 [5.0]	0.028
BMI (kg/m^2) ^	24.0 [20.9-28.5]	26.1 [23.1-30.9]	28.6 [24.8-35.0]	<0.001
Ethnicity*				
Caucasian	190 (33.7)	83 (39.3)	148 (47.0)	0.001
Asian	165 (29.3)	45 (21.3)	49 (15.6)	<0.001
Indigenous	10 (1.8)	2(0.9)	13 (4.1)	0.029
Indian	73 (13.0)	39 (18.5)	36 (11.4)	0.057
Other	125 (22.2)	42 (19.9)	69 (21.9)	0.782
Parity*				
0	236 (41.9)	83 (39.3)	111 (35.2)	0.151
1	197 (35.0)	76 (36.0)	106 (33.7)	0.848
2	70 (12.4)	28 (13.3)	53 (16.8)	0.188
≥3	60 (10.7)	24 (14.3)	45 (11.4)	0.272
ART*	29 (5.2)	15 (7.1)	21 (6.7)	0.488
Hypertension*	45 (8.0)	23 (11.0)	37 (11.7)	0.152
Thyroid disease*	54 (9.6)	15 (7.1)	26 (8.3)	0.519
Smoking*	61 (10.8)	25 (11.8)	39 (12.4)	0.836
Total length labor (mins)^	269 [282.3] (n=420)	275 [284.5] (n=138)	293 [261.5] (n=195)	1.000
Mode of Delivery*				
SVD	300 (53.3)	94 (44.6)	130 (41.3)	0.001
Instrumental	76 (13.5)	28 (13.3)	34 (10.8)	0.492
CS	187 (33.2)	89 (42.2)	151 (47.9)	<0.001
Elective CS	93 (16.5)	43 (20.4)	85 (27.0)	0.001
Emergency CS	94 (16.7)	46 (21.8)	66 (21.0)	0.149
NRFS	20 (3.6)	12 (5.7)	11 (3.5)	0.352
Other	74 (13.1)	34 (16.1)	55 (17.5)	0.199
Gestation at US (weeks) §	35.6 (0.91)	35.7 (0.86)	35.7 (0.84)	0.625
CPR ^	2.02 (1.68-2.40)	2.04 (1.69-2.43)	2.11 (2.79-2.43)	0.210
UA PI ^	0.86 (0.74-0.96)	0.82 (0.75-0.93)	0.83 (0.72-0.93)	0.071
MCA PI^	1.68 (1.46-1.91)	1.68 (1.45-1.89)	1.69 (1.51-1.93)	0.402
CPR <10th centile *	59 (10.5)	18 (8.5)	31 (9.8)	0.721
CPR >90th centile *	48 (8.5)	21 (10.0)	38 (12.1)	0.240

§ Mean (SD)
^Median (IQR)
***Number (Percentage)
BMI – Body Mass Index, ART – Assisted Reproductive Techniques, CS – Caesarean Section, SVD – Spontaneous Vaginal Delivery, NRFS – Non-Reassuring Fetal Status, SD – standard deviation, IQR – Interquartile Range, CPR – Cerebroplacental Ratio, UA – Umbilical Artery, MCA – Middle Cerebral Artery, PI – Pulsatility Index

Table 2: Perinatal outcomes stratified by GDM treatment

	Diet (n=563)	OHA (n=211)	Insulin (n=315)	p-value	OR (95%CI)‡	p-value
Gestation at delivery (weeks) [SD] §	38.2 [1.4]	38.0 [1.0]	37.6 [1.0]	<0.001	NA	NA
Delivery =<37 weeks*	142 (25.2)	46 (21.8)	116 (36.8)	<0.001	1.82 (1.37-2.41)	<0.001
BW (g) [SD] §	3210.3 [553.3]	3196.4 [487.2]	3280.1 [532.6]	0.115	NA	NA
BW <10th centile (n, %)*	64 (11.4)	16 (7.6)	29 (9.2)	0.252	0.88 (0.56-1.37)	0.574
LGA (BW≥90th centile) (n, %)*	54 (9.6)	14 (6.6)	41 (13.0)	0.051	1.55 (1.03-2.34)	0.036
Apgar score <7 at 5min (n, %) *	10 (1.8)	5 (2.4)	6 (1.9)	0.803†	0.97 (0.37-2.52)	0.956
Acidosis (pH≤<7.0 or Lactate>6) (n, %)*	35 (6.2)	17 (8.1)	16 (5.1)	0.384	0.74 (0.42-1.32)	0.312
NCCU admission (n, %)*	88 (15.6)	27 (12.8)	71 (22.5)	0.006	1.67 (1.20-2.32)	0.002
Respiratory distress (n, %)*	59 (10.5)	35 (16.6)	66 (21.0)	<0.001	1.92 (1.35-2.71)	<0.001
Hypoglycaemia (n, %)*	44 (7.9)	21 (10.0)	64 (20.3)	<0.001	2.76 (1.90-4.02)	<0.001
Perinatal Death (n, %)*	3 (0.5)	0 (0)	2 (0.6)	0.714†	1.64 (0.27-9.87)	0.54
Composite adverse neonatal outcome (n, %)*	179 (32.1)	73 (34.6)	145 (46.0)	<0.001	1.75 (1.34-2.28)	<0.001

§ Mean (SD)
* Number (percentage)
† Fishers Exact
‡ Odds ratios are for the Insulin-treated group compared to other treatment groups

BW – birth weight, LGA – large for gestational age, NCCU – neonatal intensive care unit, SD – standard deviation, IQR – interquartile range, OR – Odds Ratio, 95%CI – 95% Confidence Interval

Table 3: Intrapartum and perinatal outcomes stratified by CPR centile categories.

	CPR <10th centile (n=108)	CPR 10-90th centile (n=874)	CPR >90th centile (n=107)	p-value	OR (95%CI)‡	p-value
Mode of Delivery (n, %)*						
SVD	53 (49.1)	426 (48.7)	45 (42.1)	0.417	1.04 (0.70-1.55)	0.834
Instrumental	15 (13.9)	107 (12.2)	16 (15.0)	0.673	1.13 (0.63-2.00)	0.689
Caesarean Section	40 (37.0)	341 (39.0)	46 (43.0)	0.647	0.90 (0.60-1.36)	0.626
Elective CS	20 (18.5)	177 (20.3)	24 (22.4)	0.774	0.88 (0.53-1.47)	0.629
Emergency CS	20 (18.5)	164 (18.8)	22 (20.6)	0.899	0.97 (0.58-1.62)	0.911
NRFS	6 (5.6)	35 (4.0)	2 (1.9)	0.394†	1.50 (0.62-3.64)	0.369
Other	14 (13.0)	129 (14.8)	20 (18.7)	0.453	0.83 (0.46-1.50)	0.539
Mean gestation at delivery (weeks) [SD] §	37.2 [1.5]	38.1 [1.2]	38.2 [1.1]	<0.001	NA	NA
Delivery <37 weeks*	57 (52.8)	226 (25.9)	21 (19.6)	<0.001	3.32 (2.22-4.99)	<0.001
Mean BW (g) [SD] §	2733.5 [580.2]	3254.6 [490.2]	3507.7 [541.0]	<0.001	NA	NA
BW <10th centile (n, %)*	41 (38.0)	63 (7.2)	5 (4.7)	<0.001	8.22 (5.19-13.02)	<0.001
LGA (BW≥90th centile) (n, %)*	2 (1.9)	81 (9.3)	26 (24.3)	<0.001†	0.15 (0.04-0.63)	0.010
Apgar score <7 at 5min (n, %) *	2 (1.9)	18 (2.1)	1 (0.9)	0.917†	0.95 (0.22-4.13)	0.944
Acidosis (pH<7.0 or Lactate>6) (n, %)*	8 (7.4)	49 (5.6)	11 (10.3)	0.147	1.23 (0.57-2.64)	0.599
NCCU admission (n, %)*	40 (37.0)	131 (15.0)	15 (14.0)	<0.001	3.36 (2.19-5.16)	<0.001
Respiratory distress (n, %)*	15 (13.9)	131 (15.0)	14 (13.1)	0.845	0.93 (0.52-1.65)	0.804
Hypoglycaemia (n, %)*	19 (17.9)	101 (11.6)	9 (8.4)	0.083	1.72 (1.01-2.94)	0.046
Perinatal Death (n, %)*	2 (1.9)	3 (0.3)	0 (0)	0.156†	6.15 (1.02-37.23)	0.048
Composite adverse neonatal outcome (n, %)*	65 (60.2)	296 (34.1)	36 (33.6)	<0.001	2.93 (1.95-4.40)	<0.001

§ Mean (SD)

* Number (percentage) – data analysed by Chi-squared test except where indicated

† Fishers Exact

‡ Odds ratios are for CPR <10th centile compared to CPR ≥10th centile.

SVD – Spontaneous Vaginal Delivery, CS – Caesarean Section, BW – Birth Weight, LGA – Large for Gestational Age, NCCU – Neonatal Critical Care Unit, SD – Standard Deviation, OR – Odds Ratio, 95%CI – 95% Confidence Interval, NRFS – Non Reassuring Fetal Status

Table 4a: Intrapartum and perinatal outcomes stratified by CPR centile categories and type of treatment.

	CPR <10th centile				CPR 10th-90th centile				CPR >90th centile			
	Diet (n=59)	**OHA (n=18)**	**Insulin n=31)**	**p-value**	**Diet (n=456)**	**OHA (n=172)**	**Insulin (n=246)**	**p-value**	**Diet (n=48)**	**OHA (n=21)**	**Insulin (n=38)**	**p-value**
Mode of Delivery (n, %)*												
SVD	35 (59.3)	6 (33.3)	12 (38.7)	0.061	245 (53.7)	80 (46.5)	101 (41.1)	0.005	20 (41.7)	8 (38.1)	17 (44.7)	0.882
Instrumental	7 (11.9)	4 (22.2)	4 (12.9)	0.516†	60 (13.2)	20 (11.6)	27 (11.0)	0.676	9 (18.8)	4 (19.1)	3 (7.9)	0.292†
Caesarean Section	17 (28.8)	8 (44.4)	15 (48.4)	0.146	151 (33.1)	72 (41.9)	118 (48.0)	<0.001	19 (39.6)	9 (42.9)	18 (47.4)	0.769
Elective CS	8 (13.6)	1 (5.6)	11 (35.5)	0.017†	76 (16.7)	39 (22.7)	62 (25.2)	0.018	9 (18.8)	3 (14.3)	12 (31.6)	0.251†
Emergency CS	9 (15.3)	7 (38.9)	4 (12.9)	0.076†	75 (16.5)	33 (19.2)	56 (22.8)	0.125	10 (20.8)	6 (28.6)	6 (15.8)	0.507
NRFS	2 (3.4)	4 (22.2)	0 (0)	0.010†	17 (3.7)	8 (4.7)	10 (4.1)	0.86	1 (2.1)	0 (0)	1 (2.6)	1†
Other	7 (11.9)	3 (16.7)	4 (12.9)	0.860†	58 (12.7)	25 (14.5)	46 (18.7)	0.103	9 (18.8)	6 (28.6)	5 (13.2)	0.338†
Mean gestation at delivery (weeks) [SD] §	37.3 [1.6]	37.0 [1.7]	37.2 [0.9]	0.813	38.3 [1.3]	38.1 [0.8]	37.6 [1.0]	<0.001	38.8 [1.1]	38.1 [0.9]	37.6 [0.8]	<0.001
Mean BW (g) [SD] §	2696.6 [596.6]	2646.8 [753.9]	2854.2 [410.4]	0.375	3237.7 [501.0]	3234.9 [339.2]	3299.9 [525.2]	0.232	3581.8 [557.9]	3352.5 [579.7]	3499.8 [490.4]	0.270
Composite adverse neonatal outcome (n, %)*	33 (55.9)	11 (61.1)	21 (67.7)	0.551	133 (29.6)	53 (30.8)	110 (44.7)	<0.001	13 (27.1)	9 (42.9)	14 (36.8)	0.387

§ Mean (SD)
* Number (percentage)
† Fishers Exact

SVD – Spontaneous Vaginal Delivery, CS – Caesarean Section, BW – Birth Weight, SD – Standard Deviation, OR – Odds Ratio, 95%CI – 95% Confidence Interval, NRFS – Non Reassuring Fetal Status

Table 4b: Intrapartum and perinatal outcomes stratified by type of GDM treatment and CPR centile categories.

	Diet				OHA				Insulin			
	CPR <10th centile (n=59)	**CPR 10th-90th centile (n=456)**	**CPR >90th centile (n=48)**	**p-value**	**CPR <10th centile (n=18)**	**CPR 10th-90th centile (n=172)**	**CPR >90th centile (n=21)**	**p-value**	**CPR <10th centile (n=31)**	**CPR 10th-90th centile (n=246)**	**CPR >90th centile (n=38)**	**p-value**
Mode of Delivery (n, %)*												
SVD	35 (59.3)	245 (53.7)	20 (41.7)	0.174	6 (33.3)	80 (46.5)	8 (38.1)	0.463	12 (38.7)	101 (41.1)	17 (44.7)	0.871
Instrumental	7 (11.9)	60 (13.2)	9 (18.8)	0.518	4 (22.2)	20 (11.6)	4 (19.1)	0.279†	4 (12.9)	27 (11.0)	3 (7.9)	0.766†
Caesarean Section	17 (28.8)	151 (33.1)	19 (39.6)	0.498	8 (44.4)	72 (41.9)	9 (42.9)	0.976	15 (48.4)	118 (48.0)	18 (47.4)	0.996
Elective CS	8 (13.6)	76 (16.7)	9 (18.8)	0.758	1 (5.6)	39 (22.7)	3 (14.3)	0.208†	11 (35.5)	62 (25.2)	12 (31.6)	0.379
Emergency CS	9 (15.3)	75 (16.4)	10 (20.8)	0.705	7 (38.9)	33 (19.2)	6 (28.6)	0.114	4 (12.9)	56 (22.8)	6 (15.8)	0.342†
NRFS	2 (3.4)	17 (3.7)	1 (2.1)	1†	4 (22.2)	8 (4.7)	0 (0)	0.017†	0 (0)	10 (4.1)	1 (2.6)	0.855†
Other	7 (11.9)	58 (12.7)	9 (18.8)	0.478	3 (16.7)	25 (14.5)	6 (28.6)	0.208†	4 (12.9)	46 (18.7)	5 (13.2)	0.626†
Mean gestation at delivery (weeks) [SD] §	37.3 [1.6]	38.3 [1.3]	38.8 [1.1]	<0.001	37.0 [1.7]	38.1 [0.8]	38.1 [0.9]	<0.001	37.2 [0.9]	37.6 [1.0]	37.6 [0.8]	0.038
Mean BW (g) [SD] §	2696.6 [596.6]	3237.7 [501.0]	3581.8 [557.9]	<0.001	2646.8 [753.9]	3234.9 [339.2]	3352.5 [579.7]	<0.001	2854.2 [410.4]	3299.9 [525.2]	3499.8 [490.4]	<0.001
Composite neonatal outcome score (n, %)*	33 (55.9)	133 (29.6)	13 (27.1)	<0.001	11 (61.1)	53 (30.8)	9 (42.9)	0.026	21 (67.7)	110 (44.7)	14 (36.8)	0.025

§ Mean (SD)
* Number (percentage)
† Fishers Exact

SVD – Spontaneous Vaginal Delivery, CS – Caesarean Section, BW – Birth Weight, SD – Standard Deviation, OR – Odds Ratio, 95%CI – 95% Confidence Interval, NRFS – Non Reassuring Fetal Status

#