RETROSPECTIVE ANALYSIS OF THE RISK FACTORS FOR PRETERM DELIVERY IN GESTATIONAL DIABETES MELLITUS AND THEIR ADVERSE NEONATAL OUTCOMES

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Abstract
Objectives-This study aims to anticipate all the risk factors involved with preterm birth in women diagnosed with gestational diabetes mellitus (GDM) and to identify the adverse outcomes in their premature babies. Methods—This retrospective hospital-based case-control study was conducted at the Department of Obstetrics and Gynecology of Shri Shankaracharya Institute of Medical Sciences from August 2022 to October 2023. A total of 640 pregnant women were included in this study. Antenatal screening for gestational diabetes was done at 24 weeks of gestation as per the institutional guidelines. The diagnosis of gestational diabetes mellitus (GDM) is based on an oral glucose tolerance test with 75 grams of glucose. Results- Age ≥ 30 years (86% vs 71% p-value <0.001), BMI ≥25 (63% vs 47% p-value <0.01), and prior preterm birth (9.2% vs 3.7% p-value <0.01) were more associated with preterm delivery in mothers with GDM. LGA was more common in cases than controls (6.2% vs 2.2%, p=0.035). RDS (26.9% vs 17.4%, P=0.02) and hypoglycemia (28.4% vs 19.6%, P=0.03) are more common problems in preterm babies of GDM mothers. Conclusions- Mothers with GDM are prone to preterm delivery, with significant risk factors being age≥ 30, BMI≥ 25, prior preterm birth and LGA. GDM also increases the risk of some adverse outcomes, such as RDS and neonatal hypoglycemia.
Keywords- GDM, preterm delivery, preterm birth, risk factors, neonatal outcome

Introduction

The prevalence of GDM in India ranges from 9% to 16%, as per the systematic review and meta-analysis of 110 studies.(1) GDM is an essential concern in India since by 2040, the number of diabetic women will reach up to 313.3 million (2). According to one estimation, more than five million are affected by GDM. The main reason for increasing GDM in pregnant women is due to overweight and obesity. (3) Gestational diabetes mellitus (GDM) is a type of diabetes that develops during pregnancy and is characterised by hyperglycemia and decreased insulin sensitivity. Undiagnosed or undertreated GDM can lead to significant maternal & foetal complications. GDM screening can be done by 75g oral glucose and measuring plasma glucose 2 hours after ingestion (Oral Glucose Tolerance Test) between 24 and 28 weeks of pregnancy. (4) Management involves following a proper diet, exercising, making lifestyle changes, and using insulin as needed. It's essential to control blood sugar levels to reduce the risks for both the mother and baby. Gestational diabetes mellitus (GDM) can lead to adverse effects during childbirth and long-term issues for both the mother and baby. These issues include large for gestational age babies, including macrosomia (5), which can cause complications during delivery, such as prolonged and obstructed labour, and an increased likelihood of cesarean delivery. (6) Additionally, GDM can result in preterm birth and pregnancy-induced hypertension. (7)A variety of neonatal complications are associated with GDM, like hypoglycemia, neonatal jaundice, hypocalcemia, polycythemia, respiratory distress syndrome, and birth injury. (8)

Mothers with gestational diabetes mellitus (GDM) have a greater chance of preterm delivery as compared to the general population. This is because of metabolic disturbances, poor glycemic control, and other comorbidities. Many studies found preterm birth as a complication of gestational diabetes mellitus, but only a few studies evaluated the risk factors for preterm delivery in these patients. Also, few studies are concentrating on the outcomes of preterm babies of gestational diabetes (GDM) mothers. Additionally, the maternal complications and mortality of preterm babies of mothers with GDM have not been established. As a result, this study aimed to study the risk factors associated with preterm deliveries in mothers with GDM, and the complications and mortality in preterm infants born to mothers with GDM.

MATERIAL AND METHODS

A hospital-based case-control study was conducted at the Department of Obstetrics and Gynecology of Shri Shankaracharya Institute of Medical Sciences, Durg. The institute's ethics committee approves the study. This study includes 640 pregnant women who started antenatal visits before 24 weeks of gestation and underwent GDM screening per

the institutional guideline from Aug 2022 to October 2023. The cases are preterm birth in women with GDM, and controls are preterm birth in women without GDM. The sample size was calculated based on the estimated proportion of preterm delivery of 20% in GDM and 10% in those without GDM. So, at least 128 cases and 509 controls at a 95% confidence level and 80% power, the ratio of control to cases 4, and the least extreme odds ratio of 2.25. Roughly 130 cases and 510 controls were randomly selected. Inclusion criteria were patient consistency with the American Diabetes Association diagnostic criteria for GDM in 2019 (2), singleton pregnancy and complete clinical records. Exclusion criteria were in vitro fertilisation (IVF), multiple pregnancies, mothers with associated comorbidities (type 1 diabetes, type 2 diabetes, chronic respiratory diseases, neoplasms, gastrointestinal, hepatic, infectious tract diseases, and heart disease) and newborns with congenital anomalies or metabolic disorders.

An oral glucose tolerance test (OGTT) is performed to diagnose GDM. At first, a venous blood sample is taken on an empty stomach in the morning. Then, 75 grams of glucose dissolved in 300 ml water and taken orally. Afterwards, blood samples are taken at 1 hour and 2 hours after glucose ingestion. Plasma glucose is estimated by the GOD-POD method. The first testing was done at the antenatal visit as early as possible. The second testing was done 24-28 weeks of pregnancy if the first test was negative. A 4-week gap was maintained between the two tests. GDM is diagnosed if the fasting blood glucose level is >92 mg/dl, the 1-hour blood glucose level is >180 mg/dl and/or the 2-hour blood glucose level is >153 mg/dl. Insulin treatment started as required when the women had poor glycemic control after nutritional intervention.

The data was acquired from the hospital's medical records. The obstetric, antenatal natal, postnatal and neonatal history were taken. Risk factors for preterm delivery and GDM were assessed. Age 30 or older, family history of diabetes, BMI of 25 or more, previous GDM, previous macrosomia, previous unexplained fetal death, previous preterm delivery and pregnancy-induced hypertension were the risk factors. Preterm delivery was defined as a baby born before 37 completed weeks of gestation. The data was analysed using SPSS software. In descriptive statistics, mean, standard deviation and percentages were calculated. As required, various risk factors were compared between cases and controls using a t-test and chi-square test. A multivariate logistic regression analysis was used to determine if GDM was independently associated with preterm delivery. Odds ratio (OR) and 95% confidence intervals (CI) were estimated. P value < 0.05 was considered statistically significant.

The neonatal outcomes were calculated using problems such as neonatal sepsis, neonatal jaundice, hypoglycemia (blood glucose level <40 mg/dl), respiratory distress syndrome (RDS) and neonatal mortality. Diagnosis of neonatal sepsis, neonatal jaundice and hypoglycemia was based on clinical and laboratory criteria. RDS was diagnosed through clinical and radiological criteria.

OBSERVATIONS AND RESULTS

Table I Maternal risk factors for preterm deliveries

Maternal Risk factors	Cases (n = 130)	Controls (n = 510)	P value
AGE ≥ 30 years	112 (86%)	363 (71%)	**<0.001**
BMI ≥ 25	82 (63%)	242 (47%)	**<0.01**
Previous Abortions	11 (8.5%)	41 (8%)	0.87
Nulliparity	42 (32%)	175 (34%)	0.67
Family history of DM	40(31%)	163(32%)	0.79
Previous GDM	3(2.3%)	5(0.98%)	0.37
PROM	28(21.5%)	127(24.9)	0.46
Eclampsia	3 (2.3%)	3 (0.59%)	0.15
Chronic Hypertension	12 (9.2%)	34 (6.7%)	0.31
Preeclampsia	4 (3.1%)	15 (2.9%)	1
Previous macrosomia	2 (1.5%)	8 (1.6%)	1
Previous neonatal death	3 (2.3%)	7 (1.4%)	0.43
Prior preterm birth	12 (9.2%)	19 (3.7%)	**<0.01**
Cesarean delivery	73 (56%)	257 (50%)	0.24
Vaginal delivery	57 (44%)	253 (50%)	

Table I shows maternal risk factors for preterm delivery in cases and controls. Age ≥ 30 years (86% vs 71% p-value <0.001), BMI≥25 (63% vs 47% p-value <0.01), and prior preterm birth (9.2% vs 3.7% p-value <0.01) were more in cases than controls.

Table II Logistic Regression Analysis of Maternal Risk Factors

Risk factors	Odds-Ratio (95%CI)	P value
AGE≥ 30 years	2.48 [1.47-4.39]	**<0.01**
BMI ≥ 25	1.77 [1.18-2.69]	**<0.01**
Previous Abortions	1.36 [0.607-2.89]	0.43
Preeclampsia	0.542 [0.111-1.90]	0.38
Eclampsia	3.65 [0.491-30.1]	0.2
Hypertension	1.31 [0.599-2.72]	0.48
Family history of DM	0.658 [0.391-1.08]	0.1
Previous gdm	3.13 [0.587-14.3]	0.15
Nulliparity	0.877 [0.565-1.37]	0.56
Prior preterm birth	2.32 [0.999-5.21]	**0.043**

Table II shows a multivariate logistic regression analysis of maternal and neonatal risk factors. Age ≥ 30 (OR: 2.48,95%CI:1.47-4.39, p<0.01), BMI ≥ 25(OR: 1.77, 95% CI: 1.18-2.69, p<0.01) and prior preterm birth (OR:2.32,95%CI:0.999-5.21,p=0.043) are all associated with risk of preterm deliveries in mother with gestational diabetes.

Table III Neonatal risk factors for preterm deliveries

Neonatal Risk Factors	Cases (n = 130)	Controls (n = 510)	P value
Baby Birth Weight, mean (sd) (grams)	2365 (583)	2307 (555)	0.31
Extremely low birth weight	1(0.77%)	11(2.2%)	0.48
Very low birth weight	8(6.2%)	36(7.1%)	0.72
Low birth weight	68(52%)	259(51%)	0.76
Normal weight	53(41%)	204(40%)	0.87
Gestation, mean (sd) (Weeks)	34.5 (1.87)	34.5 (2.18)	0.81
Extremely preterm	1(0.77%)	10(2%)	0.7
Very Preterm	13(10%)	41(8%)	
Moderate preterm	12(9.2)	46(9%)	0.94
Late preterm	104(80%)	413(81%)	0.8

Large for gestational age	8(6.2%)	11(2.2%)	**0.035**
NICU Admission	40 (31%)	163 (32%)	0.79
Female	59 (45%)	277 (54%)	
Male	71 (55%)	233 (46%)	0.069
Apgar Score 1min, mean (sd)	8.26 (1.47)	8.21 (1.51)	0.74
Apgar Score 5min, mean (sd)	9.45 (0.890)	9.30 (1.13)	0.12

Table II shows Neonatal risk factors in cases and controls. There were no differences between the mean birth weight and gestational age. There were more low birth weights in both groups. There were more late preterms in both cases (80%) and controls (81%). Macrosomia was more common in cases than controls (6.2% vs 2.2%, p=0.035). Male babies were more likely to be in GDM cases than female babies (55% vs 45%).

Table IV Neonatal outcomes among preterm infants

Morbidities	Cases (n=130)	Controls (n=510)	P value
Sepsis	10(7.69%)	36(7%)	0.95
RDS	35(26.9%)	89(17.4%)	**0.02**
Hypoglycemia	37(28.4%)	100(19.6%)	**0.03**
Hyperbilirubinimea	39(30%)	148(29%)	0.91
Mortality	7(5.4%)	23(4.5%)	0.85

Table IV shows neonatal outcomes among preterm infants. RDS (26.9% vs 17.4%, P=0.02) and Hypoglycemia (28.4% vs 19.6%, P=0.03) are more common morbidities in cases. There is no difference between the mortality among cases and controls.

DISCUSSION

Preterm birth can cause a wide variety of health problems and dangerous complications to babies. Preterm birth can cause respiratory distress, lung injury, sepsis, heart diseases, intestinal problems, Intracranial bleeding, and lifelong disorders like cerebral palsy (1-3). Therefore, it is necessary to know the fundamental character of preterm delivery in gestational diabetes mellitus because this is very important for the prevention of an uneventful pregnancy. Currently, gestational diabetes mellitus (GDM) is on a rising trend and obesity and sedentary lifestyles are important risk factors. Previous studies found that perinatal complications were higher in diabetic mothers as compared to the general population.

Many studies have shown that advanced maternal age is associated with an increased risk of preterm delivery in GDM mothers. Zhang et al. compared women with GDM aged 25–29; women with GDM aged 35–44 have a significantly higher risk of preterm birth. (9) Another study found that women with GDM are more likely to experience spontaneous preterm birth than women without GDM. (10) Fuchs et al. found that the risk of preterm birth is lowest for women aged 30–34 and highest for women over 40. (11) In our research, age≥ 30 (OR: 2.48, 95% CI: 1.47-4.39, p<0.01) was associated with an increased risk of preterm delivery. Many studies found a pre-conceptional BMI of 25 or higher (OR: 1.77, 95% CI: 1.18-2.69, p<0.01) is one of the risk factors for preterm birth in pregnant women with GDM. (10, 12, 13) In our research, pre-conceptional BMI ≥ 25 was associated with an increased risk of preterm delivery. A history of preterm birth is a significant risk factor for a subsequent preterm birth, regardless of the cause of the first preterm birth. A shorter gestational period in the first pregnancy increases the risk of preterm birth and early-term birth in subsequent pregnancies. (14,15)Also, previous preterm birth and GDM independently increased the risk of spontaneous preterm delivery. (10) Similarly, our study found previous preterm birth was associated with preterm delivery in GDM. Multivariate analysis indicated that previous preterm birth increases the risk of preterm birth by 2.32 times (95% CI: 0.99-5.1, p=.043).

In our research, we found that preterm large for gestational age (LGA) babies born to mothers with gestational diabetes mellitus (GDM) are more as compared to preterm babies born to mothers without GDM. (6.2% vs 2.2%, p=0.035). Mothers with GDM have a higher chance of LGA babies. According to a study, the prevalence of LGA newborns in mothers without GDM was 7.7% to 12.7% compared to mothers with GDM, which was 13.6% to 22.3%. The increased risk of macrosomia and LGA in GDM is mainly due to the mother's increased insulin resistance. Other factors that contribute to macrosomia include maternal obesity and poorly controlled diabetes. (17) Controlling maternal weight and managing GDM promptly can help reduce the prevalence of macrosomia and LGA babies. Regular exercise and eating a healthy diet can also help reduce the risk of complications.

In our study, we found neonates born to GDM mothers have a higher rate of complications. However, our study did not observe significant differences between the two groups regarding newborn sex, gestational age, birth weight, and Apgar score. There was a higher number of male babies in cases than female babies (55% vs 45%). Although it is not clinically significant (p=0.069), it denotes male preponderance in babies of GDM mothers. A systematic review and meta-analysis found that women carrying a male fetus have a 3- 4% higher relative risk of GDM than women carrying a female fetus. (18) Our study results indicated that gestational diabetes mellitus (GDM) is linked to a higher risk of respiratory distress syndrome (RDS) in preterm infants (P=0.02). Respiratory distress syndrome (RDS) is more common in newborns of diabetic mothers than in normal mothers. (19, 20) RDS is a leading cause of perinatal mortality and morbidity. It's caused by a lack of surfactant in the lungs, a foamy substance that helps the lungs expand so newborns can breathe. Maternal diabetes can lead to hyperglycemia and hyperinsulinism in the fetus, which disrupts the production and function of surfactants. Surfactant is necessary for lung maturation. (21) Fetal lung underdevelopment: GDM can cause fetal lung underdevelopment, leading to immediate respiratory distress in newborns. (22)In our study, it was found that preterms born to diabetic mothers had a higher incidence of hypoglycemia. (P=0.03). Hypoglycemia is more common in newborns of diabetic mothers because the mother's high blood sugar levels cause the fetus to produce too much insulin. (23) Maternal hyperglycemia, fetal hyperinsulinism and insufficient glucose supply can lead to hypoglycemia in newborns. After birth, inadequate glucose supply can increase the risk of hypoglycemic shock if not appropriately managed. This can lead to cerebral insult and even death (24).

The strengths of this study may include the consistent diagnosis of GDM according to the guidelines. All samples selected were randomised correctly; therefore, the biases are minimal. However, there are also some limitations to consider. The data obtained from a tertiary care hospital may not apply to the general population. Also, there may be differences in GDM screening and newborn management across different settings. Further studies with large samples and a prospective nature are needed for the relationship between GDM and preterm birth. In the near future, if more studies give us significant evidence, we can frame a program to decrease maternal and neonatal morbidity and mortality.

Conclusions

Mothers with GDM are prone to preterm delivery, with significant risk factors being age≥ 30, BMI≥ 25, prior preterm birth and LGA. GDM also increases the risk of some adverse outcomes, such as RDS and neonatal hypoglycemia.

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