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Neonatal outcome in pregnancies complicated by gestational diabetes mellitus in a tertiary care hospital from South India

Shrikant Jamdade[1], Nibedita Mitra[2], Senthilkumar V[3], Kavitha G[4], Nithya M[5]

[1]Assistant Professor, Department of Pediatrics, Seth GS Medical College and KEM Hospital Mumbai, Maharashtra, [2]Additional Chief Health Director and Head, [3,4]Senior Consultant, Department of Pediatrics, Southern Railways Headquarters Hospital, Chennai, Tamil Nadu, [5]Consultant Pediatrician, Puvi Child Health Clinic, Coimbatore, Tamil Nadu, India

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ABSTRACT

Background: Affecting 537 million adults worldwide and counting, diabetes is spiraling out of control. Historically pregnancies complicated by abnormal glycemic control are associated with various neonatal complications, increased morbidity and mortality. Majority of abnormal glycemic control in pregnancy is attributed to gestational diabetes mellitus (GDM) rather than pregestational Diabetes Mellitus. 21 million live births (1 in 6) were affected by hyperglycemia during pregnancy worldwide in 2021, approximately 80% of which is attributed to GDM. With disease burden increasing at an alarming rate a hospital-based descriptive study was conducted to observe neonatal outcome in pregnancies complicated by GDM. **Aims and Objectives:** The present study was undertaken to observe neonatal outcome, in pregnancies complicated by GDM in terms of neonatal mortality and neonatal complications, in the study hospital. **Materials and Methods:** 115 mothers diagnosed to have GDM and their infants were enrolled in the study. Maternal antenatal records and indoor case sheets were used to collect data regarding maternal medial profile and any associated obstetric complications. Neonatal indoor case sheets were reviewed to collect data regarding gestational age, birth weight, and gender. Neonatal complications and mortality if any were recorded. Descriptive analysis was done using data collected. **Results:** Out of 115 infants 60 (52.2%) were female and 55 (47.5%) were male, 108 (93.9%) were full term and 7 (6.1%) were preterm. 93 (80.9%) infants were appropriate for gestational age, 15 (13.0%) were small for gestational age, and 7 (6.1%) were large for gestational age. Four (3.4%) infants had birth weight more than 4000 g. Neonatal complications were noted in 26 (22.6%) infants, most common being neonatal hyperbilirubinemia (n = 14) (12.2%). Other neonatal complications observed were respiratory distress (n = 5) (4.3%), perinatal asphyxia (n = 3) (2.6%), hypoglycemia (n = 2) (1.7%), meconium aspiration syndrome (n = 1) (0.9%), and neonatal convulsions (n = 1) (0.9%). Cardiac malformations noted were ventricular septal defect (n = 1) (0.9%) and atrial septal defect (n = 1) (0.9%). There was no neonatal mortality noted in the study. **Conclusion:** In our study, we observed a better neonatal outcome in terms of neonatal mortality and morbidity as compared that noted historically in the literature. Early detection and meticulous maternal diabetes management is associated with better neonatal outcome as observed in this study. This observation is also well supported in the literature along with the fact that, untreated GDM is associated with significant neonatal morbidity.

Key words: Gestational diabetes mellitus; Neonate; Outcome study; Fetal macrosomia

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INTRODUCTION

With changing lifestyles, dietary habits, mental stress, and lack of physical activity the burden of diabetes mellitus is increasing at an alarming rate in mid and low-income countries. Current global prevalence of diabetes mellitus is 573 million adults with 6.7 million deaths in 2021.[1] Diabetes mellitus has been the chief ally to COVID-19 contributing

Address for Correspondence:
Dr. Shrikant Jamdade, Assistant Professor, Department of Pediatrics, Seth GS Medical College and KEM Hospital, Mumbai - 400 012, Maharashtra, India. **Mobile:** +91-9930039135. **E-mail:** dr.shrikantjamdade@gmail.com

significantly to mortality associated with it. With 1 in 6 live births affected by hyperglycemia in pregnancy worldwide,[1] diabetes today is complicating pregnancies like never before. Apart from many short-term adverse outcomes and perinatal mortality, infants born to diabetic mothers are at higher risk developing obesity and Type II diabetes as adults. Besides, the findings of several studies that epigenetic alterations of different genes of the fetus of a GDM mother *in utero* could result in the transgenerational transmission of GDM and type II diabetes are of concern.[2-4] Ironically, this is not being recognized as major public health problem especially in developing countries.

Amongst all diabetic mothers a greater proportion is attributed to GDM. 21 million live births (1 in 6) were affected by hyperglycemia during pregnancy worldwide in 2021, approximately 80% of which is attributed to gestational diabetes mellitus (GDM). The global prevalence of GDM is 16.7%. The disease burden is even higher in India with prevalence of GDM being 29.3%.[1]

GDM is defined as carbohydrate intolerance of variable severity first diagnosed in during pregnancy. Neonatal outcome diabetic mothers is associated with significantly higher risk for developing congenital anomalies, metabolic complications, and increased perinatal mortality and morbidity. The current knowledge of adverse effects of diabetes on infants is based on studies in Type 1 diabetic mothers. However, GDM being far more prevalent and the risks associated with it need to be clarified and interventions should be tailored to those risks.[5] Untreated GDM is associated with adverse neonatal outcome including prenatal mortality and various neonatal complications such as macrosomia, shoulder dystocia, brachial plexus injury, cesarean delivery, prematurity, respiratory distress, hypoglycemia, polycythemia, hyperbilirubinemia, and admission to neonatal intensive care unit.[6-9] With disease burden increasing at an alarming rate a hospital based descriptive study was conducted to observe neonatal outcome in pregnancies complicated by GDM.

Aims and objectives

The present study was undertaken to observe neonatal outcome in pregnancies complicated by GDM in terms of neonatal mortality and neonatal complications in the study hospital.

MATERIALS AND METHODS

The present study is a hospital-based descriptive study carried out in a tertiary care public hospital. A total of 115 infant and mother pairs were enrolled in the study. A written, informed consent for participation was obtained from mothers before enrollment. The study was approved by Institutional Ethics Committee before the commencement.

Sample size calculation

The expected proportion of the primary outcome measure was considered as 10% based on the previous studies. Sample size was calculated, to estimate the study proportion to be within 5% of the true estimate with 90% power of study, as follows:

Parameters used in sample size calculation: Expected proportion of the outcome - 10%, width of confidence interval - 5%, and power of study (1-Beta) - 90%. The above mentioned parameters were fed into statcalc function of CDC Epi Info software version 7. The required sample size was found to be n=97. A total of 115 infant and mother pairs were enrolled in the study.

Inclusion criteria

Mothers diagnosed with GDM and infants born to them.

Exclusion criteria

Infants born to mothers with pregestational diabetes mellitus.

Maternal antenatal records and indoor case sheets were used to collect data. Maternal age, parity, mode of delivery, and type treatment received for diabetes (Medical Nutritional Therapy-MNT/insulin/metformin) were recorded. Any obstetric complications, if present were recorded. Neonatal indoor case sheets were reviewed to collect data regarding gestational age, birth weight, gender and weight for gestational age. Neonatal complications and mortality, if any, were recorded. Neonatal investigations were reviewed and any abnormal investigations were recorded.

Statistical analysis

Statistical was done using SPSS v23 (IBM Corp.) software. Chi-squared test was used for categorical variables; however, Fisher's Exact test was used if expected frequency in the contingency tables was found to be <5 for >25% of the cells.

RESULTS

Out of 115 infants, 60 (52.2%) were female and 55 (47.5%) were male, 108 (93.9%) were full term, and 7 (6.1%) were preterm. 93 (80.9%) infants were appropriate for gestational age (AGA), 15(13.0%) were small for gestational age (SGA) and 7(6.1%) were large for gestational age (LGA). Four (3.4%) infants had birth weight more than 4000 g (Table 1).

Table 1: Summary of all parameters

All parameters	Frequency (%)
Age of mother (years)	
<20	2 (1.7)
20–30	75 (65.2)
30–35	33 (28.7)
More than 35	5 (4.3)
Treatment given	
MNT	54 (47.0)
Insulin	31 (27.0)
Metformin	30 (26.1)
Parity of mother	
Primigravida	35 (30.4)
Multigravida	80 (69.6)
Mode of delivery	
NVD	57 (49.6)
LSCS	55 (47.8)
Vacuum delivery	2 (1.7)
Forceps delivery	1 (0.9)
Fetal maturity	
Preterm	7 (6.1)
Term	108 (93.9)
Baby gender	
Male	55 (47.8)
Female	60 (52.2)
Birth weight (kg)	
<2.5	16 (13.9)
2.5–3.5	84 (73.0)
>3.5–4	6 (5.2)
>4	4 (3.4)
Weight for GA	
AGA	93 (80.9)
SGA	15 (13.0)
LGA	7 (6.1)
Maternal complications (present)	22 (19.1)
Maternal complication	
No complication	93 (80.9)
PIH	7 (6.1)
Polyhydramnios	5 (4.3)
IUGR	4 (3.5)
Transverse Lie	4 (3.5)
Breech Presentation	2 (1.7)
Neonatal complications (present)	26 (22.6)
Neonatal complication	
No complication	89 (77.4)
Neonatal hyperbilirubinemia	14 (12.2)
Respiratory distress	5 (4.3)
Perinatal asphyxia	3 (2.6)
Hypoglycemia	2 (1.7)
Meconium aspiration syndrome	1 (0.9)
Neonatal convulsions	1 (0.9)
Cardiac malformation	
None	113 (98.3)
ASD	1 (0.9)
VSD	1 (0.9)

MNT: Medical nutrition therapy, NVD: Normal vaginal delivery, LSCS: Lower segment cesarean section, AGA: Appropriate for gestational age, SGA: Small for gestational age, LGA: Large for gestational age, PIH: Pregnancy induced hypertension, IUGR: Intrauterine growth retardation, ASD: Atrial septal defect, VSD: Ventricular septal defect

Out of 115, maternal obstetric complications were noted in 22 (19.1%) mothers. Pregnancy induced hypertension PIH was the most commonly associated obstetric complication (n=7) (6.1%). Other obstetric complication noted were polyhydramnios (n=5) (4.3%), IUGR (n=4) (3.5%), transverse lie (n=4) (3.5%), and breech presentation (n=2) (1.7%).

Neonatal complications were noted in 26 (22.6%) infants, most common being neonatal hyperbilirubinemia (n=14) (12.2%). Other neonatal complications observed were respiratory distress (n=5) (4.3%), perinatal asphyxia (n=3) (2.6%), hypoglycemia (n=2) (1.7%), meconium aspiration syndrome (MAS) (n=1) (0.9%), and neonatal convulsions (n=1) (0.9%). Cardiac malformations noted were ventricular septal defect (n=1) (0.9%) and atrial septal defect (n=1) (0.9%). There was no neonatal mortality noted in the study.

The frequency of neonatal complications was more in the infants delivered by LSCS (16 out of 55) (29%), vacuum assisted delivery (2 out of 2) (100%), and forceps application (1 out of 1) (100%) as compared to those delivered by normal vaginal delivery (7 out of 57) (12.2%). This observation was statistically significant with a P=0.001 (Table 2). Neonatal complications were more common in preterm infants (4 out of 7) (57.1%) as compared to term infants (22 out of 108) (20.3%). This observation was statistically significant with p value of 0.045. None of the other observed parameters had statistically significant association with occurrence of neonatal complications.

DISCUSSION

Affecting 537 million adults worldwide and counting, diabetes is spiraling out of control.[1] Over three out of 4 adults with diabetes, now live in low- and middle-income countries. 90 million adults with diabetes mellitus are living in South East Asia region, out of which India alone accounts for 74 million. Diabetes in its various forms affected 21 million pregnancies (1 in 6) worldwide in 2021 with GDM accounting for approximately 80% of it. Magnitude of disease burden in India is even worse. The prevalence of GDM in India is 29.3% as compared to 16.7% globally.[1]

In our study, we studied 115 infants born to mothers with GDM. No neonatal mortality was observed in our study. Neonatal complications were noted in 26 (22.6%) infants, most common being neonatal hyperbilirubinemia (n=14) (12.2%). Other neonatal complications observed were respiratory distress (n=5) (4.3%), perinatal asphyxia (n=3) (2.6%), hypoglycemia (n=2) (1.7%), MAS (n=1) (0.9%), and neonatal convulsions (n=1) (0.9%).

In an outcome study by Prakash et al., 132 infants (n=132) born to gestational diabetic mothers were studied. Neonatal

Table 2: Association between neonatal complications and observed parameters

Parameters	Neonatal complications (%)		P-value
	Present (n=26)	Absent (n=89)	
Age of mother (years)			0.833[1]
<20	0 (0.0)	2 (2.2)	
20–30	18 (69.2)	57 (64.0)	
30–35	8 (30.8)	25 (28.1)	
More than 35	0 (0.0)	5 (5.6)	
Treatment given			0.319[2]
MNT	10 (38.5)	44 (49.4)	
Insulin	10 (38.5)	21 (23.6)	
Metformin	6 (23.1)	24 (27.0)	
Parity of mother			0.658[2]
Primigravida	7 (26.9)	28 (31.5)	
Multigravida	19 (73.1)	61 (68.5)	
Mode of delivery***			0.001[1]
NVD	7 (26.9)	50 (56.2)	
LSCS	16 (61.5)	39 (43.8)	
Vacuum delivery	2 (7.7)	0 (0.0)	
Forceps delivery	1 (3.8)	0 (0.0)	
Fetal maturity***			0.045[1]
Preterm	4 (15.4)	3 (3.4)	
Term	22 (84.6)	86 (96.6)	
Baby Gender			0.846[2]
Male	12 (46.2)	43 (48.3)	
Female	14 (53.8)	46 (51.7)	
Birth weight (kg)			0.086[1]
<2	2 (7.7)	3 (3.4)	
2–2.5	2 (7.7)	14 (15.7)	
2.5–3.5	17 (65.4)	67 (75.3)	
>3.5	5 (19.2)	5 (5.6)	
Weight for GA			0.352[1]
AGA	19 (73.1)	74 (83.1)	
GA	4 (15.4)	11 (12.4)	
LGA	3 (11.5)	4 (4.5)	
Maternal complications (present)	7 (26.9)	15 (16.9)	0.265[1]
Maternal complication			0.438[1]
No complication	19 (73.1)	74 (83.1)	
PIH	2 (7.7)	5 (5.6)	
Polyhydramnios	1 (3.8)	4 (4.5)	
IUGR	1 (3.8)	3 (3.4)	
Transverse lie	2 (7.7)	2 (2.2)	
Breech presentation	1 (3.8)	1 (1.1)	

***Significant at P<0.05, [1]Fisher's Exact Test, [2]Chi-squared test; MNT: Medical nutrition therapy, NVD: Normal vaginal delivery, LSCS: Lower segment caesarean section, AGA: Appropriate for gestational age, SGA: Small for gestational age, LGA: Large for gestational age, PIH: Pregnancy induced hypertension, IUGR: Intrauterine growth retardation, ASD: Atrial septal defect, VSD: Ventricular septal defect

mortality was 3% (n=4). Neonatal complications were noted in 22% (n=24) infants and included respiratory distress (n=15), prematurity (n=14), hypoglycemia (n=6), and congenital anomalies (n=3). About 18.1% (n=24) infants were LGA.[10] In a prospective study by Antoniou et al., involving 576 patients with GDM, authors noted one stillbirth and one neonatal death. About 8.2% (n=47) infants were premature and 16.5% (n=95) were LGA, 7.8% (n=45) had a birth weight more than 4000 g. Hypoglycemia was noted in 10.7% (n=56) infants and hyperbilirubinemia was noted in 3.7% (n=21) infants. Authors further concluded that prepregnancy BMI, gestational weight gain, maternal treatment requirement, and HbA1c at the end of pregnancy can predict adverse pregnancy outcomes in women with GDM.[11] In a retrospective cohort study conducted by Kumari et al., authors compared perinatal outcome of, GDM (n=170) and normal controls (n=197), and concluded that adequate treatment of GDM on diet, oral hypoglycemic agents, or insulin to achieve euglycemia can achieve nearnormal maternal and neonatal outcome.[12]

Macrosomia is the most constant complication of GDM. The concept of excessive fetal growth is expressed by the word "Macrosomia."[6] Macrosomia is typically defined as a birth weight.

Above the 90th percentile for gestational age (LGA) or >4000 g.[2] Macrosomia is the single most predominant short term adverse outcome of GDM and the main factor linked to other neonatal complications.[6] Macrosomia predisposes infants to birth trauma, shoulder dystocia, clavicle fracture, brachial plexus injury, and cesarean delivery. Other complications such as hyperbilirubinemia, hypoglycemia, and respiratory distress are more common in macrocosmic infants.[7,8] Severity of macrosomia increases with increasing levels maternal hyperglycemia as demonstrated by Hyperglycemia and Adverse Pregnancy Outcome Study (HAPO). This landmark study involving 23,316 participant showed strong and continuous association between neonatal adiposity and maternal glycemia.[13] About 15–45% of babies born to diabetic mothers can have macrosomia, which is a three-fold higher rate when compared to normoglycemic controls.[2] In the present study, 7 (6.1%) infants were LGA including four infants with birth weight more than 4 kg. Our hospital is a tertiary care regional center providing optimal antenatal care, with early detection and adequate management of GDM insuring adequate glycemic control. This may be the reason for lesser frequency of Macrosomia as well as other complications observed in the study. Maternal obesity has been recognized as independent risk factor for fetal Macrosomia.[14]

Prematurity is one of the common associations with GDM. It could be because of either spontaneous onset of preterm labor or early induction of labor/cesarean section for maternal or fetal indication. In our study, 7 (6.1%) infants were preterm and 108 (93.9%) were term. No post-term infants were noted in the study. In a large cohort study of 46,230 pregnancies, Hedderson et al., showed that GDM had a significantly higher risk of spontaneous preterm birth. They also found that the risk of spontaneous preterm birth increased with increasing levels of pregnancy glycemia.[15]

Hypoglycemia is one of the most frequent metabolic complication of GDM. During the first few hours of life, the level of blood glucose that must be taken as hypoglycemia is unclear. In our study, only 2 (1.7%) infants developed hypoglycemia (<2.2 mmol/l). In a study by Juana et al., consisting of 109 infants born to GDM mothers, 23 (12.1%) presented with mild (2.2–2.4 mmol/l), 20 (10.5%) with moderate (1.6–2.1 mmol/l), and 5 (2.6%) with severe hypoglycemia (<1.6 mmol/l). Authors further concluded that mild and moderate neonatal hypoglycemia were common although severe episodes were unusual in infants of women with GDM.[16] Risk of neonatal hypoglycemia is more with LGA infants and maternal hyperglycemia during labor.

Hypocalcemia is one of the metabolic complications of GDM. There is some evidence that women who develop GDM are more likely to be Vitamin D deficient and better management of glycemic control is associated with reduction in neonatal hypocalcemia.[17,18] No neonatal hypocalcemia was noted in our study.

In this study, 5 (4.3%) infants developed respiratory distress. Prematurity, cesarean section/assisted vaginal delivery, and birth trauma are the factors that contribute to the risk of developing respiratory distress in infants born to women with GDM. However, recent evidence suggests GDM as an independent risk factor for neonatal respiratory distress. In a prospective study involving 444 women, Mortier et al., found GDM as an independent risk factor of severe neonatal respiratory distress syndrome after 34 weeks of gestation.[19] In a large, retrospective study of medical records of 228,438 deliveries by Kawakita et al., the authors concluded that the risk of neonatal respiratory morbidity was higher for women with GDM or pregestational DM compared to women without diabetes in pregnancy, and these risks were increased beyond what can be attributed to prematurity.[20]

Chronic fetal hyperinsulinism leads to increase metabolic and oxygen demands, and relative fetal hypoxia. Fetal and perinatal hypoxia is associated with still birth, perinatal asphyxia, and perinatal mortality.[8] Historically, significant perinatal mortality has been associated with infants of diabetic mothers, especially with type 1 and type 2 maternal diabetes. There is an increased risk of stillbirth and perinatal mortality in women with GDM as well, although this risk is lesser as compared to Type 1 and Type 2 pregestational diabetes.[21] In our study, 3 (2.6%) infants developed perinatal asphyxia while no stillbirth and perinatal mortality was observed.

Other effects of fetal hypoxia include increased erythropoiesis and polycythemia, which is associated with hyperviscosity, hypoglycemia, and hyperbilirubinemia.[6] In our study, 14 (12.2%) infants developed hyperbilirubinemia. Findings of the HAPO study demonstrated association between hyperbilirubinemia and maternal blood sugar levels. However, risk of severe hyperbilirubinemia was noted to be low.[6,22]

In a study by Yogev a matched control of 555 gestational diabetic mothers diagnosed after 37 weeks were compared with 1110 subjects treated for GDM and 1110 nondiabetic subjects. Authors found a 2–4-fold increase in metabolic complications and macrosomia/large for gestational age in the untreated group with no difference between nondiabetic and treated subjects, and further concluded that untreated GDM carries significant risks for perinatal morbidity compared to well treated GDM and non-diabetic women in all disease severity levels. Timely and effective treatment substantially improves outcome.[9] Transgenerational transmission of diabetes risk with GDM has serious implications for global health in future. Screening strategies for GDM and increasing awareness in general population in mid and low-income countries could be the next step in reducing burden of GDM.

Limitations of the study

In this study, we only observed neonatal outcome in GDM; however, long-term outcome could not be studied.

CONCLUSION

In our study, we observed a better neonatal outcome in terms of neonatal mortality and morbidity as compared that noted historically in the literature. Early detection and meticulous maternal diabetes management is associated with better neonatal outcome as observed in this study. This observation is also well supported in the literature along with the fact that, untreated GDM is associated with significant neonatal morbidity.

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Authors Contribution:
SJ - Concept, Design, Definition of intellectual content, Literature search, Data acquisition, Data analysis, Statistical analysis, Manuscript preparation, and Manuscript revision; **NM -** Concept, review of statistical analysis, and Manuscript review **SV -** Concept, Interpretation of results, and Manuscript review; **KG -** Literature search, Data analysis, and Manuscript review, **NM -** Data acquisition, Literature Search, and Manuscript review.

Work attributed to:
Southern Railways Headquarters Hospital, Constable Road, Perambur, Ayanavaram, Chennai - 600 023, Tamil Nadu, India.

Orcid ID:
Dr. Shrikant S Jamdade - https://orcid.org/0000-0003-2353-8682
Dr. Nibedita Mitra - https://orcid.org/0000-0003-3909-940X
Dr. Senthilkumar V - https://orcid.org/0000-0002-3397-3816
Dr. Kavitha G - https://orcid.org/0000-0001-5833-5653
Dr. Nithya M - https://orcid.org/0000-0001-5234-3070

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