A Prospective Case-Control Study to Compare the Clinical Outcomes and Metabolic Profile in Neonates Born to Diabetic Mothers in a Tertiary Care Armed Forces Hospital, India

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DOI: 10.3126/jnps.v41i2.30731

Submitted on: 2020-08-21

Accepted on: 2021-02-23

Acknowledgements: None

Funding: Nil

Conflict of Interest: None declared

Permission from IRB: Yes

To cite this article: Dhillon GK, Kushvanth KN, Dhillon HS, Sasidharan S, Singh V. A Prospective Case-Control Study to Compare The Clinical Outcomes And Metabolic Profile in Neonates Born to Diabetic Mothers in a Tertiary Care Armed Forces Hospital, India. J Nepal Paediatr Soc. 2021;41(2):127-33.

ABSTRACT

Introduction: The prevalence of gestational diabetes mellitus (GDM) is on the rise especially in women of Asian ethnicity. GDM carries with it a multitude of foeto-maternal complications, the management of which is still a challenge, especially in developing countries.

Methods: This was a hospital based prospective case control study conducted on 100 neonates to compare clinical outcomes and metabolic profiles in neonates of diabetic mothers and neonates of non-diabetic mothers over a period of two years.

Results: The mothers in GDM group had 66% emergency lower segment caesarean section (LSCS) compared to 32% in non-GDM group ($p = 0.001$). The infants of diabetic mothers (IDM) had statistically significant higher percentage of preterm births, NICU admission, hyperbilirubinemia, hypoglycaemia and polycythemia. The anthropometric and cord blood parameters (Haemoglobin, haematocrit, platelet, calcium and bilirubin) were comparable in both the groups.

Conclusions: GDM poses significant risks to both mother and neonate, however optimal glycemic control and meticulous monitoring and treatment protocols can reduce the incidence of certain known complications.

Keywords: Caesarean section; Case-control study; Gestational diabetes mellitus; Infants of diabetic mothers; Macrosomia

INTRODUCTION

Gestational diabetes mellitus (GDM) is characterised by carbohydrate intolerance with the onset or first recognition during pregnancy.[1] The World Health Organisation (WHO) has predicted that between 1995 and 2025, there will be a 35% increase in the worldwide prevalence of diabetes.[2] Moreover, women in Asian countries and especially of Indian ethnicity display the highest prevalence of GDM.[3]

GDM poses an increased risk of complications for the mother (especially preeclampsia and caesarean delivery) as well as the neonate. Infants of diabetic mother (IDM) are at higher risk of complications and congenital anomalies like macrosomia, hypoglycemia, hypocalcemia, hypomagnesemia, polycythemia, hyperbilirubinemia, prematurity, transient tachypnea of newborn, respiratory distress syndrome, birth asphyxia, congenital heart diseases like interventricular septal hypertrophy, transient hypertrophic subaortic stenosis, cardiomyopathy, cleft lip, cleft palate, sacral agenesis, jitteriness, seizures, movement disorders etc.[4,5]

Suboptimal prenatal care along with poor maternal glycemic control, vasculopathy, infection and pregnancy induced hypertension are some of the factors held responsible for the poor perinatal outcome.[6] A strong association between congenital anomalies and maternal glycemic control has been documented and studies have shown that strict control of maternal glucose during pregnancy has a favourable perinatal outcome.[7,8] This provides us with a window of opportunity to prevent or reduce the foetal and neonatal morbidity through scrupulous prenatal and intrapartum care.[6] The management of IDM can be done effectively based on prevention, early recognition and appropriate treatment of these complications. Comprehensive care of pregnant women with GDM has been extensively described, yet guidelines regarding the care of their infants are less well established. Moreover there are scanty reports on IDM in India compared to developed countries.

Hence the present study was conceived to compare multiple clinical outcomes and metabolic profiles of IDM and non diabetic mothers after matching subjects in both groups in a tertiary care Armed Forces Hospital in India. The results are expected to further our knowledge on the subject in a socio-economically homogenous sample from across the country. With not many studies done on Indian diaspora and especially in Armed Forces, this research will be useful in recognising potentially modifiable factors and implementing necessary remedial measures in the future.

METHODS

This was a hospital based prospective case control study conducted over two years at the Department of Paediatrics in Mumbai, India. The study was approved by the Institutional ethics committee, and a written informed consent was obtained from the parent(s). All consecutive infants born to mothers with gestational diabetes and pre-gestational (Type 1 and type 2) diabetes at our institute during the study period formed the study group. The control group had equal number of consecutively born neonates of non diabetic mothers during the same period. Subjects in the control group were matched with those in the study group for confounding maternal as well as neonatal factors like maternal age, maternal morbidity other than diabetes, period of gestation, mode of delivery and sex of the neonate.

Sample size was calculated using the formula: $n = \{z^2p\ (1-p)\}\ /d^2$, {where: n = sample size, Z = table value of alpha error from standard normal distribution table (0.95), power (p) = 80%, precision error of estimation (d) = 5.5%}. Thus the sample size was calculated as n = {0.95 x 0.95 x 0.8 (0.2)} / 0.055 x 0.055 = 47.7. Hence, each group was allocated 50 consecutively born neonates of diabetic mothers and 50 consecutive neonates born to non-diabetic mothers.

All subjects in both groups were evaluated for birth weight, length, occipito-frontal circumference, clinically detectable congenital anomalies and followed up for neonatal morbidities like hypoglycemia, hyperbilirubinemia and polycythemia. Cord blood samples of both groups were evaluated for serum bilirubin, haemoglobin, haematocrit, calcium, platelet counts and blood sugar levels.

Blood sugar levels were done under aseptic condition. Blood samples were obtained from the heel of foot from neonates of GDM mothers by prick method and checked on glucometer at 1, 2, 3, 6, 12, 24 hours of age as a routine in nursery for neonates of GDM mothers. Neonates of non GDM mothers were monitored for feed adequacy and if symptomatic, underwent glucose tests by glucometer as per the hospital protocol. All neonates were monitored clinically for polycythemia and jaundice and evaluated and managed appropriately.

The data were tabulated using Microsoft Excel software and analysed using statistical software, SPSS version 20. Level of significance was taken at a 'p' value less than or equal to 0.05. The Chi square statistic was used for testing relationships on categorical variables. Student t-test was used to compare the means of a normally distributed interval dependent variable for two independent groups. The Fisher's exact test was used instead of Chi-square test, when one or more cells had an expected frequency of five or less.

RESULTS

The mean age of mothers in GDM Group was 28.88 ± 3.11 years and in non - GDM Group was 27.74 ± 2.97 years (p = 0.064). Majority of the mothers in GDM group (64%) as well as non GDM group (56%) were from the age group of 26 to 30 years. There was no statistically significant difference in terms of co-morbidities in both the groups.

In terms of mode of delivery, non GDM group had 56% spontaneous vaginal delivery compared to 14% in GDM Group (p = 0.001), emergency lower segment caesarean section (LSCS) was 66% in GDM mothers compared to 32% in non-GDM (p = 0.001) and vacuum delivery was 10% in GDM vs 0% in non GDM mothers (p = 0.022) (Table1).

There were 52% and 48% male neonates in GDM group and non-GDM group respectively while female neonates constituted 48% and 52% respectively (p > 0.05). The mean period of gestation was 37.14 ± 1.52 weeks in mothers with GDM and 38.21 ± 1.22 weeks in non GDM group (0.001). In the non-GDM group, 84% of newborns were born between 37 - 40 weeks period of gestation in comparison to 52% in the GDM group (0.001). In the non-GDM group, 16% of newborns were born at < 37 weeks period of gestation in comparison to 48% in the GDM group (0.001).

In neonates born to non-GDM mothers, 24% were small for gestational age (SGA) compared to only 8% among mothers with GDM (p = 0.029). In

Table 1. Comparison between mothers with GDM and non GDM

		GDM		Non-GDM		p value
		N	%	N	%	
Maternal age (years)	18-20	1	2%	2	4%	0.558
	21-25	4	8%	9	18%	0.137
	26-30	32	64%	28	56%	0.414
	>30	13	26%	10	20%	0.640
	Total	50	100%	50	100%	0.064
	Mean ± SD		28.88 ± 3.11		27.74 ± 2.97	0.064
Maternal comorbidity	Hypothyroidism	8	16%	4	8%	> 0.05
	Hypertension	4	8%	2	4%	
	Polyhydramnios	2	4%	1	2%	
	Severe Preeclampsia	2	4%	1	2%	
	PIH	1	2%	2	4%	
Mode of delivery	Spontaneous Vaginal Delivery	7	14%	28	56%	0.001
	Vacuum	5	10%	0	0%	0.022
	Elective LSCS	5	10%	6	12%	0.749
	Emergency LSCS	33	66%	16	32%	0.001

Table 2. Comparison between neonates of mothers with GDM and non-GDM

		GDM		Non-GDM		p value
		N	%	N	%	
Period of gestation	< 37 weeks	24	48%	8	16%	0.001
	37 - 40 weeks	26	52%	42	84%	0.001
	Mean ± SD	37.14 ± 1.52		38.21 ± 1.22		0.001
Gender	Male	26	52%	24	48%	> 0.05
	Female	24	48%	26	52%	
	Total	50	100%	50	100%	
Weight for gestational age	SGA	4	8%	12	24%	0.029
	AGA	44	88%	38	76%	0.118
	LGA	2	4%	0	0	0.153
Neonatal Outcomes	NICU Admission	14	28%	4	8%	< 0.05
	Low birth weight	13	26%	14	32%	> 0.05
	Prematurity	24	48%	8	16%	< 0.05
	Respiratory distress	1	2%	0	-	> 0.05
	Tachypnea	1	2%	0	-	> 0.05
Neonatal Complications	Hyperbilirubinemia	32	64%	17	34%	< 0.05
	Hypoglycemia	8	16%	1	2%	< 0.05
	Polycythemia	7	14%	0	-	< 0.05

mothers with GDM, 88% neonates were appropriate for gestational age (AGA) compared to 76% in the non-GDM group (0.118).

In terms of neonatal morbidity, the incidence of prematurity and NICU admission were significantly higher in GDM group. The incidence of LBW (birth weight < 2.5 kg), respiratory distress and tachypnea was comparable between both the groups. The incidence of hyperbilirubinemia, hypoglycemia and polycythemia was significantly higher in GDM group as compared to non-GDM Group ($p < 0.05$). During the head to toe examination soon after birth, none of the neonates born to either GDM mothers or non-GDM mothers had any clinically detectable congenital malformations (Table 2).

The mean birth weight, length and occipito-frontal circumference (OFC) of neonates in GDM and non-GDM Group did not have any statistically significant difference. The cord blood sugar values were significantly higher in GDM Group as compared to non-GDM group ($p < 0.05$). The other cord blood investigative values (Haemoglobin, hematocrit, platelet, calcium and bilirubin) were comparable between both the groups ($p > 0.05$).

DISCUSSION

In our country, mortality and morbidity is still high among IDM due to poor antenatal care, non-compliance to therapy, lack of awareness about the disease and its effects on foetus, non-booked deliveries and lack of adequate neonatal services. Metabolic complications are among the most important neonatal complications. In addition to being important contributors to early neonatal morbidity, the metabolic complications can lead to long term consequences. Early recognition and timely management can help reduce the severity and long term morbidity associated with these complications.[9,10]

The study sample was homogenous with no significant difference in the age / co-morbidities other than GDM. The rate of spontaneous vaginal delivery (56% vs 14%) was significantly higher in non GDM group in current study. The incidence of LSCS (Elective and emergency) was higher in mothers with GDM group (76% vs 44%) compared to non GDM group. This is consistent with various other studies conducted in other developing countries.[11,12] The significant observation in our study was that rate of emergency LSCS was

Table 3. Comparison of Anthropometric and Biochemical parameters of neonates

		GDM		Non - GDM		p value
		Mean	SD	Mean	SD	
Anthropometry parameters	Weight (gms)	2830	570	2850	490	0.844
	Length (cm)	46.94	2.80	47.24	1.99	0.538
	OFC (cm)	33.07	1.68	33.18	1.17	0.705
Cord blood biochemical parameters	Haemoglobin (g/dL)	16.12	1.81	15.72	1.24	> 0.05
	Hematocrit (%)	47.31	4.89	46.30	3.29	> 0.05
	Platelet ($x10^3/\mu L$)	241.9	0.62	240.3	0.66	> 0.05
	Calcium (mg/dL)	9.20	0.60	9.58	0.80	> 0.05
	Bilirubin (mg/dL)	1.57	0.60	1.44	0.84	> 0.05
	Blood Sugar (mg/dL)	79.64	30.41	67.10	19.22	< 0.05

significantly higher in the GDM group (66% vs 32%) while elective LSCS were comparable between two groups, thus eliminating the confounding factor of choice of patient. Thus emergency LSCS emerged as an independent complication for GDM mothers posing additional risks and warranting enhanced preparedness and extra resources in terms of healthcare infrastructure. The increased risk of emergency caesarean was consistent with a nationwide study in Denmark.[13]

Preterm births are an important cause of neonatal morbidity and mortality and the incidence of preterm births was significantly higher in mothers with GDM (48% vs 16%) in the current study. This is in corroboration with previous study in the past.[14] Majority (88%) of IDM was appropriate for gestational age (AGA) and only 4% (n = 2) were large for gestational age (LGA). This is in contrast with multiple other studies which reported significantly higher weight for gestational age among new-borns to (30% - 40%) mothers with GDM.[15-17] There are multiple hypotheses for accelerated weight gain in mothers with GDM and as per Pedersen, a sustained hyperglycaemia in utero leads to hyperinsulinemia with its consequential anabolic effects.[18] Studies have found a linear and continuous relationship between maternal glycemic levels, foetal insulin levels and body fat percentage.[19] However, we found the mean birth weight comparable in both the groups. None of the neonates had macrosomia and no congenital anomalies were observed. This is in contrast to study by Leandro et al on IDM who reported incidence of major clinically detectable congenital malformations to be 3.12%. These major malformations were myelomeningocele, tracheoesophageal fistula and cleft lip and palate.[20]

Among the anthropological parameters, the length and OFC of neonates in GDM and non-GDM group were comparable ($p > 0.05$). This could be explained on the basis that ours being a tertiary care Armed Forces hospital, all the pregnancies are registered in the early antenatal period. The patients follow structured diagnostic protocols, follow up and adhere to diet and treatment plans. They are meticulously screened by radiological and biochemical modalities for possible congenital anomalies at the earliest. This observation also provides an indirect evidence that IDMs can have favourable outcomes with optimal glycemic control in mothers with GDM by implementing strict protocols and meticulous antenatal care.

Hyperbilirubinemia (64%) was the commonest metabolic complication followed by hypoglycemia (16%) and polycythemia (14%) in newborns of GDM mothers ($p < 0.05$) in the current study. This was consistent with multiple other studies thus giving strength to our existing knowledge and providing further impetus in implementing

measures for stricter glycemic control during antenatal period.[21,22]

The cord blood biochemistry revealed significantly higher blood sugar values in the IDM with consequent hypoglycaemia in neonatal period. This is consistent with existing literature which reports a rapid decline in plasma glucose concentration of the neonates born to diabetic mothers. The proposed pathophysiology is that maternal hyperglycaemia leads to foetal hyperglycaemia, stimulating the foetal pancreas to synthesise excessive insulin. At the time of birth, due to the separation of the placenta, there is a sudden interruption of glucose supply to the neonate but hyperinsulinemia persists leading to hypoglycaemia.[9] The other cord blood parameters (Haemoglobin, haematocrit, platelet, calcium and bilirubin) were comparable between both the groups ($p > 0.05$).

The strength of this study is that it is a case control design in a homogenous population revealing significant feto-maternal complications in GDM pregnancies with potentially modifiable characteristics leading to favourable outcomes. The limitation is that it is a single site hospital centric study with a relatively small sample size. Also, quantification of outcomes with different levels of maternal glycemic control was not done. A community-based study with a larger sample size is envisaged in future to further confirm our findings.

CONCLUSIONS

The IDM had statistically significant higher percentage of preterm births, NICU admission, hyperbilirubinemia, hypoglycemia and polycythemia. The anthropometric and cord blood parameters (Haemoglobin, haematocrit, platelet, calcium and bilirubin) were comparable in both the groups. GDM poses significant risks to both mother and neonate, however optimal glycemic control and meticulous monitoring and treatment protocols can reduce the incidence of certain known complications.

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