Original Article

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Paediatrics Section

Association between Cord Blood Haematocrit and Neonatal Outcome among Neonates of Diabetic Mothers: A Cohort Study

ARSHAD ALI CHERUKATTIL[1], MENON NARAYANANKUTTY SUNILKUMAR[2]

ABSTRACT

Introduction: The perinatal mortality rate of Neonates of Diabetic Mothers (NDMs) over the years showed a reducing trend. Polycythaemia is common in NDMs, and such neonates have a risk of hyperviscosity, renal vein thrombosis, cardiac failure, metabolic abnormalities, and necrotising enterocolitis.

Aim: To assess the association between cord blood haematocrit and neonatal outcomes among NDMs.

Materials and Methods: The present study was a cohort study that included 130 neonates, which was conducted at Amala Institute of Medical Sciences (AIMS), Thrissur, Kerala, India, from December 2019 to June 2021. The primary inclusion criteria were singleton neonates of Gestational Diabetic Mothers (GDM) (diabetes detected after 20 weeks of gestation) and Overt Diabetes Mellitus (ODM) defined under White's classification (known to be diabetic before the onset of pregnancy or detected in the initial visits). The parameters assessed were the frequency of distribution of hypoglycaemia, hypocalcaemia, and hyperbilirubinemia among the neonates of DM. Statistical analysis was done using Fisher's exact test and Student's t-test.

Results: Among the 130 neonates, the majority of the mothers had GDM 111 (85.4%) than ODM 19 (14.6%). The majority were delivered by normal vaginal delivery 67 (51.5%). 10 (7.7%) of NDMs had a birth weight >4000 g. Significant associations were noted between cord Packed Cell Volume (PCV) and the presence of hypoglycaemia (p-value=0.003), hypocalcaemia (p-value=0.0001), and Neonatal Hyperbilirubinemia (NNH) (p-value=0.0001) among NDMs.

Conclusion: Hypoglycaemia, hyperbilirubinemia, and hypocalcaemia were common complications noted in NDMs.

Keywords: Gestational diabetes mellitus, Hypocalcaemia, Hypoglycaemia, Neonatal hyperbilirubinemia

INTRODUCTION

Diabetes Mellitus (DM) is a chronic metabolic disorder characterised by an absolute or relative insulin deficiency, leading to an increased glucose concentration. DM in pregnancy is associated with very high perinatal mortality and morbidity [1,2]. The significance of DM during pregnancy lies in the fact that around 3-5% of pregnant women have a diabetogenic state, manifesting with abnormal carbohydrate metabolism [2]. Gestational Diabetes Mellitus (GDM) is defined as carbohydrate intolerance of unpredictable severity, first noticed during pregnancy, and accounts for about 90% of cases among these women. The classification system developed by Priscilla White [2] categorises mothers as those known to have diabetes before pregnancy as pregestational or ODM, and those diagnosed during pregnancy as GDM [2-4]. The HAPO study (Hyperglycaemia and Adverse Pregnancy Outcomes) demonstrated that the risk of all adverse outcomes (such as cardiac defects, neural tube defects, renal anomalies, caudal regression syndrome/sacral agenesis) correlates with maternal glycaemia at 24-28 weeks of gestation in a linear association [5].

The NDM is vulnerable to complications such as respiratory distress syndrome, metabolic issues like hyperglycaemia, hypocalcaemia, polycythaemia, hyperbilirubinemia, hyper viscosity syndromes, hypertrophic cardiomyopathy, and congenital malformations [6]. Neonatal polycythaemia, defined as a venous haematocrit ≥65% (0.65), is common in NDMs. It is due to chronic hypoxia, leading to an increase in erythropoietin and consequently an increase in red cell production. By increasing blood viscosity, polycythaemia can cause abnormalities in circulation in the end organs and has varied presentations involving all major systems [7]. Previous studies by Krishnan L and Rahim A, and Shohat M et al., mentioned that neonatal polycythaemia is seen in one-third of NDMs [7,8]. Most cases of polycythaemia are classified as active (increased fetal erythropoiesis) or passive (erythrocyte transfusion) polycythaemia. Polycythaemia can present with neurologic, cardiopulmonary, gastrointestinal, and metabolic symptoms [9,10]. This study was conducted to assess the association between cord blood haematocrit and neonatal outcomes among NDMs.

MATERIALS AND METHODS

This cohort study was conducted at Amala Institute of Medical Sciences (AIMS), Thrissur, Kerala, India, from December 2019 to June 2021. The study was initiated after Institutional Ethics Committee (IEC) approval via letter no. 30/IEC/19/AIMS-12 dated 21-11-2019.

Inclusion criteria: *Singleton NDMs - diabetes detected after 20 weeks* of gestation and overt diabetes, as defined under White's classification [2] were included in the study.

Exclusion criteria: NDMs with medical complications such as heart disease and renal disease, pregnancy-induced hypertension, eclampsia, and sepsis. Gestational age less than 37 weeks were excluded from the study.

Sample size calculation: The sample size was calculated as 130 (with a prevalence of 43.7% of polycythaemia) [10]. The sampling technique used was consecutive sampling, and the sampling tool used in the present study was the proforma.

Study Procedure

A proforma was used to record the history, findings of the physical examination, and investigations. After obtaining informed consent from the parents of the neonates or the guardian, further details were recorded: maternal details such as parity, age at conception, gestational age, any previous stillbirths, abortions, and mode of delivery were also noted.

After delivery, each neonate was assessed for weight and gestational age. A physical examination was conducted to look for any dysmorphism and congenital anomalies. Macrosomia was defined as weight above the 90th percentile {Large for Gestational

Age (LGA)] [11,12]. Cord blood PCV was sent, and a complete haemogram was performed at 24 hours. Blood glucose levels were checked at 1, 2, 3, 6, 12, 24, 36, and 48 hours using glucostix, as per the Neonatal Intensive Care Unit (NICU) protocol.

Transcutaneous bilirubin levels were monitored according to the NICU protocol, and serum bilirubin levels were assessed accordingly. Hypoglycaemia is defined as a blood glucose level below 40 mg/dL. Hypocalcaemia is defined as a total serum calcium level below 8 mg/dL (2 mmol/L) or ionised calcium below 4.4 mg/dL (1.1 mmol/L for term neonates) [12].

In clinically indicated cases, a chest X-ray was performed. Echocardiography was conducted for all babies. The distribution of hypoglycaemia, hypocalcaemia, NNH, and Congenital Heart Disease (CHD) among neonates with GDM and overt diabetes was noted and analysed. The distribution of cord PCV among the above parameters was also studied. Cord PCV was compared among modes of delivery and among sizes of neonates.

STATISTICAL ANALYSIS

The data were analysed using the Statistical Package for the Social Sciences (SPSS) version 23.0. The frequency distribution of hypoglycaemia, hypocalcaemia, and hyperbilirubinemia among neonates with gestational DM was noted. Data were analysed using the Fisher's exact test and Student's t-test for statistical significance.

RESULTS

In the present study, mothers with GDM and ODM exhibited varied presentations. GDM mothers had a higher gestational age of 38.4±1.6 weeks compared to ODM mothers, who had a gestational age of 37.9±0.6 weeks, with similar parity. The mean age of mothers with ODM (34.6±3.4 years) was higher than that of mothers with GDM (32.7±5.9 years). Within the study populations, none of the mothers experienced stillbirths, and 16 mothers had previous abortions [Table/Fig-1].

Characteristics	GDM-111-(85.4%)	ODM-19-(4.6%)
Age of mother (years), Mean±SD	32.7±5.9	34.6±3.4
Gestational age (weeks) Mean±SD	38.4±1.6	37.9±0.6
Parity of mothers Mean±SD	1.9±0.8	1.5±0.7
Mode of delivery		
• LSCS (60) 46.2%	53 (88.3%)	7 (11.7%)
• Assisted (3) 2.3%	3 (100%)	0
• NVD (67) 51.5%	55 (82.1%)	12 (17.9%)
Still birth	0	0
Abortions (16)	11 (68.7%)	5 (31.3%)

[Table/Fig-1]: Distribution maternal parameters among GDM and ODM mothers.
GDM: Gestational diabetes mellitus; ODM: Overt diabetes mellitus; LSCS: Lower segment caesarean section; NVD: Normal vaginal delivery

The majority of the neonates were males, 80 (51.5%), and 50 (38.5%) were females. Distribution of birthweight and gestational age of neonates is shown in [Table/Fig-2]. No significant difference was found when the cord PCV was compared among different modes of delivery [Table/Fig-3]; p-value=0.452). However, a significant difference was observed when the cord PCV was compared with the size of neonates, with a p-value of 0.025 [Table/Fig-4].

In comparing neonatal parameters between neonates from GDM and ODM, it was observed that the mean weight was significantly higher for neonates with ODM (p-value=0.02). A significantly higher proportion of neonates with ODM (42.10%) had hypocalcaemia compared to neonates with GDM (12.61%) (p-value=0.012) [Table/Fig-5]. Congenital Heart Defects (CHD) were found in 29 (22.3%) neonates, with Ostium Secundum Atrial Septal Defect (OS ASD) constituting 24 (18.5%), Patent Ductus Arteriosus (PDA) 10 (7.69%), Ventricular Septal Defect (VSD) 2 (1.5%), and Asymmetrical Septal Hypertrophy (ASH) 2 (1.5%) [Table/Fig-6].

Parameters	n (%)
Birth weight (kg)	
<2.5	10 (7.7)
2.5-4.0	110 (84.6)
>4	10 (7.7)
Size of the baby at birth	
AGA	110 (84.6)
LGA	16 (12.3)
SGA	4 (3.1)

[Table/Fig-2]: Distribution of babies according to the birth weight and size at birth.
AGA: Appropriate for gestational age; LGA: Large for gestational age; SGA: Small for gestational age

Cord PCV at birth	Mode of delivery			Total	p-value (Fisher's exact test)
	LSCS n (%)	Vaginal n (%)	Assisted n (%)		
<45	9 (15)	5 (7.46)	0	14	0.452
45-50	23 (38.33)	22 (32.84)	1 (33.33)	46	
50-55	14 (23.3)	22 (32.84)	1 (33.33)	37	
55-60	6 (10)	13 (19.40)	1 (33.33)	20	
60-65	6 (10)	5 (7.46)	0	11	
>65	2 (3.33)	0	0	2	
Total	60	67	3	130	

[Table/Fig-3]: Distribution of comparing cord PCV among mode of delivery.

Cord PCV at birth	Size			Total	p-value (Fisher's exact test)
	AGA n (%)	LGA n (%)	SGA n (%)		
<45	12 (10.91)	0	2 (50)	14	0.025
45-50	41 (37.27)	4 (25)	1 (25)	46	
50-55	33 (30)	4 (25)	0	37	
55-60	14 (12.72)	6 (37.5)	0	20	
60-65	9 (8.18)	2 (12.5)	0	11	
>65	1 (0.91)	0	1 (25)	2	
Total	110	16	4	130	

[Table/Fig-4]: Comparing cord PCV among the size of babies.
AGA: Appropriate for gestational age; LGA: Large for gestational age; SGA: Small for gestational age

Parameter		GDM-111 (85.4%)	ODM-19 (14.6%)	p-value (Fisher's exact test)
Mean±SD weight (gm)		3367.8±2.5	3403.33±2.7	0.02
Size of the baby at birth n (%)	AGA-110 (84.6%)	98 (88.29)	12 (63.16)	0.025
	LGA-16 (12.3%)	10 (9.01)	6 (31.58)	
	SGA-4 (3.1%)	3 (2.7)	1 (5.26)	
Hypoglycaemia- n (%)	Yes	22 (19.82)	4 (21.05)	0.542
	No	89 (80.18)	15 (78.95)	
Hypocalcaemia- n (%)	Yes	14 (12.61)	8 (42.11)	0.012
	No	97 (87.39)	11 (57.89)	
Hyperbilirubinemia- n (%)	Yes	65 (58.56)	15 (78.95)	0.424
	No	46 (41.44)	4 (21.05)	
CHD n (%)	Yes	22 (19.82)	7 (36.84)	0.077
	No	89 (80.18)	12 (63.16)	

[Table/Fig-5]: Data of distribution of all complications studied.
CHD: Chronic heart disease

Approximately, 46 (35.4%) neonates had a cord PCV between 45-50, and about 37 (28.5%) had a PCV between 50-55. The mean value of cord PCV for both GDM (50.697) and ODM (53.021) was between 50-55.9. There was no significant association between the type of maternal diabetes and cord PCV (p-value=0.138) Table/Fig-7].

CHD	n (%)
No	101 (77.7)
Yes	29 (22.3)
OS ASD	24 (18.5)
PDA	10 (7.69)
ASH	2 (1.5)
VSD	2 (1.5)

[Table/Fig-6]: Distribution of Congenital Heart Disease (CHD).
OS ASD: Ostium secundum atrial septal defect; PDA: Patent ductus arteriosus; ASH: Asymmetrical septal hypertrophy; VSD: Ventricular septal defect

Cord PCV at birth	GDM		Total	p-value (Fisher's exact test)
	Gestational	Overt		
<45	13	1	14	0.318
45-50	40	6	46	
50-55	33	4	37	
55-60	17	3	20	
60-65	7	4	8	
>65	1	1	2	
Total	111	19	130	
	N	Mean±SD		p-value (Student's t-test)
Cord PCV	GDM 111	50.697±6.0166		0.138
	ODM 19	53.021±7.6108		

[Table/Fig-7]: Fisher-exact test and student t-test for cord PCV- diabetes.

When cord PCV was assessed among neonates with different complications, significant associations were noted for neonates with hypoglycaemia (p-value=0.003), hypocalcaemia (p-value=0.0001), NNH (p-value=0.0001). However, PCV was non significantly associated with CHD (p-value=0.302) [Table/Fig-8]. Odds ratios for all four risk factors were calculated and found to be 1.010 for hypoglycaemia, 1.114 for hypocalcaemia, 1.107 for NNH, and 1.045 for CHD. Since the odds ratio was more than 1, all 4 were considered risk factors. The anomalies noted among these 130 neonates were: one neonate had features of congenital hypothyroidism (had umbilical hernia and a hoarse cry), one had polydactyly, one had unilateral talipes, three had bilateral talipes, and one had a congenital adduction deformity of the hip.

		N	Cord PCV Mean±SD	p-value (Student's t-test)
Hypoglycaemia	N	104	50.236±6.0518	0.003
	Y	26	54.242±6.3431	
Hypocalcaemia	N	108	49.947±5.6517	0.0001
	Y	22	54.375±7.0499	
NNH	N	50	48.134±5.7538	0.0001
	Y	80	52.851±5.9590	
CHD	N	101	50.731±5.4511	0.302
	Y	29	52.103±8.6567	

[Table/Fig-8]: Calculating p-value using students t-test for all the four complications.
NNH: Neonatal hypercalcitubinemia, with hypoglycaemia (p=0.003 CHD: Congenital heart disease

DISCUSSION

Diabetes Mellitus (DM) is a chronic disease associated with maternal and perinatal morbidity and mortality. The associated polycythaemia in NDMs can result in neurological, cardiopulmonary, gastrointestinal, and metabolic symptoms. This study was conducted to assess the association between cord blood haematocrit and neonatal outcomes among Infants of Diabetic Mothers (IDMs). In this study, the majority of the mothers had GDM (111 (85.4%) compared to mothers with ODM (14.6%). A significant association was found between cord haematocrit levels and neonates with hypoglycaemia (p-value=0.003), hypocalcaemia (p-value=0.0001), and Neonatal Hypoglycaemia (NNH) (p-value=0.0001).

The study highlighted a significant association between cord haematocrit levels and the size of the babies (p-value=0.025). In a study by Senthilkumar KM and Shanthi R, the incidence of LGA babies was 7.9% among NDMs [13]. In this study, the mean value of cord haematocrit for both GDM (50.697) and ODM (53.021) fell between 50-55.9. Another group of researchers in the subcontinent, namely Cetin H et al., found that neonatal venous haematocrit was higher (57.65±5.73) in Neonatal Diabetes Mellitus (NNDM) compared to controls (47.15±1.95) [14].

The present study observed some congenital anomalies such as polydactyly, congenital talipes equinovarus, and congenital adduction deformity of the hip. The most common heart disease observed was OS ASD. A study by Turunen R et al., showed an incidence of ASD, Transposition of the Great Arteries (TGA), and complex heart anomalies among neonates of mothers with diabetes [15]. In this study, no mortality was reported, which may be attributed to the small sample size.

[Table/Fig-9] illustrates a comparison of similar studies from the literature with the findings of the present study [9,13,16].

The selection of mothers based on the predetermined inclusion criteria is a strength of present study. Future strategies should focus on the early diagnosis of ODM, proper screening of mothers with risk factors for ODM and GDM such as hormonal disorders, overweight, sedentary lifestyles, nutritional habits in the family, and the psychosocial well-being of these mothers, all of which may influence the neonatal outcomes of their babies.

S. No.	Author's name and year	Place of study	Number of subjects	Objective	Parameters assessed	Conclusion
1.	Mahmood CB and Kayes MI, 2008 [9]	Chittagong, Bangladesh	52 infants of diabetic (overt and gestational) mothers	To evaluate the problems and immediate outcome of IDMs in early neonatal period and to compare the results between infants of gestational and pre gestational (Overt) diabetic mothers	21% of NDMs had birth weight >4000 g 23% developed perinatal asphyxia 23% developed hypoglycaemia 66% of NDMs had hypoglycaemia and were symptomatic 19.2% had hypocalcaemia Polycythaemia was higher in infants of GDMs (25.8%) 11 NDM were macrosomic, One expired within day 1	1. Perinatal asphyxia, hypoglycaemia, hypocalcaemia, polycythaemia were the major complications top the list. 2. Authors suggested planned pregnancy to reduce the morbidity and mortality.
2.	Senthilkumar KM and Shanthi R, 2020 [13]	Chennai, Tamil Nadu	566, All infants born to diabetic mothers during the study period	To study the clinical profile and outcome of the IDMs	16.25% mothers had pregestational diabetes mellitus and 83.75% were GDM mothers Prematurity was seen in 15.2% neonates and 7.9% were LGA 9% of the neonates had symptomatic hypoglycaemia. Hyperbilirubinemia was most common (29% of babies) CHD was seen in 7.8% neonates	1. Authors suggest early detection and optimal management of diabetic. 2. Early recognition and management of postnatal complications will reduce the mortality of IDMs.

3.	Gopal G, 2014 [16]	Mysore, Karnataka, India	69 neonates born to diabetic mothers	To study the clinical, metabolic and haematological profile in IDMs and to compare the neonatal outcome in GDM and pregestational (overt) diabetic mothers	71.01% had GDM, 28.99% had ODM Hypoglycaemia was the most common complication seen in 73.91% neonates Polycythaemia was seen in 60.80% neonates 17.40% of neonates had CHD	1. Hypoglycaemia and polycythaemia remain the most common biochemical and haematological abnormality respectively. CHD forms a major proportion in IDMs. 2. Mortality rate was higher in IDMs of GDMs.
4.	Present study, 2024	Thrissur, Kerala, India	130 babies infants of diabetic (Overt and gestational) mothers	To assess the association between cord blood haematocrit and neonatal outcome among NDMs	20% developed hypoglycaemia, 16.92% had hypocalcaemia, hyperbilirubinemia was present in 61.5% neonates Congenital Heart Disease (CHD) was present in 22.30% neonates No mortality was seen	1. Hypoglycaemia, hyperbilirubinemia and hypocalcaemia are common complications in NDMs. 2. Serially monitoring blood haematocrit and early detection of complications would surely reduce the neonatal mortality and neonatal morbidity in NDMs.

[Table/Fig-9]: Similar studies from literature [9,13,16].

Limitation(s)

Proper hydration and ensuring adequate breastfeeding for the neonate during the first days of newborn life will influence the neonatal haematocrit values. Therefore, many factors can contribute to complications that may not necessarily be attributed to the initial cord blood sample and value. Sample size was also one of the limitation in the present study.

CONCLUSION(S)

The cord blood haematocrit showed a strong association with the occurrence of complications in NDMs, such as hypoglycaemia, hyperbilirubinemia, and hypocalcaemia. Serially monitoring blood haematocrit and early detection of complications would surely reduce the neonatal mortality and neonatal morbidity in NDMs.

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PARTICULARS OF CONTRIBUTORS:
1. Postgraduate Scholar, Department of Paediatrics, Amala Institute of Medical Sciences, Thrissur, Kerala, India.
2. Professor, Department of Paediatrics, Amala Institute of Medical Sciences, Thrissur, Kerala, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Menon Narayanankutty Sunilkumar,
Amala Medical College Quarters, Chaithanya, Flat No. 13, Amala Nagar PO, Thrissur-680555, Kerala, India.
E-mail: sunilsree99@gmail.com

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AMALA INSTITUTE OF MEDICAL SCIENCES THRISSUR

Betsy

Dr. BETSY THOMAS
MD, FRCOG, DNB, MICOG
PRINCIPAL
AMALA INSTITUTE OF MEDICAL SCIENCES
AMALA NAGAR, THRISSUR-680 555