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Morbidities among babies of diabetic mothers with variable maternal glycemic control

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Abstract

Background and objectives: Diabetes in pregnancy is associated with an increased risk of complications in both the mother and the fetus. Early diagnosis by screening of pregnant women between 24 to 28 weeks of gestation with proper control of diabetes is essential to reduce these adverse neonatal outcomes. This study aims to determine morbidities in infants of diabetic mothers with variable maternal glycemic state in comparison to infants of non-diabetic mothers. **Methods:** A cross-sectional study (with a comparison group) was carried out at Maternity Teaching Hospital in Erbil City, Kurdistan region, Iraq over 6 months period. Fifty neonates of diabetic mothers were compared with 50 neonates of non-diabetic mothers, matched for gestational age and birth weight. Screening and certain investigations, such as blood glucose, serum calcium, total serum bilirubin, Echocardiography were done for both groups. **Results:** Majority of the mothers (72%) had gestational diabetes. Among various complications found in infants of diabetic mothers, hypoglycemia was the most common one (56%) which was significantly higher than that among infants of non-diabetic mothers (26%). Congenital heart disease was also significantly higher in infants of diabetic mothers (36%) compared to infants of non-diabetic mothers (4%). Conclusions: Morbidities like hypoglycemia,,polycythemia, and congenital anomalies are more common among babies of diabetic mothers when compared to those of non-diabetic mothers, and they are the most common complications observed.

Key words: Hypoglycemia, Maternal diabetes ,Newborns of diabetic mothers.

Introduction

Diabetes is one of the most common medical complications in pregnancy and refers to a group of metabolic disorders that share the common phenotype of hyperglycemia[1]. It is now estimated that 3-8% of all pregnancies are complicated by diabetes that may either antedate pregnancy (pre-gestational diabetes) or may be detected for the first time during pregnancy (gestational diabetes) [2]. Infants of diabetic mothers are at high risk of periconceptional, fetal, neonatal and long term complications[3].

The classic presentation of an infant of a poorly controlled diabetic mother is macrosomia; which is the result of biochemical events along the maternal hyperglycemia-fetal hyperinsulinemia pathway. It occurs in more than 25% of diabetic pregnancies[4]. Other morbidities are hypoglycemia, hypocalcemia, hypomagnesemia, respiratory distress, hyperbilirubinemia, and congenital malformations[5]. Major congenital anomalies are between three and five times more common in pregnancies with pre-gestational diabetes than in the population[6].

It has been shown that each year 800 babies are born in the United States with diabetes-associated anomalies. Of these congenital anomalies, cardiac malformations (ventricular or atrial septal defect, transposition of the great vessels, truncus arteriosus, double outlet right ventricle, tricuspid atresia, coarctation of the aorta) and lumbosacral agenesis are the most common. Additional anomalies include neural tube defects, hydronephrosis, renal agenesis and dysplasia, duodenal or anorectal atresia, situs inversus, double ureter, and holoprosencephaly. High blood glucose in the mother is the main teratogen as it interrupts electron transport in the mitochondria causing free oxygen radicals. Hyperglycemia also reduces antioxidants in the cells[7, 8].

These higher rates of congenital anomalies in infants of diabetic mothers (IDMs) suggest a strong association be-

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tween congenital anomalies and maternal glycemic control. Although most of the morbidity and mortality data for the IDMs improved with time, congenital anomalies remain a significant unresolved problem[9].

In view of high mortality and morbidity associated with babies born to diabetic mothers, the present study was aimed to determine metabolic complications (hypoglycemia, hyperbilirubinemia, polycythemia, hypocalcemia), respiratory complications and congenital anomalies among IDMs with variable maternal glycemic state as well as comparing the incidence of these morbidities with infants of non-diabetic mothers who were matched for gestational age and birth weight.

Patients and methods

A cross-sectional study (with a comparison group) was conducted during 6 months period, from 1st August 2018 to 1st February 2019, including 100 neonates who were delivered at Maternity Teaching Hospital in Erbil City, Kurdistan region, Iraq.

The protocol of the study was approved by the Research Ethics Committee of Kurdistan Board for Medical Specialties. Informed Consent was taken from the parents of the newborns. A total of 100 neonates, 50 infants of diabetic mothers and 50 infants of non-diabetic mothers, who were matched for their gestational age and birth weight and admitted during the same period of time, were compared. Babies of mothers with pre-gestational diabetes mellitus (Type 1 and Type 2) and Gestational Diabetes Mellitus (GDM) presented within 72 hours of delivery to the Neonatal Intensive Care Unit were included in the study. Infants whom their mothers had other pregnancy-related complications (hypertension, preeclampsia, and eclampsia), chronic medical illnesses (heart disease, hypothyroidism, etc) and acute or chronic infections were excluded from the study. The mothers were grouped into pre-gestational diabetes and GDM.

Diagnosis of GDM was made according to the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria[10]. Data that was obtained from the mothers included: age, parity, mode of delivery, type of DM, type of treatment received to control DM, and their glycemic control. Maternal blood glucose and HbA1c levels were noted during the first trimester in mothers with pre-gestational diabetes and during the second and/or third trimester for both pre-gestational and GDM patients. According to the American Diabetes Association guideline 2018, mothers with an HbA1c level of ≤6.5% were labeled as having satisfactory glycemic control, whereas those with HbA1c level of >6.5% were grouped as having unsatisfactory glycemic control[11].

Complete physical examination of the newborns was performed. Those newborns who weighed 4 kg or more were classified as macrosomic[7]. Investigations for newborns, such as blood sugar, serum Calcium, Total Serum Bilirubin (TSB), Packed Cell Volume (PCV) and echocardiography for all cases and Chest X-ray in selected cases (those with respiratory distress) were done. Hypoglycemia was defined according to Pediatric Endocrine Society guideline[12]. Diagnosis of hyperbilirubinemia was made based on the need for commencing treatment according to the American Academy of Pediatrics guideline[13].

Hypocalcemia was defined as serum calcium < 8 mg/dl in term and <7 mg/dl in preterm infant, and polycythemia was defined as PCV ≥65%[4, 14]. Data was analyzed using the Statistical Package for Social Sciences (SPSS, version 22). Chi-square test of association was used to compare proportions. Fisher's exact test was used when the expected count of more than 20% of the cells of the Table was less than 5. A p-value of ≤ 0.05 was considered statistically significant.

Results

Thirty percent of the diabetic mothers were primiparous compared with 44% of the non-diabetic mothers (p-value = 0.147).The rate of cesarean delivery was 54% for IDMs compared with 46% (32% elective and 14% emergency) of the non-diabetic mothers (p-value = 0.005), Table 1.

Table (1): Parity and mode of delivery of women.

Characteristics	Diabetic		Non-diabetic		Total		
	No.	(%)	No.	(%)	No.	(%)	p-value
Parity							
Primiparous	15	(30.0)	22	(44.0)	37	(37.0)	
Multiparous	35	(70.0)	28	(56.0)	63	(63.0)	0.147
Mode of delivery							
Vaginal	23	(46.0)	27	(54.0)	50	(50.0)	
Elective	27	(54.0)	16	(32.0)	43	(43.0)	
Emergency cesarean	0	(0.0)	7	(14.0)	7	(7.0)	0.005
Total	50	(100.0)	50	(100.0)	100	(100.0)	

The type of diabetes among the majority (72%) of the patients was GDM. The glycemic control in the first trimester was unsatisfactory for all of the diabetic women, while it was unsatisfactory among 52% of diabetic women in the second/ or third trimester, Table 2.

Table (2): Type and control of diabetes among diabetic women.

Characteristics	No.	(%)
Type of diabetes		
Pre-gestational type1	5	(10.0)
Pre-gestational type 2	9	(18.0)
GDM	36	(72.0)
Glycemic control in first trimester*		
Satisfactory	0	(0.0)
Unsatisfactory (Mean $\pm$ SD = 8.91 $\pm$ 0.53)	14	(100.0)
Glycemic control in second/third trimester		
Satisfactory (HbA1c, Mean $\pm$ SD 6.22 $\pm$ 0.15)†	24	(48.0)
Unsatisfactory (HbA1c, Mean $\pm$ SD 7.97 $\pm$ 0.55)†	26	(52.0)
Total	50	(100.0)

*There are only 14 cases with pre-gestational diabetes.
†Difference between means (p-value < 0.001).

Twelve percent of the neonates of each group were preterm (p-value > 0.999) and body weight of 48% of neonates of each group was more than 4000 grams (p-value > 0.999); this indicates that both groups were matched for gestational age and birth weight (p-value is not significant),Table 3.

Table (3): Gestational age and neonatal birth weight of the two study groups.

Characteristics	Diabetic		Non-diabetic		Total		
	No.	(%)	No.	(%)	No.	(%)	p-value
Gestational age							
< 37	6	(12.0)	6	(12.0)	12	(12.0)	
37-42	44	(88.0)	44	(88.0)	88	(88.0)	> 0.999
Weight							
≤ 2500	5	(10.0)	5	(10.0)	10	(10.0)	
2500-4000	21	(42.0)	21	(42.0)	42	(42.0)	
> 4000	24	(48.0)	24	(48.0)	48	(48.0)	> 0.999
Total	50	(100.0)	50	(100.0)	100	(100.0)	

The mean rank of the APGAR score in the first minute of life of the infants of non-diabetic mothers was 54.65, which was higher than the APGAR score of babies of the diabetic mothers (p-value = 0.138). The same can be applied for the APGAR score in the fifth minute of life (p-value = 0.337) as the difference was not significant, Table 4.

Table (4): APGAR score in the first and fifth minutes of life in both study groups

APGAR score	Mean	Median	Minimum	Maximum	Mean rank	p-value *
APGAR 1						
Diabetic	7.20	8	4	9	46.33	
Non-diabetic	7.62	8	5	9	54.65	0.138
APGAR 5						
Diabetic	7.62	8	5	9	47.83	
Non-diabetic	7.86	8	6	9	53.17	0.337
*By Mann Whitney test.						

Hypoglycemia was found in 56% of the IDMs which was significantly higher than the rate (26%) among the infants of non-diabetic mothers (p-value = 0.002). More than one quarter (30%) of the IDMs had polycythemia, while none of the control group had polycythemia (p-value < 0.001). Hypocalcemia was found in 30% of the IDMs compared with 6% of the infants of non-diabetic mothers (p-value=0.002). No significant difference was detected between the two groups regarding respiratory complications (p-value = 0.641), Table 5.

Table (5): Laboratory and respiratory complications of the two study groups.

Investigations	Diabetic		Non-diabetic		Total		
	No.	(%)	No.	(%)	No.	(%)	p-value
Blood sugar							
Hypoglycemia	28	(56.0)	13	(26.0)	41	(41.0)	
Normal	22	(44.0)	37	(74.0)	59	(59.0)	0.002
TSB							
Normal	26	(52.0)	35	(70.0)	61	(61.0)	
High	24	(48.0)	15	(30.0)	39	(39.0)	0.065
PCV							
Normal	35	(70.0)	50	(100.0)	85	(85.0)	
Polycythemia	15	(30.0)	0	(0.0)	15	(15.0)	< 0.001
Calcium							
Low	15	(30.0)	3	(6.0)	18	(18.0)	
Normal	35	(70.0)	47	(94.0)	82	(82.0)	0.002
Respiratory complications							
No respiratory Complication	26	(52.0)	31	(62.0)	57	(57.0)	
RDS	12	(24.0)	8	(16.0)	20	(20.0)	
TTN*	8	(16.0)	7	(14.0)	15	(15.0)	
Pneumonia	4	(8.0)	4	(8.0)	8	(8.0)	0.641**
Total	50	(100.0)	50	(100.0)	100	(100.0)	

* Transient tachypnea of newborn **By Fisher's exact test

Table (6): Congenital anomalies among neonates of diabetic and non-diabetic mothers.

Congenital anomalies	Diabetic		Non-diabetic		Total		
	No.	(%)	No.	(%)	No.	(%)	p-value
Normal(no anomalies)	30	(60.0)	48	(96.0)	78	(78.0)	
PDA	3	(6.0)	1	(2.0)	4	(4.0)	
VSD	3	(6.0)	1	(2.0)	4	(4.0)	
TGA	1	(2.0)	0	(0.0)	1	(1.0)	
Septal hypertrophy	11	(22.0)	0	(0.0)	11	(11.0)	
Neural tube defects	1	(2.0)	0	(0.0)	1	(1.0)	
Cleft palate	1	(2.0)	0	(0.0)	1	(1.0)	< 0.001*
Total	50	(100.0)	50	(100.0)	100	(100.0)	

*By Fisher's exact test.

Discussion

Seventy percent of the diabetic mothers were multiparous; this is similar to the findings of Ahmed et al that revealed a rate of 68.5%[15]. Fifty-four percent of the IDMs delivered their babies by elective caesarian section. This high rate of operative delivery, similar to the study of Kheir et al (60%), may be related to the high incidence of macrosomia in the IDMs and their matched controls[16]. Gestational diabetes was observed in 72% of the diabetic mothers and pre-gestational diabetes in 28%, in comparison to the findings of a recent study by Al-Nemri et al which demonstrated a rate of 84.5% and 15.5 %, respectively[17]. The glycemic control in the first trimester was unsatisfactory (mean: 8.91+0.53) for all pre-gestational diabetic women, while unsatisfactory rate (mean: 7.97 +0.55) for both pre-gestational and GDM was 52% in the second/third trimester. These findings confirmed poor diabetic control in more than half of the diabetic mothers which seems to be totally in contrast with the results of Al-Nemri et al and Anjum et al[17, 18]. A variety of neonatal complications were recorded in IDMs but the most common complication was hypoglycemia, occurring in significantly higher proportion than in the infants of non-diabetic mothers. Hypoglycemia has been identified as a marker of poor glycemic control. It was seen in 56% of the IDMs, which is comparable to the result of Opara et al with a hypoglycemia rate of 63.8% [19]. Macrosomia was found in 48% of the IDMS. Studies by Hussain M et al and Shirazi et al have found macrosomia in 40% and 16%, respectively, of IDMS[20, 21]. The incidence of jaundice was 48% among IDMs; however, it was not significantly higher than in the control group, probably because the matched control group had been admitted for jaundice with other risk factors such as blood group incompatibilities. This is in agreement with the findings of Ashraf et al who showed a hyperbilirubinemia rate of 52.2%, but it is in contrast to the result of Bheeman et al in which a lower incidence of jaundice (18%) was recorded [22, 23]. Near one-third (30%) of IDMs had polycythemia, while this complication was not found in the control group. This is similar to the study by Anjum et al, and it is in contrary with the study of Alam et al in which polycythemia was found in 35% and 8%, respectively[18, 24].

Thirty percent of the neonates of the diabetic mothers had hypocalcemia, which was significantly higher than the rate in infants of the control group. This is comparable with the study of Bheeman et al which showed a rate of 12.5% [23].

Respiratory distress was found in about half (43%) of the whole sample. The difference between the two groups was not statistically significant. RDS was the most common respiratory complication that recorded 50%; this may be related to higher insulin levels that interfere with the lung's maturity secondary to the deficiency in saturated phosphatidylcholine in the amniotic fluid. This is not closely related to the result of Kadhum et al which found RDS in only 35% of the cases 25. Transient tachypnea of newborn was also the second most common respiratory complication in IDMs with a rate of 33.3%; the cause of this complication is expected to be due to high rate of caesarian delivery which on its own is a known risk factor.

The increased risk of congenital anomalies in IDMs was predominantly for a variety of congenital heart diseases (36%), these findings were supported by the study of Shirazi et al with a rate of 32%, whereas Husain M et al have found lower incidence of congenital heart disease (4.7%) [21,20]. The most common cardiac anomaly was septal hypertrophy (24%), this is similar with the result of Akbariasbagh et al that found septal hypertrophy in 25.7% of cases[26]. Except for a single case of cleft palate and a case of myelomeningocele, no other congenital anomalies were observed among IDMs. This could be due to a higher prevalence of cardiovascular anomalies compared to the anomalies in other organ systems. All these complications can be prevented by raising awareness about DM and the increased risk of adverse pregnancy outcomes related to diabetes as well as proper treatment of diabetic women during pregnancy.

Conclusions

Unsatisfactory glycemic control was observed primarily during the first trimester in mothers with pre-gestational diabetes. Morbidities like hypoglycemia, polycythemia, and congenital anomalies were found to be more common among babies of diabetic mothers when compared to those of non-diabetic mothers. Because of the high frequency of these complications, screening for hyperglycemia of mothers early in pregnancy, referring women with

unstable metabolic control to specialized diabetes centers and meticulous monitoring of babies will improve both pre- and postnatal outcomes.

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