Original Article

Neonatal Outcome of Diabetic Pregnancy

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Objective: To observe and evaluate the significance of the complications seen in Infants of diabetic mothers
Study design: Observational, prospective.
Place and duration of study: Neonatology department of Pakistan Institute of Medical Sciences [PIMS], a tertiary care teaching hospital. The study period is from March 2009 to February 2010
Materials and Methods: All the infants born to the diabetic mother were admitted to the neonatal care department for evaluation. Maternal history was taken and detailed physical examination of these babies was performed with special emphasis on the congenital anomalies and birth injuries. Laboratory investigations like blood sugar, serum calcium, hematocrit and echocardiography was done in all babies but serum bilirubin, X-ray chest and ECG was done where ever indicated. Results were analyzed using statistical package for social sciences (SPSS) version 11
Results: A total number of 11328 mothers were delivered out of which only 142 babies were born to the diabetic mothers. The median age of diabetic mothers was 29 years which included 20% primigravida and 35% multigravida mothers. Gestational diabetes was seen in 84% while pregestational diabetes was seen in 16%. Out of 142 newborn IDMs, 58% were male and 42% were female.
Hypoglycaemia at birth was documented in 28% of cases and hypocalcaemia was seen in 25% of cases. Asymmetrical septal hypertrophy [ASH} and macrosomia were strongly associated with hypoglycaemia. [p value= 0.001] .The low birth weight babies were 23% while the macrosomic babies were 16%. Birth injuries were seen in 13% in which the cephalhaematoma was seen in 9 cases and almost all injuries were due to macrosomia. Mothers with Glycosylated haemoglobin [HbA1c] of more than 8.5% were 58%. There was a strong association of high levels of HbA1c levels with hypoglycaemia, macrosomia, LGA and ASH. Congenital anomalies were observed in 34% cases. Cardiac anomalies were predominant and constituted about 94% [n=45] of all the congenital anomalies. ASH of the heart was seen in 32 of the total 45 cases of heart anomalies
Respiratory distress syndrome [RDS] was seen in 11 cases. Resuscitation at birth was required in 11% but significant asphyxia was seen in only 2 cases. It was encouraging to note that none of our IDM died because of complications.
CONCLUSION: The study showed a high percentage of neonatal complications due to poor glycemic control in pregnancy so a good glycemic control during the pregnancy is advocated. The deliveries should be attended by the paediatric team to minimize the morbidity and mortality.

KEY WORDS: *Gestational diabetes, Macrosomia, HbA1c, congenital heart malformations, hypoglycaemia*

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Introduction

Diabetes is a fairly common medical complication of pregnancy. It has been estimated that 0.2% to 0.3 % of all pregnancies are complicated by pre-existing diabetes mellitus and another 1-5 % represent gestational diabetes mellitus.[1] The Gestational diabetes mellitus (GDM) is seen in almost 80%, whereas around 12-15 % has pregestational diabetes (PGD)[2] Our local data from Karachi also reported an 8% prevalence of GDM.[9] The prevalence of pregestational DM in Pakistan has been estimated to be

10% -14% in various regions of the country.[3]

The World Health Organization estimates that the number of people with diabetes mellitus (DM) will increase from 150 million to 333 million by the year 2025. This alarming increase in the prevalence of DM will occur mainly in the developing regions of the world and the child bearing age would be most affected.[6]

In the developed world the perinatal mortality of infants of diabetic mothers (IDMs) has declined dramatically from 250 per 1000 live births in the 1960s to almost 20 per 1000 live births in the 1980.[9] This dramatic decrease in the mortality is because of the advances in the management of diabetes in the pregnancy. However in our part of the world the situation is not encouraging.[5] Although many infants of diabetic mothers (IDMs) have an uneventful perinatal course, there is still an increased risk of complications including congenital malformations, macrosomia, hypoglycaemia and intrapartum asphyxia.[10] Long term complications include an increased rate of adolescent obesity, impaired glucose tolerance or diabetes mellitus, and subtle neuropsychological dysfunctions.[8]

Studies have shown that strict control of maternal glucose during pregnancy has a favourable influence on the perinatal outcome[10] .The objective of our study was to observe the range of complications and their significance in infants of diabetic mothers in our tertiary care setup.

Materials and Methods

This study was conducted in the department of Neonatology of the Pakistan Institute of Medical Sciences for a period of one year from March 2009 to February 2010. All deliveries of diabetic mothers were attended by an experienced paediatric registrar who admitted all babies for evaluation and management. The antenatal and natal history was recorded in the performa designed for this study. The maternal diabetes was classified according to the White's classification. [11] The mothers were grouped as Pregestational diabetics (PGD) and Gestational diabetics. (GDM). The mothers with Glycosylated Hb [HbA1c] levels of less than 8.5% were labelled as having a satisfactory glycemic control whereas the mothers with HbA1c levels of more than 8.5% were grouped as having unsatisfactory glycemic control.[15] The APGAR scores were assessed and recorded on the chart. In case of birth asphyxia, the degree of Hypoxic-Ischemic encephalopathy [HIE] was classified according to the Sarnat and Sarnat classsication.[12]

Babies were examined in detail with special emphasis on the congenital anomalies and the birth trauma. Anthropometric measurements were performed and the babies were classified as large for gestational age (LGA), appropriate for gestational age (AGA) and small for gestational age(SGA) according to the centile charts. Babies with weight of > 4000 Gms were labelled as Macrosomic and babies with birth weight < 2500 Gms were labelled as Low birth weight [LBW].

The laboratory investigations included serial blood sugars initially half hourly for 2 hours and then at 4,8,12 and 24 hours if required. Serum calcium was done at 6 and 24 hours of birth. Hypoglycaemia was labelled when the blood sugar was less than 40mg/d[13] and hypocalcaemia was labelled when the serum calcium was less than 7.5mg/dL[14] Complete blood count including hematocrit was done in every IDM but serum bilirubin was done only in jaundiced babies. A venous hematocrit level of more than 65 was labelled as polycythemia where as hyperbilirubinemia was labelled when the serum bilirubin was more than 15 mg/dL[20]. Doppler echocardiogram was done in all cases but Chest X ray and electrocardiogram was done in selected cases. On echocardiography, septal hypertrophy was diagnosed when the interventricular septum was is ≥6 mm.[7]

In case of any finding a second independent opinion was sought from the paediatric radiologist or the paediatric cardiologist. In cases of birth asphyxia ultrasound brain was also done and evaluated by the paediatric radiologist. Infectious screening was done where clinically indicated. All the data was stored and analyzed using software statistical package for social sciences (SPSS) version 11. The variables were converted to categorical variables and then compared using chi- square table.

Results

A total number of 11328 mothers were delivered during this study period. Out of all these deliveries only 142 were diabetic mothers which is 1.25 % of the total deliveries. The youngest diabetic mother was 19 years old and the eldest was 40 years old with a median age of 29 years.

The primigravida mother were 28[20%] while the multigravida mothers were 50[35%]

Diabetic mothers with Gestational diabetes were 119[84%] while pregestational diabetes was seen in 22 mothers [16%]. Among the GDM mothers 19% [23/119] received insulin therapy during pregnancy whereas 81%[96/119] were managed on the diet alone. Among the 23 PGD mothers, only 5 received insulin therapy while 17 were being managed with the oral hypoglycaemic agents. Only one mother belonged to the category of C1 who was insulin dependent since 13 years of age.

Out of 142 newborn IDMs, 82[58%] were male and 60[42%] were female. Delivery by spontaneous vertex delivery was done in 61% [87/142] while 31% [44/142] were delivered by Caesarean Section. Preterm

delivery was observed in 19% [27/142] while the rest were delivered at term.

Hypoglycaemia at birth was documented in 39[28%] of cases and hypocalcaemia was seen in 36[25%] of cases. Low blood sugars at birth were strongly associated with macrosomia, LBW and ASH. Hypoglycaemia was seen 22/32 cases of LBW [p value=0.01], 14/22 cases of macrosomia [p value= 0.03] and in 28/32 cases of ASH [p value= 0.001]. However we could not find any significant association of hypocalcaemia with any factor studied.

Respiratory distress syndrome [RDS] was seen in 11 cases. Out of these five were classified as grade 1, four as grade 2 and two as grade 3. This classification was done by two independent paediatric radiologists. Two of these babies who had grade III RDS were ventilated with a normal outcome. All 11 cases of RDS were born preterm and we could not find any association with any other factor.

It is worth to note that almost all the birth injuries seen were due to macrosomia. The injuries encountered in macrosomic babies were; cephalhaematoma in 9 cases, ocular haemorrhage in 3, brachial plexus injury in 4, clavicle fracture in 2 and facial nerve palsy in one case. Statistically significant finding was the presence of hypoglycaemia in 14 of 22 macrosomic babies [p value=0.03]. Another significant observation was the presence of septal hypertrophy in 9/11 cases of macrosomia [p value =0.01]. Polycythemia was seen in 3 and hypocalcaemia was observed in 5 cases which was not significant. The frequencies of the neonatal complications observed in this series of 142 cases are shown in table I.

Table I: Frequencies of the neonatal complications observed in the series n=142

Complications	PGM	GDM	Total
Hypoglycemia	30	9	39 [27%]
Hypocalcaemia	31	5	36 [25%]
Polycythemia	10	1	11 [8%]
Macrosomia	20	2	22 [15%]
Large for Gestation	38	8	46 [32%]
Small for Gestation	18	8	26 [18%]
Low birth weight	22	10	22 [15%]
Congenital heart anomalies	40	5	45 [32%]
Birth asphyxia	9	2	11 [8 %]
Preterm	24	3	27 [19 %]
Respiratory Distress Syndrome	10	1	11 [8%]

Hypocalcaemia was seen in 36 IDMs [25%]. However we could not find any significant correlation of hypocalcaemia with any of the factors under study. Polycythemia was observed in 11[8%] cases out of which 10 developed hyperbilirubinemia.

Glycosylated haemoglobin [HbA1c] was considered to be the indicator of the Glycemic control of the mother. Mothers with HbA1c of more than 8.5% were 81[58%] while mothers with HbA1c of less than 8.5 % were 61 [43 %]. We found no association of hypocalcaemia, polycythemia or RDS with the levels of HbA1c. However there was a strong association of high levels of HbA1c levels with hypoglycaemia, macrosomia, LGA and asymmetrical septal hypertrophy [ASH] of the heart whereas high levels of HbA1c had no association with the AGA. The incidence of neonatal complications in relation to maternal HbA1c levels is shown in table II.

Table II: Incidence of neonatal complications in relation to maternal HbA1c levels

Complications	Maternal HbA1c <8.5%	Maternal HbA1c >8.5 %	P value
LGA	16/46	30/46	0.001
ASH	4/32	28/32	0.001
Hypoglycemia	8/39	31/39	0.001
Birth Asphyxia	5/14	9/14	0.041
RDS	7/11	4/11	0.158
Polycythemia	3/11	8/11	0.01

P value < 0.05 was considered as statically significant
ASH = Asymmetrical septal hypertrophy of the heart
RDS = Respiratory distress syndrome

Congenital anomalies were observed in 48 [34%] cases. Cardiac anomalies were predominant and constituted about 94% [n=45] of all the congenital anomalies. Asymmetrical septal hypertrophy of the heart was seen in 32 of the total 45 cases of heart anomalies, whereas ventricular septal defect was seen in 5, Patent ductus arteriousus in 4, Transposition of great arteries in 2 and one case each of Atrial septal defect and Tetrology of Fallot . Only one case each of duodenal atresia, anorectal atresia and Lumosacral meningomyelocoele was seen in all 142 babies delivered.

The relationship of various factors to the ASH is shown in table III.

Table III: Relationship of factors with Asymmetrical Septal Hypertrophy

Factors	Ratio	Percent	Significance
Hypoglycemia	23/32	72%	P value 0.01
Hypocalcaemia	9/32	28%	P value 0.63
LGA	19/32	59%	P value 0.03
Macrosomia	8/32	25%	P value 0.48
LBW	7/32	22%	P value 0.38
HbA1c >8.5%	28/32	88%	P value 0.001

P value < 0.05 was considered as statically significant
ASH = Asymmetrical septal hypertrophy of the heart

Resuscitation at birth was required in 15[11%] cases. Fortunately 8/15 cases developed HIE of grade I and 3/15 developed grade II HIE. None of them required artificial ventilation and none bled intracranially. We had no death of IDM during the study period.

Discussion

Historically, the perinatal mortality rates due to diabetic pregnancy were as high as 65%, but after the development of specialized maternal and neonatal care, the outcome of diabetic pregnancies has improved tremendously. [2] Unfortunately, in our set up there is still a high perinatal mortality among infants of diabetic mother due to poor antenatal care, non compliance of therapy and lack of adequate neonatal services.[4] This problem is compounded by the lack of general awareness of the problem.

This descriptive observational study was conducted at a tertiary referral teaching hospital and the objective was to study the neonatal outcomes of diabetic pregnancies in our setup.

In our study the IDMs were only 1.25 % of all the deliveries. This is in conformation with the published data where figures vary from 0.2% to 5%.Asef et al [17] from Lahore have shown an incidence of 5% whereas another study from the same city has shown an incidence of 0.2 %[19]. We have observed that 84% of our diabetic mothers had gestational diabetes while 16% had pregestational diabetes. Studies from our country have shown the same trend[17, 26]. Study from India also shows the same pattern by documenting 86% of GDM and 14 % of pregestational DM. [25]

Although most of the morbidity and mortality data for the IDM has improved with time, congenital anomalies remain a significant unresolved problem. The reported incidence varies from 6 to 30 % [25]whereas our figures from the local data vary from 7.9 % to 25%. A study from Sheikh Zayed hospital noted congenital anomalies in 13% of the IDMs.[21] Among them congenital heart disease was the most common congenital anomaly. Cardiac anomalies are about 5 times more common among the infants of diabetic mothers and the prevalence of asymmetrical septal hypertrophy among IDM is reported as 25-45% worldwide. [16]

In our study congenital anomalies were found in 48(34%) cases out of which cardiac anomalies were seen in 94% [45/48] cases. Among patients with congenital heart disease 32 babies had evidence of ASH which correlates well with the reported incidence in the literature. We found no correlation between the ASH and the presence of hypocalcaemia, polycythemia or birth asphyxia. However, hypoglycaemia was seen in 23 out of 32[72%] infants of ASH which was statistically significant. Another significant association of ASH was with the HbA1c levels of the mother. We have observed that 87% (28/32) cases of septal hypertrophy were associated with maternal HbA1c of more than 8.5%. Like Sardesi et al, [16] we have also found a strong relationship between third-trimester maternal hyperglycaemia and neonatal asymmetric septal hypertrophy, macrosomia, and hypoglycaemia at birth. Various authors have also contributed the poor glycemic control of the diabetic mother and the foetal hyperinsulinemia directly to the septal hypertrophy.[25] We observed that 60 %(19/32) cases of ASH were large for gestational age. A study from Mexico also found an association of ASH with Large infants of diabetic mothers. [7] Our findings are also substantiated by the study from India who also found ASH as a predominant cardiac malformation in the IDMs[25] Literature shows that good glycemic control during pregnancy reduces the incidence of congenital malformations.[22]

Macrosomia, a clinical sign of poor diabetic control is associated with wide variety of adverse intrapartum and perinatal outcomes. It leads to difficult vaginal delivery resulting in birth injury or asphyxia. In our study the macrosomic babies were 15% (22/142) whereas LGA babies were 28 %(40/142). Our local data shows an incidence of 41% from Hyderabad and 35% from Rawalpindi.[26] It was significant to note that almost all the birth injuries occurred in macrosomic babies. Because of the high risks involved an early identification of macrosomia is critical. In our study the growth restricted babies were 18 % which is in accordance with the incidence reported in the literature. A study from Karachi has reported a low incidence of 5% which could be because of the short duration of the study period.[3]

We observed birth asphyxia in 8% of the cases which is accordance with the reported incidence of 8-9%. However, our local studies have reported a higher incidence of 15 -20 % .[23] The low incidence of asphyxia in our study could be because of the simple fact that every delivery was attended by a trained registrar of paediatrics who prevented many cases of birth asphyxia. The same logic can hold true for the low incidence of birth asphyxia reported in the developed world.

We observed Respiratory Distress Syndrome in 8% (11/142) cases. Two of them needed intensive care and fortunately none of them expired. Robert et al have shown that the relative risk of Respiratory Distress Syndrome (RDS) is 5.6 times higher in the IDM compared with infants of nondiabetic mothers even after excluding all specific confounding variables.[24]

A decline in plasma glucose concentration following delivery is characteristic of the IDM, especially among neonates who are macrosomic or whose mothers had poor glycemic control during their

pregnancies. Glycosylated haemoglobin [HbA1c] is considered to be good indicator of the glycemic control of the mother. In our study 58% of the diabetic mothers had HbA1c of more than 8.5%. This level had a significant association with hypoglycaemia, ASH, macrosomia and LGA. The incidence of hypoglycaemia in IDMs is from 30-40 %.[13] We noted hypoglycaemia in 28%(39/124) cases. This hypoglycaemia was directly associated with the levels of HbA1c levels. It was observed that 31/39 cases of hypoglycaemia had a HbA1c levels of more than 8.5%. We also found a significant association of macrosomia and hypoglycaemia. Study from Sheikh Zayed hospital reported hypoglycaemia in 45% of their patients and half of them were asymptomatic. [21]

Hypocalcaemia ranks as one of the important metabolic derangements observed in the IDM.10 We found hypocalcaemia in 25 %(36/142) cases which is in accordance to the published literature. Though Tsang and associates [18] have shown an association of hypocalcaemia with the prematurity and birth asphyxia but we have found no such association.

Polycythemia is observed more frequently in the IDM than in the normal neonate. We found polycythemia in 8 %(12/142) cases out of which 83 % (10/12) developed hyperbilirubinemia. The polycythemia itself is associated with an unsatisfactory glycemic control in late pregnancy. Green and colleagues [20] have also showed an improved maternal glycemic control during late gestation decreased the incidence of neonatal polycythemia. In our study also the polycythemia was associated with the poor glycemic control during late gestation.

Fortunately we have observed no death of the infant of the diabetic mother in our study period. Though this figure is in accordance to the literature reports from the West but the figures from own country are higher. A study from Lahore reported 8% mortality [21] and study from Karachi reported 7.5%. [3] This good survival rate in our study could be due to good neonatal services in our hospital otherwise other factors contributing to the mortality were the same.

Recommendations

The data in our series indicate that there was a high frequency of complications associated with IDMs. Poor glycemic control in the pregnancy led to large for gestation babies with higher frequencies of congenital malformations and birth injuries. It is recommended that regular antenatal visits should be done with special emphases on good glycemic control during pregnancy and early detection of large babies. It has also been observed that the presence of a paediatric registrar has saved many lives by managing the babies in time. Therefore, it is recommended that all deliveries of diabetic mothers should be attended by a senior person trained in paediatrics. The hypoglycaemia in these IDM is usually asymptomatic so prompt recognition and treatment of asymptomatic neonates is necessary to minimize the sequelae. Today we have the knowledge and tools to properly treat both pregestational and gestational diabetes. Therefore, increased education of the general practitioner and the target population regarding early referral of pregestational diabetic mothers and the implementation of screening programs for gestational diabetes will further reduce diabetic pregnancy related morbidity.

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