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PERINATAL AND NEONATAL OUTCOMES AMONG INFANTS OF DIABETIC MOTHERS – COMPARISON OF INSULIN, ORAL HYPOGLYCEMIC AGENT, AND DIET CONTROL

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Abstract

Background: Gestational Diabetes Mellitus (GDM) affects approximately 6.6% of pregnancies worldwide. It is a significant cause of prenatal and newborn morbidity. In developing nations like Pakistan, the management of diabetes during pregnancy remains a challenge.

Methods: A retrospective cohort study was conducted over a period of one year, in a tertiary care hospital of Pakistan. Following the inclusion criteria, a total of 350 newborns (born at ≥ 24 weeks gestation, to mothers with GDM), were enrolled. Primary neonatal outcomes were gestational age, mode of delivery and complications. Complications included: preterm delivery, small for gestational age (SGA), large for gestational age (LGA), macrosomia, respiratory distress syndrome (RDS), transient tachypnea of the newborn (TTN), meconium aspiration syndrome (MAS), hypoglycemia (24 hours after birth), hypocalcemia (first 48 hours of life), polycythemia, hyperbilirubinemia, congenital anomalies, need for neonatal intensive care unit (NICU) and birth injuries. The enrolled infants were then stratified in 3 groups based on the GDM treatment their mothers had received during pregnancy: diet control, oral hypoglycemic agents (OHA), or insulin. Secondary outcomes were the difference of number of complications in infants of diabetic mothers (IDM), in the 3 different groups.

Results: During the study period, 5186 births took place, of which 427 newborns were IDMs. The mean duration of GDM treatment in mothers was 12.8 weeks ± 3.8 weeks in all three groups. Of the 350 babies, 178 (50.9%) were male and 172 (49.1%) were female, with a mean weight of 2.85kg. The incidence of prematurity (defined as gestational age <37 weeks) was 26.6% (n=93), with a mean gestational age of 36.8 weeks ±2.0 weeks. The frequencies of the morbidities under study were as follows: small for gestational age (SGA) 18.9% (n=66), large for gestational age (LGA)

4.0% (n=14), hypoglycemia in first 48 hours of life 20% (n=70), hypocalcemia the first 48 hours of life 4.0% (n=14), hyperbilirubinemia throughout the first week of life 25.7% (n=90), respiratory distress syndrome (RDS) 6.3% (n=22), transient tachypnea of newborn (TTN) 3.4% (n=12), birth asphyxia 2.9% (n=10), meconium aspiration syndrome (MAS) 0.9% (n=3), congenital anomalies 11.7% (n=41), (of which 68.3% (n=28) were cardiac anomalies), birth injury 0.3% (n=1), and babies needing NICU admission 15.7% (n=55), of which. The mortality rate was 1.4% (n=5). All babies with TTN and RDS required, and were given, oxygen (n=34).

Practical Implication: we only included diabetic mothers with GDM and not those who already had Type 1 or 2 DM before pregnancy. Furthermore, our comparison comprises morbidities in neonates of three groups of diabetic mothers based on treatment regimens; however, we did not analyze the data concerning the duration for which each treatment was given.

Conclusion: Our results indicate that IDMs with mothers on insulin have significantly higher rates of certain complications as compared to mothers on diet control or OHA. Earlier detection of GDM leading to early and better glycemic control can possibly reduce the need for insulin and simultaneously improve outcomes in neonates.

Keywords: Neonatal, DM before pregnancy, Diabetic Mothers, Tertiary Care Hospital, Pakistan

Introduction:

Diabetes has been associated with maternal and neonatal morbidity and mortality for a long time. [1]Brian et al. defined gestational diabetes mellitus (GDM) as any degree of glucose intolerance with onset or first recognition during pregnancy .[2] According to World Health Organization (WHO), GDM screening in pregnant woman should be done between 24-28 weeks with a standard 2-hour 75g oral glucose tolerance test (OGTT). 75g of anhydrous glucose in 250-300ml of water is administered orally after overnight fasting of 8-14 hours. Venous plasma glucose is measured 2 hours after glucose administration, and a cut-off of ≥140 mg/dl (7.8mmol/l) is classified as having GDM.[3] The prevalence of GDM is reported to vary from 1.4 to 14% globally. Among racial and ethnic groups, Asian women have a higher prevalence of GDM than Caucasian women [4]. The prevalence of GDM in Pakistan is estimated to range from 4.2% to 26%. Although there is no certain bureau to record GDM prevalence in Pakistan, some research statistics indicates a prevalence as high as 26% in Peshawar, 11.8% and 17.8% in Karachi, 1% in Lahore's primigravida females, 22% in Baluchistan, 14% in Bahawalpur, 11.8% and 14.8% in Hyderabad [.5-12]

The placenta secretes diabetogenic substances such as growth hormone, corticotropin-releasing hormone, human placental lactogen, prolactin, and progesterone throughout pregnancy. Additionally, pregnancy is associated with insulin resistance. Combined with inadequate pancreatic function, insulin resistance raises the risk of developing GDM [1, 13]. Any level of glucose intolerance can cause adverse maternal and fetal outcomes. Compared to infants born to mothers without diabetes mellitus (DM), infants born to women with DM have an increased risk for both; preterm birth (PTB) and being large for gestational age (LGA) [14]. In addition, they have a higher risk of neonatal complications such as cardiovascular system (CVS) and central nervous system (CNS) defects, hyperbilirubinemia, low iron stores, perinatal asphyxia, respiratory distress syndrome (RDS), hypoglycemia, hypocalcemia, polycythemia, transient hypertrophic cardiomyopathy [15-17], and macrosomia with its subsequent complications [18]. Medical resources, diagnosis, and treatment must improve in developing countries. There are limited resources: access to medical and health resources; knowledge about disease; awareness, trainings, and awareness about health[. 44-50]

Therefore, it is important to diagnose GDM early and treat it promptly to prevent complications. Conducted in a tertiary care center in Karachi, our study aims to record the incidence of adverse outcomes in neonates born to mothers taking different treatment regimens for GDM. Due to the high prevalence of GDM in Pakistan, our secondary objective is to influence early detection and treatment of GDM, which would help reduce the detrimental effects of this illness on infants.

Methodology:

The setting for this population-based cohort study was over one year, from January to December 2016, in the post-natal ward and Neonatal Intensive Care Unit (NICU) of Aga Khan University Hospital (AKUH), after getting approval from the Ethical Review Committee (ERC) of the hospital. AKUH is a large tertiary care hospital in Karachi, a metropolitan city in Pakistan.

Inclusion criteria: Any neonates ≥ 24 weeks of gestation age born to pregnant females having GDM, receiving any treatment of any duration.

Exclusion criteria: Babies born to mothers having co-morbidities other than GDM, like pregnancy-induced hypertension (PIH), autoimmune disorders, obesity, and polycystic ovary syndrome (PCOS), were excluded from the study.

All information was taken from the medical record. All neonates fulfilling inclusion criteria were enrolled in the study at birth. Informed consent was obtained from the mothers/caregivers for their infant's participation in the study. All the mothers received antenatal care in the AKUH.

Data regarding the mothers includes age, parity, gestation, diagnostic tests for GDM, different regimens of treatment and their duration, and glycemic control. Mothers with GDM were divided into three groups based on treatment received; diet control, oral hypoglycemic agent (OHA) intake, and insulin administration, on the basis of hospital protocol. Data recorded regarding the babies comprises natal and post-natal events, including gestational age, Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score, gender, birth weight, and mode of delivery. Morbidity and mortality were recorded. Morbidities and complications include preterm delivery (defined as gestational age <37 weeks in NICE guidelines 44]), small for gestational age (SGA), LGA, macrosomia, RDS, transient tachypnea of the newborn (TTN), meconium aspiration syndrome (MAS), congenital anomalies, polycythemia, and birth injuries. Hypoglycemia, and hypocalcemia were recorded for the first 48 hours of life. Hyperbilirubinemia was followed throughout the first week of life.

Statistical analysis:

The subjects were divided into three groups based on treatment taken by their mothers and the frequency of positive findings for each was calculated. Quantitative and categorical data were presented as mean, standard deviation (SD), and frequencies (percentages).

Quantitative data between three independent groups were analyzed using Chi-square. Stratification with respect to maternal age, parity, gender, and weight of the baby was done. Post-stratification chi-square test applied. P-value ≤0.05 is considered significant.

Results:

The age range of the mothers of IDMs was 18 - 42 years, with a mean of 30.72 ± 4.6 years. 58.8% of women were more than 30 years, and the rest were 30 years or less. 35% of the women were primigravida, and 65% were multigravida. During the one-year study period, 5186 babies were born, of which 427 newborns were IDMs, with an incidence rate of GDM being 8.2% in AKUH. 350 IDMs were enrolled in the study as per inclusion criteria, divided into three groups depending on the mother's treatment regimen during pregnancy: OHA, insulin, or diet control only. 70.6% of mothers were diagnosed with GDM in the second trimester, and 29.4% were diagnosed in the third trimester. The mean duration of treatment for GDM was 12.8 weeks ± 3.8 weeks in all three groups. Of the 350 babies included in the study, 178 (50.9%) were male, and 172 (49.1%) were female, with a mean weight of 2.85kg. There was no significant difference between the mean weight of babies among the three treatment groups (p=0.009). The IDM delivered with normal vaginal delivery were 95 (27.1%), and those born with cesarean deliveries (CD) were 255 (72.9%), of which 110 (43.1%) and 145 (56.9%) were elective and emergency CDs, respectively (Table 1).

Table 1: Maternal and Newborn Demographic Data

		Treatment Groups			p-value
		Oral Hypoglycemic (n=116)	Insulin (n=117)	Diet Control (n=117)	
		N (%)	N (%)	N (%)	
Mother age in years	<30	47 (40.5%)	36 (30.8%)	61 (52.1%)	0.004
	>30	69 (59.5%)	81 (69.2%)	56 (47.9%)	
Time of Diagnosis	2nd Trimester	72 (62%)	99 (84.6%)	76 (65%)	0.001
	3rd Trimester	44 (38%)	18 (15.4%)	41 (35%)	
Treatment Duration	≤8 weeks	24 (20.8%)	9 (7.7%)	14 (12%)	0.001
	9-14 weeks	46 (39.6%)	46 (39.3%)	66 (56.4%)	
	≥15 weeks	46 (39.6%)	62 (53%)	37 (31.6%)	
Birth Weight	>2.5kg	99 (85.3%)	84 (71.8%)	103 (88%)	0.009
	1.5-2.49kg	12 (10.3%)	26 (22.2%)	11 (9.4%)	
	1 - 1.49kg	5 (4.4%)	4 (3.4%)	3 (2.6%)	
	<1kg	0 (0%)	3 (2.6%)	0 (0%)	
Mode of Delivery	NVD	26 (22.4%)	25 (21.4%)	44 (37.6%)	0.009
	Elective LSCS	32 (27.6%)	41 (35%)	37 (31.6%)	
	Emergency LSCS	58 (50%)	51 (43.6%)	36 (30.8%)	

The incidence of premature birth was 28% (n=98), with a mean gestational age of 36.8 ±2.0 weeks. The frequencies of the morbidities under study were as follows: SGA 18.9% (n=66), LGA 4.0% (n=14), hypoglycemia 20% (n=70), hypocalcemia 4.0% (n=14), hyperbilirubinemia 25.7% (n=90), RDS 6.3% (n=22), TTN 3.4% (n=12), Birth Asphyxia 2.9% (n=10), MAS 0.9% (n=3), congenital anomalies 3.7% (n=13), cardiac anomalies 8% (n=28), birth injury 0.3% (n=1), and babies needing NICU admission 15.7% (n=55). The mortality rate was 1.4% (n=5) (Table 2).

Table 2: Frequency of Different Morbidities in Infants of Diabetic mothers

Complication		**Frequency (n)**	**Percentage (%)**
Premature		98	28
Hyperbilirubinemia		90	25.7
Small for gestational age		66	18.9
Hypoglycemia		70	20
Hypocalcemia		14	4
Large for gestational age		14	4
Babies requiring oxygen	Respiratory Distress Syndrome	22	6.3
	Transient Tachypnea of the Newborn	12	3.4
Birth Asphyxia		10	2.9
Meconium Aspiration Syndrome		3	0.9
Congenital anomalies		41	11.7
Birth Injuries		1	0.3
NICU Stay		55	15.7
Mortality		5	1.4

Regarding prematurity recorded in IDMs, a significant difference was seen among mothers on diet control only, those taking OHA, and those on insulin ($p < 0.001$), with the insulin group having the

highest percentage of PTBs (44.4%). Other neonatal morbidities that showed a significant difference between the three treatment groups were SGA ($p = 0.005$), hypoglycemia ($p = 0.01$), hyperbilirubinemia ($p = 0.023$), cardiac anomalies ($p = 0.03$), and babies requiring NICU admission ($p < 0.001$). Like SGA, all of the above occurred in the greatest frequency in IDMs of mothers in the insulin treatment group (Table 3).

LGA occurrence in IDMs was 5.3%, 4.3%, and 2.5% in the insulin, OHA, and diet control group, respectively, while 6.8%, 3.4%, and 1.7% of IDMs had hypocalcemia in the insulin, OHA and diet control group, respectively. 22 neonates born to mothers with GDM suffered from RDS; 9.4% in the insulin group, 6% in the OHA group, and 3.4% in the diet control group. The frequency of MAS was overall low in IDMs (n=3), and none of the babies of diabetic mothers on diet control suffered from MAS. Congenital anomalies were observed at 5.1% in the insulin group, 2.5% in the OHA group, and 3.4% in the diet control group. The mortality rate observed was 3.4% in the insulin group and 0.8% in the diet control group (Table 3).

Risk estimation of the morbidity was done with maternal age, parity, gender, and baby weight using the Chi-square test (confidence interval 95%), and it was found that there was no significant relationship between parity and maternal age with morbidity ($p > 0.05$). However, morbidity was significantly associated with gender and birth weight of the neonates ($p < 0.05$).

Table 3: Morbidities in Infant of Diabetic Mothers On Basis of Different Treatment Regimens

Complications		Regimen			P-value
		Oral Hypoglycemic	Insulin	Diet Control	
		Frequency (%)	Frequency (%)	Frequency (%)	
Prematurity		28 (28.6%)	52 (53.1%)	18 (18.4%)	<0.001
SGA		19 (28.8%)	33 (50%)	14 (21.2%)	0.005
LGA		5 (35.7%)	6 (42.9%)	3 (21.4%)	0.593
Hypoglycemia		19 (27.1%)	34 (48.6%)	17 (24.3%)	0.010
Hypocalcemia		4 (28.6%)	8 (57.1%)	2 (14.3%)	0.126
Hyperbilirubinemia		32 (35.6%)	38 (42.2%)	20 (22.2%)	0.023
RDS		7 (31.8%)	11 (50%)	4 (18.2%)	0.168
TTN		3 (25%)	7 (58.3%)	2 (16.7%)	0.165
Birth Asphyxia		3 (30%)	5 (50%)	2 (16.7%)	0.489
MAS		1 (33.3%)	2 (66.7%)	0 (0%)	0.366
Congenital Anomaly		3 (23.1%)	6 (46.2%)	4 (30.8%)	0.578
Cardiac Anomaly		7 (25%)	16 (57.2%)	5 (17.9%)	0.003
Birth Injury		0 (0%)	0 (0%)	1 (100%)	0.368
Mortality		0 (0%)	4 (80%)	1 (20%)	0.073
NICU Admission		16 (29.1%)	31 (56.4%)	8 (15.5%)	<0.001
Length of Stay	≤4	102 (87.9%)	82 (70.1%)	109 (93.2%)	<0.001
	≥5	14 (12%)	35 (29.9%)	8 (6.8%)	

Discussion:

GDM is a serious public health concern worldwide, particularly in underdeveloped nations. In AKUH, the overall incidence of GDM is 8.2%. While many studies have compared babies of diabetic mothers to those of non-diabetic mothers, there is a paucity of data comparing morbidities in neonates of diabetic mothers receiving different treatment regimens for GDM. According to our study, IDMs whose mothers are on insulin have an elevated risk of mortality and morbidity.

Prematurity is the most prevalent complication in our study, adding up to 28% of cases, which is about double the overall prevalence of prematurity in Pakistan. Although multiple studies have reported an increased risk of premature birth in association with different levels of glucose intolerance [19-24], our study shows that diabetic mothers on insulin were at a significantly higher risk of giving preterm birth, than those on OHA or diet control. Mothers with increased severity of glucose intolerance were administered insulin, which may elucidate a higher incidence of PTB.

Yogev et al. also found a relationship between higher glucose values in the OGTT or higher mean blood glucose levels and preterm birth [26]. Furthermore, 72.9% of diabetic mothers in our study underwent cesarean deliveries. In general, the higher number of premature deliveries and CDs among women with GDM can be explained by faster intrauterine growth due to overexposure to the energy source. [27]

A frequent adverse effect of GDM in IDMs is neonatal hypoglycemia. Children suffering from this may develop learning difficulties and motor impairment [28-30]. In contrast with Metzger et al., who found that up to 50% of babies in GDM pregnancies developed hypoglycemia [31] in our setup, 20% of IDMs experienced hypoglycemia, with 48.6% of those being neonates of mothers taking insulin for GDM ($p = 0.01$). In addition, the data collected by the HAPO study confirmed that: neonatal hypoglycemia was strongly associated with elevated cord serum C-peptide levels. An IDM is at risk of transient hyperinsulinism and increased glucose consumption by tissues, causing hypoglycemia [32-33.] Regardless of an IDM's birth weight, early and frequent breastfeeding remains the key to preventing hypoglycemia as long as he/she can feed autonomously. Therefore, keeping IDMs close to mothers is preferable as long as they do not require NICU admission [34].

In our study, other morbidities found to be more frequent in IDMs overall, especially IDMs born to mothers on insulin, included SGA, cardiac abnormalities, NICU admission, and length of stay ($p < 0.05$). Research suggests that the most commonly reported cardiac anomalies in IDMs include hypertrophic cardiomyopathy [17], truncus arteriosus, transposition of the great arteries, hypoplastic left heart syndrome, ventricular septal defects, and double outlet right ventricle [35]. Antenatal ultrasounds in pregnant women with GDM also play an essential role in monitoring fetal cardiac anatomy and function. In the presence of clinical signs of cardiac anomalies, including murmurs, cyanosis, or signs of heart failure, IDMs should receive an echocardiogram [36]. Neonates whose mothers had worse glycemic control and hence were taking insulin were more often subject to heart problems, suggesting a proportionate relationship between higher glucose intolerance and cardiac anomalies.

Acknowledging the above neonatal complications associated with diabetic mothers, higher rates of NICU admission are foreseeable. Quinn et al. and Khasawneh et al. established prematurity as a significant factor for NICU admission [37, 38]. According to multiple studies, babies born via CD are at increased risk for NICU admission [38-40]. 72.9% of diabetic mothers in our study gave birth via CD, and most (36.1%) took insulin. Numerous research is present regarding the increased incidence of congenital heart disease in babies admitted to NICU [41-43], elucidating that symptoms secondary to cardiac anomalies in neonates usually require special care. Since these morbidities are more frequent in mothers on insulin, we also found that significantly higher number of babies of mothers receiving insulin required NICU care ($p < 0.001$).

Large-scale local research work is necessary to uncover more robust data. Awareness regarding GDM and its early diagnosis and treatment can potentially reduce the occurrence of premature birth in Pakistan. Comparing the three groups of treatment, morbidities were directly proportional to poor hypoglycemic control. The insulin group had almost 1.5-2 times more incidence of morbidities compared to the oral hypoglycemic agent group and the diet control group.

In this paper, we only included diabetic mothers with GDM and not those who already had Type 1 or 2 DM before pregnancy. Furthermore, our comparison comprises morbidities in neonates of three groups of diabetic mothers based on treatment regimens; however, we did not analyze the data concerning the duration for which each treatment was given.

Conclusion:

Despite the multi-disciplinary antenatal diabetic care management, there is still increased prematurity, SGA, and an increased prevalence of hyperbilirubinemia among IDMs. Delivery by caesarian sections is very high among GDM women; hence this should be addressed earlier.

More efforts and education should be given to improve the known modifiable factors, such as screening and early detection of diabetes and glycemic control, to help reduce mortality and

morbidity among IDMs. Detection of congenital cardiac defects should be part of the routine evaluation in IDMs.

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