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COMPARISON OF MORBIDITIES BETWEEN INFANTS OF PREGESTATIONAL & GESTATIONAL DIABETIC MOTHERS

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ABSTRACT

To describe and compare the clinical outcome of infants born to mothers with gestational and pregestational diabetes mellitus, this study was conducted between January 2000 to January 2002 in Tehran Vali -E- Asr Hospital. Among 4472 deliveries, we found 107 infants born to diabetic mothers out of whom 6 were twins.

The prevalence of diabetes in total deliveries was 2.39%. Mean age of gestational and pregestational diabetic mothers was 30.9 ±5.86 and 31 ± 5.37 respectively.

74 infants (69%) belonged to gestational diabetic mothers. 50% of infants were male. Mean birth weight of infants was 3067±784.917 (700 -5600g). Gestational age in 57% of infants was less than 38 weeks. APGAR score at 1 & 5 minutes was <6 in 10 and 5 cases respectively.

Hypoglycemia was detected in 31%, hypocalcemia in 13%, hypomagnesemia in 4.5%, polycythemia in 6.8%, macrosomia in 28.6%, small for gestational age in 2%, respiratory distress syndrome in 8.2%, early sepsis in 9.2%, NICU admission in 23.7%, and hyperbilirubinemia in 34%.

The incidences of most of these morbidities were higher in infants of pregestational diabetic mothers. The differences between the incidence of hypoglycemia, hypocalcemia & 5 minute APGAR score in infants of pregestational and gestational diabetic mothers were significant ($p<0.05$).

There was a significant correlation between the incidence of hypoglycemia and birth weight of infants ($p<0.05$). The existence of congenital anomalies in infants of gestational diabetic mothers could be due to unrecognized cases of noninsulin dependent diabetes mellitus, and with respect to mean age of mothers it is advisable to detect diabetes before pregnancy in high risk groups and correct the level of hemoglobin A_{1c} before pregnancy. Cleft palate and undescended testes among the anomalies support this hypothesis that prostaglandin deficiency may have a role in the pathophysiology of congenital malformations in these infants.

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INTRODUCTION

Infants of insulin dependent diabetes mellitus (IDDM) and noninsulin dependent diabetes mellitus (NIDDM), and also gestational diabetic (GDM) women have more

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perinatal problems than those of normal mothers. These complications have usually been attributed to poor control of hyperglycemia and iatrogenic or emergency preterm delivery.[1] There is a significant correlation between maternal glycemic control and perinatal outcome for the incidence of neonatal hypoglycemia, macrosomia and respiratory distress syndrome.[2] Neonatal respiratory distress, jaundice, hypoglycemia, hypocalcemia, polycythemia, macrosomia, perinatal asphyxia, prematurity, congenital malformation, hyperbilirubinemia, large and small for gestational age, and renal vein thrombosis are seen more in these infants.[3] The neonatal mortality rate is over five times that of infants of nondiabetic mothers; several of these metabolic and morphologic abnormalities can be reversed with fastidious management of the mother. Recent data from several studies have shown that IDMs who have been managed rigorously through pregnancy do not become hypoglycemic and maintain normal rates of glucose production and basal metabolism.[4]

If optimal care is delivered to the diabetic woman, the perinatal mortality rate, excluding major congenital malformations, is nearly equivalent to that observed in normal pregnancies.[5]

GDM is usually detected in the second half of pregnancy when placental synthesis of peptide and steroid hormones reach a peak.[6]

Sacral agenesis syndrome, with agenesis of the sacrum and lumbar spine and hypoplasia of the lower extremities, is almost never seen except in IDMs. Poor maternal control of diabetes at conception is associated with a higher incidence of congenital malformations in infants of IDDM and NIDDM women but not those of women with truly gestational diabetes (e.g., occurrence > 20 weeks' gestation, normal HbA_{1c} concentration and reversible postpartum).[1]

Women with NIDDM are at special risk for fetal malformations because they are frequently asymptomatic and often have unrecognized diabetes; they usually enter prenatal care after embryogenesis is complete. Among many low income older women with NIDDM access to modern diabetic care is unavailable or limited in the United States. This group represents a large pool of one million women of childbearing age at risk for major and minor fetal malformations.[7]

Some morbidities such as hypocalcemia may be due to severity and duration of maternal diabetes.[4]

With this background we supposed that gestational in comparison with pregestational diabetes should have a lower incidence of morbidity and embryopathy. To show the amount of difference that could be due to poor control and severity of diabetes among pregestational diabetic mothers, we decided to describe the clinical outcome of infants born to mothers with gestational and pregestational diabetes mellitus (PGDM) and compare related morbidities in these two groups.

MATERIAL AND METHODS

All infants of diabetic women who were born at Tehran Vali-E-Asr Hospital were entered into this study between January 2000 to January 2002.

Morbidities like hypoglycemia (blood glucose level <40 mg/ dL), hypocalcemia (Ca < 8 mg/dL in term & Ca < 7.5 mg/ dL in preterm neonates), hypomagnesemia (Mg > 1.5 mg / dL), hyperbilirubinemia (bilirubin > 15 mg / dL), early sepsis (positive blood culture during 48 hours of age), late sepsis (positive blood culture after 48 hours of age), polycythemia (venous hematocrit> 65%), macrosomia defined as birth weight greater than 90th percentile of the intrauterine growth curves of Lubchenco, cardiac and noncardiac mothers, type of glycemic control in women, and route of delivery were entered into the data sheet. We divided these characteristics in to two groups of gestational and pregestational diabetes and compared them by Chi-square test and determined odds ratios for each of these variables.

RESULTS

Among 4472 deliveries, we found 107 (2.39%) infants of diabetic mothers out of whom 6 were twins. The prevalence of gestational and pregestational diabetes was 1.56% and 0.69% respectively. Mean ages of GDM and PGDM mothers, the mean age of mothers at the time of diagnosis of diabetes, mean of gravidity, and mean duration of diabetes are depicted in Table I.

Before pregnancy 23 (69.69%) of these women used insulin to control glycemic levels. All the pregestational and 83% of gestational diabetic women used insulin during their pregnancies. The route of delivery in 85% of women was cesarean section.

Mean birth weight and mean gestational age are shown in Table I. Gestational age of 57% of infants was less than 38 weeks. 1. 50% of infants were male. APGAR score at and 5 minutes was <6 in 10 and 5 cases respectively. Incidence of morbidities are depicted in Table II.

Table I. Maternal & demographic characteristics.

Mean age of GDM mothers	30.9± 5.86 (years)
Mean age of PGDM mothers	31 ± 5.37 (years)
Mean of gravidity	2.8 ± 1.4
Mean duration of diabetes	5.65 ± 5.79 (years)
Mean birth weight	3067 ± 784.917 (grams)
Mean gestational age	36.065 ± 4.272 (weeks)

Table II. Incidence of morbidities in infants of diabetic mothers.

Variables	GDM 74	PGDM 33	Total % CI (95%)	Odds ratio Chi-square	*P*-value
Hypoglycemia	17 (22.9)	14 (42)	31(28.9)	0.33	0.016
Hypocalcemia	5 (6.7)	8 (24)	13(12.14)	0.205	0.006
Hypomagnesemia	3(4.05)	1(3.03)	4(3.7)	1.4	0.74
Polycythemia	2(2.7)	3(9.09)	5 (4.68)	0.31	0.19
Icterus	23(31.08)	11(33.3)	34(31.77)	1.04	0.95
Early sepsis	8(10.08)	1(3.03)	9(8.4)	3.67	0.20
Late sepsis	2(2.7)	3(9.09)	5(4.6)	0.25	0.11
RDS	1(1.35)	3(9/.09)	4(3.7)	0.68	0.62
Oligohydramnious	7(9.45)	4(12.12)	11(10.28)	0.75	0.67
Polyhydramnious	6(8.1)	2(6.06)	8(7.47)	1.3	0.70
ROM	7 (9.4)	5(15.15)	12(11.21)	0.58	0.38
LGA	18(24.32)	10(30.3)	28(26.1)	0.62	0.32
SGA	2(2.7)	0(0)	2(1.86)	0.97	0.36
NICU admission	16 (21.6)	7(21.12)	23(21.49)	0.96	0.94
Prematurity	38 (51.35)	19 (57.57)	57 (53.27)	0.77	0.55
Apgar 1 min >6	5(6.75)	5(15.15)	10(9.34)	0.42	0.18
Apgar 5 min <6	1(1.3)	4(12.12)	5(4.6)	0.102	0.017
Death	6(8.1)	4(12.12)	10(9.34)	0.62	0.48

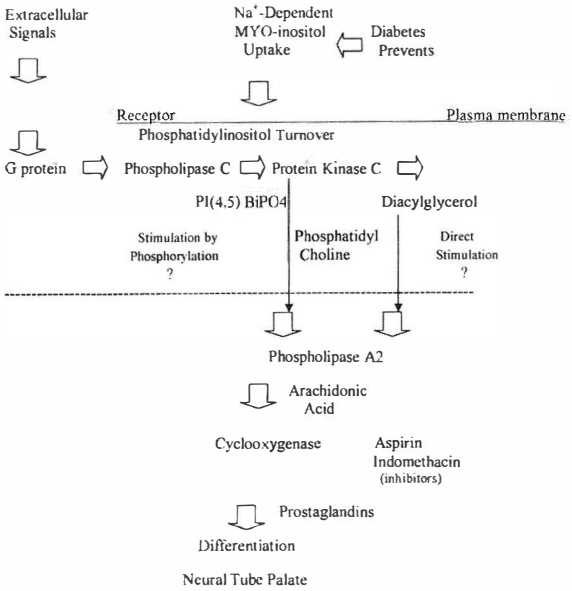

Fig. 1. Scheme of the signal transduction pathway from phosphatydylinositol turnover to the arachidonic acid cascade and the site of inhibitory action of diabetes.

Table III. Comparison of anomalies and cardiac signs and symptoms according to type of diabetes.

Case	GDM	PGDM
1		Murmur*
2	TR & murmur	
3		Microphthalmia
4		Murmur*
5	Murmur& TR, pigmented scrotum, & Undescended testis	
6	TR,Hypertrophic septum, murmur	
7	Dilated PA	
8	PDA,mild TR, murmur	
9	polydactyly	
10	PDA, hypertrophic septum, murmur	
11	Central Bell's palsy,ear atresia	
12		Severe TR,PI
13	Cleft palate	
14		Murmur*, periauricular tag
15	PDA, club foot,murmur	
16	Undescended testis, Ambiguous genitalia & murmur*	
17		TGV (Cyanosis)

TR= tricuspid regurgitation PA= pulmonary artery PI= pulmonary insufficiency

PDA= patent ductus arteriosus TGV= transposition of great vessels

* Echocardiography wasn't performed

Case one, eleven, and sixteen died before performing echocardiography.

The risk of most morbidities was higher in infants of PGDM than GDM mothers. There was a significant difference between the incidence of hypoglycemia, hypocalcemia and 5 minutes APGAR score in infants of PGDM compared to GDM mothers ($p<0.05$).

It is interesting that most of the noncardiac and cardiac anomalies are in infants of GDM mothers. Unfortunately some parents didn't bring their children for echocardiography.

With logistic regression there was a significant correlation between incidence of hypoglycemia and birth weight of infants ($p< 0.05$).

Cardiac anomalies consisted of patent ductus arteriosus, transposition of great vessels, septal hypertrophy, and most of these of patients had tricuspid regurgitation. None of the infants with PDA were premature.

Klebsiella and staphylococcus species were the predominant organisms in septic patients.

DISCUSSION

From 3 to 5% of pregnancies complicated by diabetes mellitus 80 to 90% are gestational diabetes that is defined as glucose intolerance with onset or first recognized during pregnancy.[8]

The available data suggest that the frequency of diabetes in pregnancy is highly variable, generally reflecting the underlying pattern of NIDDM in this particular population. Different ethnic groups in the same environmental setting experience a widely variable risk. Impaired glucose tolerance is usually more prevalent than diabetes in women of childbearing age. Incidence of GDM is low in the absence of risk factors, suggesting that selective screening programs may be cost-effective.

The worldwide epidemic of glucose intolerance predicted by the latest World Health Organization studies will undoubtedly increase the burden of GDM, especially in developing countries.[9] Women who are found to have markedly abnormal oral glucose tolerance tests early in pregnancy and elevated hemoglobin A_{1c} concentrations are more likely to have NIDDM rather than GDM even though hyperglycemia was detected for the first time during pregnancy.[6]

In true GDM, e.g. evoked by pregnancy, the risk for embryopathy is not increased.[7] In our study about 2.39% of total deliveries belonged to diabetic mothers and 69.15% of these pregnancies were GDM that are lower than could be expected.

It is interesting that congenital malformations were also common in this group.

When we compare the mean age of women in these two groups there is no significant difference and the mean age in total women was 30.75±5.6 years.

This discrepancy between our findings and what should be expected could be due to unrecognized cases of NIDDM that were first diagnosed in pregnancy and were not true gestational diabetes. With respect to risk factors for gestational diabetes which include age above 25 years, obesity, having a first degree relative with diabetes mellitus, being a member of an ethic group at high risk (Hispanic, American Indian, Asian, African American), history of abnormal glucose metabolism, history of obstetric outcome, history of previous gestational diabetes mellitus, and concomitant glucocorticoid therapy,[8] we suggest screening programs be performed in high risk groups before pregnancy especially in women above 25 years old and to measure HbA_{1c} in suspected patients. It should be noted that in pregnancy, erythropoesis is increased, leading to younger red blood cells, which cause the RBCs of pregnant women to be less glycated than those in nonpregnant women[8] and detection of this type of hemoglobin before pregnancy is more accurate.

Screening based on risk factors has recently been advocated by the American Diabetes Association. Screening should be performed between 24 and 28 weeks of gestation.

Some advocate earlier screening in women with significant risk factors.[10]

In one study cardiovascular malformations were present in 23% of infants.[11]

In all reviews, the number of significant malformations is underreported since many abnormalities do not have clinical signs or symptoms in the early perinatal period.

No specific congenital defect is peculiar to diabetes but malformations are overpresented.[1]

Virtually all birth defects are more frequent in IDMs, with caudal regression syndrome being the most specific to diabetes, but congenital cardiac and neural tube defects are the most common. It becomes evident that higher first trimester glycosylated hemoglobin levels are associated with a greater likelihood of anomalies suggesting that poor metabolic control may be part of the responsible mechanism.

Intervention trials have consistently demonstrated that prepregnancy and early pregnancy counseling and improvement in control are associated with a decrease in the rate of anomalies. Exactly how tight metabolic control should be is not settled at present. The important principle is that women with diabetes should start self glucose monitoring before planned conception, and pregnancy should be deferred until glycosylated hemoglobin is relatively normal.[12]

These malformations occur before the seventh week of gestation and apparently result from the mother's milieu. There were several hypotheses concerning a possible mechanism for diabetic embryopathy. These included alterations in maternal levels of trace metals such as zinc, enhanced synthesis of proteoglycans, such as hyaloronic acid, abnormally high levels of ketone bodies in poorly controlled diabetic state and partial blockade of glycolysis in the teratogenic action of the glucose isomer, mannose.

Because the embryologic processes in the differentiation of the neural tube are similar to those of embryonic palate, it is suggested that the teratogenic pathway of the neural tube and palate in the diabetic embryopathy model may similarly involve the arachidonic acid cascade (Fig. 1). If diabetic embryopathy is mediated by a deficiency of prostaglandins in the embryo, supplementation with prostaglandin may be able to prevent the diabetic embryopathy.

Hyperglycemia is not the sole cause of diabetic embryopathy. This is consistent with findings which have shown that components of diabetic serum, β-hydroxybutyrate, somatomedin inhibitor, and D-glucose, act synergistically or additively to produce malformations.

These results suggested that several factors in diabetic serum may collectively affect the synthesis of prostaglandins and produce anomalies. A deficiency of myo-inositol has also been implicated in the cause of diabetic embryopathy. Organizing action of testosterone on the genitalia involves the arachidonic acid cascade leading to prostaglandins at a critical period of genital development. It appears that the interference with testosterone synthesis or action leads to a teratogenic deficiency of arachidonic acid during this time in the genital anlagen.[13]

In our study the observation of ambiguous genitalia, undescended testis and cleft palate support the hypothesis of the role of prostaglandin deficiency in the patho-

Table IV. Comparison of incidences of morbidities between our study and others.

Morbidities	This study	Other studies
Diabetes in pregnancy	2.39% of total deliveries	3-5%
Prematurity	57%	14-36%
Macrosomia	28.6%	20-30%
Hypocalcemia	13%	10-20%
Hypoglycemia (GDM)	22.9%	15-25%
Hypoglycemia (PGDM)	42%	25-50%
Hyperbilirubinemia	34%	20-25%
Polycythemia	6.8%	10-20%
Small for gestational age	2%	2%
NICU admission	23%	47%
Cesarean section	85%	62%
RDS	4%	2-34%
Mortality	10%	5.3%

genesis of congenital malformation in infants of diabetic mothers.

When we compare anomalies in two groups we see severe malformations in infants of GDM compared to PGDM mothers. Observation of these anomalies in gestational diabetic women may suggest that in women with unrecognized diabetes and mild symptoms, low levels of hyperglycemia could induce less severe anomalies like undescended testis or cleft palate, but a severe and prolonged hyperglycemic state results in more severe malformations like TGV and neural tube defects.

The pathogenesis of some cases of diabetic embryopathy may involve a primary insult to developing somite mesoderm and associated cephalic neural crest cells. In one study the studied cases had abnormal ears in association with vertebral defects.[14]

In our study we had abnormal ear atresia and peculiar tags without vertebral defects. Gestational age in 57% of infants was less than 37 completed weeks which is higher than other reports [Table IV][15,16] In one study there was no association of preterm labor with maternal age, parity, gravidity, diabetes class according to White, presence of renal disease, retinopathy, previous elective abortion, chronic hypertension, preeclampsia, cigarette smoking, vaginal bleeding in 1st trimester of after 20 weeks of gestation, maternal serum magnesium level or hydramnious.[17]

In this study the prevalence of most neonatal morbidities was in the range of other reports [Table IV].[3,4,18]

In our study there were significant differences between the frequency of hypoglycemia, hypocalcemia and APGAR score in infants of GDM & PGDM mothers that could be due to poor glycemic control and more severe diabetes in PGDM mothers. It seems the systems most affected by poor glycemic control have been recognized for decades. Fetal hyperglycemia in poorly controlled diabetic women can lead to progressive fetal hypoxemia, acidosis and eventually death with perinatal asphyxia.[7]

Cardiac malformations, ventricular or atrial septal defect, transposition of great vessels, truncus arteriosus, double outlet right ventricle, and coarctation of aorta are most common. Infants of diabetic mothers are at increased risk for various cardiomyopathies. Many have thickening of the interventricular septum and the left or right ventricular wall. The increased cardiac muscle mass results from the fetal hyperinsulinemic state.[1]

PDA, TR, TGV, PI, and septal hypertrophy were the most reported signs in echocardiography in our patients.

Early sepsis in 8.4% of these infants is remarkable but prematurity in most of these septic patients confounds the exact role of diabetes in the production of sepsis in these infants.

According to WHO the diabetic population will increase until the year 2025 and the major part of this numerical increase will occur in developing countries. There are more women than men with diabetes, especially in developed countries. This report supports the earlier prediction of the epidemic nature of diabetes in the world during the first quarter of the 21st century. It also provides a provisional picture of the characteristics of the epidemic. Worldwide surveillance of diabetes is a necessary first step toward its prevention and control, which

is now recognized as an urgent priority.[19]

With repect to this study and regarding the age of mothers of whom most were over 25 years, the importance of prevention and control of diabetes before pregnancy in high risk groups is confirmed.

Each couple requires an individualized approach with ample opportunity for discussion and questions. The importance of diabetic control before conception is stressed and each woman is advised to have a comprehensive medical assessment, instruction in home blood glucose monitoring, a retinal examination, renal evaluation, and nutrition counselling. Frequent supervisory appointments every few weeks at a diabetes center or by a diabetologist are essential to achieve and maintain diabetic control. It usually takes 2-4 months to reach a normal HbA_{Ic} concentration along with changes in nutrition and activity that are compatible with the patient's life style, occupation, and quality of life.[20]

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