Original Research Paper

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Gynaecology

ANALYSIS OF CONGENITAL MALFORMATIONS IN OFFSPRINGS BORN TO WOMEN WITH GLUCOSE INTOLERANCE IN PREGNANCY

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ABSTRACT

AIM:40 pregnant women with glucose intolerance who gave birth to congenitally malformed babies were studied during and after pregnancy and data with regards to the type of congenital malformations and various degrees of glucose intolerance were analysed.

METHODOLOGY: 40 pregnant women with glucose intolerance who gave birth to congenitally malformed babies were studied with a standard questionnaire.They were categorized into Pre GDM and GDM group. In addition to maternal ,clinical and historical parameters , the initial fasting plasma glucose (derived either from diagnostic GTT or at entry to prenatal care and initial HbA1c before insulin therapy were taken into account and analysed for a correlation to various anomalies.

PLACE OF SUDY - Kasturba Gandhi hospital ,Madras medical college Chennai.

TYPE OF STUDY- Prospective observational study

RESULTS AND ANALYSIS-Among the GDM group , in women who did not have glucose intolerance after delivery the initial mean HbA1c was 5.8%.HbA1C was 7.1% in women who continued to be diabetic after delivery and HbA1C was 6% in the group who had impaired glucose tolerance 6 weeks after delivery. 59% in GDM group and 70% in Pre-GDM had previous pregnancy outcomes such as abortion, IUD and previous congenital anomalies. Among the anomalies, CVS involvement was the most in both the groups.While following up the GDM group to postpartum 13 of the 27 patients (48%) required postpartum insulin. The 17 (not on insulin) patients in the gestational diabetes group were subjected to postpartum 75 gms OGTT, 3 were reclassified as overt diabetes, 6 into impaired glucose tolerance and only 8 of them were normal.

CONCLUSION: It is suggested that in the GDM group exists a subgroup with an increased risk for a diabetic embryopathy, perhaps due to preexisting but undetected Type 2 Diabetes Mellitus. This shows the importance of screening for glucose intolerance early in pregnancy and pre pregnancy counselling for known diabetics who are planning for pregnancy. This study therefore highlights the importance of preconception screening for DM to prevent congenital anomalies occurring during pregnancy.

KEYWORDS : gestational diabetes mellitus,, congenital malformations, oral glucose tolerance test,hbA1c

INTRODUCTION

Maternal diabetes has toxic effects on the development of the embryo and significantly increase the risk of congenital malformations in the offspring.The incidence of foetal structural defects caused by maternal pre gestational diabetes mellitus is is three to five fold higher than that seen in non diabetic pregnancy .

Diabetic embryopathy can effect any developing organ system including Central nervous system,cardiovascular,skeletal ,renal and GI system .Pregnant women with foetuses with diabetic embryopathy may have chronic or unrecognised hyperglycaemia and elevated levels of glycosylated haemoglobin.

This emphasises the need to consider hyperglycaemia induced teratogenesis during genetic counselling of parents with prenatally detected foetal malformations.Successful preconceptional counselling for women with diabetes mellitus and metabolic control will reduce birth defects and metabolic abnormality.

OBJECTIVE

To describe the clinical profile,maternal and foetal outcomes and the conversion rates to diabetes in women with gestational diabetes mellitus seen at a tertiary care hospital& Govt maternity hospital.

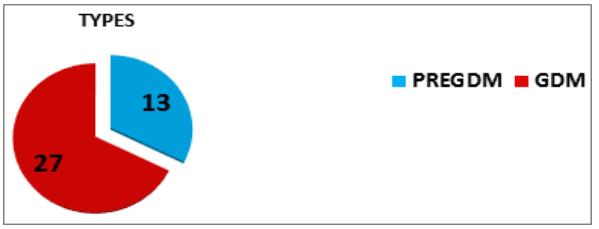
METHODOLOGY

It is a prospective observational study conducted over a period of one year at Kasturba Gandhi govt Maternity hospital,Madras medical college Chennai.40 pregnant women with an impaired glucose tolerance or diabetes mellitus who gave birth to congenitally malformed offspring were included in the study.

MATERIALAND METHODS

Antenatal mothers with pre GDM /GDM who were found to have foetal anomalies were included in the study .In addition to maternal ,clinical and historical parameters the initial fasting plasma glucose derived either from Glucose tolerance test or initial prenatal visit along with a hbA1c was recorded.The relationship of these values to the type of congenital anomaly was analysed..The congenital anomalies were categorised by the type of organ affected .

TABLE 1-DISTRIBUTION OF CASES



TYPE	PRE-GDM	GDM
TOTAL=40	13 (32.5%)	27 (67.5%)

TABLE 2-DISTRIBUTION OF CASES ACCORDING TO AGE

It was observed that out of the 40 women 29 were less than 30 yrs of age chi square -0.1032 p=0.73

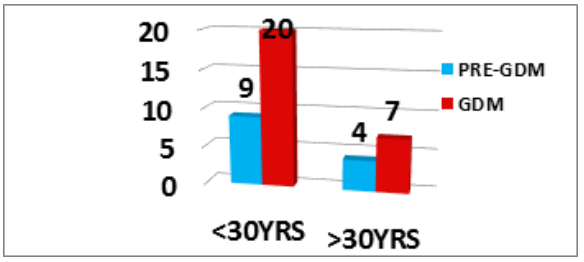
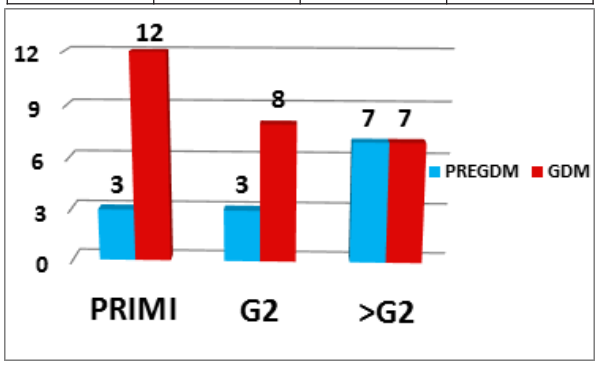


TABLE 3-DISTRIBUTION OF CASES ACCORDING TO PARITY

PARITY	PRIMI	G2	>G2
PRE GDM	3 (23%)	3 (23%)	7 (54%)



CHI SQUARE-3.16 P=0.20
In the GDM group 44% were primigravida.

TABLE 4-DISTRIBUTION OF CASES ACCORDING TO CONSANGUINITY

CONSANGUNITY	yes	no	
PREGDM	5 (38%)	8 (62%)	
GDM	9 (33%)	18 (67%)	

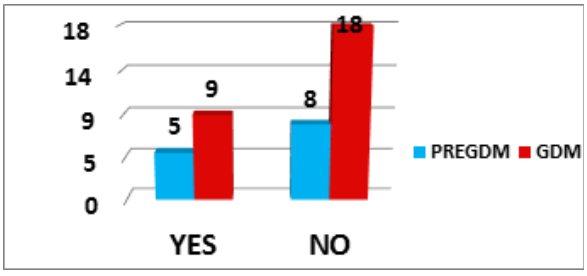
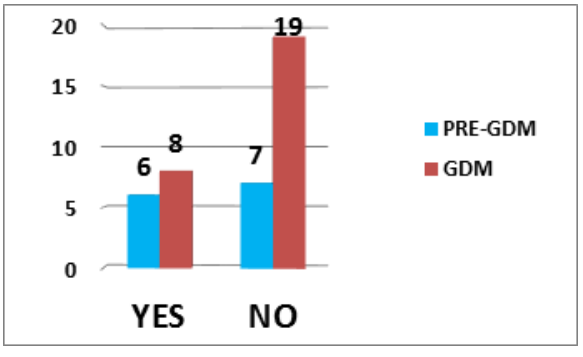


TABLE 5-DISTRIBUTION OF CASES ACCORDING TO FAMILY HISTORY

CHI SQAURE =0.1014 p=0.7501

FAMILY H/O	YES	NO
PREGDM	6 (46%)	7 (54%)
GDM	8 (30%)	19 (70%)



CHI CHI SQUARE-1.053 P=0.3066

TABLE 6-DISTRIBUTION OF CASES AS PER PREGNANCY OUTCOME

59% in GDM group and 70% in Pre-GDM had previous pregnancy outcomes such as abortion, IUD and previous congenital anomalies

PREV.PREG.OUTCOME	NIL SIGNIFICANT	ABORTION/IUD	CONG.ANOMALIES
Pre GDM(10)	3 (30%)	6 (60%)	1 (10%)
GDM(15)	6 (40%)	7 (47%)	2 (13%)
Yates corrected Chi square test	P=0.58 NS	P=0.80	P=0.65

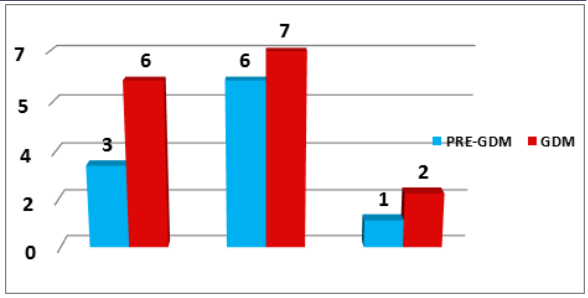


TABLE 7-DISTRIBUTION OF CASES AS PER TREATMENT

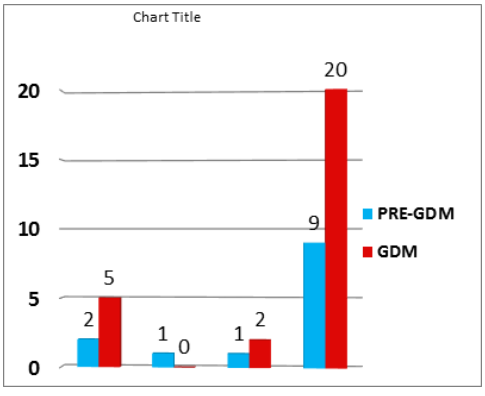
PRESENT PREGNANCY OUTCOME	ABORTION	STILL BIRTH	EARLY NEONATAL DEATH	ALIVE
PRE GDM	2 (15%)	1 (8%)	1 (8%)	9 (69%)
GDM	5 (19%)	0	2 (7%)	20 (74%)

TABLE 8 -DISTRIBUTION OF CASES AS PER PRESENT PREGNANCY OUTCOME

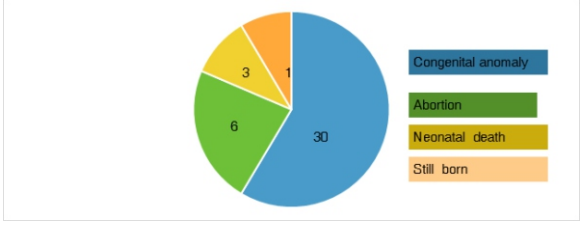
CHI SQUARE-2.156 P=0.5408

TREATMENT	MEAL PLAN	MEAL PLAN----INSULIN	INSULIN
GDM(27)	5 (19%)	3 (11%)	19 (70%)

ABORTION STILL BIRTH EARLY NEONATAL DEATH ALIVE



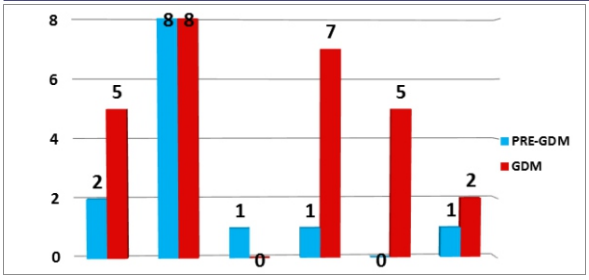
SURVIVED WITH ANOMALY	29	75%
SPON.ABORTION/MTP	7	15%
STILL BORN	1	2.5%
EARLY NEONATAL DEATH	3	7.5%



9-DISTRIBUTION OF CASES ACCORDING TO THE SYSTEM EFFECTED IN THE ANOMALOUS BABY

SYSTEM INVOLVED	CNS	CVS	GIT	SKELETAL	GENITO-URINARY	MULTIPLE
PREGDM	2 (15%)	8 (62%)	1 (7.5%)	1 (7.5%)	0	1 (8%)
GDM	5 (19%)	8 (30%)	0	7 (26%)	5 (19%)	2 (6%)

CNS CVS GIT SKELETAL GENITOURI MULTIPLE



Among the anomalies, CVS involvement was the most in both Pre GDM and GDM groups. CNS involvement was marginally higher in GDM group when compared to pre-GDM group (19% Vs 14%). The skeletal system involvement in GDM group was 26% when compared to 8% in Pre-GDM group. Involvement of multiple systems anomalies was almost similar in both groups.

TABLE 10-DISTRIBUTION OF CASES AS PER RE QUIREMENT OF INSULIN IN POSTPARTUM PERIOD

POSTPARTUM INSULIN STARTED	FBS/PPBS	6-wks 75 GMS OGTT
13	10 (80%)	3 (20%)

While following up the GDM group to postpartum, 13 of the 27 patients (48%) required postpartum insulin. Out of them, 10 patients continued insulin in the immediate postpartum period and 3 were started on insulin following reclassification after 6 wks postpartum OGTT.

TABLE 11-POSTPARTUM GLYCEMIC STATUS ASSESSM ENT

POSTPARTUM 6 wks 75 GMS OGTT	NORMAL	IMPAIRED GLUCOSE TOLERANCE	OVERT DIABETES
17	8 (47.0%)	6 (35%)	3 (18%)

CHI SQUARE- 8.227 P=0.1442

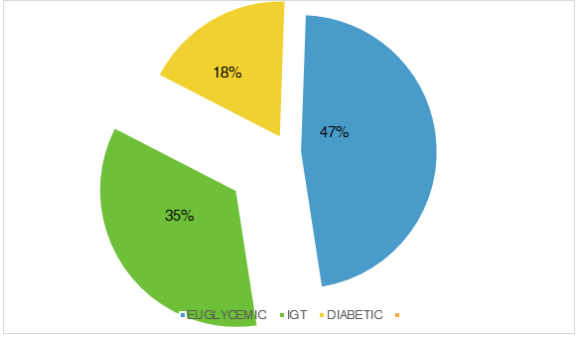
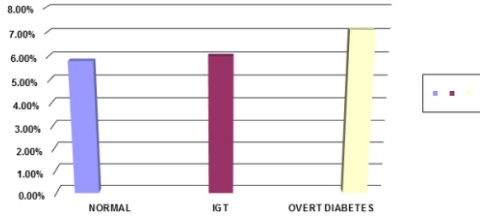


Table 12 BASELINE HbA1C AND ITS CORRELATION TO POSTPARTUM GLYCEMIC STATUS

CHI SQUARE-8.227
P= 0.1442

MEAN HBA1C	NORMAL	IGT	OVERT DIABETES
GDM(27)	5.8%(8)	6.0%(6)	7.1%(13)



Among the GDM group , in women who did not have glucose intolerance after delivery the initial mean HbA1c was 5.8%,7.1% in women who continued to be diabetic after delivery and 6% in the group who had impaired glucose tolerance 6 weeks after delivery. 59% in GDM group and 70% in Pre-GDM had previous pregnancy outcomes such as abortion, IUD and previous congenital anomalies. 81% of GDM group were treated with insulin and rest were treated with medical nutrition therapy alone. While following up the GDM group to postpartum 13 of the 27 patients (48%) required postpartum insulin. Out of them, 10 patients continued insulin in the immediate postpartum period and 3 were started on insulin following reclassification after 6 wks postpartum OGTT. Out of the 17 (not on insulin) patients in the gestational diabetes group who were subjected to 6 wks postpartum 75gms OGTT, 3 were reclassified as overt diabetes, 6 into impaired glucose tolerance and 8 were euglycemic.

Conclusion

Among women who had children with congenital anomaly the GDM group had the highest number and majority of them turned out to be having preexisting diabetes mellitus mellitus .It has been found that in the group with GDM there lies a subgroup with an increased risk of diabetic embryopathy perhaps due to preexisting but undetected type 2 diabetes mellitus .This shows the importance of screening for glucose intolerance early in pregnancy and pre pregnancy counselling for known diabetic mothers planning for pregnancy .Hence the importance of preconceptional screening for diabetes mellitus is of importance to prevent congenital anomalies occurring during pregnancy .

DISCUSSION

The cell biological reason for the teratogenic effect of the diabetic state is not known. However, both environmental factors (maternal diabetic state and intrauterine conditions) and genetic predisposition seem to be of importance in diabetic embryopathy, i.e. this is a case of environment–gene interaction. The congenital malformations are likely to be induced in early gestation and the risk for giving birth to a child with a malformation is enhanced by increased maternal metabolic dysregulation .

Among women with overt diabetes before conception, the risk of a structural anomaly in the fetus is increased threefold to eightfold, compared with the 1% to 2% risk for the general population.(1)There is no increase in birth defects among offspring of diabetic fathers and nondiabetic women or in women who develop GDM after the first trimester, indicating that glycemic control during embryogenesis is the main factor in the genesis of diabetes-associated birth defects. A classic report by Miller and associates (2)compared the frequency of congenital anomalies in patients with normal or high first-trimester maternal glycohemoglobin levels and found only a 3.4% rate of anomalies with an Hb A 1C value lower than 8.5%, whereas the rate of malformations in patients with poorer glycemic control in the periconceptional period (Hb A 1C >8.5%) was 22.4%.

Bell and coworkers studied 1677 pregnant women with diabetes and more than 400,000 controls. (3). The rate of nonchromosomal major congenital anomalies in women with diabetes was 71.6 per 1000 pregnancies (95% confidence interval [CI], 59.6 to 84.9), an RR of 3.8 (CI, 3.2 to 4.5) compared with women without diabetes. There was a threefold to sixfold increased risk across all common anomaly groups. In multivariate analysis, periconceptional glycemic control (adjusted OR [aOR] = 1.3; [CI, 1.2 to 1.4] per 1% [11 mmol/L] linear increase in Hb A 1C above 6.3% [45 mmol/L]) and preexisting nephropathy (aOR = 2.5; CI, 1.1 to 5.3) were independent predictors of congenital anomaly. Unadjusted risk was higher for women who did not take folate. The typical congenital anomalies observed in diabetic pregnancies and their frequency of occurrence are listed as follows Congenital malformations account for approximately 50 percent of the perinatal deaths in IDMs (4) This risk can be reduced by strict glycemic control during the pre- and periconceptual (first eight weeks of pregnancy) periods.

Two-thirds of the anomalies in IDMs involve the cardiovascular system (8.5 per 100 live births) or central nervous system (CNS) (5.3 per 100 live births) (4) Cardiovascular malformations occur in 3 to 9 percent of diabetic pregnancies (5). Cardiac defects that present more frequently in IDMs than in the normal newborn population include transposition of the great arteries (TGA), double outlet right ventricle (DORV), ventricular septal defect (VSD), truncus arteriosus, tricuspid atresia, and patent ductus arteriosus (PDA) Anencephaly and spina bifida are 13 and 20 times more frequent, respectively, among IDMs compared with infants of nondiabetic mothers Flexion contracture of

the limbs, vertebral anomalies, cleft palate, and intestinal anomalies are more likely to occur in IDMs than in infants of nondiabetic mothers The majority of cases of small left colon syndrome occur in IDMs . Small colon syndrome is a rare condition that presents as a transient inability to pass meconium, which resolves spontaneously.

The majority of cases of caudal regression syndrome occur in IDMs This syndrome consists of a spectrum of structural defects of the caudal region, including incomplete development of the sacrum and, to a lesser degree, the lumbar vertebrae and occurs approximately 200 times more frequently in IDMs than in other infants

ANOMALY	APPROXIMATE RELATIVE RISK	PERCENT RISK
All cardiac defects	18	8.5%
CNS Anomalies	16	5.3%
Anencephaly	13	
Spina bifida	20	
All congenital anomalies	8	18.4%

The mechanism by which hyperglycemia disturbs embryonic development is multifactorial. The glucose transporter GLUT2 plays a prominent role in mediating embryonic glucotoxicity. **(6)** .A variety of environmental changes with teratologic consequences for diabetic embryopathy have been identified. Diabetic teratogenesis has been associated with oxidative stress, enhanced lipid peroxidation, decreased antioxidative defense capacity, and sorbitol accumulation. Along these lines, high doses of vitamins C and E decreased fetal dysmorphogenesis to nondiabetic levels in vivo and in rat embryo culture. **(7)**

Likewise, addition of prostaglandin inhibitors to cultures of mouse embryos prevented glucose-induced embryopathy. The underlying biochemical and molecular mechanisms of diabetic embryopathy have started to be deciphered. Disturbed arachidonic acid metabolism, alteration in activity of protein kinase C, increased apoptosis, and enhanced JNK1 and JNK2 activity have been well documented. Decreased expression of the gene PAX3 is central to the appearance of neural tube defects. Recent studies have indicated that the detrimental effect of PAX3 in embryos during a diabetic pregnancy are mediated by adenosine monophosphate–activated protein kinase (AMPK) signaling pathways.

Prevention.

Because the critical time for teratogenesis is during the period 3 to 6 weeks after conception, nutritional and metabolic intervention must be instituted preconceptionally to be effective. Several clinical trials of preconceptional metabolic care have demonstrated that malformation rates equivalent to those in the general population can be achieved with meticulous glycemic control.

Wahabi and colleagues analyzed 12 cohort studies with low or medium risk of bias involving 2502 women with diabetes who did or did not participate in preconception care. Their results showed that preconceptional care was effective in reducing the occurrence of congenital malformations (RR = 0.25; CI, 0.15 to 0.42); preterm delivery (RR = 0.70; CI, 0.55 to 0.90); and perinatal mortality (RR = 0.35; CI, 0.15 to 0.82). In these studies, preconception care lowered Hb A 1C in the first trimester of pregnancy by an average of 2.43% (CI, 2.27 to 2.58) and reduced diabetes-related congenital malformations, preterm delivery, and maternal hyperglycemia. **(8)**

Van Beynum and coworkers, in a case-control study assembled over a 10-year period (1996-2005), compared mothers who delivered infants with isolated heart defects (n = 611) and controls from the general population (n = 2401). 99 Folic acid was taken as a supplement or as a multivitamin in a dose of at least 400 µg daily. Those receiving periconceptional folic acid had an OR for all types of congenital heart defects of 0.82 (CI, 0.68 to 0.98) relative to other malformations. The estimated OR for congenital heart defects of folic acid supplementation was 0.74 (CI, 0.62 to 0.88) compared with the general population. These results demonstrated that periconceptional folic acid use was related to a reduction of approximately 20% in the prevalence of any congenital heart defect.**(9)**

Women with prediabetes should be counseled about their subsequent risk for developing overt diabetes and referred for discussion of management options (eg, lifestyle modification such as medical nutritional therapy, indications for metformin. They should try to achieve their ideal body weight through diet and exercise and, if possible, they should avoid drugs that may adversely affect glucose tolerance (eg, glucocorticoids). They should have yearly assessment of glycemic status. Women with prediabetes results should also be informed that breastfeeding may decrease their long-term risk of developing type 2 diabetes Women with overt diabetes mellitus should receive appropriate education and treatment. They should also be given advice regarding contraception and the planning of future pregnancies.In addition, women with prediabetes or overt diabetes should be counseled regarding the importance of good metabolic control prior to any future pregnancies.

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