Original Article

Congenital Anomalies among the Babies of Diabetic Mothers with Uncontrolled Blood Sugar -A Study in a Tertiary Hospital

Taslima K[1]

Abstract

Diabetes mellitus is a silent killer which affects at any stage of life. Worldwide incidence of major malformation among the offspring of diabetic mothers ranges from 5-10%. Though 65-75% of birth defects are multifactorial, poor diabetic control in pregnancy predisposes congenital malformation. The aim of this retrospective study is to see the actual picture of congenital anomalies among the babies of uncontrolled diabetic mothers. Cases are taken from the hospital records of the patients who delivered congenitally abnormal babies & were admitted in SCABU of BIRDEM during the period of January, 2006 to December, 2010. After going through all records, patients were divided into DM/GDM/ND groups and different variables are studied. Among the patients (163), 57 (35%) were DM, 38 were (23.3%) GDM and 68 (41.7%) were ND. Major congenital anomalies were found 82.45% in DM and 71.05% in GDM and 83.82% in ND patients. Rests were minor anomalies. Among the anomalies maximum were congenital heart diseases, then CNS anomalies, then renalanomalies and then others. In this study congenital anomalies were found 1.4 times more in DM patients. Among DM and GDM patients maximum had uncontrolled blood sugar. Neonatal mortality was higher in DM and GDM groups. Both cardiac and CNS abnormalities were 1.2 times higher in diabetic groups. Renal anomalies were 2.8 times higher. Limb abnormalities were 7.15 times higher in diabetic groups. So it is concluded that pregnancy with uncontrolled diabetes increases the risk of birth defects, mainly CVS, CNS and Renal system related.

Key words: Congenital anomalies, Babies of diabetic mother, Uncontrolled blood sugar

1. Corresponding Author:
Dr. Kazi Taslima
Junior Consultant
Department of Obs & Gynae
Upazila Health Complex, Matlab (South), Chandpur

Introduction

Congenital anomalies are recognised in 2-3% of newborn babies[1]. Anomalies are more common in pregnancies with diabetes, among aborted foetus, pre-term and still-born infants. Birth defects are the leading cause of infant deaths in USA[2]. In past, anomalies were responsible for 10% of all perinatal deaths. Now with the reduction of other causes malformation accounts for 30-50% of perinatal mortality. In worldwide studies incidence of major malformation among off-springs of IDDM (insulin dependant diabetes mellitus) mothers ranges from 5-10 %[3].

20-25% congenital malformations are the result of chromosomal abnormalities or single gene defect. 65-75% of birth defects are due to multiple causes such as maternal infections (e.g. CMV, syphilis, rubella, toxoplasma), maternal disease (e.g. diabetes, epilepsy, alcohol abuse), exposure to drugs (alcohol, thalidomide, folic acid antagonist, DES, androgen, anticonvulsant, high dose of vitamin A, synthetic oestrogen, radioactive iodine etc.) and radiation[2].

The cause of diabetic embryopathy is not fully understood. Maternal hyperglycaemia has proposed by most investigators as primary teratogenic factor but various factors are related such as hyperketonaemia, hypoglycaemia, somatomedin inhibitor excess, excess free radical production, reduced intracellular myoinositol, arachidonic acid deficiency, yolk sac failure and maternal vasculopathy[4]. Profile of a woman most likely to produce an anomalous infant would include a patient with poor periconceptional diabetic control, long standing diabetes with vasculopathy. Genetic susceptibility to the teratogenic influence of diabetes may be a factor. However, teratogenic effect of hyperglycaemia has been suggested by human study and has been confirmed by animal study[5].

Prior to the advent of insulin co-existence of DM with successful pregnancy was a rare event. William reported maternal mortality of 30% and perinatal loss of 70% in 1909. Discovery of insulin in 1921 changed the outlook for the pregnant patient completely. Maternal mortality was reduced to nil and perinatal mortality to 3-5 % over the years. High incidence of congenital malformation of about 12% is reduced to 5-6 % by pre-pregnancy counseling and control of diabetes. In pre-gestational diabetes, foetal mortality and morbidity occurs more than in gestational diabetes (GDM)[6].

Poor diabetic control predisposes congenital malformation, particularly of CNS, cardiac and renal systems. It occurs 3 to 4 times more commonly than in non-diabetic woman[7]. Comparable prevalence figures for congenital anomalies, ranging from 41 per 1000 to 97 per 1000, although these

studies have been based predominantly on the babies of women with type 1 diabetes[12]. In one study the prevalence of major anomalies in the offspring of diabetic mother was 46 per 1000 total births. This compares with 21 per 1000 total birthsfrom the EUROCAT data for 2002 (prevalence ratio 2.2, 95% confidence interval 1.8 to 2.6; P < 0.001). The prevalence of major anomalies associated with type 1 diabetes was 48 per 1000 total births, and the prevalence associated with type 2 diabetes was 43 per 1000 total births. Statistically significant increases were confined to anomalies of the nervous system (prevalence ratio 2.7, 1.5 to 4.4; P <0.001) and congenital heart disease (prevalence ratio 3.4, 2.5 to 4.6; P < 0.001). The increase in anomalies of the nervous system was driven by an increase in the observed number of neural tube defects (prevalence ratio 4.2, 2.0 to 7.8; P < 0.001)[11].

Sacral agenesis and caudal regression syndrome is almost pathognomonic of diabetes and occurs 256 times more often in diabetic than non-diabetic[13].

Rapid development of techniques allowing early and accurate pre-natal diagnosis of foetal disorder reduces the rate of congenital anomaly among newborn babies. Antenatal diagnosis of some cardiac conditions decreases the risk of neonatal mortality[8]. Routine ultrasound scanning foranomalies in the UK has been reported to identify 23% of cardiac defects[9]. Implementing specialist views of the fetal heart may increase the pick-up rate of cardiac anomalies up to 75%[14]. This study showed that cardiac lesions were the most frequent anomaly in the off spring of women with diabetes and 55% were detected ante-natally. If blood glucose concentration during diabetic pregnancy is maintained near normal level and available techniques for assessment of foetal growth and well-being are used appropriately, then a pregnancy outcome approaching that of non-diabetic mother can be achieved[15]. Congenital malformation developed during early gestational period. So its prevention necessitate pre-conceptional care. In 14 cohort studies, major congenital malformation swere assessed among 1192 off spring of mothers who had received preconception care and 1459 off spring of women who had not. The pooled rate of major anomalies was lower among preconceptioncare recipients (2.1%) than non-recipients (6.5%) (RR 0.36,95% CI 0.22-0.59)[16].

The aim of my study is to see the actual picture of congenital anomaly among diabetic mothers in our BIRDEM hospital and the association of poorly controlled DM with occurrence of congenital anomaly. My study will provide information to doctors, help them in pre-natal counseling and thus reduce the rate of occurrence of birth defects among babies of diabetic mothers.

Materials & Methods

This cross -sectional study was done in the Department of obstetrics and gynaecology in BIRDEM hospital, Dhaka from, January, 2006 to December, 2010. Permission was taken from the concerned Department & authorities after getting recommendation of ethical committee. Informed consent was taken from all the study subjects after full explanation of nature and purpose of study. Total 163 subjects of age ranged from 20 - 40 years were selected from the Department of Obs & Gynae and also from SCABU of same institute detail record files were searched to collect all data. Study subjects were selected according to inclusion and exclusion criteria Exclusion criteria were age >40 years, patients having congenital heart disease, patients with known autoimmune disorder like SLE, Hypothyroidism etc, patients with history of exposure to radiation, patients with history of teratogenic drugs taking. Inclusion criteria were after exclusion of above patients, all women who delivered congenitally abnormal babies in BIRDEM hospital and the mothers whose congenitally abnormal babies admitted in SCABU in same hospital. Sample were selected randomly according toinclusion and exclusion criteria. All data were checked and edited after collection. Then the data were entered into the computer and analyzed with the help of SPSS 12 program me.

Results

Among the mothers of congenitaly abnormal babies, maximum (58.3%) and among them 3.5% gave history of previous congenitally abnormal babies. Blood sugarwas found uncontrolledin 82.5% of diabetic and 89.5% are gestational diabetic patient. Among diabetic patient HbAIc was raised more indiabetic than gestational diabetes (96.5% versus 84.2%.

Multiple types of congenital anomalies was found and maximum was cardiac and CNS related. Among CNS anomalies hydrocephalus, meningocele and anencephaly was found.

Table-I shows out of 163 cases, majority 58.3% [95] were diabetic. Among them 35% [57cases] were pregestational and 23.3% were gestational.

Table-I :Glycaemic status of patients

Glycaemic status	No. of patient	Percentage
DM	57	35
GDM	38	23.3
ND	68	41.7
Total Diabetic Patients	95	58.3

Table II shows the history of congenitally abnormal baby in previous pregnancy. In the study population only in DM group 2 patients [3.50%] had the history of congenitally abnormal baby in previous pregnancy.

Table-II: History of congenitally abnormal baby in previous pregnancy.

Positive History of congenitally abnormal baby	No. of patient	Percentage
DM	2	3.50
GDM	0	0
ND	0	0

Table III shows the blood sugar level in DM and GDM. In DM patients 82.50% [47cases] were uncontrolled, where as in GDM group it was 89.50% [34 cases].

Table-III: Blood sugar level in DM and GDM.

No. of patient & Percentage	Blood sugar level [mmol/L]	
	Controlled (mmol/L)	Uncontrolled (mmol/L)
DM	10 (17.5%)	47 (82.5%)
GDM	4 (10.5%)	34 (89.5%)

Table IV shows the Haemoglobin A1C level in DM and GDM. In DM patients it was raised in 96.50% [55cases], where as in GDM group it was raised 84.20% [32 cases].

Table -IV: Haemoglobin A1C level in DM and GDM.

Haemoglobin A1C level		No. of patient	Percentage
DM	Within normal limit	2	3.5
	Raised	55	96.5
GDM	Within normal limit	6	15.8
	Raised	32	84.2

Table -V: Types of congenital anomalies in all groups[b].

Congenital anomalies		No of pt.	Percent
Hyrdocephalus	DM	8	14.03
	GDM	4	10.52
	ND	8	11.76
Meningocele/ With Encephalocele	DM	4	7.01
	GDM	3	7.89
	ND	7	10.29
Anancephale	DM	7	12.28
	GDM	3	7.89
	ND	3	4.41
Congenital heart disease	DM	13	22.80
	GDM	4	10.52
	ND	13	19.11
Renal anomalies	DM	7	12.28
	GDM	1	2.63
	ND	4	5.88
Cleft lip/ with Cleft palate	DM	1	1.75
	GDM	7	18.42
	ND	6	8.82
Coanal stenosis with lerangeal obstruction	DM	0	0
	GDM	3	7.89
	ND	0	0
Facial dismorphism	DM	4	7.01
	GDM	1	2.63
	ND	0	0
Congenital hydrocele, hypospadias, ambigousgenitalia	DM	4	7.01
	GDM	4	10.52
	ND	4	5.88
Congenital hydrocele, hypospadias, ambigousgenitalia	DM	4	7.01
	GDM	4	10.52
	ND	4	5.88
Limb abnormalities	DM	6	10.52
	GDM	4	10.52
	ND	1	1.47
Caudal regression syndrome	DM	1	1.47
	GDM	0	0
	ND	0	0
Diaphramatic hernia	DM	1	1.75
	GDM	1	2.63
	ND	0	0
Omphalocele	DM	1	1.75
	GDM	0	0
	ND	1	1.47

Table -VI: Rate of congenital anomalies.

Glycaemic status	Total deliveries	No. of anomalies	Percentage
DM	1865	57	3.05
GDM	1858	38	2.04
DM+GDM	3723	95	2.55
ND	1979	68	3.43

Discussion

Congenital anomalies are common causes of perinatal morbidity and mortality. In this study it is shown the types of congenital anomalies among the babies of diabetic mothers and comparison with that of non-diabetic mothers. This study done in BIRDEM hospital where diabetic patients are common and non-diabetic patients are also attended there.

This study has been done among the patients who delivered congenitally abnormal babies in BIRDEM hospital during the period extending from January 2006 to December 2010 [5 years]. It was a retrospective study. During the period I have seen 163 patients and I subdivided them in DM, GDM and ND groups. I compared them in various parameter. Blood sugar level was mentioned controlled/ uncontrolled; HbA1c was mentioned within normal limit/ raised according to ADA criteria. I found CNS, cardiac, renal anomalies, limb abnormalities, facial dysmophysm, omphocele and diaphragmatic hernia, congenital hydrocele and hypospadias are more common in diabetic than non-diabetic patients. Cleft lip/ with cleft palate are more common in non-diabetic group. Caudal regression syndrome found in one DM patients.

Age distribution

Most patients are between 30 - 34 years of age. Most congenital anomalies occurs after 30 years of age and least patients are before 20 years of age.

It reflects that most congenital anomalies occurs in aged pregnancy than early. Higher rate of education and improvement of consciousness about early marriage and child bearing is discouraged in educated society. In my study area [BIRDEM hospital] most patients come from middle class or higher class families.

Duration of Diabetes

Here duration of pregnancy is < 5 years in majority of cases which does not correlate with other studies[19]. Endocrinology & Metabolism news-September 2006, where major congenital anomalies associated with duration of diabetes >10 years in IDDM patients. In our study most patients are NIDDM [type -II] and here onset of diabetes occurs at a latter age, so most patient's duration of diabetes is < 5 years [68%] and least duration is 10 years (only 5%).

Glycaemic status of patient

Among 163 patients most patients are diabetic { DM (57) + GDM (38) = 95 (58.2%) }. That is congenital anomalies are 1.4 times more in diabetic patients. This result correlate with the study done by Marry C M Macintosh et al which indicates risk of major congenital anomalies are two fold in DM patients than general population.

History of IUD/still birth

In our study the incidence of IUD/ still birth is 2.38 times more in diabetic patients. Higher incidence of IUD &still birth in our study than that of Steel J. M. et al. Significantly higherstillbirth rates (4.7 times) and perinatal mortality (3.8 times) compared withthe general maternity population were found in a cohort study done by Mary C M Macintosh et al.

History of neonatal death

Neonatal mortality is higher in GDM [15.7%] and DM than in ND group [0%]. There is possibility of congenital anomalies and also other factor [birth asphyxia, PNS, prematurity] correlate with the study of Khatun F. Neonatal mortality found to be 2.6 times higher in a study done by Mary C M Macintosh et al.

History of abortion

Abortion is maximum in diabetic group [50.87%] and 1.3 times more in DM than ND patients which correlate with the study done by Dicker [1998], where it is 1.3 times more in IDDM patients.

History of congenitally abnormal baby

Among 57 diabetic cases 2 had positive H/O congenitally abnormal babies in previous pregnancy. So, recurrence of congenitally abnormal babies positive in diabetic patient and not in other groups.

Blood sugar level

The American College of Obstetricians and Gynecologists (ACOG) recommends that women with pregestational diabetes maintain fasting plasma glucose levels between 60-90 mg/dL and 2-hour postprandial levels <120 mg/dL[8]. For women with gestational diabetes who are not controlled within these targets on dietary therapy alone, ACOG recommends the additional of insulin therapy[9].

The American Diabetes Association recommends that women with pregestational diabetes maintain capillary plasma glucose levels of 80-110 mg/dL before and <155 mg/dL 2 hours after meals before pregnancy and while trying to conceive[10]. The ADA does not list target glucose level for women with pregestational diabetes once they become pregnant. The ADA recommends the use of diet and insulin therapy to maintain preprandial plasma glucose levels of <105 mg/dL and 2-hour postprandial levels below <130 mg/dL in gestational diabetes.

In our study we followed ADA criteria for the target of control blood suger level during pregnancy. So, controlled are grouped as fasting < 6.1 mmol/L [105 mg/dl] and post prandial < 7.6 mmol/L [130mg/dl].

Among 57 diabetic patients only 10 patents [17.5%] had controlled blood sugar level. Among 38 GDM patients 4 patients [10.5%] had controlled blood sugar level. So, it is clear that congenital anomalies are more common among the uncontrolled group. Rosenn and Tsang (1991) summarize several studies with compared incidences of congenital malformations in women with poor versus good control. The rate of birth defects among women with poor control ranges from 4.5% - 35.3%. However, with good glycaemic control, these risks are greatly reduced with a range from 0% - 10.7%.

HbA1c level

Among 57 diabetic patients only 55 patents [96.5%] had HbA1c level above normal level. In case of GDM patients it was 84.2%. Study done by Marry C M Macintosh et al showed that good control defined by glycosylatedhaemoglobin (HbA1c) of less than 7%, was achieved by 596 (37%) women. The median HbA1c was 7.9% for the women whose pregnancies resulted in a congenital anomaly. The result is similar to my study. In another study shows that, when the frequency of congenital anomalies in patients with normal or high first-trimester maternal glycosylated hemoglobin values was compared to the frequency in healthy patients, the rate of anomalies was only 3.4% with glycosylated hemoglobin (HbA1C) values of less than 8.5%, whereas patients with poorer glycemic control in the periconceptional period (HbA1C>8.5%) had a 22.4% rate of malformations. An overall malformation rate of 13.3% was reported in 105 patients with diabetes, but the risk of delivering an infant who is malformed was comparable to a normal population when the HbA1C value was less than 7%.

IUD/Still birth

It is 12.3% in DM group and 0% in GDM group and ND group [8.8%]. So, it is 1.4 times more in Diabetic group.The study of Mary C M Macintosh et al showed that neonatal mortality (2.6 times) in this cohort compared with the general maternity population in 2002.

Low birth weight

Incidence of LBW baby is almost similar in both diabetic [DM - 29.8% and GDM - 36.8%] and ND group [39.7%]. The study of Mangala R, et al showed that the mean difference in the birth weight of offspring between diabetic and non-diabetic women (133 g; -29 g to 296 g) was not significant (P=0.11)

The study of Metzger BE et al showed that in a total of 3764 women with GDM and 416 women with known type 2 diabetes mellitus. Maternal historical (age, prepregnancy

BMI, prior pregnancy with macrosomia, stillbirth or anomalies) and clinical parameter (gestational age at first prenatal visit, first trimester exposure to sulfonylurea agents) and value of the initial fasting glucose and HbA1c were investigated regarding their relation to anomalies. 143 infants (3.4%) with major anomalies were identified, with a prevalence of 2.9% in GDM and 8.9% in type 2 diabetes. The most frequently affected organ systems were cardiac (37.6%), musculo-skeletal (16%) and nervous system (9.8%).

In conclusion, DM in mother has been suggested an important risk factor for the development of congenital anomalies among the offspring. Mills [1988] reported rate of major malformation 2-3 times greater in infants of IDDM mother 3 even 10 times when DM is severe at conception. Others had found the rate of anomalies in offspring of diabetic women to be 2-5 times greater than the general population. The overall rate of congenital anomalies in infants born to diabetic mothers may be as high as 10% when there is not good glycemic control. The prevalence of malformations appears to increase with more severe degrees of diabetic disease 04 Mary C.M. Macintosh et al seen the risk of major congenital anomalies in the offspring of women with diabetes was more than two fold increased than in general population[17]. In our study we have found major anomalies are about 1.2 times more in diabetic patients. In our study most diabetic patients had uncontrolled blood sugar [96.5% in DM and 84.2% in GDM] and HbA1c level more than normal limit [> 7%]. Rosenn and Tsang (1991) summarize several studies with compared incidences of congenital malformations in women with poor versus good control. The rate of birth defects among women with poor control ranges from 4.5% - 35.3%. However, with good glycaemic control, these risks are greatly reduced with a range from 0% - 10.7%. As most of the anomalies of the foetus occur between 4th to 7th weeks of gestation after conception, so periconceptional diabetic control is important. In pre-conceptional care [in diabetic patients] strict blood sugar control is advised. In one study major congenital anomalies were lower among pre-conception care recipients [2.1%] than non-recipients [6.5%]. In 14 cohort studies, major congenital malformations were assessed among 1192 off spring of mothers who had received preconception care, and 1459 offspring of women who had not. The pooled rate of major anomalies was lower among preconception care recipients (2.1%) than non-recipients (6.5%) (RR 0.36, 95% CI 0.22-0.59). In nine studies, the risk for major and minor anomalies was also lower among women who received preconception care (RR 0.32, 95% CI 0.17-0.59)[15]. We found commonest anomalies were cardiac anomalies in IDDM. Tamura and Dooley, (1991). Becerra (1990) reports a relative risk of 18 for cardiovascular anomalies associated with IDDM, with an absolute risk of 8.5/100 live births. Others report a 2-4 times increased risk for CHD, with the severity and duration of the diabetes impacting on the rate. Rowland et al (1973) found as many as 4% of infants born to diabetic mothers have CHD. Mary C.M. Macintosh found CHD 3.4 times than in general population.

Rate of birth defect among women with poor control ranges from [4.5%-35.3%], However, with good glycaemic control. The study of Mary C M Macintoshet al[17] showed that it was similar to that of nondiabetic group. As diabetic embriopathy occurs at early gestational age [4-7 wks after conception], periconceptional blood sugar control is obligatory.

Referances

1. Arias F. Diabetes and pregnancy. In: Practical guide to high risk pregnancy and delivery. 2nd ed. USA: Mosby-Year Book Inc; 1993:23.

2. Cunningham F.G, Mac Donald P.C, Gant. N.F, Leveno K.J, Gilstrap E.C, Hankins G.V.D et al. Diabetes. In: William's Obstetrics. 20th ed. Stamford, CN: Appleton and Lange; 1993:1203.

3. Landon M.B. Diabetes and other endocrine disease. In: Gabbe S.G, Niebyl J.R, Simpson J.L. editors. Obstetrics (Normal and problem pregnancy 3rd Ed. New York: Churchill Livingstone Inc; 1996:1040-42.

4. Hawdon J.M, Green A.A. The infant of a diabetic mother. In: Rennie J.M, Robertson N.R.C. editors. Textbook of neonatology. 3rd ed. London: Harcourt Brace and company limited; 1999:404.

5. Platt MJ, Stanisstreet M, Casson IF, Howard CV, Walkinshaw S, Pennycook S, et al. St Vincent's declaration 10 years on: outcomes of diabetic pregnancies. Diabet Med. 2002;19:216-20.

6. Diabetes and Pregnancy Group. French multicentric survey of outcome of pregnancy in women with pregestational diabetes. Diabetes Care. 2003;26:2990-3.

7. Perinatal mortality and congenital anomalies in babies of women with type 1 or type 2 diabetes in England, Wales, and Northern Ireland: population based study. BMJ. 2006 22 July;333:177. doi:10.1136/bmj. 38856.692986. AE (published 16 June 2006).

8. Khoshnood B, De Vigan C, Vodovar V, Goujard J, Lhomme A, Bonnet D, et al. Trends in prenatal diagnosis, pregnancy termination, and perinatal mortality of newborns with congenital heart disease in France, 1983-2000: a population-based evaluation. Pediatrics. 2005;115:95-101.

9. Dutta D C. In: Text book of Obstetrics. 5thedn. Calcutta: New central book agency (P) Ltd; 2001:28-40.

10. Okley NW, Beard RW and Turner RC. Effect of carbohydrate in norma and diabet pregnancies. British Medical Journal. 1972;1:466-468.

11. Simpson, JL, Elias set al. Diabetes in pregnancy. Revised ADA criteria 2006.

12. Prospective study of anomalies in offspring of mothers with DM. AMJ ObstGynaecol. 1983;146:263.

13. Mary C M Macintosh, Kate M Fleming, Jaron A Bailey. BMJ. 2006 July 22;333:177 (doi:10.1136/bmj. 38856.692986. AE (published June 16, 2006)

14. Nagy G. Management of gestational diabetes. Journal Zentrabel Gynaecol. 1993;115(4):147-153.

15. Metzger BE, Coustan DR. Summary and Recommendations of the 4th International Workshop-Conference on Gestational Diabetes. Diabetes Care. 1998;3221 (Suppl.):161-167.

16. J.G. Ray, T.E O`Brien, W.S. Chan. Preconceptional care and the risk of congenital anomalies in the offspring of women with DM. Q J Med. 2001;94:435-444.

17. Thomas R Moore, Ylinen K, Aula P, Stenmen U-H, Kesaniemi-Kuokkanen T, Teramo K. Risk of minor and major fetal malformations in diabetics with high haemoglobin A1c values in early pregnancy. Br Med J. 1984;289:345-6.