

CONGENITAL ABNORMALITIES AND PREGESTATIONAL DIABETES MELLITUS IN PREGNANCY

Y T Chia, S Chua, A C Thai, L P Kek, S S Ratnam

ABSTRACT

Despite falling perinatal mortality rate, congenital malformation remains the major cause of mortality in infants of mothers with established diabetes. The perinatal mortality rate in this group of infants is 5 times the overall perinatal mortality rate in this hospital. It is well established that pre-pregnancy counselling and maintenance of euglycaemia during the periconception period are the keys to prevention of congenital malformation. We are able to offer pre-pregnancy counselling to 29% of our diabetic mothers who are diagnosed to have pregestational diabetes mellitus only after the 6 weeks postnatal oral glucose tolerance test. Even in the known established diabetes mellitus, 95% of the patients were first seen after the period of organogenesis (>8 weeks). This could explain our high congenital malformation rate of 15.7%

Keywords: congenital malformation, pregestational diabetes mellitus

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INTRODUCTION

Major congenital abnormalities occur in 7.5%-12.9% of infants of mothers with established diabetes who register for care post-conception⁽¹⁻⁵⁾. This rate is seven or more times greater than the rate seen among infants of non-diabetic women. Over the past 30 years, despite falling perinatal mortality rate, congenital malformation is difficult to eliminate and now is the major cause of mortality⁽⁶⁾.

The time of greatest risk of structural defects is before the 9th week gestation. Poor metabolic control during this period is accepted as a major explanation for the phenomenon of infants of mothers with insulin dependent diabetes having an increased frequency of congenital malformations. Indeed, many investigators look upon hyperglycaemia as almost the sole teratogenic mechanism⁽¹⁾. It is important to improve glycaemia control during pre-conception to reduce major congenital abnormalities in the offspring, to rates equivalent to the expected rate in the non-diabetic population.

In our population, pregnancy is complicated by diabetes mellitus in 5% of patients, 25% of which are established

diabetics⁽⁷⁾. There is a high rate of major congenital malformation in our patients with established diabetes. We embarked on a retrospective study to look at the clinical characteristics of our established diabetic patients that might contribute to the high incidence of congenital malformation.

METHODS

The case records of 44 antenatal patients with pregestational diabetes mellitus, attending the Diabetic Clinic in the Department of Obstetrics and Gynaecology, National University Hospital, Singapore, between October 1989 - March 1993, were studied retrospectively. Of these, 21 (48%) were diagnosed to have diabetes mellitus or impaired glucose tolerance after the 6 weeks postnatal oral glucose tolerance test, the rest being known diabetics for between 1 and 16 years. All patients were admitted to hospital for initial control of the blood sugar and subsequently discharged for follow-up in the outpatient diabetic clinic. Monitoring of the diabetic condition include weekly 7-point home glucose profile, monthly glycosylated haemoglobin, and a 2-hour postprandial hypocount at the weekly diabetic clinic visit. If the diabetic control is unsatisfactory, they were then readmitted. An ultrasound scan is scheduled at 12-13 weeks' amenorrhoea to date the pregnancy as well as to detect gross neural tube defect and cardiovascular abnormality. At 22 weeks, a detailed fetal abnormality scan is performed, followed by a repeat growth scan at 32 weeks. Subsequently, growth scans and non-stress test and amniotic fluid index assessment are used for fetal surveillance. For well-controlled diabetics, pregnancy is terminated between 38-39 weeks of amenorrhoea.

Assessment of mean blood sugar level up to 27 weeks, between 28-35 weeks and after 36 weeks was done by averaging the blood glucose level in each period. The outcome of the pregnancy was assessed by type of labour, mode of delivery, neonatal outcome in terms of congenital malformation, birthweight, Apgar score at 5 minutes, presence of hyperbilirubinaemia, neonatal hypoglycaemia and respiratory distress syndrome.

RESULTS

Forty-four women were recruited into the study. Their mean age was 31.75 years (range 24-40 years) and 40.9% of them were primiparous. Historical risk factors include previous stillbirth (6.8%), previous babies with birthweight of more than 4 kg (11.3%), and miscarriages (31.2%), with 4.5% or 2 patients having 3 miscarriages; 61% of patients had first degree relatives with diabetes mellitus.

Department of Obstetrics and Gynaecology
National University Hospital
5 Lower Kent Ridge Road
Singapore 119074

Y T Chia, MRCOG
Lecturer

S Chua, MRCOG
Senior Lecturer

S S Ratnam, FRCOG
Professor and Head

Department of Medicine
National University Hospital

A C Thai, M Med (Int Med)
Associate Professor

3 Mt Elizabeth #12-18
Mt Elizabeth Medical Centre
Singapore 228510

L P Kek, MRCOG
Consultant

Correspondence to: Dr Y T Chia
3 Mt Elizabeth #13-13
Mt Elizabeth Medical Centre
Singapore 228510

Sixty-one percent (27) of our patients were booked only after the first trimester. Of these, 37% (10) were known overt diabetics before pregnancy. Forty-eight percent (21) of the patients were diagnosed retrospectively to be established diabetes mellitus only after the 6 weeks postnatal oral glucose tolerance test. A diagnosis of gestational diabetes mellitus was made in the index pregnancy in these 21 patients (48%).

Of the women who were known diabetics before pregnancy, only 50% (23) had treatment of their diabetic condition from the team in the first trimester, with one patient being treated at 5 weeks amenorrhoea, and the rest at 7-10 weeks amenorrhoea. Therefore, 95% of the pregnancies were seen after the period of organogenesis. Of the 22 patients treated only after 7 weeks, 31.8% (7) showed poor control at booking with a blood sugar level >6.7 mmol/L; this could account for the high rate of congenital malformation.

The duration of diabetes mellitus ranges from those detected in index pregnancy (47.7%), 1-5 years (36.3%), 6-10 years (11.3%), 11-15 years (2.3%) and 16-20 years (2.3%). Known diabetics had some form of treatment (diet, oral hypoglycaemic, insulin) before pregnancy. During pregnancy, 22.7% required dietary advice alone, the rest were on insulin and diet. In 38% of the patients, treatment was initiated in the first trimester by the team, 40.9% in the second trimester and 20.5% in the third trimester.

Using a normal range for HbA1c of 4%-6% (9), 54.5% (24) were abnormal when treatment was initiated. There were 20 (43%) women with HbA1c <6%, of which 3 (15%) had congenital malformations, compared with the group of 24 women with HbA1c >6% in whom 4 (16.6%) had malformations; the difference was not statistically significant. There were 5 patients with HbA1c >10%, in whom one patient had congenital malformation (20%) compared with the group of 39 patients with HbA1c <10% where 6 (15.4%) had congenital malformation; the difference was also not statistically significant.

Of the 35 patients who had blood sugar profile performed in the first 27 weeks of amenorrhoea, 82.8% had average hypoglycaemia level of < 6.7 mmol/L. Between 28-35 weeks, data of blood glucose profile of 39 patients were collected and 95% had average hypoglycaemia levels <6.7 mmol/L; while after 35 weeks, 30 patients had blood glucose profiles with 90% average blood glucose <6.7 mmol/L.

The congenital malformation rate was 15.7% (7 of 44) with cardiac malformation and/or cleft lip and palate being the 2 malformations in all the patients (Table I). Three of these patients had normal HbA1c at booking (including one patient who had poorly controlled blood sugar level in pre-pregnancy and complications of diabetic nephropathy and retinopathy) and were booked at 8, 28 and 36 weeks (Table I).

Table I – Profile of diabetic patients who had babies with congenital malformation.

Patients	Age/ Race/ Gravity/ Parity	Risk factors	At booking		BSL control during pregnancy	Delivery: gestation/mode	Congenital malformations	Neonatal Outcome
			Gestation (wks)	HbA1c(%)				
1.	33, Malay G2P1	previous child BW > 4kg. DMx1 yr on hypoglycaemic	36	5.8	good	40 wks Emergency LSCS for no progress	cleft lip and palate, complete AV septal defect, mitral regurgitation, TGA and PDA	3 kg Alive
2.	33, Chinese G2P0	F/H DM. 1 miscarriage. DM x 10 yr with nephropathy and retinopathy. On insulin.	28	5.9	poor	34 wks Elective LSCS for poor DM control, poor renal function and hypertension	Pulmonary stenosis, Ebsteinoid malformation, Tricuspid stenosis and regurgitation, mild hypoplastic right ventricle and confluent pulmonary arteries	1.8 kg Died after surgery at 1.5 yrs
3.	44, Malay G1P0	F/H DM. DM x 6 yrs on oral hypoglycaemic	12	6.3	good	38 wks NVD	Double outlet and inlet left ventricle, coarctation of aorta, PDA, patent foramen ovale, pulmonary valve incompetence, left superior venae cava, dilated coronary sinus	2.6 kg Jaundice, cyanosed at birth. Alive
4.	33, Malay G3P1	1 miscarriage. DM x 2 yrs on oral hypoglycaemic	7	10.3	good	34 wks preterm labour. Emergency LSCS for no progress	TGA, PDA, patent foramen ovale	3 kg Apnoeic attacks D11: died post-surgery
5.	28, Malay G1P0	DM diagnosed at 13 weeks amenorrhoea	13	9.1	good	36 wks, NVD	Hypoplastic left ventricle, mitral atresia, coarctation of aorta, VSD, PDA	2.1 kg Jaundice, RDS Died at 1 mth
6.	28, Malay G3P1	1 miscarriage. Patient has cleft lip. DM diagnosed at 8 wks amenorrhoea	8	5.8	good	36 wks NVD	Complete cleft lip and palate.	4.3 kg Jaundice hypoglycaemia Alive
7.	33, Indian G2P0	F/H DM. 1 miscarriage. DM diagnosed at 9 weeks amenorrhoea	9	10.0	good	36 wks, surgical induction, emergency LSCS for no progress	Cardiomyopathy	4.3 kg hypoglycaemia Alive

BW – Birthweight
DM – Diabetes mellitus
AV – Atrial ventricle
TGA – Transposition of great arteries
PDA – Patent ductus arteriosus

F/H : Family history
NVD : Normal vaginal delivery
RDS : Respiratory distress syndrome

DISCUSSION

This diabetic population has a high rate of congenital malformation (15.7%). This is against a background rate of structural defects of 2.8% in the general obstetric population in this hospital, of which, cardiac and central nervous malformations are equally common, each constituting 23.1% of the total malformation. The high rate of congenital malformation in this study is attributable to late booking, late diagnosis of gestational diabetes mellitus and poor glycaemia control in periconception period. This study did not look into the number of patients who had oral glucose tolerance test performed specifically after structural abnormality had been found.

Healthcare providers attending to diabetic women should emphasise preconception glycaemia control and the importance of planned pregnancy and early booking. Patients who have high risk factors, specifically maternal obesity, advanced maternal age, previous stillbirth, family history of affected first degree relatives, and previous large babies could be screened for diabetes mellitus early in pregnancy and perhaps seen before planning a pregnancy. This could theoretically uncover the large proportion of diabetic women who were discovered only late in the index pregnancy. However, O'Sullivan et al⁽¹⁰⁾, using these historical risk factors, have shown that they have a sensitivity of only 63% and a specificity of only 56% which means that 37% of gestational diabetics in a population were missed when historical risk factors were used in choosing patient for testing, while 44% of the normal patients were subjected for diagnostic test before they were declared normal.

The use of glycated haemoglobin serves a dual purpose in that it gives an indication of glycaemia control⁽¹¹⁾ and high levels in the first trimester is thought to be predictive of congenital malformation⁽²⁾. In our patients, HbA1c levels were done at the first visit and subsequently at monthly intervals. More than half (52.3%) of our patients had abnormal HbA1c level at first antenatal visit. Among the 7 patients with congenital malformation, 4 (57.1%) patients had abnormal level of HbA1c (Table I). Of the 3 patients with malformation and normal HbA1c, one patient, a pregestational diabetes mellitus on insulin had poorly controlled blood sugar levels > 6.7 mmol/L at diagnosis and complications of diabetic nephropathy and retinopathy.

We found poor specificity and correlation between HbA1c and congenital malformation, contrary to Miller et al⁽²⁾ who found that patients with HbA1c level >10% in the first trimester had high incidence of congenital malformation. Our data support the findings of animal and other human teratogenic studies which suggested that hyperglycaemia, although an important teratogenic mechanism, is not the sole cause for diabetic teratogenicity. Because diabetes mellitus has a strong genetic component, the possibility that there is a genetic predisposition to diabetic related malformation has been raised⁽¹³⁾. Another possible contribution to poor correlation between HbA1c and malformation could be that those with very high HbA1c and poorly controlled diabetes had higher rate of spontaneous abortion. This possibility is not analysed in this study.

Although oral agents have been opposed as therapeutic option in gestational diabetes mellitus due to fear of teratogenesis, Coetze and Jackson⁽⁸⁾ in South Africa used it as the mainstay of therapy. They found no increase in teratogenesis. This is in contrast with Piacquo et al⁽¹⁵⁾ in the United States. This group found malformation rate which was significantly different between the Type II diabetic women on oral agents versus Type II diabetes not on oral agent at the time of conception (50% vs 15%). Those patients on oral hypoglycaemic agents at the time of conception had ear malformation not usually associated with diabetic embryopathy. In our study, it is unlikely that the high rate of congenital malformation is attributed to oral

hypoglycaemic agent. Of the 7 mothers with congenitally malformed babies, 3 (41.8%) were on oral hypoglycaemic in early pregnancy, as compared with 57.1% (4 of 7) who had malformed babies and were not on oral hypoglycaemic agents which was not statistically significant. Furthermore, none of the babies had ear malformation which was specifically attributed to oral hypoglycaemic agents.

Congenital heart disease is probably the most common malformation in infants of diabetic mothers, occurring between 1.7%-4% of the infants⁽¹²⁾. We have only 2 types of congenital malformation in our study – congenital heart disease and cleft lip and palate. Six out of 7 infants had congenital heart disease. Ultrasonography at 12-13 weeks by both the abdominal vaginal route, followed by a detailed fetal echocardiography at 22 weeks and a repeat scan at 32 weeks detected 4 out of 6 congenital heart malformation. In 2 of the 6 patients, fetal cardiac abnormality was not diagnosed antenatally. The shortfall of ultrasound echocardiography is the poor pictures in our diabetic patients who are more likely to be obese.

Although there has been marked improvement in the perinatal mortality and morbidity rate in infants of diabetic mothers over the past 30 years, congenital malformation still remains the foremost cause of perinatal mortality and morbidity. In this series, 3 out of the 7 infants with congenital malformation died, giving an overall mortality rate of 6.8% and a perinatal mortality of 45/1000 (1 infant died at 1.5 years of age), which is 5 times that of our overall perinatal mortality rate in this hospital. Only by screening patients at high risk of diabetes before pregnancy and by offering prepregnancy counselling in a known diabetic patient of child bearing age can we bring down the high congenital malformation rate.

REFERENCES

1. Kalter H, Warkany J. Congenital malformations: etiologic factors and their role in prevention. *N Engl J Med* 1983; 308: 424.
2. Miller E, Hare JW, Cloherty JP. Elevated maternal hemoglobin A1c in early pregnancy and major congenital anomalies in infants of diabetic mothers. *N Engl J Med* 1981; 304: 1331.
3. Furhmann K, Reiher H, Semmler K, Fischer F, Fischer M, Glockner E. Prevention of congenital malformations in infants of insulin-dependent diabetic mothers. *Diabetes Care* 1983; 6: 219.
4. Ylinen K, Aula P, Stenman UH, 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.
5. Steel JM. Prepregnancy counselling and contraception in the insulin-dependent diabetic patient. *Clin Obstet Gynecol* 1985; 28: 553.
6. Gabbe S. Medical complications of pregnancy. Management of diabetes: Six decades of experience. In: Pitkin RM, Zlatnik FJ. eds. *Year book of Obstetrics and Gynaecology. Obstetrics Year Book Of Medical complications*. Chicago: Yearbook 1980; 1: 37-49.
7. Kek LP, Ng CSA, Ching KP, Cheah JS, Yeo PB, Gwee HM et al. Extremes of foetal birthweight for gestation in infants of diabetic mothers. *Ann Acad Med Singapore* 1985; 14: 303.
8. WHO Expert Committee. Second report on diabetes. Geneva: WHO 1980 (Tech. Rep. Ser. 646).
9. Ylinen K, Raivo K, Teramo K. Haemoglobin A1c predicts the perinatal outcome in insulin dependent diabetics pregnancies. *Br J Obstet Gynaecol* 1981; 88: 961.
10. O'Sullivan JB, Mahan CM, Charles D, Dandrow RV. Screening criteria for high risk gestational diabetic patients. *Am J Obstet Gynecol* 1973; 116: 895.
11. Dunn PJ, Cole RA, Soeldner JS. Temporal relationship of glycosylated haemoglobin concentrations to glucose control in diabetics. *Diabetologia* 1979; 17: 213.
12. Rowland TW, Hubbel JPP, Nadas AS. Congenital heart disease in infants of diabetic mother. *J Pediatr* 1973; 83: 815.

13. Mills JL, Baker L, Goldman AS. Malformation in infants of diabetic mothers occur before seventh gestational week: implication for treatment. *Diabetes* 1979; 28: 292.
14. Churchill JA, Berendes HW, Nemore J. Neuropsychological defects in children of diabetic mothers. *Am J Obstet Gynecol* 1969; 105: 257-68.
15. Petersen MB, Pedersen SA, Greisen G, et al. Early growth delay in diabetic pregnancy: relation to psychomotor development at age 4. *Br Med J* 1988; 296: 598-600.