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Fetal growth patterns in fetuses of women with pregestational diabetes mellitus

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KEYWORDS: diabetes; fetal growth; fetal ultrasound; high risk obstetrics; pregnancy care

ABSTRACT

Objective *To assess the effect of glucose control on the rate of growth of fetuses in women with pregestational diabetes mellitus (Types 1 and 2).*

Methods *All pregestational diabetic women booked at Mater Mothers' Hospital, Brisbane, Australia, between 1 January 1994 and 31 December 2002, were included. Pregnancies with congenital fetal anomalies, multiple pregnancies, and pregnancies terminated prior to 20 weeks' gestation were excluded. Dating scans were performed before 14 weeks' gestation and serial scans were performed at 18, 24, 28, 32 and 36 weeks. Fetal parameters, including biparietal diameter, femur length and abdominal circumference, were recorded. The daily growth rates for biparietal diameter, femur length, and fetal abdominal area were calculated and compared with those in a low-risk (non-diabetic) population. The growth rates in fetuses of women with satisfactory diabetic control (HbA1c < 6.5%) and unsatisfactory control (HbA1c ≥ 6.5%) in the three trimesters were compared.*

Results *A total of 174 diabetic pregnancies were included and a total of 997 ultrasound scans were performed. The growth rates for fetuses of mothers with diabetes mellitus were significantly higher than for those in the low-risk population. The* z*-scores for biparietal diameter, femur length, and fetal abdominal area were 0.18, 0.59 and 1.44, respectively. Fetuses of diabetic mothers with high HbA1c in the first trimester had significantly greater fetal abdominal area growth rate than those with normal HbA1c (fetal abdominal area* z*-score of 1.7 vs. 0.75,* $P = 0.009$*). Although the fetal abdominal area* z*-scores in fetuses of diabetic mothers with high HbA1c in the second or third trimesters were also higher than those with normal HbA1c levels, the differences did not reach statistical significance. Maternal obesity did not influence the fetal growth rate.*

Conclusion *The rate of growth of fetuses of diabetic mothers differs from that of the normal population. Growth acceleration persists until the late third trimester. Moreover, periconceptional glucose control appears to have a significant effect on accelerated growth of the fetal abdominal area. Copyright © 2006 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Macrosomia occurs in a significant proportion of fetuses in women with insulin-dependent diabetes, even in those with relatively good glycemic control[1]. Recently, Raychaudhuri *et al.* and our group found that macrosomic babies of diabetic mothers have increased fetal size from the second trimester onwards, and that the difference in size persists despite improvements in diabetic control[2,3]. We found that macrosomic babies have a larger abdominal circumference from 18 weeks' gestation onwards, but failed to show that diabetic control has any significant effect on fetal size[3]. Other maternal factors such as obesity, excessive weight gain in pregnancy, duration of diabetes, type of diabetes, and presence of vasculopathy can confound the risk for macrosomia[4–11].

Many studies have failed to demonstrate a consistent relationship between macrosomia and diabetic control[5–7,12–15]. Some researchers have proposed that such poor correlation might relate to differing recommendations for target blood glucose concentration or the gestational age at which tight control was achieved[5–7,12–15]. Other growth factors or hormonal factors may also affect the rate of fetal growth[16]. Such confusion can be partially resolved if growth rate rather than absolute fetal

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size is studied. Studying the relationship between growth rate and glucose control should be more meaningful than studying fetal size alone[17]. Fetal growth rate will also provide us with more information on the dynamic changes in the first, second and third trimesters in relation to maternal glucose control. The aim of this study was to assess fetal growth rate in pregnant women with diabetes mellitus.

PATIENTS AND METHODS

This study was conducted at Mater Mothers' Hospital, a tertiary obstetric hospital in Brisbane, Australia. All pregestational diabetic women (Types 1 & 2) booked between 1 January 1994 and 31 December 2002 were included. Pregnancies complicated by congenital fetal anomalies, multiple pregnancies, or those terminated prior to 20 weeks' gestation were excluded. Dating scans were performed before 14 weeks' gestation and estimated due dates were adjusted accordingly. Serial scans were performed at intervals of less than 6 weeks from 18 weeks onwards; the majority had ultrasound scans at 18, 24, 28, 32 and 36 weeks. Thus, women delivered at term would have had at least five ultrasound scans (excluding the booking scan), while women who delivered prematurely might have had fewer than five scans.

Fetal biometric parameters – including biparietal diameter, femur length and abdominal circumference – were recorded. Fetal abdominal circumference was converted to abdominal area using the formula: abdominal area = (abdominal circumference)$^2/4\pi$.

To analyze fetal growth rates, pairs of observations made between 14 and 28 days apart were used. Fetal abdominal area was compared with the nomogram for daily abdominal area that was published by Owen *et al.*[17]. Daily growth rate for each individual was calculated by the following formula:

$$\frac{(\text{Observation 2} - \text{Observation 1})}{\text{number of days between Observations 1 and 2}}.$$

Daily growth was tabulated against the value obtained by the second measurement. *Z*-scores for the mean daily growth rates for biparietal diameter, femur length, and fetal abdominal area were calculated based on the data published by Owen *et al.* *Z*-score was calculated by the following formula[17]:

$$\frac{\begin{array}{c}(\text{Observed measurement} \\ - \text{ mean gestation-specific measurement})\end{array}}{\text{gestation-specific standard deviation.}}$$

The effects of maternal diabetic control and obesity on the rate of fetal growth were assessed. Obesity was defined as a pre-pregnancy body mass index of more than 25 kg/m^2. Satisfactory diabetic control was defined as HbA1c of less than 6.5%. Mean HbA1c levels were determined at each trimester for all the women. Mean first-, second- and third-trimester HbA1c were defined as mean HbA1c measured at < 13 weeks, 13–28 weeks and > 28 weeks, respectively. The effects of elevated first-trimester, second-trimester and third-trimester HbA1c on fetal growth rate were assessed.

Statistics

Statistical analyses were performed using the Statistical Package for Social Science (SPSS Inc., Chicago, IL, USA). The unpaired Student's *t*-test was used to compare continuous variables with normal distribution. The Mann–Whitney test was used when the data were distributed in a non-Gaussian fashion. Repeated measures ANOVA testing was used to compare the three different trimesters. Values of $P < 0.05$ on two-tailed analyses were considered statistically significant.

RESULTS

During the study period, there were a total of 213 diabetic pregnancies, of which 174 met the inclusion criteria and had ultrasound dating and serial ultrasound scans for fetal size. A total of 997 ultrasound scans were performed on these women. The mean maternal age was 28 ± 5.5 years, and median parity was 1. There were 93 pregnancies (53.4%) complicated by Type 1 diabetes mellitus. These women required insulin before pregnancy, and serum C-peptide confirmed insulin deficiency. The other women had insulin resistance, the majority of whom (57, 70%) were on an oral hypoglycemic agent prior to pregnancy, while the others were being treated with insulin (9, 11%) or diet alone (15, 19%). The mean pre-pregnancy maternal weight was 74 ± 21.1 kg and the mean body mass index was 27.8 ± 7.2 kg/m^2. The mean HbA1c measured during the first trimester was 7.9 ± 2.1%; mean second-trimester HbA1c was 6.8 ± 1.3%; and mean third-trimester HbA1c was 6.8 ± 1.2%.

The mean daily increments for biparietal diameter, femur length, and fetal abdominal area are listed in Table 1. Increments for biparietal diameter, femur length, and fetal abdominal area were higher than for those in a low-risk population from 26 weeks' gestation onwards[17]. The mean *z*-scores for biparietal diameter, femur length, and fetal abdominal area were 0.18, 0.59 and 1.44, respectively. Owen *et al.* found that the growth rate for a low-risk population (without medical complication or growth restriction) reached a plateau or decreased after 34 weeks' gestation[17]. In this study, the accelerated growth rate persisted until 38 weeks of gestation. The maximal growth rates for biparietal diameter, femur length and abdominal circumference were achieved at around 32 to 34 weeks of gestation.

There was no difference in the overall growth rate of fetuses in women with Types 1 and 2 diabetes. On analysis of the growth rate at 4-weekly intervals, no difference was found between the groups (data not shown). Therefore, data from women with Type 1 and Type 2 diabetes were grouped together in the subsequent analysis, thus

providing a larger sample size and greater statistical power.

Comparing fetal growth rate in women with satisfactory diabetic control versus those with unsatisfactory control, there were no differences in the daily increment of biparietal diameter and femur length, as well as their respective *z*-scores between the two groups of fetuses (Table 2). The fetuses of women with elevated first trimester HbA1c had a significantly higher fetal abdominal area growth rate. The fetal abdominal area *z*-score was 1.7 versus 0.75, $P = 0.009$ (Table 2). On the other hand, although the fetal abdominal area *z*-scores were also higher in fetuses whose mothers had high levels of HbA1c in the second or third trimesters, the results were not significantly different from fetuses whose mothers had normal HbA1c levels (Table 2). Among the population, 65.5% (114/174) of the women were obese. We failed to demonstrate that maternal obesity has an effect on fetal growth rate. The growth rates for biparietal diameter (*z*-score: 0.52 vs. 0.42, $P = 0.25$), femur length (*z*-score: 0.81 vs. 0.36, $P = 0.15$) and fetal abdominal area (*z*-score: 1.51 vs. 1.37, $P = 0.68$) were comparable between the obese and non-obese women.

DISCUSSION

Strict metabolic control has been shown to improve perinatal outcomes in pregnancies complicated by pregestational diabetes mellitus. Despite improved perinatal mortality, macrosomia is still common in these pregnancies, which are often associated with higher perinatal morbidity. Macrosomia is commonly associated with poor diabetic control, but maternal characteristics such as obesity may also contribute to fetal macrosomia[3,6–11]. The present study attempted to differentiate the effect of maternal weight, the most common confounding factor, from the effects of diabetic control. Fetal growth rate, instead of fetal size, was assessed. As shown in our previous study, fetal size differences have already occurred by the early second trimester in fetuses destined to become macrosomic in obese diabetic mothers[3]. Assessment of growth rate will enable one to appreciate changes in fetal size, rather than size alone.

This study showed that growth rates for biparietal diameter, femur length and fetal abdominal area among the fetuses of diabetic mothers were higher than those in the low-risk population from 26 weeks' gestation onwards. The differences were greatest for fetal abdominal area, followed by femur length and biparietal diameter. This finding is expected, as fetal size is most accurately reflected by the size of the abdomen[18]. Biparietal diameter is the least affected fetal parameter among fetuses of women with diabetes mellitus.

In our analysis of the effect of glucose control, periconceptional control seemed to have the most significant effect on fetal growth rate, at least as far as the abdominal area is concerned. Previous studies on fetal macrosomia have confirmed that preconception and first-trimester glucose control has the greatest effect on fetal size[6,19–23]. We postulate that an elevated glucose level in the first trimester may result in early programming of the fetus and result in subsequent accelerated growth rate. This would explain why many studies have failed to show that subsequent satisfactory glucose control has any significant effect on the incidence of macrosomia[24–27]. Recent publications have suggested that adverse intrauterine conditions are linked to adult diseases such as diabetes mellitus, hypertension and cardiovascular diseases[28–31].

Our current findings support the hypothesis that fetal growth rate is programmed at the periconceptional period. In our previous study, we showed that macrosomia could

Table 1 The mean daily increment in biparietal diameter (BPD), fetal abdominal area (FAA) and femur length (FL) between 23 and 38 weeks of gestation

GA (weeks)	*BPD (mm)*		*FAA (mm^2)*		*FL (mm)*	
	Mean ± SD	n	*Mean ± SD*	n	*Mean ± SD*	n
23	0.5357 ± 0.0844	13	0.4974 ± 0.1421	13	0.4525 ± 0.1276	13
24	0.3863 ± 0.1419	34	0.4636 ± 0.2106	34	0.3985 ± 0.0933	34
25	0.4243 ± 0.1190	14	0.3826 ± 0.1802	14	0.3886 ± 0.1353	14
26	0.4024 ± 0.0922	26	0.5661 ± 0.1845	26	0.3149 ± 0.1386	26
27	0.4003 ± 0.1337	34	0.6222 ± 0.1553	34	0.3127 ± 0.1392	34
28	0.4237 ± 0.0947	87	0.5672 ± 0.2148	87	0.3615 ± 0.1524	87
29	0.4284 ± 0.1243	20	0.5905 ± 0.4049	20	0.3076 ± 0.0826	20
30	0.4015 ± 0.1082	38	0.6931 ± 0.3161	38	0.2869 ± 0.0997	38
31	0.3638 ± 0.1066	52	0.7139 ± 0.3234	52	0.3311 ± 0.1268	52
32	0.3920 ± 0.1176	53	0.8689 ± 0.4411	53	0.2987 ± 0.1388	53
33	0.3423 ± 0.1208	26	0.7988 ± 0.4314	26	0.3759 ± 0.1548	26
34	0.3488 ± 0.1263	69	0.9211 ± 0.4173	69	0.3209 ± 0.0998	69
35	0.3112 ± 0.1487	23	0.7601 ± 0.3409	23	0.2644 ± 0.1380	23
36	0.2768 ± 0.1343	79	0.8294 ± 0.3382	79	0.3451 ± 0.1964	79
37	0.2344 ± 0.1393	38	0.7493 ± 0.7477	38	0.2299 ± 0.1644	38
38	0.2360 ± 0.097	40	1.0862 ± 0.4372	40	0.2507 ± 0.1420	40

GA, gestational age.

Table 2 The mean daily increment and *z*-score for biparietal diameter (BPD), femur length (FL) and fetal abdominal area (FAA) based on overall glucose control at different trimesters

	First-trimester HbA1c			*Second-trimester HbA1c**			*Third-trimester HbA1c†*			*Overall HbA1c*		
Parameter	< 6.5%	≥ 6.5%	P	< 6.5%	≥ 6.5%	P	< 6.5%	≥ 6.5%	P	< 6.5%	≥ 6.5%	P
BPD (mm)	0.37 ± 0.13	0.36 ± 0.13	0.95	0.35 ± 0.13	0.35 ± 0.15	0.78	0.31 ± 0.14	0.30 ± 0.16	0.91	0.36 ± 0.14	0.35 ± 0.13	0.36
BPD *z*-score	0.23	0.27	0.92	0.59	0.036	0.15	1.31	0.52	0.30	0.14	0.03	0.69
FL (mm)	0.34 ± 0.10	0.33 ± 0.16	0.84	0.33 ± 0.09	0.34 ± 0.18	0.46	0.32 ± 0.13	0.34 ± 0.18	0.57	0.32 ± 0.11	0.32 ± 0.17	0.73
FL *z*-score	0.72	0.61	0.76	0.74	0.72	0.95	1.03	0.77	0.65	0.51	0.59	0.81
FAA (mm^2)	0.65 ± 0.25	0.74 ± 0.32	0.049	0.73 ± 0.29	0.81 ± 0.47	0.17	0.72 ± 0.34	0.77 ± 0.44	0.27	0.75 ± 0.32	0.79 ± 0.44	0.38
FAA *z*-score	0.75	1.70	0.009	1.15	1.67	0.20	1.11	1.99	0.19	1.41	1.55	0.71

*Cases only included from 28 weeks onwards. †Cases only included from 34 weeks onwards.

be detected from the early second trimester, but failed to show any association between first-, second- and third-trimester HbA1c[3]. The current study has shown that periconceptional glucose control has a direct effect on the fetal growth rate and possibly the fetal birth weight, but we failed to demonstrate that maternal obesity has an effect on the growth rate.

The implication of our study is that to further improve the perinatal outcome for pregnant women with pre-existing diabetes, every attempt should be made to achieve euglycemia during the periconceptional period. Such effort should be made in collaboration with physicians, endocrinologists and general practitioners caring for women of reproductive age with diabetes mellitus. Further studies may provide information on the feasibility, effectiveness and outcome of such programs.

The weakness of this study includes the use of HbA1c to define satisfactory and poor control groups. Mean glucose level would probably provide a better reflection of diabetic control. As this is a retrospective study, we did not have the complete set of daily glucose readings. Among our non-compliant women, many did not provide good home monitoring records. In these women the effect of poor control is of interest, and exclusion of these women would make this study incomplete. Therefore, we decided to use HbA1c of more than 6.5% to define poor diabetic control. In this study we also included both insulin dependent and non-insulin dependent diabetes (Types 1 and 2 diabetes). Ideally, the two groups should be analyzed separately. As the total sample size was small and there were no statistically significant differences between the two groups, we decided to combine both groups. Bearing in mind these deficiencies, the study provides us with evidence that the growth rate of fetuses in women with pre-existing diabetes is in fact different from that in the normal low-risk population. Furthermore, high periconceptional HbA1c is associated with a higher rate of growth of the fetal abdominal area.

In conclusion, the growth rate of fetuses of diabetic mothers differs from that in the normal population. The growth acceleration persists until the late third trimester. Moreover, periconceptional glucose control appears to have a significant effect on accelerated growth of the fetal abdominal area.

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