# Fetal Growth Spurt and Pregestational Diabetic Pregnancy

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**OBJECTIVE** — To assess the timing of fetal growth spurt among pre-existing diabetic pregnancies (types 1 and 2) and its relationship with diabetic control. To correlate fetal growth acceleration with factors that might influence fetal growth.

**RESEARCH DESIGN AND METHODS** — This retrospective study involved all pregestational diabetic pregnancies delivered at a tertiary obstetric hospital in Australia between 1 January 1994 and 31 December 1999. Pregnancies with major congenital fetal anomalies, multiple pregnancies, small-for-gestational-age pregnancies (<10th centile), and those that were terminated before 20 weeks were excluded. In this cohort, pregnancies delivered at term had at least four ultrasound scans performed. The first scans were performed before 14 weeks of gestation and were regarded as dating scans. Abdominal circumference measurements were retrieved from the ultrasound reports. The *z*-scores for abdominal circumferences, according to the gestational age, were calculated. The gestations when the ultrasound scans were performed were stratified at four weekly intervals beginning at 18 weeks and continuing through the rest of the study. Majority of these diabetic pregnancies had ultrasound scans performed at 18, 28, 32, and 36 weeks. The abdominal circumference *z*-scores for pregnancies with large-for-gestational-age (LGA) babies (>90th centile for gestation) were compared with babies with normal birth weights.

**RESULTS** — A total of 101 diabetic pregnancies were included. Diabetic mothers, who had LGA babies, had significantly higher prepregnancy body weight and BMI ($P < 0.05$). There were no differences in maternal age or parity among the two groups. There were also no differences in the first-, second-, and third-trimester $HbA_{1c}$ levels between the two groups. The abdominal circumference *z*-scores were significantly higher for LGA babies from 18 weeks and thereafter. The differences increased progressively as the gestation advanced. Maximum difference was noted in the third trimester (30–38 weeks).

**CONCLUSIONS** — Fetal growth acceleration in LGA fetuses of diabetic mothers starts in the second trimester, from as early as 18 weeks. In this study, glucose control did not appear to have a direct effect on the incidence of LGA babies, and such observation might result from the effects of other confounding factors.

*Diabetes Care* **25:1681–1684, 2002**

Macrosomia occurs in a significant proportion of fetuses of pregnant women with type 1 diabetes, despite relatively good glycemic control (1). With the advent of modern obstetric care, the incidence of congenital malformations has reduced, but large-for-gestational-age (LGA) babies and associated complications remain high. One might postulate that this is related to the varying recommendations for target blood glucose concentration (2–5). Nevertheless, maternal factors such as obesity and excessive weight gain in pregnancy might also contribute to the development of LGA neonates (6,7). Poor correlation between blood glucose concentration and birth weight might also be related to the gestational age at which tight control was achieved. These might account for the conflicting results in many of the reported studies (8–10). Apart from diabetic control, maternal characteristics have also been shown to be associated with LGA babies (8–14).

Recently, growth acceleration among fetuses of diabetic mothers was reported to start at 22 weeks of gestation and to continue despite improvements in diabetic control (15). Such acceleration was determined by prevailing maternal glucose concentrations in the early trimesters. However, it is unclear whether fetal growth spurt occurs even earlier than the late second trimester. It is still controversial whether fetal growth rate is determined by diabetic control in the first or second trimester. In the current study, we assessed the timing of fetal growth spurt in pre-existing diabetic pregnancies (type 1 and 2) and its relationship with diabetic control ($HbA_{1c}$ levels in the first, second, and third trimesters). We also attempted to correlate growth acceleration with other factor(s) that might influence fetal growth. These include maternal parity and prepregnancy BMI.

## RESEARCH DESIGN AND METHODS

— This retrospective study was conducted at Mater Mothers' Hospital, a tertiary obstetric hospital in Brisbane, Australia. All pregestational diabetic pregnancies (types 1 and 2) delivered between 1 January 1994 and 31 December 1999 were included. Type 1 diabetes was defined as women having insulin deficiency requiring injectable insulin prior to becoming pregnant and documentation of insulin deficiency by C-peptide measurement or history of diabetic ketoacidosis. Type 2 diabetes was defined as women having late-onset diabetes secondary to insulin resistance.

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Received for publication 19 November 2001 and accepted in revised form 5 July 2002.

**Abbreviations:** AC, abdominal circumference; LGA, large-for-gestational-age.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

**Table 1—*Maternal characteristics and first-, second-, and third-trimester $HbA_{1c}$ levels for pregnancies with normal birth weight versus those with LGA babies***

| | Normal | LGA | *P* |
|---|---|---|---|
| *n* | 58 | 43 | NA |
| Age (years) | 27.8 ± 5.2 | 28.5 ± 6.1 | 0.55 (NS) |
| Parity | 1.12 ± 1.24 | 1.29 ± 1.22 | 0.193 (NS) |
| Type 2 diabetes | 21 (36) | 19 (44) | 0.418 (NS) |
| Prepregnancy weight (kg) | 73.5 ± 19.1 | 82.2 ± 18.2 | 0.018 |
| BMI (kg/m$^2$) | 27.7 ± 7.0 | 30.5 ± 6.3 | 0.045 |
| $HbA_{1c}$ | | | |
| First trimester | 8.1 ± 2.0 | 7.5 ± 2.0 | 0.104 (NS) |
| Second trimester | 7.1 ± 1.3 | 6.4 ± 1.2 | 0.055 (NS) |
| Third trimester | 6.8 ± 1.3 | 6.8 ± 1.2 | 0.797 (NS) |
| Satisfactory sugar control* | 19 (33) | 16 (37) | 0.554 (NS) |
| Gestation at delivery (weeks) | 36.2 ± 2.8 | 36.7 ± 1.7 | 0.306 (NS) |
| Birth weight | 2903 ± 701 | 3916 ± 531 | <0.0005 |

Data are means ± SD or *n* (%). *Satisfactory control: prepandial < 6 mmol/l and postprandial < 7 mmol/l. NA, not applicable; NS, not significant

Pregnancies that did not have dating scans and serial growth scans were excluded from this study. Pregnancies with major congenital fetal anomalies, multiple pregnancies, small-for-gestational-age (<10th centile) pregnancies, and those pregnancies that were terminated before 20 weeks were also excluded. Sonographers performing the ultrasound scans had no prior knowledge of the current study. The medical records of these pregnancies were reviewed.

In this cohort, pregnancies delivered at term had at least four ultrasound scans performed. The first ultrasound scan was usually performed before 14 weeks of gestation and was regarded as a dating scan. This was used as the estimated date for women who had an uncertain menstrual date. For women with a certain menstrual date, the estimated date would be adjusted if there was a discrepancy of >10 days. Pregnancies delivered prematurely might have had less than four ultrasound scans performed.

Abdominal circumference (AC) measurements were retrieved from the ultrasound reports. The *z*-scores for abdominal circumferences, according to the gestational age, were calculated. The nomogram used to calculate the AC *z*-score was based on data published by Hadlock et al. (16). The *z*-score was calculated by the following formula: 1−[AC − mean AC (gestation specific)/1 SD for AC (gestation specific)]. AC was chosen because it was found to reflect the birth weight more accurately in diabetic pregnancies (17). The gestational age when the ultrasound scans were performed were stratified at four weekly intervals beginning at 18 weeks and continuing through the rest of the study. The majority of these diabetic pregnancies had ultrasound scans performed at 18, 28, 32, and 36 weeks. The AC *z*-scores for pregnancies with LGA babies were compared with those who had babies with normal birth weights. An LGA baby was defined as having a birth weight >90th centile for gestation, based on a birth weight centile chart derived from babies delivered in the same hospital.

Glucose control was assessed with home glucose monitoring and $HbA_{1c}$. In these series, all women were managed with outpatient home glucose monitoring. Satisfactory home glucose monitoring was defined as a preprandial glucose level <105 g/dl and a postprandial glucose level <120 g/dl in the majority of the readings (>80%). These results were coupled with a normal $HbA_{1c}$ <6.5%.

**RESULTS** — During the study period, there were a total of 129 diabetic pregnancies. Of these, 101 diabetic pregnancies met the inclusion criteria and had received a dating ultrasound scan as well as serial scans for fetal growth. Of the women, 65 (64%) had type 1 diabetes and the rest (36%) had type 2 diabetes. The prevalence of LGA babies was slightly higher among type 2 diabetic women (50 vs. 38%, $P = 0.26$). There was no difference in the incidence of pregnancy-induced hypertension among women with LGA and average-for-gestational-age babies (15 vs. 16%, $P = 1.0$). The maternal characteristics, $HbA_{1c}$ results, gestation at delivery, and birth weight are listed in Table 1. Diabetic mothers, who had LGA babies, had significantly higher prepregnancy body weight BMI ($P < 0.05$). There were no differences in the maternal age or parity among the two groups. There were also no differences in the first-, second-, and third-trimester $HbA_{1c}$ levels between the two groups. There was no difference in the number of women with satisfactory home glucose monitoring. The gestation at delivery was comparable but, as expected, the birth weight for the LGA group was significantly heavier than that for the normal group (3,916 vs. 2,903 g, $P < 0.0005$).

The *z*-scores of the ACs are listed in Table 2. The AC *z*-scores were significantly higher for LGA babies, which were measured at 18 weeks and thereafter. The AC *z*-scores for the 22- to 26-week period

**Table 2—*AC z-score for normally grown and LGA fetuses***

| | Control group ($N = 58$) | | LGA group ($N = 43$) | | | |
|---|---|---|---|---|---|---|
| Gestation (weeks) | *n* | Mean AC *z*-score | *n* | Mean AC *z*-score | Difference in mean *z*-score | *P* |
| 18–22 | 37 | −1.1224 ± 1.3 | 30 | 0.4411 ± 1.0 | 0.6813 | 0.025 |
| 22–26 | 14 | −0.1659 ± 1.8 | 9 | 0.9053 ± 1.57 | 1.0712 | 0.16* |
| 26–30 | 48 | −0.0561 ± 1.2 | 26 | 1.0464 ± 1.6 | 1.1025 | 0.001 |
| 30–34 | 53 | 0.09874 ± 1.38 | 40 | 2.07 ± 1.5 | 1.9713 | <0.0005 |
| 34–38 | 53 | 0.94 ± 1.12 | 43 | 2.9 ± 1.5 | 1.960 | <0.0005 |

Data are means ± SD. *The scores for the 22- to 26-week period were not statistically significant because of the small sample size in both groups, despite a difference in the mean *z*-score by 1.071.

were not statistically significant because of the small sample size in both groups, despite a difference in the mean *z*-score by 1.071. The differences increased progressively as the gestation advanced and reached maximum difference in the third trimester (30–34 weeks).

**CONCLUSIONS** — Macrosomia is one of the common adverse outcomes associated with diabetic pregnancy. This condition is commonly associated with poor diabetic control, but maternal characteristics such as obesity may also contribute to LGA babies (8–14). Strict metabolic control has been shown to improve perinatal outcome. However, despite improved perinatal mortality, macrosomia is still common and is associated with higher perinatal morbidity.

The current study showed that the ACs of the LGA fetuses were significantly larger than their normal size counterparts at as early as 18 weeks. This difference was accentuated even more in the third trimester. Such a finding suggests that fetal growth was determined very early, possibly even earlier than the second trimester. Thus, LGA may be influenced by factors affecting fetuses during the first and second trimesters. These may include diabetic control, maternal obesity, genetic factors, or severity of maternal diabetes, such as duration of diabetes, vasculopathy, and type of diabetes.

Since the *z*-score for the normal birth weight group was below zero (*z*-score = −1.1), such an observation might be partly due to inclusion of Asian and Aborigine subjects. Both races had lower mean birth weight and therefore might have lower AC *z*-score. In this study, we used a North American AC database; thus, the mean second-trimester AC might be higher than the Asian and Aboriginal counterparts.

Another possible explanation for the lower second-trimester *z*-score in the normal birth weight group, might imply "early growth retardation." In this group, there were more women with type 1 diabetes (Table 1) and these women had higher first- and second-trimester $HbA_{1c}$, reflecting poorer control. Women with type 1 diabetes were more likely to have vasculopathy, longer duration of diabetes, difficult diabetic control during early gestation, and associated medical disorders. All these factors could contribute to smaller fetuses during the second trimester. Thus, the lower *z*-score for the normal birth weight group might reflect smaller fetuses resulting from more severe maternal diabetes. Subsequent influence of poorly controlled maternal diabetes, as implied by the raised $HbA_{1c}$ in this group, might nullify the effect of "growth restriction" and give rise to an apparently normal size fetuses and babies. In this study, we did not have data on the duration of diabetes, vasculopathy, smoking status, treatment before pregnancy, and the overall mean glucose level. Therefore, we did not know how the fetal size was affected by these factors. Moreover, the small sample size in the two groups would not allow meaningful statistical analysis.

In the current study, women who had LGA babies did not have higher $HbA_{1c}$ levels. However, the mean first-trimester $HbA_{1c}$ of 7.5 and 8.1% observed in this study were high and unacceptable controls by current standards. A better glucose control should be achieved before conception. A few possible explanations could account for such an observation. First, maternal obesity may be a major contributing factor for LGA babies. Studies on women with gestational diabetes have confirmed that maternal BMI has a strong association with LGA babies (12–14). In the current study, women who gave birth to LGA babies did have higher prepregnancy weight and maternal BMI- and women with type 2 diabetes were more likely to have LGA babies. There was strong association between maternal obesity and type 2 diabetes.

Second, early programming of fetal growth by elevated maternal glucose levels during the periconceptional period may result in subsequent LGA babies. Previous studies have shown that first- and second-trimester $HbA_{1c}$ levels were associated with macrosomia (18–20). Gold et al. (18) has shown that periconceptional glucose control was most predictive of birth weight in type 1 diabetic pregnancies (18). Unfortunately, the majority of the women included in this study had their first $HbA_{1c}$ readings at or after 8 weeks of gestation. Thus, we had insufficient data to assess the role of periconceptional diabetic control on the incidence of LGA babies.

Thirdly, $HbA_{1c}$ might not be a good predictor for LGA babies. Kyne-Grzebalski et al. (21) has shown that episodic hyperglycemia could be associated with normal $HbA_{1c}$ results. There was plenty of evidence that poorly controlled diabetes was associated with fetal macrosomia (22,23). It is also well known that many women with satisfactory glucose control based on $HbA_{1c}$ or sugar profile still had LGA babies. These may be due to episodic hyperglycemia, which is not reflected by $HbA_{1c}$ results.

Fourthly, as described before, babies of the normal birth weight group might have a combination of intrauterine growth restriction due to bad maternal diabetic characteristics and subsequent growth acceleration due to raised maternal glucose level. Fetal growth is a complicated process with an interplay of many factors. Therefore, it was difficult to identify a specific factor that could fully explain the result observed in this study.

In conclusion, the current study showed that fetal growth acceleration in LGA fetuses of diabetic mothers starts in the second trimester, beginning as early as 18 weeks. In this study, glucose control did not appear to have direct effect on the incidence of LGA babies. Various confounding factors might have contributed to this contradicting finding. Interplay between the factors causing intrauterine growth retardation, such as vasculopathy and long-standing type 1 diabetes, in combination with those causing large babies, such as poor glucose control and maternal obesity, might have resulted in such a conflicting outcome.

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