Intrauterine growth rate in pregnancies complicated by type 1, type 2 and gestational diabetes

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Summary: Fetal macrosomia is a feature of all subtypes of maternal diabetes. The intrauterine time course of development of macrosomia in type 1, type 2 and gestational diabetes (GDM) could identify the times of more rapid growth, which differ as a result of different influences in subtypes of diabetes. Higher maternal weight in type 2 and GDM may be expected to contribute to macrosomia and the blood glucose control will exert an additional influence. Information was collected prospectively on 217 pregnancies in insulin-treated women at a single centre over a six-year period. All women were managed by a single team of obstetricians and diabetologists at a Joint Obstetric Medical Clinic. The rate of increase in abdominal circumference from 28 weeks was identical in each subtype of diabetes and there were no differences between subtypes at the earliest gestation assessed. Use of customized growth centiles showed rates of macrosomia to be similar in type 1, type 2 and GDM (43.0%, 50.0% and 41.8%, respectively). The intrauterine time course to macrosomia is similar in type 1, type 2 and GDM. The relationship of macrosomia to extent of elevation of mean blood glucose control is weak, implying a low threshold for maximal effect on the rate of fetal growth.

Keywords: intrauterine growth, diabetes, macrosomia, customized growth centile

INTRODUCTION

Macrosomic babies remain a major problem associated with diabetic pregnancy and the underlying factors are not well defined. However, the time course of intrauterine growth requires to be defined. The prevalence of macrosomia has been reported to be similar in types 1 and 2 compared with gestational diabetes (GDM),¹ even though the major known influences, maternal weight and HbA_{1c}, differ between subgroups. HbA_{1c} levels are higher in first trimester of type 1 diabetes compared with type 2 diabetes and GDM,² and blood glucose levels only rise in later pregnancy in GDM.

Maternal weight exerts a major influence on birth weight.^{3–5} The weight of women with type 2 or GDM tends to be considerably higher than those of women with type 1 diabetes.^{1,6} The relative influences on intrauterine growth rates require to be more closely defined, especially as maternal obesity is a constant throughout pregnancy and HbA_{1c} tends to decrease throughout pregnancy in types 1 and 2 diabetes, but rise in GDM. Macrosomia is the endpoint of a long process. Although the intrauterine time course to macrosomia may not be the same in subtypes of diabetes, this has not been previously evaluated. Serial ultrasound data permit description of the time course of intrauterine growth.

Comparison of birth weight data between groups of women with type 1, type 2 and GDM is complicated by differences in several factors, notably ethnicity, age and weight. The customized growth centile statistic was derived to allow examination

of growth corrected for these potential confounders.⁷ This analysis has not hitherto been applied to test the hypothesis that this will change the distribution of birth weights, when groups of women with different subtypes of diabetes are compared.

We report a six-year, single-centre prospective study of time course of intrauterine growth in consecutive singleton births in diabetic women who were insulin-treated during pregnancy. In addition, customized growth centiles between women with type 1, type 2 and GDM were compared.

Patients and methods

Information was collected prospectively on 217 pregnancies in insulin-treated women who booked for antenatal care and subsequently delivered of singleton pregnancies at the Royal Victoria Infirmary, Newcastle upon Tyne, between 1 January 2000 and 31 December 2005. There were five sets of twins and these were not included in the analysis to avoid violation of statistical requirements. All the women were managed by a single team of obstetricians and diabetologists at the Joint Obstetric Medical Clinic. The women with pre-gestational diabetes were seen at booking, monthly until 28 weeks gestation, fortnightly between 28 and 36 weeks gestation and weekly thereafter until delivery. Women were telephoned frequently by one diabetes specialist nurse and more frequent visits were arranged if blood glucose control was not optimal. The women with GDM were identified by the District screening programme of testing non-fasting plasma glucose at 28 weeks gestation and oral glucose testing of all women with levels ≥ 6.5 mmol/L.⁸ All such women were seen in the clinic, given dietary advice and

commenced on home blood glucose testing. Insulin therapy was commenced using the criterion of two-hour post-prandial blood glucose levels >7.5 mmol/L or fasting blood glucose >6.0 mmol/L. They were reviewed in the clinic according to the schedule for pre-gestational diabetes from the time of commencing insulin therapy, but as for pre-gestational diabetes women frequent telephone contact with diabetes specialist nurse was important.

HbA_{1c} and total insulin requirements were checked at each visit. The estimated due date was derived from a scan at around 12 weeks gestation. All booked women had an anomaly scan at 19 weeks gestation and a fetal echocardiogram at 23 weeks. This was followed by serial growth scans from 28 weeks gestation and every visit thereafter. From 2003, 24 week scans were introduced to assess growth and uterine artery Doppler. Ultrasound growth parameters included abdominal circumference and femur length. The unit policy is to electively deliver all insulin-treated women between 38 and 39 weeks gestation. Maternal blood glucose during labour was controlled by a standardized combined glucose, insulin and potassium infusion as previously described.⁹ Neonates were fed as soon as practicable after delivery and not routinely admitted to special care baby unit (SCBU). The neonatal blood glucose pre-second feed was collated. Neonatal whole blood glucose was measured using a Yellow Springs glucose analyser (YSI Inc, OH, USA).

HbA_{1c} was measured monthly by Bio-Rad high-performance liquid chromatography (coefficient of variation 1.3% at mean HbA_{1c} of 10.0% and 1.9% at mean HbA_{1c} of 5.8%). The HbA_{1c} assay was standardized upon that used in the Diabetes Complications and Control Trial Central Laboratory at the University of Minnesota, with an upper limit of normal of 6.1%.¹⁰

The customized growth centile is calculated using a computer programme [Gardosi J, Francis A. Gestation-related optimal weight (GROW) customized centile calculator] GROW-CC software, version 5.1, 2006 and gestation network (see www.gestation.net) using the principles of the GROW programme.^{7,11} The three main underlying principles are: (1) weights are assessed in reference to a standard, which is individually adjusted for physiological pregnancy variables, e.g. at 40 weeks, a 3 kg baby is small for an average size mother but may be normal for a small mother; (2) the standard is 'optimized' to obtain the growth potential, i.e. pathological variables such as smoking are excluded – this means that the expected term

baby weight for a mother who smokes is calculated as if she was a non-smoker; and (3) optimal weight is calculated using a fetal rather than a neonatal weight standard. This software generates an individual 'customized' standard by adjusting for physiological factors known to affect fetal growth compared with population centiles. The version 5.1 individual calculator gives the option of customization based on data-sets from Nottingham, UK ($n = 40,000$), Sweden ($n = 400,000$) and New Zealand ($n = 5000$). In our analysis, customization based on data-set from Nottingham was selected.

Signed consent was obtained from each woman to allow data storage and ongoing analysis of clinical outcomes for audit and monitoring purposes. The study was approved by the Newcastle upon Tyne Foundation Trust.

Continuous data were given as mean $\pm$ SD and categorical data presented as proportions. Differences between means were tested by Student's *t*-test and Mann-Whitney *U* test as appropriate. Correlations were tested by Pearson's correlation coefficient using the Minitab Statistical Package (Minitab Inc., State College, PA, USA). Statistical significance was accepted at $P < 0.05$.

RESULTS

The clinical characteristics of the women in each group are shown in Table 1. The type 2 diabetes group were older, heavier, had higher parity compared with the type 1 diabetes group and contained significantly more women of Asian ethnicity. The 17.4 kg difference in booking weight between these groups was striking. The GDM group was similar in age to the type 1 group, but were heavier. The group weights reflect the later first attendance at the Obstetric Medical Clinic of the GDM women (11.6, 13.0 and 28.4 weeks; type 1, type 2 and GDM, respectively). Despite a 0.9% higher mean HbA_{1c} at eight weeks gestation age in type 1 diabetes compared with type 2 diabetes women (8.0% versus 7.1%, $P < 0.05$), mean HbA_{1c} during pregnancy was similar in the types 1 and 2 diabetes groups, but significantly lower in the GDM group (Figure 1, Table 1). Mean blood pressure was notably similar between the groups despite the weight differences.

The mean gestation at delivery was not significantly different between the groups (Table 2). The rates of elective caesarean section were 15.5%, 21.4% and 16.1% for type 1, type 2 and

Table 1 Maternal characteristics

	Type 1	Type 2	GDM
Number of pregnancies	129	31	57
Number of women	107	30	53
Maternal age (years)	29.7 $\pm$ 5.6*	35.7 $\pm$ 5.0*†	30.7 $\pm$ 4.7†
Number of primigravidas	37/129	4/31	12/56
Median parity + IQR	1 $\pm$ 2 (range 0–6)	3 $\pm$ 3 (range 0–10)	1 $\pm$ 2 (range 0–6)
Number of Asian women	0/107 (0%)	8/30 (26.7%)	14/53 (26.4%)
Number of caucasian women	107/107 (100%)	19/30 (63.3%)	39/53 (73.6%)
Mean systolic BP (mmHg)	118 $\pm$ 8	118 $\pm$ 8	117 $\pm$ 9
Mean diastolic BP (mmHg)	72 $\pm$ 6	73 $\pm$ 6	73 $\pm$ 8
Mean HbA _{1c} throughout pregnancy	7.0 $\pm$ 1.0† (range 5.1–11.1)	6.8 $\pm$ 1.0† (range 5.3–9.1)	6.2 $\pm$ 0.9†‡ (range 4.7–9.7)
Mean weight at initial visit (kg)	71.2 $\pm$ 12.1*†	88.6 $\pm$ 23.7*	87.9 $\pm$ 21.6†
Mean gestation at initial visit (weeks)	11.6 $\pm$ 6.0†	13.0 $\pm$ 7.0†	28.4 $\pm$ 8.2†‡

The parity data reflect individual pregnancy records, not individual woman

IQR = interquartile range

* $P < 0.05$ between type 1 and type 2

† $P < 0.05$ between type 2 and GDM

‡ $P < 0.05$ between type 1 and GDM

Figure 1 Mean HbA_{1c} during pregnancy in type 1 (solid circles), type 2 (open triangles) and gestational diabetes women (open squares). * $P < 0.05$

GDM, respectively, and for emergency section were 41.1%, 28.6% and 33.9%, respectively. During labour, blood glucose levels were close to the midpoint of the target range of 4–8 mmol/L and were similar in the type 1 (mean 6.6 ± 2.0 mmol/L) and GDM women (mean 6.1 ± 1.4 mmol/L). Mean blood glucose during labour was approximately 1 mmol/L lower in the type 2 (5.8 ± 1.4 mmol/L) than type 1 group, although this did not attain statistical significance ($P = 0.08$). Neonatal blood glucose levels were similar between the groups, but the rate of SCBU admissions was higher in the type 2 group (39.3%) compared with either type 1 (28.6%) or GDM (17.0%) ($P < 0.05$ between type 2 and GDM; $P > 0.05$ between type 1 and GDM and between type 1 and type 2; Table 2). Although the rates of neonatal hypoglycaemia (defined by blood glucose < 2.5 mmol/L) was highest in type 2 group (12 of 27 cases with recorded neonatal blood glucose [44.5%]) and lowest in GDM group (10 of 33 cases with recorded neonatal blood glucose [30.3%]), hypoglycaemia only accounted for half of the SCBU admissions. The rates of preterm delivery, defined as delivery at < 37 gestation

Figure 2 Rate of increase in fetal abdominal circumference measured by ultrasound. The measurements were derived by tracing abdominal circumference as described by Chitty *et al.*³¹ The 5th, 50th and 95th centile data for infants of non-diabetic mothers are plotted as dashed lines³¹

weeks, were similar in types 1 and 2 groups, but significantly lower in the GDM group ($P < 0.05$; Table 2).

Between 28 weeks and term, rates of growth as assessed by ultrasound measurement of fetal abdominal circumference (Figure 2) and femur length (Figure 3) were similar in all

Table 2 Maternal and neonatal outcomes

	Type 1	Type 2	GDM
Mean gestation at delivery (days)	262 $\pm$ 11	260 $\pm$ 9	265 $\pm$ 10
Elective C-section rate	20/129 (15.5%)	6/28 (21.4%)	9/56 (16.1%)
Emergency C-section rate	53/129 (41.1%)	8/28 (28.6%)	19/56 (33.9%)
Mean maternal blood glucose during labour (mmol/L)	6.6 $\pm$ 2.0	5.8 $\pm$ 1.4	6.1 $\pm$ 1.4
Neonatal blood glucose (mmol/L)	2.8 $\pm$ 0.9	2.7 $\pm$ 1.0	2.9 $\pm$ 0.9
Neonatal blood glucose < 2.5 mmol/L	46/116 (39.7%)	12/27 (44.5%)	10/33 (30.3%)
SCBU admission rate	36/126 (28.6%)	11/28 (39.3%)*	9/53 (17.0%)*
Birth weight (kg)	3.49 $\pm$ 0.69 (range 1.08–5.27)	3.49 $\pm$ 0.65 (range 2.28–4.69)	3.54 $\pm$ 0.56 (range 2.43–5.19)
Birth weight > 4 kg	28/129 (21.7%)	4/28 (14.3%)	13/56 (23.3%)
Customized growth centile > 90 th	55/128 (43.0%)	14/28 (50.0%)	23/55 (41.8%)
Birth weight < 2.5 kg	8/129 (6.2%)	3/28 (10.7%)	13/56 (1.8%)
Customized growth centile < 10 th	7/128 (7.0%)	1/28 (3.6%)	3/55 (5.5%)
Preterm delivery (< 37 weeks gestation)	39/129 (30.2%) [†]	10/28 (35.7%)*	7/57 (12.3%)* [†]

SCBU, special care baby unit

* $P < 0.05$ between type 2 and GDM

[†] $P < 0.05$ between type 1 and GDM

Figure 3 Rate of increase in fetal femur length as measured by ultrasound. The 5th, 50th and 95th centile data for infants of non-diabetic mothers are plotted as dashed lines³²

groups of women. The mean abdominal circumference accelerated from between the 50th and 90th centiles for the background population to being greater than the 90th centile with no difference in the time course of change between the three groups. Femur length showed similar pattern of growth in all the groups.

The mean birth weights were 3.49 ± 0.69 , 3.49 ± 0.65 and 3.54 ± 0.56 kg for type 1, type 2 and GDM groups, respectively (Table 2), with no significant differences between groups. There was no relationship between the mean maternal HbA_{1c} during pregnancy and birth weight in type 1 ($r = 0.033$, $P > 0.05$) and type 2 diabetes ($r = 0.138$, $P > 0.05$). A weak but statistically significant relationship was observed in the GDM group between birth weights and mean maternal HbA_{1c} during pregnancy ($r = 0.362$, $P < 0.05$). Examination of the distribution of birth weights between large-for-gestation-age (LGA), appropriate-for-gestation-age and small-for-gestation-age (SGA) suggests that the mean values conceal a greater number of SGA babies in the type 2 diabetes group, balanced by a smaller number of babies over 4 kg (Table 2). An opposite trend was observed in the GDM group, with a significantly lesser number of SGA babies. The mean customized growth centile for babies born to type 1 mothers was 71, and 72 and 65 for babies born to type 2 and GDM mothers, respectively, showing that when birth weight data were additionally corrected for maternal weight, ethnicity and parity, these differences

disappeared. The greatest influence behind this effect was noted to be ethnicity.

DISCUSSION

This single-centre, six-year study of singleton pregnancies in insulin-treated women observed no difference in the rates of intrauterine growth from 28 weeks gestation to term in type 1, type 2 and GDM groups. No previous comparative data have been reported. It was striking that both abdominal circumference, a marker of soft tissue accretion during intrauterine growth, and femur length which reflects linear growth were similar in the three groups at 28 weeks. Despite a considerably greater maternal booking weight in the type 2 diabetes group, fetal macrosomia correcting for the impact of body weight, ethnicity and other factors using the customized growth centiles showed that rates of macrosomia were not different between the groups.

Maternal body weight has a major influence on birth weight of offspring. Ricart *et al.*¹² observed relative risks for macrosomia (defined as >4 kg) of 1.82 for overweight women with normal glucose tolerance compared with 1.32 for normal weight women with abnormal glucose tolerance. In a study of 12,950 women, obesity was associated with a 1.6-fold increased prevalence of LGA (>90 th centile).¹³ Maternal weight correlates better with macrosomia than does maternal blood glucose⁴ and, conversely, 82% of macrosomic infants are born to women who were normoglycaemic in pregnancy.¹⁴ However, within type 1 diabetes there is no relationship between maternal weight and macrosomia.¹⁵ This is in sharp contrast to the non-diabetic population.^{16,17} In previous reports, prevalence of infants greater than the 90th centile has been reported as 36–62% in type 1 diabetes,^{15,18,19} and as 32–56% in type 2 diabetes.^{1,6} The current data show prevalence of actual birth weights >4 kg in 21.7% of women with type 1 diabetes compared with only 14.3% of women with type 2 diabetes, despite the latter group being 17.4 kg heavier at booking ($P < 0.001$).

Application of customized growth centiles changes the apparent paradoxical under-representation of macrosomia in the type 2 diabetes group. The prevalence of customized growth centile greater than the 90th centile was similar in each of the three groups. The degree of weighting for each factor in the calculation causes the effect of maternal weight to be subsumed by the effect of ethnicity. In a multi-ethnic population of women with type 2 diabetes comprising Polynesian, Asian and Caucasian women, Hughes *et al.*²⁰ observed that Asian women had significantly smaller babies and lower rates of macrosomia as defined by standard growth charts. Despite being a mean 500 g lighter, neonatal morbidity was similar in the Asian infants compared with the other ethnic groups.

The need to screen with high accuracy for macrosomia is important in clinical practice as it is a major risk for obstetric complications and fetal morbidity.^{21–23} Existing conventional charts are not accurate for clinical assessment in heterogeneous maternity populations. Customized antenatal growth charts can optimize the assessment of fetal growth and birth weight by taking individual physiological variables, including gestational age, ethnic group, maternal weight at booking, maternal height and parity, into account to derive an optimal curve that delineates the potential weight gain in each pregnancy. This results in an increased detection rate of true growth restriction and a reduction in false-positive diagnoses for intrauterine growth restriction. Such use of the customized growth centiles is therefore likely to detect more babies at risk of perinatal morbidity

and mortality than would be detected by population centiles.^{24,25} Even though six babies were additionally identified as SGA in our series by this classification, they were not associated with the adverse perinatal events found in other studies.²⁶ While the introduction of customized growth has the improved capacity to identify fetus with growth restriction, this has not to date been applied in a maternity population with diabetes.

It must be considered whether the normal weight type 1 diabetic women have over 40% rate of macrosomia (as judged by customized growth centile) because of factors unique to this form of diabetes. As assessed in the present series, average blood glucose control was similar in type 1 and type 2 diabetes and somewhat better in GDM. It has to be acknowledged that HbA_{1c} data are only available for the GDM women from 28 weeks gestation and is likely to have been lower in early pregnancy. However, HbA_{1c} is a poor predictor of macrosomia, explaining a relatively small proportion of the variance of birth weight.^{15,27,28} Also, it reflects only mean maternal blood glucose, whereas the fetus is exposed to a range of absolute levels of blood glucose. The nature of absorption of subcutaneous insulin, together with the effect of having no basal intraportal secretion of insulin, makes the profile of blood glucose much more erratic in type 1 diabetes than in either type 2 or GDM, even when the latter requires insulin therapy. In sheep, maintenance of constant high blood glucose does not produce fetal hyperinsulinaemia, whereas intermittent spikes of high blood glucose did so.²⁹ In human type 1 diabetes, during pregnancy, direct observation by electronic meter recording has shown the extent of spikes of hyperglycaemia despite excellent HbA_{1c} values.³⁰ This led to the hypothesis that the lack of relationship between HbA_{1c} and macrosomia was due to intermittent marked hyperglycaemia in type 1 diabetes not contributing significantly to HbA_{1c}, yet bringing about intermittent hyperinsulinaemia in the fetus. As insulin is a growth factor *in utero*, and as in extrauterine life growth hormone exerts its prolonged effects by intermittent spikes of secretion, such a phenomenon could at least partially explain the disproportionate macrosomia, in view of maternal weight, in type 1 diabetes in relation to type 2 diabetes and GDM.³⁰

In summary, this study has demonstrated that the intrauterine trajectory of growth does not differ in subtypes of diabetes treated with insulin during pregnancy. Correction of birth weight data especially for ethnicity reveals similar rates of SGA and macrosomic infants in women with type 1, type 2 and GDM. Further work is required to define the factors which result in accelerated intrauterine growth in each subtype of diabetes from mid-pregnancy onwards.

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