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Congenital anomalies in the offspring of women with Type 1, Type 2 and gestational diabetes

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Abstract

Aim To determine the frequency of major congenital anomalies in the offspring of women with gestational diabetes (GDM), classified according to their postpartum glucose tolerance status.

Methods A prospective study of pregnancies in women with Type 1 diabetes (n = 221), Type 2 diabetes (n = 317) and GDM (n = 1822) between 1985 and 2000 (15 years). Congenital anomalies were detected by antenatal ultrasound or postnatal examination.

Results The frequency of major congenital anomalies in the offspring was 5.9% (95% confidence interval (CI) 3.2–9.8) for women with Type 1 diabetes; 4.4% (95% CI 2.4–7.3) for women with Type 2 diabetes; and 1.4% (95% CI 0.9–2.0) for women with GDM. Two hundred and thirty-seven women with GDM (13%) had diabetes diagnosed on early (6-week) postpartum glucose tolerance testing. The frequency of major congenital anomalies in their offspring was 4.6% (95% CI 2.3–8.2), compared with 0.9% (95% CI 0.5–1.5) for the remainder of the GDM group ($P < 0.0001$).

Conclusions GDM is not a homogeneous group with regard to the risk of major congenital anomalies. In those with diabetes on early postpartum testing, who are likely to have had unrecognized Type 2 diabetes antedating their pregnancy, the rate of major congenital anomalies is the same as for women with established Type 1 or Type 2 diabetes. In the remainder of the GDM group, the rate does not differ from the non-diabetic background rate.

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Keywords congenital anomalies, gestational diabetes, Type 2 diabetes, Type 1 diabetes

Abbreviation GDM, gestational diabetes mellitus

Introduction

Pregestational diabetes, whether Type 1 or Type 2, is associated with a two to eight-fold increase in the rate of major congenital defects in the fetus [1–6]. This association is thought to be secondary to the teratogenic effect of hyperglycaemia in early pregnancy. Studies examining glycaemic control and birth defects have demonstrated a dose–response effect: the poorer the periconceptional blood glucose control, the greater is the risk of congenital defects [7–10]. Whilst the association of established pregestational diabetes and congenital birth defects is well documented, it remains controversial whether gestational diabetes is also associated with an increased prevalence of congenital anomalies [4,11–13].

Gestational diabetes is not a homogeneous grouping. Defined as glucose intolerance of onset or first recognition in pregnancy [14], it includes women who may have unrecognized diabetes antedating their pregnancy, along with women who develop glucose intolerance only in late pregnancy [15]. An explanation for the inconsistent reports associating gestational diabetes with an increased risk of congenital anomalies may therefore be that the populations with gestational diabetes

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studied have had differing proportions of women with unrecognized Type 2 diabetes. The fetuses of the latter would be more exposed to more severe hyperglycaemia in early pregnancy than those of women with milder degrees of gestational glucose intolerance. Studies in Latino women in Southern California (a community with a high background rate of Type 2 diabetes) would support this hypothesis, with the incidence of congenital anomalies clearly increased in the fetuses of women with gestational diabetes who have fasting hyperglycaemia [16].

The community served by National Women's Hospital in Auckland includes a large proportion of women of Maori or Pacific Island origin, and an increasing number of women of South or East Asian origin, groups which also have a high prevalence of glucose intolerance [17,18]. A high proportion of women from these communities who are diagnosed with gestational diabetes have newly recognized Type 2 diabetes [15]. In this study we examined the frequency of congenital birth defects in women with pregestational diabetes and gestational diabetes, in particular the frequency in subgroups of gestational diabetes, classified according to postpartum glucose tolerance status.

Materials and methods

A review of our prospectively collected database of all women referred to the combined Diabetes Pregnancy Clinic at National Women's Hospital was undertaken. The clinic provides the diabetes pregnancy service for the central, northern and western regions of Auckland, and serves a population of mixed ethnicity. Gestational diabetes was diagnosed by two-step testing, usually undertaken at 24–28 weeks gestation, but earlier if there were clinical indications to do so. Initially, a blood glucose was measured 1 h after a 50-g glucose load (non-fasting). If the blood glucose level ≥ 7.8 mmol/l, then a formal glucose tolerance test was arranged. Prior to 1993 a 100-g 3-h glucose tolerance test was used, with gestational diabetes diagnosed if the area under the glucose tolerance curve (0, 1, 2, 3 h) exceeded 50 mmol/l · h [19], but since 1993 a 75-g glucose tolerance test has been used, with a fasting blood glucose of ≥ 5.5 mmol/l and/or a 2-h value > 9.0 mmol/l confirming the diagnosis of gestational diabetes [20].

Following a diagnosis of gestational diabetes a further 75-g glucose tolerance test was performed 6 weeks after delivery, in order to re-classify glucose tolerance status. Diabetes was diagnosed if the World Health Organization criteria for diabetes (fasting blood glucose of ≥ 7.0 mmol/l and/or a 2-h value ≥ 11.1 mmol/l) were met. In this report, the population identified as having gestational diabetes has been subdivided into those who had diabetes on the early postpartum test (which we have termed 'newly recognized diabetes') and those who did not (or declined postpartum testing).

In this population, 96% of women with Type 2 diabetes were treated with insulin therapy during pregnancy, compared with 78% of the women with newly recognized diabetes and 36% for the remaining women with gestational diabetes. All women undertook self blood glucose monitoring and insulin doses were adjusted to meet glycaemic targets of control of fasting 4.0–5.5 mmol/l and 1.5 h postprandial < 7.5 mmol/l.

Standard antenatal care included an ultrasound scan performed between 18 and 22 weeks gestation to screen for fetal malformations. In cases of suspected cardiac anomalies, or if first trimester glycaemic control was poor, then a fetal echocardiogram was also undertaken.

If detected early enough in pregnancy, women with fetuses with major malformation were offered termination of pregnancy as an option, following appropriate counselling. All fetal anomalies were confirmed following delivery by a paediatric or pathology specialist. Women with pregestational or gestational diabetes transferred from other clinics to National Women's Hospital specifically for tertiary care because of severe malformations detected by ultrasound were excluded from the analysis. Fetal malformations were classified as major if they were gross physical or anatomical developmental anomalies that required either major surgery or substantial medical treatment, or had the potential to affect survival, or caused substantial physical or psychological handicap or death.

The prevalence of anomalies is given as a percentage, with 95% confidence intervals. Proportions are compared using the χ^2 test.

Results

Between 1 July 1985 and 30 June 2000 (15 years) there were 568 pregnancies in women with pregestational diabetes who attended the combined Diabetes Antenatal Clinic at National Women's Hospital. Two hundred and twenty-one pregnancies were in women known to have Type 1 diabetes and 315 in women known to have Type 2 diabetes prior to pregnancy. Of the 1822 women diagnosed with gestational diabetes, 237 (13%) women had a positive glucose tolerance test following delivery. This subgroup is described in this paper as 'newly recognized diabetes', on the assumption that the majority of these women must have had diabetes antedating their pregnancy (in almost all instances Type 2 diabetes). As expected, Europeans were the main ethnic group in the Type 1 diabetes population (93%) compared with Type 2 and newly recognized Type 2 diabetes groups, where the main ethnic groups were Maori or Pacific Islanders (73% and 76%, respectively; $P < 0.0001$).

During the study period there were 55 fetuses or infants identified in the whole population (Type 1, Type 2 and GDM) with major congenital anomalies. Three of the fetuses had aneuploidy (one woman with Type 1 diabetes had a baby with trisomy 18, and one woman with Type 1 diabetes had two terminations of pregnancy for trisomy 21). Excluding the aneuploidy cases, the incidence of major anomalies in women with Type 1 diabetes was 5.9% (95% confidence interval (CI) 3.2–9.8) and in women with Type 2 diabetes it was 4.4% (95% CI 2.4–7.3), compared with 1.4% (95% CI 0.9–2.0) in women with GDM. When the GDM group was subanalysed, women with newly recognized diabetes had a major anomaly rate of 4.6% (95% CI 2.3–8.2), which was not significantly different to that seen in women with Type 1 and Type 2 diabetes. The remainder of the GDM group had a rate of major anomalies that was significantly lower than that of the other three groups ($P < 0.0001$, Table 1), and did not differ from the

Table 1 Rates of congenital anomalies for the diabetes populations studied

	No. of infants or fetuses	All major congenital anomalies		Major congenital anomalies (excluding aneuploidy)	
		n	% (95% CI)	*n*	% (95% CI)
Type 1 diabetes	221	16	7.2 (4.2–11.5)	13	5.9 (3.2–9.8)
Type 2 diabetes:					
known	317	14	4.4 (2.4–7.3)	14	4.4 (2.4–7.3)
newly recognized	237	11	4.6 (2.3–8.2)	11	4.6 (2.3–8.2)
Other GDM	1585	14	0.9 (0.5–1.5)	14	0.9 (0.5–1.5)
Total GDM	1822	25	1.4 (0.9–2.0)	25	1.4 (0.9–2.0)

Table 2 Numbers of fetuses or offspring with major congenital anomalies according to type of diabetes and major system affected

	Type 1	Type 2 (known)	Type 2 (newly recognized)
Cardiac	6	7	3
Musculoskeletal	3	2	1
Reno-genital	2	1	2
Neurological	1	2	1
Multiple	1	2	4
Aneuploidy	3	0	0

background rate for major anomalies in births at National Women's Hospital.

Table 2 demonstrates the nature of the major anomalies in the three diabetic groups. The majority of anomalies involved the cardiovascular, musculoskeletal and genito-renal systems. There were eight cases of multiple major anomalies. The pattern of congenital anomalies did not differ between the Type 1, Type 2 and the newly recognized diabetes groups.

Discussion

This study has confirmed the findings of other studies, that the incidence of major congenital malformations for women with pregestational diabetes is in the order of 5–10% [1–3]. The incidence was similar for women with Type 1 and Type 2 diabetes, but gestational diabetes was associated with a much lower incidence of major congenital malformations (1.4%). However, for the subgroup of women with GDM who had newly recognized diabetes, the risk was the same as that of women with pregestational diabetes. Gestational diabetes in women who either had a postpartum glucose tolerance test which was normal, or demonstrated impaired glucose tolerance or impaired fasting glucose, or who declined postpartum testing, appears to have had a negligible impact on the fetal malformation rate.

Our definition of newly recognized diabetes is predicated on the postpartum glucose tolerance test. It is of course impossible to prove in retrospect that all the women in this category had diabetes antedating their pregnancy. It is likely to be true of the majority, although some could have had impaired fasting glucose or impaired glucose tolerance before pregnancy and decompensated to diabetes, perhaps because of a failure to lose pregnancy weight gain. Further support for the concept that the majority of women in the newly recognized diabetes category had diabetes antedating pregnancy comes from measurements of glycated haemoglobin at presentation. Data on this are only available from 1997, but the mean value in 46 women with newly recognized diabetes on booking at the clinic of 7.2% (SD 1.4) was not significantly different from that in 64 women with Type 1 diabetes (7.4%, SD 1.4), or 77 women with Type 2 diabetes (7.6%, SD 1.6). The non-diabetic values in our laboratory are 4.5–6%. Most women with newly recognized diabetes had Type 2 diabetes. Only five of 237 subjects (2.1%) subsequently proved to have Type 1 diabetes.

A potential weakness of our study is that 30% of women with gestational diabetes did not have postpartum glucose tolerance testing. Some of these too may have had unrecognized diabetes, and it is possible that if more effort was made to confirm diabetes postpartum in women with infants with major congenital anomalies, it would tend to exaggerate the impact of newly recognized diabetes on congenital anomaly rates. Whilst it is impossible to refute this completely as a potential source of bias, we think that it is unlikely to have been significant. First, by international standards our rate of achieving postpartum glucose tolerance testing is high (70%). Second, even if we assume that the same proportion (13%) of the untested 30% had unrecognized diabetes, and that none of these 62 subjects had infants with major congenital anomalies, the rate in the unrecognized/newly diagnosed diabetes group (11/299, 3.67%) would still exceed the rate in the remainder of the gestational diabetes group (14/1379, 0.92%) four-fold.

The risk of congenital anomalies in the fetuses of women with gestational diabetes has been reported to be increased if insulin therapy is required [4,14]. Presumably the group of

women with gestational diabetes who require insulin have more severe hyperglycaemia, and are likely to include those with unrecognized diabetes, whose fetuses would have been exposed to first trimester hyperglycaemia before organogenesis. Our study confirms that the incidence of malformations in those women with gestational diabetes who have newly recognized diabetes, in whom first trimester glycaemic control is likely to have been poor, is as high as for women with established diabetes, and emphasizes that the category of gestational diabetes encompasses a wide range of glucose intolerance.

Gestational diabetes is thus not a homogeneous category as far as the risk of congenital malformation is concerned. Our data fully support those of Schaefer *et al*. [16], who, in a population similar to ours with a high prevalence of Type 2 diabetes, demonstrated a linear relationship between fasting blood sugar and the rate of congenital anomalies in women diagnosed with gestational diabetes, many of whom clearly had previously unrecognized diabetes.

We have recently demonstrated that women with newly recognized diabetes also have a higher perinatal mortality rate than women with gestational diabetes who do not have diabetes on early postpartum testing, the rate being similar to that in women with known Type 2 diabetes [15]. The high perinatal mortality rate cannot, however, be explained by the increased congenital anomaly rate [15]. The data presented here on congenital malformations reinforce the view that in future, reports of outcomes in gestational diabetes should stratify their populations in some way to reflect differing degrees of hyperglycaemia. The risks of both perinatal mortality and major congenital malformations are clearly elevated in those women with the most severe hyperglycaemia [15,16].

The metabolic insult that causes the malformation impacts on most organ systems and has its effect before the week 7 of gestation [21]. The infants of diabetic mothers are not prone to any particular pattern of structural defects, which supports a non-specific effect of hyperglycaemia on the development of a wide number of organs and systems. The pattern of anomalies we observed in women with newly recognized diabetes is in keeping with those stated in the literature for women with Type 1 and Type 2 diabetes [22], and did not differ from that in women with Type 1 or Type 2 diabetes. Our findings are again very similar to those reported by Schaefer-Graf *et al*. in a predominantly Latino population in Southern California [23]. We have previously emphasized the late presentation of women with newly recognized diabetes to the pregnancy service as a potential contributor to their high perinatal mortality rate [15]. However, earlier presentation would have little impact on the incidence of fetal malformations, as the teratogenic effect occurs before the week 7 of gestation [21].

Our results highlight the problem of newly recognized Type 2 diabetes within a population which has a high background rate of Type 2 diabetes. As the prevalence of Type 2 diabetes increases, the age of onset is falling, and an increasing number of women of childbearing age are affected. The experience in both California [16,23] and Auckland indicates that a rise in the incidence of major congenital anomalies in the offspring of women with unrecognized Type 2 diabetes in pregnancy is yet another unwelcome consequence.

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