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*Short communication*

# Glycaemic control during early pregnancy and fetal malformations in women with Type I diabetes mellitus

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**Abstract**

*Aims/hypothesis*. To assess the relation between glycaemic control in early pregnancy and the risk of congenital malformations in offspring of mothers with Type I (insulin-dependent) diabetes mellitus.
*Methods*. From 1988–1997, we prospectively collected data from 691 pregnancies and 709 offspring of 488 women with Type I diabetes in a specific geographic area in Southern Finland. Glycated haemoglobin $A_{1c}$ at less than 14 weeks of gestation was used as the indicator of glycaemic control. The malformations were diagnosed either by ultrasonography in pregnancy or during the neonatal period. We also studied 729 non-selected control pregnancies in women without diabetes.
*Results*. The numbers of major fetal malformations were 30 (4.2%) in patients with Type I diabetes and 10 (1.2%) in the control subjects (relative risk 3.1; 95% confidence interval: 1.6 to 6.2). Even women whose $HbA_{1c}$ was only slightly raised (5.6 to 6.8%, ie 2.0 to 5.9 standard deviation units) showed a relative risk of 3.0 (95% confidence interval: 1.2 to 7.5). Haemoglobin $A_{1c}$ retained its statistically significant association with the occurrence of malformations after adjusting for White's class, age at onset of diabetes, duration of diabetes, parity, smoking and participation in pre-pregnancy counselling.
*Conclusions/interpretation*. Even a slightly raised $HbA_{1c}$ during early pregnancy in women with Type I diabetes carries an increased risk for fetal malformations. Therefore normoglycaemia should be strived for during early pregnancy. [Diabetologia (2000) 43: 79–82]

**Keywords** Diabetes mellitus, haemoglobin $A_{1c}$, pregnancy, fetus, malformations, congenital anomalies, relative risk, prenatal diagnosis.

The incidence of congenital malformations is reportedly two to four times higher in pregnancies of women with Type I (insulin-dependent) diabetes mellitus than in normal pregnancies [1, 2]. Hyperglycaemia in early pregnancy has been most often implied as the reason because an association between maternal $HbA_{1c}$ in early pregnancy and the frequency of fetal malformations has been reported.

Although it has been suggested that the risk of fetal malformations in women with Type I diabetes increases only when $HbA_{1c}$ is above a certain value, e.g. 8 or 10 SD units above the non-diabetic mean [3, 4], existence of such thresholds has recently been challenged. It is still not clear whether only slightly impaired glycaemic control during early pregnancy in women with Type I diabetes is teratogenic.

We assessed the risk of fetal malformations in women with Type I diabetes and compared it with that in a background population. We also related this risk to glycaemic control in early pregnancy as determined by $HbA_{1c}$.

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## Subjects and methods

*Patients with Type I diabetes.* From 1988 to 1997 691 pregnancies in 488 women with Type I diabetes and their 709 offspring (including 16 sets of twins and one set of triplets) were followed up at the Department of Obstetrics and Gynaecology at Helsinki University Central Hospital. The study protocol was accepted by the local ethics committees. During the study period, the prevalence of Type I diabetes among the parturients of this area was 0.4 %.

*Control subjects.* The control subjects were 735 offspring (including 6 sets of twins) from 729 consecutive pregnancies in 706 unselected residents of Kerava (a city located in the middle of the catchment area of our hospital) who attended the routine ultrasound screening at 16–19 weeks of gestation in 1993–1994. Subjects with pre-existing Type II (non-insulin-dependent) diabetes mellitus and those needing insulin during pregnancy were excluded. Of the diabetic women and control subjects, 98 % were Finnish Caucasians.

*Follow-up during pregnancy.* The patients with Type I diabetes were registered at the hospital as soon as the pregnancy was diagnosed, usually at 5 to 10 weeks of gestation (the median was 7 weeks). In 93 % of these the first visit was earlier than 14 completed weeks of gestation. The women with diabetes, like the control group, attended a 16 to 19 week examination by ultrasonography.

*Diagnosis and definitions of the malformations.* The infants of women with diabetes and control subjects were similarly examined by specialist neonatologists for possible malformations both at birth and at the age of 2 to 5 days.

A malformation was classified as 'major' if it was fatal, likely to cause a serious handicap or if it required surgery. Other malformations were classified as 'minor', in which group we also included undescended testis, hydrocele and dislocation of the hip. Each offpring was classified according to the most serious disorder as having either major, minor, or no malformation.

*Laboratory analyses.* Haemoglobin $A_{1c}$ was assessed by HPLC (Diamat, Bio-Rad Laboratories, Hercules, Calif., USA). The mean $HbA_{1c}$ with this method is 4.93 % (SD: 0.32 %) for healthy Finnish adults. Values of less than 5.6 % ( + 2 SD) were considered to be normal in the patients with diabetes. Haemoglobin $A_{1c}$ was not assessed in the control subjects.

*Outcome.* The outcomes of the pregnancies were ascertained from the obstetric and paediatric records of all diabetic patients and control subjects. For central nervous system malformations, a comparison was also made with the national rate of this disorder from 1988–1997, which was 1:1300 (excluding defects due to chromosomal abnormalities and known inherited syndromes).

*Statistical analyses.* Power calculations indicated that 602 diabetic patients and 602 control subjects would be needed to show doubling of the rate of malformations in the diabetic group (4 vs 8 %; one-sided comparison) with 90 % power at the $p$ value of 0.05.

For continuous variables, the $t$ test and the Mann-Whitney test were used. Proportions were compared by calculating the rate difference and its 95 % CI. Relative risks of malformations and their 95 % CIs were calculated for different values of $HbA_{1c}$.

Multiple logistic regression was applied with occurrence of a fetus with malformation as the dependent variable. A $p$ value of less than 0.05 was considered statistically significant. The calculations were done by Arcus Quickstat Biomedical (Longman Software Publishing, Cambridge, UK).

## Results

*Baseline characteristics.* The mean (SD) age at onset of diabetes was 15.1 ( ± 8.5) years, and its duration averaged 14.5 ( ± 7.9) years. Compared with the control subjects, the women with diabetes were more often nulliparous (50 % vs 42 %; $p = 0.006$), had a shorter gestation (mean 37.3 vs 39.7 weeks; $p < 0.001$) due to the earlier elective deliveries, and had more multiple pregnancies (2.3 % vs 0.8 %; $p = 0.02$). No differences were observed in the maternal ages or in the proportion of smokers.

Haemoglobin $A_{1c}$ was labelled as 'not known' in those 7 % of the pregnancies in which it had not been assessed by 13 weeks 6 days of gestation. The mean ± SD $HbA_{1c}$ in the whole series was 7.5 ± 1.4 %. Of the women with diabetes, 39 % had participated in pre-pregnancy counselling offered by our institution.

The distribution of the women with diabetes according to White's classification was as follows: class B 23 %, class C 26 %, class D 34 % and class F/R 17 %.

*Frequency of offspring with malformations.* The frequency of fetuses with major malformations was 30/709 (4.2 %) in the patients with diabetes and 10/735 (1.4 %) in the control subjects (difference: 2.8 %; 95 % CI of the difference: 1.2 to 4.7 %) (Table 1).

Of the pregnancies in the women with diabetes five and in the control subjects none were terminated due to fetal malformations diagnosed by ultrasonography (Table 1).

There were 43/709 (6.1 %) minor malformations among the offspring of women with diabetes and 22/735 (3.0 %) among the control subjects (difference: 3.1 %; 95 % CI of the difference: 1.0 to 5.3 %). Including both major and minor malformations, the rates were 10.3 % for the diabetic subjects and 4.4 % for the control subjects (difference: 5.9 %; 95 % CI of the difference: 3.3 to 8.6 %). One malformation occurred in the twins of women with diabetes and none in the twins of control subjects.

*Logistic regression.* With occurrence of a fetus with malformation as the dependent variable and $p$ less than 0.2 as the entry criterion, only $HbA_{1c}$, parity and White's class F/R qualified as predictors in the model, with $p$ values of 0.02, 0.15 and 0.09, respectively. A high $HbA_{1c}$ value and nulliparity were associated with an increased risk, whereas White's class F/R showed a reduced risk for a malformation. Factors such as age at onset of diabetes, duration of diabetes, age, smoking and participation in pre-pregnancy counselling were dropped from the model.

**Table 1.** Offspring with major malformations and maternal $HbA_{1c}$

| Malformations | Diabetes $n = 709$ | | Controls $n = 735$ |
|---|---|---|---|
| | $HbA_{1c}$ % | $n$ | $n$ |
| Anencephaly | 7.8 | 1[a] | |
| Hydranencephaly | 6.1 | 1 | |
| Hydrocephaly | 5.9 | 1[a] | |
| Multiple CNS, visceral and limb anomalies | 5.9 | 1[a] | |
| Caudal regression syndrome | (10.3) | 1 | |
| Left heart hypoplasia | 7.0 | 1 | 1 |
| Left heart hypoplasia | (8.0) | 1 | |
| Tetralogy of Fallot | 6.3 | 1 | 1 |
| VSD | 7.3 | 5 | 3 |
| VSD and hydrocephaly | (6.5) | 1 | |
| VSD, short limbs, anterior anus, hypertelorism | | | 1 |
| Coarctation of aorta | 8.9 | 2 | |
| PDA (operated) and multicystic kidney | 6.5 | 1 | |
| Pulmonary stenosis | | | 1 |
| Gastroschisis, amnion adhesion syndrome | 7.2 | 1[a] | |
| Anal atresy, vesicourethral reflux | 8.7 | 1 | |
| Duodenal atresy | 7.7 | 1 | |
| Intestinal malrotation | 6.6 | 1 | |
| Hydronephrosis (operated) | 6.2 | 1 | |
| Hypospadia | 9.6 | 2 | 1 |
| Pelvic cyst and vaginal atresy | 10.2 | 1 | |
| Craniosynostosis | | | 2 |
| Limb reductions, missing antebrachium and foot | 7.9 | 1[a] | |
| Hip anomaly (operated) | 9.2 | 1 | |
| Metatarsovarus, equinovarus (operated) | 10.0 | 2 | |
| Metatarsovarus (operated) | (7.5) | 1 | |
| Total | 7.9 | 30 | 10 |

[a] Induced abortion. $HbA_{1c}$ was assessed at less than 14 weeks except those in parentheses at 14–17 weeks. $HbA_{1c}$ is a mean when $n$ is more than 1. CNS, central nervous system; PDA, patent ductus arteriosus; VSD, ventricular septal defect

*Relative risk for malformations compared with $HbA_{1c}$ value.* Comparing the women with Type I diabetes with the control subjects (Table 2), the relative risk for major malformations was 3.0 even in those diabetic women whose $HbA_{1c}$ was only slightly raised (2 to 5.9 SD units). The risk then remained at a plateau of about 3 for higher $HbA_{1c}$ values until it shifted up to 4.8 for $HbA_{1c}$ values above 9.4% ( + 14 SD units) (Table 2). The patients in whom the early $HbA_{1c}$ was 'not known' (ie first assessed at 14 weeks of gestation or later) also showed a high relative risk of 6.0. Only the diabetic patients with normal $HbA_{1c}$ (less than + 2 SD units) displayed a risk similar to the control subjects (Table 2).

There were five central nervous system malformations among the offspring of women with diabetes and none in the offspring of the control subjects (Table 2). Compared with the national rate, the relative risk for this disorder among the offspring of women with diabetes was 8.8 ( 95% CI: 3.8 to 19.9). The mean $HbA_{1c}$ was 6.4% in those with a central nervous system malformation ($p = 0.1$ compared with 7.5% in the rest of the series).

**Table 2.** Haemoglobin $A_{1c}$ in early pregnancy in women with Type 1 diabetes and the risk for major fetal malformations compared with non-diabetic control subjects

| $HbA_{1c}$ < 14 weeks | | No. offspring malformed/all | Relative risk (95% CI) |
|---|---|---|---|
| % | SD | | |
| Not known | Not known | 4/49 | 6.0 (2.0–17.1) |
| ≥ 9.4 | ≥ 14 | 4/61 | 4.8 (1.6–13.9) |
| 8.1–9.3 | 10.0–13.9 | 6/133 | 3.3 (1.3–8.6) |
| 6.9–8.0 | 6.0–9.9 | 8/252 | 2.3 (1.0–5.7) |
| 5.6–6.8 | 2.0–5.9 | 7/170 | 3.0 (1.2–7.5) |
| < 5.6 | < 2.0 | 1/47 | 1.6 (0.3–9.5) |
| All offspring of diabetic women | | 30/709 | 3.1 (1.6–6.2) |
| Control offspring | | 10/735 | 1.0 |

## Discussion

Our results suggest that an increased risk for fetal malformation occurs at even slightly raised $HbA_{1c}$ values (2 to 6 SD units) during early pregnancy and only those women with Type I diabetes who have a normal $HbA_{1c}$ show a rate similar to the general population. This is in accordance with a study on subjects with pre-gestational diabetes (mainly Type II diabetes) [5].

Our findings contradict suggestions that there is a relatively broad range of glycaemic control, within which the risk of malformations is not substantially increased [6].

Many of the previous studies lack a control group and hence the malformation rates could be compared only within the group of patients with diabetes [6]. In contrast, this study includes a control group which makes it possible to compare even diabetic patients with a 'good' glycaemic control with the background population. This may explain our finding that even diabetic mothers with a slightly raised $HbA_{1c}$ in early pregnancy showed an increased risk for fetal malformations.

Our study gives further support to the concept that maternal hyperglycaemia is associated with congenital fetal malformations; this association persisted after several potential confounding factors were taken in account. The exact pathogenesis of fetal malformations in diabetic pregnancies is not known and it most probably is multifactorial. That the central nervous system anomalies in our series were associated with rather low $HbA_{1c}$ values suggests that factors other than maternal hyperglycaemia could be involved.

At our centre, the rate of major malformations in offspring of women with Type I diabetes decreased from 7.7% in 1978–1982 [4] to 4.4% in 1988–1997

and, at the same time, the mean $HbA_{1c}$ was reduced from 8.2 % to 7.5 %.

The American Diabetes Association recommends that diabetic women contemplating pregnancy should achieve a $HbA_{1c}$ value within 3 SDs of the normal mean [7], which is in agreement with the findings of our study.

Despite the availability of an effective pre-pregnancy programme, some women with diabetes never attain good glycaemic control. Detailed ultrasonography (including fetal echocardiography) and the assessment of serum alpha-fetoprotein aid, however, the idenfication of most major fetal anomalies [8, 9]. Thus, even patients with poor glycaemic control in early pregnancy can be assured of a relatively small residual risk, provided appropriate prenatal diagnostic methods have been applied.

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