PAPERS AND SHORT REPORTS

Early fetal growth delay detected by ultrasound marks increased risk of congenital malformation in diabetic pregnancy

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Abstract

Ninety-nine insulin-dependent diabetic women with regular menstrual histories were examined by ultrasonic scanning in the seventh to 14th weeks of pregnancy. As judged by the crown-rump length 38 fetuses were smaller than normal. The term early growth delay is suggested for this phenomenon. Nine fetuses had major congenital malformations, and seven of them were smaller than normal in early pregnancy ($p < 0.02$). The risk of fetal malformation in diabetic pregnancy increases with the severity of the diabetes. Early fetal growth delay is apparently another risk marker, in this series indicating a risk of 18% (7/38). The combination of severe maternal diabetes (White's classes D and F) and early growth delay yielded a risk of major congenital malformation of 27% (6/22).

These observations suggest a common mechanism behind early growth delay and induction of abnormal embryogenesis (and maybe even fetal death). The mechanism is unknown but probably influenced by the quality of regulation of diabetes.

Introduction

Infants of diabetic mothers have an increased incidence of congenital malformation,[1-3] which now accounts for half the perinatal mortality. The incidence of malformations is significantly higher in White's[4] classes D and F, in which the mothers have longstanding diabetes or vascular complications, or both, than in the less severe classes A, B, and C.[1 3] We previously reported that some fetuses in the early diabetic pregnancy are smaller than normal[5] and now present the results of a study that suggest that these fetuses carry a significantly higher risk of being malformed.

Patients and methods

In the autumn of 1976 we started to follow diabetic pregnancies by ultrasonic scanning from early pregnancy till term. The first infant in this programme was delivered in April 1977. We extracted data on all pregnancies occurring during 1 April 1977 to 1 October 1980 to women who fulfilled the following criteria. (1) They were insulin dependent (thus those in White's class A were excluded) with a reliable menstrual history of 28- to 30-day intervals and had not been using oral contraception for the last three months before conception. (2) They had reported to the diabetes centre early enough in pregnancy for us to have obtained at least one ultrasound measurement of fetal crown-rump length, estimated with the technique of Robinson,[6] of between 10 and 80 mm. This corresponds to an age of 7 to 14 weeks. (3) They had given birth to a singleton infant of 1000 g or over. A total of 99 patients—that is, about half of our insulin-dependent pregnant diabetics—met these criteria.

We used a Nuclear Enterprises Diasonograph Scanner NE 4102, and the patients were examined with a full bladder. All ultrasound examinations were performed by one of us (JFP). Unless otherwise indicated quantitative results were analysed by the Mann-Whitney unpaired rank sum test and qualitative results by the fourfold table test (Fisher's exact test).

Results

From data obtained from a series of normal pregnancies, which was virtually identical with that reported by Robinson,[6] we constructed a table that permitted estimation of fetal age from the crown-rump length. For each measurement of crown-rump length in the diabetic patients the corresponding fetal age was read and compared with the age calculated by using the first day of the last menstrual period. The average of the differences between "ultrasound age" and menstrual

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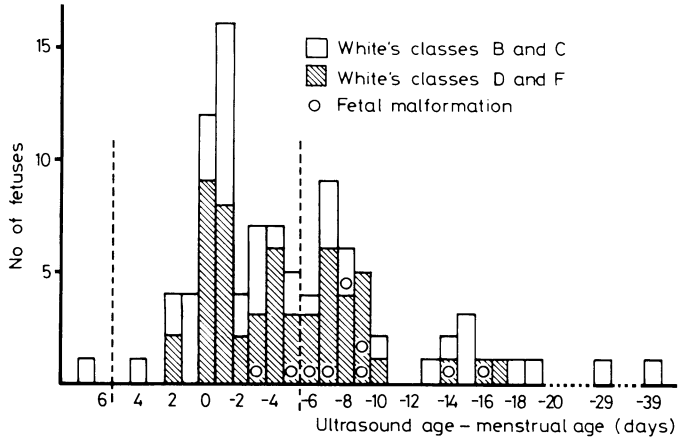
age for each fetus was taken. The distribution of these differences was skewed to the right (figure). Ninety-five per cent of the single determinations of crown-rump length in our normal series deviated by five days or less from the menstrual age: this normal range is indicated by the dashed lines in the figure. Thirty-eight of the 99 fetuses in the diabetics were smaller than the lower limit of normal; this is highly significant. For this phenomenon we suggest the term early growth delay, as opposed to the growth retardation seen in the third trimester in, for example, placental insufficiency.



Distribution of differences between ages as assessed by ultrasound and by using menstrual dates in 99 early diabetic pregnancies. Dashed lines indicate normal range (= ±5 days).

The circles in the figure indicate fetuses with major congenital malformation diagnosed at birth or in the first 10 days of life. Seven of the nine malformed fetuses were smaller than normal in early pregnancy ($p < 0.02$). Table I gives details of these fetuses. In one fetus (case 4) the morphology of the malformation (a large sacral myelomeningocele) may have influenced the determination of crown-rump length: the length may have been overestimated and the delay therefore underestimated. Table II shows the combined effect of early growth delay and the well-established risk marker severe maternal diabetes. The two factors enhance each other so that a considerably delayed fetus of a mother in White's class D or F has a risk of severe congenital malformation of six in 22, or 27% (11-50%, 95% confidence interval).

Comparison between the 38 pregnancies in which the fetus was too small in early pregnancy and the remainder (table III) shows a difference in birth weight of 500 g ($p < 0.001$) despite an almost identical age at birth. In fact, the delayed fetuses were on average three days older than the normal ones, but the ultrasound age, which takes the delay into account, showed the delayed fetuses to be seven days younger than the unaffected ones. There was no difference in maternal height or parity between the two groups.

TABLE I—*Details of nine malformed fetuses**

Case No	Birth weight (g)	"Delay" (days)	Type of malformation
1	2380	9	Unilocular heart + other; died
2	2050	9	Atrial septal defect, ventricular septal defect, common trunk + other; died
3	2890	14	Ventricular septal defect
4	4190	3	Sacral meningomyelocele + other; died
5	2860	7	Ventricular septal defect + urinary tract malformation
6	3240	5	Renal-cell tumour; died postoperatively
7	1925	16	Lumbar meningomyelocele, hydrocephalus; died
8	3150	6	Single ventricle, pulmonary stenosis
9	3865	8	Single ventricle, died postoperatively
Average	2950	8·7	

*In cases in which more than one organ system was affected only the most severe lesions are listed.

TABLE II—*Incidence of congenital malformation related to fetal size in early pregnancy (crown-rump length) and severity of diabetes in 99 insulin-dependent diabetic women*

	Early fetal size		Total
	< 6 days too small	≥ 6 days too small	
White's classes B + C	0/29	1/16 (6%)	1/45 (2%)
White's classes D + F	2/32 (6%)	6/22 (27%)	8/54 (15%)
Total	2/61 (3%)	7/38 (18%)	9/99 (9%)

TABLE III—*Clinical characteristics of pregnancy in 99 women with insulin-dependent diabetes related to fetal size (crown-rump length) in early pregnancy*

	Early fetal size	
	< 6 days too small	≥ 6 days too small
No of mothers	61	38
Mean birth weight (g)	3482	2964
Mean gestational age at birth (days)	256·3	258·9
Mean difference between ultrasound age and menstrual age in early pregnancy (days)	1·3	11·2
Mean ultrasound age at birth (days)	255·0	247·7
No of fetuses with congenital malformation	2	7

Discussion

The reliability of the menstrual histories was crucial in this study, and any doubt led to exclusion from the series. The measurements of crown-rump length were performed by one examiner, and there was no overrepresentation of observations from weeks 12-14, when the shifting curvature of the spine adds some variability to the rectilinearly measured lengths. We are therefore convinced that some fetuses in early diabetic pregnancy really are smaller than normal. We are not aware of similar studies in man, but in experimental diabetes in the rat Eriksson *et al* found pregnancy to be prolonged by two days and fetal weight at day 20 of pregnancy to be lower than normal.[7] These observations might be explained by early growth delay.

The fetuses that were too small in early pregnancy weighed 518 g (±273 g (2 SED)) less than the unaffected ones. Excluding the nine malformed fetuses did not appreciably change this figure. This difference in birth weight may well be explained by the difference in ultrasound age of seven days, bearing in mind the rapid gain in fetal weight in late diabetic pregnancy. We followed the growth of the fetuses by ultrasound, and those who were too small in early pregnancy showed on average no reduction (and no increase) in growth velocity when compared with the remainder; the fetuses appeared to be growth delayed rather than growth retarded.

The incidence of congenital malformation of 9% in this series is similar to figures given elsewhere.[2,3] Our results show that fetuses more than five days too small in early pregnancy have a significantly higher risk of malformation. This in turn supports our finding of early growth delay in some diabetic pregnancies.

We previously thought that early fetal growth delay, somewhat surprisingly, was not related to the severity of the maternal diabetes,[5] and table II shows a fairly equal distribution of the White classes between the delayed and unaffected fetuses. The figure, however, shows a significantly wider distribution of fetal size in classes B and C than D and F ($p < 0.001$, F test). Only two out of 10 fetuses whose ultrasound age was greater than the menstrual age were in classes D and F. If this means that fetuses in classes D and F are more likely to be delayed then some of these fetuses are lacking among the severely delayed ones. An explanation might be that extreme early growth delay in classes D and F, which we have shown is related to fetal malformation, might be related also to such severe damage to the fetus that it dies. This hypothesis finds support in White's

observation that the rate of spontaneous abortion increases with the duration and severity of maternal diabetes.[8]

Because of the regularity of the menstrual histories of our patients and the association between delay and malformation we find a delay in ovulation of up to more than three weeks inconceivable as an explanation of the observed growth delay. We hope to measure basal body temperatures in patients, which should provide us with final proof. We have seen only a normal rate of growth after the first determination of crown-rump length in the first trimester. Thus the delay must be introduced somewhere between ovulation and the first ultrasound examination in weeks 7-14. For comparison, embryologic considerations have shown that the factor causing the malformation must be active before the seventh week.[9]

There is some indirect evidence that good regulation of diabetes reduces the number of malformed fetuses[10 11] and of appreciably delayed fetuses.[5] We hope to obtain further substantiation by measuring $HbA/_{1c}$[10] Perhaps, therefore, the same mechanism that is responsible for the early delay of up to several weeks in fetal growth and the biological clock sometimes also induces abnormal embryogenesis (or even causes death of the embryo). The biochemical nature of this mechanism is unknown.

We have shown that considerable early growth delay, especially in White's classes D and F, entails a severe risk of fetal malformation. Paediatric follow-up might even show an overrepresentation of additional minor malformations or impaired development in this group. If a larger series and studies from other centres confirm our findings these must influence counselling to the prospective and early pregnant diabetic.

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Child-resistant containers: are we kidding ourselves?

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Abstract

A 20-month-old child was accidentally poisoned after biting through the bottom of a medicine container and ingesting the tablets inside. Consequently a study was carried out to determine the force required to fracture 20 randomly selected 25 and 32 ml polystyrene containers to see whether this exceeded the bite force of a child's jaw. Tests were performed at displacement rates of 0·5 and 10 cm/min. All the containers failed at well below the bite force recorded for children, which is 392 N.

All containers must conform to a British Standards test that requires that they withstand a force of only 35 N. Clearly this is not enough to safeguard small children. The use of polystyrene containers should be scrutinised closely, as the case of accidental poisoning reported may not be unique.

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Introduction

We re-examined the effectiveness of child-resistant containers after an unusual case of accidental poisoning in a 20-month-old child and report here our results.

Case report

A child, aged 20 months, was admitted to the paediatric unit having taken an unknown quantity of red tablets. These were later identified as dothiepin (Prothiaden) 75 mg. According to the mother, the child had bitten through the bottom of a medicine container and gained access to the tablets (fig 1). Saliva had entered the container via the hole and had struck most of the tablets together. This had caused the colour to run and rendered them unidentifiable.

There were no abnormal findings on examination. The child was treated with ipecacuanha, observed for 48 hours, and discharged after showing no ill effects.

Experimental method and results

The container that the child had bitten had been made of polystyrene and was 32 ml in size. We tested the force required to fracture 25 ml and 32 ml containers manufactured by the firm that had made the original container; these were selected because they are commonly used by hospital pharmacies and fit readily into a child's mouth.

Tests to fracture were performed, on 20 randomly selected containers of each size, by an Instron Universal testing machine. The