PAPERS AND SHORT REPORTS

Increased incidence of true type I diabetes acquired during pregnancy

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Abstract

A longitudinal study was carried out of all patients with newly acquired insulin dependent diabetes during pregnancy (as distinct from non-insulin-dependent gestational diabetes) seen at the Copenhagen Centre for Diabetes and Pregnancy during 1966 to 1980. The series comprised 63 patients with a mean age of 27 (SEM 1) years. At diagnosis the mean fasting blood glucose concentration was 15.6 (1.3) mmol/l and mean maximal insulin dose 49 (3) IU/day.

At a prospective follow up examination a mean of 8 (SEM 1) years after diagnosis 46 of 60 patients (77%) were being treated with insulin (35 (2) IU/day) and had a very low mean stimulated plasma C peptide value (0.12 (0.02) nmol/l) suggesting absent or nearly absent β cell function. The remaining 14 patients (23%), not currently receiving insulin, appeared to be severely glucose intolerant, having a mean fasting blood glucose concentration of 13.4 (1.2) mmol/l. Thus most of these patients developing insulin dependent diabetes during pregnancy had true type I disease.

Compared with the age specific incidence of type I diabetes in the background population of women the incidence was at least 70% higher in pregnant than non-pregnant women ($p < 0.001$; $\chi^2 = 11.6$; $f = 1$). This increased incidence occurred in the third trimester when the risk of developing type I diabetes was 3.8 times that of non-pregnant women ($p < 0.000001$; $\chi^2 = 35.6$; $f = 1$). Finally, the risk of developing insulin dependent diabetes during pregnancy was lower when conception occurred in the winter ($p < 0.05$; $\chi^2 = 4.18$; $f = 1$).

Introduction

Insulin dependent (type I) diabetes newly acquired in pregnancy may be distinguished from the far more common gestational diabetes, which is defined as carbohydrate intolerance with onset or first recognition during pregnancy.¹ True insulin dependent diabetes arising during pregnancy does not appear to have been investigated systematically, and our main object was therefore to describe this disease. Since the pathogenesis of type I diabetes is still not fully understood another main object was to study the development of type I diabetes in a special group—namely, pregnant women—which we hoped might provide new knowledge about the disease. The study was possible only because since 1946 treatment of pregnant diabetics in eastern Denmark has been centralised at the University of Copenhagen's diabetes centre. The study was longitudinal, consisting of a retrospective investigation of patients with newly acquired diabetes during pregnancy and a subsequent prospective follow up study.

Patients and methods

We studied all 63 patients who during 1966 to 1980 developed insulin dependent diabetes during pregnancy and began treatment with insulin at the diabetes centre. At diagnosis all patients had definite symptoms of hyperglycaemia and a high fasting blood glucose concentration (mean 15.6 mmol/l), and 42 out of 52 patients (81%) for whom information was available showed appreciable ketonuria; all therefore began taking insulin immediately. None of the patients received oral hypoglycaemic agents. The patients came from eastern Denmark and had been referred to the centre when diabetes was diagnosed.

We cannot exclude the possibility that a few patients from peripheral areas may not have been referred, so we based our calculations of incidence on patients from only three administrative areas where we were certain that referrals were complete. The three areas were the city of Copenhagen (urban), county of Copenhagen (suburban), and county of Western Zealand (mostly rural), which respectively contain 11.4%, 12.2%, and 5.4% of the total Danish population of five million. Fifty two of the 63 patients in the series came from these three areas, and they were similar to the patients living in the other areas with respect to the variables examined. During the study period there was no significant trend for a change in the yearly number of cases (χ^2 test for number of births = 3.44; $f = 1$) or the patients' mean age (regression analysis, Student's t test = 0.59; $f = 61$; $p > 0.10$).

Data were collected in two parts: firstly, data from the time of diagnosis and from the pregnancy were recorded and, secondly, after 1982 the patients were contacted and asked to attend for a follow up examination; 60 patients

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(95%) participated wholly or partially in the second part, the remaining three patients having emigrated. Patients who participated in the follow up study were similar to the patients who did not with regard to all the variables recorded for both groups.

Analysis of incidence—The number of patients in whom newly acquired insulin dependent diabetes was diagnosed during pregnancy was compared with the number expected had the age specific incidence been the same as for the background population of women. The expected number was calculated as follows: the data of Christy *et al* collected in Denmark in the period 1970-6 (predominantly in the same areas as our study)² were used to establish the incidence in the age groups 15-19, 20-24, and 25-29. The incidence of type I diabetes in the age group 30-49 was assumed to be the same as in the 25-29 year olds.³ The incidence for nine months was multiplied by the number of deliveries (including stillbirths) in the area and age group concerned for the years 1966-80 (information from the Danish Statistical Department). The number of expected type I diabetics was then calculated, taking into account the relative incidence of drop outs (5%) in the follow up study.

β Cell function was evaluated at the follow up examination by measuring plasma C peptide concentrations after an overnight fast. Blood samples were taken from a peripheral vein six minutes after an intravenous injection of 1 mg glucagon.⁴ C Peptide was determined as described⁵ using antiserum M1230.

Biochemical analyses—Plasma was assayed for glucose by a glucose oxidase method,⁶ and for insulin⁷ and glucagon⁸ by radioimmunoassays.

Statistical analyses—Data are presented as mean or median and standard error of mean (SEM). Significance of differences was evaluated by the χ^2 test or Mann-Whitney U test. The level of type I error was set at 0.05. All p values are two sided.

Results

COURSE OF TREATMENT

Figure 1 shows the course of treatment in the 63 patients. At follow up nine patients had been treated with insulin without interruption. The mean

stimulated C peptide response in these nine patients was 0.13 (0.07) nmol/l and their mean daily insulin dose 34 (5) IU. Fifty one patients had stopped taking insulin after delivery (median 9 days (range 1-377) after delivery) but 37 (73%) had started taking insulin again by a median of 256 days after delivery (range 8-4123 days; two thirds of the patients within one year). These patients had a mean stimulated C peptide response of 0.11 (0.03) nmol/l and were receiving an average daily insulin dose of 35 (2) IU. Thus at follow up 77% of the patients (46 of the 60 for whom information was available) were having insulin and, given their stimulated C peptide responses of 0.12 (0.02) nmol/l, must be characterised as definite type I diabetics. Fourteen patients were not taking insulin at follow up. Seven of these patients had a fasting blood glucose concentration of ≥ 14 mmol/l and glucose tolerance test was therefore not carried out. Their median follow up period was 1640 days (range 1157-4667) compared with 2898 days (range 578-5870) for the currently insulin treated patients.

Four patients not currently taking insulin had fasting blood glucose concentrations below 14 mmol/l and were therefore subjected to glucose tolerance tests; all gave highly abnormal results, with a mean peak value of 17.3 (1.1) mmol/l. The median follow up period in these patients was only 608 days (range 558-766).

DATA FROM ONSET OF INSULIN DEPENDENT DIABETES

Patients currently taking insulin were significantly younger (25.9 (0.8) years) than those not currently taking insulin (30.4 (1.7) years; $p < 0.05$) (table I). At the beginning of pregnancy patients not currently taking insulin were heavier ($p < 0.01$) than the insulin treated group (table I). When grouped by weight⁹ 38 (83%) of the currently insulin treated patients were "underweight" and only 6 (13%) more than 10% overweight compared with 9 (64%) of those not currently taking insulin ($p < 0.005$). At diagnosis the mean fasting blood glucose concentration was 15.6 (1.3) mmol/l ($n = 56$) (table I). In patients for whom only random blood glucose values were obtained the mean was 20.7 (2.9) mmol/l. Ketonuria was recorded by Ketostix in 42 (81%) of 52 patients tested (mean value 2.6 (0.4)+; scale 0-3+), while the mean standard bicarbonate concentration in 25 patients

FIG 1—Diagrammatic representation of course of treatment of patients studied.

TABLE 1—Clinical and biochemical data from onset of insulin dependent diabetes. Except where stated otherwise values are means (SEM in parentheses)

	Age (years)	Parity	Weight before pregnancy (kg)	Height (cm)	Fasting blood glucose (mmol/l)	No (%) with ketonuria	Maximal insulin dose in pregnancy (IU/day)	Maximal insulin dose/kg body weight (IU/day/kg)
All patients [n=63]	27 (1)	2.0 (0.2)	62 (2)	164 (1)	15.6 (1.3) [n=56]	42/52 (81)	49 (3)	0.80 (0.05)
Currently insulin treated patients [n=46]	26 (1) *	1.8 (0.2)	59 (1) **	165 (1)	15.1 (1.3) [n=40]	33/38 (87)	45 (3)	0.79 (0.05)
Not currently insulin treated patients [n=14]	30 (2)	2.5 (0.3)	74 (5)	162 (1)	14.0 (1.4) [n=13]	8/12 (67)	61 (11)	0.82 (0.14)

* $p < 0.05$. ** $p < 0.01$.

NB: Three patients could not be contacted for follow up.

examined was 17.9 (1.1) mmol/l. Though the values in patients currently having insulin tended to be somewhat more abnormal than in the others, the differences were not statistically significant. The maximum daily dose of insulin during pregnancy was 49 (3) IU, corresponding to 0.80 (0.05) IU/kg body weight (table I).

DATA FROM FOLLOW UP STUDY

No patient currently taking insulin had a stimulated plasma C peptide value above 0.6 nmol/l, and in most patients tested (19/32; 59%) C peptide was below 0.05 nmol/l, indicating lack of β cell function (fig 2). A few patients not currently taking insulin showed stimulated C peptide values below or around 0.6 nmol/l, which has been considered to be the limit below which insulin should be given.¹⁰ Fasting C peptide values showed the same tendency as the stimulated C peptide values (table II). Free insulin and

FIG 2—Distribution of stimulated plasma C peptide concentrations in patients at follow up.

TABLE II—Biochemical data at follow up. Values are means (SEM in parentheses)

	C Peptide (nmol/l)		Free Insulin (pmol/l)	Glucagon (pmol/l)	Glucose (mmol/l)
	Fasting	Stimulated			
All patients [n=42]	0.24 (0.04)	0.39 (0.08)	154 (30)	23 (2)	13.9 (0.8)
Currently insulin treated patients [n=32]	0.10 (0.02)***	0.12 (0.02)***	174 (42)	24 (3)	14.3 (1.0)
Not currently insulin treated patients [n=10]	0.66 (0.09)	1.18 (0.17)	111 (14)	22 (3)	13.4 (1.2)

*** $p < 0.00001$.

glucagon concentrations in plasma showed no statistically significant differences between the two groups; fasting blood glucose was greatly and similarly raised in both groups (table II).

INCIDENCE

Had the age specific incidence been the same as for the background population of women 22.9 newly detected cases of insulin dependent diabetes would have been expected among pregnant women from 1966 to 1980 in the three areas with full ascertainment. In fact, 52 pregnant women developed the disease, representing a 2.3-fold increase in incidence (95% confidence limits 1.7 and 3.0; $p < 0.000001$, $\chi^2 = 35.6$, $f = 1$). This increase, however, should be regarded with caution, as the 52 women included 12 not currently receiving insulin and two for whom information about current insulin treatment was not available. When results were recalculated including only the 38 patients currently taking insulin, and taking into account the two patients with no follow up data, the incidence of type I diabetes was increased by 1.7 (confidence interval 1.3-2.4) in pregnant compared with non-pregnant women ($p < 0.001$; $\chi^2 = 11.6$, $f = 1$). We emphasise that this figure includes only patients currently taking insulin, so it must be considered to be a minimum value.

Grouping by age (table III) showed a non-significant variation in incidence from 1.4 (confidence interval 0.8-2.3) in the 20-24 year age group to 2.2 (1.3-3.6) in the 25-29 year group. There were also no significant differences in incidence ratios among patients coming from the different areas.

Table III shows the patients grouped according to the trimester of pregnancy in which insulin dependent diabetes occurred and figure 3 the distribution in relation to gestational age. There was a significant difference in incidence ratios among the three trimesters ($p < 0.00001$; $\chi^2 = 26.1$; $f = 2$). During the first two trimesters the number of cases was somewhat (but not significantly) smaller than expected. The increase in incidence occurred entirely in the third trimester, during which insulin dependent diabetes

TABLE III—Incidence of insulin dependent diabetes during pregnancy in relation to age, area of residence, and trimester of pregnancy

Currently insulin treated patients (areas with full ascertainment)	Actual No of patients	Expected No of patients*	Incidence ratio (95% confidence interval)	p Value for equal incidence ratio
Age (years):				
15-19	3	1.8	1.7 (0.6-5.0)	NS
20-24	14	10.0	1.4 (0.8-2.3)	
25-29	14	6.4	2.2 (1.3-3.6)	
30-49	7	3.9	1.8 (0.8-3.6)	
Area of residence:				
Urban	18	9.0	2.0 (1.3-3.2)	NS
Suburban	14	8.7	1.6 (1.0-2.7)	
Rural	6	4.2	1.4 (0.7-3.1)	
Trimester of pregnancy:				
First	5	7.6	0.7 (0.3-1.5)	$p < 0.00001$ ($\chi^2 = 26.1$; $f = 2$)
Second	6	7.6	0.8 (0.4-1.7)	
Third	27	7.2	3.8 (2.6-5.5)	

* Expected numbers corrected for two patients for whom information on insulin treatment at follow up was not available.

occurred 3.8 (confidence interval 2.6-5.5) times more often than among the corresponding non-pregnant background population of women ($p < 0.000001$; $\chi^2 = 54.7$; $f = 1$).

During 1966-80 a total of 302 656 deliveries occurred in the three areas with full ascertainment, giving an absolute risk of 12.6 new cases of type I diabetes per 100 000 deliveries when including only the 38 patients in our series currently taking insulin. When the "normal" incidence in the background population of women was deducted the "excess" incidence was 5.0 new cases of type I diabetes per 100 000 deliveries.

FIG 3—Gestational week of onset of insulin dependent diabetes.

SEASONAL VARIATION

Fewer patients had had their last menstrual period during the winter (fig 4). This was statistically significant ($p < 0.05$; $\chi^2 = 4.18$; $f = 1$) even after correcting for a minor seasonal variation in birth rate (and thereby timing of the last menstrual period) in the background population (correction factors for expected numbers: winter 0.946, rest of year 1.018). There was no other statistically significant seasonal variation in the diagnosis of insulin dependent diabetes.

FIG 4—Date of last menstrual period before pregnancy. (Expected numbers (winter/rest of year) 15.75/47.25; expected numbers adjusted for seasonal variation (winter/rest of year) 14.90/48.10; observed numbers (winter/rest of year) 8/55.)

Discussion

These results show that most patients who develop insulin dependent diabetes mellitus during pregnancy have true type I diabetes. These patients must therefore be followed up regularly after their pregnancy, irrespective of whether remissions occur during which they can manage without insulin. The study also shows that the incidence of type I diabetes is at least 70% higher in pregnant than non-pregnant women. The entire increase in incidence appears to occur during the third trimester, when the risk of developing type I diabetes is more than 3.5 times that of the background population of women.

At follow up 77% of the patients (46/60) were taking insulin; they had very low stimulated plasma C peptide concentrations and hence were definitely type I diabetics.¹⁰ The remaining patients (14/60; 23%) were not currently having insulin, but all showed greatly impaired glucose tolerance. Their follow up period was fairly short, and presumably there was the likelihood that some may have had type I diabetes; they were not included in the incidence calculations, which must be assumed to express minimum values.

The distribution of tissue types among the patients showed a high proportion with HLA-DR3,4 (Møller-Jensen *et al.*, paper in preparation), which is a similar picture to that seen in non-pregnant type I diabetics but very definitely "skewed" in relation to the normal background population. Since gestational diabetics¹¹ as well as patients with type II diabetes¹² have a tissue type distribution which

does not differ from that of the normal population, the "skew" distribution among our patients is further evidence that their diabetes was true type I.

There was no statistically significant seasonal variation in the onset of disease. This agrees with a Danish study¹³ and a Scottish study¹⁴ which found no seasonal difference in the incidence of type I diabetes in female patients.

Our study disclosed a lower incidence of type I diabetes when conception took place in the winter. Women who conceive in the winter have their third trimester (risk period for diabetes) in the summer, but how this may contribute to a lower incidence of diabetes is unknown.

Given the incidence of type I diabetes in pregnancy it might be thought that the more frequent patient-doctor contact during pregnancy would by itself result in more type I diabetics being detected. This, however, is unlikely to be true in Denmark, which has a well informed population with free and easy access to medical care, so that new cases of insulin dependent diabetes are quickly diagnosed and treated. Furthermore, the characteristic symptoms of insulin dependent diabetes experienced by patients such as those in our study would make it difficult to miss the disease.

It might also be suggested that insulin dependent diabetes was being "overdiagnosed" in pregnancy, so that insulin was being started in some diabetics who were not genuinely insulin dependent. Since this possibility cannot entirely be excluded, only patients currently receiving insulin were included in the incidence calculation. The possibility of overdiagnosis, however, is strongly refuted by the fact that the patients had severely deranged carbohydrate metabolism at the time of diagnosis and, furthermore, that patients with gestational diabetes in Copenhagen were not being treated with insulin at the time of our study.

The reason for the increased incidence of type I diabetes in pregnancy is unknown. Nevertheless, it is reasonable to believe that the increased strain on carbohydrate metabolism in pregnancy⁷ is contributory, and as this increases as pregnancy advances it would be compatible with the incidence of type I diabetes being highest in the third trimester. In animal experiments an increased metabolic strain increased the severity of virus induced diabetes,¹⁵ while a low carbohydrate diet reduced the diabetogenic effect of streptozocin.¹⁶ Increased β cell activity in rats subjected to ventromedial hypothalamic injury increased the sensitivity to streptozocin.¹⁷ Thus there is good reason to think that the increased β cell activity during pregnancy might at least partly explain the higher incidence of type I diabetes.

Of the 46 patients taking insulin at follow up, 37 (80%) had stopped taking insulin for a median of eight months after delivery. This is interpreted as a period of remission during which the processes underlying type I diabetes stopped or proceeded very slowly, so that some β cells still functioned. It must have been of additional importance in our patients that at the same time the insulin requirement decreased after delivery.

Type I diabetes is thought to be an autoimmune disease involving the thymus dependent immune system.¹⁸ Autoimmune diseases such as systemic lupus erythematosus¹⁹ and rheumatoid arthritis²⁰ often improve during pregnancy and worsen after delivery. This is believed to be related to a reduced functional response by lymphocytes in pregnant patients as shown in vitro.²¹ Subpopulation studies of peripheral blood lymphocytes during pregnancy and a couple of months after delivery have shown a reduced number of helper T lymphocytes and a subnormal ratio of helper to suppressor T cells.²¹ This ratio is raised in active autoimmune diseases, including type I diabetes.²² Thus these immunological phenomena would theoretically entail decreased destruction of β cells during pregnancy and for some time thereafter. It might be suggested, therefore, that the pathogenetic mechanisms underlying type I diabetes provoked by strain on β cells during pregnancy are partially at rest until a few months after delivery when the normal immunological cellular balance is re-established, and the disease progresses.

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Prevalence of asthma and hay fever in England and Wales

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Abstract

The results concerned with the prevalence of asthma and hay fever in the large surveys of morbidity in general practice in 1970-1 and 1981-2 were compared. In data standardised for age the prevalence of asthma in men increased from 11.6 to 20.5 people consulting per 1000 population ($p < 0.001$) and in women from 8.8 to 15.9 per 1000 population ($p < 0.001$). Similar increases were also evident in data analysed from the 19 practices contributing to both surveys. The prevalence of asthma increased in each age group examined. Increases of similar magnitude were reported for hay fever—the prevalence in men increased from 10.8 to 19.8 people consulting per 1000 population ($p < 0.001$) and in women from 10.3 to 19.7 per 1000 population ($p < 0.001$) and occurred in all age groups. The prevalence of acute bronchitis was reduced significantly in the age group 5-14 and increased among the elderly. The prevalence of chronic bronchitis was reduced substantially in 1981-2.

The reported increased prevalence of both asthma and hay fever represented a real increase and was not accounted for by changes in diagnostic preference. Only in the age group 5-14 was there any likelihood that some of the increased prevalence of asthma might have resulted from a reduction in the prevalence of acute bronchitis.

Introduction

The annual period prevalence of asthma reported in three large morbidity surveys in general practice increased from 8.5 people consulting per 1000 registered population in 1955-6¹ to 10.2 in 1970-1² and to 17.8 in 1981-2.³ The corresponding prevalence of hay fever was 5.1, 10.6, and 19.7. Each of these surveys was based on a population of about 300 000 and a nationwide distribution of

practices in which total recording of morbidity from every consultation was sustained over 12 months.

During recent years several reports, taken together, have suggested that the prevalence of asthma has increased. The sales of drugs for treating asthma increased consistently from 1975 to 1981.⁴ Rates of hospital discharge of men with asthma increased from 7.0/10 000 in 1975 to 8.7 in 1978 and 12.3 in 1981. Corresponding rates for women were 6.7, 8.1, and 10.3. In each year there was a distinct excess of men in the age group 0-14 years.⁵ Social security claims for absence from work owing to asthma doubled between 1968 and 1982.⁶

In 1960 there were 1188 deaths from asthma in England and Wales, and this figure increased to a maximum of 1245 in 1965, returning to 1245 in 1970. The increase and decline prompted much speculation about the possible role of aerosol inhalers as a contributory factor, and this matter never has been fully resolved.⁷ In a study of published national mortality statistics for England and Wales from 1974 to 1984, in which account was taken of the impact of the ninth revision of the *International Classification of Diseases* in 1979, Burney concluded that mortality for asthma was increasing.⁸ The trend occurred during a period in which most doctors would accept that substantial advances had been made in the management of asthma.

The difficulties of defining asthma and of its epidemiological study are well known.^{9,10} Among these the preferences of doctors in their choice of diagnostic label may change, resulting in diagnostic transfer between the classificatory headings. Opinions on management vary considerably among both consultants¹¹ and general practitioners.¹² Among children underrecognition of the condition leads to avoidable suffering.¹³ Response to histamine challenge has been used as a diagnostic test, but this is not uniformly reliable.¹⁴

In the study reported here data about asthma and related illnesses during 1981-2 were compared with data obtained in a similar survey about 10 years before to try to discover if the prevalence of asthma and hay fever is increasing.

Methods

Data for this study were obtained during the national morbidity surveys in general practice in 1970-1² and 1981-2.³ Figure 1 shows the geographical distribution of the participating practices. Data available in the material

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