Birth characteristics of women who develop gestational diabetes: population based study

Grace M Egeland, Rolv Skjærven, Lorentz M Irgens

Locus for Registry-based Epidemiology, Department of Public Health and Primary Health Care, University of Bergen, N-5021 Bergen, Norway
Grace M Egeland *researcher*

Section for Medical Statistics, Department of Public Health and Primary Health Care, University of Bergen
Rolv Skjærven *professor*

Medical Birth Registry of Norway, University of Bergen
Lorentz M Irgens *professor*

Correspondence to: G M Egeland grace.egeland@isf.uib.no

BMJ 2000;321:546–7

Women with gestational diabetes are at increased risk of non-insulin dependent diabetes and their babies are at increased risk of adverse perinatal outcomes.[1] These risks can be reduced by better detection and control of diabetes.[2] Identifying risk factors for gestational diabetes may improve screening programmes. As low birth weight has been related to non-insulin dependent diabetes in elderly populations,[3] we decided to investigate whether women's characteristics at birth could predict their subsequent risk of gestational diabetes.

Subjects, methods, and results

We used linked generation data from the medical birth registry of Norway to study all women born in 1967-84 who had given birth between 1988 and 1998. The registry is a compulsory reporting system and files used for analysis are anonymised. Although there were 141 107 women in the cohort, we excluded 2393 who were not singletons.

We compared the birth characteristics of women with and without self reported gestational diabetes in one or more pregnancies. Data were analysed in relation to categories of birth weight; the ponderal index at birth ($m/g^3 \times 100$); gestational age (excluding women who were considered misclassified)[4]; weight for gestational age; and whether the woman had a mother whose pregnancy had been complicated by diabetes (any type), pre-eclampsia, eclampsia, placental abruption, or hypertension. We also considered diabetes in relation to the women's age and parity and their mothers' age and parity when they were born. We calculated odds ratios obtained from logistic regression analyses in which we adjusted for the women's age and parity and their mothers' diabetes.

Altogether 498 of these women aged less than 32 reported gestational diabetes. Prevalence increased with age, from 1.5 per 1000 deliveries for women aged ≤20 to 4.2 for women aged ≥30 (odds ratio 2.8; 95% confidence interval 1.9 to 4.3). Parity increased the risk of gestational diabetes; age adjusted odds ratios (95% confidence intervals) for women with two, three, and four or more deliveries compared with one delivery were 1.5 (1.2 to 1.9), 1.9 (1.4 to 2.5), and 3.3 (2.1 to 5.1) respectively.

Women whose mothers had had diabetes during pregnancy were at increased risk of gestational diabetes (table). The table also shows that there were significant inverse trends in diabetes in relation to birth weight and weight for gestational age ($P < 0.001$). The increased risks of gestational diabetes were 80%, 60%, and 40% in women whose birth weights were ≤2500 g, 2500-2999 g, and 3000-3499 g respectively compared with women in the 4000-4500 g group. We observed similar findings in relation to categories of weight for gestational age. Birth weight and weight for gestational age are strongly related; the three highest birthweight categories occur primarily in the three highest categories of weight for gestational age. We therefore limited further analyses of both variables to women whose birth weight was less than 3500 g. The inverse trend in diabetes in relation to weight for gestational age remained significant (table , $P < 0.01$), but the variation attributed to the truncated range of birth weight was not significant. No other variables examined were associated with diabetes.

Comment

Low birth weight or low weight for gestational age or having a mother who was diabetic during pregnancy

Prevalence rates and adjusted odds ratios (95% CI) for self reported gestational diabetes in relation to women's own birth characteristics

Birth characteristics	No of women (n=138 714)	Rate (per 1000 women)	Odds ratio (95% CI)†
Mother with diabetes during pregnancy:			
No (referent)	138 518	3.5	1.0
Yes	196	30.6	9.3 (4.1 to 21.1)
Birth weight (g):			
<2500	4 652	4.9	1.8 (1.1 to 3.0)**
2500-2999	18 948	4.3	1.6 (1.1 to 2.3)
3000-3499	51 737	4.0	1.4 (1.0 to 2.0)
3500-3999	45 524	3.0	1.1 (0.8 to 1.5)
4000-4500 (referent)	14 852	2.8	1.0
>4500	2 640	4.2	1.5 (0.8 to 2.9)
Weight for gestational age (centiles):			
<10	16 034	4.6	1.7 (1.2 to 2.5)**
10-25	23 480	4.4	1.6 (1.1 to 2.3)
>25-50	36 413	3.6	1.3 (0.9 to 1.8)
>50-75	31 329	2.9	1.0 (0.7 to 1.5)
>75-90 (referent)	15 576	2.8	1.0
>90	10 125	3.4	1.2 (0.7 to 1.8)
Ponderal index at birth (g/cm^3) ×100:			
<2.5	25 752	3.5	1.0 (0.8 to 1.4)
2.5-2.635	28 568	4.5	1.3 (1.0 to 1.7)
2.635-2.752 (referent)	27 441	3.4	1.0
2.752 to 2.89	28 441	3.4	1.0 (0.8 to 1.4)
≥2.89	27 809	3.2	0.9 (0.7 to 1.3)
Gestational age (weeks):			
28-34	1 414	5.7	1.6 (0.8 to 3.3)
35-36	3 261	3.7	0.9 (0.5 to 1.7)
37-39	39 010	3.4	1.0 (0.8 to 1.2)
40 (referent)	37 815	3.4	1.0
41-42	43 818	3.8	1.1 (0.9 to 1.4)
43-44	5 652	3.7	1.1 (0.7 to 1.7)
Weight for gestational age in women <3500 g at birth (centiles):			
<10	16 034	4.6	2.9 (0.7 to 12.0)*
10-25	23 480	4.4	2.8 (0.7 to 11.5)
>25-50	25 803	3.6	2.2 (0.5 to 9.1)
>50-75	5 688	3.5	2.1 (0.5 to 8.9)
>75-90 (referent)	975	2.1	1.0
>90	272	3.7	1.3 (0.1 to 18.9)

Because of missing variables, not all characteristics were included for all women.
†Adjusted for women's age and parity and their mother's diabetic status.
*P<0.01; **P<0.001.

increases the risk of gestational diabetes. In women who weighed less than 3500 g at birth, weight for gestational age may provide additional predictive information on risk. No other birth characteristics were predictive of gestational diabetes. The non-significant raised risk in women weighing 4500 g or more at birth could indicate undiagnosed or unrecorded maternal diabetes. Low birth weight and low weight for gestational age may be common risk factors for gestational diabetes and non-insulin dependent diabetes. The results are compatible with the fetal origins of disease hypothesis.[5] Future studies combining birth information with risk factors in adulthood may improve predictive models for identifying women at risk of gestational diabetes.

Barbro Mork Emblem was instrumental in linking the generational birth information and in setting up the generational analytical database.

Contributors: GE had the idea for the study, conducted analyses, and wrote the report. RS provided guidance in using the registry, discussed core ideas and study design, and edited the report. LI supervised data collection, discussed core ideas and study design, and edited the report. All authors are guarantors of the paper.

Funding: Medical Birth Registry of Norway and Locus for Registry-based Epidemiology, University of Bergen.

Competing interests: None declared.

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(Accepted 5 April 2000)

Drug points

Prolonged cholestasis associated with irbesartan

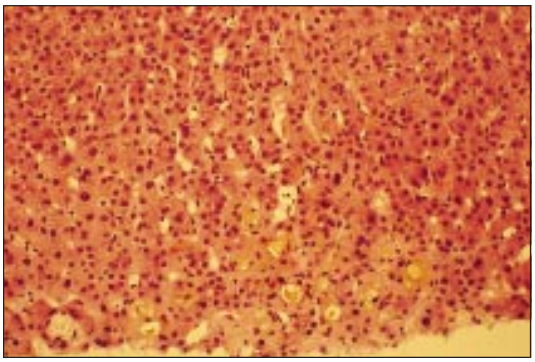
R Hariraj, E Stoner, S Jader, D M Preston, Princess Alexandra Hospital, Harlow, Essex CM20 1QX

A 62 year old woman was admitted with a week's history of jaundice. Examination showed deep icterus and hepatomegaly. She had no history of liver disease, blood transfusion, alcohol or drug misuse, or travel abroad. She had been hypertensive for 15 years and took atenolol 50 mg daily. Treatment had been changed to irbesartan (Aprovel, Bristol-Myers Squibb, Hounslow) 300 mg daily one month before admission.

Liver function tests showed concentrations of albumin 240 g/l (normal range 360-520 g/l), bilirubin 403 µmol/l (0-17 µmol/l), alkaline phosphatase 3193 IU/l (20-125 IU/l), γ-glutamyltransferase 1924 IU/l (10-50 IU/l), and aspartate aminotransferase 177 IU/l (0-40 IU/l). Serology for hepatitis A, B, and C, cytomegalovirus, Epstein-Barr virus, and autoimmune screen gave negative results. Tests for haemochromatosis and α_1 antitrypsin deficiency gave normal results. An ultrasonogram and computerised tomogram were normal.

Irbesartan was stopped one week after admission and substituted with amlodipine and atenolol. The patient remained jaundiced, with a bilirubin concentration of 324 µmol/l after two months. A liver biopsy sample obtained on two different occasions showed notable portal tract expansion with minimal inflammation, ectatic bile ductules, and cholestatic rosettes (figure). These features were more pronounced in the second biopsy sample. Endoscopic retrograde cholangiopancreatography gave normal results. Her condition gradually improved and the bilirubin concentration returned to normal in about 16 weeks. She continues to be anicteric at more than one year's follow up.

The temporal profile of her cholestatic jaundice in relation to the irbesartan and the lack of an alternative cause for liver dysfunction suggests a drug reaction. The diagnosis also fulfils the international consensus criteria for drug induced hepatotoxicity.[1]



Parenchymal cholestasis with "cholestatic rosettes" and ballooning degeneration of hepatocytes in liver biopsy sample (haematoxylin and eosin × 20)

A review of hepatotoxicity with angiotensin converting enzyme inhibitors showed that a cholestatic pattern was present in the liver of eight out of 13 patients.[2] There have been reports of severe acute hepatic injury as well as 80 reports of minor liver injury in association with losartan.[3–5] The manufacturers of irbesartan were, however, previously unaware of any association between this drug and severe hepatic dysfunction.

We thank Dr A P Dhillon at the Royal Free Medical School, London, for reviewing the histopathology slides.

Competing interests: None declared.

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