Papers

Outcomes of pregnancy in insulin dependent diabetic women: results of a five year population cohort study

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Abstract

Objective: To monitor pregnancies in women with pre-existent insulin dependent diabetes for pregnancy loss, congenital malformations, and fetal growth in a geographically defined area of north west England.
Design: Population cohort study.
Setting: 10 maternity units in Cheshire, Lancashire, and Merseyside which had no regional guidelines for the management of pregnancy in diabetic women.
Subjects: 462 pregnancies in 355 women with insulin dependent diabetes from the 10 centres over five years (1990-4 inclusive).
Main outcome measures: Numbers and rates of miscarriages, stillbirths, and neonatal and postneonatal deaths; prevalence of congenital malformations; birth weight in relation to gestational age.
Results: Among 462 pregnancies, 351 (76%) resulted in a liveborn infant, 78 (17%) aborted spontaneously, nine (2%) resulted in stillbirth, and 24 (5%) were terminated. Of the terminations, nine were for congenital malformation. The stillbirth rate was 25.0/1000 total births (95% confidence interval 8.9 to 41.1) compared with a population rate of 5.0/1000, and infant mortality was 19.9/1000 live births (5.3 to 34.6) compared with 6.8/1000. The prevalence of congenital malformations was 94.0/1000 live births (63.5 to 124.5) compared with 9.7/1000 in the general population. When corrected for gestational age, mean birth weight in the sample was 1.3 standard deviations greater than that of infants of non-diabetic mothers. Infants with congenital malformations weighed less than those without.
Conclusion: In an unselected population the infants of women with pre-existent insulin dependent diabetes mellitus have a 10-fold greater risk of a congenital malformation and a fivefold greater risk of being stillborn than infants in the general population. Further improvements in the management of pregnancy in diabetic women are needed if target of the St Vincent declaration of 1989 is to be met.

Introduction

The St Vincent declaration of 1989 set as a five year target reduction of adverse pregnancy outcomes among insulin dependent diabetic women to a level equal to that among non-diabetic women.[1] This was seen as achievable because there had been widespread acceptance that perinatal mortality and morbidity in offspring of mothers with insulin dependent diabetes had fallen as a result of changes in preconceptional, antenatal, and neonatal care,[2] some workers claiming that the outcome can approach that of the non-diabetic population.[3] Many of these data, however, are derived from specialist centres with substantial experience in the care of pregnant diabetic women.[4 5] In contrast, data from non-specialist units indicate that offspring of diabetic mothers are at a disadvantage compared with the general population,[3] severe congenital malformations continuing to play a prominent part in both mortality and long term morbidity. In the United Kingdom most insulin dependent diabetic mothers receive care at their local hospital rather than at specialist centres. There is no population based information on the outcome of pregnancies in diabetic mothers in these settings. We report the pregnancy loss, congenital malformation rates, and measures of fetal growth in pregnancies in a population based cohort of insulin dependent diabetic women.

Methods

The study cohort was drawn from a geographically discrete area in the north west of England (population about 2.4 million) which included 10 maternity units in Cheshire, Lancashire, and Merseyside. These maternity units and their associated gynaecological services provided care to women in the region over the study period, 1990-4. Though there were no regional guidelines for the management of pregnancy in diabetic women, individual units had their own policies. Local diabetes care teams also had responsibility for prepregnancy counselling, so the extent of such counselling may have varied.

Pregnancies in insulin dependent diabetic women were identified from several sources, including maternity booking clinics, gynaecology wards, operating theatre records, diabetic clinic records, and independent clinic data sources kept by individual units. Annual retrospective checks at each unit were made from both hand and computer birth registers and from operating theatre records to ensure inclusion of all relevant pregnancies. Maternal data collected

See editorial by Simmons and p 279

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Table 1 Pregnancy outcomes (n=462) of established insulin dependent diabetic women in sample population (1990-4)

Outcome	No (%)	No of infants with congenital malformations
1st Trimester therapeutic abortion	16 (3.5)	2
1st Trimester spontaneous abortion	76 (16.5)	1
2nd Trimester therapeutic abortion	8 (1.7)	7
2nd Trimester spontaneous abortion	2 (0.4)	0
Stillbirth	9 (1.9)	2
Early neonatal death	4 (0.9)	3
Late neonatal death	2 (0.4)	2
Postneonatal death	1 (0.2)	1
All live births	351 (76.0)	33
Live birth, survival to 1 year	344 (74.5)	27

included age and parity and details of glycaemic control in the first trimester. Pregnancy outcome recording included termination for social and medical reasons, spontaneous abortions, stillbirths, and neonatal (0-28 days) and postneonatal (29 days to 1 year) deaths. Necropsy records were examined when relevant. Variables measured in infants included birth weight, body length, gestational age, sex, and congenital malformations. Congenital malformations were classified according to EUROCAT criteria.[6]

The study findings were compared with national and regional data published by the Office of Population Censuses and Surveys (now the Office for National Statistics). Descriptive and analytical statistics (sign test[7] and Student's *t* test) were calculated with the Statistical Package for the Social Sciences (SPSS), version 6.1. The standard normal deviate (z score) of birth weights in the study sample was calculated by using the mean and standard deviation for each gestational age from the recent Scottish low birthweight study.[8]

Results

Data were recorded on 462 pregnancies in 355 women with pre-existent insulin dependent diabetes who completed their pregnancy during the study period. They comprised 162 first, 137 second, 89 third, and 74 fourth or later pregnancies. The mean age of mothers at the birth of a live infant was 28.3 (range 16-45) years, similar to the national average.[9] The mean duration of diabetes was 10.9 years (range 1 month to 31 years 8 months). Table 1 summarises the outcome of pregnancies in the study population; 351 (76%) resulted in live births. The perinatal mortality rate was over four times and the stillbirth rate five times that in the general population of England and Wales and the population of Merseyside and Cheshire over the same period (table 2).[9-13]

Forty five infants with congenital abnormalities were identified, of whom 33 were liveborn and two stillborn. A further nine pregnancies were terminated because of a congenital malformation and one aborted spontaneously (table 1). The prevalence of congenital malformations in the study population was 10 times that in the general population of England and Wales[14] (table 2). Of the congenital malformations in stillborn and liveborn infants, 14 (40%) were of the cardiovascular system, a rate of 38.9 (95% confidence interval 18.9 to 58.9)/1000 total births compared with a national rate of 0.81/1000.[14] The prevalence of renal abnormalities was 16.7 (3.4 to 29.9)/1000 and hypospadias among boys 13.9 (1.8 to 26.0)/1000. Despite the small numbers of cases these rates were substantially higher than those in the general population (0.07/1000 for renal malformations, 0.98/1000 for hypospadias).[14] The prevalence of skeletal malformations was 8.3/1000, which was not significantly higher than in the general population. There were six neonatal deaths and one postneonatal death; all except one of these infants had congenital malformations.

Hospitals covered by the study varied in the tests used to monitor glycaemic control, seven centres using glycated haemoglobin concentration and three fructosamine concentration. In addition, results of these measurements were specific to each centre. However, for all centres except one the mean measure of first trimester glycaemic control values among women whose infants had a congenital malformation was higher than or equal to the mean for women who had an unaffected liveborn infant ($P < 0.04$, sign test).

The mean weight of liveborn infants at delivery was 3509 g (range 990-5560 g), there being no association between infant birth weight and maternal weight at booking. Only 13.7% (43/344) of the study sample weighed less than the median birth weight for gestational age of the reference cohort.[8] Figure 1 shows the distribution of standard normal deviates (z scores) of birth weights of infants in the study group. Rather than being distributed about a mean of zero (the predicted mean from the reference data) scores for infants without congenital abnormalities had a mean of 1.38, confirming that infant macrosomia remains a problem in diabetic pregnancies. Figure 1 also shows the z score distribution for infants of diabetic mothers with congenital malformations. These infants were on

Table 2 Mortality and congenital malformation rates in study sample and in England and Wales and Merseyside and Cheshire (1990-4)

	Study population (95% confidence interval)	England and Wales	Merseyside and Cheshire
Stillbirth rate/1000 total births	25.0 (8.9 to 41.4)	5.0	4.7
Perinatal mortality rate/1000 total births	36.1 (16.8 to 55.4)	8.3	7.6
Infant mortality rate/1000 live births	19.9 (5.3 to 34.6)	6.8	6.1
Prevalence of congenital malformations/1000 total births	97.2 (66.6 to 127.8)	9.8*	NA
Prevalence of congenital malformations among all liveborn infants/1000 live births	94.0 (63.5 to 124.5)	9.5*	NA
Prevalence of congenital malformations among liveborn boys/1000 live births	101.8 (55.9 to 147.7)	10.8*	NA
Prevalence of congenital malformations among liveborn girls/1000 live births	88.4 (47.0 to 129.8)	7.9*	NA

*Figures for 1990-3.
NA=Figures not available.

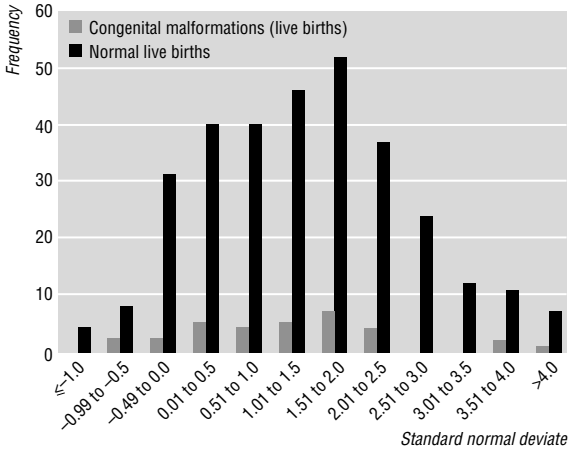

Fig 1 Birth weights of liveborn infants of women with pre-existent insulin dependent diabetes expressed as standard normal deviates (z scores) for gestational age (Merseyside and Cheshire, 1990-4). Mean scores were 1.27 for infants with congenital malformations and 1.36 for infants without congenital malformations (n=344)

average only 1.26 standard deviations heavier than the reference cohort. Thus, though infants with congenital malformations who had diabetic mothers were heavier than infants of non-diabetic mothers, they had a lower birth weight than infants with no congenital malformations who had diabetic mothers. Hence despite the overall higher weights for dates the reduced birth weight associated with congenital abnormality was maintained in the diabetic sample.

In the reference population, boys were heavier than girls at all gestational ages. In contrast, among the study population girls (3559 g) were heavier than boys (3456 g), though the difference was not significant ($P = 0.19$; Student's t test). Thus the heavier weight of infants of diabetic mothers was more pronounced in girls than boys.

Discussion

Fetal loss

This study shows the magnitude of the problem confronting clinicians who counsel and manage the care of pregnant women with insulin dependent diabetes mellitus. Though the incidence of pregnancy loss has declined dramatically since the introduction of insulin at the beginning of the 20th century,[15] our findings confirm that among unselected populations of women with insulin dependent diabetes mellitus, pregnancy loss remains significantly higher than in the normal population.[16]

It is difficult to quantify the increased risk of early fetal loss among insulin dependent diabetic women because the rate of loss in the non-diabetic population is unknown and because insulin dependent diabetic women with early pregnancy loss are more likely to present to secondary care. The rate reported here was only a little higher than that reported in 1996 in the diabetes control and complications trial, in which 13.3% of the intensively treated group and 10.4% of controls had spontaneous abortions.[17] Women with poor glycaemic control are reportedly at higher risk of spontaneous abortion,[18 19] but without knowledge of the background rate of first trimester pregnancy loss it is difficult to confirm or refute these findings.

The magnitude of the increased risk of late fetal loss in this series was similar to other recent reports, with a fourfold increase in perinatal death and a fivefold increase in stillbirths.[16 20] Also, despite an improvement in the general population in perinatal mortality rate over the past 10 years, the magnitude of increased risk among diabetic women has remained about fourfold. In 1979-80, when the population perinatal mortality rate was 9.4/1000,[21] the rate among infants of diabetic mothers was 55.6/1000.[22] Even among the highly selected volunteers in the diabetes control and complications trial, in whom diabetic control had been optimised, perinatal loss was higher than in the non-diabetic population.[17]

Congenital malformations

The prevalence of congenital malformations at birth also remains higher in infants of women with insulin dependent diabetes. A prevalence of 9.4% was observed in this study, an almost 10-fold increase in risk compared with the general population. General population figures for congenital malformations are available only from the congenital malformations notifications submitted to the Office for National Statistics. It is generally acknowledged that congenital malformations are underreported to that office,[23] which may result in surveillance bias. Reporting is voluntary and concerns only those congenital malformations identified within 10 days of birth. From 1990 certain minor congenital malformations have been excluded. Based on current notifications, the prevalence of congenital malformations at birth among the general population of England and Wales is about 1%.[14] However, as only major congenital malformations identified during the postnatal stay were included in this study, comparison with Office for National Statistics' figures is probably valid.

The prevalence of malformations in this study was similar to that in comparable studies; in a 1979-80 study the prevalence was 7.1%.[22] More recently rates of 10%[24] and 6.1%[18] in the United States and 8% in the United Kingdom[20] have been reported. The diabetes control and complications trial found a prevalence of 4.7% among controls. However, among the offspring of women in the intervention group in that trial a prevalence of only 1.1% was reported. Thus in a randomised controlled trial well motivated, self-selected diabetic women given intensive treatment before pregnancy have a birth prevalence of congenital malformations in their infants similar to that of non-diabetic women.[17]

The raised infant mortality among diabetic mothers is explicable by the excess of congenital malformations, which accounted for six of the seven infants who died during their first year of life. The infant mortality rate among infants without congenital malformations was not significantly different from the national rate.[14] The pattern of congenital malformations in this series was similar to that reported elsewhere,[17 18 22] and the prevalence of cardiovascular malformations was of the same magnitude as in two other large studies.[18 22]

Fetal size

The raised prevalence of macrosomia in the study population was similar to that reported previously,[25] though absence of a sex difference in birth weight has not been reported before. A possible explanation is

Key messages

- Infants of women with established insulin dependent diabetes mellitus have 10 times the population risk of congenital malformations and five times the stillbirth rate
- Excess mortality among infants of women with pre-existent insulin dependent diabetes mellitus is predominantly due to congenital malformations
- The birth prevalence of congenital malformations can be reduced by good periconceptional glycaemic control, but the challenge remains to implement this on a population basis
- Macrosomia remains a problem among infants of women with established insulin dependent diabetes mellitus

that there is a "ceiling" for fetal size, independent of sex, by which excess growth in macrosomic fetuses is constrained. This may limit the growth of male fetuses in diabetic women sooner than that of female fetuses, resulting in similar mean birth weights. Confirmation is needed, as it may provide evidence for the aetiology of macrosomia in infants of insulin dependent diabetic mothers.

Among pregnancies in diabetic women, infants with congenital malformations were of lower mean birth weight than other infants. Congenital malformations in the general population are often seen in infants who are small for gestational age. Though the birth weight of infants with congenital malformations in the study population did not fall into the classic definition of growth retardation (below the 10th centile for gestational age), these infants had lower mean birth weights than the rest of the study population. Thus a fetus of a diabetic mother which seems to be following a normal, non-diabetic growth trajectory may in effect be a low weight fetus and vulnerable to the complications linked with small for dates infants.

The St Vincent declaration set a target to reduce adverse pregnancy outcomes among insulin dependent diabetic women to a level equal to that in non-diabetic women by implementing "effective measures." It did not, however, identify these measures.[1] That such a reduction is possible is shown by the findings of the diabetes control and complications trial. In that trial, women whose insulin dependent diabetes was well controlled (as evidenced by a low glycated haemoglobin concentration at the time of conception) had a reduction in the birth prevalence of congenital malformations.[26] However, our findings show that this reduction does not occur in an unselected population. The challenges now are the technical, psychological, social, and political issues in helping all insulin dependent diabetic women who hope to become pregnant to achieve and maintain optimal glycaemic control.

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1 Workshop report. Diabetes care and research in Europe: the Saint Vincent declaration. *Diabet Med* 1990;7:360.
2 Oats JN. Diabetes. *Ballières Clin Obstet Gynaecol* 1995;9:481-95.
3 Kitzmiller JL, Gavin LA, Gin GD, Jovanovic-Peterson L, Main EK, Zigrang WD. Pre-conception care of diabetes: glycemic control prevents congenital anomalies. *JAMA* 1991;265:731-6.
4 Landon MB, Gabbe SG, Piana R, Mennuti MT, Main EK. Neonatal morbidity in pregnancy complicated by diabetes mellitus; predictive value of maternal glycemic profile. *Am J Obstet Gynecol* 1987;156:1089-95.
5 Steel JM, Johnstone FD, Hepburn DA. Can prepregnancy care of diabetic women reduce the risk of abnormal babies? *BMJ* 1990;301:1070-4.
6 Dolk H, Groyens S, Lechat MF, eds. *Description of EUROCAT registries, 1979-90.* Brussels: Commission of the European Communities, 1991.(Medicine series, EUR 13615.)
7 Zar JH. *Biostatistical analysis.* 2nd ed. New Jersey: Prentice-Hall, 1984:386-90.
8 Scottish Health Service Common Services Agency, Scotland. *Birthweight, head circumference and length for gestational age.* Edinburgh: SHSCSAS, 1991.
9 Office of Population Censuses and Surveys. *Birth statistics.* London: HMSO, 1992-6. (Ser FM1.)
10 Office for National Statistics. *Population trends 84.* London: HMSO, 1996.
11 Office of Population Censuses and Surveys. *Infant and perinatal mortality—social and biological factors.* London: HMSO, 1992-5. (Ser DH3.)
12 North West Regional Health Authority. *North West region: 1994 public health common dataset. Monitoring data.* Warrington: NHS Executive North West, 1995.
13 North West Regional Health Authority. *The health of the north west of England. Common dataset, 1995.* Warrington: NHS Executive North West, 1996.
14 Office of Population Censuses and Surveys. *Congenital malformation statistics.* London: HMSO, 1992-6. (Ser MB3.)
15 Landon MB, Gabbe SG. Diabetes mellitus. In: Barron WM, Lindheimer MD, Davison JM, eds. *Medical disorders during pregnancy.* 2nd ed. St Louis: Mosby, 1995:63-88.
16 Hawthorne GC, Robson S, Ryall EA, Sen D, Roberts SH, Ward-Platt M. Can St Vincent's target be met for diabetic pregnancy outcome? The results from the northern diabetic pregnancy audit, 1994. *Diabet Med* 1996;13(suppl 3):S44.
17 Diabetes Control and Complications Trial Research Group. Pregnancy outcomes in the diabetes control and complications trial. *Am J Obstet Gynecol* 1996;174:1343-53.
18 Rosenn B, Miodovnik M, Combes CA, Khoury J, Siddiqi TA. Glycemic thresholds for spontaneous abortion and congenital malformations in insulin dependent diabetes mellitus. *Obstet Gynecol* 1994;84:515-20.
19 Mills JL, Simpson JL, Driscol SD. Incidence of spontaneous abortion among normal women and insulin dependent diabetic women whose pregnancies were identified within 21 days of conception. *N Engl J Med* 1988;319:1617-23.
20 Dunlop DC, Purewal TS, Kelly LC, O'Hare JP. Folic acid and diabetic pregnancy: are we giving the correct advice? Results of a nationwide survey. *Diabet Med* 1996;13(suppl 3):S44.
21 Office of Population Censuses and Surveys. *Infant and perinatal mortality—social and biological factors, 1980.* London: HMSO, 1982. (Ser DH3, No 9.)
22 Lowy C, Beard RW, Goldschmidt J. Congenital malformations in babies of diabetic mothers. *Diabet Med* 1986;3:458-62.
23 Weatherall JAC. Congenital malformations: surveillance and reporting. *Popul Trends* 1978;11:27-9.
24 Albert TJ, Landon MB, Wheller JJ, Samuels P, Cheng RU, Gabbe S. Prenatal detection of fetal abnormalities in pregnancies complicated by insulin-dependent diabetes mellitus. *Am J Obstet Gynecol* 1996;174:1424-8.
25 Cordero L, Landon MB. Infant of diabetic mother. *Clin Perinatol* 1993;20:635-48.
26 Miller E, Hare LW, Cloherty JP. Elevated maternal hemoglobin A_{1c} in early pregnancy and major congenital malformations in infants of diabetic mothers. *N Engl J Med* 1981;304:1331-4.

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Endpiece

Hume's bonfire

If we take in our hand any volume, let us ask, Does it contain any abstract reasoning concerning quantity and number? No. Does it contain any experimental reasoning, concerning matter of fact or existence? No. Commit it then to the flames: for it can contain nothing but sophistry and illusion.

David Hume, *An Enquiry Concerning Human Understanding* (1748)