

# Association between outcome of pregnancy and glycaemic control in early pregnancy in type 1 diabetes: population based study

Rosemary Temple, Vivien Aldridge, Richard Greenwood, Philip Heyburn, Michael Sampson, Katharine Stanley

Recent studies of pregnancy in women in the United Kingdom with type 1 diabetes have shown a fourfold to tenfold increased risk of congenital malformation and a fivefold increased risk of perinatal mortality compared with non-diabetic women.<sup>1,2</sup> These studies used different measures of glycaemic control (concentrations of glycated haemoglobin and fructosamine) both within and between centres so no conclusions were reached about the relation between outcome and glycaemic control. We conducted a population study examining the relation between glycaemic control in early pregnancy and outcome of pregnancy in women with type 1 diabetes.

## Participants, methods, and results

This observational study was carried out in a single centre in Norwich from January 1991 to December 2000. The resident population is 510 000 and mainly white. We defined adverse pregnancy outcome as spontaneous abortion (first or second trimester), major congenital malformation (potentially life threatening or associated with serious long term disability), stillbirth, or neonatal death. We measured glycated haemoglobin concentration at booking for prenatal care and then monthly using the Biomen 8140 method.

Women were divided into two groups according to their glycated haemoglobin concentration at booking: women with values <7.5% (mean of normal range plus 5 standard deviations) were defined as having fair control and those with values ≥7.5% were defined as having poor control. The study was approved by the local ethics committee.

We included only the first pregnancy for each woman during the study in the statistical analyses to avoid possible biases. We analysed data with SPSS software using Student's *t* test, Mann-Whitney U test, and  $\chi^2$  test as appropriate. Fisher's exact test was used for small numbers.

There were 242 pregnancies in 158 women. Thirty two pregnancies had an adverse outcome, with 18 (7%) spontaneous abortions, eight (3%) major congenital malformations (six neural tube defects), four stillbirths, and two neonatal deaths.

We studied the relation between glycated haemoglobin concentration at booking and adverse outcome in the 158 first pregnancies. The table shows the patient characteristics and pregnancy outcomes. Adverse outcome was significantly higher in the poor control group than the fair control group (relative risk 4.3, 95% confidence interval 1.8 to 10). Compared with the fair control group, the poor control group had a fourfold increase in the spontaneous abortion rate (relative risk 4.0, 1.2 to 13.1) and ninefold increase in

the congenital malformation rate (relative risk 9.2, 1.1 to 79.9). Perinatal mortality was higher in the poor control group than the fair control group (54/1000 births *v* 19/1000, relative risk 2.8, 0.41 to 19.4) but with the small numbers the difference was not significant. Perinatal mortality in the background population is 7.8/1000.

## Comment

We found a significant relation between adverse outcome of pregnancy and poor glycaemic control in early pregnancy in women with type 1 diabetes. There was a fourfold increase in adverse outcome, a fourfold increase in spontaneous abortion, and a ninefold increase in major congenital malformation in women with a glycated haemoglobin concentration above 7.5% at booking. Our study has substantial advantages over earlier studies, being a complete, prospective, population based, single centre study analysing only one pregnancy per woman. It confirms earlier reports of increased risk of spontaneous abortion and malformation with poor glycaemic control in early pregnancy in women with type 1 diabetes.<sup>3-5</sup> Our findings suggest that good glycaemic control around the time of conception is necessary to optimise outcome of pregnancy in diabetic women. Diabetic women and their carers need to be advised of the risks and encouraged to optimise glycaemic control before and during pregnancy.

Contributors: RCT had the key idea for the study. All authors contributed to development of the study. RCT and VJA collected data for the study and RCT did the data entry and statistical analysis and compiled the first draft of the manuscript. All authors contributed to interpretation of results and revised critically and approved the final report. We thank Moira Kelly

Elsie Bertram  
Diabetes Centre,  
Norfolk and  
Norwich University  
Hospital NHS  
Trust, Norwich  
NR4 7UY

Rosemary Temple  
consultant physician  
Vivien Aldridge  
diabetes nurse  
specialist

Richard  
Greenwood  
consultant physician  
Philip Heyburn  
consultant physician  
Michael Sampson  
consultant physician

East Anglia Centre  
for Fetal and  
Maternal Medicine,  
Norfolk and  
Norwich University  
Hospital NHS Trust  
Katharine Stanley  
consultant  
obstetrician

Correspondence to:  
R Temple  
rosemary.temple@  
Norfolk-norwich.  
thenhs.com

BMJ 2002;325:1275-6

Characteristics and outcome of pregnancy in women with type 1 diabetes according to glycaemic control at booking. Values are numbers (percentages) of women unless stated otherwise

	Fair control (HbA <sub>1c</sub> <7.5%)	Poor control (HbA <sub>1c</sub> ≥7.5%)	P value
No of women	110	48	
Mean (SD) age (years)	29.0 (4.4)	26.2 (6.1)	0.007
Mean (SD) weight at booking (kg)	67.3 (10.3)	68.5 (10.4)	NS
Mean (range) duration of diabetes (years)	12.0 (1-28)	12.5 (1-32)	NS
Mean (SD) time of booking (weeks)	7.6 (2.4)	8.2 (2.5)	NS
Primiparous	76 (69)	33 (69)	NS
Smokers	21 (19)	14 (29)	NS
Microvascular complications	13 (12)	10 (21)	NS
Pregnancy outcome:			
Spontaneous abortion	4 (4)	7 (15)	0.019
Major congenital malformation	1 (1)	4 (8)	0.03
Stillbirth	1 (1)	1 (2)	NS
Neonatal death	1 (1)	1 (2)	NS
Total pregnancy loss	7 (6)	13 (27)	<0.0001

and Lynette Yaxley for help in initial development of the study and Michael Grande for statistical advice. RCT is guarantor for the study.

Funding: None.

Competing interests: None declared.

- 1 Casson IF, Clarke CA, Howard CV, McKendrick O, Pennycook S, Pharoah POD, et al. Outcomes of pregnancy in insulin dependent women: results of a five year cohort study. *BMJ* 1997;315:275-8.
- 2 Hawthorne G, Robson S, Ryall EA, Sen D, Roberts SH, Ward Platt MP. Prospective population based survey of outcome of pregnancy in diabetic

women: results of the northern diabetic pregnancy audit, 1994. *BMJ* 1997;315:279-81.

- 3 Hanson U, Persson B, Thurnell S. Relationship between haemoglobin A1c in early type 1 (insulin-dependent) diabetic pregnancy and the occurrence of spontaneous abortion and fetal malformation in Sweden. *Diabetologia* 1990;33:100-4.
- 4 Nielson GL, Sorensen PH, Nielson PH, Sabroe S, Olsen J. Glycosylated hemoglobin as predictor of adverse fetal outcome in type 1 diabetic pregnancies. *Acta Diabetol* 1997;34:217-22.
- 5 Rosenn B, Miodovnik M, Combs CA, Khoury J, Siddiqi TA. Glycaemic thresholds for spontaneous abortions and congenital malformations in insulin-dependent diabetes mellitus. *Obstet Gynecol* 1994;84:515-20. (Accepted 22 April 2002)

## Observational study of type of surgical training and outcome of definitive surgery for primary malignant melanoma

Rona M MacKie, Caroline A Bray, David J Hole

Department of Public Health, University of Glasgow, Glasgow G12 8RZ

Rona M MacKie  
*Leverhulme professorial research fellow*

Caroline A Bray  
*medical statistician*  
David J Hole  
*professor of epidemiology and biostatistics*

Correspondence to  
R M MacKie  
R.M.Mackie@clinmed.gla.ac.uk

*BMJ* 2002;325:1276-7

The incidence of primary cutaneous malignant melanoma continues to rise,<sup>1</sup> coinciding with narrower excision margins of normal skin being recommended around primary melanomas.<sup>2-3</sup> The bulk of surgery for primary melanoma is now done on an outpatient basis under local anaesthesia. This change has occurred at a time when training in dermatological surgery has developed, leading to a much higher proportion of excisions of primary melanoma being done by dermatologists. In 1979 in the west of Scotland only 3% of all primary melanomas were removed by dermatologists. By 1998 this figure had risen to 40%. Plastic surgeons now excise 26% of primary melanomas compared with 65% 20 years ago, and general surgeons excise 34% compared with 32%.

We aimed to establish if the change in type of surgeon removing primary cutaneous malignant melanoma has affected the prognosis, and also whether any evidence exists for a specialist treatment effect such as has been observed for breast cancers, with better outcomes for surgeons carrying out breast cancer surgery regularly.<sup>4</sup>

### Participants, methods, and results

We identified 4159 melanoma patients from the files of the Scottish melanoma group. All patients had had their primary melanoma removed between 1979 and 1998. We divided the surgeons performing the defini-

tive excision of the primary melanoma into dermatological, plastic surgery, or general surgery training. We recorded age, sex, tumour thickness, presence of ulceration, and maximum diameter of the primary tumour and noted mortality and cause of death up to 1998. We also looked at the effect within the three surgical groups of treating up to six or more than six primary melanomas annually.

An average of 10 years' follow up information was available for all patients. To test for an association between tumour thickness and type of surgical experience we used the  $\chi^2$  statistic for trend, aggregated over the period of diagnosis. We used the Cox proportional hazards model to compare the survival of patients in relation to surgical experience,<sup>5</sup> with adjustment for thickness, ulceration, and maximum diameter of tumour and sex, age, and deprivation category of patients.

The table shows the division of patients by tumour thickness, ulceration, maximum diameter of primary melanoma, and outcome by surgical training. Dermatologists treated a significantly higher proportion of thin melanomas ( $P < 0.001$ ). The proportion of ulcerated melanomas was higher in the plastic surgery group than in the dermatological group ( $P < 0.001$ ) and higher in the general surgical group than the plastic surgery group ( $P < 0.001$ ).

After adjustment for thickness, the best outcome was in the dermatological surgeon treatment group

Details of melanomas treated, by surgical groups adjusted for type of surgical training. Values are numbers (percentages) unless stated otherwise

Characteristics of melanomas	Dermatologist surgeon (n=1076)	Plastic surgeon (n=1691)	General surgeon (n=1392)	Total (n=4159)
Primary tumours <1.5 mm thick	739 (69)*	809 (48)	589 (42)	2137 (51)
Primary tumours 1.5-3.49 mm thick	217 (20)	447 (26)	342 (25)	1006 (24)
Primary tumours $\geq$ 3.5 mm thick	120 (11)	435 (26)	461 (33)	1016 (24)
No of primary tumours ulcerated	129 (12)*	432 (26)*	499 (36)	1060 (25)
<b>Relative hazard ratios† (95% CI) (risk of death)</b>				
Adjusted for thickness‡	1.0	1.33 (1.07 to 1.65)	1.41 (1.14 to 1.75)	P=0.008
Adjusted for thickness and ulceration	1.0	1.22 (0.97 to 1.54)	1.23 (0.97 to 1.55)	P=0.19
Adjusted for thickness, ulceration, and maximum diameter	1.0	1.14 (0.88 to 1.48)	1.18 (0.90 to 1.54)	P=0.48

\* $P < 0.001$  for comparison of proportion of thin melanomas treated by dermatological surgeons compared with other surgeons; also for proportion of ulcerated melanomas both between dermatological and plastic surgeons and between plastic and general surgeons.

†Sex, age, deprivation category, and year of diagnosis were considered in the model but did not contribute any significant impact on surgical training differences.

‡Thickness of primary tumour has been entered as a stratification variable owing to non-proportionality of the hazard functions.