Value of family history in identifying women at risk of venous thromboembolism during oral contraception: observational study

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BMJ 2001;322:1024–5

Common inherited thrombophilic defects such as factor V Leiden and G20120A mutation of the prothrombin gene interact synergistically with oral contraceptives to increase the risk of venous thromboembolism.[1 2] The best approach to identify women at higher risk of venous thromboembolism before taking oral contraceptives is controversial. Universal screening is not cost effective because 8000 women need to be screened for factor V Leiden to detect 400 mutations and prevent one episode of venous thromboembolism.[1] Many authors recommend selective screening in women with a personal or family history of venous thromboembolism.[1] However, the effectiveness of this approach has not been proved. The aim of our study was to evaluate the sensitivity and positive predictive value of a family history of venous thromboembolism for identifying common thrombophilic defects in women without thrombosis before taking oral contraceptives.

Participants, methods, and results

We prospectively evaluated a cohort of women (age range 15-49 years) consecutively referred to our thrombophilia unit by gynaecologists at family planning clinics in Bologna, Italy, between 1998 and 2000. The gynaecologists had established that the women were eligible to take oral contraceptives and had no history of venous thromboembolism. Before the women were screened, experienced investigators administered a modified structured questionnaire[3] that was designed and validated to evaluate both personal and family history (first degree = parents and siblings, second degree = grandparents, aunts, uncles, and cousins) of venous thromboembolism (see *BMJ*'s website for details). We considered family history positive if a thromboembolism was reported in any first or second degree relatives.

Thrombophilia screening was conducted as previously described.[4] Prothrombin activity was measured by chromogenic assay[5] and lupus anticoagulant by LA-test and LA-check assays (Organon Teknika, Rome, Italy). If prothrombin activity was confirmed to be above 1.10 U/ml, we analysed the DNA for the G20120A mutation according to the method of Poort et al.[5] The tests were performed by staff blind to the results of the questionnaire.

We calculated sensitivity and positive predictive values according to standard methods. The 95% confidence intervals for proportions were calculated by an approximate method, and we used the χ^2 test when appropriate. A two sided probability value <0.05 was considered significant. All data were analysed with the statistical package SOLO (BMDP, Los Angeles).

We evaluated 324 women (mean age 34 years) who had a negative personal history for venous thromboembolism confirmed by our questionnaire. Thirty four women reported a positive family history (10%, 95% confidence interval 7% to 14%), of whom two were heterozygous for factor V Leiden and one had protein S deficiency. Thrombophilic defects were identified in 19 women (6%, 3% to 8%), only three of whom had a positive family history. Among the 290 women with a negative family history, thrombophilic defects were detected in 16 (6%, 3% to 8%); eight were heterozygous for factor V Leiden and eight were heterozygous for the G20120A mutation.

The table shows the sensitivity and positive predictive value of family history for identifying thrombophilic defects. The proportion of women with thrombophilia was similar among those with a positive history and those with a negative history of venous thromboembolism when first and second degree family history was considered (9% (3/34) *v* 5% (16/290), P = 0.44) and when only first degree family history was considered (8% (2/26) *v* 6% (17/298), P = 0.68).

Comment

Family history of venous thromboembolism has unsatisfactory sensitivity and positive predictive value for identifying carriers of common thrombophilic defects before taking oral contraceptives. A policy of selective screening may therefore miss a substantial number of women at increased risk of thromboembolism when taking oral contraceptives.

We thank the gynaecologists at Bologna family planning clinics who referred women for screening.

Contributors: BC was involved in the conception and design of the study and drafting the article. GP was involved in the con-

Sensitivity and positive predictive values of family history as a predictor of thrombophilic defects in 324 women with no personal history of venous thromboembolism

	All defects		Factor V Leiden		G20120A	
Family history	**No (%)**	**95% CI**	**No (%)**	**95% CI**	**No (%)**	**95% CI**
First and second degree						
Sensitivity	3/19 (16)	0.0 to 32	2/10 (20)	0.0 to 45	0/8	—
Postive predictive value	3/34 (9)	0.0 to 18.3	2/34 (6)	0.0 to 14	0/34	—
First degree only						
Sensitivity	2/19 (11)	0 to 24.7	1/10 (10)	0 to 28	0/8	—
Postive predictive value	2/26 (8)	0 to 18	1/26 (4)	0 to 11.2	0/26	—

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The questionnaire is available on the BMJ's website

ception and design of the study and critical revision of the article and is the paper's guarantor. CL and SG analysed and interpreted the data and helped revise the article. All authors approved the final draft.

Funding: This project was supported by a grant from the University of Bologna.

Competing interests: None declared.

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(Accepted 19 December 2000)

Gestational impaired glucose tolerance does not increase perinatal mortality in a developing country: cohort study

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The high prevalence of diabetes and impaired glucose tolerance in women of childbearing age in Mauritius provides an opportunity to assess prospectively the risks of adverse outcome in pregnancy of these conditions, whether the conditions are known to be present at conception or diagnosed during pregnancy.[1] The findings are likely to have consequences for healthcare planning in developing countries.

Participants, methods, and results

The study hospital (catchment population 250 000; 4500 deliveries a year) accounts for 22% of deliveries of babies in Mauritius, hospital deliveries being 80% of all deliveries on the island.[1] Cases were registered in 1993-6 at a joint obstetric and medical service for diabetes, and were also found by monitoring admissions to the obstetric wards, and by monitoring all requests for obstetric oral glucose tolerance tests. Data were collected from the mother and from hospital and national records. Diabetes and impaired glucose tolerance were diagnosed using the 1985 WHO criteria.[2] Outcomes were assessed as miscarriage (<28 weeks), stillbirth, live birth, or neonatal death (<1 week). Neonatal data were obtained from neonatal records, and background information was obtained from national statistics and routinely collected hospital obstetric data. Standard statistical tests were used for analysis of categorical and continuous data.

A total of 294 glucose intolerant pregnancies were registered in 270 women with diabetes or impaired glucose tolerance (mean age 31; SD 6 years). Of these, 110 cases were of pregestational onset and the remainder were diagnosed during pregnancy (86 diabetes, 98 impaired glucose tolerance); nine were lost to follow up and 18 miscarried.

Outcome in the 267 pregnancies resulting in live birth or stillbirth is shown in the table. Perinatal

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BMJ 2001;322:1025–6

Outcome of pregnancy in Mauritius, 1993-6, according to diagnostic category of glucose intolerance. Values are number (percentage) unless otherwise indicated

	Pregestational diabetes	Gestational diabetes	Gestational impaired glucose tolerance	Background population
Perinatal mortality per 1000 births	124	116	22	26
Relative risk (95% CI)	4.7 (2.7 to 8.2)	4.4 (2.5 to 7.9)	0.8 (0.2 to 3.3)	
Stillbirth per 1000 births	67	81	11	14
Relative risk (95% CI)	4.8 (2.2 to 10.3)	5.7 (2.8 to 11.7)	0.8 (0.1 to 5.4)	
Early neonatal mortality per 1000 live births	60	38	11	12
Relative risk (95% CI)	4.9 (2.1 to 11.6)	3.1 (1.0 to 9.4)	0.9 (0.1 to 6.3)	
Mean (SD) birthweight (g)	3059 (641)	3293 (714)	3083 (603)	2953 (567)
P value (*v* background population)	NS	0.001	0.05	
Macrosomia (≥4000 g)	7 (8)	14 (16)	6 (7)	147 (3)
Relative risk (95% CI)	2.4 (1.2 to 4.9)	4.9 (3.0 to 8.1)	2.0 (0.9 to 4.3)	
P value (*v* background population)	0.05	0.001	NS	
Mean (SD) gestational age (weeks)	37.0 (2.4)	37.7 (2.3)	38.5 (1.8)	NA
P value (*v* pregestational diabetes/gestational diabetes)	NS	0.05	0.001/0.05	
Prematurity (<37 weeks)	33 (37)	19 (22)	10 (11)	NA
P value (*v* pregestational diabetes/gestational diabetes)	NS	0.05	0.001/0.05	
Caesarean section	51 (58)	49 (57)	40 (43)	16
P value (*v* background population)	0.001	0.001	0.001	
Hypoglycaemia in infant (<1.7 mmol/l)	17 (21)	11 (14)	4 (4)	NA
P value (*v* gestational impaired glucose tolerance)	0.001	0.05	NS	
Hyperbilirubinaemia in infant	28 (35)	30 (39)	19 (21)	NA
P value (*v* gestational impaired glucose tolerance)	0.05	0.05	NS	

NA=data not available.NS=not significant.