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Cardiovascular sequelae of toxaemia of pregnancy

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Abstract

***Objective*—To determine whether the rate of cardiovascular disease is different among parous women with a general practitioner reported history of toxaemia of pregnancy than among those not reported to have experienced toxaemia, or among nulliparous women.**

***Design*—Prospective cohort study.**

***Setting*—1400 general practitioners throughout the United Kingdom.**

***Subjects*—Women who had never used oral contraceptives who were recruited to the Royal College of General Practitioners' oral contraception study (original cohort about 23 000).**

***Main outcome measures*—Age, social class, and smoking standardised incidence rates for hypertensive disease, acute myocardial infarction, other acute ischaemic heart disease, other chronic ischaemic heart disease, angina pectoris, total ischaemic heart disease, total cerebrovascular disease, and total venous thromboembolic disease in the three groups.**

***Results*—Compared with parous women with no history of toxaemia, those who had experienced toxaemia had a significantly increased risk of hypertensive disease (relative risk (RR) 2·35), acute myocardial infarction (RR 2·24), chronic ischaemic heart disease (RR 1·74), angina pectoris (RR 1·53), all ischaemic heart disease (RR 1·65), and venous thromboembolism (RR 1·62). The rates for all cerebrovascular disease and peripheral vascular disease were also increased but not significantly. Nulliparous women were more likely to develop hypertension or all cerebrovascular disease later in life than parous women without a history of toxaemia.**

***Conclusions*—A history of toxaemia of pregnancy increases the risk of several distinct cardiovascular conditions later in life. Although causality cannot be inferred (other characteristics of the women may account for both an increased risk of toxaemia and a risk of subsequent vascular disease), the findings merit further research because of their potential importance.**

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In the United Kingdom, over 150 000 women die each year from vascular causes,[1] many dying prematurely.[2] Many more experience a non-fatal event which often leaves them permanently handicapped. It has been reported that angina may be as common in Scottish women as in their male counterparts.[3] So far, most of the aetiological research in women has concentrated on risk factors that are shared by men—for example, smoking, social class, family history, obesity, lipids, and clotting factors. Women are exposed, however, to various factors which are gender specific and which might affect the risk of cardiovascular disease: pregnancy, menopause, hysterectomy, and use of exogenous hormones. An effect of pregnancy is suggested by vital statistics data collected in England and Wales between 1938 and 1960 which showed that parous women had a higher mortality from hypertension, ischaemic and degenerative heart disease, and cerebrovascular disease than nulliparous women.[4]

Many women experience hypertensive problems during pregnancy (chronic hypertension, pre-eclampsia/eclampsia, pre-eclampsia superimposed on chronic hypertension, and transient (gestational) hypertension), especially during the first pregnancy.[5] It is estimated that almost 10% of all pregnancies are complicated by these problems.[5] Despite this high frequency of occurrence, relatively little research has been conducted into the long term sequelae of hypertensive problems in pregnancy. Most studies have only looked at the subsequent risk of hypertension;[6–17] many only included a small number of subjects,[6–8 10 11 13–15] lacked a suitable comparison group,[7 9 14–17] and were of relatively short duration.[6 9 15] In a previous analysis of data from the Royal College of General Practitioners' (RCGP) oral contraception study, women with a recorded diagnosis of toxaemia of pregnancy had nearly three times the risk of myocardial infarction as women without this history.[18] This finding supported an earlier case-control study which also found a threefold increased risk of myocardial infarction in women who had received treatment for pre-eclamptic toxaemia,[19] and contradicted another which did not find any risk.[20] More recently, a case-control study found that a history of pre-eclampsia was associated with a significant threefold increased risk of subarachnoid haemorrhage.[21] The World Health Organisation study of cardiovascular disease in young women also found that a history of pre-eclampsia increased a woman's chances of

experiencing a venous thromboembolic event[22] or haemorrhagic stroke.[23] In view of the paucity of studies, we have re-examined the RCGP oral contraception study database in order to determine whether women with a history of toxaemia of pregnancy have an increased risk of various cardiovascular events later in life.

Methods

The RCGP oral contraception study was established in 1968 in order to determine the long term effects of oral contraceptives.[24] Over a 14 month period from May 1968, 1400 general practitioners throughout the United Kingdom recruited 23 000 women who were then using the pill and 23 000 who had never used this method of birth control. The two groups were of similar age (average 29 years at recruitment), all were married or living as married and most were Caucasian. Information collected at recruitment included social class (as determined by the occupation of the woman's husband), parity, smoking habits, and previous use of the pill. In addition, a significant medical history was indicated on a checklist of specified medical conditions which included toxaemia of pregnancy (the term then used to describe the hypertensive problems in pregnancy now usually called pre-eclampsia). At regular intervals thereafter the general practitioners have supplied details of any hormonal preparations prescribed, all reported new episodes of illness, any operations, any pregnancies and their outcome, and when appropriate the date and cause of death. Most women had completed their families when recruited to the study. Thus most episodes of toxaemia of pregnancy were documented in the significant medical history section of the recruitment form. The rest were reported as a complication of pregnancy during routine follow up in the study. By July 1995, about one quarter of the original cohort remained under observation, most women being lost because they moved from the practice area of the recruiting doctor. All information, however, is used up to the time of loss, so the proportion of total person-years observation lost has been smaller (49%).

Combined oral contraceptives are known to cause blood pressure changes in some users.[25] In order to avoid contamination from these effects, we restricted our analyses to the 214 356 women-years of observation that had accumulated by July 1995 relating to women who had never used oral contraceptives. These data were divided into those relating to nulliparous women and those relating to parous women either with or without a history of toxaemia of pregnancy. First ever diagnosis rates of hypertensive disease (International Classification of Disease (ICD), 8th revision, codes 400 to 404), acute myocardial infarction (ICD code 410), other acute ischaemic heart disease (411), other chronic ischaemic heart disease (412), angina pectoris (413), total ischaemic heart disease (410–413), total cerebrovascular disease (430–438), total peripheral vascular disease (440–442, 4439), and total venous thromboembolic disease (450, 453) were calculated for each group. The rates were directly standardised using the total population as the standard. The adjustments allowed for differences between groups in age at diagnosis, smoking, and social class at recruitment. When comparing the incidence rates, the referent group was parous women without a history of toxaemia of pregnancy. The data for parous women were also stratified by reported history of hypertension before the vascular event, in order to examine whether this variable was confounding the results. Ninety five per cent confidence intervals (CI) were calculated on the assumption that the variance of the log relative risk is equal to the sum of the reciprocals of the observed number of cases in the two groups being compared.

Results

Table 1 shows that compared with parous women without a history of toxaemia of pregnancy, parous women with such a history had more than twice the risk of developing hypertension later in life. Parous women with a history of toxaemia also had a statistically significant overall increased risk of ischaemic heart disease; increases which were seen in three major subcategories—acute myocardial infarction, chronic ischaemic heart disease, and angina pectoris. Parous women with a history of toxaemia also had a significantly increased risk of venous thromboembolism. Increased relative risks for total cerebrovascular

Table 1 Incidence of vascular disease in parous women with and without a preceding history of toxaemia of pregnancy, and in nulliparous women. Standardised rate per 1000 women-years (numbers)

Condition	Parous, toxaemia rate† (n)	Parous, no toxaemia rate† (n)	Nulliparous rate† (n)	Relative risk parous toxaemia: parous no toxaemia (95% CI)	Relative risk nulliparous: parous no toxaemia (95% CI)
Hypertensive disease	13·02 (377)	5·55 (922)	7·54 (140)	2·35 (2·08 to 2·65)	1·36 (1·14 to 1·62)
Total ischaemic heart disease*	2·05 (69)	1·24 (216)	1·25 (25)	1·65 (1·26 to 2·16)	1·01 (0·67 to 1·53)
Acute myocardial infarction	0·83 (26)	0·37 (65)	0·60 (11)	2·24 (1·42 to 3·53)	1·62 (0·86 to 3·07)
Other acute ischaemic heart disease	0	0·01 (2)	0·05 (1)	—	5·00 (0·45 to 55·14)
Chronic ischaemic heart disease	0·61 (21)	0·35 (61)	0·36 (7)	1·74 (1·06 to 2·86)	1·03 (0·47 to 2·25)
Angina pectoris	1·27 (43)	0·83 (145)	0·82 (17)	1·53 (1·09 to 2·15)	0·99 (0·60 to 1·64)
Total cerebrovascular disease	0·75 (25)	0·54 (93)	0·96 (19)	1·39 (0·89 to 2·16)	1·78 (1·09 to 2·92)
Total peripheral vascular disease	0·40 (14)	0·33 (58)	0·31 (6)	1·21 (0·68 to 2·17)	0·94 (0·41 to 2·18)
Total venous thromboembolism	0·99 (32)	0·61 (105)	0·67 (13)	1·62 (1·09 to 2·41)	1·10 (0·62 to 1·96)
Periods of observation (women-years)	28 055	163 010	22 390		

*Only the first ever episode in this category is counted, therefore the total is less than the sum of individual subcategories of heart disease.
†Directly standardised for age (–29, 30–34, 35–39, 40–44, 45–49, 50+), smoking (0, 1–14, 15+), social class (non-manual, manual).
CI, confidence interval.

Table 2 Incidence of vascular disease in parous women with and without a preceding history of toxaemia of pregnancy stratified by history of pre-existing hypertension before the vascular event. Standardised rate per 1000 women-years (number)

	No history of hypertension			*History of hypertension*		
	Toxaemia rate† (n)	*No toxaemia rate† (n)*	*Relative risk parous toxaemia: parous no toxaemia (95% CI)*	*Toxaemia rate† (n)*	*No toxaemia rate† (n)*	*Relative risk Parous toxaemia: parous no toxaemia (95% CI)*
Total ischaemic heart disease*	1·39 (38)	1·01 (157)	1·38 (0·97 to 1·97)	5·88 (31)	3·70 (59)	1·59 (1·03 to 2·46)
Acute myocardial infarction	0·50 (13)	0·26 (40)	1·92 (1·03 to 3·59)	2·86 (13)	1·31 (25)	2·17 (1·11 to 4·24)
Other acute ischaemic heart disease	0	0·01 (1)	—	0	0·09 (1)	—
Chronic ischaemic heart disease	0·48 (14)	0·30 (46)	1·62 (0·89 to 2·95)	0·88 (7)	0·84 (15)	1·05 (0·43 to 2·58)
Angina pectoris	0·85 (23)	0·69 (108)	1·23 (0·78 to 1·93)	3·34 (20)	2·37 (37)	1·41 (0·82 to 2·43)
Total cerebrovascular disease	0·53 (15)	0·38 (59)	1·39 (0·79 to 2·45)	1·70 (10)	3·24 (34)	0·52 (0·26 to 1·05)
Total peripheral vascular disease	0·36 (10)	0·25 (39)	1·46 (0·73 to 2·92)	0·61 (4)	1·03 (19)	0·59 (0·20 to 1·73)
Total venous thrombotic disease	0·97 (27)	0·59 (95)	1·64 (1·07 to 2·51)	1·03 (5)	1·68 (10)	0·61 (0·21 to 1·78)

*Only the first ever episode in this category is counted, therefore the total is less than the sum of individual subcategories of heart disease.
†Directly standardised for age (−29, 30–34, 35–39, 40–44, 45–49, 50+), smoking (0, 1–14, 15+), social class (non-manual, manual).
CI, confidence interval.

and total peripheral vascular disease did not reach statistical significance.

Stratification of the data by history of pre-existing hypertension before the vascular event (table 2) reduced the power to detect significantly increased relative risks. Even so, increased relative risks were seen for all of the vascular conditions examined among women with a history of toxaemia of pregnancy and no history of hypertension; those for acute myocardial infarction and venous thromboembolism reached statistical significance. The results for women with a history of both toxaemia and hypertension were less consistent, although significantly increased risk estimates were observed for all ischaemic heart disease and acute myocardial infarction. These observations suggest that any effect of toxaemia on the subsequent risk of vascular disease may only partially be mediated by hypertension.

Comparison of parous women without a history of toxaemia with nulliparous women (table 1) showed that the nulliparous group had a significantly increased risk of developing hypertension and total cerebrovascular disease. None of the other relative risks was significantly increased.

Discussion

Our results suggest that a history of toxaemia of pregnancy increases the risk of several vascular problems later in life. Since these findings were, however, based on data derived from an observational study, causality cannot be inferred; other characteristics of the women may increase the risk of both toxaemia and subsequent vascular disease. We were unable to adjust for some possible confounding factors, such as family history of cardiovascular disease, raised cholesterol, and so on. On the other hand, the results are supported by other studies which have found that hypertensive problems in pregnancy, of various descriptions, are associated with an increased risk of hypertension,[6–17] myocardial infarction,[19] subarachnoid haemorrhage,[21] haemorrhagic stroke,[23] and venous thromboembolism.[22]

An important feature of our study was the ability to use prospectively collected information relating to a large number of women followed for up to 26 years. This increased the opportunity to detect associations, particularly those that might be long delayed. The study was unlikely to suffer from serious misclassification of exposure status because the history of toxaemia was recorded by the general practitioners, using their medical notes, relatively soon after the event. Case-control studies are much more likely to suffer from this bias, since they usually rely on patients recalling a toxaemic pregnancy that occurred many years previously. Another advantage of our investigation was the ability to examine the risk for a number of cardiovascular outcomes. Thus we found that the risk of ischaemic heart disease was increased in three of the main subcategories, not just confined to acute myocardial infarction. A further advantage was the ability to compare the risk of vascular disease in nulliparous and parous women. Like others,[10 12] we found that women who successfully complete a pregnancy without the development of toxaemia had a lower risk of subsequent hypertension than nulliparous women. The effect may not be only limited to hypertension: parous women without a history of toxaemia also appeared to have a lower risk of stroke later in life. These interesting observations raise the possibility that normal pregnancy reduces the risk of subsequent cardiovascular disease.

Our data, however, do have several important limitations. First, the reporting general practitioners were not asked to specify the criteria used to make the diagnosis of toxaemia of pregnancy. It is likely that a variety of hypertensive problems of pregnancy were included. Other studies have found that gestational hypertension,[6–8] pre-eclampsia,[7 9–15] and eclampsia[12 16 17] appear to increase the chances of subsequent hypertension. The size of the effects, however, may be different in each group. For example, Adams and MacGillivray found that women who experienced "mild pre-eclampsia" had higher systolic and diastolic blood pressures later in life than women who experienced "severe pre-eclampsia" or a normotensive pregnancy.[10] The date of the diagnosis of toxaemia was not available for most women. We were, therefore, unable to determine the interval before the vascular sequelae became apparent. Also, we did not know which pregnancy (or pregnancies) had been affected. We could not, therefore, ascertain whether the risks changed with the order

of the affected pregnancy. Nor did we have the total number of pregnancies affected by hypertensive problems for each woman. Consequently, we could not examine whether the risks changed as the number of toxaemic pregnancies increased.

The cardiovascular outcomes were those recorded by the reporting general practitioners; diagnostic criteria such as specified levels of blood pressure recordings for hypertension were not specified. For some events (perhaps especially hypertension), the diagnosis will have been that made in the general practice. Table 2 shows that the rates of vascular disease were higher among women with a history of hypertension, irrespective of their history of toxaemia, lending some weight to the notion that these data were of reasonable quality. For the other events, the family doctor may have simply reported the opinion of hospital colleagues who may have had access to the results of appropriate investigations, operation notes, or necropsy findings. As well as having access to the results of hospital investigation, the general practitioners in the oral contraception study have the benefit of being able to observe their patients over a prolonged period of time. Diagnoses which are initially uncertain may become clearer later. Indeed, study data are often revised as additional information becomes available. Evidence that hypertensive problems in pregnancy may cause vascular problems has been reported only relatively recently. It seems unlikely, therefore, that the general practitioners' diagnosis of vascular problems was biased by this association, or that they were more likely to refer these women for investigation. Similarly, although incomplete recording of medical history and cardiovascular problems could have occurred during the study, there is no reason to suspect that these events were systematically underreported (and therefore biased) because of a woman's history of toxaemia of pregnancy.

Although there have been large losses to follow up in the oral contraception study, these are mainly due to women moving practices. We have previously shown that these large losses have not materially affected mortality results from the study.[26] Furthermore, in order to produce the results presented here, one would have to postulate that women with a history of toxaemia who were going to develop vascular disease were less likely to leave the cohort than those without toxaemia who were going to develop vascular problems. This seems unlikely.

Our results suggest an important relation between hypertensive disease in pregnancy and future vascular disease. If substantiated, these findings would have important public health implications given the size of the risk estimates and the high prevalence of the exposure (almost 10% of all pregnancies[5]). Long term follow up of women with a history of toxaemia might be warranted. The findings may also throw some light on the aetiology of cardiovascular disease in women. For example, perhaps the development of toxaemia in pregnancy indicates a predisposition to cardiovascular disease later in life, which may or may not be mediated by the development of hypertension. Given the limitations of the data, however, it is essential that our findings are confirmed or refuted, using other prospectively collected data based on rigorous and standardised definitions of hypertensive disorders in pregnancy and cardiovascular outcomes. The Aberdeen study of cardiovascular health in women, recently funded by the British Heart Foundation, is currently undertaking such an investigation using a historical cohort approach based on the Aberdeen maternity and neonatal databank. However, the results of this study, which is being conducted in collaboration with colleagues at the University of Aberdeen, will not be available for several years.

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