Hypertensive diseases of pregnancy and risk of hypertension and stroke in later life: results from cohort study

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Abstract

Objective To examine the association between hypertensive diseases of pregnancy (gestational hypertension and pre-eclampsia) and the development of circulatory diseases in later life.
Design Cohort study of women who had pre-eclampsia during their first singleton pregnancy. Two comparison groups were matched for age and year of delivery, one with gestational hypertension and one with no history of raised blood pressure.
Setting Maternity services in the Grampian region of Scotland.
Participants Women selected from the Aberdeen maternity and neonatal databank who were resident in Aberdeen and who delivered a first, live singleton from 1951 to 1970.
Main outcome measures Current vital and cardiovascular health status ascertained through postal questionnaire survey, clinical examination, linkage to hospital discharge, and mortality data.
Results There were significant positive associations between pre-eclampsia/eclampsia or gestational hypertension and later hypertension in all measures. The adjusted relative risks varied from 1.13-3.72 for gestational hypertension and 1.40-3.98 for pre-eclampsia or eclampsia. The adjusted incident rate ratio for death from stroke for the pre-eclampsia/eclampsia group was 3.59 (95% confidence interval 1.04 to 12.4).
Conclusions Hypertensive diseases of pregnancy seem to be associated in later life with diseases related to hypertension. If greater awareness of this association leads to earlier diagnosis and improved management, there may be scope for reducing a proportion of the morbidity and mortality from such diseases.

Introduction

Nearly 30% of first pregnancies are thought to be affected by gestational (transient) hypertension, pre-eclampsia, or eclampsia.[1] Despite their frequent occurrence, relatively little research has been conducted into the long term effects of hypertensive problems in pregnancy. Both gestational hypertension and pre-eclampsia or eclampsia may be associated in later life with raised blood pressure[2–6] or hypertension[7–10] and cardiovascular disease.[11 12] Many of the reported studies have examined only hypertension as an outcome and have been limited by small sample sizes,[2 4–8 10] inappropriate comparison groups,[3 7 10 13] or relatively short follow up.[2 3]

We designed a retrospective cohort study using the Aberdeen maternity and neonatal databank, a computerised database which has collated validated data on all obstetric events in women attending the Aberdeen maternity hospital since 1951.[14] We determined whether a recorded history of gestational hypertension or pre-eclampsia or eclampsia predicted cardiovascular disease in later life, as indicated by measures of mortality and morbidity.

Methods

Identification and tracing of women

From the databank we identified a cohort of women who were living in Aberdeen city at the time of delivery. The cohort comprised three groups: all women who had a diagnosis of pre-eclampsia or eclampsia during their first singleton pregnancy in the years 1951 to 1970; an individually matched sample of women with a diagnosis of gestational hypertension during their first singleton pregnancy and matched for age to the nearest year and year of delivery with the previous group; and an individually matched sample of women with no history of raised blood pressure during their first singleton pregnancy likewise matched with the first group. For clinical definitions, see bmj.com. Women with chronic hypertension were separately categorised on the databank and excluded from this study.

We carried out two tracing exercises for the cohort. The first, carried out in 1996, was at the local level using the Grampian community health index (a comprehensive regional primary care register[15]) to identify all cohort members still alive and resident in the Grampian area. The second tracing exercise was at national level and was undertaken in 1999. The information and statistics division (ISD) of the NHS in Scotland, used probability matching to identify any women from the cohort who were admitted to hospital in Scotland from 1980 to 1999. In collaboration with the NHS central registry in Southport, the division also ascertained the vital status of women in the cohort and obtained death certificates for any who had died, including those who died in the United Kingdom but outside Scotland.

Ascertainment of outcomes

Questionnaire and clinical examination

After obtaining consent from her general practitioner, we sent each woman still living in Grampian a self completion questionnaire, with questions covering general health, lifestyle and wellbeing, and obstetric history, including illnesses related to pregnancy. The questions were taken from previously validated questionnaires. The study hypothesis was not disclosed to prevent bias in reporting current health status. The questionnaire included an invitation to attend for a medical examination.

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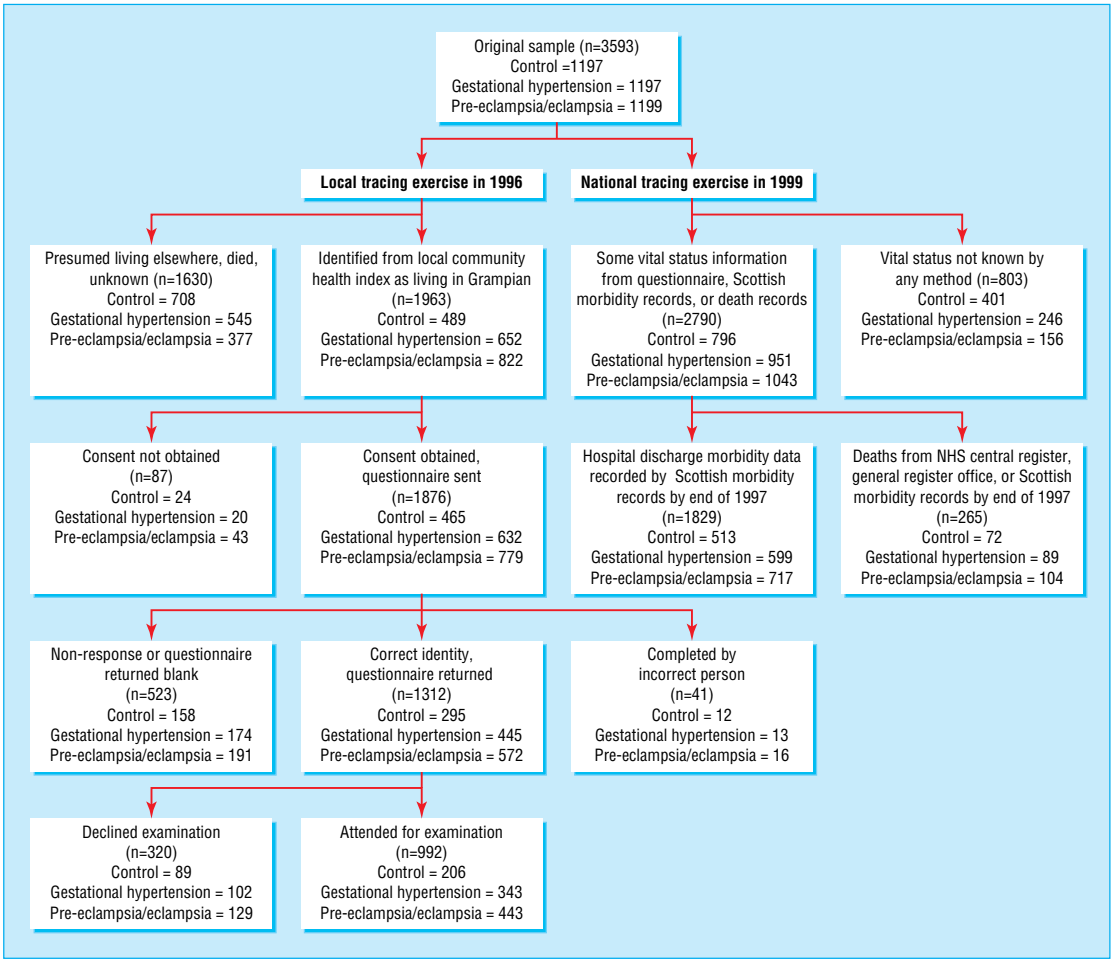

Cohort tracing in two different exercises including events up to 1997 (death and hospital discharge frequencies are not mutually exclusive; many women who died also had hospital discharges)

Each medical examination was conducted by one of two trained research nurses in accordance with an examination protocol developed for the project. The nurses were blind to study group status of the women they were examining All women had their blood pressure measured. They also had an electrocardiogram, were measured for height, and were weighed.

Hospital discharges

In collaboration with the information and statistics division (ISD) of the NHS in Scotland we conducted a data linkage exercise[16] to obtain details of all hospital discharges in cohort members. The division holds data on hospital discharges and cancer registrations of individuals who have been resident in Scotland at any point.

Deaths

We obtained details of the dates and causes of death from the UK NHS central register.

Statistical analysis

We used χ^2 and *t* tests as appropriate to test for baseline differences between the three groups, and, for all analyses, we used the control group as reference for comparisons with each of the two "exposed" groups (gestational hypertension and pre-eclampsia or eclampsia). For the questionnaire and clinical examination data, we computed odds ratios and used logistic regression methods to adjust for the influences of age, body mass index, social class, and smoking behaviour at follow up. For the mortality and hospital discharge outcomes, we constructed diagnosis groups using international classification of diseases (ninth/tenth edition) codes: "hypertension" (401-4/I10-14); "ischaemic heart disease" (410-4, 428/I20-25, I50); "cerebrovascular disease" (430-8/I60-9); "kidney disease" (580-99/N00-39); "other circulatory disease" (390-8, 405, 415-27, 440-59/ I00-9, I15, I26-8, I30-49, I51-2, I70-99). We computed incident rate ratios for deaths and hospital discharges and used logistic regression to adjust for potential confounders, age at delivery and social class.

Results

The total cohort comprised 3593 women, with a mean age of 24.2 at delivery. Compared with the control group, women in the gestational hypertension and pre-eclampsia or eclampsia groups were less likely to be in occupational classes I-III non-manual (professional/ administrative). They were also less likely to ever have been smokers (although smoking data at the time of pregnancy were obtained for only 28% of the cohort).

Tracing

The figure shows the results of local and national tracing. Local tracing identified 1963 women (54.6%) who

were still alive and resident in Grampian (figure). Questionnaires were sent to 1876 (95.6%) women, and 1312 were returned with usable responses (71% of questionnaires). National tracing ascertained the current vital status of 2790 (77.7%) of the original cohort, of whom 265 (9.5%) were known to have died. Linkage with hospital discharge data identified 1829 (65.6%) women of the original cohort who had been admitted at least once to a Scottish hospital between 1980 and 1999. Compared with untraced women, traced women were a year older at delivery (on average), slightly fatter (mean body mass index 0.6 kg/m^2 higher), and less likely to come from non-manual social classes (31% (778/2481) *v* 39% (267/680)). The success of the tracing differed across the three comparison groups (figure).

Questionnaire assessed outcomes

After adjustment for known risk factors for hypertension, women in both the gestational hypertension and pre-eclampsia or eclampsia groups had higher odds ratios for indicators of hypertension (table 1). This was not seen for the other conditions of interest, except for kidney disease in the pre-eclampsia or eclampsia group, which may have related to the original episode in pregnancy. Similar results were observed in the clinical examination data (table 2), with increased risk of hypertension defined by WHO criteria in both gestational hypertension and pre-eclampsia or eclampsia groups. In total, 41.1% of the former and 48.8% of the latter provisionally fulfilled the WHO criteria for hypertension compared with 26.7% in the control group.

Hospital admissions

Women in the gestational hypertension group were more likely to have been admitted to hospital for cerebrovascular disease, ischaemic heart disease, hypertension, and "other" circulatory disease, although this reached significance only for hypertension and other circulatory disease (table 3). Women in the pre-eclampsia or eclampsia group were also more likely to be admitted for hypertension, cerebrovascular disease, and other circulatory disease.

Table 1 Odds ratios (control group=1.0) for measures of hypertensive and other cardiovascular disease in questionnaire respondents

		Gestational hypertension				Pre-eclampsia/eclampsia			
Outcome	Control*	No*	Odds ratio (unadjusted)	Adjusted† odds ratio (95% CI)	P value	No*	Odds ratio (unadjusted)	Adjusted† odds ratio (95% CI)	P value
Hypertension, doctor diagnosis	76/277	215/428	2.67	2.47 (1.74 to, 3.51)	<0.001	327/542	3.02	3.98 (2.82 to 5.61)	<0.001
Currently taking anti-hypertensive medication	43/295	113/442	2.01	1.89 (1.23 to 2.88)	0.003	151/565	2.14	1.90 (1.27 to 2.86)	0.002
Stroke, doctor diagnosis	3/266	10/404	2.23	2.42 (0.59 to 9.98)	0.22	19/511	3.39	3.41 (0.95 to 12.2)	0.06
Angina, doctor diagnosis	24/273	40/413	1.11	1.02 (0.58 to 1.81)	0.94	69/518	1.59	1.61 (0.95 to 2.73)	0.08
Angina, Rose criteria	22/290	34/441	1.02	0.93 (0.52 to 1.65)	0.80	47/559	1.12	0.90 (0.52 to 1.55)	0.69
Possible MI, doctor diagnosis	14/268	16/408	0.74	0.73 (0.32 to 1.63)	0.44	20/512	0.74	0.76 (0.35 to 1.63)	0.48
Possible MI, Rose questionnaire	22/292	19/444	0.55	0.48 (0.25 to 0.95)	0.03	36/569	0.83	0.84 (0.47 to 1.50)	0.56
Intermittent claudication, Rose criteria	3/292	7/440	1.56	1.54 (0.38 to 6.19)	0.55	9/565	1.56	1.57 (0.41 to 6.05)	0.51
DVT, doctor diagnosis	22/269	25/404	0.74	0.65 (0.35 to 1.20)	0.17	33/510	0.78	0.75 (0.42 to 1.34)	0.32
"Kidney disease", doctor diagnosis	7/267	9/398	0.85	0.64 (0.22 to 1.82)	0.40	28/508	2.17	2.39 (1.01 to 5.65)	0.05

MI=myocardial infarction; DVT=deep vein thrombosis.
*Denominator excludes missing responses.
†Adjusted for age, BMI, social class, and smoking habit.

Table 2 Odds ratios (control group=1.0) for measures of hypertensive and other cardiovascular disease at clinical examination

		Gestational hypertension				Pre-eclampsia/eclampsia			
	Control	No	Odds ratio (unadjusted)	Adjusted* odds ratio (95% CI)	P value	No	Odds ratio (unadjusted)	Adjusted* odds ratio (95% CI)	P value
Currently taking anti-hypertensive drugs	25/206	80/343	2.20	1.95 (1.18 to 3.24)	0.009	129/443	2.97	2.77 (1.72 to 4.47)	<0.001
Not on anti-hypertensive drugs but raised blood pressure at time of examination†	30/206	61/343	1.26	1.13 (0.69 to 1.86)	0.63	87/443	1.43	1.40 (0.87 to 2.26)	0.16
Provisionally fulfilling WHO criteria for hypertension	55/206	141/343	1.90	1.70 (1.13 to 2.56)	0.01	216/443	2.60	2.62 (1.77 to 3.86)	<0.001
Changes on ECG (any abnormality)‡	20/205	32/342	0.95	0.96 (0.52 to 1.77)	0.90	61/437	1.50	1.96 (0.96 to 2.98)	0.07

*Adjusted for age, BMI, social class, and smoking habit.
†Mean diastolic ≥95 mm Hg or mean systolic ≥ 160 mm Hg or both.
‡Minnesota coding.

Table 3 Incident rate ratios (control group=1.0) for hospital admissions for specific conditions for all traced women

Discharge diagnosis*	Admissions in control group (n=796)	Gestational hypertension (n=951)				Pre-eclampsia/eclampsia (n=1043)			
		No of admissions	Incident rate ratio (unadjusted)	Adjusted† incident rate ratio (95% CI)	P value	No of admissions	Incident rate ratio (unadjusted)	Adjusted† incident rate ratio (95% CI)	P value
All causes	513	599	0.97	0.96 (0.84 to 1.09)	0.53	717	1.09	1.07 (0.95 to 1.22)	0.28
Hypertension	7	28	3.36	3.72 (1.43 to 9.65)	0.007	31	3.39	3.19 (1.21 to 8.39)	0.019
Cerebrovascular disease	13	22	1.42	1.53 (0.72 to 3.27)	0.27	34	2.00	2.10 (1.02 to 4.32)	0.043
Ischaemic heart disease	38	52	1.15	1.06 (0.68 to 1.65)	0.79	48	0.96	0.89 (0.56 to 1.40)	0.61
Other circulatory	64	108	1.42	1.51 (1.06 to 2.14)	0.021	121	1.45	1.49 (1.05 to 2.11)	0.024
Kidney disease	38	34	0.75	0.76 (0.47 to 1.28)	0.29	67	1.35	1.27 (0.81 to 1.98)	0.30

*First admission only for diagnosis group.
†Adjusted for age at delivery and social class.

Table 4 Incident rate ratios (control group=1.0) for mortality for specific conditions all traced women

Cause	Deaths in control group (n=796)	Gestational hypertension (n=951)				Pre-eclampsia/eclampsia (n=1043)			
		Deaths	Incident rate ratio (unadjusted)	Adjusted* incident rate ratio (95% CI)	P value	Deaths	Incident rate ratio (unadjusted)	Adjusted† incident rate ratio (95% CI)	P value
All causes	72	89	1.03	1.03 (0.74 to 1.45)	0.85	104	1.13	1.17 (0.84 to 1.65)	0.36
Cerebrovascular disease	5	13	2.18	2.87 (0.81 to 10.2)	0.10	16	2.44	3.59 (1.04 to 12.4)	0.044
Ischaemic heart disease	10	17	1.42	1.21 (0.53 to 2.75)	0.65	26	1.98	1.95 (0.90 to 4.21)	0.091

*Adjusted for age at delivery and social class.

Mortality

Over 90% of the traced cohort were alive at the time of analysis, and there were 265 deaths available for analysis (table 4). By the time of follow up, there were 72 deaths in the control group, 89 in the gestational hypertension group, and 104 in the pre-eclampsia or eclampsia group. No deaths were coded to hypertension. After adjustment, mortality for all causes, stroke, and ischaemic heart disease was higher in both the gestational hypertension and pre-eclampsia or eclampsia groups. The pattern was consistent, though only the increased risk of stroke in the pre-eclampsia or eclampsia group was significant.

Discussion

Women with a history of gestational hypertension or of pre-eclampsia or eclampsia are at increased risk of hypertensive and associated diseases in later life. Our findings are consistent with those of previous work.[2–10] We found an increased risk of admission to hospital for stroke and mortality from stroke but no significant increased risk of morbidity and mortality from coronary heart disease as has previously been reported.[11 12] This may be because we used a study design that did not depend on recall and used standardised criteria to distinguish gestational hypertension and pre-eclampsia from chronic pre-existing hypertension. Retrospective studies of coronary heart disease that used patient recall of pre-eclampsia are subject to recall bias, while other cohort studies have combined coronary heart disease outcomes into a single cardiovascular disease group.[17]

Our study has two key advantages over many other investigations into the associations of interest: the underlying cohort design and the use of different data sources to ascertain the outcomes of interest, which permitted assessment of the consistency of the findings.

Influence of social class

Social class differed between the three study groups in the original cohort. This might be a result of chance or might indicate an association between social class and hypertensive diseases in pregnancy. Though such associations have been reported,[18 19] there is no clear social class gradient.

Women in pre-eclampsia or eclampsia group seemed less likely than controls to have ever smoked (note, however, that the data on smoking at the time of pregnancy were obtained for only 28% of the cohort). If there is a true inverse association between pre- eclampsia or eclampsia and smoking, the association would operate against our hypothesis. It's possible therefore that we have underestimated the link between pre-eclampsia or eclampsia and circulatory diseases.

The tracing rates varied across the three groups. Those who were normotensive during their first full term pregnancy were least likely to still be living in Grampian at follow up, suggesting selective migration from the area by the control group. The national tracing exercise, however, was more successful and provided vital status and hospital discharge data for a larger proportion of women in each comparison group. Broadly similar patterns of cardiovascular sequelae were observed in the different groups, irrespective of whether the outcome measure used was obtained through the local or national tracing. Another important potential bias could have occurred if there were important differences in the response rates of those traced locally. There were in fact only small differences in the response rates to the survey by the three comparison groups (70%, 77%, and 77%) suggesting that response bias is unlikely to have materially affected our results.

Consistency of findings

There was consistency of the findings across the different methods of ascertaining outcomes. The association

What is already known on this topic

Much is known about the effect of cardiovascular risks factors that are shared by men and women, but less on those specific to women

Retrospective studies, based on patient recall, suggest that hypertension in pregnancy may be associated with increased risk of cardiovascular diseases in later life

What this study adds

Prospective recording of blood pressure and proteinuria shows that women who experienced raised blood pressure in pregnancy have a long term risk of hypertension

Women who experience raise blood pressure in pregnancy have an increased risk of stroke and, to a lesser extent, an increased risk of ischaemic heart disease

Long term cardiovascular risks are greater for women who had pre-eclampsia than those who experienced gestational hypertension (hypertension without proteinuria)

between gestational hypertensive disease and hypertension in later life was seen in the questionnaire and clinical examination data and also in the hospital diagnosis data and the mortality data. We suggest that our observations cannot be explained by chance or bias. The findings have implications for the aetiology and pathogenesis of circulatory disease, both in pregnancy and in later life. They also suggest that interventions that might minimise the risk of such conditions in later life should be identified and evaluated.

We acknowledge the contribution of Dean Phillips for tracing and data management; Amanda Cardy for review of the original case notes; Nicola Torrance for assistance with the data collection and the operation of clinics; Linda Harrigan and Wendy Aiken for entering the data; Tracy Mapp for assistance with the study design; Isobel Ford and Ian Ross at Department of Clinical Biochemistry, Aberdeen, for assistance with the laboratory analysis; Val Angus of practitioner services at Grampian Health Board for tracing women; information and statistics division for record linkage; and the staff of the MONICA project at Queens University Belfast for assistance with Minnesota coding of ECGs.

Contributors: See bmj.com

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Competing interests: None declared.

Ethical approval: The study protocol was approved by the Joint Grampian Health Board and University of Aberdeen ethics committee, the information and statistics division privacy advisory committee and the Grampian Health Board general practice cubcommittee.

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Corrections and clarifications

Brain haemorrhage in babies may not indicate violent abuse

In this news article by Owen Dyer (22 March, p 616), we said that Dr Jennian Geddes of the Royal London Hospital had said that brain stem damage in babies thought to have died from "shaken baby syndrome" could be due to "a range of aetiologies, including common perinatal problems, accidental falls, infection." This was incorrect. We should have said that Dr Geddes said this type of injury could be either accidental or inflicted. Dr Geddes would like to make it clear that she does not consider that this damage could be the result of common perinatal problems or infection.

Diagnosis and management of scalp ringworm

Our preference for spelling out abbreviations led to an editing slip in this Clinical Review article by L C Fuller and colleagues (8 March, pp 539-41). We expanded "id reaction" to "identity reaction" in both the text and the legend to figure 3; sadly this made no sense. An id reaction is an immunological response that occurs at some distance from the original infection and may be triggered at the start of treatment.

German surgeon is investigated about trading of organs

This title, which we added to a News article by Annette Tuffs about alleged organ trading (15 March, p 568), wrongly suggested that a German surgeon mentioned in the article (Christoph Broelsch) was being legally investigated over such trading. The district attorney in Essen is investigating the alleged trading, but only the recipients, donors, and an agency are being investigated; neither Dr Broelsch nor his surgeon friend Johannes Scheele is being investigated.