

Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies

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Abstract

Objective To determine the risk of pre-eclampsia associated with factors that may be present at antenatal booking.

Design Systematic review of controlled studies published 1966-2002.

Data synthesis Unadjusted relative risks were calculated from published data.

Results Controlled cohort studies showed that the risk of pre-eclampsia is increased in women with a previous history of pre-eclampsia (relative risk 7.19, 95% confidence interval 5.85 to 8.83) and in those with antiphospholipid antibodies (9.72, 4.34 to 21.75), pre-existing diabetes (3.56, 2.54 to 4.99), multiple (twin) pregnancy (2.93, 2.04 to 4.21), nulliparity (2.91, 1.28 to 6.61), family history (2.90, 1.70 to 4.93), raised blood pressure (diastolic ≥ 80 mm Hg) at booking (1.38, 1.01 to 1.87), raised body mass index before pregnancy (2.47, 1.66 to 3.67) or at booking (1.55, 1.28 to 1.88), or maternal age ≥ 40 (1.96, 1.34 to 2.87) for multiparous women. Individual studies show that risk is also increased with an interval of 10 years or more since a previous pregnancy, autoimmune disease, renal disease, and chronic hypertension.

Conclusions These factors and the underlying evidence base can be used to assess risk at booking so that a suitable surveillance routine to detect pre-eclampsia can be planned for the rest of the pregnancy.

Introduction

With the exception of studies on smoking¹ the literature has not been systematically reviewed for factors that predict the relative risk of developing pre-eclampsia. The recent National Institute for Clinical Excellence (NICE) guidelines on antenatal care have reduced the number of antenatal visits recommended for healthy woman at low risk.² As the failure to identify and act on known risk factors at booking contributes to deaths from pre-eclampsia,³ it is important to define risk at the beginning of pregnancy. We carried out a systematic review of published literature to reach an overall estimate for the risk of pre-eclampsia for each risk factor.

Methods

We searched Medline (1966 to July 2002) and Embase (1974 to July 2002) for publications that considered

the association between identified risk factors detectable at an antenatal booking visit and the subsequent development of pre-eclampsia. A multidisciplinary group identified the risk factors. We also studied reference lists of published letters and classic review articles and asked experts in the field.

We initially selected studies with a cohort or case-control design that included pre-eclampsia and the risk factors of interest. See bmj.com for details of search terms and quality assessment. We used study size, and the prospective or retrospective design of cohort studies, to score for heterogeneity. We independently extracted data from the included studies and resolved any differences by discussion.

Where data were available, we calculated the unadjusted relative risk with 95% confidence intervals for each study and across studies using the random effects model. We calculated the I^2 statistic for combined studies to estimate the proportion of total variation in study estimates that is due to heterogeneity. For some risk factors where we could not combine data, the results are described narratively.

Results

We identified over 1000 studies, and, after screening abstracts, we read 149 papers. After exclusions 52 (13 prospective cohort studies, 25 retrospective cohort studies, and 14 case-control studies) were included in the systematic review. There was more evidence of heterogeneity in the case-control studies than in the cohort studies. The available published adjusted odds ratios or relative risks, however, were similar to the unadjusted relative risks calculated in the meta-analysis.

Tables 1 and 2 summarise the results by risk factor. We found no data of sufficient quality on the presence of proteinuria at booking. There were also no data to calculate unadjusted relative risks for interval between births, existing hypertension, or existing renal disease.

Age

All except one study, which looked at women aged ≥ 40 , failed to control or address differences at baseline

Editorial by Greer and Primary care p 576

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Funnel plots for the main outcomes can be found on bmj.com



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Table 1 Calculated relative risks for cohort studies of risks for pre-eclampsia

	No of studies	No of women	Unadjusted relative risk (95% CI)	I ²
Antiphospholipid antibodies v none	2	1802	9.72 (4.34 to 21.75)	55.9%
Pre-existing diabetes v none	3	56 968	3.56 (2.54 to 4.99)	0%
Previous pre-eclampsia v none	5	24 620	7.19 (5.85 to 8.83)	0%
Family history v no family history	2	692	2.90 (1.70 to 4.93)	0%
Nulliparity v multiparity	3	37 988	2.91 (1.28 to 6.61)	94.3%
Twin v singleton pregnancy	5	53 028	2.93 (2.04 to 4.21)	72.7%
Triplet v twin pregnancy	1	76	2.83 (1.25 to 6.40)	—
Raised v normal BMI at booking	3	4625	1.55 (1.28 to 1.88)	0%
Raised v normal BMI before pregnancy	6	64 789	2.47 (1.66 to 3.67)	85.9%
Systolic ≥ 130 mm Hg v < 130 mm Hg at booking	1	906	2.37 (1.78 to 3.15)	—
Diastolic ≥ 80 mm Hg v < 80 mm Hg at booking	1	907	1.38 (1.01 to 1.87)	—
≤ 17 v > 17	1	161	2.98 (0.39 to 22.76)	—
≤ 16 v > 16	4	11 589	1.24 (0.69 to 2.23)	78.3%
≤ 19 v > 19	3	15 295	1.02 (0.59 to 1.74)	23.0%
≥ 35 v < 35	3	65 314	0.64 (0.03 to 13.33)	99.8%
Age ≥ 40 v < 40 multiparas	1	3140	1.96 (1.34 to 2.87)	—
Age ≥ 40 v < 40 primiparas	1	5242	1.68 (1.23 to 2.29)	—

BMI=body mass index.

(particularly pre-existing chronic disease). Women aged ≥ 40 had approaching twice the risk of developing pre-eclampsia, whether they were primiparous or multiparous. Nationwide US data suggest that the risk of pre-eclampsia increases by 30% for every additional year of age past 34. Young maternal age did not seem to affect the risk of developing pre-eclampsia, whichever cut off age was used.

Parity

Nulliparity almost triples the risk for pre-eclampsia; this is supported by adjusted odds ratios for nulliparity from two other cohort studies. Women with pre-eclampsia are twice as likely to be nulliparous as women without pre-eclampsia.

Previous pre-eclampsia

Women who have pre-eclampsia in a first pregnancy have seven times the risk of pre-eclampsia in a second pregnancy. Women with pre-eclampsia in their second pregnancy are also more than seven times more likely to have a history of pre-eclampsia in their first pregnancy than women in their second pregnancy who do not develop pre-eclampsia.

Family history of pre-eclampsia

A family history of pre-eclampsia nearly triples the risk of pre-eclampsia. Women with severe pre-eclamptic toxemia are more likely to have a mother rather than a mother in law who had had pre-eclampsia.

Multiple pregnancy

When a woman is pregnant with twins her risk of pre-eclampsia nearly triples. One study found that a triplet pregnancy nearly triples the risk of pre-eclampsia compared with a twin pregnancy.

Table 2 Case-control studies: pre-eclampsia

Risk factor	No of studies	No of women	Unadjusted relative risk (95% CI)	I ²
Previous pre-eclampsia	7	22 352	7.61 (4.30 to 13.47)	65.7%
Family history in mother	1	262	3.60 (1.49 to 8.67)	—
Nulliparity	6	304 559	2.35 (1.80 to 3.06)	97.3%
Antiphospholipid antibodies	3	760	6.12 (0.35 to 108.35)	81.5%

Pre-existing medical conditions

Insulin dependent diabetes—The likelihood of pre-eclampsia nearly quadruples if diabetes is present before pregnancy.

Pre-existing hypertension—One population based nested case-control study found the prevalence of chronic hypertension to be higher in women who developed pre-eclampsia than women who did not (12.1% v 0.3%).⁴ In another study, women with chronic hypertension with superimposed pre-eclampsia had significantly higher rates of perinatal morbidity (odds ratio 8.8, 2.6 to 39.0), small for gestational age infants (5.6, 1.8 to 16.0), and delivery before 32 weeks (15.0, 5.7 to 38.0) compared with women with chronic hypertension without superimposed pre-eclampsia.⁵ A diastolic blood pressure before 20 weeks of either ≥ 110 mm Hg (5.2, 1.5 to 17.2) or ≥ 100 mm Hg (3.2, 1.0 to 7.8) is most predictive of the development of superimposed pre-eclampsia.

Renal disease—The prevalence of renal disease was found to be higher in women who developed pre-eclampsia compared with those that did not (5.3% v 1.8%). Only one study compared women with renal disease, due to a history of urinary tract infections, with a prospective matched control population.⁶ In 69 continuing pregnancies, 6.7% (2/30) of the women who had urinary tract infections developed pre-eclampsia (both primigravida with scarred kidneys) compared with 2.6% (1/39) of women in the control group.

Chronic autoimmune disease—In a matched case-control study women who developed pre-eclampsia were more likely to have an autoimmune disease (relative risk 6.9, 1.1 to 42.3).⁷

Antiphospholipid syndrome—The presence of anti-cardiolipin antibodies or lupus anticoagulant or both significantly increases the risk of developing pre-eclampsia. However, when women who developed pre-eclampsia were matched with women who did not, they were no more likely to be positive for lupus anticoagulant or anticardiolipin antibodies.

Time between pregnancies

In a Norwegian population study the risk of pre-eclampsia in a second or third pregnancy was directly related to the time elapsed since the previous delivery.⁸ When the interval was 10 years or more the risk of pre-eclampsia was about the same as that in nulliparous women. After adjustment for the presence or absence of a change of partner, maternal age, and year of delivery, the probability of pre-eclampsia was increased by 1.12 for each year increase in the interval (odds ratio 1.12, 1.11 to 1.13).

A cross sectional study from Uruguay found that women with more than 59 months between pregnancies had significantly increased risks of pre-eclampsia (relative risk 1.83, 1.72 to 1.94) compared with women with intervals of 18-23 months.⁹

A Danish cohort study found that a long interval between pregnancies was associated with a significantly higher risk of pre-eclampsia in a second pregnancy when pre-eclampsia had not been present in the first pregnancy and paternity had not changed.¹⁰

Body mass index

All studies suggested an overall doubling of risk of pre-eclampsia with a raised body mass index. We combined all studies that looked at raised compared with normal

body mass index at booking and found that the risk of pre-eclampsia is increased by 50%. Notably, a body mass index > 35 at booking doubles the pre-eclampsia risk. A study comparing low and normal body mass index at booking found that the risk of pre-eclampsia was significantly reduced with a body mass index < 20 (odds ratio 0.76, 0.62 to 0.92, adjusted for diabetes and smoking).¹¹

Blood pressure at booking

Reiss et al matched 30 women with pre-eclampsia for age, race, and parity with normotensive control women. Both systolic and diastolic blood pressures were significantly higher in the first trimester for women who later developed pre-eclampsia.¹²

Sibai et al found that higher systolic and diastolic blood pressures at the first visit were associated with an increased incidence of pre-eclampsia (3.8% in women with diastolic blood pressure of < 55 mm Hg, 7.4% in those with diastolic blood pressure 70-84 mm Hg).¹³

A population based nested case-control study found that a systolic blood pressure ≥ 130 mm Hg compared with < 110 mm Hg at the first visit before 18 weeks was significantly associated with the development of pre-eclampsia later in pregnancy (adjusted odds ratio 3.6, 2.0 to 6.6).¹⁴ The association with a diastolic pressure ≥ 80 mm Hg compared with < 60 mm Hg was similar but not significant (1.8, 0.7 to 4.6).

A case-control study found that a mean arterial pressure > 90 mm Hg at the first prenatal visit was significantly associated with the development of severe pre-eclamptic toxæmia (relative risk 3.7, 2.1 to 6.6).⁷

Discussion

In this systematic review of controlled studies we found that antiphospholipid antibodies, a history of pre-eclampsia, pre-existing diabetes, multiple pregnancy, family history, nulliparity, a raised BMI before pregnancy or at booking, maternal age > 40 , renal disease, hypertension, ≥ 10 years since the last pregnancy, and raised blood pressure at booking all increased the risk of a woman developing pre-eclampsia.

We reviewed only published studies; unpublished studies may contain valid results that conflict with our conclusions. There is a greater tendency towards publication bias in a meta-analysis of observational studies than there is with randomised controlled trials. Because the peer review process is an important means of ensuring quality, however, possibly only published data and studies should be used.¹⁵ Funnel plots for the risk factors where over three studies were included were symmetrical for low maternal age, parity, previous pre-eclampsia, pre-existing diabetes, and body mass index before pregnancy.

Pre-eclampsia was seldom divided into early and late onset, nor were results presented for onset of pre-eclampsia or delivery in relation to gestational age. We may therefore have underestimated the importance of risk factors for early onset pre-eclampsia, a type with considerable maternal and perinatal morbidity and mortality.

Although we examined the role of individual risk factors, little is known about the association between them.

The risk factors that we have identified can be used to assess risk at the booking visit, so that a suitable surveillance routine to detect pre-eclampsia can be

What is already known on this topic

Various factors, which can be ascertained at the first antenatal or booking visit, are thought to increase the risk of a woman developing pre-eclampsia during pregnancy

What this study adds

The most significant risk factors for developing pre-eclampsia are a history of pre-eclampsia and the presence of antiphospholipid antibodies

Pre-existing diabetes and a pre-pregnancy BMI of ≥ 35 almost quadruple the risk; nulliparity, a family history of pre-eclampsia, and twin pregnancy almost triple the risk; and maternal age ≥ 40 , a booking BMI of ≥ 35 , and a systolic blood pressure ≥ 130 at booking double the risk

Pre-existing hypertension, renal disease, chronic autoimmune disease, and ≥ 10 years between pregnancies increase the risk but it is not clear by how much

planned for the rest of the pregnancy, as recommended by the recent NICE guideline on antenatal care² and the new pre-eclampsia community guideline (PRECOG) guideline.¹⁶

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- Conde-Agudelo A, Althabe F, Belizan JM, Kafury-Goeta AC. Cigarette smoking during pregnancy and risk of pre-eclampsia: a systematic review. *Am J Obstet Gynecol* 1999;181:1026-35.
- National Institute for Clinical Excellence. *NICE Guideline CG6 Antenatal care—routine care for the healthy pregnant woman*. London: NICE, 2003.
- Confidential Enquiries into Maternal Deaths. *Why mothers die 1997-1999. The fifth report of the confidential enquiries into maternal deaths in the United Kingdom*. London: Royal College of Obstetricians and Gynaecologists Press, 2001.
- Davies AM, Czaczkes JW, Sadovsky E, Prywes R, Weiskopf P, Sterk VV. Toxemia of pregnancy in Jerusalem I. Epidemiological studies of a total community. *Isr J Med Sci* 1970;6:253-66.
- McCowan LM, Buist RG, North RA, Gamble G. Perinatal morbidity in chronic hypertension. *Br J Obstet Gynaecol* 1996;103:123-9.
- Martinell J, Jodal U, Lidin-Janson G. Pregnancies in women with and without renal scarring after urinary infections in childhood. *BMJ* 1990;300:840-4.
- Stamilio DM, Sehdev HM, Morgan MA, Propert K, Macones GA. Can antenatal clinical and biochemical markers predict the development of severe preeclampsia? *Am J Obstet Gynecol* 2000;182:589-94.
- Skjaerven R, Wilcox AJ, Lie RT. The interval between pregnancies and the risk of preeclampsia. *N Engl J Med* 2002;346:33-8.
- Conde-Agudelo A, Belizan JM. Maternal morbidity and mortality associated with interpregnancy interval: cross sectional study. *BMJ* 2000;321:1255-9.
- Basso O, Christensen K, Olsen J. Higher risk of pre-eclampsia after change of partner. An effect of longer interpregnancy intervals? *Epidemiology* 2001;12:624-9.
- Sebire NJ, Harris J, Regan L, Robinson S. Is maternal underweight really a risk factor for adverse pregnancy outcome? A population-based study in London. *Br J Obstet Gynaecol* 2001;108:61-6.
- Reiss RE, O'Shaughnessy RW, Quilligan TJ, Zuspan FP. Retrospective comparison of blood pressure course during preeclamptic and matched control pregnancies. *Am J Obstet Gynecol* 1987;156:894-8.
- Sibai BM, Gordon T, Thom E, Caritis SN, Klebanoff M, McNellis D, et al. Risk factors for preeclampsia in healthy nulliparous women: a prospective multicenter study. *Am J Obstet Gynecol* 1995;172:642-8.
- Hartikainen A, Aliharmi RH, Rantakallio PT. A cohort study of epidemiological associations and outcomes of pregnancies with hypertensive disorders. *Hypertens Pregnancy* 1998;17:31-41.
- Chalmers TC, Levin H, Sacks HS. Meta-analysis of clinical trials as a scientific discipline. I: control of bias and comparison with large co-operative trials. *Stat Med* 1987;6:315-25.
- Milne F, Redman C, Walker J, Baker P, Bradley J, Cooper C, et al. The pre-eclampsia community guideline (PRECOG): how to screen for and detect onset of pre-eclampsia in the community. *BMJ* 2005;330:576-80. (Accepted 27 January 2005)

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