Smoking in Moderate/Severe Preeclampsia Worsens Pregnancy Outcome, but Smoking Cessation Limits the Damage

F. Broughton Pipkin; on behalf of The Genetics of Preeclampsia Consortium

Abstract—We studied phenotypic and clinical outcome data in an observational, multicenter cohort study of 1001 Western European white women and their singleton babies, with stringently defined moderate-to-severe preeclampsia. Ninety women admitted to being current smokers; 71 had stopped smoking before entry to the study. Across the categories of never-smoker, stopped, and current smoker there were significant increases in the proportion of women delivering before 34 weeks’ gestation (P=0.011), delivering a baby below the third birth weight centile (P<0.001), or delivering a baby with any adverse outcome (P=0.011). By comparison with never-smokers, smoking during pregnancy was associated with a doubling of risk of being delivered before 34 weeks’ (odds ratio: 1.98; 95% CI: 1.24 to 3.16; P=0.004), of delivering babies below the third centile of corrected birth weight (odds ratio: 2.20; 95% CI 1.41 to 3.44; P<0.0001), or for their babies to have any adverse outcome (odds ratio: 1.87; 95% CI: 1.19 to 2.95; P<0.006). Worryingly, the risk of developing eclampsia was increased 5-fold (odds ratio: 4.88; 95% CI: 1.44 to 16.61; P=0.005). The proportion of smokers in these preeclamptic women was lower than in our pregnant population generally. However, preeclampsia still carries significant perinatal morbidity, and cigarette smoking in preeclamptic pregnancies exacerbates this. Stopping smoking decreases the risks. Smoking in young women should be a particular target for advice by general practitioners before pregnancy, with active encouragement after conception to enroll in such trials as the current Smoking, Nicotine and Pregnancy Trial to support cessation. (Hypertension. 2008;51:1042-1046.)

Key Words: pregnancy ■ human ■ preeclampsia ■ hypertension ■ smoking ■ fetal outcome ■ eclampsia

An association between maternal smoking and a decreased likelihood of developing pregnancy-associated hypertension have been documented for 2 generations.1,2 An epidemiological study from Sweden3 confirmed the decreased incidence of pregnancy-associated hypertension and preeclampsia in smokers but also reported that smokers who did develop preeclampsia had increased rates of placental abrupton, small-for-gestation-age babies and perinatal mortality. However, a subsequent, smaller study from the United States4 did not confirm an increase in small-for-gestation-age babies or earlier onset of preeclampsia. No published study has compared outcomes of preeclamptic pregnancy in women who have never smoked, those who used to smoke but have given up, and those who have smoked throughout their pregnancy. If outcomes differ, such information could be useful in encouraging women to give up smoking when they know that they are pregnant.

We have recently completed a genetic study of >1000 women with stringently defined moderate-to-severe preeclampsia and their babies (the Genetics of Preeclampsia Consortium Study); details are published in Reference 5. The objectives of this analysis were, thus, to determine in this large, carefully phenotyped, cohort whether women who continue to smoke in pregnancy and develop preeclampsia have a worse outcome than nonsmokers and whether stopping smoking has an impact on outcome. Our data confirm that if women who smoke do develop preeclampsia, their outcomes are worse, but, encouragingly, women who have stopped smoking have outcomes intermediate between the 2 ends of the spectrum.

Methods
This was a 10-center collaborative study undertaken within the United Kingdom. Because the study was primarily designed to study the genetics of preeclampsia, we only recruited women of white, Western European origin by grandparental ethnicity. Detailed information about design, recruitment, and the conduct of the study can be found in Reference 5. We followed the procedure laid down in 1997 by the United Kingdom Department of Health in obtaining ethical approval for this multicenter study. All of the patients recruited to the study gave informed, written consent to participation.

Cases were identified on admission with a clinical diagnosis of preeclampsia, defined as a systolic blood pressure of ≥140 mm Hg and diastolic pressure (Korotkoff V) of ≥90 mm Hg on 2 occasions after the 20th week of pregnancy in a previously normotensive woman and proteinuria in excess of 300 mg/L in a 24-hour collection.
or 500 mg per 24 hours. A total of 1001 women were recruited, of whom 801 were nulliparous.

Data were obtained from each woman and her obstetric records. Information was obtained at first antenatal (booking) clinic attendance on gestation age by ultrasound and systolic and diastolic blood pressures. Women were also asked about their smoking habit at this visit. Responses were coded as follows: never smoked; previous smoker, now stopped; or current smoker. The gestational age, systolic and diastolic pressures, and degree of proteinuria at diagnosis were noted, as were the highest recorded systolic and diastolic blood pressures before labor. Delivery data were recorded for mother and baby. The birth weight centile for each baby was computed, correcting for gestation age at delivery, sex, maternal parity, and BMI.† All of the women were seen by a research midwife ≥6 weeks after delivery (median: 11 weeks; fifth to 95th percentile range: 6 to 14 weeks) to measure their height, weight, and systolic and diastolic blood pressure at that time and to measure urinary protein concentration (dipstick).

Smoking has been associated with greater arterial stiffness in younger as well as older subjects, and in women as well as men (eg, Reference 7). The pulse pressure is partly determined by arterial stiffness. We, therefore, examined pulse pressure in the smokers and nonsmokers, using generalized linear modeling.

Statistical analysis was performed using SPSS for Windows version 14.0. Summary data are presented as means ± SDs or median (interquartile range) as appropriate for their distribution. Between-group comparisons were made using 1-way ANOVA and the χ² test. Repeated measures (generalized linear modeling) were used to examine differences between group values where data were normally distributed. The null hypothesis was rejected where P < 0.05.

Table 1. Clinical Data

<table>
<thead>
<tr>
<th>Smoking Status</th>
<th>Maternal Age, y</th>
<th>Gestation at Diagnosis, wk</th>
<th>Blood Pressure at Diagnosis, mm Hg</th>
<th>Maximum Proteinuria, g per 24 h*</th>
<th>Gestation at Delivery, wk</th>
<th>Postnatal BMI, kg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never-smoker (n=840)</td>
<td>29.9±5.3</td>
<td>35.0±4.0</td>
<td>155.8±14.1/98.1±7.7</td>
<td>1.7 [0.8 to 3.7] (n=471)</td>
<td>36.1±3.8</td>
<td>27.8±5.6</td>
</tr>
<tr>
<td>Ceased smoking (n=71)</td>
<td>28.2±5.8</td>
<td>34.5±4.1</td>
<td>154.4±14.2/98.0±7.6</td>
<td>1.8 [0.7 to 3.3] (n=45)</td>
<td>35.6±4.1</td>
<td>29.1±6.2</td>
</tr>
<tr>
<td>Current smoker (n=90)</td>
<td>26.2±5.8</td>
<td>33.8±4.4</td>
<td>156.6±16.4/97.8±7.7</td>
<td>2.2 [1.0 to 5.3] (n=52)</td>
<td>35.0±4.2</td>
<td>26.3±4.3</td>
</tr>
</tbody>
</table>

†There were significant decreases (Kendall’s τ) in maternal age (P<0.001), gestation age at the time of diagnosis (P<0.019), and gestation age at delivery (P<0.027) from women who had never smoked to those who currently smoked. The maximum observed proteinuria increased across the same groups, but this was not statistically significant (P>0.3). Data are shown as mean±SD for normally distributed data or median [interquartile range] when data were not normally distributed.

*Maximum proteinuria was recorded as grams per liter in an additional 481 women and as dipstick 2+ or more (median: 3+) in the remaining women in all of the groups. There was no significant difference across groups with either method.

Results

Ninety women admitted to being current smokers, whereas 71 had stopped smoking at varying times before entry to the study. Table 1 summarizes the maternal age, gestation age at diagnosis of preeclampsia and delivery, and the mothers’ BMI at the postpartum visit. ANOVA showed that the smoking mothers were younger (P<0.0001), preeclampsia was diagnosed earlier (P=0.019), they were delivered earlier (P=0.027), and their postnatal BMI was less (P=0.005). Blood pressures in the 3 groups were statistically indistinguishable throughout pregnancy and postpartum. Table 2 summarizes the proportions of women in the 3 groups who were delivered before 34 weeks’ gestation, delivered a baby whose birth weight was below the third centile, or delivered a baby with any adverse outcome. It can be seen that all of the outcomes worsened progressively and significantly across the groups.

We calculated relative risks for various outcomes comparing never-smokers with current smokers. In our cohort of women with established preeclampsia, smoking during preg-

nancy was associated with a doubling of risk of being delivered before 34 weeks gestation (odds ratio [OR]: 1.98; 95% CI: 1.24 to 3.16; P=0.004). Smoking mothers were twice as likely to deliver babies below the third centile of corrected birth weight compared with women in our cohort who did not smoke (OR: 2.20; 95% CI: 1.41 to 3.44; P<0.0001) or were twice as likely for their babies to have any adverse outcome (OR: 1.87; 95% CI: 1.19 to 2.95; P<0.006). Regression analysis showed that the highest recorded diastolic pressure (P<0.0001) and smoking (P=0.012) independently influenced the birth weight centile. Twelve women (1.2%) developed eclampsia in the index pregnancy. Four of the eclamptic women were current smokers; the remaining 8 had never smoked (Fisher’s exact test, comparison with noneclamptic subjects: OR: 4.88; 95% CI: 1.44 to 16.61; P=0.005). All of the women and their babies survived.

We also examined pulse pressure in the smokers and nonsmokers. Because both the mothers’ age and BMI were significantly associated with pulse pressure, they were included as independent variables. As the Figure shows, after correction for age and BMI, the current smokers had significantly higher (P=0.018) pulse pressures during the development of preeclampsia, which had not resolved by the postnatal visit at 11 weeks after delivery.

Discussion

The Genetics of Preeclampsia Consortium Study recruited from white, Western European women who developed stringently defined preeclampsia. The results from the study may, thus, not be extrapolable to other populations. However, we believe this to be the most clinically detailed large database of
Figure. Repeated-measures analysis of pulse pressure in smokers (solid line) and nonsmokers (broken line) at different points during pregnancy adjusted for maternal age and BMI. Smoking was associated with higher pulse pressures ($P=0.018$) once preeclampsia was diagnosed; this effect was maintained to a median of 11 weeks postpartum. Estimated marginal means are shown with the SEMs.

Possible mechanisms for an adverse outcome are similar to those outside pregnancy. Smoking is associated with increased platelet and leukocyte activation, adverse effects on lipids and insulin resistance, and, perhaps most importantly, damage to endothelial function. This includes decreased endothelial NO synthase activity and possibly accelerated inactivation of NO by reactive oxygen species and increased synthesis of the potent oxidant peroxynitrite. A small study of women of similar age to those in this study reported a decrease of approximately one quarter in the endogenous NO production (measured as exhaled NO) of smoking compared with nonsmoking women. There is also local dysregulation of prothrombotic and antithrombotic factors such as prostacyclin and thromboxane. Integrated, dose-dependent impairment of endothelial function has been shown in the peripheral circulation in smokers. A decrease in stimulated NO release has also been shown in women with preeclampsia compared with normotensive pregnant women. The administration of $S$-nitrosoglutathione (a platelet-specific NO donor) to women with severe preeclampsia was associated with a highly significant fall in blood pressure and in uterine artery resistance.

In our study, when women who smoked developed preeclampsia, they were at considerably greater risk of adverse outcome than nonsmokers. Preeclampsia is a multifactorial disease, and smoking may only adversely affect a subset of the at-risk population, identification of which is not yet possible. Functional polymorphisms in genes regulating antioxidant status, such as the superoxide dismutases or the glutathione peroxidases, could influence susceptibility. For example, $>$90% of patients diagnosed with chronic obstructive pulmonary disease are chronic smokers, yet only approximately one fifth of smokers develop clinically significant chronic obstructive pulmonary disease. A recent report suggested that a functional polymorphism of the SOD3 gene may, through anti-inflammatory or antioxidant effects, be protective. An individual’s sensitivity to the effects of smoking has also been suggested to be related to dietary intake of antioxidants and n-3 fatty acids. A significant inverse association between fruit and vegetable intake and subsequent occurrence of cardiovascular disease was reported in a large group ($n=39$ 876) of older, largely perimenopausal or postmenopausal women. In the multivariate models tested, smoking was the strongest confounding factor. There is currently increasing interest in the beneficial effects of an improved diet, especially intake of fruit and vegetables, on cardiovascular function in the population as a whole. The available evidence suggests that smokers could particularly benefit.

Epidemiological data from Sweden and among a predominantly African American population reported significantly increased perinatal mortality, placental abruption, and infants born small for gestational age among women who smoked...
and nevertheless did develop preeclampsia. Such studies have shown no synergy between the effects of maternal smoking and of hypertension on birth weight.\textsuperscript{23} We defined a composite variable similar to that described previously,\textsuperscript{8,24} whereby women who had any of the following, delivery before 34 weeks' gestation, delivery of an infant with a birthweight below the third centile, admission of the baby to the special care baby unit, or who suffered a perinatal death, were classified as having had an adverse outcome. Smoking mothers were nearly twice as likely to deliver a baby with such an outcome. Delivery before the watershed 34 weeks and/or severe fetal growth restriction carry increased immediate and longer-term morbidity and mortality for the baby and infant.\textsuperscript{25,26} Thus, this large study, in which all of the 1001 women had moderate/severe preeclampsia, also suggests that the greatest impact of smoking in pregnancy is on the fetoplacental unit. The potential adverse effects of smoking on the placenta itself have been well documented (eg, Reference\textsuperscript{7}).

We are only aware of 1 previous study considering smoking and eclampsia,\textsuperscript{27} an epidemiological survey of \textgreater{}3 million singleton pregnancies in the United States in 1998. The incidence of eclampsia in the United Kingdom is 4.9 per 10 000 maternities (\textasciitilde{}1:2000).\textsuperscript{28} In our study of high-risk women, 12 women suffered an eclampsia, an incidence of 120 per 10 000 maternities, \textasciitilde{}25-fold higher, and the risk of eclampsia was greatest in smokers (OR: 4.9; 95% CI: 1.4 to 16.6). Eclampsia carries a high cost to the mother as well as the fetus, \textasciitilde{}1 in 50 dying in the 1994 report\textsuperscript{28} and 35% having \textgreater{}1 major complication. Smoking is associated with increased arterial stiffness in young women as well as young men (eg, Reference\textsuperscript{7}). The greater pulse pressure in smokers once preeclampsia had developed (Figure) may indicate greater stiffness, perhaps secondary to the endothelial dysfunction associated with preeclampsia (see above and Reference \textsuperscript{7}), which might contribute to the greater risk of eclampsia.

The degree of hypertension did not differ in the 3 groups, regardless of whether delivery was before or after 34 weeks' gestation. However, the maximum recorded 24-hour urinary protein output was somewhat higher in the smokers (median: 2.24 g per 24 hours; range: 0.45 to 12.85 g per 24 hours compared with never-smokers at 1.70 g per 24 hours [range: 0.50 to 10.42 g per 24 hours]; \(P \textgreater{} 0.1\), as was the likelihood of 1+ protein or more at the postpartum visit (6.8% compared with 3.1%; \(\chi^2=3.49; P=0.067\)), but neither difference was statistically significant. Nevertheless, it may be that the somewhat higher proteinuria triggered earlier delivery in the smokers. Smoking is a known risk factor for renal damage.\textsuperscript{30,31} A recent large-scale study (\textasciitilde{}11 000) of a normal population\textsuperscript{25} linked smoking to increased urinary protein:creatinine in men but not in women, especially in the presence of high-normal systolic pressure, a trend reported from other studies. However, it seems likely that a degree of underlying smoking-induced glomerular damage will also be present in women. Thus, it may be that the proteinuria used to diagnose preeclampsia in these women is at least partly smoking related rather than pregnancy specific.

We did not measure urinary cotinine, so we cannot be certain that all of those who claimed to have given up had in fact done so. However, a recent study of pregnant and postpartum women reported excellent agreement between self-reported smoking status and urinary cotinine measurement.\textsuperscript{33} This would fit with the clear dose-related change in the risk of various outcomes from women who had never smoked, those who used to smoke but gave up, and those who smoked throughout their pregnancy reported here. This is encouraging and provides a further reason for pregnant women to stop smoking. The development and implementation of effective strategies for stopping smoking in all pregnant women should be a priority. The current Smoking, Nicotine and Pregnancy Trial is 1 such strategy (http://www.biomedcentral.com/1472-6963/7/2).

**Perspectives**

These data are from a large group (\textasciitilde{}1001) of women with well-characterized moderate-to-severe preeclampsia. Smokers as a group are less likely to develop preeclampsia, and the relatively low proportion of current smokers in this study reflects this. However, clearly, in the United Kingdom population, if a smoker does develop preeclampsia, she is considerably more likely to develop the more severe, early onset form. The effects were most pronounced on the fetus, with a significant worsening of risk from women who had never smoked through those who had stopped to those who currently smoked for delivery before 34 weeks' gestation, delivering a baby whose birth weight was below the third centile, or any adverse outcome for the baby. These outcomes have long-term consequences for the child’s cardiovascular health. Although absolute hypertension was no worse in the smokers, their pulse pressure was raised, and they were at 5-fold greater risk of eclampsia. Smokers who do develop preeclampsia may be a subset at particular risk, perhaps because of their genetic background or dietary habits. Encouragingly, if a woman stopped smoking during her pregnancy, the deleterious outcomes all decreased. This is an important observation for those caring for pregnant women, who should actively promote smoking cessation. Because smoking is associated with endothelial damage, the opportunity provided by attendance for antenatal care should also be used to give appropriate dietary advice focused on the benefits of increased intake of antioxidants.

**Appendix**

**The Genetics of Preeclampsia (GOPEC) Consortium**

Consortium members include the following: F. Broughton Pipkin, N. Kalshkever, L. Morgan, S. O’Malley, M. Henfrey, S. Arulkumaran, and I. Symonds (University of Nottingham); A. Cameron, A. Dominiczak, M. McDade, W. Kwong Lee, and J. McCulloch (University of Glasgow); M. Caulfield (Bart’s and the London, Queen Mary’s School of Medicine and Dentistry); M. Farrall (Wellcome Trust Centre for Human Genetics, Oxford); M. Kilby and L. Davies (University of Birmingham); P.M.S. O’Brien (University of Keele); M. Habiba, J. Waugh, and C. Dodd (University of Leicester); P.N. Baker (University of Manchester); S. Macphail (University of Newcastle); K. O’Shaughnessy, B. Newcombe, and P. de la Salle (University of Cambridge); C. Redman and P.
Jarrett (University of Oxford); M. de Swiet, C. Williamson, E. Byford, and F. Cheng (Imperial College London); J.J. Walker and L. Samiul (University of Leeds); G. Chapman (University Hospital of North Staffordshire); E. Dennehy (Derby Hospitals Trust); R. Keys and S. Bjornsson (Glasgow Princess Royal Hospital); C. Mercer and M. Mohajer (Royal Shrewsbury Hospital); G. Thompson (Newcastle Royal Victoria Hospital); M.N. Fitzgibbon (Wordsley Hospital); G. Hackett (Cambridge Rosie Maternity Hospital); K. Hinshaw (Sunderland Royal Hospital); B. Lim (Hinchingbrooke Hospital); D.T.Y. Liu (Nottingham City Hospital); W. Mackenzie (Birmingham Heartlands Hospital); M. Selinger (Royal Berkshire Hospital); I. Scudamore (Leicester General Hospital); C. Sparey (Leeds General Infirmary); D. Tuffnell (Bradford Royal Infirmary); S. Ward (Kings Mill Hospital); J. Waugh (Leicester Royal Infirmary); and D. Williams (Chelsea and Westminster Hospital).

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Disclosures

None.

References

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