How Does Smoking Reduce the Risk of Preeclampsia?

S. Ananth Karumanchi, Richard J. Levine

Although smoking during pregnancy may lead to many adverse effects, such as fetal growth restriction, placental abruption, stillbirth, and preterm labor, smoking is the only environmental exposure known to consistently reduce the risk of preeclampsia and gestational hypertension. The article by Wikström et al.2 is a major step forward in understanding this protective effect. Using data from the Swedish Medical Birth Register in a large epidemiological study of >600 000 Nordic women, the authors conclude that use of Swedish snuff, a smokeless tobacco, did not reduce the risk of preeclampsia and gestational hypertension but that tobacco, when smoked, did. They infer that combustion products of tobacco, such as carbon monoxide (CO), protect against preeclampsia but that constituents of tobacco, such as nicotine, do not. The data strengthen and extend results of a previous smaller study using the Swedish Medical Birth Register, which had reported a similar association.

Although snuff use did not reduce the risk of mild or severe preeclampsia, preeclampsias that began before or after 37 weeks of gestation, or preeclampsias with or without delivery of a small for gestational age (SGA) infant or stillbirth, smoking reduced the risk of all categories of preeclampsia except for preeclampsia with an SGA infant or stillbirth. Of considerable interest, using data from women who changed their tobacco habits at gestational weeks 30 to 32 from those reported at the first antenatal visit (usually before 15 weeks of gestation), Wikström et al. found that women who had reported smoking at the first antenatal visit but no use of tobacco at 30 to 32 weeks did not have reduced risk of preeclampsia or gestational hypertension compared with tobacco nonusers, whereas women who reported no use of tobacco at the first antenatal visit but smoking at 30 to 32 weeks did. This implies that smoking during the second half of pregnancy is necessary for reducing the risk of preeclampsia or gestational hypertension.

Our understanding of the pathogenesis of preeclampsia has undergone a major revolution in the last decade. It is now believed that the clinical phenotype of preeclampsia may be mediated by a circulating antiangiogenic state largely attributed to placental overproduction of soluble fms-like tyrosine kinase 1 (sFlt1), an endogenous vascular endothelial growth factor signaling inhibitor, and soluble endoglin (sEng), a transforming growth factor-β signaling inhibitor. The etiology of these alterations has been the subject of intense debate, with a number of hypotheses advanced, including oxidative stress, altered immunologic factors, insulin resistance, and enhanced angiotensin II signaling. Can we explain the effects of smoking reported by Wikström et al. in terms of our new understanding of the pathogenesis of preeclampsia?

First of all, smoking during pregnancy has been associated with lower circulating concentrations of the antiangiogenic proteins, sFlt1 and sEng, and higher concentrations of the proangiogenic protein, placental growth factor.6 Because preeclampsia usually begins after the middle of the second trimester of pregnancy coincident with substantial rises in circulating sFlt1 and sEng, it is not entirely surprising why smoking during the latter half of pregnancy has the greatest benefit. Wikström et al. report that the protective effect of smoking appears to be less for the more severe forms of preeclampsia, preterm preeclampsia and preeclampsia with an SGA infant or stillbirth. Moreover, although there is a dose-response relationship between smoking and risk for the mild forms of preeclampsia (term preeclampsia, preeclampsia without SGA or stillbirth, or mild preeclampsia), there is no such relationship for the severe forms (preterm preeclampsia, preeclampsia with SGA or stillbirth, or severe preeclampsia). It should be noted that preeclampsia with SGA in this study is preeclampsia with severe SGA (~2.5%), and it may be associated with much greater alterations of antiangiogenic proteins than preeclampsia with SGA defined as ~10.0%.

We believe that every woman has a threshold for angiogenic imbalance, which, when crossed, will lead to preeclampsia. Because alterations in angiogenic proteins are greater in severe forms of preeclampsia, it should take more of a reduction in angiogenic factor concentrations to bring them below threshold and to prevent onset of preeclampsia. Thus, a given amount of smoking will afford less protection to women destined to develop preterm preeclampsia or preeclampsia with an SGA infant or stillbirth than to women who will develop mild or term preeclampsia. Cnattingius et al.7 and Pipkin8 have both reported that, although smoking reduces the incidence of preeclampsia, it worsens pregnancy outcomes in smokers who develop preeclampsia. We suggest that smoking more frequently prevents preeclampsia from developing in women who would otherwise experience mild disease, thus increasing the proportion who experience severe disease and worse outcomes. Recently, Chappell et al.9 have reported an association of smoking with increased risk of superimposed preeclampsia in women with chronic hyper-

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tension. This finding is of great interest and remains to be explained.

Among tobacco combustion products, NO, which promotes vascular relaxation, is a possible mediator of protection against preeclampsia. However, smokers have been noted to have decreased and not increased circulating levels of NO metabolites\(^1\); therefore, NO is unlikely to mediate the protective effect. On the other hand, recent data suggest that CO may be the critical mediator. CO is a vascular protective agent in a number of vascular disorders, such as ischemia/reperfusion injuries.\(^10\) In addition to exogenous sources, such as automobile exhaust or smoking, CO is also produced endogenously during cellular metabolism via the heme oxygenase (HO) system. Cudmore et al\(^11\) reported that CO and CO-releasing molecules lower sFlt1 and sEng production in endothelial cells and placental organ cultures, thus potentially providing a molecular explanation for the lower circulating levels of sFlt1 and sEng noted in smokers during pregnancy. Cigarette smoking may also directly upregulate HO expression in placental trophoblasts, which, in turn, may stimulate endogenous CO production. It is also likely that CO may inhibit placentation apoptosis and necrosis directly, thus reducing the release of placentally derived toxic factors.\(^12\) Other evidence to support the hypothesis that the HO pathway may play an important role in the pathogenesis of preeclampsia comes from human studies that have demonstrated decreased HO gene expression in placental villous tissue during the first trimester among pregnant women destined to develop preeclampsia\(^13\) and decreased exhaled CO among women with preeclampsia.\(^14\) Whether decreased HO and CO are found only in a subset of women with preeclampsia or in all such women is not known, and whether CO contributes to other adverse outcomes of pregnancy noted among smokers, such as fetal growth restriction, should be determined.

In summary, Wikstrom et al\(^2\) suggest that smoking during pregnancy, but not the use of smokeless tobacco, is associated with lower preeclampsia risk. The protective role of smoking is most likely to be explained through the biological effects of CO that are formed during smoking. CO may act by inhibiting placental production of antiangiogenic proteins, such as sFlt1, and by inhibiting placental apoptosis and necrosis. Additional research is needed to understand more fully the molecular mechanisms of the CO-mediated vascular protective effect and to harness this knowledge to identify new therapeutic targets for preeclampsia.

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**References**

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