

Smoking and risk of preeclampsia: a systematic review

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1. ABSTRACT

Cigarette smoking adversely affects every organ system. Paradoxically, smoking during pregnancy has been associated with a reduced risk of preeclampsia. We reviewed previous epidemiologic and clinical studies on the association between smoking and preeclampsia from 1959 to March, 2006. A total of 48 epidemiologic studies were identified. Overall, smoking during pregnancy reduces the risk of preeclampsia by up to 50% with a dose-response pattern. A protective effect was consistently found in both nulliparas and multiparas, singleton and multifetal pregnancies, and for mild and severe preeclampsia. Evidence on whether quitting smoking before or in early pregnancy reduces the risk remains inconclusive. To understand possible biologic mechanism(s) of the protective effect, we reviewed literature on potential

pathophysiology of smoking and its effects on placenta, cardiovascular and immune systems. Although current literature does not lend clear evidence to support a particular mechanism for the protective effect of smoking, smoking might have effects on angiogenic factors, endothelial function and the immune system which act to lower risk of preeclampsia. More epidemiologic studies with biochemically confirmed smoking status and laboratory studies with a focus on promising pathways are warranted to further clarify this puzzling relationship. Understanding the underlying mechanisms through which smoking reduces preeclampsia risk may enhance our understanding of the pathogenesis of this disorder and contribute to the development of prevention strategies.

2. INTRODUCTION

Smoking adversely affects every organ system, and causal associations have been established between smoking and many diseases, including multiple types of cancer, cardiovascular disease, respiratory disorders, poor wound healing, low bone density in postmenopausal women, periodontal disease, and pregnancy complications including premature rupture of the fetal membranes, placenta previa, placental abruption, preterm delivery, and fetal growth restriction (1). Smoking has been associated with reduced risk for a smaller number of diseases, including ulcerative colitis, celiac disease and primary sclerosing cholangitis, Parkinson's disease, and preeclampsia (2-4).

Preeclampsia is a syndrome of reduced organ perfusion due to vasospasm and endothelial dysfunction with onset after 20 weeks gestation that is marked by proteinuria, and hypertension (5, 6). Preeclampsia is a leading cause of pregnancy-related mortality in the United States (7), and is associated with fetal growth restriction, placental abruption, and perinatal death (recently reviewed by Sibai and colleagues (6)). Epidemiologic studies have consistently shown an inverse association between smoking and preeclampsia (4). Interestingly, no other environmental factors or supplements have shown a protective effect so consistently (8).

This review summarizes findings from studies on the association between smoking and risk of preeclampsia. To reconcile findings in epidemiologic studies with those of laboratory studies, we review pathways thought to contribute to preeclampsia and examine potential effects of smoking on these pathways.

3. METHODS

We conducted a comprehensive literature search on MEDLINE using key words: cigarette, hypertension, preeclampsia, pregnancy, smoking and tobacco. All published articles in English up to March, 2006 were potentially eligible. Meeting proceedings were not searched. We retrieved all relevant articles and cross-checked the references. Because the study populations, definitions of preeclampsia and hypertensive disorders of pregnancy, and approaches to controlling for confounders differed substantially from study to study, no data synthesis or meta-analysis was attempted.

4. RESULTS

4.1. Epidemiology of Smoking and Preeclampsia

4.1.1. The overall association between smoking during pregnancy and preeclampsia

In 1999, Conde-Agudelo and colleagues published a systematic review on cigarette smoking during pregnancy and risk of preeclampsia, which summarized the literature through October 1998 (4). They identified 27 cohort studies and 7 case-control studies from 1959 to 1998 and combined results from all the cohort studies and all the case-control studies, respectively. Both types of studies

showed a 32% reduction in risk of preeclampsia with a significant dose-response pattern. In the cohort studies, women who smoked less than 10 cigarettes per day during pregnancy had a relative risk (RR) of 0.77 while women who smoked 10 cigarettes per day or more had a RR of 0.67. The corresponding RRs in the case-control studies were 0.87 and 0.61, respectively.

Studies published after October 1998 showed very similar results (9-18). As in previously published studies, the quality and type of data available for analysis varied substantially, and included birth registry records, medical records, and randomized trials. Overall, these recent studies support that smoking during pregnancy reduces the risk of preeclampsia by up to 50 percent, depending on the amount smoked. In 2 studies, the authors found no reduction in preeclampsia risk among smokers. However, these studies were limited by failure to adjust for potential confounders (19) and small sample size (20).

4.1.2. Severity of hypertensive disorder in pregnancy

Studies including examination of both preeclampsia and gestational hypertension have demonstrated that smoking during pregnancy reduces the risk of both disorders (9, 13, 21) and with a similar inverse dose-response pattern (13, 21). Some studies (13, 21) but not all (9) indicate that the protective effect may be somewhat stronger for preeclampsia than for gestational hypertension.

Clinical manifestations of preeclampsia vary considerably and severe disease is marked by earlier onset, greater hypertension, and/or greater proteinuria. Several studies have examined the relationship between smoking and severity of preeclampsia, and most have found that smoking had similar protective effects for mild and for severe preeclampsia (11, 13, 21-24). However, in two studies smoking did not appear to reduce the risk of early onset preeclampsia (23, 25) while in another protective effects for preterm and term preeclampsia were similar (11). It should be noted that early onset preeclampsia is uncommon, and in most studies the sample size was small, leading to unstable point estimates.

4.1.3. Parity

Preeclampsia and, to a lesser extent, gestational hypertension predominantly affect nulliparous women. Smoking appears to have protective effects in nulliparous and multiparous women that are similar in magnitude (17, 23, 26, 27). For example, Xiong and colleagues found that the adjusted relative risks of preeclampsia in relation to smoking during pregnancy were 0.63 (95% confidence interval [CI]: 0.50 – 0.80) in nulliparous women and 0.72 (95%CI: 0.51 – 1.02) in multiparous women, respectively (17). Odegard and colleagues found an odds ratio (OR) of 0.6 in nulliparous women, 0.8 in multiparous women with a history of preeclampsia and 0.4 in multiparous women with no history of preeclampsia (23).

4.1.4. Twin pregnancy

Twin pregnancy differs from singleton pregnancy in many ways, including increased risk of preeclampsia.

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Table 1. Relative risk of preeclampsia in women who quit smoking, comparing to that in non-smokers

Author/ Year (reference)	Study description	Smoking status	Outcome measure	Crude RR (95% CI)	Adjusted RR (95% CI)	Adjusted factors
Marcoux, 1989 (21)	A retrospective case-control study in multiple hospitals in Canada; Primipara, singleton pregnancy without chronic hypertension; 172 women with preeclampsia, 251 with gestational hypertension; 505 normotensive controls	Never smoker; Past smoker: stopped smoking before pregnancy; Quitter: stopped smoking during pregnancy; Current smoker.	Preeclampsia Gestational hypertension		For preeclampsia: Past smoker 0.74 (0.46 – 1.18) Quitter 0.82 (0.46 – 1.49) For gestational hypertension: Past smoker 0.91 (0.59 – 1.39) Quitter 1.16 (0.69 – 1.95)	Maternal body mass and education
Sibai, 1995 (30)	A multicenter prospective trial in the U.S. on the effects of low-dose aspirin on preeclampsia. 2,947 healthy nullipara with singleton gestation recruited early in pregnancy.	Never or has not smoked for more than 1 year prior to pregnancy; Quitter: Quitted at start of pregnancy; Current smoker.	Preeclampsia	Quitter 0.46 (0.23 – 0.93) Current smoker 0.63 (0.36 – 1.13)	Quitter and current smoker combined RR = 0.50, p<0.01	Body weight, systolic blood pressure, gravidity
Zhang, 1999 (13)	A large prospective cohort study in the U.S. A total of 9,651 healthy primigravida with singleton gestation were selected.	Never smoker Ex-smoker: stopped smoking anytime before enrollment (many of them smoked in early pregnancy); Current smoker	Preeclampsia Gestational hypertension		For preeclampsia: Ex-smoker 1-5 cig./day 0.8 (0.6-1.2) 6-10 cig./day 0.7 (0.4-1.3) >10 cig./day 1.1 (0.7-1.8) For gestational hypertension: Ex-smoker 1-5 cig./day 1.1 (0.9-1.3) 6-10 cig./day 0.8 (0.6-1.1) 11-20 cig./day 0.7 (0.4-0.98) >20 cig./day 0.6 (0.3-1.2)	Maternal age, race, socioeconomic status, prepregnancy body mass
Martin, 2000 (28)	Retrospective medical record data on 1,575 twin pregnancies in one hospital in U.K.	Nonsmoker; Ex-smoker: smoked in early pregnancy but quit before booking; Current smoker;	Preeclampsia	Primipara ex-smoker 0.75 (0.21 – 2.75) Multipara ex-smoker 0.68 (0.18 – 2.60)		
England, 2002 (9)	A multicenter prospective trial in the U.S. on the effects of calcium supplementation on preeclampsia. 4,589 healthy nullipara with singleton gestation recruited early in pregnancy.	Never smoker; Quit before LMP; Quit after LMP; Smoking at enrollment.	Preeclampsia Gestational hypertension		For preeclampsia: Quit before LMP 1.1 (0.7 – 1.7) Quit after LMP 0.9 (0.6 – 1.3) For gestational hypertension: Quit before LMP 1.1 (0.9 – 1.4) Quit after LMP 0.9 (0.7 – 1.1)	Maternal age, race, type of health insurance, study center, body mass index at enrollment.
Parazzini, 2003 (16)	A retrospective case-control study in multiple hospitals in Italy. 215 cases of non-proteinuric pregnancy-induced hypertension; 1,222 normotensive controls	Never smoker; Former smoker: have quit smoking > 1 year before conception; Current smoker.	Non-proteinuric pregnancy-induced hypertension		Former smoker 1.0 (0.6 – 1.5)	Maternal age, center, parity, education, body mass index, nausea

LMP: last menstrual period.

However, Martin and colleagues found that the relationship between smoking and preeclampsia risk was similar in twin pregnancies to that in singleton pregnancies (28). Similarly, Coonrod and colleagues found that the relative risks of preeclampsia in relation to smoking during pregnancy were 0.7 (95% CI: 0.5 – 1.0) for singleton and 0.8 (0.6 – 1.1) for twin pregnancies (29).

4.1.5. Smoking cessation

Many smokers quit before becoming pregnant or in early pregnancy. As clinical manifestation of

preeclampsia usually occurs in late pregnancy, examining preeclampsia risk in quitters could provide insight into mechanisms through which smoking may reduce the risk of preeclampsia.

Table 1 presents six studies that have examined the risk of preeclampsia in women who quit smoking either before or after conception (9, 13, 16, 21, 28, 30). These studies consistently showed that continued smoking during pregnancy was associated with a reduced risk of

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Table 2. Effects of smoking on selected physiologic processes

	Effect	Reference
General	Increase oxidant stress	1, 136-138
	Induce protease-antiprotease imbalance	1, 139
	Increase angiogenesis	68, 140
	Platelet activation	141-143
	Abnormal platelet-vessel wall interactions, thrombosis	141, 144, 145
	Increased arterial uptake of atherogenic plasma proteins	1, 146
	Increased lipid peroxidation	96
	Endothelial dysfunction	147
	Endothelial damage	148
	Increased inflammation	149-151
	Increased blood viscosity	152
	Decreased oxygen carrying capacity	1
Pregnancy	Placental degradation	46
	Decreased maternal blood levels of ascorbic acid	130, 153
	Chronic hypoxemia	154, 155
	Vasoconstriction of the uteroplacental vasculature	154, 156
	Impairment of maternal immune response	157, 158
	Increased production of prostaglandins	159

preeclampsia (not shown). However, women who quit smoking in early pregnancy also had a slightly reduced risk of preeclampsia (the relative risk ranging from 0.68 (28) to 0.9 (9)). These RRs are similar to that found in women who smoked less than 10 cigarettes per day throughout pregnancy (4).

The effect of quitting smoking before pregnancy on the risk of preeclampsia is less consistent. Marcoux (21) and Zhang (13) found that women who quit smoking before pregnancy, especially the heavy smokers, still had a reduced but statistically non-significant risk. However, England (9) and Parazzini (16) showed no protective effect at all.

In all studies addressing preeclampsia risk in quitters, smoking and quit status were based solely on maternal self-report and were not biochemically validated. Therefore, it is possible that apparent protective effects seen in quitters reflected misclassification of active smokers as quitters.

4.1.6. Partner smoking

Parazzini and colleagues (16) found that whether a woman's partner smoked or not did not affect her risk of preeclampsia. No dose-response pattern was observed.

4.1.7. Smokeless tobacco

Comparing effects of smokeless tobacco on preeclampsia risk to effects of smoking could provide insight into which components found in tobacco smoke are responsible for protective effects as smokeless tobacco users are exposed to nicotine but not products of combustion. England and colleagues examined the incidence of preeclampsia in women who used smokeless tobacco (snuff) during pregnancy in Sweden (31). The authors found that the incidence of preeclampsia was

increased in snuff users (adjusted RR = 1.58, 95%CI 1.09 – 2.27) compared with tobacco nonusers. This finding suggests that products of combustion rather than nicotine may be the cause of reduced preeclampsia in smokers.

4.2. Pathophysiology of Preeclampsia and Effects of Smoking

Smoking has a number of effects on physiologic processes, many of which are believed to contribute to smoking-related diseases (Table 2). None of these effects offers a clear explanation for reduced preeclampsia risk in smokers. However, a better understanding of the mechanisms underlying the protective effects of smoking could contribute to the development of effective interventions. We reviewed the literature on the possible processes underlying preeclampsia and the potential effects of smoking on these processes.

4.2.1. Placental development and function

4.2.1.1. Physiologic transformation

Preeclampsia is characterized by poor placentation with shallow invasion of the decidua and myometrium by trophoblast cells, resulting in incomplete physiologic transformation of the maternal spiral arteries, which then retain their muscular characteristics resulting in reduced placental perfusion and placental insufficiency (32, 33). Among women who smoke during pregnancy, physiologic transformation appears to be disturbed. *In vitro* studies indicate that cytotrophoblast cell column formation, which is necessary for invasion of the uterine wall, is disrupted in the presence of nicotine (34). There also appears to be a reduction in the number of cytotrophoblastic stem cells in the floating villi and in the number of anchoring villi successfully invading the uterine wall. These findings suggest that tobacco exposure may result in disturbance of cytotrophoblast invasion of the uterine wall, which in turn could lead to an increased risk of pregnancy complications (35). Since preeclampsia is characterized by incomplete transformation of the spiral arteries, it is uncertain whether/how effects of smoking on invasion of the uterine wall affect preeclampsia risk. However, the possibility remains that effects of smoking on physiologic transformation could lead to alterations in the clinical course of preeclampsia. Further research using *in vivo* models will be necessary to clarify these issues.

4.2.1.2. Villous morphology

Preeclampsia in the absence of fetal growth restriction is associated with modest reductions in the intervillous space and terminal villi volume (36), while preeclampsia in the presence of fetal growth restriction is associated with more dramatic decreases in placental villi and capillary volumes (36, 37). The clinical relevance of these morphologic changes is unknown. Studies of the effects of smoking on development of the villous capillary system are inconsistent. In several studies the placentas of smokers were found to be heavier or larger than in nonsmokers (38-41) which is consistent with expansion of the peripheral villous tree. However, in other studies no or only small increases in placental size and/or weight were found (13, 39, 42-46). In morphological studies, increased (47), decreased (42, 48-51), and no difference (52, 53) in

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the dimensions of the villous capillary system of smokers have been described. The potential contribution of smoking-related alterations in villous morphology to preeclampsia risk and clinical manifestations of the disease are unclear.

4.2.1.2. Other effects on the villous system

Preeclampsia has been associated with increased release of syncytiotrophoblast microparticles and/or syncytial cellular debris into the maternal circulation, potentially resulting in endothelial dysfunction (54-56). Placentas from preeclamptic pregnancies show evidence of an increased rate of syncytiotrophoblast proliferation and apoptosis (57). A number of changes in placental morphology of smokers have been described, including cytotrophoblast hyperplasia, increased focal syncytial necrosis, loss or distortion of syncytial microvilli, decreased vasculosyncytial membranes, decreased syncytial pinocytotic vesicles and degeneration of cytoplasmic organelles, increased syncytial knots and decreased syncytial buds, and increased collagen in the villous stroma (41, 46, 53, 58). Evidence of increased syncytial damage in smokers is suggested by increased syncytial knots and necrotic areas (46). Not all studies are consistent, however (50, 59). These cellular and molecular abnormalities of the villous system could lead to impaired exchange of metabolic products, oxygen and nutrients between the mother and fetus. Since preeclampsia has been associated with increased release of syncytiotrophoblast microparticles and/or syncytial cellular debris into the maternal circulation, research to date offers no compelling evidence that smoking protects against preeclampsia through effects on syncytial shedding into the maternal circulation.

4.2.2. Angiogenesis

An imbalance between pro- and anti-angiogenic placental factors may contribute to manifestations of preeclampsia, and it has been suggested that smoking may exert its protective effects by affecting this imbalance (60, 61). For example, vascular endothelial growth factor (VEGF) is a proangiogenic factor and major regulator of cytotrophoblast differentiation along the invasive pathway which is decreased in preeclamptic placentas. Circulating levels of free VEGF appear to be decreased in the blood of preeclamptic women (60, 62, 63). Similarly, circulating levels of free placental growth factor (PlGF), another proangiogenic protein, also appear to be reduced in affected women (60, 62, 64). While research suggests that smoking decreases cytotrophoblast proliferation and causes abnormal cytotrophoblast differentiation (35), smoking also appears to increase placental expression of VEGF (65). This increased expression of VEGF may be due to down regulation of the von Hippel Lindau tumor suppressor protein (61). It has been hypothesized that increased expression of VEGF could raise maternal blood levels of VEGF enough to reduce preeclampsia risk (35).

The soluble form of fms-like tyrosine kinase (sFlt-1) is secreted into the maternal circulation and has been found to be elevated in the maternal circulation in preeclamptic women. It has been hypothesized that sFlt-1

causes hypertension and proteinuria by antagonizing VEGF and PlGF (reviewed by Levine and Karumanchi 2005) (66). Blood levels of sFlt-1 have been found to be decreased in the plasma of smokers (67). Furthermore, results of a series of experiments performed by Heeschen and colleagues support that nicotine has proangiogenic properties (68) and it has been suggested that nicotine may be responsible for smoking-related alterations in the pro- and anti-angiogenic placental factor balance (35, 60). However, in at least one epidemiologic study, preeclampsia risk was not reduced among women using smokeless tobacco, suggesting that nicotine may not be responsible for protective effects of smoking (31).

Taken as a whole, studies of the potential effects of smoking on increasing proangiogenic factors and decreasing antiangiogenic factors offer a plausible explanation as to why preeclampsia is reduced in smokers. Additional research is needed to confirm or dispute that effects of smoking on VEGF-A and/or sFlt-1 explain the reduced risk of preeclampsia in smokers.

4.2.3. Thromboxane/prostacyclin

It has been suggested that preeclampsia is the result of an imbalance between prostaglandin (a vasodilator) and thromboxane (a vasoconstrictor and platelet aggregation stimulator). Studies suggest that women who later develop preeclampsia have lower levels of PGI₂ and a higher TXA₂/PGI₂ ratio compared with women with nonhypertensive pregnancies (69). Nicotine may have inhibitory effects on thromboxane production (70), leading to a more favorable TXA₂/PGI₂ ratio.

4.2.4. Gaseous transmitters

Gaseous transmitters are small molecules of endogenous gases, permeable to membranes, which can have endocrine, paracrine, and autocrine effects and are not dependent on membrane receptors (reviewed by Wang, 2003)(71). Nitric oxide is one well-studied gaseous transmitter synthesized by nitric oxide synthase in vascular endothelial cells (eNOS) (72). In pregnancy, nitric oxide is present in placental villi and is believed to play an important role in the vasodilatory response of the fetoplacental circulatory system (73-75). Nitric oxide synthase activity was found to be reduced in placental villi from preeclamptic and IUGR pregnancies (76), and *in vitro* research indicates that mRNA and protein expression of eNOS are decreased in endothelial cells from preeclamptic pregnancies (77). Smoking has been associated with a dose-dependent decrease in endothelial dependent vessel dilation (78, 79), and can inhibit eNOS activity, depending on the eNOS genotype (80). The effects of smoking on eNOS activity could lead to lower NO levels, resulting in a loss of dilatory capacity, contributing to intrauterine growth retardation. If true, smoking should act through this mechanism to increase risk of preeclampsia rather than to decrease risk.

Carbon monoxide is a more recently discovered gaseous transmitter which may have important vasoregulatory physiologic effects including decreasing platelet aggregation and vasorelaxant properties. Carbon

monoxide is produced by hemeoxygenases HO-1 and HO-2. HO-2 may have effects in the placenta that are complimentary to endothelial nitric oxide synthase (81). Placental perfusion studies have shown that both carbon monoxide and nitric oxide can have vasodilatory effects on placental flow (81, 82) and it has been suggested that exogenous carbon monoxide from cigarette smoke could play a role in the protective effects of smoking against preeclampsia by causing vasodilation of placental vessels in the face of incomplete physiologic transformation of maternal spiral arterioles (82). However, more research is needed to further define the effects of exogenous carbon monoxide on placental perfusion *in vivo*.

4.2.5. Endothelial dysfunction

Preeclampsia is marked by endothelial dysfunction and increased neutrophil activation (83-85). Activation of neutrophils results in the release of proteases, reactive oxygen species, and leukotrienes which can mediate vascular damage, endothelial cell destruction, membrane lipid peroxidation, and increased vascular permeability (86). The recruitment and attachment of neutrophils to endothelial cells is controlled by cell surface adhesion molecules in circulating cells and in the vascular endothelium, including E-selectin, intercellular adhesion molecule 1 (ICAM-1), and vascular cell adhesion molecules (VCAM) 1 and 2 (87). Women with preeclampsia have increased plasma concentrations of the soluble VCAM-1, the endothelial adhesion molecule E-selectin (83) and the soluble intercellular adhesion molecules sICAM and CD54 (88, 89).

Researchers have found that nicotine administration in animal models results in decreased leukocyte adhesion to uterine vascular endothelial cells (90), and that nicotine inhibits endothelial cell surface ICAM expression and neutrophil integrin expression of CD11a, and CD11b (91). These inhibitory effects of nicotine on endothelial cell and neutrophil adhesion molecule expression could decrease leukocyte-endothelial cell adhesion, contributing to the protective effects of smoking against preeclampsia.

4.2.6. Oxidative stress

Oxidative stress is a condition in which production of oxidative species outpaces antioxidant defenses, resulting in oxidative damage. Oxidative stress is thought to underlie many conditions related to tobacco exposure (1) and it is thought that hypoxic conditions in the placenta can lead to oxidative stress. This, in combination with an exaggerated inflammatory response, could contribute to the clinical syndrome of preeclampsia. Women with preeclampsia have decreased plasma and placental concentrations of antioxidants and increased placental production of lipid peroxides and thromboxane found in preeclamptic placentas has been described (reviewed by Rumbold and colleagues, 2006 (92) and by Gupta and colleagues, 2005 (93)). However, recent large randomized clinical trials of the use of antioxidants (such as vitamins C and E) as prophylaxis against preeclampsia showed no benefit in reducing preeclampsia risk (94, 95).

Studies of the acute effects of exposure to tobacco smoke on oxidative stress suggest that smoking results in increased products of lipid peroxidation and degradation products of extracellular matrix proteins (reviewed by van der Vaart and colleagues, 2004)(96). Smokers have evidence of greater oxidative damage to DNA than nonsmokers, as measured by 8-hydroxydeoxyguanosine (8-OH-dG), regardless of the biologic material studied (1). Exposure of human plasma to cigarette smoke results in increased damage to proteins, as evidenced by elevated levels of protein carbonyls (97-99). In addition, there is evidence that smokers have reduced blood levels of antioxidant micronutrients (such as vitamin C, alpha-carotene, beta carotene, and cryptoxanthin) compared with nonsmokers. While reduced dietary intake may play a role, depletion of antioxidants appears to contribute (1). Based on our current understanding, the effects of smoking on oxidative stress do not offer a plausible explanation for the protective effects of smoking against preeclampsia.

4.2.7. Immune system

Immunologic factors have been implicated in the pathophysiology of preeclampsia and preeclampsia has been described as a maternal alloimmune reaction triggered by rejection of the fetal allograft. Infections and/or inflammatory conditions such as genitourinary tract infections and periodontal disease appear to increase preeclampsia risk (reviewed by Sibai and colleagues 2005)(6). Smoking has multiple effects on the immune system and is associated with an increased risk for many types of infection (reviewed by Arcavi and Benowitz 2004 (100)), likely through complex effects involving both innate and adaptive immune responses. Smokers appear to have a relative leukocytosis (101-106), while some types of immune cell function appear to be suppressed. For example, lymphocytes in smokers appear to have a decreased response to T cell mitogens (reviewed by Soporì 2002 (107)), and polymorphonuclear leukocytes show decreased chemotaxis and migration (108, 109). Smokers appear to have reduced titers of antibodies to influenza virus and lower serum levels of all immunoglobulin classes except IgE (107, 110). Smoking may also affect the balance between Th1 and Th2 cell function, as increases in Th2-related cytokines and/or Th1-related cytokines in smokers has been observed (111, 112). *In vitro* experiments suggest that nicotine impairs the immunostimulatory activity of dendritic cells (antigen-presenting cells), and adversely affects differentiation of monocytes into dendritic cells (113, 114). Finally, smoking has also been associated with a decreased number and cytotoxic activity level of natural killer cells, which are important components of innate immunity (115, 116). Because preeclampsia appears to involve an exaggerated maternal immune response, immunosuppressive effects of smoking could contribute to protective effects against preeclampsia.

Potential mechanisms through which tobacco or nicotine exposure might result in altered immune function include induction of glucocorticoid hypersecretion, and increased release of catecholamines, both of which have been shown to inhibit the immune response (107, 117). In

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addition, exposure to exogenous carbon monoxide could have immunosuppressive effects (82). In animal models, exogenously administered carbon monoxide has anti-inflammatory effects such as inhibition of LPS-induced tumor necrosis factor α production and augmented interleukin-10 production. Carbon monoxide also appears to suppress xenograft rejection in rodents, resulting in improved transplant success (118).

5. DISCUSSION

There is strong epidemiologic evidence that preeclampsia risk is reduced in smokers. However, it has been challenging for epidemiologists to determine with certainty whether this association is causal because a randomized trial demonstrating an increased incidence of preeclampsia in quitters does not exist and such a trial would be difficult to conduct due to the large study population required. Hennekens and Buring describe eight factors to consider when judging whether an epidemiologic observation is likely to be causal, including strength of the association, chance, bias, confounding, biological plausibility, consistency of the association, the time sequence (whether the exposure precedes the outcome) and dose-response relationship (119).

Numerous studies from many parts of the world have shown a consistent, statistically significant inverse relationship between smoking and preeclampsia, virtually ruling out the possibility that the association is due to chance. Multiple studies (10, 13, 21) but not all (120) have confirmed a dose-response relationship in which risk of preeclampsia decreases as the number of cigarettes smoked per day increases. The temporal sequence has never really been in doubt as the vast majority of women who smoke during pregnancy are smokers at the time of conception, well before development of preeclampsia. Well designed and carefully conducted prospective cohort studies, including large randomized clinical trials have been conducted which minimize the possibility that major biases due to selection, recall, and loss-to-follow-up explain the reduced preeclampsia risk in smokers.

In general, the stronger the association, the less likely it is due to confounding (119). The strength of the association between smoking and preeclampsia (approximately a 50% reduction in heavy smokers) is not as strong as that observed for some tobacco-related diseases. For example, current smokers have a 10-fold increased risk of lung cancer compared with nonsmokers, while heavy smokers have a 20-fold risk (119). On the other hand, the strength of the association between smoking and preeclampsia is similar to that of several other established effects of smoking, such as stroke (121, 122), bladder and kidney cancer (123), and endometrial cancer (protective effect from smoking)(124).

The relatively weak association between smoking and preeclampsia may in part be attributable to uncertainty around smoking status. The vast majority of studies on smoking and preeclampsia based smoking assessment on self-report, which is known to result in misclassification (125, 126). In prospective studies, cigarette exposure was

often based on what women reported smoking at enrollment, typically at or before 20 weeks of gestation (9, 13, 30). However, women tend to vary their cigarette use during the course of pregnancy, and may reduce the amount with advancing gestation (127). Conversely, women may report quitting smoking in early pregnancy but later resume smoking, or even misreport their smoking status altogether. Therefore, self-reported cigarettes smoked per day in early pregnancy may not accurately reflect true exposure, which could reduce the strength of the association among active smokers. To date, only one study to our knowledge used urinary cotinine level to quantify tobacco exposure (OR 0.31, 95% confidence interval, 0.12-0.79), confirming that a dose-response relationship exists (128).

While many studies of smoking and preeclampsia include adjustment for potential confounders (9, 13, 17, 18, 21, 129), the possibility remains that the association is due to unmeasured confounding. Smokers differ from nonsmokers in many ways, including diet and exercise habits (130-134). However, as Zhang and colleagues argued, this seems an unlikely explanation. In studies where the prevalence of smoking was high and the association was robust, a confounder would have to have been a risk factor that was common in the population, and the distribution of the confounder in smokers and nonsmokers would have had to differ remarkably to explain the relationship between smoking and preeclampsia (13). Such a confounder, if it exists and is measurable by epidemiologic instruments, is likely to have been identified by now. Therefore, it is unlikely that the apparent protective effect of smoking on preeclampsia is due to confounding.

Identification of a clear biological mechanism through which smoking reduces preeclampsia risk would provide compelling evidence for a causal association and could contribute to the identification of an effective treatment or prevention strategy for this disorder. However, such a mechanism has not yet been identified. Many of the known effects of smoking (Table 2) suggest that smoking should increase risk. None of the mechanisms hypothesized to protect smokers against preeclampsia has led to identification of an underlying cause of preeclampsia.

Identification of the component in tobacco responsible for reducing preeclampsia risk is critical to weighing the benefits against the potential toxic effects of any tobacco- or nicotine-based therapeutic or preventive interventions. For example, although not yet proven, it has been hypothesized that nicotine reduces preeclampsia risk. However, administering nicotine to pregnant women is not without risk as nicotine is a neuroteratogen that has been associated with numerous adverse effects on fetal brain development (135). Therefore, it remains unknown whether understanding the mechanisms underlying the protective effects of tobacco against preeclampsia will lead to safe treatment options.

It would also be useful to understand where smoking exerts its effects in the cascade of events leading

to clinically apparent preeclampsia. Does tobacco exposure affect events in early pregnancy, such as on placentation, or does it have systemic effects far downstream from the inciting events? Research that could help answer this question includes additional studies of preeclampsia risk in quitters with biochemical validation of quit status, additional epidemiological studies of preeclampsia risk in smokeless tobacco users, and further study of the effects of smoking and nicotine exposure on placental development and function. Further investigation into those pathways which offer biologically plausible explanations for reducing preeclampsia risk, such as effects of smoking on angiogenic factor balance, and the immune function, is warranted.

In conclusion, preeclampsia risk is reduced in smokers by as much as 50 percent. Although a clear biological mechanism has not yet been identified, based on current epidemiologic literature, the relationship is likely to be causal. Furthermore, plausible mechanisms for this association have been described. Current research regarding the pathophysiology of preeclampsia is promising, and new intervention strategies are currently under investigation. Understanding the mechanism through which smoking reduces preeclampsia risk has the potential to help us to better understand the pathogenesis of this disorder, and eventually to develop effective prevention strategies for preeclampsia.

6. ACKNOWLEDGMENT

Dr Lucinda England and Dr Jun Zhang contributed equally to this manuscript. The authors gratefully acknowledge the helpful contributions of Rebecca Buus, PhD and Terry Njoroge, MPH of the Division of Reproductive Health, Division of Reproductive Health, Centers for Disease Control and Prevention, Department of Health and Human Services, Atlanta, GA. This research was supported in part by the Intramural Research Program of the NICHD, NIH.

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Key Words: Pregnancy, Preeclampsia, Smoking, Review

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