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Teratogen Update: Smoking and Reproductive Outcomes

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The potential effects of cigarette smoke exposure on reproductive outcomes are a major scientific and public health concern, as evidenced by the myriad of published studies on outcomes ranging from germ cell morphology to morbidity among subsequent generations of offspring. Although the prevalence of maternal smoking has decreased over the past two decades, ~15% of women smoke throughout pregnancy (Kendrick and Merritt, '96). Given that cigarette smoke contains hundreds of toxic components, it follows that maternal smoking may have adverse effects on certain reproductive outcomes. For the most part, specific components of cigarette smoke have not been studied in humans, but pieces of evidence point toward certain pathways. Some examples include: nicotine is known to be vasoactive and is thought to reduce placental and fetal circulation (Lehtovirta and Forss, '78; Goodman, '90; Mochizuki et al., '94; Philipp et al., '94); cotinine, a major metabolite of nicotine, has been measured in follicular fluid (Bureau et al., '82; Weiss and Eckert, '89); cyanide is a known toxin and has been studied as a marker for smoking because thiocyanate correlates well with smoking exposure (Sophian, '68; Andrews and McGarry, '72; Bottoms et al., '82); carbon monoxide is known to deplete both maternal and fetal oxygen supplies (Bartlett, '68; Meyer, '78; Bureau et al., '84); excess cadmium has been observed in the ovaries, follicular fluid, and placentas of smokers (Van der Velde et al., '83; Kuhnert et al., '88; Zenzes et al., '93); lead is a known neurotoxin (Doull et al., '80); and some polycyclic aromatic hydrocarbons are mutagenic (USDHHS, '82). The more general exposure—cigarette smoking—is the focus of this review.

Because of the abundance of published papers on smoking, the outcomes presented here were selected on the basis of public health relevance and the availability of published data from epidemiologic studies in humans. For each reproductive outcome covered, important epidemiologic issues are described and the findings are summarized in terms of an estimated relative effect of smoking (i.e., relative risk) (Rothman, '86). For those outcomes that have been linked to smoking consistently across studies, the proportion of the outcome attributed to the exposure (i.e., attributable proportion) is estimated (Rothman, '86).

SUBFERTILITY

Subfertility is methodologically difficult to study in humans. Typically, cohorts of women are followed and the time to conception (or the interval between cessation of birth control to conception) is measured. Because these studies usually focus on women who are trying to become pregnant, there is potential for selection bias or confounding by factors associated with planning a pregnancy, smoking, and fertility. Studies show that time to conception is increased by ~30% for smokers (Baird and Wilcox, '85; Bolumar et al., '96). Smokers have an approximately two- to threefold increased risk of not conceiving within 1 year of trying (Baird and Wilcox, '85; Bolumar et al., '96). More detailed studies have been conducted on women receiving treatment for infertility, showing impaired ovarian function and more tubal infertility among smokers; however, pregnancy rates are not reduced among women who quit smoking (Van Voorhis et al., '96). Paternal smoking has been linked to inferior sperm quality in some studies (Vine et al., '94, '96), but time to conception was not increased among male smokers when their partners' smoking was taken into account (Baird and Wilcox, '85).

SPONTANEOUS ABORTION

Maternal smoking appears only slightly to increase the risk of spontaneous abortion, if at all (Risch et al., '88; Armstrong et al., '92; Kline et al., '95). Observed relative risks fall below 1.5 and approach the null when other factors, such as previous history of spontaneous abortion and alcohol consumption, are taken into account. Although there are inconsistencies across studies, factors that modify the smoking and spontaneous abortion relationship include alcohol consumption (Harlap and Shiono, '80; Kline et al., '95; Windham et al., '92), reproductive history (Windham et al., '92), gestational timing of the spontaneous abortion (Windham et al., '92), fetal karyotype (Kline et al., '95), and indicators of socioeconomic status (Kline et al., '95; Windham et al., '92).

ABNORMAL PLACENTATION

Abnormal placentation has been linked to maternal smoking in most studies. The effect is small; ~50% (i.e., relative risk of ~1.5) increases in the risks of placenta

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previa (Naeye, '80; Kramer et al., '91; Zhang and Fried, '92; Ananth et al., '96) and abruption (Naeye, '80; Williams et al., '91; Raymond and Mills, '93; Ananth et al., '96). In addition, the risk of placental abruption and previa increases with the increasing number of cigarettes smoked daily (Naeye, '80; Williams et al., '91; Zhang and Fried, 1992; Raymond and Mills, '93) and with increasing duration of smoking (Naeye, '80). Abruption placentae can lead to perinatal death, but among women with abruption, the perinatal death rate is ~2–3 times higher for smokers than for nonsmokers (Naeye, '80; Raymond and Mills, '93).

The mechanisms of abnormal placentation are not completely understood, but the ready availability of placentas following delivery has permitted study of several measures of placental structure and function. A number of placental abnormalities have been linked to maternal smoking, including increased syncytial knots, cytotrophoblastic cells, and false knots in the umbilical cord (Denir et al., '94), syncytiotrophoblastic necrosis (Denir et al., '94), increased basement membranes (Van Der Velde et al., '83; Van der Veen and Fox, '92; Denir et al., '94); and microvilli (Van Der Velde, '83; Van der Veen and Fox, '92; Denir et al., '94). In addition, studies of pregnant women have revealed uterine vaso-constriction and decreased placental perfusion among smokers, presumably due to nicotine (Lehtovirta and Forss, '78; Philipp et al., '84). It is assumed the placental vascular effects of smoking impair fetal growth (Philipp et al., '84), but whether these effects also lead to placenta previa and/or abruption is not known (Philipp et al., '84).

The attributable risk, or the proportion of all abnormal placentation cases that can be attributed to maternal smoking, is ~10%. In other words, it is estimated that ~10% of abnormal placentation cases could be prevented if all women stopped smoking in pregnancy.

INTRAUTERINE GROWTH RETARDATION

Probably the most known and well-documented reproductive outcome related to smoking is intrauterine growth retardation (IUGR). Smoking during pregnancy reduces birthweight an average of 200 g, and there is a dose-response effect where birthweight decreases as numbers of cigarettes smoked increases (Frazer et al., '61; Butler et al., '72; D'Souza et al., '81). It is important to note that there are negligible differences in birthweight among offspring of women who quit smoking early in pregnancy compared to women who never smoked (Butler et al., '72; Rush and Cassano, '83; Cliver et al., '95). Expressing the IUGR-smoking relation in terms of risk of low birthweight (defined as <2,500 g) has more meaning to both clinicians and women than a deficit in grams. The risk of a low birthweight baby is doubled among maternal smokers and the risk increases with the increasing number of cigarettes smoked (Frazer et al., '61; Meyer, '78; Cnattingius et al., '93). Also, low birthweight risk is greater among nulliparous and older smokers (Meyer et al., '76; Cnattingius, et al., '93). Again, there is no increase in risk of low birthweight for women who stop smoking early in pregnancy (Frazer et al., '61; Rush and Cassano, '83). It is estimated that low birthweight could be prevented in at least 20% of all births if all women stopped smoking in pregnancy (Alameda County, '90).

Birthweight adjusted for gestational age is a superior measure of IUGR because gestational age is strongly predictive of birthweight. Small for gestational age (SGA) is most often defined as a birthweight that is less than the fifth percentile for a given gestational age. Smoking increases the SGA risk 2.5-fold and risk increases with numbers of cigarettes smoked (Cnattingius et al., '93; Morrison et al., '93). Again, this risk is increased among nulliparous and older women (Cnattingius et al., '93). Approximately 30% of SGA infants could be prevented if smoking in pregnancy was eliminated (Cnattingius et al., '93; Morrison et al., '93).

PRETERM DELIVERY

Smoking affects birthweight independent of gestational age, but does smoking independently affect gestational age? Excluding subjects with placental problems (because smoking-attributed placental abruption and previa are also related to gestational age), risk of delivery at <37 weeks is increased an estimated 30% (RR 1.3) among women who smoke in pregnancy (Shiono, '86b). This risk increases with the increasing number of cigarettes, with an approximately twofold increase in risk of premature rupture of membranes at <33 weeks for women who smoked 20 cigarettes per day (Shiono, '86b). Approximately 5% of all premature births (<37 weeks) are attributed to maternal smoking.

The mechanisms of smoking on preterm delivery beyond that of abnormal placentation are not understood. Infection and altered nutrition have been linked to premature labor (Goldenberg et al., '95; Harlow et al., '96), but whether smoking affects prematurity through either of those pathways is not clear.

PERINATAL MORTALITY

Smoking is also related to increased risk of perinatal mortality (Kleinman et al., '88; English and Eskenazi, '92; Raymond and Mills, '93), which includes fetal deaths after 20 weeks gestation and infant deaths within 28 days of life. The approximate 30% increase in risk of perinatal mortality (RR 1.3) is attributed to excesses in low birthweight, prematurity, and abnormal placentation (English and Eskenazi, '92).

It is interesting that low birthweight infants of smokers have lower perinatal mortality rates than do infants of nonsmokers, whereas the reverse is true for normal or heavier birthweight infants. This crossover pattern in risk is due to the fact that the birthweight distribution of infants born to smokers is skewed toward lower weights compared to nonsmokers. The same pattern is observed in other oxygen-deprived populations, such as those born at high altitudes (Wil-

cox, '93). Standardizing birthweight distributions by measuring the distance from the mean for each birthweight within smoking and nonsmoking populations results in a higher perinatal mortality risk for infants of smokers than nonsmokers at all standardized birthweights, whether they are below, at, or above the means (English and Eskenazi, '92; Wilcox, '93). Interestingly, when this adjustment is made for the different birthweight distribution of infants born at high altitudes, perinatal mortality risk is the same across all standardized birthweights (Wilcox, '93). The attributable risk of perinatal mortality from smoking is estimated to be ~10%; the majority of this risk, but not all of it, is among infants with IUGR (Kleinman et al., '88).

CHILDHOOD MORBIDITY AND MORTALITY

Studies of maternal smoking in relation to infant and childhood outcomes that may develop after delivery optimally should separate fetal effects (exposure in utero) from passive effects (exposure postpartum). However, the identification of such independent effects can be difficult because one would need to follow the relatively small group of infants whose mothers smoked during, but not after, pregnancy (an estimated 1.2% of U.S. children in 1988 were exposed to cigarette smoking in utero, but not after birth) (Overpeck and Moss, '91). Due to the rarity of this pattern of exposure, there is a dearth of information on independent effects of smoking exposure in utero on childhood outcomes.

Body mass among infants of smokers has been studied to identify what tissues are affected. Smoking is related to indices of lean body mass, such as weight, length, limb lengths, and head and chest circumferences, but not to indices of fat such as skinfold thickness (D'Souza et al., '81; Harrison et al., '83; Cliver et al., '95). This raises the question of whether smoking-related IUGR in the otherwise healthy neonate is associated with subsequent adverse outcomes. Smoking in pregnancy (and presumably during the postpartum period) does not appear to have long-term effects on growth, after maternal alcohol consumption, nutrition, and other factors were taken into account (Barr et al., '84; Day et al., '94).

Sudden Infant Death Syndrome (SIDS) has been linked to passive exposure to cigarette smoke, with approximately two- to fourfold increased risks (Haglund and Cnattinguis, '90; Schoendorf and Kiely, '92; Scragg et al., '93; Klonoff-Cohen et al., '95). The risk was higher among infants who were exposed both in utero and during infancy than those exposed only after infancy in one study (Schoendorf and Kiely, '92).

It has been clearly documented in several studies that passive exposure to cigarette smoke increases the risk of respiratory illnesses, including upper and lower respiratory infections and asthma, in infants and children (AHA, '94). However, these studies were not able to estimate whether there is an independent effect of fetal exposure in the absence of postpartum exposure. One recent study observed the respiratory function of newborns (measured in hospital before the opportunity for passive exposure) was reduced among offspring of smokers (Stick et al., '96), suggesting a fetal effect.

The relationship between maternal smoking in pregnancy and cognitive development has been studied, but results are difficult to interpret. Some studies suggest decreased cognitive functioning (such as low IQ, learning disorders, hyperactivity, poor motor coordination, and poor language development) is related to smoking (Naeye and Peters, '84; Roelveld et al., '92; Drews et al., '96). Whether such associations exist is unclear, because there are a myriad of factors that are related to these outcomes, which are difficult to measure and control for in free-living populations.

CONGENITAL MALFORMATIONS

Since many structural malformations develop early in gestation, it is important to determine exposure status for the first months of pregnancy. In many studies information on smoking was obtained from medical records or birth certificates, which lack specificity on timing of exposure. For example, women who quit smoking in the third month are likely recorded as nonsmokers, but exposure occurred during much of organogenesis. Detailed questions on timing of smoking are necessary to determine accurately the exposure status, particularly given that approximately one-third of smokers quit during pregnancy (Kendrick and Merritt, '96).

Studies of smoking in relation to birth defects vary according to design (prospective vs. retrospective), accuracy of exposure information, which anomalies were included in the case group, completeness of ascertainment, accuracy of diagnostic information, size (statistical power), and in retrospective studies, the type of control group (e.g., malformed, nonmalformed); these differences may account for some of the inconsistent findings.

For studies of all birth defects grouped together as one outcome, all (Evans et al., '79; Christianson, '80; Shiono et al., '86; Malloy et al., '89; Seidman et al., '90; Van den Eeden et al., '90) but two (Himmelberger et al., '78; Kelsey et al., '78) reported no association with maternal smoking, but inaccurate measurement of smoking and/or malformation status would bias relative risks to underestimate any true association. Of the four studies that obtained smoking information directly from the mother during or shortly after pregnancy (Kelsey et al., '78; Christianson, '80; Shiono et al., '86a; Seidman et al., '90), three were null (Christianson, '80; Shiono et al., '86a; Seidman et al., '90), suggesting that maternal cigarette smoking does not have a broad teratogenic effect on all malformations as one group.

There are scattered reports in the literature about smoking and specific malformations, showing increased risks, decreased risks, and no association. The following review was restricted to those defects on which two or more studies had been conducted and in which there were at least five smoking-exposed cases.

Chromosomal anomalies. Smoking has not been associated with risk of trisomies among spontaneous abortuses, fetuses karyotyped during the second trimester, or liveborn infants, after adjusting for maternal age (Kline et al., '93, '95).

Central nervous system (CNS) defects. Neural tube defects (anencephaly, spina bifida, and encephalocele) constitute one of the most common structural malformations and have been studied in relation to a variety of risk factors. Overall, data suggest that maternal smoking is not related to an increased risk for neural tube defects (Shiono et al., '86a; Malloy et al., '89; Van den Eeden et al., '90; Shaw et al., '96a). Other CNS defects have been positively related to smoking in some studies (Shiono et al., '86a; Van den Eeden et al., '90), but not others (Evans et al., '70; Seidman et al., '90). As a group, nonneural tube CNS defects include a variety of defects, possibly with entirely different etiologies. Specific defects such as microcephaly and reduction deformities of the brain need further study.

Cardiac defects. Smoking has not been linked to cardiac malformations overall (Evans et al., '70; Christianson, '80; Malloy et al., '89; Seidman et al., '90; Van den Eeden et al., '90; Tikkanen and Heinonen, '91; Pradat, '92), but this is also an etiologically heterogeneous group. Ventricular septal defects (Kelsey et al., '78; Shiono et al., '86a; Malloy et al., '89; Tikkanen and Heinonen, '91), conotruncal defects (Kelsey et al., '78; Tikkanen and Heinonen, '91; Wasserman et al., '96) transposition of the great arteries (Wasserman et al., '96), tetralogy of Fallot (Wasserman et al., '96), and atrial septal defects (Malloy et al., '89; Tikkanen and Heinonen, '91) have not been related to maternal smoking. Risk of valvular defects was doubled for smokers in one study (Kelsey et al., '78), but no association was observed in two others (Shiono et al., '86a; Malloy et al., '89) each with only one or two exposed cases.

Gastroschisis. Primarily noted for its occurrence in the offspring of very young women, gastroschisis is a rare abdominal wall defect (Torfs et al., '90). In theory, a positive relation between maternal smoking and risk is biologically plausible, because gastroschisis is thought to arise from a vascular interruption (Hoyme et al., '83), and smoking exposure is known to have vasoactive effects (Lehtovirta and Forss, '78; Philipp et al., '84). Smaller studies have shown maternal smoking doubled gastroschisis risk (Goldbaum et al., '90; Haddow et al., '93), but the largest studies estimated relative risks between 1.2 and 1.5 with no dose-effect (Werler et al., '92; Torfs et al., '94). Also, each study that adjusted for maternal age (Goldbaum et al., '90; Werler et al., '92; Haddow et al., '93; Torfs et al., '94), or indicators of socioeconomic status (Goldbaum et al., '90; Werler et al., '92; Torfs et al., '94) showed confounding that reduced risk estimates for smoking.

Limb reduction defects. Another etiologically heterogeneous group is limb reduction defects (LRDs). Most studies have considered all LRDs as one group. Reported relative risk estimates range from 0.9 to approximately twofold (Aro, '83; Shiono et al., '86a; Van den Eeden et al., '90; Wasserman et al., '96; Kallen, '97a). For the subgroup of longitudinal type LRDs, risk estimates were below 1.0 or close to the null for any smoking in early pregnancy (Czeizel et al., '94; Wasserman et al., '96; Kallen, '97a). Because transverse LRDs, like gastroschisis, are thought to result from a vascular interruption (Hoyme et al., '82), these defects are more plausibly associated with smoking. However, findings are inconsistent; an elevated risk was observed in one study (Czeizel et al., '94), but not in two others (Wasserman et al., '96; Kallen, '97a).

Oral clefts. Of all structural defects, oral clefts have been the most widely studied in relation to smoking (Saxen, '74; Kelsey et al., '78; Ericson et al., '79; Evans et al., '79; Hemminki et al., '83; Shiono et al., '86a; Khoury et al., '87, '89; Malloy et al., '89; Seidman et al., '90; Van den Eeden et al., '90; Werler et al., '90; Hwang et al., '95; Kallen, '96b; Laumon et al., '96; Shaw et al., '96b). Some examined oral clefts as a single outcome and relative risks ranged from 0.8 to 2.3 (Saxen, '74; Kelsey et al., '78; Evans et al., '79; Hemminki et al., '83; Malloy et al., '89; Seidman et al., '90). Other studies separated oral clefts into cleft lip with or without cleft palate (CLCP) and cleft palate (CP) subgroups.

Of the 10 studies of CLCP (Ericson et al., '79; Shiono et al., '86a; Khoury et al., '87, '89; Van den Eeden et al., '90; Werler et al., '90; Hwang et al., '95; Laumon et al., '96; Shaw et al., '96b; Kallen, '97b), five showed maternal smoking increased risk; estimates ranged from 1.5 to 2.7 (Ericson et al., '79; Khoury et al., '87, '89; Van den Eeden et al., '90; Shaw et al., '96b). The four positive studies with information on level of smoking (Khoury et al., '87, '89; Ericson et al., '79; Shaw et al., '96b) all showed CLCP risk increased with the increasing number of cigarettes smoked. When cases were classified according to the presence or absence of an associated defect (Khoury et al., '87, '89; Van den Eeden et al., '90; Werler et al., '90; Laumon et al., '96; Shaw et al., '96b; Kallen, '97b), elevated risks were observed for isolated CLCP in some studies (Khoury et al., '87, '89; Van den Eeden et al., '90; Shaw et al., '96b), but not in others (Werler et al., '90; Laumon et al., '96; Kallen, '97b).

For CP, increased risks ranging from 1.4 to 2.8 were observed in seven studies (Ericson et al., '79; Khoury et al., '87, '89; Van den Eeden et al., '90; Laumon et al., '96; Shaw et al., '96b; Kallen, '97b), whereas no association was observed in three (Shiono et al., '86a; Werler et al., '90; Hwang et al., '95). Risks increased with the increasing number of cigarettes in some investigations (Khoury et al., '87; Shaw et al., '96b; Kallen, '97b), but not in others (Ericson et al., '79; Khoury et al., '89; Werler et al., '90). When CP cases were divided according to the presence or absence of associated malformations, elevated risks were found only for those with associated defects in some studies (Khoury et al., '87; Van den Eeden et al., '90) and only for isolated cases in others (Khoury et al., '89; Shaw et al., '96b; Kallen, '97b).

TABLE 1. Maternal smoking, transforming growth factor-alpha (TGF-α) gene variation, and oral cleft risk

	Hwang et al. ('95) Odds ratio (95% CI)[1]	Shaw et al. ('96b) Odds ratio (95% CI)[1]
CLCP[2]		
Smoking	0.8 (0.5–1.3)[3]	1.7 (1.1–2.4)
Uncommon TGF-α allele	1.2 (0.7–2.1)	1.0 (0.6–1.5)
Smoking and uncommon TGF-α allele[@]	1.9 (0.6–6.5)[3]	2.1 (1.0–4.5)
CP[4]		
Smoking	0.8 (0.4–1.3)[3]	1.6 (1.1–2.4)
Uncommon TGF-α allele	2.2 (1.2–4.0)	1.6 (0.9–2.8)
Smoking and uncommon TGF-α allele[5]	7.0 (1.8–28)[3]	4.0 (1.7–9.2)

[1]CI = confidence interval.
[2]Cleft lip with or without cleft palate.
[3]Adjusted for maternal age and parity.
[4]Cleft palate.
[5]Reference category is nonsmokers without the uncommon TGF-α allele.

The lack of consistency across studies on smoking and types of oral clefts makes it difficult to draw conclusions. A possible explanation may be underlying interactions between genetic factors and maternal smoking. One such genetic marker is the transforming growth factor-alpha *Taq1* (TGF-α) polymorphism, which has been observed in association with CLCP and CP in some, but not all reports (Hwang et al., '95; Shaw et al., '96b). Table 1 shows that two separate studies have observed similar interactions between smoking, the uncommon TGF-α allele, and oral cleft risk, despite differences in underlying associations between maternal smoking and the risks of CLCP and CP, on the one hand, and between the TGF-α polymorphism and risks of CLCP and CP, on the other hand. For CLCP, an approximate doubling in risk was estimated for maternal smokers whose infants were either heterozygous or homozygous for the uncommon TGF-α allele (Hwang et al., '95; Shaw et al., '96b). For CP, the corresponding risk estimates were increased sevenfold in one study (Hwang et al., '95) and fourfold in the other study (Shaw et al., '96b). The results of the Hwang et al. ('95) and Shaw et al. ('96b) studies provide evidence in support of the long-held view that oral clefts have a multifactorial etiology (Fraser, '70).

In summary, maternal cigarette smoking in pregnancy has conclusively been linked to many adverse reproductive outcomes, including IUGR, abnormal placentation, and perinatal mortality. Recent evidence suggests that maternal smoking in the presence of the uncommon TGF-α allele increases oral cleft risk. Although evidence is less strong for many other reproductive outcomes, there are suggestions that smoking carries increased risks of subfertility, SIDS, and childhood illnesses. Further studies are needed to evaluate maternal smoking in relation to specific malformations, particularly those thought to have a vascular etiology.

The overall prevalence of smoking in pregnancy has decreased over the past few decades (Kleinman and Kopstein, '87; Kendrick and Merritt, '96), due in part to public education about smoking-related adverse reproductive outcomes. However, increases in smoking prevalence have been reported for young women and women in poverty (MMWR, 1994), and it remains one of the most common hazardous behaviors among pregnant women (Kendrick and Merritt, '96). Continued public health efforts aimed at reducing initiation of cigarette smoking and at increasing cessation of cigarette smoking clearly are warranted.

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