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Effects of exposure to environmental tobacco smoke on reproductive health

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The scientific evidence on the effects of preconceptional and prenatal exposure to environmental tobacco smoke on reproductive health is reviewed in this article. The evidence is the most convincing for the adverse effects of environmental tobacco smoke on birthweight. In meta-analyses, exposure to environmental tobacco smoke has been estimated to reduce mean birthweight by about 25–40 grams. The majority of the studies on low birthweight also show a moderately or slightly increased risk among infants of exposed women. There is also some support for an association between high exposure to environmental tobacco smoke and preterm birth. The evidence on the effects of environmental tobacco smoke on spontaneous abortion and birth defects is weak and inconsistent. Very little is known about the impact of exposure on fertility, menstrual function, reproductive health of men, and childhood cancer. Further studies, paying attention to study design and careful exposure assessment, are therefore needed on these associations.

Key terms birth defects, fertility, fetal growth, menstrual function, preterm birth, review, spontaneous abortion.

The harmful developmental and reproductive effects of active smoking are well known. Smoking reduces birthweight and fertility, and it increases the risk of abnormal placentation, spontaneous abortion, preterm delivery, and perinatal mortality (1). Evidence of these effects has raised concern about the reproductive effects of environmental tobacco smoke. Environmental tobacco smoke is a prevalent exposure at workplaces, as well as at home and during leisure time. Many of the components of the mainstream smoke inhaled by smokers are present also in environmental tobacco smoke, although the pattern and amounts of the constituents differ.

Our aim was to assess scientific evidence on the effects of exposure to environmental tobacco smoke on reproductive health. We have mainly addressed epidemiologic studies on the effects of preconceptional and prenatal exposure. The outcomes of interest include fertility, spontaneous abortion, preterm delivery, fetal growth, birth defects, and childhood cancer. Studies on the association of exposure to environmental tobacco smoke with menstrual function and age at menopause, as well as biological mechanisms of the reproductive toxicity of environmental tobacco smoke, have been reviewed. In some studies maternal prenatal exposure to environmental tobacco smoke has been related also to the sudden infant death syndrome and to neurodevelopmental and behavioral effects on children (2, 3), but these outcomes are beyond the scope of our paper.

Biological mechanisms

There is no direct evidence for the mechanisms of reproductive toxicity for environmental tobacco smoke. In general, when reproductive toxicity is assessed, human and animal data on the harmful effects are evaluated. Carcinogenic and mutagenic constituents of tobacco smoke are likely to cause changes in the chromosomes or in the DNA (deoxyribonucleic acid) of germ cells or

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in the cells of the developing offspring. Childhood cancer is also an important end point to suspect.

The chemical exposure from passive smoking is qualitatively similar but quantitatively different from that of the smoker. The undiluted sidestream smoke contains many harmful chemicals in greater amounts than the inhaled cigarette smoke (eg, three times more tar, seven times more nicotine, five times more benzene, and 100 times more carcinogenic nitrosoamines) (4, 5).

The level of exposure to the harmful chemicals of environmental tobacco smoke can be estimated from a comparison of the urine cotinine (U-cotinine) concentrations of smokers and passive smokers (6). Nonsmoking women who were not exposed to environmental tobacco smoke had a U-cotinine concentration of 3 ng/mg creatinine. Women exposed at work had a U-cotinine concentration of 5 ng/mg creatinine, whereas women exposed at home, or both at home and at work, had a U-cotinine concentration of about 10 ng/mg creatinine (7). Workers in dining restaurants had U-cotinine concentrations of up to 12 ng/mg creatinine, for women in pubs the corresponding value was 65 ng/mg creatinine, and in night clubs and dance restaurants it ranged up to 26 ng/mg creatinine (8). The highest concentration is about 3% of the mean U-cotinine concentration among currently smoking women. Among pregnant women exposed to environmental tobacco smoke, higher cotinine levels have been measured in fetal fluids (celomic, amniotic, and fetal serum) than in the mother's serum (9).

The concentrations of individual chemicals in sidestream smoke seem to stay very low when compared with the occupational exposure limits. The produced concentration of carbon monoxide is about 100 mg/cigarette, but when diluted in the air volume of a room, the concentration is not high enough to cause toxic effects on a person. Tobacco smoke and sidestream smoke contain over 100 toxic compounds, and more than 40 of them are classified as human or animal carcinogens (4, 10). Sidestream smoke contains chemicals that are known or suspected reproductive toxicants (carbon monoxide, benzene, ethylbenzene, formaldehyde, hydrazine, limonene, methylamine, methylene chloride, nicotine, pyridine, toluene), but the concentrations in the air are low. Sidestream smoke also contains radioactive polonium-210, producing 0.1 Bq/g tobacco.

Smoking disturbs the morphology and the function of the placenta (11, 12). A substantial decrease in the mitotic potential of cytotrophoblast has been found in smoking women, and the effect was present also in vitro, tested by nicotine (13). This occurrence may point to a mechanism for abnormal placental development and explain the fetal growth restriction effect of environmental tobacco smoke. A marker of fetal hypoxia, the absolute number of circulating red blood cells, was increased among children of mothers exposed to environmental tobacco smoke (14). The mechanism behind this finding may be relative fetal hypoxia, nicotine-induced placental vasoconstriction and placental vascular disease.

A mutagenic mechanism may be important in the reproductive toxicity of benzene. The metabolites of benzene may be the active agents in its genotoxic effects (15). For male mice, exposure was associated with cytotoxic effects on germ cell histogenesis (16).

Inhalation exposure to an airborne concentration of 40 ppm of formaldehyde (close to a lethal dose) caused some degenerative changes in the uterus and ovaries in mice (17) and therefore suggested that formaldehyde may be a direct gonadotoxin. Formaldehyde decreased the sperm count, sperm mobility, and sperm viability of male rats given a 10 mg/kg dose daily for 30 days (18). The levels of formaldehyde in the fetuses were comparable to those found in pregnant mice. This finding indicated that formaldehyde crosses the placenta. Mouse fetuses eliminated formaldehyde more slowly than did the mothers (19).

Hydrazine was mutagenic when tested in microbial assays (20), in mouse lymphoma cell assays (21), and in pregnant mice (22). Hydrazine inhibited the development of intestinal enzymes in hamsters at a dose of 260 mg/kg (23).

A reduction in uterine blood flow has been demonstrated in rats, sheep, rhesus monkeys, and humans exposed to nicotine (24–27). This may be the mechanism by which nicotine impairs fetal growth. More recent data suggest that maternal nicotine exposure may also alter placental circulation by means of direct toxic effects on the fetal cardiovascular system (28).

Polycyclic aromatic hydrocarbons (PAH) form a class of compounds, and many of them are indirect toxins (ie, they demand metabolic activation to yield reactive intermediates). Benzo(a)pyrene (BP), one of the procarcinogenic PAH compounds, is metabolized in the ovary and in the endometrium, and the biotransformation products are carcinogenic (29, 30). PAH compounds can destroy oocytes by causing necrosis (31). They can also destroy premordial follicles, induce chromosome aberrations in oocyte meiosis, and cause ovarian tumors. BP is a direct ovarian toxicant in mice (32, 33). It decreases uterine weight and cyclic nucleotide levels (34) and inhibits the formation of corpora lutea and thus also the production of progesterone. BP is known to cross the placenta in humans and animals, and there is evidence of adduct formation in animal fetal tissues (35–37). DNA adducts of PAH derivatives were present also in term placentas of smokers (38). Cigarette smoke exposure increases the PAH metabolism potential in placental tissues about twofold (39).

Exposure to environmental tobacco smoke significantly increased the concentration of polychlorinated

biphenyls (PCB) and hexachlorobenzene in newborns (40). Both chemicals are carcinogenic and teratogenic and, in animal tests, have demonstrated tumor-promoting properties together with transplacental carcinogens (41). A derivative of a transplacental carcinogen, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, is present in the newborns of smoking mothers (42).

Although numerous harmful effects have been reported for the chemicals in sidestream smoke, their concentrations in situations involving exposure to environmental smoke are much lower than experimental doses. It has been questioned whether the dose of reproductive toxicants from environmental tobacco smoke can be high enough to cause adverse reproductive effects. On the other hand, the possibility of the harmful effects of the combination of a great number of chemicals, even at low concentrations, cannot be overlooked.

Exposure of the fetus has been assessed by estimating cotinine levels in fetal fluids, cord blood, and newborn urine and hair. The cotinine levels in cord serum of women exposed to environmental tobacco smoke have been low when compared with the levels of smokers. The geometric mean concentration of cotinine in the cord serum of those exposed to environmental tobacco smoke was 2.76 ng/ml, which is about 5% of the concentration of smokers (59.33 ng/ml) (43). However, in hair, amniotic fluid, and fetal meconium, the levels of metabolite concentrations in passive smokers have been closer to the levels of active smokers. The hair concentration of cotinine in newborns was 0.26 ng/mg for nonsmokers, 0.62 ng/mg for passive smokers, and 2.81 ng/mg for active smokers (44). Cotinine accumulates in the fetus already from the seventh week of gestation. In the first half of pregnancy the cotinine level in the amniotic fluid of passive smokers reached 44% of the level in active smokers (9). At term, the cotinine level in amniotic fluid was 2.5 times higher in passive smokers and 8 times higher in active smokers than in nonsmokers (45). Meconium analyses indicated that the nicotine metabolite concentration in infants of passive smokers (31.6 ng/ml) did not significantly differ from that in infants of light active smokers (34.7 ng/ml) (46). These latter observations suggest that fetal exposure may be substantial as a result of maternal exposure to environmental tobacco smoke.

The chemical composition of mainstream smoke is quantitatively different from the composition of sidestream smoke. Thus the effects of exposure to environmental tobacco smoke on reproductive health cannot necessarily be compared with the effects of active smoking on reproduction. Differences in metabolism between active and passive smokers have also been suggested as an explanation for the adverse effects of low exposure levels in passive smokers. Remmer (47) has suggested that cigarette smoke induces drug-metabolizing enzymes among active smokers, but passively inhaled tobacco smoke is ineffective as an inducer. The induction of placental enzymes probably protects the fetus against the toxic agents among active smokers, whereas the small amounts of smoke inhaled by passive smokers are supposedly not detoxified in the placenta.

Menstrual function

Active smoking has been associated with a variety of menstrual disorders, such as oligomenorrhea, amenorrhea, prolonged bleeding, heavy bleeding, and dysmenorrhea. In a prospective study, a decreased duration of bleeding, an increased daily amount of bleeding, and an increased duration of dysmenorrhea were observed among current smokers (48). Active smoking was associated with these outcomes in a dose-response manner. Women with exposure to environmental tobacco smoke reported more days with painful menses (2.6 days) than unexposed women (2.0 days). The difference between the unexposed and passive smokers was not tested, however.

Another prospective study focused on the effects of passive smoking and dysmenorrhea (49). Women completed the baseline questionnaire interview upon enrollment and were prospectively followed by the use of a daily diary. Dysmenorrhea was defined as diary recording of abdominal pain or low-back pain for at least 2 days during a menstrual period. Exposure to environmental tobacco smoke was defined as the mean number of cigarettes smoked per day at home by household members over an entire menstrual cycle. The incidence of dysmenorrhea was 9.7% and 13.3% among unexposed and exposed cycles, respectively. Moreover, among the cycles exposed to environmental tobacco smoke, a positive dose-response relation was observed between the numbers of cigarettes smoked and the relative risk of dysmenorrhea. The adjusted odds ratios (OR) for dysmenorrhea associated with tertiles of environmental tobacco smoke exposure (<0.8, 0.8–2.5, and >2.5 cigarettes/day) were 1.1 [95% confidence interval (95% CI) 0.5–2.6], 2.5 (95% CI 0.9–6.7), and 3.1 (95% CI 1.2–8.3), respectively, when compared with no exposure.

Age at menopause

Only few studies have focused on the effects of environmental tobacco smoke on lowered age at menopause (50). The findings of two studies (51, 52) suggest an association between environmental tobacco smoke and

early menopause. In one study (51), the mean age at menopause was reduced by two years among nonsmoking women whose spouses smoked, in comparison with nonsmokers whose spouses did not smoke. Passive smokers had a twofold risk of early menopause (adjusted OR 2.1, 95% CI 1.0–4.5). Both these measures were similar to the associations observed among active smokers. In another study (52), passive smokers had their menopause earlier than nonsmokers (–0.7 years, 95% CI –1.9 – 0.5). In contrast, passive smoke exposure was not related to lowered age at menopause in a third study (53). The mean age at menopause was 0.6 years higher (95% CI -0.2–1.4) among women exposed to passive smoking than among never smokers without exposure to environmental tobacco smoke. To conclude, there is a paucity of data on the association between environmental tobacco smoke and lowered age at menopause, and the findings are conflicting.

Fertility

Active female smoking has been associated with reduced fecundability in several studies. [For example, see Jensen et al (54) and references therein.] Only few studies have aimed at assessing the impact of environmental tobacco smoke on fertility, and no firm conclusions can be drawn. The focus of interest has been exposure in utero, childhood exposure or paternal smoking and, to a less extent, mothers' exposure to environmental tobacco smoke.

Exposure to environmental tobacco smoke in utero has been associated with reduced fertility in two prospective studies on time to pregnancy with retrospectively collected data on exposure to environmental tobacco smoke (54, 55). The reference group was composed of nonsmoking adults not exposed to environmental tobacco smoke in utero. In the earlier study (55) women with prenatal exposure to maternal smoking had a 50% reduced fecundability ratio (FR) (FR 0.5, 95% CI 0.4–0.8). Similar findings were described in the Danish study (54). The fecundability odds ratio (FOR) for nonsmoking women exposed in utero was 0.70 (95% CI 0.48–1.03). Nonsmoking men exposed in utero also had reduced fecundability (FOR 0.68, 95% CI 0.48–0.97). For a small number of subjects, the information was provided by their mothers. In that subset, the association was present only for the males. No clear association (FR 0.9, 95% CI 0.7–1.1) between exposure to environmental tobacco smoke in utero and subsequent fecundability was found in an earlier retrospective study (56).

In two studies, women exposed to environmental tobacco smoke as children displayed increased fecundability (FR 1.3 to 1.6) as compared with unexposed women (55, 56), whereas in one study (57) the observed FR values of 1.1 to 1.2 (one or both parents smoking) did not indicate any clear association.

A recent retrospective study aimed at discriminating between the effects of active and passive smoking on the fecundability of women (58). Active female smoking was associated with delayed conception. For example, the odds ratio for taking more than 12 months to conceive was increased by 58% among heavy smokers (≥ 20 cigarettes daily). For a woman's passive smoking, all the sources of exposure (smoking of her partner, other household member, or environmental tobacco smoke at work) were combined in the analysis. Passive smoking by the woman was slightly associated with delayed conception, the odds ratios being 1.17 (95% CI 1.02–1.37) and 1.14 (95% CI 0.92–1.42) for taking longer than 6 or 12 months to conceive, respectively. As the authors acknowledged, it was not entirely possible to separate the direct effects of the man's smoking and the effects of passive smoking.

Spontaneous abortion

Maternal cigarette smoking has been associated with spontaneous abortion in some but not all studies on this topic (1, 59). Only three studies examined the effect of passive smoking on spontaneous abortion. Two studies showed a moderate association of spontaneous abortion with exposure to environmental tobacco smoke. In a Swedish prospective study (60) an excess risk of intrauterine death (spontaneous abortion and stillbirth) was observed among working women spending most of their time at work in rooms where other people smoked [relative risk (RR) 1.53, 95% CI 0.98–2.38]. Exposure at home (living with a person who smokes inside the home) was not related to abortion. In a case-referent study, Windham et al (61) also observed an increased risk of spontaneous abortion for exposure of 1 hour or more per day among nonsmokers (OR 1.6, 95% CI 1.2–2.1). In the most recent prospective study (62), no evidence was found for an association of spontaneous abortion with exposure to environmental tobacco smoke at home or at work (OR 1.01, 95% CI 0.80–1.27). However, some effect modification by alcohol and caffeine consumption was seen; the risks were increased among exposed women who also consumed alcohol or caffeine in moderate to high amounts.

A positive association between paternal smoking and risk of spontaneous abortion may reflect a direct male-mediated effect of smoking on the fetus, rather than an effect of environmental tobacco smoke on the mother. Two studies examined the effects of environmental tobacco smoke among nonsmoking women living with

a nonsmoking partner (60, 61). Both noted a slightly elevated risk of spontaneous abortion for the exposed women [OR 1.38, 95% CI 0.81–2.36 (60) and OR 1.5, 95% CI 1.1–2.1 (61)]. A third study (62) showed, however, no association between any exposure to environmental tobacco smoke at work and spontaneous abortion.

The associations noted between passive exposure and spontaneous abortion are of similar magnitude as the associations found between spontaneous abortion and active smoking, although the effect of passive exposure might be expected to be much lower than that of active smoking. The chemical composition of mainstream smoke and sidestream smoke is not identical, however. Many of the constituents present in mainstream and sidestream smoke are the same, but there are important differences in the rates at which they are emitted into the air; some constituents have a higher rate of release into sidestream than mainstream smoke, while for others the reverse is true (50). All in all, the evidence of the effects of environmental tobacco smoke is inconclusive, but a potential relationship between exposure and spontaneous abortion cannot be excluded.

Preterm birth

Maternal active smoking during pregnancy has been associated with preterm delivery (1, 63). Few studies have examined the effects of environmental tobacco smoke on preterm birth (usually defined as delivery before 37 weeks of gestation). Three studies reported no difference in the risk or frequency of preterm birth between exposed and unexposed women (64–66). Three other studies examined the effects of environmental tobacco smoke by the level of exposure. The results indicated an increased risk of preterm birth among highly exposed women. In two studies the risk was related to daily exposure for 7 hours or more [OR 1.86 (95% CI 1.05–3.45) and OR 1.6 (95% CI 0.87–2.9) for preterm birth and OR 2.4 (95% CI 1.0–5.3) for very preterm birth] (67, 68). In the third, most recent study (69), exposure assessment was based on nicotine concentration of maternal hair sampled after the child's delivery. The risk of preterm birth was related to hair nicotine concentration; the odds ratio was 6.1 (95% CI 1.3–28.7) for the high exposure category (≥4.00 μg/g). A positive dose-response relation was also noted between exposure and the risk of preterm birth in all of these three studies (67–69). In a Swedish study, a slightly elevated risk was noted for preterm birth among working women who spent most of the time at work in rooms where other people were smoking (RR 1.27, 95% CI 0.70–2.31) (60). This definition seems to refer also to fairly heavy exposure. The findings of two studies indicated that the association between exposure and preterm birth is modified by maternal age, the risk being increased among older (>30 years) but not younger women (68, 70). Altogether, the available evidence is scarce, but it does suggest that high exposure may increase the risk of preterm birth.

Fetal growth

Maternal active smoking is known to reduce the mean birthweight of the fetus by about 150–200 grams and to double the risk of low birthweight (< 2500 g). Several studies have reported the association between environmental tobacco smoke and mean birthweight, low birthweight, or intrauterine growth retardation (small for gestational age). The results of these studies have been reviewed in a report of the Californian Environmental Protection Agency (50) and in two review articles (71, 72) and meta-analyses (71, 73). In our paper we review briefly the older studies based on these reviews and consider in more detail the recent studies not included in these publications.

Mean birthweight

Windham et al (71) comprehensively reviewed the data from 25 studies on environmental tobacco smoke and birthweight, published between 1966 and 1995. Studies were not included if there was no consideration of maternal smoking, the methods were not described, an effect measure was not presented, or the report was in a foreign language. The authors grouped the studies by the method of measuring exposure to environmental tobacco smoke: ascertainment of spousal smoking status, estimation of exposure from multiple sources, or measurement of biomarkers. In 16 studies that used spouse smoking as a measure of exposure, the mean birthweight of the infant was lower in the exposed group than in the unexposed group. The decrement ranged from 3 to 200 grams. When only the highest quality studies were included, the range of weight decrement was reduced to about 15–60 grams.

It has been shown that overall exposure to environmental tobacco smoke is underestimated if only exposure to the partner's tobacco smoke is measured (74). A methodological limitation of the aforementioned studies is that exposure outside the home (at work or during leisure time) was not considered. When Windham et al (71) restricted their analysis to the five studies that attempted to ascertain total exposure from multiple

sources and adjusted for confounders, the range of the decrement was 10–50 grams.

Misra & Nguyen (72) reviewed the results of 11 studies on environmental tobacco smoke and mean birthweight published all through 1998. Studies were excluded from the review if they did not separate active smokers exposed to environmental tobacco smoke from nonsmokers exposed to environmental tobacco smoke, did not consider potential confounders, did not provide assessment of statistical significance, or did not characterize the study population. Misra & Nguyen (72) concluded that the reduction in birthweight associated with environmental tobacco smoke ranged from 25 to 90 grams. In two of the most recent studies, however, no association was observed between birthweight and exposure to tobacco smoke at home or at work (68, 71). Only the infants of the most highly exposed women, 12 hours or more per day, had an adjusted weight decrement of 88 (SE 103) grams.

Most studies have based exposure assessment on self-reports of exposure to environmental tobacco smoke, and the validity of self-reports has been questioned. Five studies used a biological marker to measure exposure: cotinine (a nicotine metabolite) in blood or saliva of the mother or the nicotine concentration in maternal hair (table 1). Two of these studies indicated a statistically significant decrease in mean birthweight: 104 grams with serum cotinine levels of ≥1 ng/ml (75) and 87 grams with salivary cotinine levels of >1.7 ng/ml (76). Eskenazi et al (77) and Jaakkola et al (69) noted a smaller decrement (45 g and 17 g, respectively), and in the study of Peacock et al (73) there was hardly any difference in the adjusted mean birthweight between the exposed and unexposed children (7 g).

The different categorization of exposure or the use of a different type of biomarker hampers comparisons of the results of the aforementioned studies on the basis of biomarkers. The study of Eskenazi et al (77) has been criticized for including possible hazardous low-level exposures in the reference group (serum cotinine <2 ng/ml) and thus possibly diluting the real effect of higher level exposure (72). Similarly, the classification used by Peacock et al (73) may have diluted the effects, because the high exposure group (serum cotinine 0.796–14.9 ng/ml) may have also included women with a relatively low level of exposure.

Two meta-analyses have been published on the effects of environmental tobacco smoke on birthweight (table 2). Windham et al (71) conducted a meta-analysis of 22 studies from which an effect measure and study weight could be calculated. Based on 11 studies that assessed exposure among nonsmokers and provided

Table 1. Studies on mean birthweight and exposure to environmental tobacco smoke determined by the measurement of biomarkers.

Study	Exposure assessment	Cotinine level or nicotine level	Mean birthweight difference [a] (g) between exposed and unexposed	95% CI
Haddow et al, 1998 (75)	Serum cotinine	<0.5 ng/ml	+4	-65–73
		0.5–1.0 ng/ml	Reference	.
		1.1–9.9 ng/ml	-104	-173 – -35
Rebagliato et al, 1995 (76)	Salivary cotinine	0–0.5 ng/ml	Reference	.
		0.6–0.8 ng/ml	-42	..
		0.9–1.1 ng/ml	-53	..
		1.2–1.7 ng/ml	+54	..
		1.8–14.0 ng/ml	-87	-174 – -1
Eskenazi et al, 1995 (77)	Serum cotinine	<2 ng/ml	Reference	.
		2–10 ng/ml	-45	-126–36
Peacock et al, 1998 (73)	Serum cotinine	0–0.18 ng/ml	Reference	.
		0.796–14.9 ng/ml	-7	-97–84
Jaakkola et al, 2001 (69)	Hair nicotine	<0.75 µg/g	Reference	.
		≥4.00 µg/g	-17	-178–145

[a] Adjusted for potential confounders.

Table 2. Meta-analyses of studies on mean birthweight and exposure to environmental tobacco smoke.

Study	Studies included and subgroups selected	Number of studies	Pooled weight difference (g) between exposed and unexposed	95% CI
Windham et al, 1999 (71)	All studies	22	-24.9	-33.7 – -16.1
	Nonsmoking mothers, adjusted estimates	11	-28.5	-40.8 – -16.2
	Multiple sources of exposure, adjusted estimates	8	-24.0	-39.3 – -8.6
Peacock et al, 1998 (73)	All studies	11	-31	-44 – -19

adjusted effect measures, the pooled estimate of the difference in birthweight was –28.5 grams (95% CI –40.8 – –16.2) between the exposed and unexposed children. Among the eight studies that ascertained exposure from multiple sources, the pooled birthweight difference was –24 grams (95% CI –39.3 – –8.6). Peacock et al (73) pooled the results of 10 previous studies and their own study. One study was excluded because of the missing denominator and another because the outcome could not be converted to grams of birthweight. The pooled estimate of the difference in mean birthweight between the exposed and unexposed children across these studies was –31 g (95% CI – 44 – –19).

The overall scientific evidence suggests that exposure to environmental tobacco smoke reduces slightly the mean birthweight of the fetus. Based on their literature reviews, Windham et al (71) concluded that the best studies show weight decrements from 25 to 100 grams, whereas Misra & Nguyen (72) concluded that the reduction in birthweight ranges from 25 to 90 grams. The pooled estimates of the meta-analyses showed decrements from 24 to 31 grams, with a greater decrement (35–40 g) seen in more homogeneous and higher quality studies (71). In the report of the Californian Environmental Protection Agency (50), an average weight decrement of 25–50 grams is considered plausible. Overall, the effect is small compared with the effects of maternal active smoking. It means, however, that the birthweight distribution shifts down with exposure to tobacco smoke. At the population level this shift would lead to increases in the number of low birthweight infants. It may also put infants who are already compromised into even higher risk categories (71, 72). Low birthweight is strongly associated with perinatal mortality.

Low birthweight

The effects of environmental tobacco smoke on low birthweight (<2500 g or small for gestational age) have been analyzed in several studies (50, 71, 72). Windham et al (71) reviewed the results of studies published between 1966 and 1995 and conducted a meta-analysis of the results of 16 studies that examined low birthweight or small for gestational age (table 3). When all the studies were considered, the pooled summary measure was close to unity (OR 1.07, 95% CI 1.0–1.15). Limiting the analysis to the 11 studies of only low birthweight at term or small for gestational age yielded a pooled estimate of 1.19. Further limiting the analysis to studies that presented adjusted estimates reduced the summary measure to 1.11.

After the meta-analysis, seven studies have been published on environmental tobacco smoke and low birthweight or small for gestational age. Most of them have shown an increased risk for exposure to environmental tobacco smoke (table 3). The highest risk estimate was noted in a Swedish study on small-for-gestational-age infants, the adjusted odds ratio for nonsmoking women exposed to passive smoking being 3.9 (95% CI 1.4–10.7) (78). Ahluwalia et al (70) reported an increased risk of low birthweight among older (≥30 years) women exposed to environmental tobacco smoke but not among younger women. Hanke et al (67) noted an odds ratio of 1.26 for small for gestational age at birth for the children of women exposed for 7 hours a day or more. Sadler et al (79) found no effects of environmental tobacco smoke on fetal growth in a relatively homogeneous upper-middle-class group of women exposed at low levels. In the most recent study (68), high exposure to environmental tobacco smoke (≥7 hours/day) was moderately associated with low birthweight, but not with small for gestational age.

Three studies based exposure assessment on the measurement of biomarkers. Nafstad et al (80) observed an increased odds ratio for small-for-gestational-age births among women with a hair nicotine concentration of 0.75–4.00 μg/g or >4.00 μg/g (table 3). The risk of low birthweight (<3000 g) was weakly related to maternal hair nicotine concentration also in the study of Jaakkola et al (69), although the lower confidence limits were below one. In the study of Eskenazi et al (77), the unadjusted odds ratio for low birthweight among women with serum cotinine levels of >2 ng/ml was 1.35 (95% CI 0.60–3.03). The number of subjects was, however, small in all three studies.

The majority of studies on low birthweight or small for gestational age has shown a moderate or slight, but often statistically nonsignificant, increase in risk among the infants of women exposed to environmental tobacco smoke. The results of the meta-analysis from studies published in 1966–1995 (71) indicate that the increase in risk is about 20%, ranging from 10% to 30%. The results of more recent studies have, however, often indicated a greater increase in risk.

Validity of birthweight studies

The most important methodological weaknesses in the studies on environmental tobacco smoke and fetal growth include a potential for misclassifying exposure, uncontrolled confounding, and small sample size. In several studies, exposure to environmental tobacco smoke has been assessed solely on the basis of paternal

Table 3. Studies of low birthweight (LBW) or small for gestational age (SGA) and exposure to environmental tobacco smoke (including a meta-analysis of studies published between 1966 and 1995 and individual studies published thereafter). (OR = odds ratio, 95% CI = 95% confidence interval)

Author (reference)	Design, source of exposure data, size	Outcome	Exposure definition	Effect (pooled estimates)	
				OR [a]	95% CI
Windham et al, 1999 (71)	Meta-analysis: 11 studies	Term LBW or SGA	Generally any exposure	1.19	1.08– 1.32
	Meta-analysis: 6 studies	Adjusted estimates	Generally any exposure	1.11	0.92– 1.34
Ahluwalia et al, 1997 (70)	Cross-sectional, interview, 17 412 persons	LBW	Mothers' age: < 30 years [b]	0.97	0.76– 1.23
			Mothers' age: ≥30 years [b]	2.42	1.51– 3.87
		SGA	Mothers' age: < 30 years [b]	0.97	0.75– 1.26
			Mothers' age: ≥30 years [b]	1.28	0.76– 2.15
Dejin-Karlsson et al, 1998 (78)	Prospective cohort and self-administered questionnaire, 826 persons	SGA	Any exposure	3.9	1.4 –10.7
Sadler et al, 1999 (79)	Cohort, postpartum interview, 2283 persons	SGA	Exposed ≥1 hour/week	0.82	0.51– 1.33
Hanke et al, 1999 (67)	Cohort, postpartum interview, 1751 persons	SGA	Exposed ≤1 hour/day	0.68	0.34– 1.38
			Exposed 2–3 hours/day	1.05	0.60– 1.83
			Exposed 4–6 hours/day	1.01	0.51– 2.01
			Exposed ≥7 hours/day	1.26	0.68– 2.35
Windham et al, 2000 (68)	Prospective cohort and interview, 4454 persons	LBW	Exposed 0.5–6.5 hours/day	1.0	0.61– 1.7
			Exposed ≥7 hours per day	1.8	0.82– 4.1
		SGA	Exposed 0.5–6.5 hours/day	1.1	0.74– 1.5
			Exposed ≥7 hours/day	0.62	0.25– 1.5
Nafstad et al, 1998 (80)	Case-referents, maternal hair sample, 58 cases, 105 referents	SGA	0.75–4.00 µg/g [c]	3.4	1.3 – 8.6
			≥4.00 µg/g [c]	2.1	0.4 –10.1
Jaakkola et al, 2001 (69)	Cohort, maternal hair sample, 389 persons	LBW	0.75 to < 4.00 µg/g [c]	1.28	0.59– 2.60
			≥4.00 µg/g [c]	1.55	0.55– 4.43
		SGA	0.75 to < 4.00 µg/g [c]	1.05	0.44– 2.49
			≥4.00 µg/g [c]	1.18	0.34– 4.19

[a] Adjusted for potential confounders except for Nafstad et al (80).
[b] Any exposure at home.
[c] Hair nicotine concentration.

smoking status. This assessment may result in exposure being misclassified because locations outside the home (work, leisure) are also important sources of exposure (74, 81). Therefore, the results of studies that consider all sources of exposure are usually more valid.

An explanation for any effect observed for environmental tobacco smoke is that the effect is due to the misclassification of smokers as nonsmokers. The possibility of misclassification is, however, small in studies conducted in China and India, where the levels of passive smoke exposure are high, but very few women smoke cigarettes. These studies (65, 82, 83) have reported slightly reduced birthweight and an increased risk of growth retardation for the infants of exposed women. These findings suggest that this kind of misclassification does not explain all the observed effects (79).

Assessments of exposure to environmental tobacco smoke have usually been based on the subjects' own reports, which may be inaccurate. This procedure tends to dilute the potential effects, or, if it is related to the outcome, it introduces bias that overestimates or underestimates an effect. A few investigations have used biomarkers in assessing exposure to tobacco smoke, cotinine in blood, or saliva (73, 75–77) or nicotine in hair (69, 80). A limitation of serum and salivary cotinine is that they reflect exposure over a relatively short period, the previous 2 to 3 days, whereas nicotine levels in hair collected shortly after birth describe exposure during the past few months. Compared to self-reports, misclassification of exposure is much less likely in studies using a biomarker of exposure. Four (69, 75, 76, 80) of the six studies based on biomarkers showed an association between environmental tobacco smoke and fetal growth.

There are several factors that have been considered possible determinants of birthweight, such as length of gestation, gender of the infant, maternal age, maternal stature, previous reproductive history, and socioeconomic status. The effect of many of these potential confounding factors has usually been controlled for in the analyses, especially in the more recent studies.

All in all, the results of the most valid studies, which have considered multiple sources of exposure and adjusted for potential confounding factors, suggest that maternal exposure to environmental tobacco smoke during pregnancy slightly reduces mean birthweight. Likewise, they suggest that the risk of intrauterine growth retardation is elevated in the infants of exposed women.

Birth defects

The existing studies on birth defects were reviewed in detail recently by the California Environmental Protection Agency in "Health Effects and Exposure to Environmental Tobacco Smoke" (50). The most consistent finding was the increased risk of nervous system defects; this finding was noted in all but one study out of five. Increased risk for facial cleft was reported in three out of five studies, with the relative risks or odds ratios varying: 7.0 (significant), 1.7, and 1.6 (not significant). Associations in a dose-response manner have been suggested for paternal smoking and clefts, urethral stenosis (84), spina bifida, diaphragmatic hernia, and the pigmentary anomalies (85).

The risk for severe birth defects was increased in one study in a dose-response manner depending on the smoking of the father. The rate of severe congenital malformations among the children was 0.8% if the fathers did not smoke, 1.4% if the fathers smoked 1–10 cigarettes per day, and 2.1% if the fathers smoked >10 cigarettes per day (86). The increase in risk was independent of maternal and paternal age and socioeconomic status. The reviewer calculated a crude odds ratio of 2.6 (95% CI 1.5–4.7) for children whose fathers smoked >10 cigarettes per day (50). Deleting smoking women from the analysis did not change the results for paternal smoking. Paternal heavy smoking (>30 cigarettes per day) seems to be associated with an increase in the rate of major malformations (87); the relative risk calculated by the reviewers was 1.45 (95% CI 0.73–2.8) (50). In some studies [eg, in that by Zhang et al (85)], elevated rates of malformations were observed in association with paternal smoking but without a dose-response effect [reviewer calculated RR 1.2, 95% CI 1.0–1.5 (42, 75)].

Complete teratological animal studies with sidestream smoke are lacking. Two studies did not reveal any defects in the gross examinations, and one study found no defects in a skeletal examination, but soft tissues were not examined (50). In a recent study, no macroscopically visible gross anomalies were observed in rat fetuses after maternal passive exposure to sidestream smoke, but widespread ossification retardation was seen in the exposed group (88). Many chemicals in sidestream smoke have teratogenic potential [developmental disturbances in some animal tests, for example, nicotine (89, 90), pyridine (91, 92), hydrazine (93), and methylamine (94)] in higher doses than the produced concentration from sidestream smoke. Harmful effects are possible, but at the moment the evidence from animal studies is insufficient.

An ideal design with which to study the effects of environmental tobacco smoke on human birth defects would include nonsmoking couples for whom the exposure to environmental tobacco smoke could be compared at several dose levels, measurements of U-cotinine for the classification of exposure whenever available, and there would be information on other relevant exposures of women from work and leisure time. Pregnant women should be comparable also with respect to other relevant factors, like age, socioeconomic status, time period, ethnicity, and geographic region. Thus far such studies do not exist. In most existing reports the effects of environmental tobacco smoke have been estimated on the basis of paternal smoking, and smoking of the pregnant women has not always been controlled for in the analyses. Possible confounders have not been taken into account in all studies. A possible direct effect via the father's sperm cannot be ruled out when the father has been the source of exposure to environmental tobacco smoke. Due to these limitations of the studies it is not possible to be certain whether there is an association between exposure to environmental tobacco smoke and birth defects.

Childhood cancer

Data distinguishing the effects of exposure to tobacco smoke before, during, or after pregnancy are sparse in studies on childhood cancer. In the following discussion, exposure is defined as the time of pregnancy. There is one recent review (95) and one recent meta-analysis (96) on the risk of childhood cancers and childhood exposure to passive smoking. A small increase in the risk of childhood cancer seems to be associated with maternal smoking during pregnancy (95, 96). In the meta-analysis of 12 studies, a relative risk of 1.10 (95% CI 1.03–1.19) was found for all neoplasms (96). However, the risks were not elevated for central nervous system tumors (12 studies, RR 1.04, 95% CI 0.92–1.18) or leukemia (8 studies, RR 1.05, 95% CI 0.82–1.34). According to the review (95), the positive findings seem to be consistent for brain tumors and some forms of leukemia and lymphomas. The results on exposure to paternal tobacco smoke suggest an association with brain tumors (10 studies, RR 1.22, 95% CI 1.05–1.40) and lymphomas (4 studies, RR 2.08, 95% CI 1.08–3.98) in children (95).

Recently, the risk of brain cancer was investigated among children of nonsmoking women exposed to the smoke of the husband (97). The relative risk for exposure was 1.8 (95% CI 1.2–2.5) for early pregnancy and 1.7 (95% CI 1.2–2.6) for late pregnancy. Notably, the fathers' smoking during the 5 years before the pregnancy was not related to the risk of brain cancer. This finding, together with earlier studies conducted among nonsmoking mothers (95, 96), suggests that a part of the observed effect may be related to the mothers' exposure to passive smoking during pregnancy.

Male reproductive toxicity

Male reproductive toxicity includes altered semen quality and effects on fertility. The sperm density of active smokers is, on the average, 13–17% lower than that of nonsmokers (98). Alterations in sperm morphology and motility have also been linked with active smoking. There are no studies on the effects of environmental tobacco smoke on semen quality. The data of Pacifici et al (99) indicate, however, that exposure to environmental tobacco smoke results in measurable cotinine and nicotine levels in seminal plasma.

There are problems in distinguishing between the transgenerational, transplacental, and direct effects of exposure to passive smoking (ie, between the effects of preconceptional, prenatal, and postnatal exposure) (96). Many studies have defined maternal exposure based on paternal active smoking. The fathers' smoking is solely passive only if he has started to smoke after the conception of the child and he has smoked in the same rooms where the mother is.

Male smoking seems to have only a weak influence on time to pregnancy; this finding suggests that the summary effect of male active smoking and female passive smoking on fecundability is weak. Some studies suggest an association (58, 100, 101), whereas others (102–104), including two prospective studies (54, 105), do not indicate an association. The studies on in vitro fertilization are mechanistically and methodologically of interest. One can focus on the direct effects of male smoking to fertilization or implantation. In a recent retrospective cohort study on in vitro fertilization, male smoking was related to a reduced likelihood of achieving a 12-week pregnancy (106). No significant differences were found in the occurrence of a clinically detected pregnancy (ie, ultrasonic evidence of fetal heart activity or evidence of an early spontaneous abortion or ectopic pregnancy). Thus the findings suggest that male smoking may be associated with pregnancy loss following the early clinical detection of pregnancy. Actually no conclusion on the potential effects of passive smoking can be drawn on the basis of these studies, since female exposure to environmental tobacco smoke has not been documented. There are no published studies aimed at examining the effects of environmental tobacco smoke on adult male reproductive health (50).

Concluding remarks

The most convincing evidence on the reproductive effects of environmental tobacco smoke is its adverse effect on birthweight. Based on literature reviews of published studies, the range of birthweight decrement is from 25 to 100 grams. The results of meta-analyses indicate that exposure to environmental tobacco smoke reduces the mean birthweight by about 25 to 40 grams. Most of the studies on low birthweight show also a moderate or slight increase in risk among the infants of exposed women.

The available evidence suggests that high exposure to environmental tobacco smoke may also increase the risk of preterm birth. The evidence on the effects of environmental tobacco smoke on spontaneous abortion and birth defects is weak and inconclusive. Very few studies have examined the association between environmental tobacco smoke and spontaneous abortions. The findings of different studies on birth defects have been conflicting, and the validity of the studies is weakened by limitations in assessing exposure. Similarly, very little is known about the impact of environmental tobacco smoke on fertility, menstrual function, male reproductive health, or childhood cancer.

A methodological shortcoming of reproductive studies on exposure to environmental tobacco smoke has been the difficulty to distinguish whether the findings are due to the direct effect of male active smoking or the woman's exposure to passive smoking. Further studies are needed among nonsmoking women exposed to environmental tobacco smoke at work or during leisure time, but living with a nonsmoking partner. In these studies, the effects of other work-related reproductive risk factors should also be considered and, because of the infertile worker effect, it might be prudent to restrict them to employed women only.

References

1. Werler MM. Teratogen update: smoking and reproductive outcomes. Teratology 1997;55:382–8.
2. Anderson HR, Cook DG. Passive smoking and sudden infant death syndrome: review of the epidemiological evidence. Thorax 1997;52:1003–9.
3. Eskenazi B, Castorina R. Association of prenatal maternal or postnatal child environmental tobacco smoke exposure and neurodevelopmental and behavioral problems in children. Environ Health Perspect 1999;107:991–1000.
4. US Environmental Protection Agency (EPA), Department of Health and Human Services. Respiratory health effects of passive smoking: lung cancer and other disorders. Washington (DC): EPA, Department of Health and Human Services, 1993:93–3605. NIH publication: Smoking and tobacco control monograph 4.
5. National Research Council. Environmental tobacco smoke: measuring exposures and assessing health effects. Washington (DC): National Academy Press, 1986.
6. Husgafvel-Pursiainen K. Biomarkers in the assessment of exposure and the biological effects of environmental tobacco smoke. Scand J Work Environ Health 2002;28 suppl 2:21–29.
7 Riboli E, Preston-Martin S, Saracci R, Haley NJ, Trichopoulos

D, Becher H, et al. Exposure of nonsmoking women to environmental tobacco smoke.: a 10-country collaborative study. Cancer Causes Control 1990;1:243–52.
8. Husgafvel-Pursiainen K, Sorsa M, Engström K, Einistö P. Passive smoking at work: biochemical and biological measures of exposure to environmental tobacco smoke. Int Arch Occup Environ Health 1987;59:337–45.
9. Jauniaux E, Gulbis B, Acharya G, Thiry P, Rodeck C. Maternal tobacco exposure and cotinine levels in fetal fluids in the first half of pregnancy. Obstet Gynecol 1999;93:25–9.
10. International Agency for Research on Cancer (IARC). Tobacco smoking. Lyon: IARC, 1986. IARC monographs on the evaluation of the carcinogenic risk of chemicals in humans, no 35.
11. Salafia C, Schiverick K. Cigarette smoking and pregnancy, II: vascular effects. Placenta 1999;20:273–9.
12. Schiverick KT, Salafia C. Cigarette smoking and pregnancy, I: ovarian, uterine and placental effects. Placenta 1999;20: 265–72.
13. Genbacev O, McMaster MT, Lazic J, Nedeljkovic S, Cvetkovic M, Joslin R, et al. Concordant in situ and in vitro data show that maternal cigarette smoking negatively regulates placental cytotrophoblast passage through the cell cycle. Reprod Toxicol 2000;14:495–506.
14. Dollberg S, Fainaru O, Mimouni FB, Shenhav M, Lessing JB, Kupferminc M. Effect of passive smoking in pregnancy on neonatal nucleated red blood cells. Pediatrics 2000; 106(3):e34.
15. Yager JW, Eastmond DA, Robertson ML, Paradisin WM, Smith MT. Characterization of micronuclei induced in human lymphocytes by benzene metabolites. Cancer Res 1990;50:393–9.
16. Spano M, Pacchierotti F, Uccelli R, Amendola R, Bartoleschi C. Cytotoxic effects of benzene on mouse germ cells determined by flow cytometry. J Toxicol Environ Health 1989;26:361–72.
17. Maronpot RR, Miller RA, Clarke WJ, Westerberg RB, Decker JR, Moss OR. Toxicity of formaldehyde vapor in B6C3F1 mice exposed for 13 weeks. Toxicology 1986;41:253–66.
18. Majumder PK, Kumar VL. Inhibitory effects of formaldehyde on the reproductive system of male rats. Indian J Physiol Pharmacol 1995;39:80–2.
19. Katakura Y, Kishi R, Okui T, Ikeda T, Miyake H. Distribution of radioactivity from ^{14}C-formaldehyde in pregnant mice and their fetuses. Br J Ind Med 1993;50:176–82.
20. Keller WC. Toxicity assessment of hydrazine fuels. Aviat Space Environ Med 1988;59:100–6.
21. Rogers AM, Back KC. Comparative mutagenicity of hydrazine and 3 methylated derivatives in L5178Y mouse lymphoma cells. Mutat Res 1981;89:321–8.
22. Neuhauser-Klaus A, Chauhan PS. Studies on somatic mutation induction in the mouse with isoniazid and hydrazine. Mutat Res 1987;191:111–6.
23. Schiller CM, Walden R, Kee TE. Effects of hydrazine and its derivatives on the development of intestinal brush border enzymes. Toxicol Appl Pharmacol 1979;49:305–11.
24. Hammer RE, Goldman H, Mitchell JA. Effects of nicotine on uterine blood flow and intrauterine oxygen tension in the rat. J Reprod Fertil 1981;63:163–8.
25. Resnik R, Brink GW, Wilkes M. Catecholamine-mediated reduction in uterine blood flow after nicotine infusion in the pregnant ewe. J Clin Invest 1979;63:1133–6.
26. Suzuki K, Minei LJ, Johnson EE. Effect of nicotine upon uterine blood flow in the pregnant rhesus monkey. Am J Obstet Gynecol 1980;136:1009–13.
27. Lehtovirta P, Forss M. The acute effect of smoking on intervillous blood flow of the placenta. Br J Obstet Gynaecol 1978;85:729–31.
28. Bruner JP, Forouzan I. Smoking and buccally administered nicotine. J Reprod Med 1991;36:435–40.
29. Lu LJ, Wang MY. Modulation of benzo[a]pyrene-induced covalent DNA modifications in adult and fetal mouse tissues by gestation stage. Carcinogenesis 1990;11:1367–72.
30. Iannaccone PM, Fahl WE, Stols L. Reproductive toxicity associated with endometrial cell mediated metabolism of benzo[a]pyrene: a combined in vitro, in vivo approach. Carcinogenesis 1984;5:1437–42.
31. Shiromizu K, Mattison DR. The effect of intraovarian injection of benzo(a)pyrene on primordial oocyte number and ovarian aryl hydrocarbon [benzo(a)pyrene] hydroxylase activity. Toxicol Appl Pharmacol 1984;76:18–25.
32. Swartz WJ, Mattison DR. Benzo(a)pyrene inhibits ovulation in C57BL/6N mice. Anat Rec 1985;212:268–76.
33. Miller MM, Plowchalk DR, Weitzman GA, London SN, Mattison DR. The effect of benzo(a)pyrene on murine ovarian and corpora lutea volumes. Am J Obstet Gynecol 1992; 166:1535–41.
34. Bui QQ, Tran MB, West WL. A comparative study of the reproductive effects of methadone and benzo[a]pyrene in the pregnant and pseudopregnant rat. Toxicology 1986;42:195–204.
35. Madhavan ND, Naidu KA. Polycyclic aromatic hydrocarbons in placenta, maternal blood, umbilical cord blod and milk of Indian women. Hum Exp Toxicol 1995; 14(6):503–6.
36. Shugart L, Matsunami R. Adduct formation in hemoglobin of the newborn mouse exposed in utero to benzo[a]pyrene. Toxicology 1985;37:241–5.
37. Kihlstrom I. Placental transfer of benzo(a)pyrene and its hydrophilic metabolites in the guinea pig. Acta Pharmacol Toxicol [Copenh] 1986;58:272–6.
38. Everson RB, Randerath E, Santella RM, Cefalo RC, Avitts TA, Randerath K. Detection of smoking-related covalent DNA adducts in human placenta. Science 1986;231 (4733):54–7.
39. Sanyal MK, Li YL, Belanger K. Metabolism of polynuclear aromatic hydrocarbon in human term placenta influenced by cigarette smoke exposure. Reprod Toxicol 1994; 8(5):411–8.
40. Lackman GM, Angerer J, Töllner U. Parental smoking and neonatal serum levels of polychlorinated biphenyls and hexachlorobenzene. Pediatr Res 2000;47:598–601.
41. Beebe LE, Kim YE, Amin S, Riggs CW, Kovatch RM, Anderson LM. Comparison of transplacental and neonatal initiation of mouse lung and liver tumors by N-nitrosodimethylamine (NDMA) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and promotability by a polychlorinated biphenyls mixture (Aroclor 1254). Carcinogenesis 1993;14: 1545–8.
42. Lackman GM, Salzberger U, Hecht SS, Töllner U. Rauchen während der Schwangerschaft: Neue Erkenntnisse zum Einfluss auf den Fetus und das neugeborene Kind. Dtsch Ärztebl 1999;96:A2080–3.
43. Pichini S, Basagana X, Pacifici R, Garcia O, Puig C, Vall O, et al. Cord serum cotinine as a biomarker of fetal exposure to cigarette smoke at the end of pregnancy. Environ Health Perspect 2000;108:1079–83.
44. Klein J, Koren G. Hair analysis — a biological marker for

passive smoking in pregnancy and childhood. Human Exp Toxicol 1999;18:279–82.
45. Jordanov JS. Cotinine concentrations in amniotic fluid and urine of smoking, passive smoking and non-smoking pregnant women at term and in the urine of their neonates on 1st day of life. Eur J Pediatr 1990;149:734–7.
46. Ostrea EM Jr, Knapp DK, Romero A, Montes M, Ostrea AR. Meconium analysis to assess fetal exposure to nicotine by active and passive maternal smoking. J Pediatr 1994; 124:471–6.
47. Remmer H. Passively inhaled tobacco smoke: a challenge to toxicology and preventive medicine. Arch Toxicol 1987; 61:89–104.
48. Hornsby PP, Wilcox AJ, Weinberg CR. Cigarette smoking and disturbances of menstrual function. Epidemiology 1998;9:193–8.
49. Chen C, Cho SI, Damokosh AI, Chen D, Li G, Wang X, et al. Prospective study of exposure to environmental tobacco smoke and dysmenorrhea. Environ Health Perspect 2000; 108:1019–22.
50. California Environmental Protection Agency. Health effects of exposure to environmental tobacco smoke. San Francisco (CA): California Environmental Protection Agency, 1997.
51. Everson RB, Sandler DP, Wilcox AJ, Schreinemachers D, Shore DL, Weinberg C. Effect of passive exposure to smoking on age at natural menopause. BMJ 1986;293:792.
52. Tajtakova M, Farkasova E, Klubertova M, Konradova I, Machovcakova L. The effect of smoking on menopause [In Slovak]. Vnitr Lek 1990;36:649–53.
53. Cooper GS, Sandler DP, Bohlig M. Active and passive smoking and the occurrence of natural menopause. Epidemiology 1999;10:771–3.
54. Jensen TK, Henriksen TB, Hjollund NHI, Scheike T, Kolstad H, Givercman A, et al. Adult and prenatal exposures to tobacco smoke as risk indicators of fertility among 430 Danish couples. Am J Epidemiol 1998;148:992–7.
55. Weinberg CR, Wilcox AJ, Baird DD. Reduced fecundability in women with prenatal exposure to cigarette smoking. Am J Epidemiol 1989;129:1072–8.
56. Wilcox AJ, Baird DD, Weinberg CR. Do women with childhood exposure to cigarette smoking have increased fecundability? Am J Epidemiol 1989;129:1079–83.
57. Schwingl PJ. Prenatal smoking exposure in relation to female adult fecundability [dissertation]. Ann Arbor (MI): United Microfilms International, 1992.
58. Hull MGR, North K, Taylor H, Farrow A, Ford WCL, the Avon Longitudinal Study of Pregnancy and Childhood Study Team. Delayed conception and active and passive smoking. Fertil Steril 2000;74:725–33.
59. Ness RB, Grisso JA, Hirschinger N, Markovic N, Shaw LM, Day NL, et al. Cocaine and tobacco use and the risk of spontaneous abortion. N Engl J Med 1999;340:333–9.
60. Ahlborg G, Jr., Bodin L. Tobacco smoke exposure and pregnancy outcome among working women: a prospective study at prenatal care centers in Örebro County, Sweden. Am J Epidemiol 1991;133:338–47.
61. Windham GC, Swan SH, Fenster L. Parental cigarette smoking and the risk of spontaneous abortion. Am J Epidemiol 1992;135:1394–403.
62. Windham GC, Von Behren J, Waller K, Fenster L. Exposure to environmental and mainstream tobacco smoke and risk of spontaneous abortion. Am J Epidemiol 1999;149:243–7.
63. Kyrklund-Blomberg NB, Cnattingius S. Preterm birth and maternal smoking: risks related to gestational age and onset of delivery. Am J Obstet Gynecol 1998;179:1051–5.
64. Martin TR, Bracken MB. Association of low birth weight with passive smoke exposure in pregnancy. Am J Epidemiol 1986;124:633–42.
65. Mathai M, Vijayasri R, Babu S, Jeyaseelan L. Passive maternal smoking and birthweight in a south Indian population. Br J Obstet Gynaecol 1992;99:342–3.
66. Fortier I, Marcoux S, Brisson J. Passive smoking during pregnancy and the risk of delivering a small-for-gestational-age infant. Am J Epidemiol 1994;139:294–301.
67. Hanke W, Kalinka J, Florek E, Sobala W. Passive smoking and pregnancy outcome in central Poland. Hum Exp Toxicol 1999;18:265–71.
68. Windham GC, Hopkins B, Fenster L, Swan SH. Prenatal active or passive tobacco smoke exposure and the risk of preterm delivery or low birth weight. Epidemiology 2000;11: 427–33.
69. Jaakkola JJK, Jaakkola N, Zahlsen K. Fetal growth and length of gestation in relation to prenatal exposure to environmental tobacco smoke assessed by hair nicotine concentration. Environ Health Perspect 2001;109:557–61.
70. Ahluwalia IB, Grummer-Strawn L, Scanlon KS. Exposure to environmental tobacco smoke and birth outcome: increased effects on pregnant women aged 30 years or older. Am J Epidemiol 1997;146:42–7.
71. Windham GC, Eaton A, Hopkins B. Evidence for an association between environmental tobacco smoke exposure and birthweight: a meta-analysis and new data. Paediatr Perinat Epidemiol 1999;13:35–57.
72. Misra DP, Nguyen RH. Environmental tobacco smoke and low birth weight: a hazard in the workplace? Environ Health Perspect 1999;107(suppl 6):897–904.
73. Peacock JL, Cook DG, Carey IM, Jarvis MJ, Bryant AE, Anderson HR, et al. Maternal cotinine level during pregnancy and birthweight for gestational age. Int J Epidemiol 1998;27:647–56.
74. Rebagliato M, Bolumar F, Florey CdV. Assessment of exposure to environmental tobacco smoke in nonsmoking pregnant women in different environments of daily living. Am J Epidemiol 1995;142:525–30.
75. Haddow JE, Knight GJ, Palomaki GE, McCarthy JE. Second-trimester serum cotinine levels in nonsmokers in relation to birth weight. Am J Obstet Gynecol 1988;159:481–4.
76. Rebagliato M, Florey CdV, Bolumar F. Exposure to environmental tobacco smoke in nonsmoking pregnant women in relation to birth weight. Am J Epidemiol 1995;142:531–7.
77. Eskenazi B, Prehn AW, Christianson RE. Passive and active maternal smoking as measured by serum cotinine: the effect on birthweight. Am J Public Health 1995;85:395–8.
78. Dejin-Karlsson E, Hanson BS, Ostergren PO, Sjoberg NO, Marsal K. Does passive smoking in early pregnancy increase the risk of small-for-gestational-age infants? Am J Public Health 1998;88:1523–7.
79. Sadler L, Belanger K, Saftlas A, Leaderer B, Hellenbrand K, McSharry JE, et al. Environmental tobacco smoke exposure and small-for-gestational-age birth. Am J Epidemiol 1999;150:695–705.
80. Nafstad P, Fugelseth D, Qvigstad E, Zahlen K, Magnus P, Lindemann R. Nicotine concentration in the hair of nonsmoking mothers and size of offspring. Am J Public Health 1998;88:120–4.
81. O'Connor TZ, Holford TR, Leaderer BP, Hammond SK, Bracken MB. Measurement of exposure to environmental tobacco smoke in pregnant women. Am J Epidemiol 1995;

142:1315–21.
82. Chen Y, Pederson LL, Lefcoe NM. Passive smoking and low birthweight. Lancet 1989;2:54–5.
83. Zhang J, Ratcliffe JM. Paternal smoking and birthweight in Shanghai. Am J Public Health 1993;83:207–10.
84. Savitz DA, Schwingl PJ, Keels MA. Influence of paternal age, smoking and alcohol consumption on congenital anomalies. Teratology 1991;44:429–40.
85. Zhang J, Savitz DA, Schwingl PJ, Cai WW. A case-control study of paternal smoking and birth defects. Int J Epidemiol 1992;21(2):273–8.
86. Mau G, Netter P. The effects of paternal cigarette smoking on perinatal mortality and the incidence of malformations. Dtsch Med Wochenschr 1974;99:1113–8.
87. Seidman DS, Ever-Hadani P, Gale R. Effect of maternal smoking and age on congenital anomalies. Obstet Gynecol 1990;76(6):1046–50.
88. Nelson E, Jodscheit K, Guo Y. Maternal passive smoking during pregnancy and fetal developmental toxicity, part 1: gross morphological effects. Hum Exp Toxicol 1999;18:252–6.
89. Schardein JL. Chemically induced birth defects. 2nd ed. New York (NY): Marcel Dekker Inc, 1993.
90. Saad AY, Gartner LP, Hiatt JL. Teratogenic effects of nicotine on palate formation in mice. Biol Struct Morphog 1991; 3:31–5.
91. Landauer W, Salam N. Quantitative and qualitative distinctions in developmental interference produced by various substituted pyridines: molecular shape and teratogenicity as studied on chicken embryos. Acta Embryol Exp 1973;2:179–97.
92. Landauer W, Salam N. The experimental production in chicken embryos of muscular hypoplasia and associated defects of beak and cervical vertebrae. Acta Embryol Exp 1974;1:51–66.
93. Druckrey H. Specific carcinogenic and teratogenic effects of indirect alkylating methyl and ethyl compounds, and their dependency on stages of ontogenic developments. Xenobiotica 1973;3:271–303.
94. Murphy ML, Moro AD, Lacon CR. The comparative effects of five polyfunctional alkylating agents, with additional notes on the chick embryo. Ann NY Acad Sci 1958;68:762–81.
95. Sasco AJ, Vainio H. From in utero and childhood exposure to parental smoking to childhood cancer: a possible link and the need for action. Hum Exp Toxicol 1999;18:192–210.
96. Boffetta P, Trédaniel J, Greco A. Risk of childhood cancer and adult lung cancer after childhood exposure to passive smoke: a meta-analysis. Environ Health Perspect 2000; 108:73–82.
97. Filippini G, Farinotti M, Ferrarini M. Active and passive smoking during pregnancy and risk of central nervous system tumours in children. Paediatr Perinat Epidemiol 2000; 14:78–84.
98. Vine MF. Smoking and male reproduction: a review. Int J Androl 1996;19:323–37.
99. Pacifici R, Altieri I, Gandini L, Lenzi A, Passa AR, Pichini S, et al. Environmental tobacco smoke: nicotine and cotinine concentration in semen. Environ Res 1995;68:69–72.
100. Olsen J. Cigarette smoking, tea and coffee drinking, and subfecundity. Am J Epidemiol 1991;133:734–9.
101. Curtis KM, Savitz DA, Arbuckle TE. Effects of cigarette smoking, caffeine consumption, and alcohol intake on fecundability. Am J Epidemiol 1997;146:32–41.
102. Baird DD, Wilcox AJ. Cigarette smoking associated with delayed conception. JAMA 1985;253:2979–83.
103. Joffe M, Li Z. Male and female factors in fertility. Am J Epidemiol 1994;140:921–9.
104. Bolumar F, Olsen J, Boldsen J. Smoking reduces fecundity: a European multicenter study on infertility and subfecundity: The European Study Group on Infertility and Subfecundity. Am J Epidemiol 1996;143:578–87.
105. de Mouzon J, Spira A, Schwartz D. A prospective study of the relation between smoking and fertility. Int J Epidemiol 1988;17:378–84.
106. Joesbury KA, Edirisinghe WR, Phillips MR, Yovich JL. Evidence that male smoking affects the likelihood of a pregnancy following IVF treatment: application of the modified cumulative embryo score. Hum Reprod 1998;13:1506–13.