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Infertility, Pregnancy Loss and Adverse Birth Outcomes in Relation to Maternal Secondhand Tobacco Smoke Exposure

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Abstract

A substantial proportion of the etiology involved in female infertility and adverse pregnancy outcomes remains idiopathic. Recent scientific research has suggested a role for environmental factors in these conditions. Secondhand tobacco smoke (STS) contains a number of known or suspected reproductive toxins, and human exposure to STS is prevalent worldwide. Robust evidence exists for the toxic effects of active smoking on fertility and pregnancy, but studies of passive exposure are much more limited in number. While the association between maternal STS exposure and declined birth weight has been fairly well-documented, only recently have epidemiologic studies begun to provide suggestive evidence for delayed conception, altered menstrual cycling, early pregnancy loss (e.g. spontaneous abortion), preterm delivery, and congenital malformations in relation to STS exposure. There is also new evidence that developmental exposures to tobacco smoke may be associated with reproductive effects in adulthood. To date, most studies have estimated maternal STS exposure through self-report even though exposure biomarkers are less prone to error and recall bias. In addition to utilizing biomarkers of STS exposure, future studies should aim to identify vital windows of STS exposure, important environmental co-exposures, individual susceptibility factors, and specific STS constituents associated with female infertility and adverse pregnancy outcomes. The role of paternal exposures/factors should also be investigated.

Keywords

ETS; infertility; pregnancy; secondhand smoke; spontaneous abortion; tobacco

INTRODUCTION

Approximately 15% of all couples have difficulty achieving pregnancy, and female factors are the main (approximately 40%) or contributory cause (approximately 20%) of infertility in a large percentage of cases [1]. Over the past 25 years, estimates of the percentage of infertile women in the US (aged 15–44) have ranged from 7.4% to 10.2% [2, 3]. Adverse birth outcomes such as low birth weight and preterm birth also remain common, and rates

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

have even been increasing over recent decades in some countries including the US [4–6]. Although several risk factors for female infertility and hindered embryo and fetal development have been identified, the etiology of a substantial proportion of female fertility problems remains idiopathic. There is increasing scientific and regulatory concern for the role that environmental factors may play in these conditions. Animal and human studies have shown associations between active smoking or specific constituents of tobacco smoke and altered female fertility and embryo development [7], but human data on exposure to secondhand tobacco smoke (STS; also known as environmental tobacco smoke) and female fertility, early pregnancy loss, and fetal development remain somewhat limited. Because a large portion of women in the general population are exposed to STS, even associations of small magnitude for these health endpoints may have large public health significance.

REVIEW METHODS

Literature searches for the present review were conducted using PubMed of the US National Library of Medicine, National Institutes of Health. Searches included various combinations of the following terms: *infertility, pregnancy, pregnancy loss, spontaneous abortion, miscarriage, stillbirth, birth outcomes, birth weight, preterm birth, birth defects, congenital malformations, secondhand tobacco smoke, passive smoking*, and *environmental tobacco smoke*. Results from human studies written in English that assessed statistical relationships between STS and infertility, pregnancy loss, adverse birth outcomes, or latent reproductive difficulties were included. Studies of actively smoking women were excluded except for a few instances where the main findings of previously-reviewed studies are summarized. Studies of paternal STS exposure were also excluded.

EXPOSURE TO SECONDHAND TOBACCO SMOKE

Although exposure to STS is preventable, it remains prevalent worldwide. Antismoking legislation is gaining support, but many countries have no such laws, and as of 2011, only 27 states in the US had comprehensive smoke-free laws in place [8]. Many non-smoking adults and children are regularly exposed to STS which can occur in a home, in a vehicle, at work, or in other public places such as bars or restaurants. The Second and Third US National Reports on Human Exposure to Environmental Chemicals (part of the National Health and Nutrition Examination Survey; NHANES 1999–2000 and 2001–2002, respectively) reported measurable levels of serum cotinine, a biomarker of tobacco smoke, in approximately 50% of the non-smoking US population [9, 10]. The majority of STS is in the form of sidestream smoke generated from the burning end of a lighted cigarette, while the remainder is composed of mainstream smoke exhaled by individuals actively smoking. Both mainstream and sidestream smoke contain thousands of compounds, many of them harmful to humans. Mainstream and sidestream smoke are produced at differing temperatures and oxygen conditions, and harmful constituents exist in varying proportions between the two types of smoke. For example, sidestream smoke contains more CO and less CO_2, and higher levels of combustion products formed by nitrosation and amination, than mainstream smoke [11]. In addition to CO, STS contains other chemicals that are known or suspected reproductive toxicants—for example, benzene, cadmium, ethylbenzene, formaldehyde, hydrazine, lead, limonene, methylamine, methylene chloride, nicotine, pyridine, toluene, and radioactive polonium-210 [12].

ASSESSING EXPOSURE TO SECONDHAND TOBACCO SMOKE

NHANES III, which took place between 1988 and 1991, estimated that STS exposure occurred in 33% of all women in the U.S. based on self-reports [13]. However, measurable levels of cotinine, a metabolite of nicotine, were found in serum from 87.8% of all non-tobacco users in the study. This suggests that many people may be unaware of passive

exposure, and that self-reported exposure to secondhand smoke may not be a sensitive estimate for true exposure [14, 15]. The use of personal or environmental air monitoring is an alternative strategy for estimating STS exposure [16], though this approach can become quite costly and labor-intensive in large epidemiologic studies. In addition, many air monitoring strategies utilize particulate matter as a surrogate for STS exposure, which leads to measurement error if other particulate sources are present. Biological markers (known as biomarkers) of STS exposure provide a more valid, quantitative measure of exposure in epidemiology studies compared to self-report and environmental measures [17]. The main advantage of using biomarkers in exposure assessment for epidemiology is that they provide a measure of absorbed dose as opposed to the potential dose (exposure) in the external environment [18], and self-reports of time spent exposed to STS are imprecise due to recall biases, variations in the number of cigarettes smoked, proximity of nonsmokers to smokers, room ventilation, and other environmental characteristics.

Cotinine is the primary metabolite of nicotine and is currently regarded as the best biomarker in active smokers and in nonsmokers exposed to STS [9, 17, 18]. Measuring cotinine is preferred over measuring nicotine because cotinine persists longer in the body (20–24 hours, compared with two hours for nicotine). Cotinine can be measured in saliva, hair, nails, or more commonly serum or urine. Commercially-available cotinine immunoassay kits are available, although recent advances in liquid chromatography/ tandem mass-spectrometry offer a rapid and highly sensitive (but more costly) analytical method currently considered the "gold standard". Urine is often the preferred medium due to the ease of sample collection and because cotinine is present at higher concentrations in urine than in serum [17]. It has been recommended that exposed and unexposed nonsmokers be separated by using a urinary cotinine cutoff concentration of 50 ng/ml [18, 19]. Urine output is highly variable depending on hydration, so cotinine concentrations measured in urine are often adjusted for dilution using specific gravity or the concentration of creatinine in the sample [20]. A limitation of using cotinine concentrations as a biomarker for STS exposure is its relatively short half-life in biological fluids, reflecting exposure on the order of several days. Using cotinine in epidemiology studies to estimate STS exposure over several months or years may result in exposure misclassification. For this reason, although often imprecise, self-report is still a useful supplement to biomarkers for the estimation of longer-term intermittent STS exposure [21]. Exposure over the past several months can also be estimated *via* cotinine measures in hair and nails [22].

Other biologic matrices for measuring exposure to environmental chemicals have not been as widely used, but have great potential as a way of estimating exposure in reproductive health studies. For example, follicular fluid has been analyzed for cotinine in several studies [23–27]. This fluid surrounds the oocyte prior to ovulation and is aspirated and usually discarded during oocyte retrieval as part of *in vitro* fertilization (IVF) treatment. A recent study measured cotinine concentrations in matched follicular fluid and urine samples from nonsmoking women to examine STS exposure classification agreement [28]. The authors reported a high degree of exposure misclassification when relying only on urinary cotinine. Because the ovarian follicle does not have a direct blood supply, and since cotinine levels in follicular fluid reflect to what extent the oocyte was directly exposed to the constituents of tobacco smoke during late its development, follicular fluid cotinine is likely a more relevant measure of biologically effective dose in studies of early reproduction compared to cotinine in urine or blood samples. Other matrices useful for measuring cotinine or other components of tobacco smoke during pregnancy may include amniotic fluid, cord blood, umbilical cord or placental tissue, meconium or breast milk [29]. Biomarkers such as carbon monoxide, polycyclic aromatic hydrocarbons, and thiocyanate have been measured in biological samples, but these are not specific to tobacco smoke and can result in exposure

misclassification [22]. These markers may also not be relevant to the health outcome of interest in studies of reproduction and pregnancy.

TOBACCO SMOKE AND PREGNANCY

There is growing concern surrounding potential adverse reproductive health effects and pregnancy outcomes resulting from exposure to STS among both men and women. Only 50 to 60 percent of all conceptions advance beyond 20 weeks of gestation [30], and up to seventy-five percent of the lost pregnancies are a result of blastocyst implantation failure and are never clinically recognized as pregnancies [31]. Thus, these early losses may manifest clinically as female infertility. For the most part, factors involved in failed implantation remain unidentified. The ability of a blastocyst to implant in the endometrial surface may be associated with endometrial receptivity, oocyte quality, or delayed implantation, though oocyte quality is likely the most important factor [31]. Oocyte quality can be significantly affected by its surrounding environment [32], and the follicular microenvironment is influenced by a complex balance of many physiological, biochemical and potentially environmental factors.

Active smoking is associated with female subfertility resulting from a number of potential mechanisms [reviewed by 33–35], while similar studies among passively exposed women remain quite limited. Constituents of cigarette smoke (cadmium and cotinine) have been measured in follicular fluid of both active and passive smokers [23–27], indicating that exposure to cigarette smoke may allow toxic compounds to interact directly with the cells of the follicle and the developing oocyte. In laboratory animals, cadmium exposure resulted in an increased proportion of oocytes and embryos with chromosomal anomalies, and a decline in the number of oocytes reaching metaphase II [36]. Intrafollicular exposure to cigarette smoke, measured as cotinine concentration in follicular fluid, was associated with a significant increase in follicular lipid peroxidation intensity in active smokers [23] and an increased risk of DNA damage in granulose-lutein cells of both active and passive smokers [24]. Oocytes from women with follicular fluid cotinine levels above 20 ng/ml (representing active smokers) experienced significantly lower fertilization rates (44%) than oocytes from women with follicular fluid cotinine levels less than 20 ng/ml (72%) [26]. Oocyte numbers, function, and viability have also been found to be quantitatively and qualitatively impaired in smoking patients undergoing IVF-embryo transfer [37, 38]. A study of 499 women seeking IVF treatment found decreased pre-retrieval serum estradiol concentrations, lower numbers of retrieved oocytes, fewer embryos, and a 50% reduction in implantation rate among smokers compared to women who had never smoked [38].

Approximately one-third of pregnancies are lost after implantation [30]. Causes of post-implantation loss are also poorly understood. A large percentage of cleaved embryos have chromosome aberrations [39], mostly as a result of abnormalities during oogenesis leading to abnormal gametes, which likely contributes to a portion of the high rate of embryonic arrest [40]. Active smoking is associated with spontaneous abortion, abnormal placentation, intrauterine growth retardation, preterm delivery, perinatal mortality, congenital malformations [reviewed by 41], and lower rates of implantation and IVF success [38, 42]. Less is known about these outcomes among passive smokers, but metabolites of cigarette smoke have been measured in fetal blood at higher concentrations than in that of the mother [43–45], suggesting that nicotine and other compounds in secondhand smoke concentrate in the fetus. In addition, fetal serum and amniotic fluid metabolite levels from passive smokers reached 30 to 44% of the corresponding levels from active smokers, respectively [45], higher than what would be expected considering passive smokers typically have serum metabolite concentrations at less than 1% to 10% of those found in active smokers [13]. In hamsters, exposure to sidestream cigarette smoke at concentrations that reflect secondhand

smoke exposure in humans was found to delay the rate of embryo transport through the oviduct, and sidestream smoke actually exhibited greater toxicity than mainstream smoke concentrations that were representative of active smokers [46]. Thus, the potential reproductive and developmental effects associated with STS exposure are of concern.

SECONDHAND TOBACCO SMOKE EXPOSURE, FEMALE INFERTILITY AND ADVERSE PREGNANCY OUTCOMES

While more data are available on reproductive health and pregnancy outcomes related to active smoking there is a growing body of literature of these effects among women exposed to STS (see Table 1). Studies conducted prior to 2006 were reviewed in the U.S. Surgeon General's report, *The Health Consequences of Involuntary Exposure to Tobacco Smoke* [47]. The body of literature at that time was inadequate to infer the presence or absence of a causal relationship between maternal STS exposure and infertility, pregnancy loss, or congenital malformations. Since the Surgeon General's report, several studies have investigated the associations between maternal exposure to STS and adverse reproductive effects or pregnancy outcomes. However, a majority of the studies used self-reported STS exposure categories and are susceptible to exposure misclassification and/or bias, underscoring the need for further study using biomarkers of exposure.

Infertility

Studies of declined female fecundity in relation to STS exposure are quite limited. One study that utilized cotinine concentrations in follicular fluid to categorize exposure reported no significant differences in pregnancy and fertilization rates between active, passive and nonsmokers [48]. That study's small sample size however (N = 197; 103 active smokers; 26 passive smokers) and resultant lack of statistical power may partially explain its null findings. Furthermore, a negative association between STS exposure and fertility has been reported in other larger studies, though their findings were based on self-reported exposure. A retrospective study of fertile women found that the risk of experiencing delayed conception for at least six months was significantly elevated among women that reported STS exposure, and the risk estimate was similar in magnitude to that for women who actively smoked [49]. In a more recent study, women self-reporting STS exposure had greater difficulty becoming pregnant and experienced increased fetal loss (see "pregnancy loss" below) compared to those reporting no exposure [50].

Results from a few additional studies suggest that STS exposure may be associated with infertility *via* altered endocrine and menstrual function. Prolactin is involved in many reproductive processes [51], and hyperprolactinemia may be a cause of infertility in a small number of women [52]. A statistically significant increase in prolactin concentrations among STS-exposed nonsmokers compared to unexposed nonsmokers was recently observed among 314 women undergoing IVF treatment [53]. In that study, STS exposure was determined by cotinine concentrations in follicular fluid. In another study, healthy nonsmoking Chinese women attempting to become pregnant who self-reported STS exposure had lower levels of estrogen metabolite (E_1C) in urine during cycles where conception did not take place [54]. Self-reported STS exposure was also associated with increased risk of dysmenorrhea among the women [55]; however, this relationship may be confounded by other factors. Finally, exposure to STS has been linked to increased FSH levels in women 38–49 years of age [56], while another study reported increased risk of early onset of menopause among STS-exposed women [57].

Pregnancy Loss

The effects of STS exposure on pregnancy loss at varying stages have been explored in several epidemiologic studies. Some of these were recently reviewed in a meta-analysis [58]. A small but significant increase in the risk of stillbirth (pooled-odds ratio [OR] = 1.23; 95% confidence interval [CI] = 1.09–1.38) was reported after reanalyzing data from four studies among women exposed to STS during pregnancy. No significantly increased risk, however, was observed for spontaneous abortion or specific congenital abnormalities (see "adverse birth outcomes" below) after reanalyzing data from six and seven studies, respectively.

Individual studies of pregnancy loss have employed varied methodologies and have reported inconsistent results. A study using daily urinary hCG levels to detect early pregnancy loss among 526 nonsmoking Chinese female textile workers investigated associations between early pregnancy loss and having a husband who smoked [59]. Increased odds of early pregnancy loss (OR = 1.81; 95% CI = 1.00–3.29) among women with husbands that smoked more than 20 cigarettes per day were reported. Associations with paternal smoking may reflect either effects related to maternal exposure to STS or sperm damage associated with active smoking in the male partner, or possibly a combination of both factors. A study of non-smokers among 3,000 California women enrolled in a 1992 prenatal screening program reported associations between maternal serum cotinine levels and increased odds for fetal death, preterm delivery, and term-low birth weight [60], though the association for fetal death was not statistically significant due to a small number of cases. An earlier, large case-control study (626 cases and 1,300 controls) from California also showed an increased risk for spontaneous abortion among mothers exposed to STS for one hour or more per day [61], while another Californian prospective cohort study reported null findings [62]. A large study of Swedish women undergoing prenatal care found increased risk for first-trimester fetal loss among women reporting STS exposure in the workplace [63]. A more recent Swedish case-control study utilizing biomarkers of STS exposure as opposed to self-report found a statistically significant increased odds of spontaneous abortion among women classified as STS-exposed based on plasma cotinine concentrations (between 0.1 and 15 ng/mL cotinine) [64]. Furthermore, a large US study reported increased risk of fetal loss (OR = 1.23; 95% CI 1.08–1.40) among women self-reporting STS exposure in adulthood [50]. The authors also observed a dose-response relationship between increasing current daily hours of STS exposure and fetal losses, though this trend was only statistically suggestive (p-trend = 0.10).

The advent of assisted reproductive technologies (ART) has allowed for improved ability to design studies investigating factors in failed conception or early pregnancy loss. Several reports to date have utilized two sizable ART cohort studies to investigate associations between STS exposure and early pregnancy. A study among 225 women undergoing *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI) in a Canadian reproductive clinic in years 2003–2004 [65] reported significantly lower implantation rates and pregnancy rates among both active smokers and passive smokers compared to nonsmokers. However, passive smoking (STS exposure) among the women in the study was measured only by self-report. In addition, the statistical analyses were somewhat limited in that they did not account for potential confounding variables in multivariate analyses. A US report of couples utilizing ART in Boston in years 1994–1998 measured cotinine concentrations in urine (adjusted for dilution using creatinine) from 921 women [66], but found no associations between urinary cotinine and failed implantation or spontaneous abortion in multivariate analysis. However, the authors did report an unexpected predictor of spontaneous abortion using self-reported STS exposure data (see "latent effects" below). Two larger (N = 2,162 and N = 1,909, respectively) follow-up studies of couples in the Boston-area ART cohort were conducted. The first reported a suggestive increased risk for failed implantation among

women with self-reported STS exposure at home and/or at work [67]. The second study utilized data from all IVF treatment cycles and cotinine concentrations in follicular fluid to classify STS exposure [68]. The authors reported a significantly increased risk of implantation failure and significantly decreased probability of a live birth among women exposed to STS compared with those unexposed.

Adverse Birth Outcomes

The majority of human studies investigating the impact of STS exposure on reproduction have been limited to pregnancy outcomes (e.g. low birth weight, preterm birth) as opposed to infertility or early clinical measures of successful pregnancy. Both active and passive smoking have been found to alter expression of key mediators of placental development [69], which may describe a potential mechanism for the decreased birth weights and increased risk of low birth weight (<2500 grams) that were associated with maternal STS exposure in a number of studies [previously reviewed by 12, 70–72]. In several meta-analyses, exposure to STS has been estimated to reduce mean birthweight by approximately 25–40 grams [reviewed by 12]. This estimate is consistent with a more recent study of over 18,000 singleton births from data collected by the UK Millennium Cohort Study, which found that self-reported maternal exposure to STS lowered the adjusted mean infant birth weight by 36 grams (95% CI = 5–67 grams) compared to women with no exposure to tobacco smoke [73].

The effects of maternal STS exposure on gestational length are still unclear. Several studies have reported significantly increased risk of preterm delivery among STS-exposed women [74–79], while others have reported null findings [80–82]. Studies published prior to 2008 have been previously reviewed in a meta-analysis which found no effect of STS exposure on gestational length [72]. A recent cross-sectional study of 33 Malaysian women also found no association between preterm birth and STS exposure which was estimated *via* cotinine in maternal saliva [83].

Results from the limited studies investigating associations between STS exposure and birth defects have been inconsistent, but suggestive [12]. Increased risks for severe congenital malformations and facial clefts, urethral stenosis, spina bifida, diaphragmatic hernia and pigmentary anomalies have been reported [84–87]. However, STS exposure assessment in each of these studies was limited to presence of paternal smoking during pregnancy. Thus, observed effects may be due to maternal/fetal environment factors, male germ cell factors, or a combination of both. A recent meta-analysis reanalyzed the results from seven studies of the effects of maternal STS exposure and congenital malformations [58]. Individual studies included in the analysis showed no significant increase in the risk of various types of malformations due to STS exposure. When analyzed together, however, the authors reported a significant increase of congenital malformations in general from maternal STS exposure (pooled-OR = 1.13; 95% CI = 1.01–1.26).

Latent Effects

There is currently growing concern over the potential for adverse health effects that arise in adulthood as a result of harmful environmental exposures *in utero* or during childhood [88, 89], and several studies have examined reproductive difficulties in particular in the offspring of women who smoked. Declined semen quality has been documented in men exposed to active maternal smoking *in utero* [90–92]. Likewise, in females, three studies have linked fetal exposure to active maternal smoking with reduced fecundability in adulthood [93–95]. There is a paucity of similar studies of latent reproductive effects following early exposure to secondhand smoke. In a study of patients at a US cancer hospital, 4,800 women contributed data on self-reported pregnancy outcomes and STS exposure [50]. Increased

odds of infertility (OR = 1.57; 95% CI = 1.15–2.15) was observed among women who were exposed to STS as a child but not as an adult. As a secondary aim, the Boston (US) study of 921 couples undergoing ART assessed the female partner's self-reported exposure to parental smoking as a child in relation to ART cycle outcomes [66]. After adjusting for age, year of treatment, and number of embryos transferred, there was a significantly increased risk of spontaneous abortion (OR = 4.35; 95% CI = 1.04–18.1) among women reporting that both parents smoked during their childhood compared with women reporting that neither parent smoked. In a follow-up study that included 2,162 couples, the increased risk for spontaneous abortion among women with parents that smoked during childhood remained, with a dose-dependent increase in odds ratios when 0, 1 or 2 parents smoked [67].

CONCLUSION

There is a growing body of literature suggesting adverse effects on fertility and early pregnancy loss in relation to STS exposure. However, human studies of these outcomes remain limited and more epidemiologic research is required. Human studies of exposure to STS and fetal growth are rather numerous and present strong evidence that exposure decreases birth weight, although more research is needed to shed light on biologic mechanisms and dose-response relationships. It is unclear whether and to what extent STS exposure reduces gestational length and increases congenital malformations or latent reproductive health effects. To the degree possible, future studies should employ more complete and state-of-the art exposure assessment strategies. This may include the use of relevant exposure biomarkers, identification and characterization of crucial windows of exposure, and improved methods to address timing, frequency, duration and temporal variability of STS exposure. Because STS is a mixture of hundreds of compounds (dozens of which are known or suspected reproductive toxins), more information is needed on the specific agents to which observed health effects can be attributed. Future research should also aim to determine the relative contributions of paternal and maternal factors to reduced fecundity and adverse pregnancy outcomes in relation to smoking and STS exposure. In addition, a number of other environmental agents have been implicated in reduced fecundity and/or adverse pregnancy outcomes (e.g. pesticides), and studies to date have not considered potential confounding or modification (e.g. environment-environment interactions) of effect estimates by hazardous co-exposures or other environmental factors. Finally, it is known that responses to xenobiotic exposures are not uniform across individuals and populations, and future studies should set out to identify individual susceptibility factors that modify the dose-response relationship between STS exposure and adverse reproductive outcomes (e.g. gene-environment interactions).

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Table 1

Reproductive Difficulties Observed in Relation to Maternal Secondhand Tobacco Smoke (STS) Exposure

Reproductive Difficulty	Reference	Study Design	Exposure Assessment	Specific Endpoint(s)	Effect Estimate(s)	95% CI
Infertility/ART Failure	Benedict *et al.*, 2011 [68]	Retrospective analysis of prospective cohort	Follicular fluid cotinine	Implantation failure	1.52[a] 1.17[b]	1.20–1.92 1.10–1.25
	Hull *et al.*, 2000 [49]	Retrospective analysis of prospective cohort	Self-reported	Delayed conception	1.17[a]	1.02–1.37
	Meeker *et al.*, 2007a [66]	Retrospective analysis of prospective cohort	Urinary cotinine	Implantation failure	0.98[a]	0.70–1.37
	Meeker *et al.*, 2007b [67]	Retrospective analysis of prospective cohort	Self-reported	Implantation failure	1.43[a]	0.97–2.09
	Neal *et al.*, 2005 [65]	Retrospective cohort	Self-reported	Implantation rate	Difference in rate[c]	N/A (p-value <0.01)
				Pregnancy rate	Difference in rate[d]	N/A (p-value <0.001)
	Peppone *et al.*, 2009 [50]	Retrospective cohort	Self-reported	Difficulty becoming pregnant	1.24[a]	1.03–1.51
	Sterzik *et al.*, 1996 [48]	Prospective cohort	Follicular fluid cotinine	Fertilization rate	Difference in rate[e]	N/A (p-value = 0.59)
				Pregnancy rate	Difference in rate[f]	N/A (p-value = 0.99)
Pregnancy loss	Ahlborg and Bodin, 1991 [63]	Prospective cohort	Self-reported	First-trimester fetal loss	2.16[b]	1.23–3.81
	George *et al.*, 2006 [64]	Case-control	Plasma cotinine	Spontaneous abortion	1.67[a]	1.17–2.38
	Kharrazi *et al.*, 2004 [60]	Case-control	Serum cotinine	Fetal death	3.36[a]	0.81–13.96
	Leonardi-Bee *et al.*, 2011 [58]	Meta-analysis	Varied	Stillbirth	1.23[g]	1.09–1.38
				Spontaneous abortion	1.17[g]	0.88–1.54
	Meeker *et al.*, 2007a [66]	Retrospective analysis of prospective cohort	Urinary cotinine	Spontaneous abortion	0.51[a]	0.21–1.24
	Meeker *et al.*, 2007b [67]	Retrospective analysis of prospective cohort	Self-reported	Spontaneous abortion	0.80[a]	0.30–2.14
	Peppone *et al.*, 2009 [50]	Retrospective cohort	Self-reported	Fetal loss	1.23[a]	1.08–1.40
				Fetal loss or difficulty becoming pregnant	1.30[a]	1.15–1.47
	Venners *et al.*, 2004 [59]	Prospective cohort	Self-reported	Early pregnancy loss	1.81[a]	1.00–3.29

Reproductive Difficulty	Reference	Study Design	Exposure Assessment	Specific Endpoint(s)	Effect Estimate(s)	95% CI
	Windham *et al.*, 1992 [61]	Case-control	Self-reported	Spontaneous abortion	1.5[a]	1.2–1.9
	Windham *et al.*, 1999 [62]	Prospective cohort	Self-reported	Spontaneous abortion	1.01[a]	0.80–1.27
Adverse birth outcomes	Arffin *et al.*, 2012 [83]	Cross-sectional	Salivary cotinine	Preterm birth or miscarriage	Cotinine difference[h]	N/A (p-value = 0.598)
	Leonardi-Bee *et al.*, 2008 [72]	Meta-analysis	Varied	Gestation period	−0.04[i]	−0.22–0.13
				Low birth weight	1.32[g]	1.07–1.63
	Leonardi-Bee *et al.*, 2011 [58]	Meta-analysis	Varied	Congenital malformations	1.13[g]	1.01–1.26
Latent effects	Meeker *et al.*, 2007a [66	Retrospective analysis of prospective cohort	Self-reported (childhood)	Spontaneous abortion	4.35[a]	1.04–18.
	Meeker *et al.*, 2007b [67]	Retrospective analysis of prospective cohort	Self-reported (childhood)	Spontaneous abortion	1.75[a]	1.01–3.04
	Peppone *et al.*, 2009 [50]	Retrospective cohort	Self-reported (childhood)	Difficulty becoming pregnant	1.27[a]	1.03–1.56
				Fetal loss	1.02[a]	0.89–1.18
				Fetal loss or difficulty becoming pregnant	0.99[a]	0.82–1.16

[a] Adjusted odds ratio

[b] Adjusted risk ratio

[c] Implantation rate was 25.0% for unexposed nonsmokers and 12.6% for women exposed to STS

[d] Pregnancy rate per embryo transferred was 48.3% for unexposed nonsmokers and 20.0% for women exposed to STS

[e] Fertilization rate was 68%for unexposed nonsmokers and 58% for women exposed to STS

[f] Pregnancy rate was 33%for unexposed nonsmokers and 33% for women exposed to STS

[g] Pooled odds ratio

[h] There was no significant difference in cotinine concentrations between the test group (women with preterm birth or miscarriage) and control group

[i] Mean difference in gestational period (in weeks) between women exposed to STS and unexposed nonsmokers