



Original Contribution

Risk of Spontaneous Abortion in Women with Childhood Exposure to Parental Cigarette Smoke

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There is increasing concern over whether environmental exposures early in life may impact health in adulthood. Recent evidence suggests that prenatal or childhood exposure to cigarette smoke may result in poorer reproductive health later in life. Among 2,162 nonsmoking women recruited from three Boston, Massachusetts, clinics who underwent assisted reproductive treatments between 1994 and 2003, adjusted odds ratios for pregnancy outcomes in the initial treatment cycle were calculated in relation to self-reported childhood exposure to parental cigarette smoke. Women who reported having two parents who smoked during their childhood had increased odds of a spontaneous abortion compared with women reporting that neither parent smoked (adjusted odds ratio = 1.8, 95% confidence interval: 1.0, 3.0). A trend for increased risk was observed for women reporting that zero, one, or two parents smoked. In secondary analysis, the authors also found suggestive evidence for increased risk of failed embryo implantation among women reporting current secondhand tobacco smoke exposure. Future large studies of pregnancy loss are needed that can distinguish women's tobacco smoke exposure in childhood from that taking place in utero.

abortion, spontaneous; maternal exposure; parents; risk; tobacco smoke pollution; women

Abbreviations: CI, confidence interval; OR, odds ratio.

There is growing concern over whether in utero and/or childhood exposures to xenobiotics result in adverse health outcomes later in life (1–5). Among a multitude of potentially harmful toxicants in the environment, tobacco smoke is one of the most prevalent and preventable exposures among the general population (6). Evidence for associations between prenatal exposure to maternal cigarette smoking and decreased male reproductive health (reduced semen quality) has been recently reported in large European epidemiologic studies (7–9). Similar reports for early female exposure to tobacco smoke and adverse reproductive effects

as adults are limited to studies of fecundability (10). We recently conducted a study of maternal exposure to secondhand tobacco smoke and pregnancy outcomes (11). In that study, a compelling finding emerged from a secondary aim, where the odds of experiencing a spontaneous abortion following assisted reproduction technologies were fourfold higher (odds ratio (OR) = 4.4, 95 percent confidence interval (CI): 1.0, 18.1) for women who reported that both of their parents smoked while the women were children compared with women who reported that neither of their parents smoked. It was hypothesized that the observed association

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was either due to chance, since a number of comparisons were made in the study, or perhaps represented an important exposure period for female reproductive development either in utero or as a child. The present study adds considerable size to the previous cohort to further test the robustness of the association. It includes subjects recruited over 10 years instead of 4 years from the previous work, with data from over 2,300 couples undergoing assisted reproduction technologies compared with 921 couples in the previous study.

MATERIALS AND METHODS

Couples in the present study overlap with those from our previous report. Study details have been described previously (11). Briefly, from August 1994 until June 2003, couples undergoing in vitro fertilization or intracytoplasmic sperm injection were recruited through three Boston, Massachusetts, area clinics. Study protocols were approved by human research committees at Brigham and Women's Hospital, Harvard School of Public Health, and the University of Michigan. Approximately 65 percent of couples who were approached agreed to participate. Couples who required either donor eggs or donor semen were excluded, as were couples who were gestational carriers and those who underwent gamete intrafallopian transfer. Following these exclusions, 2,350 couples were enrolled. An additional 188 couples were excluded from the analysis because the female partner was a smoker at the time of the first clinic visit, and another 713 couples diagnosed with male-factor infertility were excluded. Self-administered questionnaires obtained information about medical history and lifestyle factors, and details about first-cycle in vitro fertilization/intracytoplasmic sperm injection treatment and outcome were abstracted from clinical records. Self-reported secondhand tobacco smoke exposure at home (due to partner or other household member smoking) or at work was obtained through the self-administered questionnaire. In addition, participants' childhood exposure to secondhand tobacco smoke was estimated through questions on parental smoking while growing up. The following questions appeared on the questionnaire.

1. Did your mother or father smoke any tobacco products when you were growing up?
 - ☐ Neither smoked
 - ☐ Mother smoked
 - ☐ Father smoked
 - ☐ Both smoked
2. At home or at work are you regularly exposed to tobacco smoke in any of the following ways? (Check all that apply.)
 - ☐ At home from a spouse who smokes
 - ☐ At home from another household member who smokes
 - ☐ At work from a coworker in an unregulated smoking environment
 - ☐ At work from a coworker in a regulated smoking environment

Conditional logistic regression analyses were performed by fitting multiple logistic regressions to estimate the odds of a spontaneous abortion only on the subset of subjects that had not experienced a failure up to that point, instead of among all subjects (i.e., must have had a clinical pregnancy). For example, a woman/couple who experienced a failed implantation would not be included in the analysis for spontaneous abortion. Because implantation was the most common failure experience by the couples, it was included in the analysis as a secondary aim. Variables considered as potential confounders were age, race, body mass index, months trying to get pregnant, year of in vitro fertilization treatment, clinic/site of in vitro fertilization treatment, ovarian stimulation method, ampules of gonadotropin, number of oocytes transferred, assisted hatching, and day of embryo transfer. Inclusion of covariates in the final models was based on biologic and statistical considerations (12).

RESULTS

Female partners from the couples recruited into the study had a mean age of 35 (standard deviation: 4.3) years, were primarily White (90 percent), and had never smoked (71 percent) (table 1). Ninety-six (4 percent) of the couples experienced a spontaneous abortion in their first cycle of assisted reproduction technologies (table 2). Among the first cycles, a high proportion (42 percent) of the couples experienced a failure at implantation, while just over one quarter (28 percent) experienced a successful livebirth. After exclusion of active smokers and couples with male factor infertility, 1,449 couples remained in the final analysis.

In logistic regression models adjusted for age, year, and the number of embryos that were transferred (table 3), women who reported that both parents smoked while they were growing up had increased odds of experiencing a spontaneous abortion following their first cycle of assisted reproduction technologies treatment (OR = 1.8, 95 percent CI: 1.0, 3.0). Women who reported that only their mother smoked or only their father smoked had effect estimates near unity, while combining those into an "either (but not both) parent smoked" group resulted in a suggestively increased odds ratio (OR = 1.6, 95 percent CI: 0.8, 3.1). A test for trend showed that the odds of spontaneous abortion increased among women with zero, one, or two parents who smoked (per added parent, OR = 1.5, 95 percent CI: 1.1, 2.1). No associations between current exposures to secondhand smoke and spontaneous abortion were found, but those analyses had limited power because of a low number of women who reported secondhand exposure.

There were no associations between parental smoking during the women's childhood and risk of experiencing failure of implantation (table 4). However, women reporting any current exposure to secondhand smoke at home or at work had a suggestive increase in the odds of failed implantation compared with women reporting no secondhand exposure (OR = 1.4, 95 percent CI: 1.0, 2.1). When that variable was divided into exposure at home or at work, women exposed to a partner's smoke had a suggestive increased odds of implantation failure (OR = 1.7, 95 percent CI: 0.9, 3.0).

TABLE 1. Study demographics for 2,162 nonsmoking women seeking fertility treatment, Boston, Massachusetts, 1994–2003*

	No.	%
Race		
White	1,942	90
Non-White	220	10
Ever smoked		
No	1,532	71
Yes	630	29
Primary infertility diagnosis		
Male factor	713	33
Ovulatory	266	12
Endometriosis	273	13
Tubal inflammation/occlusion	443	21
Cervical/uterine	68	3
Unexplained	391	18
Year of treatment		
1995–1999	1,111	51
2000–2003	1,051	49
No. of embryos transferred		
0	356	16
1	131	6
2	621	29
3	597	28
4	285	13
≥5	172	8
Self-reported current secondhand tobacco smoke exposure		
At home, from smoking partner	89	4
At home, other household member	27	1
At work	143	7
Any reported secondhand tobacco smoke exposure	236	11
Parental smoking while growing up		
Neither parent smoked	737	34
Mother only smoked	407	19
Father only smoked	401	19
Both parents smoked	605	28
	Mean	SD†
Female age (years)	35.4	4.3

* Information on infertility diagnosis and parental smoking was missing for eight subjects and 10 subjects, respectively.

† SD, standard deviation.

DISCUSSION

The primary aim of the present study was to extend our earlier results using a larger study population to investigate the association between exposure to parental smoking as a child and increased risk of spontaneous abortion among pregnancies as an adult. We found that women reporting that both parents smoked when they (the women in the study)

TABLE 2. Outcome of first in vitro fertilization cycle for 2,162 couples, Boston, Massachusetts, 1994–2003

Reason for failure	No. of couples	%
Initiated in vitro fertilization treatment	2,162	
Began medicines but canceled before retrieval	163	8
Retrieval unsuccessful or of poor quality	7	0
Failure of fertilization (semen of poor quality)	7	0
Embryo creation of poor quality	110	5
All embryos frozen and cycle canceled	67	3
Failure of implantation (i.e., never achieved chemical or clinical pregnancy)	915	42
Failure of development		
Chemical pregnancy but never achieved clinical pregnancy	146	7
Clinical pregnancy was molar	1	0
Clinical pregnancy was ectopic	23	1
Clinical pregnancy was therapeutically aborted	5	0
Clinical pregnancy was spontaneously aborted	96	4
Fetus was stillborn	6	0
Successful livebirth	603	28
Unknown outcome	13	1

were children had increased odds of experiencing a spontaneous abortion as compared with women who reported that neither parent smoked. Secondary aims of the study were to explore associations between self-reported current exposure to secondhand smoke and risk of spontaneous abortion, as well as associations between current and past exposure to tobacco smoke and implantation failure—the most prevalent point of failure for those attempting to conceive via assisted reproduction technologies. Self-reported current exposure to secondhand tobacco smoke either at home or at work, or more specifically due to a smoking partner, was suggestively associated with increased odds of implantation failure.

Potential mechanisms involved in these reported associations have yet to be elucidated. However, tobacco smoke contains thousands of chemicals, a number of which are known or suspected reproductive toxicants (e.g., cadmium, lead, benzene, and so on) (13). In addition, fetal and childhood stages are critical developmental periods for virtually all tissues, organs, and systems in the body, and increased sensitivity to harmful exposures during these periods is of concern for immediate and latent adverse health outcomes.

Strengths of the present study include its size and the detailed, clinically verified documentation of pregnancy outcomes. In addition, because the study was conducted among couples undergoing assisted reproduction, it involved a motivated study group that likely resulted in a higher participation rate than would be achieved in a similarly invasive study among the general population. A study among couples undergoing assisted reproduction technologies also allowed for the exploration of contributing factors to early pregnancy loss (e.g., failed implantation) that is not possible to

TABLE 3. Adjusted* odds ratios and associated 95% confidence intervals for spontaneous abortion associated with parental and current exposure to smoking, Boston, Massachusetts, 1994–2003†

	No. of exposed cases	Odds ratio	95% confidence interval
Childhood exposure			
Only mother smoked‡	12	0.98	0.50, 1.93
Only father smoked‡	13	1.07	0.55, 2.09
Either parent smoked‡	25	1.60	0.81, 3.12
Both parents smoked‡	26	1.75	1.01, 3.04
Current exposure			
Any reported secondhand exposure§	5	0.80	0.30, 2.14
Secondhand exposure at work§	4	0.64	0.08, 5.20
Secondhand exposure from partner§	1	0.45	0.06, 3.49

* Adjusted for age, year, and number of embryos transferred.

† There were 460 nonsmoking women with non-male factor infertility at risk for spontaneous abortion.

‡ Comparison group: neither parent smoked.

§ Comparison group: no reported secondhand tobacco smoke exposure.

measure in a study among couples in the general population trying to get pregnant.

The present study also has several limitations. First, the exposure measures were based on self-report, which may introduce error and the potential for recall bias, though recall bias was not a concern since in vitro fertilization outcome was not known when the questionnaire was completed. Second, our ability to estimate the precise exposure window that was most relevant to the outcome was limited because we were unable to separate fetal exposures to direct or passive smoking from secondhand exposure in childhood. We assume that the group of women exposed to parental smoking as a child likely included a subset of women whose mothers also smoked during their pregnancy, and that mothers were unlikely to smoke during pregnancy and then quit while the women in the present study were children. However, the lack of an association between women whose mother was the only parent who smoked and spontaneous abortion provides limited evidence against the contribution of prenatal exposures to maternal smoking (11), unless maternal smoking during pregnancy was for some reason associated with having two parents that smoked during childhood but not with having only a mother who smoked during childhood. Another limitation of the present study was that information on frequency or magnitude of exposure was not collected to allow for the exploration of dose response. We also did not collect detailed exposure information from male partners, as paternal exposures to agents such as solvents may impact outcomes from assisted reproduction technologies (14). In the present study, this potential source of confounding would likely have been controlled to some degree by the exclusion of couples diagnosed with

TABLE 4. Adjusted† odds ratios and 95% confidence intervals for failed implantation associated with parental and current exposure to smoking, Boston, Massachusetts, 1994–2003‡

	No. of exposed cases	Odds ratio	95% confidence interval
Childhood exposure			
Only mother smoked§	128	1.17	0.86, 1.58
Only father smoked§	109	1.01	0.75, 1.38
Either parent smoked§	237	1.09	0.82, 1.44
Both parents smoked§	184	0.91	0.70, 1.19
Current exposure			
Any reported secondhand exposure¶	78	1.43*	0.97, 2.09*
Secondhand exposure at work¶	45	1.60	0.76, 3.37
Secondhand exposure from partner¶	32	1.67*	0.91, 3.06*

* $p < 0.1$.

† Adjusted for age, year, and number of embryos transferred.

‡ There were 1,208 nonsmoking women with non-male factor infertility at risk for failed implantation.

§ Comparison group: neither parent smoked.

¶ Comparison group: no reported secondhand tobacco smoke exposure.

male-factor infertility (i.e., poor semen quality) from the primary data analyses. Finally, if infertile couples undergoing assisted reproduction technologies respond to cigarette smoke exposure differently from people in the general population, then the ability to generalize the results may be limited. Nevertheless, even if infertile couples undergoing assisted reproduction technologies represent only a population sensitive to tobacco smoke exposure, the results are still of interest.

In conclusion, results from the present study are in part consistent with our previous findings. In the present study, which was conducted among a larger population than was our previous report, the increased risk of having a spontaneous abortion when both parents smoked remained, although the magnitude of the effect was smaller (but with narrower confidence intervals). Other larger studies are needed to account for the low prevalence of spontaneous abortions. They should include more detailed exposure assessments that are also designed to distinguish women's tobacco smoke exposure in childhood from that taking place in utero.

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