Nitrous Oxide and Spontaneous Abortion in Female Dental Assistants

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The relation between anesthetic gas exposure and spontaneous abortion remains unresolved. We examined the effect of nitrous oxide on spontaneous abortion among female dental assistants. Questionnaires were sent to 7,000 dental assistants aged 18–39 years who were registered in California in 1987; 4,856 (69%) responded. Analysis was based on 1,465 respondents whose most recent pregnancy was conceived while working full time. Women were asked how many hours a week they worked with nitrous oxide during this pregnancy and whether the excess gas was scavenged (vented). Relative risk of spontaneous abortion (through week 20) was calculated using a person-week model. This allowed women with current pregnancies (13%) or induced abortions (10%) to be included for appropriate time periods of risk. A total of 101 pregnancies (7%) ended as spontaneous abortions. An elevation in risk of spontaneous abortion was seen among women who worked with nitrous oxide for 3 or more hours per week in offices not using scavenging equipment (relative risk = 2.6, 95% confidence interval 1.3–5.0, adjusted for age, smoking, and number of amalgams prepared per week), but not among those using nitrous oxide in offices with scavenging equipment. This relation changed little when analyses were restricted to confirmed pregnancies or examined for several types of potential bias. Scavenging equipment appears to be important in protecting the reproductive health of women working with nitrous oxide. Am J Epidemiol 1995;141:531–8.

abortion, spontaneous; air pollutants, occupational; cohort studies; dental staff; nitrous oxide; occupational diseases

The relation between occupational exposure to anesthetic gases (including nitrous oxide) and spontaneous abortion has never been resolved, despite being one of the most frequently studied topics in reproductive epidemiology. Six studies with 500 or more pregnancies reported moderate associations (1-6), but four others reported relative risks of only 1.1 or 1.2 (7-10). Three of the null studies (8-10) involved were conducted recently, however, after almost all hospitals had installed scavenging (venting) equipment and exposure levels had been dramatically reduced. It therefore is difficult to know whether the previously reported positive association between anesthetic gases and spontaneous abortion was the result of selection bias and other flaws, as some researchers have suggested (11-13), or of higher exposures in the earlier time period.

Even in the positive studies, the reported spontaneous abortion effect was often only weak to moderate, with relative risks of between 1.3 and 2.0. However, in almost all studies, exposure was assessed crudely, on the basis of job titles alone (e.g., operating room staff vs. other hospital personnel). Thus, a possible explanation for the weakness of the reported associations was that exposure was poorly characterized. The one study that collected detailed exposure information on the number of hours of exposure per week (4) reported a relative risk of about 2.4 for their highest exposure group.

Nitrous oxide is believed to be the toxicant responsible for the adverse reproductive outcomes reported among workers exposed to anesthetic gases (14), most of which are administered with nitrous oxide. In laboratory animals, nitrous oxide causes malformations, increases fetal resorptions, and decreases live litter size (15-17). These effects have been consistently demonstrated with continuous exposures of 1,000 ppm or higher. At lower exposure levels or with shorter, more intermittent exposure, increased fetal loss is not seen consistently (18, 19), although increased loss has...
been reported in rats exposed to as little as 100 ppm nitrous oxide for 8 hours a day (20).

Nitrous oxide exposure levels tend to be higher in dental offices than in hospital operating rooms. In operating rooms, nitrous oxide is usually used as a carrier gas for other, more potent anesthetics. Exposures there typically are better controlled because there is frequent air exchange and scavenging equipment is almost always in place to vent exhaled gas. In dental offices, nitrous oxide is mixed only with oxygen and is usually administered as a sedating agent, not as an anesthetic. Because a face mask cannot be placed over the dental patient’s mouth and office air exchange rates are lower, exposure levels can be quite high, particularly if scavenging equipment is not used. In dental offices without scavenging equipment, exposure levels during administration of nitrous oxide often exceed 1,000 ppm (21, 22), 40 times the 25 ppm standard recommended by the National Institute for Occupational Safety and Health and possibly 10 times the levels found in operating rooms or dental offices that use scavenging equipment (21-23).

Previously, we reported that exposure to 5 or more hours of unscavenged nitrous oxide per week was associated with reduced fertility in a cohort of female dental assistants of reproductive age (24). We use data from the same cohort to examine the relation between nitrous oxide exposure and spontaneous abortion.

MATERIALS AND METHODS

Study participants

We randomly selected 7,000 dental assistants, aged 18–39 years, from the 1987 dental assistant registry of the California Department of Consumer Affairs and sent them a four-page self-administered questionnaire. Questionnaires were mailed between June and October 1987. Nonrespondents were sent follow-up letters. Women with incorrect addresses were traced by using California driver’s license and vehicle registration files and postal service address corrections. After three mailings at 3-week intervals, nonrespondents with a listed telephone number were given a reminder call. The remaining nonrespondents were asked a shortened version of the questionnaire by telephone or sent a fourth follow-up letter.

Of the 7,000 dental assistants to whom a questionnaire was mailed, eight were dead or living out of the country. Of those remaining, 4,856 (69 percent) completed a questionnaire, 232 (3 percent) could not be traced, 204 (3 percent) acknowledged receipt but refused to participate, and 1,700 (24 percent) did not respond. Of the 4,856 respondents, 1,805 had been pregnant and, thus, at risk at the beginning of the week they conceived their most recent pregnancy and who reported that they had been working full time (30 or more hours per week) as a dental assistant at that time. These women comprise the sample used for analysis.

Questionnaire

The mail questionnaire included questions about a woman’s most recent pregnancy, her marital status, race, birth date, number of cigarettes per day smoked each year during the previous 7 years, work history as a dental assistant, and information about pregnancy history. For each of her dental assistant jobs, she was asked to provide information on nitrous oxide exposure, average number of hours worked per week, number of amalgams placed per week (an indirect measure of mercury exposure), and the methods used to sterilize instruments. To explore perceptions about risk of disease, participants were asked whether they believed working as a dental assistant increases a person’s risk of spontaneous abortion, infertility, acquired immune deficiency syndrome, and hepatitis B.

Occurrence of spontaneous abortion was ascertained from a woman’s report of her most recent pregnancy outcome. The most recent pregnancy was selected to maximize recall of pregnancy and exposure information. Women were asked the length of their pregnancy in weeks, whether they had had a positive pregnancy test, and if so, how many weeks into the pregnancy the test was done. Spontaneous abortions were defined as any pregnancy loss occurring before 21 weeks (excluding ectopic and molar pregnancies).

Exposures were assessed as of the date of the woman’s last menstrual period preceding her most recent pregnancy by cross-referencing last menstrual period dates with the work history information. To assess nitrous oxide exposure, for each job the questionnaire asked, “How many hours per week did you work in a room at the same time nitrous oxide was being used?” and “Was the nitrous oxide scavenged?” Dental scavenging equipment typically consists of a nasal mask and tubing that delivers nitrous oxide to the patient, captures unused gas and gas exhaled from the patient’s nose, and vents it away from the work area through a vacuum line.

Analytic approach

Spontaneous abortion data were analyzed using a person-week model that treated the occurrence of a spontaneous abortion in each gestational week as a dichotomous outcome. Separate risk sets consisting of all women who were pregnant and, thus, at risk at the beginning of the week were created for each gesta-
tional week. Pregnancies were entered into the risk sets starting at the estimated first week of pregnancy. The analysis was truncated at 20 weeks. Induced abortions were considered noninformative censoring events, assumed to have occurred at the end of the reported week, and current pregnancies were censored at the end of the gestational week of pregnancy during which the questionnaire was completed or, for pregnancies longer than 20 weeks, at 20 weeks. Analysis was done with logistic regression. This was approximately equivalent to using a Poisson regression model because of the use of person-weeks and the rarity of the outcome at each week. This approach provides a natural way to include induced abortions and current pregnancies through their observed period of risk, with right censoring at the appropriate point. This model yields a summary measure of the absolute risk of spontaneous abortion over gestational time.

Nitrous oxide exposure was divided into two separate variables: scavenged hours (hours of exposure per week in the presence of scavenging equipment) and unsca venged hours of exposure per week. Each of these exposures was examined as continuous and as multilevel categorical variables. Our earlier work on time to pregnancy had identified 5 hours of unsca venged nitrous oxide as a level at which biologic effects might occur (24). We further divided unsca venged nitrous oxide above and below this point in order to understand the exposure response relations in the data. On the basis of exploratory analysis, 3 hours of unsca venged nitrous oxide per week was ultimately selected as a cutpoint.

There were 102 women without nitrous oxide exposure data and seven exposed women without information on the number of hours they worked with nitrous oxide who were dropped from analysis. There were also 169 exposed women who reported the number of hours per week they worked with nitrous oxide, but did not report whether it was scavenged or not. These women were also omitted from the analysis, but those with a complete set of covariates (n = 142) were also included in a sensitivity analysis to determine what effect this missing data might have had on the point estimates presented.

Other covariates considered in univariate and multivariate models included race, age, cigarette smoking, years working as a dental assistant, seniority in current job, time since conception, current exposure to mercury amalgams, cumulative number of amalgams prepared in all dental assistant jobs before the last menstrual period date, and method of sterilization of instruments, including autoclave, chemiclave, cold sterilants, and ethylene oxide gas. Gravidity and history of previous spontaneous abortion were examined but were not included in the statistical models. Controlling for such prior outcomes can bias results (25). Other covariates with associations to spontaneous abortion that approached statistical significance were retained in the model. Interaction effects of factors related to spontaneous abortion and nitrous oxide were tested, but none contributed significantly to the model.

RESULTS

Table 1 presents a demographic profile of the study sample. Most were young; 86 percent were age 30 years or younger at the beginning of their pregnancy. Entry criteria required that everyone had been pregnant at least once; 44 percent had been pregnant only once. About 20 percent of the women were members of a minority; of these, over 70 percent were Hispanic. Almost three-quarters reported contact with mercury amalgams in their jobs, and about half reported working with nitrous oxide. Sixty-nine percent of the pregnancy outcomes included in the analysis were livebirths, 7 percent were spontaneous abortions, 10 percent were induced abortions, and 13 percent were current pregnancies (table 2).

There was a slight excess of spontaneous abortions (and deficit of livebirths) among women who worked in offices with unsca venged nitrous oxide (10.2 percent compared with 6.7 percent among the unexposed (table 2)). The follow-up time was differential by exposure since a smaller percentage of the women who worked with unsca venged nitrous oxide were pregnant at the time of interview. Therefore, a person-week analysis was indicated.

We then examined scavened nitrous oxide and unsca venged nitrous oxide in a multivariate model (table 3). Each exposure was a continuous variable measured by number of hours of exposure per week and entered as a linear term in the model. Estimates were adjusted for gestational week, age, smoking, and

| TABLE 1. Demographic description of the study sample of dental assistants registered in California in 1987 (n = 1,465) at the time of their most recent pregnancy |
|-----------------------------|--------|------|
| Age 31 years or older       | 201    | 13.7 |
| Primigravid                 | 632    | 43.7 |
| Minority†                   | 274    | 19.5 |
| Hispanic                    | 198    | 13.9 |
| Cigarette smokers           | 165    | 14.1 |
| Worked with mercury         | 1,058  | 73.8 |
| Worked with nitrous oxide   | 672    | 49.3 |

* Percentages based on the number of nonmissing values for each variable.
† Includes Hispanics, African Americans, Asians, and Native Americans.
TABLE 2. Birth outcomes by nitrous oxide exposure status, dental assistants registered in California, 1987

<table>
<thead>
<tr>
<th>Birth outcome</th>
<th>Unexposed</th>
<th>Unscavenged nitrous oxide</th>
<th>Scavenged nitrous oxide</th>
<th>Missing or incomplete nitrous oxide</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Livebirths</td>
<td>479</td>
<td>70.0</td>
<td>96</td>
<td>66.7</td>
<td>229</td>
</tr>
<tr>
<td>Currently pregnant</td>
<td>88</td>
<td>12.9</td>
<td>15</td>
<td>10.2</td>
<td>61</td>
</tr>
<tr>
<td>Spontaneous abortions</td>
<td>46</td>
<td>6.7</td>
<td>15</td>
<td>10.2</td>
<td>23</td>
</tr>
<tr>
<td>Induced abortions</td>
<td>63</td>
<td>8.2</td>
<td>16</td>
<td>10.9</td>
<td>41</td>
</tr>
<tr>
<td>Other*</td>
<td>8</td>
<td>1.2</td>
<td>3</td>
<td>2.0</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>684</td>
<td>100.0</td>
<td>147</td>
<td>100.0</td>
<td>356</td>
</tr>
</tbody>
</table>

* Includes two stillbirths, one molar pregnancy, and 10 ectopic/tubal pregnancies.

TABLE 3. Adjusted* relative risk of spontaneous abortion associated with nitrous oxide (measured as two continuous variables) and covariates, dental assistants registered in California in 1987

<table>
<thead>
<tr>
<th>Variable</th>
<th>No.</th>
<th>Relative risk</th>
<th>95% confidence interval</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrous oxide exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unexposed</td>
<td>559</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unscavenged nitrous oxide†</td>
<td>113</td>
<td>1.1</td>
<td>0.9-1.3</td>
<td>0.36</td>
</tr>
<tr>
<td>Scavenged nitrous oxide†</td>
<td>311</td>
<td>1.0</td>
<td>0.8-1.1</td>
<td>0.71</td>
</tr>
<tr>
<td>Covariates</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥31 years</td>
<td>161</td>
<td>1.7</td>
<td>1.0-2.9</td>
<td>0.05</td>
</tr>
<tr>
<td>Smoking (≥1 pack/day)</td>
<td>38</td>
<td>2.3</td>
<td>1.0-5.4</td>
<td>0.05</td>
</tr>
<tr>
<td>≥50 amalgams/week</td>
<td>130</td>
<td>1.8</td>
<td>1.0-3.2</td>
<td>0.06</td>
</tr>
</tbody>
</table>

* Variables adjusted for each other and for gestational week. Women with missing gestational week, age, smoking, or amalgams (n = 204) or incomplete or missing nitrous oxide data (n = 298) are not included.
† Point estimates for nitrous oxide given at 4 hours, which is the median value for both distributions.

the number of dental amalgams prepared per week. Neither nitrous oxide coefficient was significantly different from zero.

To explore a possible nonlinear association between nitrous oxide and spontaneous abortion, we examined the exposures categorically. Women exposed to scavenged nitrous oxide continued to be indistinguishable from the unexposed. When unscavenged nitrous oxide exposure was divided into four levels (0.5-2, 3-4, 5-9, and 10 or more hours per week), elevated risks of spontaneous abortion were found in each of the three highest groups but the estimated relative risk declined in the highest (10 or more hours per week) group (table 4). This model (four levels of unscavenged nitrous oxide and an unexposed group) was then compared with a model that collapsed the three highest exposure categories into one group (3 or more hours of unscavenged exposure), combined the two low exposure categories (less than 3 hours of unscavenged exposure and scavenged nitrous oxide), and compared both with the unexposed. The five-level exposure model did not fit the data significantly better than the three-level exposure model (delta twice log likelihood = 12.34; 4 df: p = 0.015).

After we adjusted for age, gestational week, smoking, and number of amalgams prepared per week, the point estimate for the low exposed group was 0.9 (95 percent confidence interval (CI) 0.5-1.4, p = 0.56), but there was a 2.6-fold increase in the risk of spontaneous abortion among 64 women exposed to unscavenged nitrous oxide for 3 or more hours per week (95 percent CI 1.3-5.0, p = 0.006).

A nitrous oxide effect is apparent even in the unmodeled data (figure 1). The estimated cumulative
probability of spontaneous abortion among the unexposed and the low exposed were very similar (7.3 percent and 6.6 percent respectively), but women with 3 or more hours per week of unscavenged nitrous oxide exposure had a substantially higher rate of loss (16.6 percent). All of the reported losses in the exposed group occurred during weeks 6–11 of pregnancy.

We explored the possibility that the apparent nitrous oxide effect was the result of bias (table 5). Early losses are easily missed and can potentially distort study results. To evaluate this, we restricted analysis in the multivariate model to pregnancies confirmed by a pregnancy test and then limited analysis to pregnancies of 7 or more weeks gestation and therefore combined with the low exposed group, and assigned the remaining 77 women to the low exposed group. The relative risk for spontaneous abortion among the high exposed was reduced to 2.0 (95 percent CI 1.1–3.6). When women with unknown scavenging status were instead all assumed to have worked with scavenged nitrous oxide and therefore combined with the low exposed group, the relative risk was 2.9 (95 percent CI 1.4–5.7).

**TABLE 5. Effect of using different subsets of the study population on the association between nitrous oxide and spontaneous abortion, dental assistants registered in California in 1987**

<table>
<thead>
<tr>
<th>Subset Included for analysis</th>
<th>No. of pregnancies</th>
<th>RR* for ≥3 hours per week unscavenged nitrous oxide†</th>
<th>95% CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full dataset</td>
<td>983</td>
<td>2.6</td>
<td>1.3–5.0</td>
</tr>
<tr>
<td>Using only pregnancies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>confirmed by pregnancy test</td>
<td>951</td>
<td>3.1</td>
<td>1.5–6.4</td>
</tr>
<tr>
<td>Using only pregnancies of 7 or more weeks gestation</td>
<td>912</td>
<td>3.2</td>
<td>1.6–6.8</td>
</tr>
<tr>
<td>Using only first pregnancies</td>
<td>423</td>
<td>2.4</td>
<td>0.8–7.2</td>
</tr>
<tr>
<td>Eliminating women who believed working as a dental assistant increased the risk of spontaneous abortion</td>
<td>751</td>
<td>3.2</td>
<td>1.4–7.4</td>
</tr>
<tr>
<td>Adjusting for time since conception also‡</td>
<td>983</td>
<td>2.8</td>
<td>1.4–5.5</td>
</tr>
</tbody>
</table>

* RR, relative risk; CI, confidence interval. † Adjusted for age, smoking, number of amalgams, gestational week, and low nitrous oxide exposure (defined as scavenged nitrous oxide exposure or unscavenged hours ≤3 hours/week).

DISCUSSION

Post hoc selection of exposure cutpoints can exaggerate both the size of the odds ratio and its precision of estimation (26). The a priori linear model for dose response showed minimal evidence for an effect of nitrous oxide exposure (table 3). However, when levels of exposure were reduced to categories, the risks did not appear to be linear in dose and, in fact, the selection of 3 hours of unscavenged nitrous oxide as a cutpoint fit the data well. Thus, on the basis of exploratory analysis, the data are consistent with an effect beginning at 3 hours a week and confined to women in...
offices without scavenging equipment. This group, although identified post hoc, showed more than a two and a half-fold increased risk of spontaneous abortion. In evaluating this association, the limitations of these data should be considered. First, the method used to estimate exposure, although more detailed than in previous studies, is based on questionnaire responses rather than on actual measurements. Second, there is limited information on potential confounders, with no data on caffeine intake, alcohol use, or paternal occupation. Third, there was a considerable amount of missing data because the questionnaire was self-administered.

Spontaneous abortion is a difficult outcome to study epidemiologically because it is vulnerable to selection bias and problems in ascertainment. To the extent possible, these have been explored in the analysis. For example, women who have a child often leave the paid workforce or work part time, while women who have had difficulty becoming pregnant or who have had a spontaneous abortion are likely to keep working (27). Consequently, in the United States, populations of working women tend to be less reproductively healthy than women of similar social class background who work part time or who do not work outside the home. This “unhealthy worker effect” can be mistaken for an occupational exposure effect (28, 29). Our analysis is limited to women employed full time. Even among women working full time, a sorting process based on the outcome of the first pregnancy can introduce bias (30). Restricting analysis to first pregnancies compensates somewhat for this problem (but reduces statistical power). In these data, the point estimate for nitrous oxide was reduced only slightly with such restriction.

The gestational age at which pregnancy is recognized will also affect the spontaneous abortion rates. Earlier detection of pregnancy by an exposed group can increase the number of recognized spontaneous abortions and therefore create the appearance of an occupational hazard. In this study, 97 percent of the women reported having a positive pregnancy test, and the gestational week of pregnancy when tests were performed was similar for exposed and unexposed women; 68 percent of the high exposed had their pregnancy tests before week 7 compared with 74 percent of the unexposed and 75 percent of the low exposed.

Response bias can pose particular problems for occupational studies of spontaneous abortion; exposed women with poor reproductive outcomes are more likely to volunteer, which can artificially inflate the risk estimates of a study (11, 31). Our relatively low response rate (69 percent) makes this study potentially vulnerable to such response bias. Although we could not determine exposure and outcome status for the nonresponders, we did try to identify the level of concern among responders. Twenty-four percent of the women in the final sample responded that they believed working as a dental assistant increased a person’s risk of spontaneous abortion. When these women were excluded from the analysis, unscavenged nitrous oxide remained strongly associated with spontaneous abortion (relative risk = 3.2, 95 percent CI 1.4–7.4). This does not eliminate the possibility that response bias may have inflated the risk estimates in this study but suggests that response bias does not entirely account for the nitrous oxide effect we observed.

Ascertainment of spontaneous abortion using questionnaire data is problematic. The estimated risk of spontaneous abortion (6.7 percent) reported for the unexposed in this sample is lower than the 10–15 percent reported in most cohorts (32, 33). The low proportion of spontaneous abortions may reflect the young age of the cohort and the use of a sampling frame restricted to each woman’s most recent pregnancy.

Moreover, sampling on the most recent pregnancy creates an artificial time trend in spontaneous abortion rates within the group of pregnancies being studied (34). Intended pregnancies ending in spontaneous abortion are usually followed by subsequent attempts at pregnancy until a livebirth is achieved. Women whose most recent pregnancy occurred in the more distant past are more likely to have replaced any pregnancy that ended in spontaneous abortion. Therefore, spontaneous abortion rates would artificially appear lower for women whose most recent pregnancy was years ago. We adjusted for time since conception in our statistical models since exposure to nitrous oxide was likely to have been higher in the past.

The potential for time since conception to act as a confounder is further exacerbated by recall bias because some losses are forgotten over time (35). The median time since the last menstrual period for women included in the final model was 1.8 years, and the range was 1 month to 7 years. When time since conception was added to our model, it was highly significant ($p = 0.004$) and, as expected, was inversely associated with spontaneous abortion. However, this adjustment only slightly changed the relative risk estimate for unscavenged nitrous oxide (table 5).

There are few known risk factors for spontaneous abortion. Age greater than 30 years, cigarette smoking, and preparing more than 50 mercury amalgams a week were all risk factors of borderline significance in this dataset. Although prior spontaneous abortion is also a strong risk factor, we did not control for this because
Nitrous Oxide and Spontaneous Abortion

Nitrous oxide is an important neuronal messenger whose physiologic importance in reproduction is just beginning to be investigated (47, 48). Many of the toxic by-products of nitrous oxide (45); nitrogen radicals (44). Nitrogen dioxide and nitric oxide are reducible hormones during pregnancy is possible. Nitrous oxide also is subject to oxidation reduction reactions and the possible creation of harmful free radicals (44). Nitrogen dioxide and nitric oxide are potential by-products of nitrous oxide (45); nitrogen dioxide is a potent reproductive toxicant (46), and nitric oxide is an important neuronal messenger whose physiologic importance in reproduction is just beginning to be investigated (47, 48). Many of the toxic effects of nitrous oxide observed in the laboratory have been examined only at high levels of exposure.

Which mechanisms might be relevant for health workers with lower, intermittent exposures is not known. There is currently no mandatory Occupational Safety and Health Administration standard for nitrous oxide, although possible standards have been suggested (49). Animal studies to explore the biologic mechanisms of the reproductive effects are needed, as are additional epidemiologic studies that measure exposure directly. In the meantime, minimizing exposure seems prudent. Scavenging equipment can make large differences in exposure levels at moderate cost (50-53) and appears to be important in protecting the reproductive health of women who work with nitrous oxide.

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