

## REDUCED FERTILITY AMONG WOMEN EMPLOYED AS DENTAL ASSISTANTS EXPOSED TO HIGH LEVELS OF NITROUS OXIDE

ANDREW S. ROWLAND, PH.D., DONNA DAY BAIRD, PH.D., CLARICE R. WEINBERG, PH.D.,  
DAVID L. SHORE, PH.D., CARL M. SHY, M.D., PH.D., AND ALLEN J. WILCOX, M.D., PH.D.

**Abstract Background.** Fertility is reduced in female rats exposed to levels of nitrous oxide similar to those found in some dental offices. Epidemiologic studies have suggested an association between exposure to mixed anesthetic gases and impaired fertility. We investigated the effects of occupational exposure to nitrous oxide on the fertility of female dental assistants.

**Methods.** Screening questionnaires were mailed to 7000 female dental assistants, ages 18 to 39, registered by the California Department of Consumer Affairs. Sixty-nine percent responded. Four hundred fifty-nine women were determined to be eligible, having become pregnant during the previous four years for reasons unrelated to the failure of birth control, and 91 percent of these women completed telephone interviews. Detailed information was

collected on exposure to nitrous oxide and fertility (measured by the number of menstrual cycles without contraception that the women required to become pregnant).

**Results.** After controlling for covariates, we found that women exposed to high levels of nitrous oxide were significantly less fertile than women who were unexposed or exposed to lower levels of nitrous oxide. The effect was evident only in the 19 women with five or more hours of exposure per week. These women were only 41 percent (95 percent confidence interval, 23 to 74 percent;  $P < 0.003$ ) as likely as unexposed women to conceive during each menstrual cycle.

**Conclusions.** Occupational exposure to high levels of nitrous oxide may adversely affect a woman's ability to become pregnant. (N Engl J Med 1992;327:993-7.)

**NITROUS OXIDE** is a widely used inhalation analgesic. In hospitals, it is usually a carrier gas for other, more potent anesthetics. In dental offices, it is administered with oxygen, primarily as a sedative to reduce anxiety. Nitrous oxide is also used in veterinary clinics, in ambulances, and as an obstetrical analgesic.

In the 1970s, nitrous oxide came under suspicion as a reproductive toxin because studies linked occupational exposure to anesthetic gases to birth defects and spontaneous abortion.<sup>1-5</sup> Those studies were criticized, however, most notably for their lack of adequate data on concomitant factors that might adversely affect reproduction and for possible oversampling of exposed women with reproductive problems.<sup>6,7</sup> No previous epidemiologic studies have focused on the effects of nitrous oxide on fertility, but decreased fertility has been reported among women occupationally exposed to mixed anesthetic gases.<sup>4,8</sup>

Rats exposed to 500 ppm nitrous oxide had reduced fertility.<sup>9,10</sup> This exposure level is 1/1000 of the experimental dose of nitrous oxide that produces malformations<sup>11</sup> and is comparable to the levels of occupational exposure among many dental personnel.<sup>12</sup>

We investigated the effect of exposure to nitrous oxide on the fertility of female dental assistants. Fertility was assessed retrospectively by collecting information on the number of menstrual cycles women required to become pregnant. Although some couples achieve pregnancy quickly, others require years, reflecting their lower fertility. Only couples who are sterile are not represented in a sample of gravid women.

From the Epidemiology Branch (A.S.R., D.D.B., A.J.W.) and the Statistics and Biomathematics Branch (C.R.W.), Division of Biometry and Risk Assessment, National Institute of Environmental Health Sciences, Research Triangle Park, N.C.; Westat, Inc., Durham, N.C. (D.L.S.); and the Department of Epidemiology, University of North Carolina School of Public Health, Chapel Hill (C.M.S.). Address reprint requests to Dr. Rowland at the Epidemiology Branch A3-05, NIEHS, P.O. Box 12233, Research Triangle Park, NC 27709.

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This retrospective method of studying fertility<sup>13</sup> has been used to investigate the effects of oral-contraceptive use<sup>14</sup> and cigarette smoking,<sup>15</sup> but it is applicable to occupational exposures as well.

### METHODS

#### Study Participants

We randomly selected 7000 female dental assistants, ages 18 to 39, from the dental-assistant registry of the California Department of Consumer Affairs. We used a four-page, mailed questionnaire to screen these women for eligibility. Women who did not respond were sent follow-up letters. Incorrect addresses were traced through the state files of driver's licenses and vehicle registrations and through address corrections from the Postal Service. After three mailings at three-week intervals, nonrespondents with listed telephone numbers were given reminder calls. The remaining nonrespondents were asked to complete a shortened version of the questionnaire by telephone or were sent a fourth follow-up letter.

Of the 7000 dental assistants sent the screening questionnaire, 8 were dead or living outside the country. Of the remaining women, 4856 (69 percent) completed the screening questionnaire, 232 (3 percent) could not be traced, 204 (3 percent) acknowledged receipt but declined to participate, and 1700 (24 percent) did not respond. There were five criteria for further participation: the women had to have been pregnant within the past four years, with the pregnancy not due to the failure of birth control; they had to have been married at the time they discontinued contraception; they had to have worked full time (at least 30 hours per week) during the six months before they began to have unprotected intercourse; their exposure to mercury (a potential reproductive toxin<sup>16</sup> used in dental amalgam) must not have changed during this period; and they had to have provided a correct telephone number. Four hundred fifty-nine women (9 percent) met these requirements. The most common reasons for exclusion were never having been pregnant (35 percent) and not having been pregnant in the past four years (27 percent). Of the 459 eligible women, 418 (91 percent) completed an extensive interview by telephone. The protocol for the study was approved by the Clinical Review Subcommittee of the National Institute of Environmental Health Sciences.

#### Data Collection

Telephone interviews were conducted between August 1987 and May 1988 by trained female interviewers who were not told the specific hypotheses of the study. The interviews (averaging 38 minutes) included questions about reproductive and contraceptive his-

tory, occupational exposures, and other factors, including medical history, that might have affected fertility. To assess perceived risks, the women had also been asked on the screening questionnaire whether they believed working as a dental assistant increased a person's risk of infertility, miscarriage, the acquired immunodeficiency syndrome (AIDS), or hepatitis B.

Time to pregnancy was ascertained by establishing the length of time before the most recent pregnancy during which the woman was having unprotected sexual intercourse.<sup>13</sup> Women were included regardless of whether they actually intended to become pregnant. The beginning of this interval without contraception was designated the reference date. The number of menstrual cycles until pregnancy was calculated by taking the time between the reference date and the date of the last normal menstrual period, dividing by the usual cycle length, and adding one cycle (to include the cycle in which conception occurred). Any menstrual cycles during which the woman was sexually abstinent were subtracted (affecting time-to-pregnancy data for six women). Menstrual cycles during which birth control was used sporadically were added as half cycles and were rounded down to the nearest whole cycle (affecting time-to-pregnancy data for 23 women). The analysis was based on cycle-by-cycle successes and failures for up to 13 menstrual cycles. This censoring at 13 cycles (about one year) was done to exclude possible effects of medical treatment for infertility, which typically is begun after one year of attempting to become pregnant.

Exposure to nitrous oxide was assessed as of the reference date (as was other information used for analysis). Those reporting exposure were asked how many hours per week they worked in a room where nitrous oxide was being used and whether the nitrous oxide was scavenged. Dental scavenging equipment typically consists of a nasal mask and tubing that deliver nitrous oxide to the patient, capture unused gas and gas exhaled from the patient's nose, and vent it away from the work area through a vacuum line. Thirteen women who did not know whether their workplace used scavenging were dropped from our analysis. Exposure to other anesthetic gases was reported by only two women and was not considered in the analysis.

### Statistical Analysis

Time-to-pregnancy data were analyzed with a discrete-time analogue of the Cox proportional-hazards model.<sup>17</sup> Models were fitted by maximum likelihood, with nested models compared by likelihood-ratio testing.<sup>18</sup> The model coefficients were used to calculate an adjusted fecundability ratio (analogous to a risk ratio or hazard ratio). The fecundability ratio estimates the conception rate for exposed women relative to that for unexposed women in each menstrual cycle of unprotected intercourse. If, for example, an exposed group has a fecundability ratio of 0.5, its members are half as likely as unexposed women to conceive in each menstrual cycle.

Exposures to nitrous oxide in offices with and without scavenging equipment were treated as separate variables, each measured in hours per week. We explored a possible nonlinear dose-response relation for each, using grouped exposure data. Five hours of exposure per week (one hour per workday) was ultimately used as a cutoff point on the basis of exploratory analyses and the distribution of hours of exposure to unscavenged nitrous oxide. That division produced five exposure groups: unexposed, low scavenged, high scavenged, low unscavenged, and high unscavenged.

Other factors that might have affected fecundability were examined in preliminary analyses. Those of potential importance were included in the multivariate model: age, race, family income, exercise, body mass, alcohol use, use of recreational drugs, smoking, douching, history of using intrauterine devices, age at menarche, history of pelvic inflammatory disease, frequency of sexual intercourse, lifetime number of sexual partners, and recent use of an oral contraceptive. Variables were tested as dichotomous, continuous, and multilevel categorical. With the exception of age and race, variables that were not significantly related to fecundability were dropped. Occupational exposure to the following was also examined: x-rays, methylmethacrylate (used in composite resins and

dental prostheses), ethylene oxide, chemoclaves (heated chemical sterilizing systems), cold sterilants, and mercury. None substantially changed the association between nitrous oxide and fecundability, and they were therefore dropped. Two-way interactions of fertility-related factors and exposure to nitrous oxide were tested, but none contributed significantly to the fit.

### RESULTS

Twenty-eight percent of the dental assistants became pregnant in the first menstrual cycle of unprotected intercourse. As in other studies,<sup>19</sup> the rate of conception tended to decline as the number of cycles increased (Fig. 1). By the end of 13 cycles (about one year), 87 percent had become pregnant; according to clinical criteria the other 13 percent would have been classified as infertile.

An increased number of hours of exposure to unscavenged nitrous oxide was associated with decreased fecundability ( $P < 0.01$ ), after adjustment for recent use of oral contraceptives, number of cigarettes smoked per day, age, history of pelvic inflammatory disease, number of sexual partners, frequency of intercourse, and race (Table 1). On the basis of a linear fit, each hour of exposure to unscavenged nitrous oxide per week corresponded to a 6 percent reduction in the probability of conception in each menstrual cycle. There was no relation between the number of hours of exposure to scavenged nitrous oxide and fecundability.

When the numbers of hours of exposure to scavenged and unscavenged nitrous oxide were categorized separately to allow for a possibly nonlinear dose-response relation, reduced fecundability was found primarily in women with five or more hours of exposure to unscavenged nitrous oxide per week. The adjusted fecundability ratios associated with exposure to unscavenged nitrous oxide were 0.94 for women exposed for 1 hour per week or less ( $n = 21$ ), 1.03 for those exposed for 2 to 4 hours per week ( $n = 20$ ),

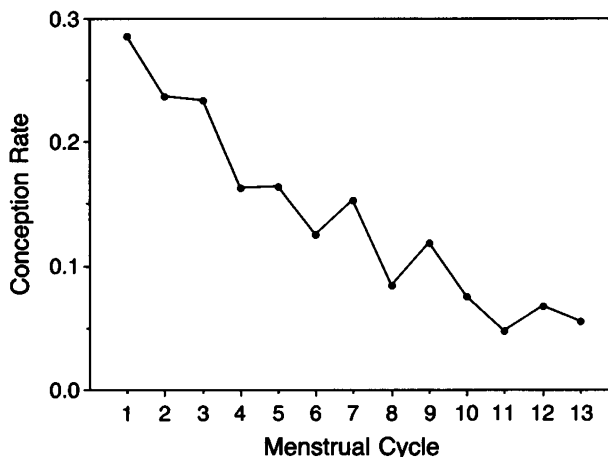


Figure 1. Conception Rate among 418 Dental Assistants. The rate is the number of women who conceived during each menstrual cycle of unprotected intercourse (crude fecundability) as a fraction of those who were at risk in that cycle.

Table 1. Adjusted Fecundability Ratios for Nitrous Oxide and Covariates.\*

VARIABLE	FECUNDABILITY RATIO (95% CI)
Nitrous oxide exposure (each hr/wk)	
Scavenged	1.00 (0.98–1.02)
Unscavenged	0.94 (0.90–0.98)
Covariates	
Oral-contraceptive use†	0.50 (0.29–0.86)
Cigarettes (each pack/day)	0.54 (0.27–1.06)
Age (each decade)	1.16 (0.86–1.55)
History of pelvic inflammatory disease	0.39 (0.17–0.91)
≥6 previous sexual partners	1.52 (1.18–1.95)
Frequency of intercourse‡	1.28 (1.06–1.54)
Nonwhite race	0.83 (0.63–1.10)

\*In this analysis 203 unexposed women, 121 women exposed to scavenged nitrous oxide, and 60 women exposed to unscavenged nitrous oxide were considered. Thirty-four women with missing data for one or more covariates were excluded. CI denotes confidence interval.

†Estimated effect during the first cycle after discontinuing oral contraception. (Such effects become negligible after the first few cycles.)

‡Comparing two groups of women with a difference of three times per week in the frequency of intercourse, on the basis of a linear fit.

0.45 for those exposed for 5 to 9 hours per week ( $n = 9$ ), and 0.37 for those with 10 or more hours of exposure per week ( $n = 10$ ). In the combined group with five or more hours of exposure to unscavenged nitrous oxide per week, the estimated probability of conception in each menstrual cycle was almost 60 percent lower than among unexposed women (adjusted fecundability ratio, 0.41; 95 percent confidence interval, 0.23 to 0.74;  $P = 0.003$ ) (Table 2). No reduction in fecundability was evident in any other exposure group.

Although women with five or more hours of exposure to unscavenged nitrous oxide per week (the high-unscavenged group) had markedly lower fecundability, they were otherwise similar to the rest of the dental assistants in the study. There were minor differences between the high-unscavenged group and the others in age (100 percent of the high-unscavenged group were under 30, as compared with 87 percent of the others), race (26 percent vs. 13 percent Hispanic), sexual frequency (5 percent vs. 17 percent reported having intercourse less than twice a week), and oral-contraceptive use (11 percent vs. 20 percent had used oral contraceptives as their last method of contraception before attempting pregnancy). In addition, the high-unscavenged group had more women working with amalgams (90 percent vs. 73 percent), but this variable was not significantly related to fecundability. Statistical adjustment for covariates had little influence on the estimated effect; the unadjusted fecundability ratio for exposure to five or more hours of unscavenged nitrous oxide per week was 0.45 (95 percent confidence interval, 0.25 to 0.79).

Other measures of subfertility (with unadjusted

data) revealed the same pattern. The mean time to conception among the women who worked with scavenged nitrous oxide was similar to that among the unexposed women, but it was much longer among the women who worked with unscavenged nitrous oxide for five or more hours a week (Table 3). The cumulative probability of conception was also markedly lower at each menstrual cycle for women in the high-unscavenged group (Fig. 2). Only 11 percent became pregnant in the first cycle of unprotected intercourse, as compared with 27 percent of the unexposed women, and 42 percent required more than one year to conceive, as compared with 11 percent of the unexposed women.

Concern about occupational risk was more prevalent for hepatitis B (85 percent of the women), AIDS (63 percent), and miscarriage (24 percent) than for infertility (11 percent). When the women who believed that working as a dental assistant increased a person's risk of infertility (a group that might be prone to response bias) were excluded from the analysis, the adjusted fecundability ratio for a high level of exposure to nitrous oxide became 0.49 (95 percent confidence interval, 0.26 to 0.91).

The occurrence of spontaneous abortions among the women in this study was also examined. Excluding the 93 women who were pregnant at the time of data collection, we found that 10 of the remaining women reported exposure to five or more hours of unscavenged nitrous oxide per week at the time of their pregnancies. Five of these pregnancies (50 percent) ended in spontaneous abortion, as compared with 8 percent of the other 315 pregnancies.

## DISCUSSION

We found an association between occupational exposure to high levels of unscavenged nitrous oxide and reduced fertility in female dental assistants. This finding is consistent with both laboratory studies of nitrous oxide and epidemiologic studies of women exposed to mixed anesthetic gases that included nitrous oxide.<sup>4,8</sup> The association did not depend on adjustment for other variables, including other occupational

Table 2. Effect of Nitrous Oxide on Fecundability, According to the Use of Scavenging and Hours of Exposure.

NITROUS OXIDE EXPOSURE	NO. OF WOMEN	ADJUSTED FECUNDABILITY RATIO (95% CI)*	P VALUE
Scavenged (hr/wk)			
<5	85	1.05 (0.83–1.32)	0.69
≥5	36	1.15 (0.83–1.59)	0.40
Unscavenged (hr/wk)			
<5	41	1.01 (0.73–1.39)	0.53
≥5	19	0.41 (0.23–0.74)	0.003

\*As compared with 203 unexposed women. The ratio was adjusted for oral-contraceptive use, smoking, age, history of pelvic inflammatory disease, number of previous sexual partners, frequency of intercourse, and race. CI denotes confidence interval.

Table 3. Time to Conception, According to Exposure Group.\*

NITROUS OXIDE EXPOSURE	NO. OF WOMEN	CYCLES TO CONCEPTION	PREGNANT IN FIRST CYCLE	percent	
Unexposed	215	6.4±0.8	27		11
Low scavenged	88	4.7±0.6	33		9
High scavenged	39	5.6±1.3	33		10
Low unscavenged	44	9.0±2.4	30		18
High unscavenged	19	32.2±11.1	11		42

\*Thirteen women who could not provide complete information on exposure are omitted. Plus-minus values are means ±SE.

exposures in dental offices. Confounding by other unmeasured factors potentially related to subfertility was minimized because we compared exposed dental assistants with unexposed dental assistants who were demographically similar. By restricting our sample to women who worked full-time, we avoided the bias that arises from comparing an employed group of women with homemakers or part-time workers (groups likely to be reproductively healthy).<sup>20</sup>

Although we studied only women who eventually became pregnant, the range of times to pregnancy was wide (some of the women tried for more than 10 years). However, if nitrous oxide had rendered some women sterile, those women would have been ineligible for our study, and the adverse effect of exposure would have been underestimated.

The widespread availability of nitrous oxide, combined with its reputation as a safe anesthetic, has led

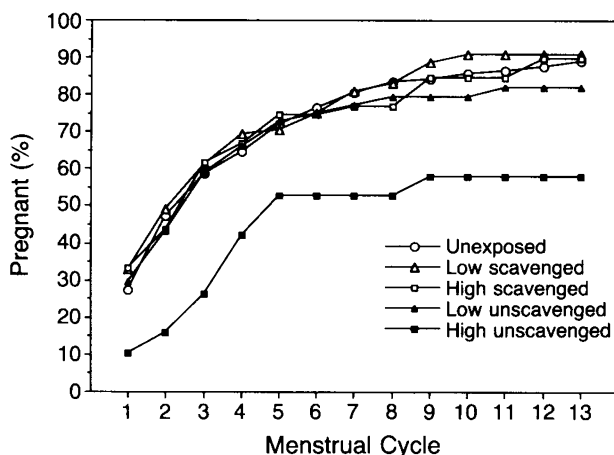


Figure 2. Cumulative Percentage of 405 Dental Assistants Who Were Pregnant at Each Menstrual Cycle, According to Exposure Group.

The unexposed group (n = 215) reported no exposure to nitrous oxide. The low-scavenged group (n = 88) reported less than five hours of exposure to scavenged nitrous oxide per week. The high-scavenged group (n = 39) reported five or more hours of exposure to scavenged nitrous oxide per week. The low-unscavenged group (n = 44) reported less than five hours of exposure to unscavenged nitrous oxide per week. The high-unscavenged group (n = 19) reported five or more hours of exposure to unscavenged nitrous oxide per week. Thirteen women could not be classified according to use of scavenging and were excluded.

to its abuse as a recreational drug.<sup>21</sup> We were concerned that our results might partially reflect recreational, not occupational, exposure. However, all the women in offices where nitrous oxide was used presumably had equal recreational access to the gas, but we observed an effect only among women with high levels of exposure to unscavenged gas, suggesting an effect due to occupational exposure.

Retrospective time-to-pregnancy studies are vulnerable to distortions in the estimate of effect if there are time trends in the exposures being studied. Exposure to unscavenged nitrous oxide has declined since 1978, when dental offices began to use scavenging equipment. Women who took a long time to become pregnant were more likely to have earlier reference dates and to have had the opportunity to be exposed to unscavenged nitrous oxide. Statistical methods were developed to estimate the possible bias in the fecundability ratio created by the decreasing opportunity for exposure.<sup>22</sup> After accounting for this bias, the association between unscavenged nitrous oxide and reduced fecundability remained statistically significant.

Response bias has been a problem in reproductive studies involving anesthetic gases.<sup>23</sup> In our study, women who had trouble conceiving and who were concerned about workplace exposure may have been more motivated to participate. When asked about perceived risks, however, few women said that working as a dental assistant increased the risk of infertility. The degree of response bias may therefore have been relatively small. When we excluded from analysis the 40 women who believed working as a dental assistant affected fertility (the group likely to contribute most to response bias), the fecundability ratio for high levels of exposure to nitrous oxide did increase, but the estimated effect remained strong (0.49 [95 percent confidence interval, 0.26 to 0.91] vs. 0.41 [95 percent confidence interval, 0.23 to 0.74]).

Evidence of impaired fertility was confined to the group with high exposure, but our exposure measures were relatively crude and the statistical power of the study was limited for women who reported low or intermittent exposure (less than one hour per day). As a result, there may be undetected but biologically important effects at lower levels of exposure. A prospective study with measurements made with industrial-hygiene techniques would be required to characterize the dose-response relation more precisely.

The mechanism by which nitrous oxide might impair fertility is unclear. Increased time to pregnancy can result from a range of biologic disruptions, including ovulatory impairment, tubal dysfunction, and loss of a conceptus before or after implantation, before pregnancy is clinically recognized. Nitrous oxide may block the secretion of gonadotropin-releasing hormone by the hypothalamus, disrupting ovulation, as it does in rats.<sup>10,24</sup> Nitrous oxide can also oxidize vitamin B<sub>12</sub> and inactivate methionine synthase, an enzyme important in DNA synthesis.<sup>25</sup> Decreased methionine

synthase activity might disrupt any biologic process requiring rapid mitosis, such as folliculogenesis or early development of a conceptus. Depressed methionine synthase activity has been reported in patients who receive nitrous oxide and in dentists with occupational exposure to nitrous oxide at a level of more than 1500 ppm.<sup>26,27</sup> It is this mechanism that has been hypothesized to cause teratogenic effects in laboratory rats, but recent studies cast doubt on the hypothesis.<sup>28,29</sup> It is not known whether depressed levels of methionine synthase are important for nonteratogenic end points, such as subfertility or spontaneous abortion.

Nitrous oxide is used by 35 to 50 percent of all dentists in the United States.<sup>30,31</sup> Although scavenging equipment is standard in hospital operating rooms, it is still not used in all dental offices. In a dental office, a scavenging mask cannot be placed over the patient's mouth to catch exhaled gas, which makes controlling exposure inherently more difficult than in a hospital. Scavenging can nevertheless reduce levels of exposure by 90 percent or more.<sup>12,32</sup> According to our screening questionnaire, over 20 percent of the dental assistants in California in 1987 worked in offices that used nitrous oxide but did not have scavenging equipment.

Although the National Institute for Occupational Safety and Health proposed a recommended standard of 25 ppm for nitrous oxide in 1977,<sup>33</sup> the Occupational Safety and Health Administration has never adopted a mandatory standard for the gas. In most parts of the United States, nitrous oxide has therefore gone virtually unregulated. Levels of exposure in dental offices remain high, frequently around 100 ppm in offices that use scavenging equipment and over 1000 ppm in offices that do not.<sup>12,34</sup>

There are more than 175,000 dental assistants, 80,000 dental hygienists, and 15,000 female dentists in the United States<sup>35</sup>; most are women of reproductive age. Our data suggest that exposure to high levels of unscavenged nitrous oxide can impair fertility and scavenging equipment is important in protecting the reproductive health of women who work with the gas.

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