Exposure to Anesthetic Gases and Reproductive Outcome

A Review of the Epidemiologic Literature

Terry N. Tannenbaum, M.D., and Robert J. Goldberg, Ph.D.

A variety of evidence suggests that chronic exposure to low doses of anesthetic gases, as occurs in the occupational setting, is a risk factor for spontaneous abortion and congenital defects. The major epidemiologic studies are reviewed, and it is suggested that, due to significant flaws in the design and conduct of these observational studies, there is inadequate evidence to conclude that occupational exposure to anesthetic agents causes increased rates of spontaneous abortion or congenital anomalies.

During the past 25 years a variety of experimental, clinical, and epidemiologic studies have examined the health effects of exposure to anesthetic gases, including their carcinogenic and teratogenic potential.[1-8] The purpose of this article is to review in detail the epidemiologic studies that have examined the effects of occupational exposure to trace concentrations of anesthetic gases on reproductive outcomes.

Epidemiologic Studies

The initial report on the health problems of anesthesiologists appeared in the Russian literature in 1967. Vaisman,[9] in a survey of 345 anesthesiologists, found a relatively high frequency of headache, fatigue, irritability, and nausea among the 303 respondents. The 110 female respondents reported 31 pregnancies; 18 of the pregnancies (58%) ended in spontaneous abortions and one resulted in a child born with a congenital anomaly.

In a subsequent study, questionnaires were sent to 752 nurses and physicians.[10] Data on 212 pregnancies that occurred prior to employment (nonexposed) and 392 pregnancies in the same population that occurred during employment (exposed) were compared. The incidence rate of spontaneous abortions in the exposed group was found to be 18.6 per 100 pregnancies, as compared with a rate of 8.9 in the nonexposed group ($p<.001$)

These preliminary studies brought attention to the fact that chronic exposure to trace concentrations of anesthetic gases may have an adverse effect on reproductive outcome, specifically leading to an increased rate of spontaneous abortions, and led to a series of further investigations in the United States, Great Britain, and Europe.

The first epidemiologic survey in the United States was reported in 1971.[11] Personal interviews were conducted among 67 operating room nurses and 92 general duty nurses, examining their obstetric history for the previous five years. The rate of spontaneous abortions was found to be significantly elevated in the exposed group (operating room nurses) as compared with that of the nonexposed group (general duty nurses).

In the second aspect of this study, questionnaires were mailed to female anesthesiologists and a comparison group of other female physicians. Consistent with the initial findings of this study, the 50 exposed physicians were found to have a significantly increased risk of spontaneous abortions as compared with that of the 81 nonexposed physicians ($p<.001$).

In 1972 a survey of practicing physicians from the United Kingdom was reported.[12] Questionnaires were sent to 1,241 female anesthetists and a control group of 1,678 female physicians. A total of 1,073 pregnancies among the anesthetists and 2,150 pregnancies in the control group were reported. These results suggested that the anesthetists did not differ significantly from the controls with respect to the ratio of abortions to total pregnancies, but the ratio was significantly greater among anesthetists who were practicing during their pregnancy compared with that of the control group ($p<.025$). The incidence rate of congenital anomalies was significantly greater (6.5%) when the mother had worked than when she had not been working (2.5%) ($p<.002$), but was not significantly differ-

From the Departments of Family and Community Medicine (Dr. Tannenbaum) and Medicine (Dr. Goldberg), University of Massachusetts Medical School, 55 Lake Ave. N., Worcester, MA 01605 (Dr. Tannenbaum for further correspondence).

ent from the rate among members of the control group (4.9%).

In a subsequent study by these investigators, the obstetric histories of wives of male anesthetists were examined.[13] Questionnaires were sent to anesthetists in the United Kingdom and to a sample of male physicians registered in the United Kingdom, which served as a comparison group. Working as an anesthetist or a surgeon during a pregnancy was defined as having an exposed pregnancy. No significant differences were found in the spontaneous abortion rates of the group in which only paternal exposure had occurred and the nonexposed group, but maternal exposure again was associated with an increased risk of spontaneous abortions.

A report from Finland also suggested an elevated risk of spontaneous abortion among nurses working in the operating room,[14] and nurse-anesthetists in Michigan[15] who were practicing during their pregnancy were reported to have significantly elevated rates of congenital anomalies in their offspring (16.4%) as compared with both nonpracticing nurse-anesthetists (5.7%) and a group of nonanesthetists (8.4%) (p<.01).

Following these initial studies, the American Society of Anesthesiologists (ASA) appointed an ad hoc committee to prepare a protocol for a nationwide study.[16] This study surveyed 49,585 operating room personnel in the United States, including all members of the ASA, the American Association of Nurse Anesthetists (AANA), and the Associations of Operating Room Nurses and Operating Room Technicians (AORN/T). The comparison groups consisted of 23,911 members of the American Academy of Pediatrics and the American Nursing Association. Members of the study societies who were not working in the operating room provided further means of comparison.

A significantly higher rate of spontaneous abortions was found among exposed female anesthetists when compared with the rate among female pediatricians (17% *v* 9%, p<.01). A significantly elevated rate was also found among female members of the AORN/T (19.5%) as compared with nonexposed female nurses (15%) (p<.01). There was no difference in the rate of spontaneous abortions among the female members of the AANA (17%) as compared with nonexposed nurses. In comparing exposed and nonexposed members within each society, only the AORN/T was found to have a significantly increased rate of spontaneous abortions. These data did not show any evidence that exposure of males resulted in spontaneous abortion in their spouses; only the spouses of male members of the AORN/T were found to have an increased rate.

Congenital anomaly rates were found to be consistently higher in the exposed groups and significantly elevated among children of exposed female members of the AANA and of wives of male anesthetists.

Two further studies by the same investigators[17,18] examined the effect of exposure to anesthetic agents among members of the dental profession. The initial study,[17] a survey of 2,798 oral surgeons and 4,800 dentists, reported an elevated rate of spontaneous abortion among wives of exposed dentists as compared with wives of dentists not exposed to anesthetic gases.

In the latter study,[18] 138,000 members of the American Dental Association were initially surveyed to identify those who were using anesthetic agents in their practice. Among the 108,000 respondents, 15,000 exposed and 15,000 unexposed dentists were selected to be enrolled in a survey that examined the obstetric history of their wives. Thirty thousand dental assistants were also surveyed.

Among both female dental assistants and wives of male dentists the rate of spontaneous abortions was found to be significantly increased according to degree of exposure. The highest rate (19.1%) was seen among female dental assistants with heavy exposure. The nonexposed subjects in each group had a spontaneous abortion rate of approximately 7.0%, slightly lower than the reported population rate of 10% to 15%.

Further smaller studies among physicians and nurses[19-22] reported no increases in the incidence rates of either spontaneous abortion or birth defects among operating room personnel, while elevated rates of both spontaneous abortions and congenital anomalies were found in a study from the West Midlands region of Great Britain.[23]

A study from Sweden was reported in 1982.[24] This investigation was performed as a questionnaire study among female employees in a large hospital. Exposed and nonexposed employees were identified from personnel registers of various departments and were sent questionnaires asking for their obstetric history, occupational history, and other pertinent data. Responses obtained from the questionnaire concerning miscarriages and malformations were compared with data obtained from hospital and birth records.

Significant differences between the incidence rates of spontaneous abortion among highly exposed (16%) and nonexposed personnel (8%) were found only when miscarriages occurring prior to the 16th week of pregnancy were compared (p<.05). The spontaneous abortion rate for all exposed employees was 12%, not significantly different from that observed among members of the nonexposed group.

One hundred thirteen pregnancies were identified from medical records within the group of nonrespondents. Twenty (18%) of these pregnancies ended in spontaneous abortions; all of these miscarriages occurred among nonexposed women. When data from these nonrespondents were added to the data obtained from the respondent group, the spontaneous abortion rate among exposed personnel was found to be 15% as compared with 11% among nonexposed personnel. This difference was not statistically significant.

Table 1 summarizes the design features of the 14 studies described previously. Several methodologic flaws were observed in these studies and are addressed below in greater detail.

1. Study Design — All studies used a retrospective cohort design, in which members of the study group were defined by current membership in a professional society or by current work in an operating theater. Only one study[21] used a different study design; the exposed group in this study was chosen by matching birth records and occupational data so that all exposed "births" were identified. There have been no concurrent prospective studies. While historical cohort studies are of importance, they are subject to potential biases in sample selection, inadequate response rates, losses to follow-up, and difficulties in

Table 1 — Epidemiologic Study Design						
	Study Population*			Response Rate (%)		
Source	Exposed	Nonexposed	Total No. Surveyed	Exposed	Nonexposed	Total
Cohen et al, 1971[11]	1. F OR nurses (n=67)	1. F general duty nurses (n=92)	1. 159	. . .	. . .	1. 100
	2. F anesthetists (n=50)	2. Other F physicians (n=81)	2. 131	. . .	. . .	2. 77
	Exposure Criteria: Any OR exposure in previous 5 yr					
Knill-Jones et al, 1972[12]	All F anesthetists, UK	1. F anesthetists, unexposed	1. 1,241	82	80	. . .
	Exposure Criteria: work in OR during first and/or second trimester	2. Other F physicians, UK	2. 1,678	. . .	. . .	. . .
Rosenberg & Kirves, 1973[14]	1. F OR nurses (n=124)	1. F emergency room nurses (n=75)	1. 199	. . .	. . .	70-75
	2. F nurse-anesthetists (n=58)	2. F intensive care unit nurses (n=48)	2. 101	. . .	. . .	. . .
	Exposure Criteria: Work in OR during pregnancy; subjective exposure to halothane rated between 0 (low) and 3					
Corbett et al, 1974[15]	F nurse-anesthetists, exposed	F nurse-anesthetists, unexposed	621	. . .	. . .	82.5
	Exposure Criteria: Work in OR during pregnancy					
ASA, 1974[16]	1. Anesthetists, US (n=11,192)	1. Pediatricians, US (n=7,910)	49,585 (Exposed)	58 (F)	44 (F)	. . .
	2. Nurse-anesthetists, US (n=14,594)	2. General nurses, US (n=16,001)	23,911 (Control)	66 (M)	41 (M)	. . .
	3. OR nurses/technicians, US (n=23,799)	3. Unexposed OR personnel	. . .	. . .	. . .	. . .
	Exposure Criteria: Work in OR 1 yr prior to pregnancy and during first trimester					
Knill-Jones et al, 1975[13]	Surgeons and anesthetists, UK, either parent exposed	Physicians, UK, neither parent exposed	7,949	. . .	. . .	70
	Exposure Criteria: Work in OR during first trimester					
Cohen et al, 1975[17]	M oral surgeons & dentists, US, exposed	M oral surgeons and dentists, US, unexposed	7,439	. . .	. . .	65 (oral surgeons), 39 (dentists)
	Exposure Criteria: Work in dental surgery 3 hr/wk 1 yr before pregnancy					
Pharoah et al, 1977[19]	F anesthetists, UK, exposed	1. F physicians, working, unexposed	7,992	. . .	. . .	72
	Exposure Criteria: Work in OR at time of conception	2. F physicians, not working	. . .	. . .	. . .	. . .
Rosenberg & VanHinen, 1978[20]	All anesthetists, Finland (n=212)	Pediatricians, Finland (n=356)	568	85	64	. . .
	Exposure Criteria: Work in OR during pregnancy; subjective exposure to halothane, rated between 0 (low) and 3					

(Continued)

Table 1 — Epidemiologic Study Design (Continued)

Source	Study Population*			Response Rate (%)		
	Exposed	Nonexposed	Total No. Surveyed	Exposed	Nonexposed	Total
Ericson & Kallen, 1979[21]	F OR personnel who delivered live-born, infants, 1973 or 1975 (n = 541) Exposure Criteria: Work in OR during pregnancy (hospital records)	Unexposed medical personnel who delivered live-born, infants, 1973 or 1975 (n = 19,127)	19,668	. . .	. . .	94
Tomlin, 1979[23]	Anesthetists, West Midlands, exposed (n = 254) Exposure Criteria: Work in OR 20 hr/wk during pregnancy	All anesthetics, unexposed (n = 60)	314	. . .	. . .	92
Cohen et al, 1980[18]	1. M dentists, US, exposed (n = 15,000)	1. M dentists, US, unexposed (n ≅ 15,000)	30,650	75	72 (F)	. . .
	2. F dental assistants, US, exposed Exposure Criteria: Work in OR 1 yr before pregnancy; heavy, 8 hr/wk; light, 4-8 hr/wk	2. F dental assistants, US, unexposed	30,547	. . .	. . .	. . .
Lauwerys et al, 1981[22]	1. Anesthetists, Belgium	1. Physicians, Belgium, unexposed	1,305	. . .	. . .	42-55
	2. OR nurses Belgium Exposure Criteria: Work in OR 1 yr before pregnancy	2. Nurses, Belgium, unexposed	1,715	. . .	. . .	. . .
Axelsson and Rylander, 1982[24]	F Nonphysicians, OR personnel, exposed (n = 288) Exposure Criteria: Exposure—high, low, none	F nonphysicians, hospital personnel, unexposed (n = 322)	610	80	75	. . .

* M indicates male; F, female; OR, operating room; UK, United Kingdom; US, United States

standardization and interpretation of exposure and outcome endpoints.

2. Population at Risk — Most investigators have studied anesthesiologists and nurses working in the operating room. Other study groups have included operating room technicians[16] and surgeons.[13] Two studies examined dentists as a population at risk.[17,18] Different occupations, however, have different levels of exposure to anesthetic gases, and it cannot be expected that these groups would have the same risks for adverse effects. Furthermore, some investigators studied only women while others surveyed both sexes; it is certainly possible that exposed women might exhibit different effects from wives of exposed males. Any conclusions, therefore, can only be generalized to the specific population investigated in that study, and it would not be surprising to find different effects across different groups.

3. Selection of Study Group — In all of the studies involving large numbers of subjects, the study group was identified through a survey of a professional organization, (e.g., the ASA).[12,13,16-20,22] From the responses, subjects were divided into exposed and nonexposed groups. In the smaller surveys[11,14,15,21,23,24] the subjects were identified through hospital personnel records, and the respondents again were separated by their work history and classified according to exposure. The British investigators used medical registries as the source of their study groups. This method excluded individuals who left their work permanently, a group whose reproductive history might be quite different from that of those who continued to work.

4. Selection of Comparison Group — In general, either of two methods of selecting a control group was used. Some investigators selected a separate population (e.g., general duty nurses) who had not had operating room exposure as a comparison group.[11-14,16,20-22,24] The potential problem with this comparison group is that its members might differ from those of the exposed group in other aspects such as working conditions, stress, or radiation exposure. In some studies the comparison group included operating room personnel who were not working at the time of their pregnancy.[12,13,15-19,23] In this situation, a woman could be in the exposed group for one pregnancy and the non-exposed group for another. With this method there are several additional problems. The life-style of a working woman may differ considerably from that of a nonworking woman, and it would be very difficult to control for stress, irregular working hours, and other occupational exposures that may be associated with an increased rate of spontaneous abortions. In addition, the reasons that members of the comparison group were not working were not known; one could imagine that a woman who has had a poor reproductive history might decide to stop working during a later pregnancy, in the hopes that adequate rest and less stress would increase her chance for a healthy outcome. One study of dental personnel attempted to overcome the problem of finding an appropriate comparison group by first surveying a population to identify users and nonusers of anesthetic agents who were similar in all other known respects.[18] However, the two groups were found to differ by age, which suggests that they may have not been comparable in other aspects. Also the problems of recall bias, response bias, and lack of validation of data were still present.

5. Methods of Data Collection — In the majority of studies a mailed questionnaire was used to obtain both exposure and outcome data from the subjects. Ericson and Källén's[21] design differed in that the reproductive outcome was assessed from birth records, and these records were used to generate the cohort under study. Axelsson and Rylander[24] were the sole investigators who actually verified the data collected from the questionnaires by reviewing medical records.

With the questionnaire method of data collection, there is a great potential for inaccurate recall of both exposure and outcome events. Different interpretations of the terms "abortion," "miscarriage," and "congenital anomaly" may occur and the relationship between time of exposure and pregnancy cannot always be accurately recalled. Also recognition of an abnormal reproductive event may vary with an individual's socioeconomic status, degree of medical knowledge, and prior obstetric and medical history. Certainly there is the potential for a selective response bias among those women who have had an abnormal reproductive event. Although Axelsson and Rylander[24] found that 93% of the reported spontaneous abortions could be verified, they did not look for unreported abortions among respondents.

Another problem with this method is that there is a potential for a "loaded" questionnaire, in which the relationship being investigated becomes obvious to the subject, increasing the risk of a biased response. This can be seen in the ASA study,[16] in which the questionnaire was entitled "Effect of Waste Anesthetic Gases on Health." This same questionnaire, or a very similar one, was used in the investigators' subsequent studies[17,18] and in one of the United Kingdom surveys[11] so that any biased questions may have been repeated in several investigations.

6. Definition of Exposure — In most studies, exposure was defined as working in the operating room before and during the pregnancy. Some investigators[18,24] have tried to divide their groups into various levels of exposure, depending on duration of exposure. However, given the large variability in levels of gas concentrations in different operating suites, it is difficult to compare doses of exposure between as well as within studies.

7. Definition of Outcome — In all the studies except those of Ericson and Källén[21] and Axelsson and Rylander,[24] outcome was accepted as reported by the respondent with no further validation. Most authors did not state their criteria for spontaneous abortion (i.e., number of weeks of gestation) or congenital anomalies. In reviewing hospital records, Axelsson and Rylander[24] found in fact that the information given by the respondent as to the week of pregnancy in which miscarriage occurred was often inconsistent with the data as reported in the record.

The reliability of outcome data is also limited because of the duration of the study periods. Respondents were asked to recall their occupational and obstetric histories for the previous five[11] to 20 years.[21] Most investigators chose study periods of eight to 10 years.[14,16-18,24] There is obviously opportunity for error in asking the respondent to remember events that occurred to themselves or to their spouses 10 to 20 years previously. There is also the opportunity for error in recalling the temporal association between such events and the respondent's occupation at that time.

8. Confounding Variables — Potential confounding variables for the reproductive outcomes under study include prior obstetric history, age, nutrition, smoking habits, alcohol use, illness and medications used during pregnancy, exposure to radiation, and the presence of other medical problems. In none of the studies were the members of the study and the comparison groups matched on these variables. Most investigators controlled for maternal age and smoking habits in the data analysis,[11,16-22,24] while some also examined radiation exposure, prior obstetric history, drug use during pregnancy, and alcohol use.[14,20,22,24] In only two studies[20,24] were working conditions and stress levels addressed as potential confounding variables. It is therefore very possible that confounding variables account for some of the differences found in rates of spontaneous abortions between exposed and unexposed personnel in some of the studies; in those studies in which working hours, stress, radiation exposure, maternal age, and smoking behavior were controlled,[20,22,24] overall significant differences in reproductive outcome between the exposed and nonexposed groups were not found.

9. Response Rate — It can be seen from Table 1 that the response rates were often quite low, ranging from 41% to 94%, with the response rates among the study group often differing considerably from that of the comparison group. In the ASA study,[16] telephone interviews of the nonrespondent comparison group were carried out, and the investigators claimed that their rates of spontaneous abortions were similar to the rates among respondents. Axelsson and Rylander,[24] however, found that nonrespondent controls had a significantly higher rate of spontaneous abortions than the respondents; in contrast, in a record search no spontaneous abortions were found among the nonrespondent exposed women. Such a difference in the reproductive histories of the nonrespondents in the exposed and the nonexposed groups could lead to false conclusions. Indeed, numerous epidemiologic studies have found significant differences with regard to selected outcomes between respondents and nonrespondents that could lead to a distortion of the relative risk ratios.[25-27]

10. Results — Table 2 lists the incidence rates of spontaneous abortions among female physicians exposed to anesthetic gases during their pregnancy. In all but one of the relatively smaller studies, an elevated risk was found, with rates ranging from 9 to 38 miscarriages per 100 pregnancies; the relative risk found in the larger studies among the exposed group appears to be approximately twice the risk of the comparison group and is consistent across all studies.

Table 3 lists the rates of spontaneous abortions found among women other than physicians exposed to anesthetic gases, including studies that did not describe maternal occupation. Rates among the exposed groups ranged from eight to 30 spontaneous abortions per 100 pregnancies. In most studies relative risks among exposed personnel were found to be elevated, ranging from approximately 1.3 to 2.5. Among the largest studies,[11,16,18] whose study populations comprised over 90% of the total population surveyed, the incidence rates of spontaneous abortion among exposed personnel ranged from 15 to 20 per 100 pregnancies; the relative risks were found to be elevated in all of these studies, ranging from 1.1 to 2.5 times that of the nonexposed group.

Several problems and inconsistencies are to be noted in these two tables, however. First, the rate of spontaneous abortions found among the comparison groups ranges from six to 15 per 100 pregnancies and actually overlaps that found in the exposed group. The statistical difference found between groups could be due to a low rate of reported miscarriages in the comparison group. This is exactly what Axelsson and Rylander[24] discovered in their study. Second, no difference was found between exposed and nonexposed women; this suggests that either exposure has a long-term effect or that something other than anesthetic gas exposure contributes to the apparent increase in miscarriage rate among operating room personnel. Third, while data on exposure are poor, one might speculate that physicians and nurse-anesthetists have higher exposure levels than technicians and nurses. In fact, rates of spontaneous abortions are similar for both groups.

Table 4 describes the miscarriage rates found among pregnant wives of males exposed to anesthetic agents. Only one investigator found elevated rates.[16-18]

The results of all 14 studies are summarized in Table 5. While several studies, including those with the largest study populations,[11,16-17,18] do show an increased risk of spontaneous abortions among exposed females, there is little evidence to suggest an elevated risk among wives of exposed male anesthetists. There is some evidence that wives of exposed dentists may have an elevated risk. There are also little data to suggest an increased risk of congenital malformations among offspring of exposed personnel.

Discussion

It has been known for many years that anesthetic agents have an inhibitory effect on the dividing cell.[28,29] These agents have also been found to cause increased rates of abnormal cell formation and chromosomal aberrations[30-36] Toxic effects on organ systems in humans have also been documented for several agents when administered at anesthetic doses. The use of halothane has been associated with hepatitis[37,38] and methoxyflurane has been linked to renal failure.[39] Nitrous oxide, when administered for several days at high doses, has been noted to lead to neutropenia[40-42] and megaloblastic hematopoiesis.[43-45] Several cases of neuropathies have also been reported among persons exposed to nitrous oxide for prolonged periods.[46-48] Recently, it has been shown that the mechanism of this effect is through the ability of nitrous oxide to oxidize vitamin B12 and impair the synthesis of methionine, folate, and thiamine.[49-53] Some investigators have also reported hepatic injury in animals exposed to halothane, methoxyflurane, and other agents.[54-58]

Numerous studies have been conducted on the effects of various inhalational agents on reproductive events in rodents. At anesthetic doses most agents have been found to have toxic effects, primarily causing decreased fertility, decreased fetal weight, skeletal anomalies, and fetal death.[59-64] At subanesthetic levels, however, most investigators have not found specific fetotoxic effects. Fetal growth retardation has been reported by some investigators after exposure to high subanesthetic doses of nitrous oxide,[65-67] halothane,[64] methoxyflurane,[61,67] and enflurane,[68,69] and low-dose exposure to nitrous oxide has been reported to cause decreased litter size and fetal resorption.[70] Most recent studies, however, of nitrous ox-

Table 2 — Incidence Rates of Spontaneous Abortion Among Exposed Female Anesthetists

Source	Rate (per 100 Pregnancies) Exposed	Unexposed	Control	Relative Risk*
Cohen et al, 1971[11]	38		10	3.7†
Knill-Jones et al, 1972[12]	18	14	15	1.2†
ASA, 1974[16]	17	6	9	1.9‡
Pharoah et al, 1977[19]	14	14	12	1.2†
Rosenberg & VanHinen, 1978[20]	9	1	13	0.69

* Incidence rates of spontaneous abortions in exposed group vs incidence rates in control group
† $p<.05$
‡ $p<.01$

Source	Study Group	Rate (per 100 Pregnancies) Exposed	Unexposed	Control	Relative Risk*
Cohen et al, 1971[11]	Nurses	30	. . .	9	3.5†
Rosenberg & Kirves, 1973[14]	Nurses	20	. . .	11	1.7†
ASA, 1974[16]	Nurse-anesthetists	17	14	15	1.1
	Nurses/technicians	20	15	15	1.3‡
Knill-Jones et al, 1975[13]	Maternal exposure	16	. . .	11	1.5‡
	Maternal exposure (with matching)	15	. . .	6	2.5§
		High Low			
Cohen et al, 1980[18]	Dental assistants	19 14	. . .	8	2.4‡
Lauwerys et al, 1981[22]	Nurses, physicians (combined)	9	6	. . .	1.4
Tomlin, 1979[23]	Maternal exposure	30	. . .	10	2.9†
Axelsson & Rylander, 1982[24]	Operating room personnel	High Low 16 4	. . .	9	1.7
	Abortions <16 wk	16	. . .	8	2.0†
	With results of nonrespondents	15	. . .	11	1.2

Table 3 — Incidence Rates of Spontaneous Abortion Among Nonphysician Female Operating Room Personnel

* Incidence rates of spontaneous abortions in exposed group versus incidence rates in control group
† $p<.05$
‡ $p<.01$
§ $p<.001$

Table 4 — Incidence Rates of Spontaneous Abortion Among Wives of Exposed Males

Source	Study Group	Rate (per 100 Pregnancies) Exposed	Unexposed	Control	Relative Risk*
ASA, 1974[16]	Anesthetists	12	. . .	13	0.9
	Nurse-anesthetist	12	. . .	10	1.2
	Nurse/technicians	18	. . .	10	1.8†
Knill-Jones et al, 1975[13]	Physicians	11	. . .	11	1.0
Cohen et al, 1975[17]	Dentists	16	9	. . .	1.8‡
Rosenberg & VanHinen, 1978[20]	Physicians	10	. . .	9	1.1
Tomlin, 1979[23]	Anesthetists	16	. . .	10	1.6
		High Low			
Cohen et al, 1980[18]	Dentists	10 8	. . .	7	1.4‡
Lauwerys et al, 1981[22]	Nurses and physicians	7	. . .	6	1.1

* Incidence rates of spontaneous abortions in exposed group versus incidence rates in control group
† $p<.05$
‡ $p<.01$

ide,[71] enflurane,[72-74] and halothane[74-76] have found no fetotoxic effects in animals exposed to levels well above those found in occupational exposure. Problems with these studies have been in the difficulty of separating the specific effects of anesthetic agents from the adverse effects of stress, hypoxia, inadequate nutrition, and hypotension. The similarity of effects noted in pregnant animals when anesthetic or high subanesthetic doses of all agents are administered has led some investigators to suggest that they are due to a general effect of anesthetic agents perhaps in combination with one or more predisposing factors.[67]

If there are human health hazards from anesthetic agents, this would represent a significant public health problem. In the United States approximately 50,000 individuals are occupationally exposed to anesthetic agents, including anesthesiologists, nurse-anesthetists, operating room nurses, and technicians. Thirty-five thousand of the exposed personnel are women. This group excludes surgeons, dental personnel, and veterinarians who have variable exposures.[6]

It has been difficult to determine the actual concentrations of these agents that occur during occupational exposure. The amount of exposure varies, depending on the

Table 5 — Summary of Results*				
	Study Group			
Source	Males	Females	Spontaneous Abortion	Congenital Anomaly
Cohen et al, 1971[11]		Operating room nurses/	+	. . .
		anesthetists	+	NS
Knill-Jones et al, 1972[12]		Anesthetists	+	+ (Exposed vs nonexposed only)
Rosenberg & Kirves, 1973[14]		Operating room nurses	+	. . .
Corbett et al, 1974[15]		Nurse-anesthetists	. . .	+
ASA, 1974[16]		Anesthetists	+	NS
		Nurse-anesthetists	NS	+
		Operating room nurses	+	NS
ASA, 1974[16]	Anesthetists		NS	+
	Nurse-anesthetists	. . .	NS	NS
	Operating room nurses		NS	NS
Knill-Jones et al, 1975[13]	Anesthetists		NS	+ (minor anomalies only)
		Exposed females	+	NS
Cohen et al, 1975[17]	Dentists		+	NS
Pharoah et al, 1977[19]		Anesthetists	. . .	+ (Congenital heart anomalies only)
Rosenberg & VanHinen, 1978[20]	Anesthetists		NS	NS
		Anesthetists	NS	NS
Ericson & Källén, 1979[21]		Operating room personnal	. . .	NS
Tomlin, 1979[23]	Anesthetists		NS	NS } +
		Exposed + females	+	NS } +
Cohen et al, 1980[18]	Dentists		+	NS
		Dental assistants	+	NS
Lauwerys et al, 1981[22]	Operating room personnel		NS	NS
		Operating room personnel	NS	NS
Axelsson & Rylander, 1982[24]		Operating room personnel	NS	NS
		Abortions <16 wk. only	+	NS
		With nonresponders	NS	NS

* Plus sign indicates rate of outcome significantly increased ($p<.05$) in exposed as compared with nonexposed group; NS, no significant difference between exposed and nonexposed groups; and ellipses, not measured

presence and function of scavenging systems. Studies have reported atmospheric levels of nitrous oxide ranging from 130 to 7,000 ppm in the anesthesiologists' breathing zone, and halothane levels of 10 to 85 ppm have been measured.[1,6,57] Presently, U.S. hospital regulations limit contamination levels in the operating room to 25 ppm of nitrous oxide and 1 to 2 ppm of halogenated agents. These low levels can be maintained at a relatively low cost by removal of the waste gases with a gas-scavenging trap over the escape valve of the tank and a length of tubing to provide a conduit to the outside.[77]

Summary and Conclusions

A variety of data collected from clinical, experimental, and animal studies suggests that anesthetic gases may have an adverse effect on the reproductive outcome of exposed pregnant females. However, whether chronic exposure to low doses of these agents, as occurs in the occupational setting, has an adverse health effect in humans is not yet known. Several investigators have reported that women working in the operating room theater prior to and during their pregnancy have 1.5 to two times the risk of spontaneous abortion as compared with unexposed medical personnel, and this relationship has been widely accepted as a causal one. However, after examination of the methodology of these studies, it appears that the validity of the results can be seriously questioned. The consistency of the results may be explained in part by the consistency of the methodologic problems, specifically lack of criteria for exposure or outcome, poor survey response rates, selection bias, lack of validation of outcome, recall bias, and lack of control of potentially confounding variables. Results from the majority of these studies do suggest that there is no increase in spontaneous abortions among wives of exposed male personnel and that there is no increase in birth defects among the offspring of exposed parents.

Due to the limitations of historical cohort studies in this area, a prospective study should provide reliable data from which a reliable estimate of the true risks of exposure to anesthetic agents can be determined. A cohort of exposed female personnel could be identified — for example, resident physicians as they begin their training in anesthesia or newly graduated nurses who begin work in the operating room and a selected comparison group that ideally would be similar to the exposed women in terms of age, smoking behavior, working conditions, and prior obstetric history. Both groups should be monitored closely, with data obtained frequently concerning both exposure and outcome events. Such a study would involve monitoring of exposure levels, both by recording hours spent in the operating room and by periodic measurements of levels of nitrous oxide and halothane during exposure hours from which an exposure index for each cohort member could be calculated. Most important would be accurate measurement of outcome; this would require frequent interviews with both cohort and control group members to obtain data on involuntary infertility and pregnancy history, as well as examination of potentially confounding variables such as exposure to radiation, drugs, and smoking. These data should be verified through examination of obstetric records and any additional sources. Accurate information on both exposure and pregnancy outcome would allow a reliable estimate of the risk of spontaneous abortion in the exposed and comparison groups, and the relationship between degree of exposure and outcome could be examined. Such a study would require a very large cohort, however, and would be very expensive and time-consuming.

Another method of addressing this problem from a population-based perspective would be the formation of statewide surveillance systems for spontaneous abortions and birth defects, similar to cancer registries, with inclusion of information on occupational and environmental exposures, cigarette smoking habits, obstetric history, and other pertinent data for each case. This would allow investigators to examine the effects of a variety of exposures on reproductive outcome and would provide a valuable data base for future studies.

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Compromising the Doctor-Patient Relationship

It is reasonable to expect doctors to do everything in their power to preserve the lives of their patients. But where new drugs, devices, or surgical techniques are involved, physicians must temper the desire to help against the moral obligation to adequately test techniques and to obtain informed consent.

If medical research is allowed to proceed without adequate testing and without informed consent, then before long patients would begin to wonder whether their physicians really had their best interests at heart or simply chose to use them as guinea pigs to advance medical research.

The price of evading existing regulations is to introduce mistrust and fear into every doctor-patient interaction. Ultimately, that is too high a price for society to pay.

— From " 'Good Intentions' Just Aren't Enough" by Arthur Caplan
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