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Fetal Risk of Anesthesia and Surgery during Pregnancy

Peter G. Duncan, M.D., F.R.C.P., William D. B. Pope, M.D., F.R.C.P.,†*
Marsha M. Cohen, M.D., M.H.Sc., F.R.C.P.,‡ Nancy Greer, B.A.§

In an attempt to define the risk to the fetus associated with anesthesia and surgery during pregnancy, a study was performed using health insurance data from the province of Manitoba (1971 to 1978). Each of the 2,565 women undergoing incidental surgery during pregnancy (Group A) was paired with a pregnant female not undergoing surgery (Group B) by maternal age and area of residence. Both groups were linked to a separately maintained provincial congenital-anomalies registry to ascertain the frequency of anomalies. There was no signficant difference in the rate of congenital anomalies between the two groups, implying no strong teratogenic effect. However, there was an increased risk of spontaneous abortion in those undergoing surgery with general anesthesia in the first or second trimester, most notably after gynecologic procedures (estimated risk ratio = 2.00), but also following procedures anatomically remote from the conceptus (estimated risk ratio = 1.54). While it is concluded that surgery with general anesthesia is associated with a higher incidence of abortion, it is conjectural at present which factor(s) account for the observed increase in fetal risk. (Key words: Anesthesia: morbidity; pregnancy; obstetric; teratology.)

IT IS ESTIMATED that between 0.5% and 2.0% of pregnant women will at some time during pregnancy undergo anesthetic or surgical procedures for incidental medical illness.[1,2] However, the information available regarding the safety of such procedures from a teratogenic point of view is limited. Postponing elective procedures for pregnant women may result in unnecessary hardship by prolonging suffering from or intensifying the intercurrent illness. When emergency surgery is performed, the viability of either the pregnancy or fetus should be minimally affected. We sought to define what, if any, risk exists to a pregnancy by the administration of anesthesia or performance of surgery during gestation.

Materials and Methods

With the consent of appropriate provincial and University regulatory bodies, health insurance records for the population of Manitoba (approximately 1 million) were used for this study. From these records, all hospitalizations for pregnancy-related conditions were determined for the years 1971 to 1978 inclusive. The health records for each woman were scanned to determine which had had any surgical procedure during the preceding 10 months. These individuals comprised the surgical study group (Group A). All surgical events, including procedures performed under local anesthesia and traumatic injuries, were included. For each woman in Group A, the next woman on the Provincial file from the same geographic area and within 2 yr of age of the Group A subject with a pregnancy-related condition but without any operative procedure (Group B) was entered to form a matched pair. As the Manitoba Health Services Commission (MHSC) records all health care utilization, regardless of where it took place, it was possible to record events despite movement of women to different hospitals. As virtually all residents are insured by the universal medical care system, the study included all pregnancies occurring in Manitoba during the time frame in question.

For each pregnancy-related hospitalization, information was obtained concerning maternal age, date of hospitalization, and outcome of the pregnancy (*i.e.*, normal delivery, abnormal delivery, or abortion) for all the women in the study group. Outcomes and surgical procedures (if performed) were coded according to the eighth revision of the International Classification of Diseases. Those pregnancies terminated by therapeutic abortion were excluded from analysis. For Group A women, operative procedures performed, type of anesthetic used (nil, local, general, or nerve block) and date of procedure were documented. In those individuals undergoing multiple procedures, all were included in the data set, but only the most complex surgical event was used for analysis. On-site review of the hospital records of randomly selected cases (25% of total) established the validity of the MHSC data.

Manitoba maintains a centralized data bank to monitor birth defects as part of a national and international surveillance program.¶ Birth defects were determined from hospital separation-sheet diagnostic information or physician claim forms for the first year of life. Children born in the province with recordable defects over the time frame of the study were linked to the mothers without

* Associate Professor, Anesthesia and Pediatrics.
† Associate Professor, Anesthesia.
‡ Assistant Professor, Social and Preventative Medicine.
§ Research Assistant.

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Address reprint requests to Dr. Duncan: Associate Professor, Anesthesia and Pediatrics, University of Manitoba, 315 Lennox Bell Lodge, 60 Pearl Street, Winnipeg, Manitoba R3E 1X2.

¶ Sherman GJ: The Canadian congenital anomalies surveillance system: A brief description. Chronic Disease in Canada 2:48–50, 1982.

knowledge of study status (blind) by maternal name, maternal age, date, and hospital of birth of the child. Pregnancies of 24 weeks or more not attributed to a child with a known anomaly were assumed to have delivered a normal child.

The two groups were compared for abortion rate and type and frequency of anomalies. The data were subsequently stratified by the estimated trimester of exposure (40 weeks was considered as gestational date), operative site (intraabdominal, obstetric/gynecologic or other), and type of anesthetic. For Group A, each mother–child match was reviewed to ensure that the operation had occurred within 40 weeks of date of delivery. McNemar's chi-square statistic was used to test the hypothesis concerning association of the matched operation/nonoperation women with regard to outcomes studied (abortion, congenital anomalies).[3] This statistic tests the difference between discordant pairs of women where one has a characteristic that is lacking in the other member of the pair. Estimated risk ratios, with 95% confidence intervals, were calculated and a confidence interval not including "1" was considered statistically significant ($P \leq 0.05$).

Results

A total of 2,565 pregnant women were identified as having undergone intercurrent surgery, and each was successfully matched to one woman with a surgery-free pregnancy. On-site chart review found 9% coding errors, the majority of which did not bear on the question of the study (*i.e.*, surgical procedures performed not precisely identical to that coded but of similar site and severity).

Eighty-two babies with congenital anomalies were found in the data set. In the Group A women, the incidence was 1.68% (43 anomalies) as compared with 1.52% (39 anomalies) in women in Group B. Using matched pairs, no association was found between the incidence of anomalies and operation during pregnancy as seen in table 1. For Group A women, stratification by timing of exposure, type of anesthetic used, and surgical procedure performed did not reveal any significant differences in the incidence of anomalies. No single anomaly appeared with unusual frequency in either group.

There were 181 abortions in Group A women (7.1%) and 166 abortions in Group B women (6.5%). The matched analysis revealed no association between the rate of abortion and an operation and anesthesia. Table 2 (fig. 1) shows no difference between groups in abortion rate when stratified by site of operation without regard to anesthetic administered. However, as shown in table 3 (fig. 2), there was a significant increase in abortion rate in those women who received a general anesthetic (estimated risk ratio = 1.58 [95% confidence limits 1.19, 2.09]) when compared with their matched controls. When further analyzed as to the type of surgery performed under general anesthesia (table 4, (fig. 3)), the increased risk was found to be most marked among those women having obstetric or gynecologic procedures (estimated risk ratio = 2.0 [95% confidence limits 1.1, 3.6]). There were too few obstetric or gynecologic procedures done under alternative techniques to relate the effect to surgical procedure alone. The findings for the obstetric/gynecologic surgery were not explained by the presence of Shirodkar procedures for women who are habitual aborters, as there were only three such procedures among the discordant pairs. The relationship between general anesthesia and abortion is also found for "other" surgical procedures remote from the conception as well as for obstetric/gynecologic, thus strengthening the likelihood of a true association of abortion with general anesthesia rather than a random occurrence or an effect attributable to the operative procedure.

TABLE 1. Congenital Anomalies in Matched Pairs of Offspring

Type	No.
Both infants of a pair	6
In neither infant of a pair	2,136
Group A infant only	40
Group B infant only	36
Total pairs	2,218
McNemar's chi-square, 1 df	0.21
P	0.65

df = degrees of freedom.

Discussion

In the 1970s maternal exposure to trace concentrations of anesthetic drugs in "polluted" operating theaters was suggested as a cause of a higher-than-normal incidence of abortions, congenital anomalies, or even carcinogenic transformation in the developing fetus.[4] In contrast, the influence of an acute, high-dose anesthetic exposure during an operation has received little attention. It is possible that such an exposure may be harmful, because as little as 8 h of exposure to nitrous oxide has been shown to

TABLE 2. Abortions by Surgical Site

Surgical Site	Discordant Pairs: Group A Woman+ Group B Woman−	Discordant Pairs: Group A Woman− Group B Woman+	Total Pairs	Estimated Risk Ratio (95% confidence limits)
Abdominal	34	26	481	1.31 (0.67, 2.55)
Ob/gyn	37	38	747	.97 (0.63, 1.51)
Other sites	96	83	1928	1.16 (0.86, 1.55)

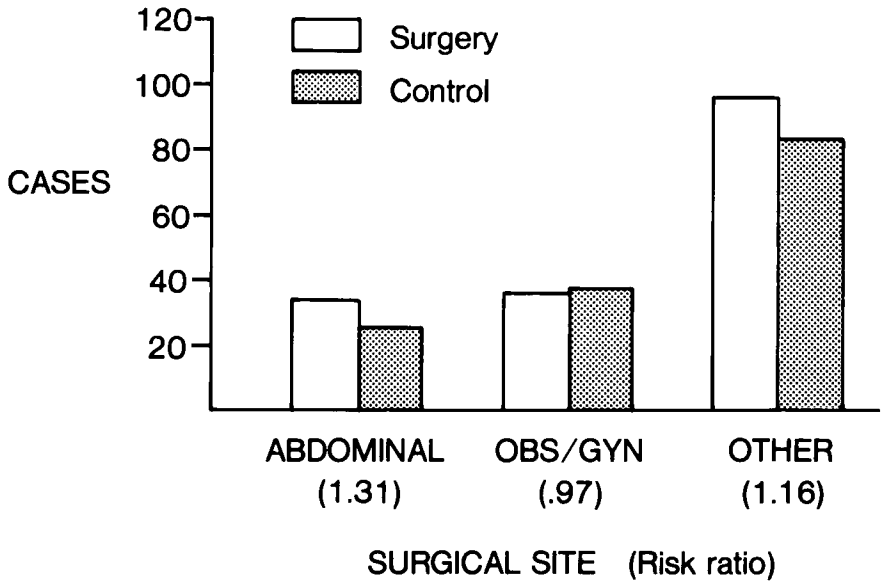

FIG. 1. Abortions by surgical site. Number of cases is the number of discordant pairs where one member (either Group A or Group B) had an abortion and the matched subject did not. Stratification of the women undergoing surgical procedures, regardless of anesthetic used, did not reveal any significant difference in risk when compared with their paired controls.

interfere with hematopoesis in human subjects.[5] This is due, presumably, to a mechanism similar to the interference shown in rats with nucleic acid synthesis by inhibition of methionine synthetase.[6] Whether other anesthetics in clinical concentrations have similar effects, or whether the rapidly multiplying cells of the human fetus are similarly affected, remains unknown.

Three previous studies have addressed the effect of anesthetic administration upon fetal outcome. The first[7] examined 67 pregnant women, only ten of whom had an operation in the first trimester. Fetal death rate was 11.1%, and no congenital anomalies were found. No control group was studied for this small series. A second study[1] examined 147 women operated on during pregnancy compared with those not undergoing operative procedures. Surgery in the first trimester was associated with an 8.5% fetal death rate (2.0% in controls) and a 9.3% incidence of congenital anomalies (6.0% in controls). The latter difference was not significant due to the small number of cases. In the second trimester, anesthesia and operation were associated with a 10.3% fetal death rate and an 11.5% incidence of congenital anomalies. However, the majority of these procedures were Shirodkar procedures to prevent abortions. The authors concluded that the indication for and the site of operation were more important than the type of anesthetic employed. The most recent study[2] employed a mail-survey approach to dentists

TABLE 3. Abortions by Anesthetic Type

Anesthetic Type	Discordant Pairs: Group A Woman+ Group B Woman−	Discordant Pairs: Group A Woman− Group B Woman+	Total Pairs	Estimated Risk Ratio (95% confidence limits)
Nil	17	28	503	.607 (0.42, .876)
General	125	79	911	1.58* (1.19, 2.09)
Spinal/block	1	1	46	1.00
Local	24	39	337	.62 (0.37, 1.02)

* $P < 0.05$.

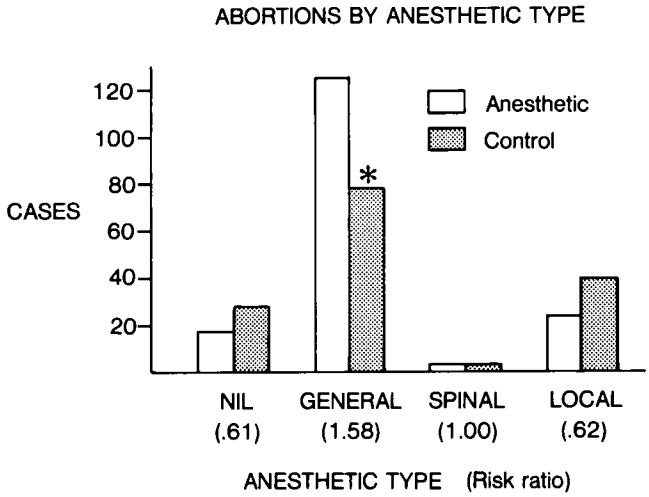

FIG. 2. Abortions by anesthetic type. Number of cases is the number of discordant pairs where one member (either Group A or Group B) had an abortion and the matched subject did not. Stratification of women undergoing operative procedures, regardless of the procedures performed, revealed a significantly increased risk of abortion (P 0.05) in those receiving general anesthetic when compared with their paired control women. A similar effect was not demonstrable in those receiving no anesthetic (trauma), major regional, or local anesthetics for their procedures.

and dental assistants, achieving a 70% response rate. They found 187 women who had been operated on in the first trimester of pregnancy and 100 in the second trimester; again, they noted an increased fetal wastage in women exposed to anesthesia and operation during both trimesters (first trimester 9.6% *vs.* 5.1%; second trimester 2.6% *versus* 1.4%) when compared with controls. No increased incidence of congenital anomalies was found. Unfortunately, there was no information given of the indication for or the type of operation performed.

It is, perhaps, simplistic to consider the risk to the pregnant patient undergoing surgery only in terms of exposure to anesthetic drugs. The period of gestation is a time of multiple physiologic changes, many of which may be disturbed by anesthetic and surgical techniques.[8,9] Many other agents employed in the perioperative period, including diagnostic x-rays, analgesics,[10] and sedatives such as diazepam,[11,12] barbiturates,[13,14] and antiemetics[15] have been found to be associated epidemiologically with birth defects. Indeed, even anxiety and life stress have been associated with an adverse pregnancy outcome.[16] Any documented effects of anesthesia and operation on the human fetus must, therefore, be interpreted as multifactorial in origin.

The present study used a large sample involving an entire province, yet did not detect a difference in congenital anomalies. Our study findings of 76 discordant pairs and a difference of 2.6% between groups at a 95% confidence limit had only a 13% chance of revealing a difference (if one existed). This difference would be difficult to detect without using huge sample sizes, estimated at over 500 discordant pairs, and would require a study of over 17,000 women exposed to anesthesia during pregnancy. Fortunately, the rate of congenital anomalies was so low in both groups that even if there were an effect due to anesthesia and operation, the number of infants involved would be very small. One could also question whether our anomaly rate (1.6%) was excessively low, perhaps because of underreporting to the central registry. While this cannot be ruled out, incomplete records of congenital anomalies would apply to all women in the study and, therefore, should not bias the comparison between the Group A and Group B women.

The use of health insurance data, as validated, affords an unbiased analysis of the entire study population.[17] By matching, we attempted to control for age and, to some extent, the influence of environmental and socioeconomic factors. Unfortunately, the data base did not permit controlling for the other factors such as smoking, maternal medical illness, or parity, which may have a bearing on pregnancy outcome. Furthermore, it is not possible to determine if any women had surgery during the pregnancy but before moving to the province. However, be-

TABLE 4. Abortions by Surgical Site under General Anesthesia

Site of Surgery	Discordant Pairs: Group A Woman+ Group B Woman−	Discordant Pairs: Group A Woman− Group B Woman+	Total Pairs	Estimated Risk Ratio (95% confidence limits)
Abdominal	33	24	277	1.38 (0.66, 2.83)
Ob/gyn	32	16	229	2.0* (1.10, 3.64)
Other Sites	60	39	518	1.54* (1.03, 2.30)

* $P < 0.05$.

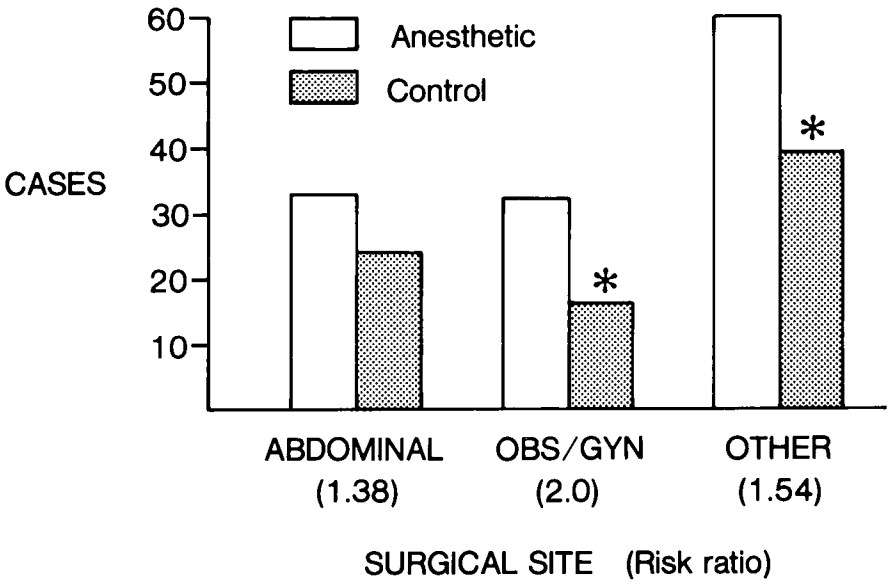

FIG. 3. Abortions by surgery site (general anesthetics). Number of cases is the number of discordant pairs where one member (either Group A or Group B) had an abortion and the matched subject did not. Stratification of women exposed to general anesthesia by operative site demonstrated a significantly increased risk ($P \leq 0.05$) compared with control subject (confidence limit not including 1.0) when obstetric/gynecologic and "other" procedures were examined. The risk for abdominal surgery, while demonstrating the same trend, was not statistically significant.

cause the population of Manitoba is very stable,** and because the sample size in this study was large, this consideration should not affect the study results. Such factors could only be controlled in future prospective studies that would be costly and difficult to justify unless a clear risk to the pregnancy can be defined.

Our results indicate that receiving an anesthetic does not appear to be associated with an increased incidence of congenital anomalies in the offspring of exposed mothers. On the other hand, general anesthesia, particularly for obstetric or gynecologic procedures, does appear to be associated with increased risk of abortion. It is conjectural at the present time whether such an effect is due solely to the operative procedure, or whether other factors such as the uterine relaxant effects of the volatile anesthetic drugs, the compromise of uterine blood flow occurring with nitrous oxide and stress, or mutagenic effects of the administered drugs are contributory. In any event it is probably prudent at the present time to avoid, if possible, operations and anesthesia during pregnancy. If an operative procedure is necessary to preserve comfort or prevent maternal morbidity, it should be acknowledged that fetal transformation is unlikely, but that an increased risk of abortion might be anticipated.

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