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# Maternal surgery and anesthesia during pregnancy and risk of birth defects in the National Birth Defects Prevention Study, 1997–2011

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## Abstract

**Background:** There is little recent research on the teratogenicity of maternal anesthesia exposure. We used National Birth Defects Prevention Study data to describe surgical procedures conducted during pregnancy and to estimate the risk of birth defects associated with periconceptional anesthesia exposure.

**Methods:** We used logistic regression to assess associations between general and local anesthesia for surgery during the periconceptional period and specific birth defects. We calculated odds ratios and 95% confidence intervals for 25 birth defects with at least five exposed cases (11,501 controls, 24,337 cases), adjusted for maternal race/ethnicity, age, body mass index, periconceptional exposure to X-ray, CT, or radionuclide scans, and study site.

**Results:** The most commonly reported procedures were dental, dermatologic, and cervical cerclage procedures, regardless of gestational timing. Overall, 226 case and 73 control women reported periconceptional general anesthesia; 230 case and 89 control women reported periconceptional local anesthesia. Women who reported general or local anesthesia were disproportionately non-Hispanic white and were more likely to report periconceptional opioid use and at least one periconceptional X-ray/CT/radionuclide scan. Women who reported general

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CONFLICT OF INTEREST
The authors report no conflict of interest.

DISCLOSURE OF INTEREST
The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

DATA AVAILABILITY STATEMENT
Data from the NBDPS are not released to the public. Qualified researchers can be granted access to NBDPS data for analysis through collaboration with one of the Centers for Birth Defects Research and Prevention.

anesthesia were also more likely to report periconceptional injury. We did not observe any significant associations between either type of anesthesia exposure and the birth defects studied. Odds ratios were generally close to null and imprecise.

**Conclusions:** Our study population reported a wide range of surgical procedures during pregnancy, requiring both general and local anesthesia. Our findings suggest that periconceptional anesthesia is not strongly associated with the birth defects assessed in this study.

### Keywords

anesthesia; birth defects; National Birth Defects Prevention Study; pregnancy; surgery

## 1 | INTRODUCTION

There are few population-based epidemiological studies on surgery and anesthesia during pregnancy and the risk of birth defects in offspring. Most are limited by small numbers and either analyze all birth defects together or only include a select few types of malformations. Additionally, the existing literature is outdated and does not reflect modern anesthetic practices. The American College of Obstetricians and Gynecologists recommends that elective surgery be performed after pregnancy, but that necessary nonobstetric surgery should not be denied (Committee on Obstetric Practice and the American Society of Anesthesiologists, 2017). Exposure to anesthetics during nonobstetric surgeries occurs in approximately 2% of pregnant women (Kuczkowski, 2004; Rosen, 1999; Sylvester, Khoury, Lu, & Erickson, 1994). Maternal general anesthesia exposure during late pregnancy has been linked to negative effects on neurodevelopment in offspring ("FDA Drug Safety Communication: FDA review results in new warnings about using general anesthetics and sedation drugs in young children and pregnant women," 2016), but the effect of periconceptional exposures on fetal development is less clear. It is important to better understand the types of anesthesia and procedures pregnant women are exposed to, as well as the potential risks of birth defects those exposures pose to the fetus.

Studies of women undergoing surgery during pregnancy have reported conflicting results on teratogenicity. Neither the Hungarian Case–Control Surveillance of Congenital Abnormalities Study nor the Collaborative Perinatal Study found any significant associations between surgery under general anesthesia and increased risk of congenital defects (Czeizel, Pataki, & Rockenbauer, 1998; Heinonen, Slone, & Shapiro, 1977). However, two other studies found associations with central nervous system defects, particularly neural tube defects (Kallen & Mazze, 1990) and hydrocephalus with eye defects (Sylvester et al., 1994). The Collaborative Perinatal Study did note a nonsignificant elevation in eye and ear malformations in 1,340 women exposed to a local anesthetic, procaine, during early pregnancy (Heinonen et al., 1977). in vitro studies in mice and chicks have shown lidocaine, another local anesthetic, to cause neural tube closure defects (Lee & Nagele, 1985; O'Shea & Kaufman, 1980). In human cells, nitrous oxide has been shown to interfere with the action of vitamin B12 (Kano et al., 1983). Animal studies have also demonstrated skeletal malformations, as well as eye defects and laterality alterations, associated with high levels of nitrous oxide exposure (Fujinaga, Baden, & Mazze, 1989; Mazze, Wilson, Rice, & Baden, 1984).

Given its size and breadth, the NBDPS is in a unique position to more closely assess potential associations between modern anesthetic exposures and a wider range of specific malformations than previous studies have analyzed. Our study had two main objectives: (a) describe the prevalence and types of surgical procedures and related anesthesia exposures that women undergo during pregnancy; and (b) assess whether periconceptional anesthesia exposure is associated with risk of birth defects among offspring.

## 2 | METHODS

The NBDPS was a multisite, population-based, case–control study in the United States designed to investigate risk factors for more than 30 major structural birth defects (Reefhuis et al., 2015). The NBDPS enrolled women from study sites in 10 states (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah) who had pregnancies that ended on or after October 1, 1997 and had estimated delivery dates (EDDs) through December 2011. A woman was eligible to participate in the study if she could complete the interview in English or Spanish, had legal custody of her child, was not incarcerated, and had not participated in the NBDPS following a previous pregnancy. Each study site and the Centers for Disease Control and Prevention obtained institutional review board approval for the study protocol and participants provided informed consent.

Controls were liveborn infants without a major birth defect, randomly selected from birth records or hospital discharge lists to represent the underlying population from which the cases were drawn. Cases were ascertained from birth defect surveillance programs in each site. With some variation across sites, cases could be liveborn, stillborn (≥20 gestational weeks), or induced abortions. Clinical geneticists at each site reviewed medical record information to determine case eligibility, according to a standardized case definition. Cases with known chromosomal abnormalities or single gene disorders were excluded. Eligible cases were classified as having either isolated, multiple, or complex birth defects (Rasmussen et al., 2003; Reefhuis et al., 2015). Briefly, a case with two or more major birth defects that are considered unrelated was classified as multiple; a case with a pattern of embryologically related birth defects was classified as complex (e.g., Pentalogy of Cantrell or Omphalocele–Exstrophy–Imperforate anus–Spinal defects [OEIS] complex). Congenital heart defects (CHDs) were further classified according to the cardiac phenotype, complexity, and presence of extra-cardiac defects (Botto, Lin, Riehle-Colarusso, Malik, & Correa, 2007). With the exception of amniotic band sequence, single ventricle, and heterotaxy, we excluded complex cases from our study. For analyses of hypospadias, we excluded female controls.

Trained interviewers collected information on maternal surgery and anesthesia exposures during pregnancy, as well as demographic, behavioral, medical history, and socioeconomic characteristics, via computer-assisted telephone interview with participants between 6 weeks and 2 years after the EDD. Women reported surgical procedures in response to the question: "From 3 months before you became pregnant to the end of your pregnancy, did you have any surgical procedures?" Follow-up questions asked women to report "what was done" in the surgical procedure, whether general or local anesthesia was used, and the gestational month of the procedure. We excluded women who were missing responses to the surgery questions

($n$ = 228 cases, 95 controls) or who reported fetal surgery or obstetric procedures that may have directly affected the fetus (fetal blood transfusion, amniotic fluid reduction/infusion, or multifetal pregnancy reduction) ($n$ = 151 cases, eight controls). Women who reported only delivery-related surgical procedures (cesarean section, episiotomy, contraceptive or sterilization procedures, or induced abortion) or fertility treatment-related procedures (in vitro fertilization or contraceptive device removal) were considered unexposed. The only remaining obstetric procedure that did not meet these two criteria was cervical cerclage; we considered women who reported cerclage as exposed in our analyses. Women who reported a surgical procedure were also asked whether they received general or local anesthesia for that procedure, as well as the month in which the procedure took place.

For our descriptive analysis of surgical and anesthetic exposures during pregnancy, we limited our study population to control women who reported an eligible surgical procedure during the month before through the end of pregnancy. We categorized exposures by timing ("peri-conception" included the month before through the third month of pregnancy; "second/third trimester" included months four through the end of pregnancy), and by type of anesthesia (general or local). We used chi-square tests to compare selected demographic, clinical, and risk factor characteristics among women exposed to anesthesia, by type and timing, compared to unexposed women. Women who reported more than one procedure or anesthesia type were counted in each relevant exposure category and/or time period. We (SCF and KS) reviewed women's open-ended responses to the type of surgery undergone and categorized them according to general body system.

For our analysis of the association between anesthesia and birth defects, we considered women who reported anesthesia for an eligible surgical procedure any time during the periconceptional period to be exposed. Women who did not report any anesthesia during pregnancy were considered unexposed. We excluded from this analysis women who reported anesthesia for surgical procedures only after the first trimester. We used logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between anesthesia exposure, by type, and each birth defect case group for which there were at least 100 interviewed cases. Women who reported both types of anesthesia exposures were included in both analyses. For groups with at least five exposed cases, we adjusted our estimates for maternal age at delivery (continuous years), race/ethnicity (non-Hispanic white vs. other), prepregnancy body mass index (continuous kg/m$^2$), periconceptional exposure to a radiation-emitting scan (X-ray, CAT/CT, or radionuclide; any vs. none), and study site. We selected covariates a priori, based on content area expertise and review of the existing literature. For defect categories with 3–4 exposed cases, we calculated crude ORs and Fisher's exact 95% CIs. We did not calculate ORs for defects with less than 3 exposed cases. Cervical cerclage was the only obstetric procedure directly related to the index pregnancy that we included in our analysis and may indicate complications that could be related to birth defect risk, so we conducted a subanalysis in which we excluded women who reported anesthesia for cervical cerclage. We conducted all analyses in SAS 9.4 (Cary, NC).

## 3 | RESULTS

We included 11,725 control women in our descriptive analysis, of whom 383 (3.3%) reported a surgical procedure during pregnancy (Figure 1). More control women reported surgical procedures in the second or third trimesters (59.3%, $n = 227$) than in the periconceptional period (44.6%, $n = 171$), with some reporting procedures during both time periods (3.9%, $n = 15$). Most control women reported local anesthesia for their surgical procedure(s), although less so among periconceptional procedures (42.7% general anesthesia, 52.0% local anesthesia) than among later pregnancy procedures (25.6% general anesthesia, 63.8% local anesthesia).

Control women's knowledge of pregnancy prior to surgery increased with higher gestational ages (data not shown). Of those who reported anesthesia type and postconception surgery ($n = 113$; $n = 43$ general anesthesia, $n = 74$ local anesthesia), control women with an unrecognized pregnancy at the time of surgery represented at least 37.2% ($n = 16$) of control women who underwent general anesthesia and 21.6% ($n = 16$) of control women who underwent local anesthesia during gestational months 1–3. An additional 29.2% of control women ($n = 33$; $n = 13$ general anesthesia, $n = 20$ local anesthesia) reported surgery in the same gestational month as pregnancy recognition, but we do not have data on more specific timing to determine which occurred first.

Among control women, most of those who reported surgery (91.6%, $n = 351$) only reported one surgical procedure during pregnancy. Twenty-two control women reported two separate procedures, and 10 control women reported three or more (data not shown). Overall, dental procedures were the most commonly reported surgical procedure during pregnancy (23.6%, $n = 103$ procedures), followed by dermatologic procedures (e.g., mole/cyst removal and/or biopsy, ingrown fingernail/toenail removal) (17.2%, $n = 75$ procedures) and cervical cerclage (13.3%, $n = 58$ procedures) (Table 1). In the periconceptional period, the most commonly reported procedures requiring general anesthesia were dental procedures (16.7%, $n = 14$), cholecystectomy (9.5%, $n = 8$), and cervical cerclage (9.5%, $n = 8$). The most commonly reported local anesthesia procedures in the periconceptional period were dental procedures (34.8%, $n = 32$), dermatologic procedures (20.7%, $n = 19$), and cervical cerclage (16.3%, $n = 15$). The distributions by anesthesia type were similar for second/third trimester procedures. Procedures to treat acute abdominal conditions were notably more prevalent among control women who reported general anesthesia in the second or third trimesters: appendectomy (12.1%, $n = 8$), cholecystectomy (15.2%, $n = 10$), and kidney stone/ureteral stent procedures (13.6%, $n = 9$). For dental procedures during the periconceptional period, 30% involved general anesthesia; for the second/third trimester this dropped to 6%. Although not the focus of our formal descriptive analysis, these distributions were similar among cases (data not shown).

Control women who reported anesthesia exposure, regardless of type or timing, were statistically more likely than unexposed control women to report periconceptional opioid use and at least one periconceptional X-ray/CT/radionuclide scan (Table 2). They also differed in terms of race/ethnicity, with a higher proportion of women across all exposure groups reporting non-Hispanic white race/ethnicity and a lower proportion reporting Hispanic ethnicity. Women with general anesthesia exposure during the periconceptional period were also more likely to report a periconceptional injury. Compared to unexposed women, higher proportions of women with periconceptional local anesthesia exposure reported at least some college education, household income of $50,000 or more, unintended pregnancy (mistimed or unwanted), and prenatal care during the periconceptional period. Women with late pregnancy general anesthesia exposure were more likely to report hypertension and a periconceptional injury. A higher proportion of women with late pregnancy local anesthesia exposure reported having completed a bachelor's degree or higher.

The results of our analysis of the association between periconceptional anesthesia exposure, by type, and birth defects are presented in Table 3. We analyzed a total of 30,184 cases and 11,501 controls, of whom 443 cases and 158 controls were exposed to general and/or local anesthesia during the periconceptional period ($n$ = 13 cases and four controls reported periconceptional exposure to both anesthesia types). In our study, 0.8% of case and 0.6% of control women reported general anesthesia exposure; 0.8% of case and 0.8% of control women reported local anesthesia exposure. We did not observe any statistically significant crude or adjusted ORs between either type of anesthesia exposure and any birth defect category. We calculated 47 adjusted ORs, which ranged from 0.5 (95% CI 0.2–1.4) for general anesthesia and perimembranous VSD to 1.9 (95% CI 0.8–4.2) for local anesthesia and longitudinal limb deficiency. Several crude ORs were elevated: for general anesthesia, anophthalmia/microphthalmia (cOR 2.9, 95% CI 0.8–7.7), pulmonary atresia (cOR 2.5, 95% CI 0.7–6.8), and tricuspid atresia (cOR 3.7, 95% CI 1.0–10.1); for local anesthesia, holoprosencephaly (cOR 2.3, 95% CI 0.5–7.2), anophthalmia/microphthalmia (cOR 2.3, 95% CI 0.6–6.3), and conoventricular VSD (cOR 3.3, 95% CI 0.6–10.4). However, these estimates were based on small numbers (3–4 exposed cases) and confidence intervals were wide. Our subanalysis excluding women who reported anesthesia for periconceptional cervical cerclage yielded similar results to our main analyses (data not shown).

## 4 | DISCUSSION

Approximately 3% of women in our study population reported undergoing a surgical procedure during pregnancy. They reported a broad range of procedures, both in early and late pregnancy, utilizing both general and local anesthesia. We did not find any clear evidence that periconceptional anesthesia exposure as part of a surgical procedure was associated with meaningfully increased risk of birth defects. This is consistent with the results from most of the available human studies, primarily from administrative datasets, on surgery or anesthesia and birth defects (Czeizel et al., 1998; Duncan, Pope, Cohen, & Greer, 1986; Heinonen et al., 1977; Mazze & Kallen, 1989; Reedy, Kallen, & Kuehl, 1997).

Although the NBDPS is the largest population-based case–control study of birth defects in the United States, periconceptional anesthesia exposure was rare among participants. As a result, our study was generally underpowered to detect moderate effect sizes (ORs <2), even for the largest case groups. We did observe elevated crude ORs for anophthalmia/microphthalmia, regardless of type of anesthesia. Unspecified eye malformations have been reported among rats exposed to nitrous oxide, although only at concentrations much higher than would be administered to humans in practice (Mazze et al., 1984). Sylvester et al.

reported an association between general anesthesia exposure and hydrocephalus with eye defects; however, that association was primarily driven by cases with cataracts (Sylvester et al., 1994). In our study, we did not observe evidence of an association between cataracts and general anesthesia, based on three exposed cases (cOR 1.4, 95% CI 0.3–4.5), or hydrocephaly and general anesthesia, based on five exposed cases (aOR 1.6, 95% CI 0.6–4.4); there were no exposed cases in our sample with both hydrocephaly and any NBD PS-eligible eye defects.

An analysis of Swedish registry data did not find an association between general anesthesia exposure and birth defects overall (Mazze & Kallen, 1989), although a reanalysis of the same database suggested a possible link between general anesthesia during gestational weeks 4–5 and neural tube defects (anencephaly, encephalocele, and spina bifida) (Kallen & Mazze, 1990). Those authors cautioned that their results may be a chance finding and encouraged further study with larger datasets. We did not observe increased risk of neural tube defects overall, nor of any specific type of neural tube defect, associated with general anesthesia exposure in our study. We did observe an increased crude OR between local anesthesia and holoprosencephaly (cOR 2.3, 95% CI 0.5–7.2), another central nervous system defect, but this estimate was imprecise and based on only three exposed cases.

We also observed elevated, but not statistically significant, adjusted ORs for associations between longitudinal limb deficiency and both general (aOR 1.8, 95% CI 0.8–4.2) and local (aOR 1.9, 95% CI 0.8–4.2) anesthesia during the periconceptional period. Limited evidence suggests limb deformities in rats may be associated with high levels of nitrous oxide exposure (Mazze et al., 1984), but this finding has not been reported in human studies (Czeizel et al., 1998; Duncan et al., 1986; Heinonen et al., 1977).

As others have reported (Czeizel et al., 1998; Kort, Katz, & Watson, 1993; Mazze & Kallen, 1989), appendectomy and cholecystectomy were common procedures for which women in our sample received general anesthesia. Women also commonly reported anesthesia (both general and local) for kidney stone removal and/or ureteral stent procedures. These reflect urgent conditions for which surgical treatment was likely unavoidable. Similarly, our analysis included women who reported anesthesia for cervical cerclage, which is a procedure aimed at preventing preterm birth and therefore cannot be delayed until a later time. Our results suggest that concerns about risk of anesthesia and birth defects likely do not outweigh these more pressing concerns about the health of the woman and fetus.

Dental and dermatologic procedures, for which women primarily reported local anesthesia, were also prevalent in our study. We speculate that pregnancy may present a time of increased engagement with the healthcare system for some women, resulting in "catchup" care for primary care needs that may have gone unattended or undiagnosed prior to pregnancy. In the United States, a routine prenatal care schedule includes as many as 14 visits for a full-term, uncomplicated pregnancy (Kilpatrick, Papile, & Macones, 2017), providing ample opportunity for an obstetric healthcare provider to observe nonobstetric care needs and potentially recommend treatment or referral.

We observed that many women who reported a surgical procedure during gestational months 1–3 did not know of their pregnancy until at least the next gestational month. The proportion of women undergoing surgery with an unrecognized pregnancy was similar whether the procedure involved general or local anesthesia. The American Society of Anesthesiologists Task Force on Preanesthesia Evaluation suggests that preanesthesia pregnancy testing “may be offered to female patients of childbearing age and for whom the result would alter the patient’s management,” but declines to recommend it as a standard practice (Apfelbaum et al., 2012). The Task Force cites lack of evidence of the harmfulness of anesthesia during early pregnancy as justification, which our study does seem to support. However, our study also shows that anesthesia is not the only potentially harmful exposure associated with surgical procedures; for instance, women who reported anesthesia were also substantially more likely to report periconceptional opioid use. Even when the procedure itself cannot be avoided during pregnancy, clinical decisions about the best pain management options may differ depending on the patient’s pregnancy status. Given the high proportion of unrecognized pregnancies at the time of surgery in our study, health care providers may consider the risks and benefits of preoperative pregnancy testing.

Our study was limited by the level of detail provided by maternal self-report. Women described the procedure(s) undergone, but we did not have access to clinical details on the indication for the procedure, duration or specific type of procedure (e.g., laparoscopic or open), any complications encountered, or any information about the type or dosage of anesthetic agent(s) used. This makes it difficult to assess the effect of anesthesia independently from the underlying reason for the surgery, such as infection or other chronic medical condition. It also makes it impossible to evaluate the risk or safety of particular anesthetic agents or practices. However, these types of limitations would primarily be of concern if we found increased risk of birth defects associated with anesthesia during surgery. Given that we did not observe strong evidence to this effect, they have limited practical impact on our conclusions. Additionally, our reliance on self-reported anesthesia may have resulted in exposure misclassification. Because both cases and controls would have been equally likely to misreport anesthesia exposure, this could bias our estimates toward the null. Finally, our study did not assess risks associated with occupational exposure to anesthetic gases, so we cannot comment on any potential risk of birth defects and chronic, as opposed to acute, anesthesia exposure.

Despite its limitations, our study has several strengths. The NBDPS’s large size and standardized case classification protocol enabled us to analyze many specific birth defects that have not been previously described in relation to anesthesia. Additionally, women in our study reported procedures occurring between 1997 and 2011, reflecting more current anesthetic practices than most other available studies (Czeizel et al., 1998; Duncan et al., 1986; Heinonen et al., 1977; Kallen & Mazze, 1990; Mazze & Kallen, 1989; Reedy et al., 1997; Sylvester et al., 1994). Finally, our maternal interview format allowed us to collect detailed information on a number of relevant pregnancy exposures, to allow for more complete control of potential confounders than studies utilizing administrative data have been able to do (Duncan et al., 1986; Kallen & Mazze, 1990; Mazze & Kallen, 1989; Reedy et al., 1997).

## 5 | CONCLUSIONS

Our findings suggest that periconceptional anesthesia exposure for a surgical procedure is not associated with the birth defects assessed in this study. The prevalence of reported surgical procedures in our study population was similar to what has been reported elsewhere. Many of the surgeries reported are generally performed for urgent, medically necessary conditions that cannot be delayed until after pregnancy; our results should be reassuring to those women. Additionally, during pregnancy, women may have the opportunity to access dental care or diagnostic services for conditions that may not be life threatening, but are important for preventive health and quality of life. Our study adds to the evidence that the benefits of this care, based on individual clinical decision making, likely outweigh any potential risk of birth defects due to the anesthesia exposure during a surgical procedure. However, it is important to keep in mind our study did not assess all factors associated with surgery, such as antibiotics or pain medication.

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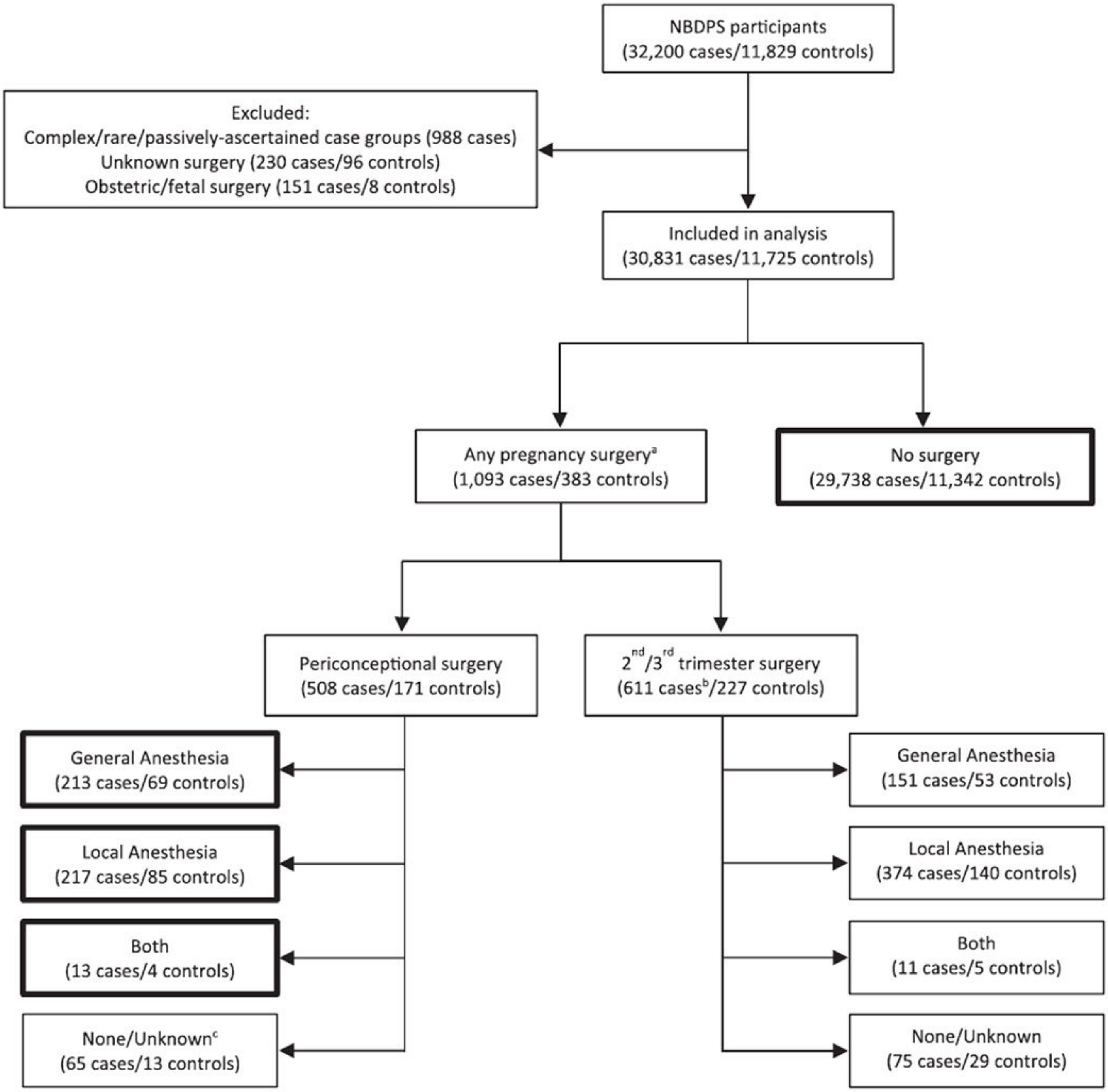


**FIGURE 1.**
Study population and exclusions, National Birth Defects Prevention Study, 1997–2011. Boxes with bold outlines indicate subjects who were included in logistic regression analyses (Tables 2 and 3). [a]$n$ = 15 controls and 26 cases reported at least one surgical procedure in both time periods (periconception and second/third trimester). [b]Cases are quantified here, but were not formally analyzed. [c]Of these, $n$ = 1 control and three cases reported no anesthesia. These women are included as “unexposed” in logistic regression analyses of ane

sthesia exposure. Cases with un known anesthesia exposure are quantified here but were excluded from any formal analysis

## TABLE 1

Reported types of surgical procedures among controls, by time period and anesthesia type, National Birth Defects Prevention Study, 1997–2011

| | Total | | Periconceptional period | | | | Second/third trimester | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | General anesthesia | | Local anesthesia | | General anesthesia | | Local anesthesia | |
| **Procedure type** | ***n*** | **%** | ***n*** | **%** | ***n*** | **%** | ***n*** | **%** | ***n*** | **%** |
| All procedures[a] | 436 | | 84 | | 92 | | 66 | | 153 | |
| Dermatologic | 75 | 17.2% | 5 | 6.0% | 19 | 20.7% | 1 | 1.5% | 41 | 26.8% |
| Breast lumpectomy/biopsy | 17 | 3.9% | 2 | 2.4% | 4 | 4.3% | 4 | 6.1% | 6 | 3.9% |
| Dental | 103 | 23.6% | 14 | 16.7% | 32 | 34.8% | 3 | 4.5% | 51 | 33.3% |
| Ear/nose/throat | 6 | 1.4% | 4 | 4.8% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| Gastrointestinal | | | | | | | | | | |
| Endoscopy | 6 | 1.4% | 2 | 2.4% | 1 | 1.1% | 1 | 1.5% | 1 | 0.7% |
| Appendectomy | 14 | 3.2% | 4 | 4.8% | 0 | 0.0% | 8 | 12.1% | 1 | 0.7% |
| Colonoscopy | 5 | 1.1% | 2 | 2.4% | 0 | 0.0% | 1 | 1.5% | 0 | 0.0% |
| Cholecystectomy | 18 | 4.1% | 8 | 9.5% | 0 | 0.0% | 10 | 15.2% | 0 | 0.0% |
| Other | 10 | 2.3% | 0 | 0.0% | 2 | 2.2% | 3 | 4.5% | 3 | 2.0% |
| Genitourinary | | | | | | | | | | |
| Kidney stone removal | 21 | 4.8% | 4 | 4.8% | 4 | 4.3% | 9 | 13.6% | 8 | 5.2% |
| Ureteral stent | 13 | 3.0% | 1 | 1.2% | 3 | 3.3% | 6 | 9.1% | 7 | 4.6% |
| Colposcopy/cervical biopsy | 22 | 5.0% | 1 | 1.2% | 5 | 5.4% | 1 | 1.5% | 6 | 3.9% |
| Cyst/fibroid removal | 13 | 3.0% | 7 | 8.3% | 0 | 0.0% | 5 | 7.6% | 1 | 0.7% |
| Cervical cerclage | 58 | 13.3% | 8 | 9.5% | 15 | 16.3% | 11 | 16.7% | 23 | 15.0% |
| Other | 15 | 3.4% | 4 | 4.8% | 2 | 2.2% | 3 | 4.5% | 3 | 2.0% |
| Orthopedic | 14 | 3.2% | 7 | 8.3% | 2 | 2.2% | 2 | 3.0% | 3 | 2.0% |
| Other[b] | 39 | 8.9% | 12 | 14.3% | 6 | 6.5% | 4 | 6.1% | 6 | 3.9% |

*Note:* “Periconceptional” refers to the month before through the third month of pregnancy.

[a]Total column may not equal the sum of reported procedures by time period and anesthesia type, as some women reported both types of anesthesia for the same procedure or did not report a type of anesthesia.

[b]Specific types of procedures for which <5 were reported are combined together in the “Other” category.

## TABLE 2

Selected characteristics among controls, by timing of anesthesia exposure, National Birth Defects Prevention Study, 1997–2011

| | | Periconceptional period | | | | Second/third trimester | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Characteristic** | **Unexposed (*n* = 11,343)** | **General anesthesia (*n* = 73)** | **$\chi^2$ *p*-value** | **Local anesthesia (*n* = 89)** | **$\chi^2$ *p*-value** | **General anesthesia (*n* = 58)** | **$\chi^2$ *p*-value** | **Local anesthesia (*n* = 145)** | **$\chi^2$ *p*-value** |
| Age, mean (*SD*) | 27.7 (6.1) | 27.6 (6.7) | .88 | 29.8 (5.9) | .001 | 27.5 (5.9) | .85 | 28.3 (6.2) | .24 |
| Race/ethnicity | | | .02 | | .02 | | .09 | | <.001 |
| Non-Hispanic white | 6,520 (57.5) | 54 (74.0) | | 62 (69.7) | | 42 (72.4) | | 100 (69.0) | |
| Non-Hispanic black | 1,239 (10.9) | 8 (11.0) | | 12 (13.5) | | 5 (8.6) | | 19 (13.1) | |
| Hispanic | 2,837 (25.0) | 9 (12.3) | | 10 (11.2) | | 7 (12.1) | | 13 (9.0) | |
| Other | 741 (6.5) | 2 (2.7) | | 5 (5.6) | | 4 (6.9) | | 13 (9.0) | |
| Completed education | | | .25 | | .002 | | .06 | | .02 |
| <High school | 1877 (16.9) | 6 (8.3) | | 4 (4.7) | | 3 (5.2) | | 11 (7.6) | |
| High school diploma | 2,633 (23.7) | 21 (29.2) | | 14 (16.3) | | 20 (34.5) | | 33 (22.9) | |
| Some college | 2,957 (26.7) | 20 (27.8) | | 30 (34.9) | | 15 (25.9) | | 42 (29.2) | |
| Bachelor's degree or higher | 3,625 (32.7) | 25 (34.7) | | 38 (44.2) | | 20 (34.5) | | 58 (40.3) | |
| Annual household income | | | .51 | | .01 | | .56 | | .06 |
| <\$30,000 | 4,677 (45.8) | 26 (38.8) | | 25 (30.5) | | 25 (43.9) | | 54 (39.7) | |
| \$30,000–\$50,000 | 1,780 (17.5) | 13 (19.4) | | 15 (18.3) | | 13 (22.8) | | 34 (25.0) | |
| ≥\$50,000 | 3,746 (36.7) | 28 (41.8) | | 42 (51.2) | | 19 (33.3) | | 48 (35.3) | |
| Prepregnancy body mass index, mean (*SD*) | 25.3 (6.0) | 26.9 (8.0) | .09 | 25.6 (5.2) | .65 | 25.7 (6.2) | .56 | 25.3 (5.3) | .91 |
| Hypertension (chronic or gestational) | 1,057 (9.4) | 9 (12.5) | .38 | 10 (11.4) | .54 | 10 (17.2) | .04 | 14 (9.7) | .93 |
| Pregestational type 1 or 2 diabetes | 79 (0.8) | 0 (0) | - | 0 (0) | - | 2 (3.7) | - | 2 (1.6) | - |
| Parity ≥ 1 | 6,890 (60.8) | 46 (63.0) | .70 | 55 (62.5) | .74 | 35 (60.3) | .94 | 91 (62.8) | .63 |
| Pregnancy intention | | | .93 | | .01 | | .09 | | .69 |
| Intended | 6,848 (60.6) | 43 (58.9) | | 41 (47.1) | | 40 (69.0) | | 86 (60.1) | |

| Characteristic | Unexposed ($n$ = 11,343) | Periconceptional period: General anesthesia ($n$ = 73) | $\chi^2$ $p$-value | Local anesthesia ($n$ = 89) | $\chi^2$ $p$-value | Second/third trimester: General anesthesia ($n$ = 58) | $\chi^2$ $p$-value | Local anesthesia ($n$ = 145) | $\chi^2$ $p$-value |
|---|---|---|---|---|---|---|---|---|---|
| Mistimed/unintended | 3,635 (32.2) | 25 (34.3) | | 41 (47.1) | | 18 (31.0) | | 49 (34.3) | |
| Ambivalent | 819 (7.3) | 5 (6.9) | | 5 (5.8) | | 0 (0) | | 8 (5.6) | |
| Any periconceptional folic acid use[a] | 5,942 (52.7) | 43 (58.9) | .29 | 50 (56.8) | .44 | 33 (56.9) | .52 | 78 (53.8) | .79 |
| Any first trimester prenatal care | 4,599 (40.7) | 33 (45.2) | .53 | 48 (54.6) | .02 | 21 (36.2) | .56 | 66 (45.5) | .27 |
| Any periconceptional cigarette smoking | 1989 (17.9) | 19 (26.4) | .06 | 18 (20.9) | .46 | 14 (24.1) | .21 | 31 (21.5) | .25 |
| Any periconceptional binge alcohol use[b] | 1,373 (12.4) | 14 (19.4) | .07 | 13 (15.3) | .43 | 6 (10.5) | .66 | 18 (12.5) | .98 |
| Any periconceptional opioid use | 179 (1.6) | 40 (54.8) | <.001 | 17 (19.3) | <.001 | 7 (12.1) | <.001 | 5 (3.5) | .08 |
| Any periconceptional radiation-emitting scan[c] | 455 (4.4) | 24 (39.3) | <.001 | 31 (40.8) | <.001 | 5 (13.2) | .01 | 7 (7.6) | .13 |
| Any periconceptional injury | 95 (0.8) | 5 (6.9) | <.001 | 1 (1.1) | .77 | 2 (3.5) | .03 | 1 (0.7) | .85 |

*Notes:* Unless otherwise noted, values are $n$(%) and “periconceptional” refers to the month before through the third month of pregnancy. Women with multiple anesthesia exposures ($n$ = 15) were counted in each category.

[a]“Periconceptional” is defined as 1 month before and after conception.

[b]Defined as consuming at least four alcoholic drinks on one occasion.

[c]X-ray, CT/CAT, radionuclide.

## TABLE 3

Associations between periconceptional anesthesia exposure, by type, and birth defects, National Birth Defects Prevention Study, 1997–2011

| Defect | Unexposed | General anesthesia | | Local anesthesia | |
|---|---|---|---|---|---|
| | *n* | *n* | OR (95% CI)[a] | *n* | OR (95% CI)[a] |
| Controls, *n* (%) | 11,343 (98.6) | 73 (0.6) | | 89 (0.8) | |
| Any birth defect, *n* (%) | 29,741 (98.5) | 226 (0.7) | | 230 (0.8) | |
| Noncardiac defects | 19,269 | 145 | | 148 | |
| Amniotic band syndrome and limb body wall complex (ABS-LBWC) | 324 | 2 | | 1 | |
| ABS-LBWC: Limb anomalies only | 203 | 1 | | 0 | |
| Neural tube defects | 2,073 | 16 | 1.2 (0.6–2.2) | 21 | 1.4 (0.8–2.4) |
| Anencephaly | 633 | 7 | 1.5 (0.6–3.9) | 6 | 1.1 (0.4–3.0) |
| Spina bifida | 1,222 | 7 | 0.9 (0.4–2.1) | 12 | 1.5 (0.8–2.9) |
| Encephalocele | 218 | 2 | | 3 | 1.8 (0.4–5.4) |
| Hydrocephaly | 488 | 5 | 1.6 (0.6–4.4) | 4 | 1.0 (0.3–2.8) |
| Dandy–Walker malformation | 178 | 2 | | 1 | |
| Holoprosencephaly | 164 | 2 | | 3 | 2.3 (0.5–7.2) |
| Cataracts[b] | 346 | 3 | 1.4 (0.3–4.5) | 2 | |
| Anophthalmia/microphthalmia | 218 | 4 | 2.9 (0.8–7.7) | 4 | 2.3 (0.6–6.3) |
| Glaucoma/anterior chamber defects[b] | 179 | 2 | | 0 | |
| Anotia/microtia | 684 | 4 | 0.9 (0.2–2.4) | 2 | |
| Choanal atresia | 158 | 0 | | 1 | |
| Oral clefts[c] | 4,610 | 29 | 0.8 (0.5–1.4) | 33 | 1.0 (0.6–1.5) |
| Cleft palate only[c] | 1,574 | 9 | 0.8 (0.3–1.7) | 7 | 0.6 (0.2–1.3) |

| Defect | Unexposed | General anesthesia | | Local anesthesia | |
|---|---|---|---|---|---|
| | *n* | *n* | OR (95% CI)[a] | *n* | OR (95% CI)[a] |
| Cleft lip with or without cleft palate[c] | 3,036 | 20 | 0.9 (0.5–1.5) | 26 | 1.2 (0.8–1.9) |
| Cleft lip with cleft palate[c] | 1,964 | 13 | 0.8 (0.4–1.6) | 17 | 1.2 (0.7–2.2) |
| Cleft lip only[c] | 1,072 | 7 | 1.0 (0.5–2.3) | 9 | 1.2 (0.6–2.4) |
| Esophageal atresia | 726 | 1 | | 9 | 1.3 (0.6–3.0) |
| Intestinal atresia/stenosis | 467 | 1 | | 2 | |
| Duodenal atresia/stenosis | 230 | 1 | | 1 | |
| Anorectal atresia/stenosis | 868 | 8 | 1.1 (0.5–2.6) | 7 | 1.0 (0.4–2.4) |
| High anorectal atresia/stenosis | 210 | 2 | | 1 | |
| Low anorectal atresia/stenosis | 460 | 4 | 1.4 (0.4–3.6) | 3 | 0.8 (0.2–2.5) |
| Cloacal exstrophy | 95 | 2 | | 0 | |
| Biliary atresia | 196 | 2 | | 2 | |
| Hypospadias[d] | 2,489 | 23 | 0.9 (0.5–1.7) | 18 | 0.9 (0.5–1.6) |
| Bilateral renal agenesis/hypoplasia | 175 | 2 | | 2 | |
| Limb deficiency | 1,211 | 10 | 1.2 (0.6–2.5) | 14 | 1.4 (0.8–2.6) |
| Longitudinal or intercalary limb deficiency | 515 | 6 | 1.8 (0.8–4.2) | 8 | 1.9 (0.8–4.2) |
| Longitudinal preaxial limb deficiency | 270 | 2 | | 4 | 1.9 (0.5–5.1) |
| Transverse limb deficiency | 702 | 4 | 0.9 (0.2–2.4) | 6 | 1.0 (0.4–2.6) |
| Craniosynostosis | 1,545 | 15 | 1.5 (0.8–2.7) | 14 | 1.0 (0.5–1.9) |
| Diaphragmatic hernia | 822 | 7 | 1.5 (0.6–3.4) | 4 | 0.6 (0.2–1.7) |
| Omphalocele | 409 | 2 | | 3 | 0.9 (0.2–2.8) |
| Gastroschisis | 1,383 | 11 | 0.9 (0.4–2.1) | 9 | 1.4 (0.7–3.1) |
| Sacral agenesis | 101 | 0 | | 1 | |

| Defect | Unexposed | General anesthesia | | Local anesthesia | |
|---|---|---|---|---|---|
| | *n* | *n* | OR (95% CI)[a] | *n* | OR (95% CI)[a] |
| Cardiac defects | 11,416 | 87 | | 88 | |
| Conotruncal defects | | | | | |
| Truncus arteriosus | 129 | 0 | | 1 | |
| Tetralogy of Fallot | 1,173 | 11 | 1.2 (0.6–2.6) | 8 | 1.0 (0.5–2.2) |
| D-transposition of the great arteries (TGA) | 731 | 7 | 0.9 (0.3–2.5) | 7 | 1.3 (0.6–2.9) |
| Double outlet right ventricle with TGA | 166 | 1 | | 0 | |
| Double outlet right ventricle (non-TGA) | 100 | 0 | | 2 | |
| Conoventricular VSD[e] | 111 | 1 | | 3 | 3.3 (0.6–10.4) |
| Atrioventricular septal defect | 337 | 4 | 1.8 (0.5–5.0) | 0 | |
| Anomalous pulmonary venous return | 373 | 1 | | 2 | |
| Total anomalous pulmonary venous return | 298 | 1 | | 2 | |
| Left ventricular outflow tract defects | | | | | |
| Hypoplastic left heart syndrome | 626 | 6 | 1.0 (0.4–2.8) | 10 | 1.6 (0.8–3.5) |
| Coarctation of the aorta | 1,116 | 5 | 0.6 (0.2–1.8) | 6 | 0.7 (0.3–1.6) |
| Aortic stenosis | 475 | 1 | | 3 | 0.8 (0.2–2.4) |
| Right ventricular outflow tract defects | | | | | |
| Pulmonary atresia | 247 | 4 | 2.5 (0.7–6.8) | 1 | |
| Pulmonary valve stenosis[f] | 1,503 | 15 | 1.3 (0.6–2.4) | 12 | 1.0 (0.5–1.9) |
| Tricuspid atresia | 167 | 4 | 3.7 (1.0–10.1) | 2 | |
| Ebstein malformation | 169 | 0 | | 1 | |
| Septal defects | | | | | |
| Perimembranous VSD[e] | 1,407 | 6 | 0.5 (0.2–1.4) | 6 | 0.6 (0.3–1.5) |
| Muscular VSD[g] | 187 | 0 | | 2 | |
| ASD secundum or NOS | 2,966 | 28 | 1.3 (0.8–2.1) | 24 | 1.1 (0.7–1.9) |

| Defect | Unexposed | General anesthesia | | Local anesthesia | |
|---|---|---|---|---|---|
| | ***n*** | ***n*** | **OR (95% CI)**[a] | ***n*** | **OR (95% CI)**[a] |
| Single ventricle | 166 | 1 | | 2 | |
| Heterotaxy with CHD | 338 | 2 | | 0 | |

Abbreviations: ASD, atrial septal defect; CHD, congenital heart defect; NOS, not otherwise specified; VSD, ventricular septal defect.

[a]Groups with 5+ exposed cases are adjusted for maternal age (years, continuous), race/ethnicity (white, other), BMI ($kg/m^2$, continuous), first trimester exposure to radiation-emitting scans (Xray, CAT/CT, radionuclide), and study site.

[b]$n$ = 9,671 unexposed controls, $n$ = 58 general anesthesia exposed controls, $n$ = 74 local anesthesia exposed controls.

[c]$n$ = 11,211 unexposed controls, $n$ = 73 general anesthesia exposed controls, $n$ = 88 local anesthesia exposed controls.

[d]$n$ = 5,756 unexposed controls, $n$ = 40 general anesthesia exposed controls, $n$ = 46 local anesthesia exposed controls.

[e]$n$ = 6,555 unexposed controls, $n$ = 44 general anesthesia exposed controls, $n$ = 54 local anesthesia exposed controls.

[f]$n$ = 10,885 unexposed controls, $n$ = 70 general anesthesia exposed controls, $n$ = 88 local anesthesia exposed controls.

[g]$n$ = 695 unexposed controls, $n$ = 7 general anesthesia exposed controls, $n$ = 6 local anesthesia exposed controls.