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Epidemiology of general anesthesia prior to age 3 in a population-based birth cohort

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Summary

Background—Utilization of general anesthesia in children has important policy, economic, and healthcare delivery implications, yet there is little information regarding the epidemiology of these procedures in the United States.

Aims—The primary objective of this study was to describe in a geographically defined population the incidence of procedures requiring general anesthesia up to the child's third birthday, and the patient characteristics associated with receiving these procedures. A secondary objective was to determine the proportion of children in the population who meet the risk criteria promulgated by the Food and Drug Administration (FDA).

Methods—A retrospective cohort of children born from 1994 to 2007 in Olmsted County, MN was established. Birth certificate information and receipt of general anesthesia before age 3 were collected. Proportional hazard regressions were performed to evaluate the association between characteristics of children and incidence of general anesthesia.

Results—Among the 20 922 children in the cohort, 3120 (14.9%) underwent at least 1 general anesthesia before age 3. In multivariate regression, factors independently associated with receiving at least 1 procedure included prematurity, male sex, lower birth weight, cesarean delivery, a non-Hispanic mother, and a White mother, controlling for multiple gestation, number of children previously born, age, education, and marital status of the mother. Seven hundred and twenty-three children (3.5%) had at least 1 subsequent procedure. Estimated gestational age <32 weeks and low birth weight were independently associated with receiving repeated anesthesia. Eight hundred and twenty children (3.9%) had a single prolonged exposure above 3 hours, multiple exposures prior to age 3, or both.

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IRB APPROVAL

This study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards.

CONFLICT OF INTEREST

The authors have no conflicts of interest relevant to this article to disclose.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

Conclusion—Approximately 1 in 7 children were exposed to at least 1 episode of general anesthesia before age 3, and approximately 1 in 4 children who received general anesthesia fall within the high-risk category as defined by the recent FDA warning. The apparent disparities in surgical utilization related to race and ethnicity in this study population deserve further exploration.

Keywords

anesthesia; child; ethnic groups; general; gestational age; incidence; infant; low birth weight

1| INTRODUCTION

Children may receive invasive diagnostic or surgical procedures that require general anesthesia as a part of their medical care. Utilization of these services has important policy, economic, and healthcare delivery implications, yet there is surprisingly little information regarding the epidemiology of these procedures in the United States (USA). Population-level estimates for ambulatory and inpatient procedural utilization in children have been published,^{1,2} but there is little information regarding secular trends in utilization, characteristics of the anesthetic care provided, or patient factors associated with the receipt of such procedures.

Exposure to general anesthesia may be associated not only with short-term behavioral changes in the postoperative period^{3,4} but with long-term alterations in cognition and behavior.^{5–8} Animal studies provide strong evidence of neurotoxic effects of anesthetics on brain development.⁹ However, it is not at all clear whether these results in animals can be translated to children, and this area is a subject of lively debate and ongoing research efforts. Nonetheless, based largely on animal studies, the US Food and Drug Administration (FDA) recently issued a warning in the form of Drug Safety Communication and additional warning labels that prolonged (defined as >3 hours anesthesia duration) or repeated exposure to general anesthesia may affect brain development in children under 3.¹⁰ Defining the population frequency of “at risk” exposures thus has potential relevance to health care providers, regulators, and policy makers.

We recently defined a birth cohort of children born from 1994 to 2007 (inclusive) to mothers residing in Olmsted County, Minnesota as part of an effort to examine long-term neurocognitive outcomes of children exposed to anesthetics prior to their third birthday.¹¹ Because information is available regarding all anesthesia exposures in this population, this work provides the opportunity to explore the epidemiology of procedures requiring general anesthesia.

The purpose of this study was to describe in a geographically defined population, the incidence of procedures requiring general anesthesia up to the child’s third birthday, and the patient and family characteristics associated with receiving these procedures. A secondary objective was to determine the proportion of children in the population who meet the risk criteria promulgated by the FDA (anesthesia of >3 hours duration or repeated exposure to anesthesia prior to age 3).

2 | MATERIALS AND METHODS

2.1 | Study cohort

A prior publication described the definition of a birth cohort of children born in Olmsted County, Minnesota from January 1, 1994 to December 31, 2007 to mothers who resided in Olmsted County at the time of birth.^{11,12} Potentially eligible children were identified using the resources of the Rochester Epidemiology Project (REP). The REP provides access to the complete medical records of all Olmsted County residents and birth certificate information from the Minnesota Department of Health, Division of Vital Statistics.¹³ From the latter source, we identified 27 213 children who were born between the identified dates. Of these, 34 were excluded because an identification number or records could not be located in the REP system. A further 3330 children were excluded because they or their parents did not provide authorization for their medical records to be used in research per Minnesota statute. Finally, because the purpose of the study was to study procedural utilization prior to age 3, we excluded 2798 children who moved from Olmsted County and 129 children who died prior to their third birthday. Thus, the final study cohort included 20 922 children.

2.2 | Study measurements

Birth certificate information utilized in the current study included date of birth, sex, estimated gestational age, birth weight, cesarean section vs vaginal delivery, multiple gestation, number of children previously born as well as the age, race (White vs non-White), ethnicity (Hispanic vs non-Hispanic), education, and marital status of the mother. Estimated gestational age was categorized into 3 groups: more than 36 weeks, between 32 and 36 weeks, and <32 weeks.¹⁴ All episodes of exposure to general anesthesia before age 3 at Mayo Clinic Rochester or Olmsted Medical Center were identified from existing medical records and data were abstracted including procedure type, anesthesia duration, and anesthetics/adjuvants received. Records review did not identify evidence of these children receiving anesthesia at other medical centers.

2.3 | Statistical analysis

Characteristics of the birth cohort were compared among the 3 groups of estimated gestational age (EGA). EGA was missing in 69 patients. Continuous variables were presented as mean $\pm$ SD. Categorical variables were reported as number and percentage.

In the analysis of the initial anesthesia exposure, a subject was defined as at risk from the date of birth and contributed to person time until date of first anesthetic or their 3rd birthday. Incidence was calculated using total number of first anesthetic exposures and total person time. In the analysis of the second anesthesia exposure, a child was regarded as at risk from the date of their first anesthetic until date of their second surgery or their 3rd birthday.

Cox (proportional hazards) regressions were performed to evaluate the relationship between baseline characteristics (EGA, sex, birth weight, cesarean section vs vaginal delivery, multiple gestation, number of children previously born as well as the age, race, ethnicity, education, and marital status of the mother) and the risk of receiving a procedure. Univariate

Cox regressions were performed before a multivariate regression on EGA and having surgery was done controlling for other factors.

Duration of individual anesthesia episodes and cumulative duration of exposure in children who had multiple exposures was reported as mean $\pm$ SD and median with interquartile range (IQR). Duration was categorized as <1, 1–2, 2–3, and ≥ 3 hours (prolonged).

Analyses were performed using Stata, version 13.1 (College Station, TX), and a *P* value $< .05$ was considered statistically significant.

3| RESULTS

Characteristics of the study cohort are presented in Table 1 according to the categories of EGA. Several characteristics differed according to gestational age, with prematurity associated with lower birth weight, multiple gestation, more previously born children, cesarean delivery, older maternal age (for those born at 32–36 weeks), unmarried mothers, and lower levels of maternal education.

Of the study cohort, 3120 children (14.9%) underwent at least 1 surgical procedure requiring general anesthesia before age 3. The most common classification of first procedure received was otorhinolaryngologic (44.9%; Table 2). The first procedure occurred in the first year of life in 1208 (39.0%) children. The proportion of children receiving otorhinolaryngologic and orthopedic procedures as their first procedures increased with age, whereas the proportion of children receiving cardiovascular, general, neurologic, and urologic procedures decreased with age. The mean age at the time of first surgery was less in premature infants (15.8 ± 9.2 [mean $\pm$ SD] months, 13.0 ± 9.4 months, and 8.2 ± 8.8 months for children born at >36 weeks, 32–36 weeks, and <32 weeks, respectively, $P < .001$).

The overall incidence of first procedures was 54 per 1000 child years over the follow-up period. There was no obvious temporal trend in incidence rates from 1994 to 2007 (Figure 1).

In univariate analysis, factors related to receiving at least 1 procedure included prematurity, male sex, lower birth weight, multiple birth, cesarean delivery, a non-Hispanic mother, a White mother, and higher levels of maternal education (Table 3). In multivariate analysis that included all factors, those independently associated with receiving at least 1 procedure included prematurity, male sex, lower birth weight, cesarean delivery, a non-Hispanic mother, and a White mother—but not the mother's level of education.

Among the 3120 children who received at least 1 procedure, 723 (23.2%) had at least 1 subsequent procedure requiring anesthesia. In univariate analysis, factors related to receiving a subsequent procedure included prematurity, lower birth weight, and cesarean delivery (Table 4). In multivariate analysis that included all factors, only EGA <32 weeks and low birth weight were independently associated with receiving a subsequent procedure.

Approximately half of all anesthesia exposures were <1 hour in duration (Table 5). For first exposures, 5.9% were of ≥ 3 hours duration. Of children exposed to anesthesia, at least 1

exposure was ≥ 3 hours in 8.0%, and 14.3% had a cumulative duration of anesthesia of ≥ 3 hours. For all 3120 children who were exposed to anesthesia prior to age 3, 820 (26.3%) had a single exposure of ≥ 3 hours, had multiple exposures prior to age 3, or both.

Most children received sevoflurane (79% of anesthetics) with nitrous oxide (90% of anesthetics; Table S1).

4| DISCUSSION

In this study cohort of children born to mothers residing in Olmsted County, MN and who were resident up to age 3, 14.9% were exposed to general anesthesia before age 3. Among the children who underwent general anesthesia, 26.3% (3.9% of the study cohort) met criteria for an increased risk (ie, multiple or prolonged exposures) for potential subsequent adverse neurodevelopmental outcomes as defined in the FDA warning.

No previous study has directly measured the incidence of receiving procedures requiring general anesthesia in a population of children; rather, annual numbers of pediatric surgical procedures have been estimated from surveys and administrative datasets. According to estimates from 2003, 2006, and 2009 Kids' Inpatient Database (KID), 15.2 per 1000 children under age 3 were admitted after surgery every year.² Another study using the US National Survey of Ambulatory surgery in 2006 estimated that 49 per 1000 children under 1 and 60 per 1000 children between 1 and 4 received general anesthesia for outpatient surgical procedures.¹ Therefore, the incidence in our study cohort of 54 per 1000 child years is generally consistent with these previous reports. If this incidence is extrapolated to the USA population (with approximately 4 million births annually),¹⁵ approximately 650 000 children born each year will require anesthesia prior to age 3. The distribution of procedure type changed with age. Cardiovascular, general, neurologic, and urologic procedures were concentrated at younger ages, and otorhinolaryngological and orthopedic procedures were relatively more frequent at later ages. It does not appear that utilization is changing over time.

The characteristics associated with receiving procedures, such as prematurity and lower birth weight, are perhaps as expected from the characteristics of the conditions necessitating surgery.¹⁶ However, it was not expected that race and ethnicity would be independently associated with receiving procedures, with the children of Hispanic and non-White mothers being less likely to receive procedures. These disparities could not be attributed to differences in maternal education or the other factors examined. One potential explanation is inequality in access to specialty care in non-White and Hispanic children. A previous study using national survey data reported that Latino and African American children were more likely to be uninsured or have public insurance and less likely to report medical visits in the past year.¹⁷ Therefore, there might be a barrier to the medical visit necessary for referral to surgical service to occur. Previous surveys with pediatric surgeons in California revealed that surgeon might select patients based on insurance status.^{18,19} However, both facilities (Mayo Clinic and Olmsted Medical Center) that provided surgical care in the current study accept Medicaid patients, making insurance status unlikely to be a major cause of disparities. Future study is needed to investigate if inequality of access to specialty care pertains to

children in our local area. As this study was not designed to examine the role of race and ethnicity in the receipt of surgical care, and the numbers of Hispanic and non-White children were relatively small, the finding of apparent disparities in care related to race and ethnicity should be regarded only as hypothesis-generating.

In March of 2017 the US FDA required that the labeling of most anesthetic drugs be changed to reflect potential risk of exposure to the developing brain when exposures occurred prior to age 3 years and were either repeated or prolonged, defined as >3 hours anesthesia duration.¹⁰ In this cohort, 26.3% of the children who required general anesthesia met these criteria (representing 3.9% of the total study cohort). If this proportion is extrapolated to the USA population, 160 000 of the approximately 4 million children born annually in the USA meet the at risk criteria defined by the FDA. The current study is not able to provide information on the number of procedures that could have been avoided or delayed until a later age. Although multiple anesthetics may increase risk of later adverse outcomes,⁵ as a practical matter it is usually not possible to know whether a child will require multiple anesthetics. We did not find parental characteristics that predicted the need for multiple anesthetics. Among the child characteristics included in our study, EGA of <32 weeks and low birth weight were related to higher incidence of multiple anesthetic exposures.

This study has several limitations. First, 22% of children born during the study period were excluded from the study cohort due to either lack of research authorization or because they moved from Olmsted County before age 3. This raises the potential for biases, because the characteristics of children whose parents did not provide research authorization or who moved may have differed from the children analyzed. In a prior analysis of a subset of this birth cohort who were born from 1996 to 2000, we found that the characteristics of children and families who moved from the county prior to age 5 were similar to characteristics of those did not move and enrolled in the local school district.¹² This suggests that migration would not be a significant source of bias, although this cannot be excluded. Such biases could affect the accuracy of our estimates. Also, although most characteristics of Olmsted County residents are similar to the rest of Minnesota, some differ from the USA population as a whole, including the proportion of racial and ethnic minorities.²⁰ The small number of non-White parents do not allow for analysis of associations between receiving surgery and specific non-White racial categories. There may also be variation in surgical practices across the USA related to region or other factors. This would affect the ability to accurately extrapolate these results to the USA population as a whole, or populations elsewhere in the world. For example, the access to surgical care to children in Olmsted County may be different than that of other communities. Finally, it is possible that unmeasured covariates may be associated with factors such as race and ethnicity.

In summary, approximately 1 in 7 children in this birth cohort were exposed to at least 1 episode of general anesthesia before age 3, and approximately 1 in 4 children who required general anesthesia prior to their third birthday fell within the at risk category as defined by the recent FDA warning. Although many of the factors associated with the need for general anesthesia might be anticipated, the apparent disparities in procedural utilization

independently related to race and ethnicity in the study population were not, and deserve further exploration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What is already known

- Utilization of general anesthesia in children has important policy, economic, and healthcare delivery implications. The US Food and Drug Administration (FDA) recently issued warning that prolonged or repeated exposure to general anesthesia before age 3 may affect brain development.

What this article adds

- One in 7 children were exposed to general anesthesia before age 3, and 1 in 4 children who received general anesthesia defined as high risk by the FDA warning.

FIGURE 1.
Incidence of receiving first procedure requiring anesthesia by birth year

TABLE 1

Comparison of characteristics of study cohort across gestational age groups

	>36 wk (N = 19 140)	32–36 wk (N = 1486)	<32 wk (N = 227)
Male gender	9771 (51%)	763 (51%)	123 (54%)
Birth weight (g; n = 20 843)	3499.7 (475.8)	2500.5 (531.7)	1308.1 (445.1)
Multiple births	340 (2%)	394 (27%)	88 (39%)
Number previously born (n = 20 793)			
None	7498 (39%)	608 (41%)	99 (44%)
1	6349 (33%)	452 (30%)	61 (27%)
2	3262 (17%)	252 (17%)	30 (13%)
3 or more	1976 (10%)	170 (11%)	36 (16%)
Delivery method (n = 20 799)			
Vaginal	15 548 (81%)	947 (64%)	75 (33%)
C-section	3544 (19%)	533 (36%)	152 (67%)
Mother's age (y; n = 20 851)	28.9 (5.4)	29.3 (5.9)	29.1 (5.5)
Marital status (n = 20 848)			
Married	15 507 (81%)	1165 (78%)	177 (78%)
Not married	3629 (19%)	320 (22%)	50 (22%)
Mother's ethnicity, Hispanic (n = 20 812)	838 (4%)	67 (5%)	9 (4%)
Mother's race, White (n = 20 791)	16 471 (86%)	1284 (87%)	197 (87%)
Mother's education (y; n = 20 530)			
<12	1602 (8%)	122 (8%)	17 (8%)
12	3737 (20%)	325 (22%)	59 (27%)
13–15	4514 (24%)	374 (26%)	59 (27%)
16	5270 (28%)	391 (27%)	59 (27%)
>16	3733 (20%)	243 (17%)	25 (11%)

Sixty-nine subjects were missing gestational age and are not included in this summary. Data summarized are n (%) for categorical variables and mean (SD) for continuous variables.

TABLE 2Type of first procedure according to age^a

	Overall (N = 3120)	0–1 y (N = 1208)	1–2 y (N = 1285)	2–3 y (N = 627)
Procedure type, n (%)				
Cardiovascular	52 (2)	44 (4)	4 (0)	4 (1)
Otorhinolaryngologic	1401 (45)	337 (28)	744 (58)	320 (51)
General	434 (14)	286 (24)	93 (7)	55 (9)
Neurologic	45 (1)	35 (3)	7 (1)	3 (0)
Orthopedic	106 (3)	28 (2)	37 (3)	41 (7)
Other	621 (20)	251 (21)	226 (18)	144 (23)
Plastics	91 (3)	39 (3)	35 (3)	17 (3)
Urologic	370 (12)	188 (16)	139 (11)	43 (7)

^aOther procedures include oral surgeries, ophthalmology surgeries, diagnostic procedures, catheterization, angiography, and examination during anesthesia.

TABLE 3

Univariate and multivariate Cox regressions on the relationship between child and parent characteristics of and the risk of receiving at least 1 procedure

	Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
Estimated gestational age				
>36 wk	Reference		Reference	
32–36 wk	1.7 (1.5, 1.9)	<.001	1.5 (1.3, 1.7)	<.001
<32 wk	4.3 (3.5, 5.3)	<.001	3.2 (2.4, 4.1)	<.001
Sex, male	1.7 (1.6, 1.8)	<.001	1.7 (1.6, 1.8)	<.001
Birth weight in kg	0.7 (0.7, 0.8)	<.001	0.8 (0.8, 0.9)	<.001
Multiple gestation	1.6 (1.4, 1.9)	<.001	0.9 (0.8, 1.1)	.280
Number of previously born				
0	Reference		Reference	
1	1.0 (1.0, 1.1)	.363	1.1 (1.0, 1.2)	.084
2	1.0 (0.9, 1.1)	.484	1.0 (0.9, 1.1)	.920
>3	1.0 (0.8, 1.1)	.445	1.0 (0.9, 1.2)	.788
Cesarean delivery	1.3 (1.2, 1.4)	<.001	1.2 (1.1, 1.3)	.005
Age of mother	1.0 (1.0, 1.0)	.487	1.0 (1.0, 1.0)	.744
Married	1.0 (0.9, 1.1)	.982	1.0 (0.9, 1.1)	.376
Hispanic mother	0.6 (0.5, 0.7)	<.001	0.6 (0.5, 0.7)	<.001
White mother	1.5 (1.3, 1.7)	<.001	1.5 (1.3, 1.7)	<.001
Mother education				
<12 y	Reference		Reference	
12 y	1.2 (1.0, 1.4)	.014	1.0 (0.9, 1.2)	.593
13–15 y	1.4 (1.2, 1.6)	<.001	1.1 (1.0, 1.4)	.148
16 y	1.2 (1.1, 1.4)	.008	1.0 (0.9, 1.2)	.805
>16 y	1.2 (1.0, 1.4)	.018	1.0 (0.9, 1.3)	.691

CI, confidence interval; HR, hazard ratio.

TABLE 4

Univariate and multivariate Cox regressions on the relationship between child and parent characteristics of and the risk of receiving at more than 1 procedure

	Univariate		Multivariate		
	HR	CI	P	HR	CI
Estimated gestational age					
>36 wk	Reference			Reference	
32–36 wk	1.3	1.0, 1.6	.019	1.1	0.8, 1.5
<32 wk	2.4	1.8, 3.2	<.001	1.6	1.0, 2.5
Sex, male	0.9	0.8, 1.0	.152	0.9	0.8, 1.1
Birth weight in kg	0.8	0.7, 0.8	<.001	0.8	0.7, 1.0
Multiple gestation	1.2	0.9, 1.6	.308	0.8	0.6, 1.2
Number of previously born					
0	Reference			Reference	
1	1.1	0.9, 1.3	.408	1.2	1.0, 1.4
2	1.0	0.8, 1.3	.819	1.1	0.9, 1.4
>3	0.9	0.7, 1.1	.324	0.9	0.7, 1.2
Cesarean delivery	1.3	1.1, 1.5	.002	1.2	1.0, 1.4
Age of mother	1.0	1.0, 1.0	.144	1.0	1.0, 1.0
Married	0.8	0.7, 1.0	.080	0.9	0.7, 1.1
Hispanic mother	0.8	0.5, 1.3	.448	0.8	0.5, 1.4
White mother	0.8	0.7, 1.0	.107	0.9	0.7, 1.2
Mother education					

	Univariate			Multivariate		
	HR	CI	P	HR	CI	P
<12	Reference			Reference		
12	1.0	0.7, 1.4	.882	0.9	0.7, 1.3	.815
13–15	1.0	0.8, 1.4	.834	1.0	0.7, 1.3	.833
16	0.8	0.6, 1.1	.261	0.9	0.6, 1.3	.567
>16	0.9	0.6, 1.2	.431	1.0	0.6, 1.4	.805

CI, confidence interval; HR, hazard ratio.

TABLE 5

Duration of anesthesia exposure^a

	First exposure N = 3120	All exposures (per exposure) N = 4558	All exposures (cumulative) N = 3120
Duration of anesthetic (m)			
Mean (SD)	71.3 (65.0)	78.4 (72.9)	114.6 (191.0)
Median (Q1, Q3)	53 (26, 93)	58 (29, 100)	67 (30, 118)
<60	1691 (54.2%)	2321 (50.9%)	1410 (45.2%)
60–119	959 (30.7%)	1436 (31.5%)	948 (30.4%)
120–179	286 (9.2%)	437 (9.6%)	316 (10.1%)
180	184 (5.9%)	364 (8.0%)	446 (14.3%)

^a A total of 3120 subjects underwent 4558 surgeries or procedures requiring general anesthesia. Duration of each subject's first exposure, all exposures among all subjects, and each subject's total cumulative exposure are summarized.