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# Descriptive and risk factor analysis of infantile cataracts: National Birth Defects Prevention Study, 2000–2011

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## Abstract

Using National Birth Defects Prevention Study (NBDPS) data, we sought to estimate birth prevalence, describe clinical characteristics, and examine risk factors for infantile cataracts. We calculated birth prevalence using the numbers of NBDPS-eligible cataract cases and live births in the study area. We described case infants by the presence of associated ipsilateral eye defects (IEDs) and non-eye-related major birth defects. Using maternal exposure information collected via telephone interview, we conducted logistic regression analyses among the interviewed cases and controls. Birth prevalence of infantile cataracts was 1.07/10,000 live births. Unilateral cataracts were more often associated with IEDs, while infants with bilateral cataracts were more often preterm, full-term with low birth weight, or had non-eye-related major birth defects. Unilateral cataracts were positively associated with maternal nulliparity (adjusted odds ratio [aOR] = 1.61, 95% confidence interval [CI] = 1.18, 2.20; reference: multiparity), whereas bilateral cataracts were positively associated with maternal education <12 years (aOR = 2.08, 95% CI = 1.13, 3.82; reference: education >12 years), and foreign-born nativity (aOR = 1.92, 95% CI = 1.04, 3.52; reference: U.S.-born nativity). The current analysis can inform future epidemiological studies aimed at identifying mechanisms underlying the associations between infantile cataracts and complex maternal exposures, such as lower levels of education and foreign-born nativity.

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AUTHOR CONTRIBUTIONS

Marine Nalbandyan, Marilyn Browne, and Meredith Howley conceived and designed the analysis. Marine Nalbandyan conducted data analysis and wrote the manuscript. Marilyn Browne, Meredith Howley, Christopher Cunniff, and Emily Leckman-Westin critically reviewed and edited the manuscript. All authors have contributed to and approved the final article.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

**Keywords**

birth defect; birth prevalence; infantile cataract; risk factors

## 1 | INTRODUCTION

Cataracts are a major cause of childhood blindness with high economic burden due to loss of vision and productivity (Wittenborn et al., 2013). They are classified as congenital when present at birth or infantile when they occur within 12 months of age, although the terms congenital and infantile are often used interchangeably (American Academy of Ophthalmology, 2021). Previous studies reported a birth prevalence of infantile cataracts (diagnosed by 12 months of age) ranging from 2.03 to 3.60 per 10,000 births (Abrahamsson et al., 1999; Bhatti et al., 2003; Rahi & Dezateux, 2001). These estimates, however, were calculated using data from older birth cohorts (1968–1998), and the birth prevalence may have changed over this time period. Common nongenetic risk factors for infantile cataracts reported in previous studies include maternal first trimester infections with rubella, herpes simplex viruses, cytomegalovirus, genitourinary tract infections, and influenza/common cold/respiratory illnesses accompanied with fever (reviewed in Nalbandyan et al., 2021). The risk factors for infantile cataracts were also examined within the National Birth Defects Prevention Study (NBDPS), the largest population-based case-control study in the United States investigating risk factors for major birth defects. The authors conducted a stratified analysis by cataracts laterality (unilateral vs. bilateral) in pregnancies with estimated dates of delivery (EDDs) from 2000 through 2004 and did not observe associations with environmental exposures (Prakalapakorn et al., 2010). However, due to a limited sample size, they were unable to explore a broader range of exposures collected within the NBDPS, as well as examine exposures by varying pregnancy time windows that may be critical for lens development (first trimester) or lens maturation (second and third trimesters) (Sadler & Langman, 2012), and conduct a subanalysis within a potentially more homogeneous group of isolated cases. Currently, the risk factors remain unknown for approximately two-thirds of infantile cataract cases and the gaps in the literature include further understanding of etiological differences by cataracts laterality and birth defect classification (isolated vs. nonisolated cases), and the teratogenic effects of environmental exposures at different timings of pregnancy (Nalbandyan et al., 2021). Thus, studies providing additional insights into the prevalence and etiology of infantile cataracts are warranted.

Using the final NBDPS data with EDDs through 2011, we sought to expand upon the previous work of Prakalapakorn et al. (2010) by estimating the birth prevalence, describing clinical characteristics and associated malformations, and examining potential risk factors for unilateral and bilateral cataracts by varying pregnancy time windows. Furthermore, we sought to test the consistency of the observed associations within different groups of isolated cases.

## 2 | MATERIALS AND METHODS

The details of the NBDPS are presented elsewhere (Rasmussen et al., 2003; Reefhuis et al., 2015). Briefly, cases were ascertained from population-based birth defects surveillance systems in 10 study sites (Arkansas, California, Georgia, Iowa, Massachusetts, North Carolina, New Jersey, New York, Texas, Utah). Cases with known chromosomal or single-gene abnormalities were excluded from the study (Rasmussen et al., 2003). Controls comprised of infants without major birth defects, randomly selected from hospitals or vital records from the same time and geographical areas as cases. The NBDPS ascertained cataract cases from pregnancies with EDDs 2000–2011, and included infantile cataracts diagnosed by an ophthalmologist within 12 months of age. Cases of corneal clouding, cataracts resulting from surgery or trauma, and clinically insignificant minor lens opacities were excluded. Starting with EDDs in 2006, isolated cases with a family history of infantile cataract in a parent or a sibling were also excluded. Cataract cases were reviewed and classified by clinical geneticists as isolated (cataracts alone, without non-eye-related major birth defects) or multiple (cataracts with other non-eye-related major birth defects) (Reefhuis et al., 2015). For the current analysis, all isolated cases were re-reviewed by an ophthalmologist (M.N.), in consultation with a clinical geneticist (C.M.C.), and were further classified as isolated without an ipsilateral eye defect (IED) or isolated with IED, with the latter category indicating the presence of an eye defect in the same eye as the cataract. A clinical geneticist (C.M.C.) re-reviewed all multiple cases and classified the co-occurring non-eye-related major birth defects by structure/organ system.

Clinical data on case infants (sex, gestational age at delivery, birth weight, and medical diagnoses) were abstracted from medical records. Mothers of NBDPS-eligible cases and controls were invited to participate in a telephone interview (6 weeks to 24 months post-EDD), collecting information on maternal demographics and exposures 3 months before pregnancy through delivery. Institutional Review Board approval was received, and verbal consent was obtained before the interview.

We compared case and control infants of interviewed mothers on a wide range of exposures, including: (1) infant characteristics—sex (male, female), plurality (singleton, multiple), season of conception (spring, summer, autumn, winter); (2) maternal demographics—age at delivery (<20, 20–34, ≥35 years), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, other), education (<12, 12, ≥12 years), nativity (U.S.-born, foreign-born); (3) pregnancy-related characteristics—parity (0, ≥1), previous miscarriage (yes, no), pregnancy intention (yes, other), infertility treatment (yes, no), folic acid-containing supplement use (the month prior through the first month of pregnancy) (yes, no), gestational diabetes during current pregnancy (yes, no); (4) maternal health conditions—pregestational body mass index (<25, ≥25 kg/$m^2$), pregestational type 1 diabetes (yes, no), pregestational type 2 diabetes (yes, no), epilepsy (yes, no), hypertension during pregnancy (yes, no); (5) behavioral exposures during the periconceptional (the month before through the third month of pregnancy) period—binge drinking (yes, no), cigarette smoking (yes, no), recreational drug use (yes, no), medical radiation (yes, no); and (6) paternal age at delivery (<25, 25–34, 35–44, ≥45 years). Maternal illnesses (fever, pelvic inflammatory disease, kidney, bladder, or urinary tract infection [KBUTI], sexually transmitted infection, gastrointestinal infection,

and respiratory illness) and medication use (vasoactive, anti-hypertensive, corticosteroid, aspirin, antipyretic, anti-tussive, and anti-infective) that varied during pregnancy were categorized as periconceptional, late pregnancy only (exposure in month 4 of pregnancy or later), and no exposure.

Parity was defined as the number of previous live births or stillbirths. Maternal binge drinking was defined as having four or more drinks per occasion. We assessed maternal infertility treatment by combining information on surgical procedures for the current pregnancy and use of fertility medications/other procedures in the 2 months prior to the current pregnancy. We manually searched responses to an open-ended question on "other maternal diseases" and identified reports of sexually transmitted infection and respiratory illness. The reports of respiratory illnesses were later combined with the responses to a question on "cold and flu" into a single variable assessing maternal respiratory illness. Since the NBDPS did not collect information on specific maternal infections with known teratogenic effects, we considered maternal use of anti-infective, anti-tussive, and antipyretic medications as proxies for these infections. Finally, we grouped responses to questions on medical radiations (X-ray, magnetic resonance imaging, radionuclide, CAT scan) into a single variable assessing maternal periconceptional medical radiation.

To estimate birth prevalence per 10,000 live births, we divided the total number of NBDPS-eligible cases, obtained from the population-based birth defects surveillance systems ($n$ = 592), by the total number of live births in study areas from which cases were ascertained ($N$ = 5,522,842). Similarly, we estimated the birth prevalence per 10,000 live births for different case groups: isolated (both with and without IED) and multiple cases, unilateral and bilateral cataracts. Using Pearson's $\chi^2$ tests, we described clinical characteristics of all case infants by case classification (isolated, multiple) and cataracts laterality (unilateral, bilateral). We examined the frequencies of IEDs among all cases and non-eye-related major birth defects among multiple cases. All analyses were conducted separately for unilateral and bilateral cataracts. We conducted bivariate logistic regression analyses to estimate crude odds ratios (cORs) and 95% confidence intervals (CIs) for exposures with five and more exposed cases and exact 95% CIs for exposures with three/four exposed cases. Estimates were not calculated for exposures with less than three exposed cases. We included exposures with five and more exposed cases in the multivariable analysis if the crude Wald $p$ value was less than 0.2 for either unilateral or bilateral cataracts. Maternal age at delivery and study site did not meet both criteria but were included in multivariable logistic regression models to account for potential confounding. The same common set of covariates was included in the analysis of unilateral and bilateral cataracts. Each exposure was adjusted for other exposures included in the multivariable model and adjusted odds ratios (aOR) and 95% CIs were reported. Within each laterality, we conducted subanalyses among all isolated cases and among isolated cases without IED. All subanalyses used the same set of covariates as the main analysis. All analyses were conducted using SAS version 9.4 (SAS Corporation).

## 3 | RESULTS

Overall, 592 infantile cataract cases were eligible for the NBDPS, resulting in a birth prevalence of 1.07 per 10,000 live births (95% CI = 0.99–1.16). The prevalence per

10,000 live births was 0.96 (95% CI = 0.88–1.05) for isolated cases, 0.11 (95% CI = 0.08–0.14) for multiple cases, 0.66 (95% CI = 0.59–0.73) for unilateral cataracts, and 0.41 (95% CI = 0.36–0.47) for bilateral cataracts. Isolated cases tended to have unilateral cataracts, while two-thirds of multiple cases had bilateral cataracts (Table S1). Compared to unilateral cases, infants with bilateral cataracts more often were preterm, full-term with low birth weight, or had non-eye-related major birth defects (Table S2). Unilateral cataracts were more frequently associated with IEDs than bilateral cataracts (32.3% vs. 23.7%). The most common IED among unilateral cases was persistent fetal vasculature (18.5%), whereas microphthalmia (9.2%) was the most common IED among bilateral cases (Table 1). Common non-eye-related major birth defects among multiple cases were congenital heart defects (CHDs) (49.2%), central nervous system defects (26.2%), and orofacial defects (23.0%) (Table 2).

Mothers of 359 (61%) cases and 10,084 (64%) controls participated in the telephone interview. Case infants of interviewed and noninterviewed mothers were similar across most available characteristics but differed by infant birth year with no apparent pattern (Table S3). For cases with EDDs in 2006 or later, isolated cases with a family history of infantile cataracts were no longer eligible for the NBDPS. Fifteen cases (nine males, six females) with a positive family history of infantile cataracts with EDDs before 2006 were still included in the database, and all these cases had bilateral cataracts (14 isolated, 1 multiple). To eliminate the possibility of hereditary cataracts, we further excluded these 15 cases and 8 controls (whose mothers also reported a positive history of infantile cataracts) and conducted risk factor analyses among 344 cataract cases (227 unilateral, 117 bilateral) and 10,076 controls. For both unilateral and bilateral cataracts, estimates were generally similar for different case groups: total cases, all isolated cases, and isolated cases without IEDs. Adjusted and unadjusted estimates were also similar, with a few exceptions.

In the crude analyses of all unilateral cases, we observed positive associations for female sex (cOR = 1.34, 95% CI = 1.03, 1.75) and maternal nulliparity (cOR = 1.50, 95% CI = 1.15, 1.95), and inverse associations for maternal Hispanic race/ethnicity (cOR = 0.55, 95% CI = 0.38, 0.79) and education <12 years (cOR = 0.60, 95% CI = 0.39, 0.92) (Table S4). We observed stronger positive associations with maternal periconceptional binge drinking (cOR = 1.67, 95% CI = 1.08, 2.56) and paternal age ≥45 years (cOR = 2.17, 95% CI = 1.04, 4.52) in the subanalysis of isolated cases without IED. In the multivariable analysis of all unilateral cases, only maternal nulliparity remained associated with unilateral cataracts (aOR = 1.61, 95% CI = 1.18, 2.20), which persisted in the subanalyses of isolated (aOR = 1.64, 95% CI = 1.19–2.26) and isolated cases without IED (aOR = 1.66, 95% CI = 1.13–2.46) (Table 3).

In the crude analysis of all bilateral cases, we observed positive associations with maternal periconceptional KBUTI (cOR = 1.95, 95% CI = 1.14, 3.34) and second/third trimester aspirin use (cOR = 5.84, 95% CI = 1.14, 18.6) (Table S5). Different results were observed in the multivariable analysis, where bilateral cataracts were positively associated with maternal education <12 years (aOR = 2.08, 95% CI = 1.13, 3.82) and foreign-born nativity (aOR = 1.92, 95% CI = 1.04, 3.52) (Table 4). In the subanalyses of isolated cases, bilateral cataracts remained positively associated with maternal education <12 years among all isolated cases

(aOR = 2.39, 95% CI = 1.20–4.78) and with foreign-born nativity among isolated cases without IED (aOR = 2.10, 95% CI = 1.01–4.39).

## 4 | DISCUSSION

In the current analysis, we estimated birth prevalence, described clinical characteristics and associated malformations, and examined potential risk factors for unilateral and bilateral cataracts by varying pregnancy time windows. The birth prevalence of infantile cataracts in the NBDPS was 1.07 per 10,000 live births, which might be slightly underestimated, considering that about one-third of infantile cataracts remain undiagnosed by 12 months of age (Rahi & Dezateux, 1999). Other studies on infantile cataracts reported higher estimates (2.03–3.60 per 10,000 births), which could be explained by differences in inclusion criteria, as the NBDPS excluded cataract cases with known genetic syndromes, stillbirths/pregnancy terminations, and minor lens opacities (Abrahamsson et al., 1999; Bhatti et al., 2003; Rahi & Dezateux, 2001). In the NBDPS, all case infants with a positive family history for infantile cataracts had bilateral cataracts (predominately isolated). Similar results have been reported in Danish and Australian birth cohorts (Haargaard et al., 2004; Wirth et al., 2002). In these studies, and in NBDPS, infantile cataract cases were ascertained before the modern genetic screening methods were introduced into clinical practice (Miller et al., 2010; Yang et al., 2013), while the subsequent studies utilizing next generation sequencing showed that 60%–70% of bilateral cataracts have a genetic origin (Gillespie et al., 2016; Musleh et al., 2016). Thus, further genetic testing of bilateral cataracts might be beneficial in identifying novel mutations.

Consistent with previous reports, we observed that infants with bilateral cataracts were often preterm, full-term with low birth weight, or had co-occurring non-eye-related major birth defects (Bhatti et al., 2003; Prakalapakorn et al., 2010). A study examining the association between major birth defects and preterm birth suggested that the presence of a birth defect in a fetus may lead to a preterm birth (Honein et al., 2009). In the NBDPS, infants with bilateral cataracts often had other (more serious) major birth defects, presence of which may have triggered a preterm birth. This might be a reason for observing a higher proportion of preterm births among bilateral cases, compared to unilateral, that more often were isolated. Also, per current recommendations, all newborns with a birth weight ≤ 1500 g or gestational age ≤ 30 weeks should be screened for the retinopathy of prematurity (Fierson, 2018). We agree with previous authors that different guidelines for ophthalmological screening of preterm versus full-term newborns could partially explain higher risk of infantile cataracts among preterm births (Bhatti et al., 2003; Prakalapakorn et al., 2010). Recent increases in the number of preterm births coupled with improved survival of low birth weight newborns (Goldenberg & Culhane, 2007), may increase the prevalence of infantile cataracts in coming years.

Consistent with other studies, unilateral cataracts in the NBDPS were often associated with IEDs, and with persistent fetal vasculature in particular (Lim et al., 2010; Wirth et al., 2002). Compared to bilateral cases, surgeries on unilateral cataracts have worse outcomes (Asferaw et al., 2019), especially when associated with persistent fetal vasculature often leading to retinal detachment or glaucoma (Jinagal et al., 2018). The most common IED associated

with bilateral cataracts was microphthalmia, which also can create surgical challenges, such as postoperative corneal edema due to the small surgical space (Hoffman et al., 2015). Among multiple cases, CHDs were the most common non-eye-related major birth defects, followed by central nervous system and orofacial defects. Infantile cataracts and CHDs are two common clinical manifestations of congenital rubella syndrome (Motaze et al., 2018). The NBDPS did not collect information on maternal rubella infection, however, since the vaccine has been available in the United States since 1969 (Centers for Disease Control and Prevention, 2018), we assumed that most mothers were vaccinated against rubella. Yet, we cannot rule out cases of congenital rubella syndrome among infants of U.S.-born mothers who declined vaccination or foreign-born mothers from countries without routine rubella vaccination. Nevertheless, CHDs, central nervous system defect, and orofacial defects are relatively common in the United States (Simeone et al., 2015) and were also frequently associated with infantile cataracts in a pooled analysis of data from 30 U.S. population-based surveillance systems (Stallings et al., 2018). Studies with larger number of multiple cases that would allow analyses of birth defect co-occurrence patterns and calculation of the observed-to-expected ratio of co-occurring birth defects are warranted to identify shared pathogenic mechanisms between infantile cataracts and other major birth defects (Benjamin et al., 2019).

Previous studies reported female predominance among unilateral cases and a male predominance among bilateral cases (Haargaard et al., 2004; SanGiovanni et al., 2002). We observed a positive crude association between female sex and unilateral cataracts, which was nonsignificant after adjusting for potential confounders. We observed a higher risk for unilateral cataracts among nulliparous mothers, which was persistent in all three analytical groups: total cases, all isolated cases, and isolated cases without IED. A similar association was reported in the previous NBDPS analysis (2000–2004 EDDs) by Prakalapakorn et al. (2010) but not in an older U.S. study (1959–1965 births) by SanGiovanni et al. (2002). Two separate studies on maternal parity reported a higher risk for birth defects among nulliparous women, compared to women having their second birth (Duong et al., 2012; McNeese et al., 2015). In their paper, McNeese et al. (2015) proposed that the higher risk for birth defects among nulliparous women can be partially attributed to a smaller uterus with less vasculature. However, even if these biological features of nulliparous women truly contribute to a cataract formation in the fetus, the difference in the association for unilateral and bilateral cataracts remains unclear.

In the current analysis, maternal age was not associated with infantile cataracts, while in a Danish study the risk for infantile cataracts was elevated among mothers aged ≥40 years old (Haargaard et al., 2005). Studies on singleton births reported conflicting results on the associations between advanced maternal age and the risk of non-chromosomal major birth defects (Goetzinger et al., 2017; Reefhuis & Honein, 2004). Reefhuis and Honein (2004) observed a higher risk for some birth defects among mothers aged 35–40 years old, while in the study by Goetzinger et al. (2017), advanced maternal age (≥35 years old) was associated with reduced risk for major birth defects.

In contrast to previous studies (Prakalapakorn et al., 2010; SanGiovanni et al., 2002), we observed a positive association between maternal education <12 years and bilateral

cataracts. Also, similar to the study by Haargaard et al. (2005), we observed that foreign-born mothers were more likely to have infants with bilateral cataracts compared to U.S.-born mothers. Lower levels of maternal education and foreign-born nativity have been previously reported to be associated with the lack of prenatal care (Goldfarb et al., 2017; Stativa et al., 2014). Given that appropriate prenatal care is important for optimal pregnancy outcomes (Zolotor & Carlough, 2014), presence of untreated health conditions during pregnancy might result in a formation of a cataract in the fetus. In our analysis, the risk of bilateral cataracts was elevated (nonsignificant) among mothers reporting KBUTI during pregnancy. The positive association between KBUTI and infantile cataracts (not stratified by laterality) was significant in another NBDPS analysis by Howley et al. (2018) indicating the importance of maternal health for normal embryological development.

In the previous NBDPS analysis, Prakalapakorn et al. (2010) reported a two-fold increased risk of bilateral cataracts among women using aspirin during pregnancy. The association, however, was based on three exposed cases and was nonsignificant. We explored this association by specific timing during pregnancy and observed more than five times higher odds among women reporting second/third trimester aspirin use, compared to those who did not use aspirin during pregnancy. Yet, this elevated cOR was based on three exposed cases and imprecise. Aspirin is a nonsteroidal anti-inflammatory drug, which are commonly used for fever, pain, and inflammation (Vane & Botting, 1998). In the current analysis, maternal fever, respiratory illnesses, as well as the use of antipyretic, anti-infective, and anti-tussive medications, that served as proxies for acute maternal infections, were not associated with infantile cataracts. In another study examining acute maternal illnesses during pregnancy, the authors did not observe an association between influenza/common cold/respiratory system diseases and infantile cataracts among women who used antifever medications, while the risk was elevated among women with the same diseases and uncontrolled fever (Vogt et al., 2005).

Previous studies reported inconsistent associations between paternal age at delivery and infantile cataracts (Green et al., 2010; McIntosh et al., 1995). Green et al. (2010) reported higher risk for infantile cataracts among younger fathers (20–30 years), with the risk being higher for a 1 year increase among fathers aged 20 (vs. 19 years) and 30 (vs. 29 years) years at delivery. McIntosh et al. (1995) reported a positive association for paternal age ≥50 years, although the aOR was based on three exposed cases and was nonsignificant. In the current analysis, we observed elevated cORs for the paternal age ≥45 years for both unilateral and bilateral cataracts, which was significant only among isolated cases of unilateral cataracts without IED. This phenomenon could be explained by an increased risk for spontaneous mutation in offspring of older fathers (Sloter et al., 2007). Even though the NBDPS excluded cases with known chromosomal or single-gene abnormalities, cataract cases of unidentified genetic disorders could have been included in the study as the NBDPS data was collected before modern genetic screening methods with high capacity of detecting genetic mutations became widely used in clinical practice (Miller et al., 2010; Yang et al., 2013).

Our study had some limitations. Morphological type of cataracts was not specified for 61.0% cases, limiting our ability to describe infantile cataracts by morphology and degree of lens opacity. Some cases of genetic origin that could have not been detected by

genetic testing methods available during NBDPS data collection (2000–2010) may have been included in the study, possibly diluting true environmental associations. All exposure information was self-reported, thus some extent of information bias is possible. If recall bias strongly influenced the results, we would expect some observed positive associations to be over-estimated. Stratifications by pregnancy time windows resulted in a small number of exposed cases for some exposures, creating imprecise estimates with wide CIs or not allowing the calculation of estimates. Finally, due to multiple comparisons, some of the observed associations might have occurred due to chance.

Our study had several strengths. The NBDPS is a large population-based study including a geographically and ethnically diverse population (Reefhuis et al., 2015). All cases were reviewed and classified by clinical geneticists using standard criteria and minor lens opacities that could be unreliably diagnosed were excluded (Frost & Sparrow, 2001; Rasmussen et al., 2003). Controls were representative of the source population (Cogswell et al., 2009), and in the current analysis we did not find differences between cataract cases of interviewed and noninterviewed mothers.

Through the current analysis, we observed some differences between clinical characteristics and risk factors for unilateral and bilateral cataracts, supporting a previously suggested difference in their etiologies (Haargaard et al., 2005; Prakalapakorn et al., 2010). Within each laterality, we did not observe differences by the presence of associated non-eye-related major birth defects or IEDs. The current analysis can inform future epidemiological studies aimed at identifying mechanisms underlying the associations between infantile cataracts and complex maternal exposures, such as lower levels of education and foreign-born nativity.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## DATA AVAILABILITY STATEMENT

Data from the NBDPS are not released to the public. Qualified researchers can be granted access to the NBDPS data for analysis through collaboration with one of the Centers for Birth Defects Research and Prevention. The process for accessing the data used in this study is described at https://www.cdc.gov/ncbddd/birthdefects/nbdps-public-access-procedures.html.

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**TABLE 1**

Frequency of ipsilateral eye defects among all NBDPS-eligible cataract cases (*N* = 592), National Birth Defects Prevention Study, 2000–2011

| | | Unilateral cataracts[a] | | Bilateral cataracts[a] | |
|---|---|---|---|---|---|
| | All cases (*n* = 592) | Total (*n* = 362) | Isolated[b] (*n* = 341) | Total (*n* = 228) | Isolated[b] (*n* = 189) |
| **Ipsilateral eye defects** | ***n* (%)** | ***n* (%)** | ***n* (%)** | ***n* (%)** | ***n* (%)** |
| Persistent fetal vasculature | 73 (12.3) | 67 (18.5) | 66 (19.4) | 5 (2.2) | 4 (2.1) |
| Microphthalmia | 57 (9.6) | 35 (9.7) | 28 (8.2) | 21 (9.2) | 13 (6.9) |
| Glaucoma | 22 (3.7) | 7 (1.9) | 6 (1.8) | 15 (6.6) | 10 (5.3) |
| Coloboma | 16 (2.7) | 12 (3.3) | 11 (3.2) | 3 (1.3) | 1 (0.5) |
| Anterior segment dysgenesis | 15 (2.5) | 8 (2.2) | 5 (1.5) | 7 (3.1) | 4 (2.1) |
| Microcornea | 14 (2.4) | 5 (1.4) | 4 (1.2) | 9 (4.0) | 5 (2.7) |
| Corneal opacity | 13 (2.2) | 6 (1.7) | 3 (0.9) | 7 (3.1) | 4 (2.1) |
| Optic nerve defects | 13 (2.2) | 6 (1.7) | 4 (1.2) | 7 (3.1) | 3 (1.6) |
| Vitreoretinopathy | 10 (1.7) | 5 (1.4) | 4 (1.2) | 5 (2.2) | 4 (2.1) |
| Lens defects | 9 (1.5) | 7 (1.9) | 7 (2.1) | 2 (0.9) | 2 (1.1) |
| Retinal detachment | 7 (1.2) | 5 (1.4) | 5 (1.5) | 2 (0.9) | 1 (0.5) |
| Aniridia | 4 (0.7) | 2 (0.6) | 2 (0.6) | 2 (0.9) | 2 (1.1) |
| Nasolacrimal duct obstruction | 3 (0.5) | 2 (0.6) | 2 (0.6) | 1 (0.4) | 1 (0.5) |
| Other eye defects[c] | 9 (1.5) | 4 (1.1) | 3 (0.9) | 5 (2.2) | 2 (1.1) |

[a] Two cases with unknown laterality excluded.

[b] Includes all isolated cases, with and without ipsilateral eye defects.

[c] Includes birth defects of the orbit, eyelids, cornea, and iris.

**TABLE 2**

Frequency of non-eye-related major birth defects among NBDPS-eligible cataract cases classified as multiple (n = 61), National Birth Defects Prevention Study, 2000–2011

| | All cases (*n* = 61) | Unilateral cataracts[a] (*n* = 21) | Bilateral cataracts[a] (*n* = 39) |
|---|---|---|---|
| **Non-eye-related major birth defects** | ***n* (%)** | ***n* (%)** | ***n* (%)** |
| **Congenital heart defects** | **30 (49.2)** | **10 (47.6)** | **20 (51.3)** |
| Septal defects | 19 (31.2) | 6 (28.6) | 13 (33.3) |
| ASD, secundum/NOS | 10 (16.4) | 3 (14.3) | 7 (18.0) |
| VSD, muscular | 8 (13.1) | 3 (14.3) | 5 (12.8) |
| VSD, perimembranous | 1 (1.6) | – | 1 (2.6) |
| VSD, NOS | 3 (4.9) | – | 3 (7.7) |
| Atrioventricular septal defect | 2 (3.3) | – | 2 (5.1) |
| Left ventricular outflow tract defects | 6 (9.8) | 2 (9.5) | 4 (10.3) |
| Patent ductus arteriosus | 3 (4.9) | 1 (4.8) | 2 (5.1) |
| Coarctation of the aorta | 2 (3.3) | 1 (4.8) | 1 (2.6) |
| Hypoplasia of the aorta | 1 (1.6) | – | 1 (2.6) |
| Interrupted aortic arch, NOS | 1 (1.6) | – | 1 (2.6) |
| Aberrant subclavian artery | 1 (1.6) | – | 1 (2.6) |
| Right ventricular outflow tract defects | 6 (9.8) | 4 (19.1) | 2 (5.1) |
| Pulmonary valve stenosis | 5 (8.2) | 4 (19.1) | 1 (2.6) |
| Pulmonary atresia | 1 (1.6) | – | 1 (2.6) |
| Conotruncal defects | 3 (4.9) | 1 (4.8) | 2 (5.1) |
| Tetralogy of Fallot | 2 (3.3) | 1 (4.8) | 1 (2.6) |
| Tetralogy of Fallot with PA | 1 (1.6) | – | 1 (2.6) |
| Double inlet left ventricle | 1 (1.6) | – | 1 (2.6) |
| Heterotaxia with CHD | 1 (1.6) | – | 1 (2.6) |
| **Central nervous system defects** | **16 (26.2)** | **6 (28.6)** | **9 (23.1)** |
| Agenesis/dysgenesis of the corpus callosum | 8 (13.1) | 3 (14.3) | 5 (12.8) |
| Cerebellar hypoplasia | 2 (3.3) | 1 (4.8) | 1 (2.6) |
| Hydrocephaly | 2 (3.3) | 2 (9.5) | – |
| Schizencephaly | 2 (3.3) | 1 (4.8) | 1 (2.6) |

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| | All cases (*n* = 61) | Unilateral cataracts[a] (*n* = 21) | Bilateral cataracts[a] (*n* = 39) |
|---|---|---|---|
| **Non-eye-related major birth defects** | ***n* (%)** | ***n* (%)** | ***n* (%)** |
| Frontal lobe dysgenesis | 1 (1.6) | – | 1 (2.6) |
| Polymicrogyria | 1 (1.6) | – | 1 (2.6) |
| Hydranencephaly | 1 (1.6) | – | 1 (2.6) |
| Porencephaly | 1 (1.6) | – | 1 (2.6) |
| Meningeal hamartoma | 1 (1.6) | 1 (4.8) | – |
| Dandy-Walker syndrome | 1 (1.6) | – | – |
| Chiari malformation type 1 | 1 (1.6) | – | 1 (2.6) |
| **Orofacial defects** | **14 (23.0)** | **4 (19.1)** | **10 (25.6)** |
| Cleft lip with/without cleft palate | 4 (6.6) | 2 (9.5) | 2 (5.1) |
| Cleft palate | 4 (6.6) | 1 (4.8) | 3 (7.7) |
| Choanal stenosis/atresia | 3 (4.9) | – | 3 (7.7) |
| Hemifacial microsomia | 2 (3.3) | 1 (4.8) | 1 (2.6) |
| Thyroglossal duct cyst | 1 (1.6) | – | 1 (2.6) |
| **Genitourinary defects** | **5 (8.2)** | **1 (4.8)** | **4 (10.3)** |
| Hypospadias | 2 (3.3) | – | 2 (5.1) |
| Hydronephrosis | 2 (3.3) | 1 (4.8) | 1 (2.6) |
| Dysplastic kidney | 1 (1.6) | – | 1 (2.6) |
| **Musculoskeletal defects** | **4 (6.6)** | **1 (4.8)** | **3 (7.7)** |
| Clubfoot | 2 (3.3) | 1 (4.8) | 1 (2.6) |
| Developmental dysplasia of the hip | 1 (1.6) | – | 1 (2.6) |
| Diaphragmatic hernia | 1 (1.6) | — | 1 (2.6) |
| **Gastrointestinal defects** | **2 (3.3)** | – | **2 (5.1)** |
| Biliary atresia | 1 (1.6) | – | 1 (2.6) |
| Pyloric stenosis | 1 (1.6) | – | 1 (2.6) |
| **Respiratory defects** | **2 (3.3)** | **1 (4.8)** | **1 (2.6)** |
| Pulmonary hypoplasia | 1 (1.6) | – | 1 (2.6) |
| Adenomatoid malformation | 1 (1.6) | 1 (4.8) | – |

Bold font indicates total number of birth defects in each structure/organ system.

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

[a]One case with unknown laterality was excluded.

**TABLE 3**

Adjusted odds ratio estimates for the association between potential risk factors and unilateral cataracts, National Birth Defects Prevention Study, 2000–2011

| | | Total cases (*n* = 227) | | Isolated with/without IED (*n* = 215) | | Isolated without IED (*n* = 144) | |
|---|---|---|---|---|---|---|---|
| **Characteristics** | **Controls (*n* = 10,076) *n* (%)[a]** | **Cases *n* (%)[a]** | **aOR[b] (95% CI)** | **Cases *n* (%)[a]** | **aOR[b] (95% CI)** | **Cases *n* (%)[a]** | **aOR[b] (95% CI)** |
| Sex | | | | | | | |
| Male | 5173 (51) | 100 (44) | Ref | 92 (43) | Ref | 62 (43) | Ref |
| Female | 4891 (49) | 127 (56) | 1.31 (0.98–1.76) | 123 (57) | 1.34 (0.99–1.80) | 82 (57) | 1.17 (0.81–1.68) |
| Plurality | | | | | | | |
| Singleton | 9758 (97) | 216 (95) | Ref | 205 (95) | Ref | 136 (94) | Ref |
| Multiple | 293 (3) | 11 (5) | 1.66 (0.86–3.21) | 10 (5) | 1.53 (0.76–3.05) | 8 (6) | 1.80 (0.82–3.97) |
| Season of conception | | | | | | | |
| Spring | 2440 (24) | 57 (25) | 1.03 (0.68–1.54) | 54 (25) | 1.03 (0.68–1.57) | 36 (25) | 0.97 (0.58–1.62) |
| Summer | 2547 (25) | 56 (25) | 0.90 (0.60–1.35) | 54 (25) | 0.95 (0.63–1.43) | 33 (23) | 0.86 (0.51–1.44) |
| Autumn | 2601 (26) | 56 (25) | 0.88 (0.58–1.32) | 53 (25) | 0.89 (0.59–1.35) | 40 (28) | 1.00 (0.61–1.64) |
| Winter | 2488 (25) | 58 (26) | Ref | 54 (25) | Ref | 35 (24) | Ref |
| Race/ethnicity | | | | | | | |
| Non-Hispanic White | 5726 (56.9) | 151 (67) | Ref | 143 (67) | Ref | 94 (65) | Ref |
| Non-Hispanic Black | 1101 (10.9) | 24 (11) | 0.97 (0.58–1.62) | 24 (11) | 1.00 (0.60–1.66) | 17 (12) | 1.12 (0.61–2.05) |
| Hispanic | 2546 (25.3) | 37 (16) | 1.10 (0.62–1.96) | 34 (16) | 1.09 (0.60–1.96) | 23 (16) | 1.02 (0.49–2.15) |
| Other | 696 (6.9) | 15 (7) | 1.05 (0.58–1.90) | 14 (7) | 1.01 (0.55–1.86) | 10 (7) | 1.06 (0.51–2.19) |
| Education | | | | | | | |
| <12 years | 1633 (17) | 25 (11) | 0.71 (0.39–1.28) | 24 (11) | 0.73 (0.41–1.33) | 18 (13) | 0.70 (0.33–1.47) |
| 12 years | 2277 (23) | 50 (22) | 1.02 (0.70–1.50) | 45 (21) | 0.99 (0.67–1.46) | 31 (22) | 1.06 (0.66–1.71) |
| >12 years | 5848 (60) | 149 (67) | Ref | 143 (67) | Ref | 93 (65) | Ref |
| Nativity | | | | | | | |
| Foreign-born | 2088 (21) | 36 (16) | 0.82 (0.50–1.36) | 33 (16) | 0.82 (0.50–1.37) | 25 (18) | 0.97 (0.53–1.80) |
| U.S.-born | 7678 (79) | 187 (84) | Ref | 178 (84) | Ref | 117 (82) | Ref |
| Parity[c] | | | | | | | |
| 0 | 3911 (39) | 111 (49) | 1.61 (1.18–2.20) | 105 (49) | 1.64 (1.19–2.26) | 72 (50) | 1.66 (1.13–2.46) |
| ≥1 | 6120 (61) | 116 (51) | Ref | 110 (51) | Ref | 72 (50) | Ref |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Pregestational body mass index | | | | | | | |
| <25 kg/m$^2$ | 5540 (58) | 140 (64) | Ref | 131 (63) | Ref | 89 (64) | Ref |
| ≥25 kg/m$^2$ | 4046 (42) | 79 (36) | 0.85 (0.62–1.15) | 78 (37) | 0.89 (0.65–1.21) | 50 (36) | 0.91 (0.62–1.34) |
| Fever[d] | | | | | | | |
| Periconceptional | 1535 (17) | 38 (19) | 1.00 (0.60–1.69) | 33 (17) | 0.85 (0.48–1.49) | 21 (17) | 0.71 (0.34–1.49) |
| Second/third trimester | 1630 (18) | 24 (12) | 0.55 (0.29–1.04) | 23 (12) | 0.53 (0.28–1.03) | 15 (12) | 0.52 (0.23–1.19) |
| None | 6001 (65) | 141 (69) | Ref | 137 (71) | Ref | 91 (72) | Ref |
| KBUTI[d] | | | | | | | |
| Periconceptional | 751 (8) | 18 (8) | 1.15 (0.58–2.28) | 17 (8) | 1.31 (0.63–2.69) | 11 (8) | 1.46 (0.58–3.68) |
| Second/third trimester | 1084 (11) | 20 (9) | 1.31 (0.62–2.76) | 18 (9) | 1.31 (0.61–2.84) | 12 (9) | 1.29 (0.49–3.43) |
| None | 8064 (81) | 181 (83) | Ref | 174 (83) | Ref | 118 (84) | Ref |
| Vasoactive medication use[d] | | | | | | | |
| Periconceptional | 3191 (33) | 71 (33) | 0.77 (0.56–1.06) | 67 (33) | 0.77 (0.55–1.07) | 42 (30) | 0.72 (0.48–1.09) |
| Second/third trimester | 704 (7) | 11 (5) | 0.77 (0.41–1.44) | 10 (5) | 0.72 (0.38–1.40) | 7 (5) | 0.78 (0.35–1.70) |
| None | 5865 (60) | 136 (62) | Ref | 129 (63) | Ref | 89 (64) | Ref |
| Folic acid-containing supplement use[e] | | | | | | | |
| No | 4646 (47) | 95 (42) | 1.17 (0.85–1.60) | 92 (43) | 1.20 (0.87–1.65) | 56 (39) | 0.93 (0.62–1.39) |
| Yes | 5288 (53) | 131 (58) | Ref | 122 (57) | Ref | 87 (61) | Ref |
| | **Mean (*SD*)** | **Mean (*SD*)** | **aOR[b] (95% CI)** | **Mean (*SD*)** | **aOR[b] (95% CI)** | **Mean (*SD*)** | **aOR[b] (95% CI)** |
| Maternal age (years) | 27.7 (6.0) | 27.9 (6.2) | 1.02 (0.99–1.05) | 28.0 (6.3) | 1.02 (0.99–1.05) | 27.8 (6.3) | 1.01 (0.98–1.05) |

Bold font indicates a statistically significant association.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; IED, ipsilateral eye defect; KBUTI, kidney, bladder, or urinary tract infection; *SD*, standard deviation; U.S., United States.

[a]Numbers vary because of missing information. Percentages might not sum to 100 because of rounding.

[b]Each exposure was adjusted for all other exposures (sex, plurality, season of conception, race/ethnicity, education, nativity, parity, pregestational body mass index, fever, KBUTI, vasoactive medication use, folic acid-containing supplement use, maternal age at delivery, and study site) included in the multivariable model.

[c]Number of previous live births or stillbirths.

[d]One month prior through the third month of pregnancy. Second and third trimester exposure category excludes cases with periconceptional exposure.

[e]One month prior through the first month of pregnancy.

**TABLE 4**

Adjusted odds ratio estimates for the association between potential risk factors and bilateral cataracts, National Birth Defects Prevention Study, 2000–2011

| | | Total cases (*n* = 117) | | Isolated with/without IED (*n* = 91) | | Isolated without IED (*n* = 75) | |
|---|---|---|---|---|---|---|---|
| **Characteristics** | **Controls (*n* = 10,076) *n* (%)** | **Cases *n* (%)[a]** | **aOR (95% CI)** | **Cases *n* (%)[a]** | **aOR[b] (95% CI)** | **Cases *n* (%)[a]** | **aOR[b] (95% CI)** |
| Sex | | | | | | | |
| Male | 5173 (51) | 59 (50) | Ref | 46 (51) | Ref | 37 (49) | Ref |
| Female | 4891 (49) | 58 (50) | 1.12 (0.75–1.67) | 45 (49) | 1.13 (0.72–1.79) | 38 (51) | 1.25 (0.76–2.06) |
| Plurality | | | | | | | |
| Singleton | 9758 (97) | 114 (97) | — | 89 (98) | — | 73 (97) | — |
| Multiple | 293 (3) | 3 (3) | — | 2 (2) | — | 2 (3) | — |
| Season of conception | | | | | | | |
| Spring | 2440 (24) | 31 (27) | 1.02 (0.59–1.77) | 28 (31) | 1.35 (0.72–2.52) | 21 (28) | 1.27 (0.63–2.55) |
| Summer | 2547 (25) | 19 (16) | 0.62 (0.34–1.15) | 15 (16) | 0.77 (0.38–1.55) | 14 (19) | 0.86 (0.40–1.82) |
| Autumn | 2601 (26) | 33 (28) | 0.97 (0.56–1.66) | 24 (26) | 1.07 (0.56–2.03) | 22 (29) | 1.16 (0.58–2.31) |
| Winter | 2488 (25) | 34 (29) | Ref | 24 (26) | Ref | 18 (24) | Ref |
| Race/ethnicity | | | | | | | |
| Non-Hispanic White | 5726 (56.9) | 62 (53) | Ref | 48 (53) | Ref | 40 (53) | Ref |
| Non-Hispanic Black | 1101 (10.9) | 19 (16) | 1.35 (0.73–2.50) | 16 (18) | 1.49 (0.76–2.90) | 13 (17) | 1.59 (0.77–3.27) |
| Hispanic | 2546 (25.3) | 30 (26) | 0.94 (0.44–2.01) | 22 (24) | 0.77 (0.32–1.88) | 17 (23) | 0.84 (0.32–2.19) |
| Other | 696 (6.9) | 6 (5) | 0.59 (0.22–1.57) | 5 (5) | 0.59 (0.20–1.78) | 5 (7) | 0.68 (0.22–2.08) |
| Education | | | | | | | |
| <12 years | 1633 (17) | 27 (24) | 2.08 (1.13–3.82) | 22 (26) | 2.39 (1.20–4.78) | 15 (21) | 1.95 (0.90–4.21) |
| 12 years | 2277 (23) | 25 (23) | 1.05 (0.60–1.84) | 18 (21) | 1.14 (0.61–2.15) | 16 (23) | 1.14 (0.58–2.24) |
| >12 years | 5848 (60) | 59 (53) | Ref | 46 (53) | Ref | 40 (56) | Ref |
| Nativity | | | | | | | |
| Foreign-born | 2088 (21) | 31 (28) | 1.92 (1.04–3.52) | 23 (27) | 1.97 (0.98–3.96) | 19 (27) | 2.10 (1.01–4.39) |
| U.S.-born | 7678 (79) | 80 (72) | Ref | 63 (73) | Ref | 52 (73) | Ref |
| Parity[c] | | | | | | | |
| 0 | 3911 (39) | 52 (44) | 1.21 (0.78–1.88) | 40 (44) | 1.22 (0.74–2.02) | 34 (45) | 1.26 (0.74–2.16) |
| ≥1 | 6120 (61) | 65 (56) | Ref | 51 (56) | Ref | 41 (55) | Ref |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Pregestational body mass index | | | | | | | |
| <25 kg/m$^2$ | 5540 (58) | 56 (49) | Ref | 44 (49) | Ref | 38 (51) | Ref |
| ≥25 kg/m$^2$ | 4046 (42) | 59 (51) | 1.42 (0.94–2.15) | 46 (51) | 1.38 (0.87–2.21) | 37 (49) | 1.20 (0.73–2.00) |
| Fever[d] | | | | | | | |
| Periconceptional | 1535 (17) | 25 (23) | 0.98 (0.46–2.08) | 18 (22) | 1.00 (0.42–2.39) | 16 (23) | 1.25 (0.52–3.02) |
| Second/third trimester | 1630 (18) | 15 (14) | 0.79 (0.35–1.80) | 12 (15) | 0.79 (0.31–2.00) | 9 (13) | 0.89 (0.33–2.36) |
| None | 6001 (65) | 67 (63) | Ref | 52 (63) | Ref | 44 (64) | Ref |
| KBUTI[d] | | | | | | | |
| Periconceptional | 751 (8) | 16 (14) | 2.25 (0.95–5.37) | 12 (13) | 2.12 (0.78–5.77) | 10 (14) | 1.75 (0.62–4.94) |
| Second/third trimester | 1084 (11) | 11 (10) | 1.20 (0.47–3.05) | 9 (10) | 1.22 (0.42–3.52) | 6 (8) | 1.00 (0.32–3.16) |
| None | 8064 (81) | 88 (77) | Ref | 68 (76) | Ref | 58 (78) | Ref |
| Vasoactive medication use[d] | | | | | | | |
| Periconceptional | 3191 (33) | 44 (40) | 1.45 (0.93–2.26) | 32 (37) | 1.24 (0.75–2.05) | 23 (32) | 1.03 (0.59–1.79) |
| Second/third trimester | 704 (7) | 10 (9) | 1.74 (0.87–3.48) | 7 (8) | 1.43 (0.63–3.24) | 6 (8) | 1.35 (0.56–3.24) |
| None | 5865 (60) | 57 (51) | Ref | 48 (55) | Ref | 43 (60) | Ref |
| Folic acid-containing supplement use[e] | | | | | | | |
| No | 4646 (47) | 50 (44) | Ref | 37 (41) | Ref | 30 (40) | Ref |
| Yes | 5288 (53) | 65 (57) | 0.77 (0.50–1.20) | 53 (59) | 0.64 (0.39–1.06) | 45 (60) | 0.60 (0.34–1.04) |
| | **Mean (*SD*)** | **Mean (*SD*)** | **aOR[b] (95% CI)** | **Mean (*SD*)** | **aOR[b] (95% CI)** | **Mean (*SD*)** | **aOR[b] (95% CI)** |
| Maternal age (years) | 27.7 (6.0) | 27.9 (6.1) | 1.01 (0.97–1.05) | 27.8 (6.4) | 1.01 (0.97–1.06) | 27.9 (6.5) | 1.01 (0.96–1.06) |

Bold font indicates a statistically significant association.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; IED, ipsilateral eye defect; KBUTI, kidney, bladder, or urinary tract infection; *SD*, standard deviation; U.S., United States.

[a]Numbers vary because of missing information. Percentages might not sum to 100 because of rounding.

[b]Each exposure was adjusted for all other exposures (sex, plurality, season of conception, race/ethnicity, education, nativity, parity, pregestational body mass index, fever, KBUTI, vasoactive medication use, folic acid-containing supplement use, maternal age at delivery, and study site) included in the multivariable model.

[c]Number of previous live births or stillbirths.

[d]One month prior through the third month of pregnancy. Second and third trimester exposure category excludes cases with periconceptional exposure.

[e]One month prior through the first month of pregnancy.