Association between Maternal Age and Birth Defects of Unknown Etiology - United States, 1997–2007

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Abstract

BACKGROUND—Birth defects affect 3% of babies born, and are one of the leading causes of infant mortality. Both younger and older maternal age may pose increased risks for certain birth defects. This study assessed the relationship between maternal age at the estimated delivery date and the risk for birth defects.

METHODS—Data were obtained from the National Birth Defects Prevention Study, a population-based case-control study including mothers across 10 states. Maternal age was stratified into six categories: <20, 20 to 24, 25 to 29, 30 to 34, 35 to 39, and ≥40 years, and also analyzed as a continuous variable. Logistic regression models adjusted for maternal race/ethnicity, education, body mass index (BMI), folic acid use, smoking, gravidity, and parental age difference were used to estimate adjusted odds ratios (aORs) and 95% confidence intervals (CIs).

RESULTS—For maternal age <20 years, associations with total anomalous pulmonary venous return (aOR, 2.3; 95% CI, 1.3–4.0), amniotic band sequence (aOR, 2.4; 95% CI, 1.5–3.8), and gastroschisis (aOR, 6.1; 95% CI, 4.8–8.0) were observed. For the ≥40 year age group, associations with several cardiac defects, esophageal atresia (aOR, 2.9; 95% CI, 1.7–4.9), hypospadias (aOR, 2.0; 95% CI, 1.4–3.0), and craniosynostosis (aOR, 1.6; 95% CI, 1.1–2.4) were observed. Results using maternal age as a continuous variable were consistent with those that used categorized maternal age.

CONCLUSION—Elucidating risk factors specific to women at either extreme of maternal age may offer prevention opportunities. All women should be made aware of prevention opportunities, such as folic acid supplementation, to reduce the occurrence of birth defects.

Keywords

birth defect; maternal age; teenage pregnancy

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INTRODUCTION

Although birth defects affect 3% of births, causes are not known for about two-thirds of cases (Nelson and Holmes, 1989; Brent, 1999; Canfield et al., 2006; Centers for Disease Control and Prevention, 2008). Both younger and older maternal age may pose increased risks for birth defects (Reefhuis and Honein, 2004; Loane et al., 2009), and these risks are of significant public health importance as the birth rate in the United States to women aged 15 to 19 years is 39.1 births per 1000 teenagers, and 10.1 births per 1000 women aged 40 to 44 years (Centers for Disease Control and Prevention, 2011).

Young Maternal Age

Births to teenage mothers have decreased in recent years in the United States, but still accounted for 6.4% of annual live births in 2009 (National Center for Health Statistics, 2010). This proportion is one of the highest among industrialized countries (Centers for Disease Control and Prevention, 2011), and represents a tremendous ongoing socioeconomic cost as numerous studies have determined that teenage pregnancies are susceptible to adverse pregnancy outcomes including intrauterine growth restriction, low birthweight, and preterm delivery (Chandra et al., 2002; Khashan et al., 2010). Limited data, however, exist on the associations between young maternal age and birth defects. In a retrospective cohort study conducted in the United States, strong associations between younger maternal age, 13 to 19 years, and certain birth defects in the offspring were identified, including malformations of the central nervous system, gastrointestinal tract, and musculoskeletal system (Chen et al., 2007). More consistent results have been published with respect to the association between young maternal age and gastroschisis (Reefhuis and Honein, 2004; Loane et al., 2009; Benjamin et al., 2010; Chabra et al., 2011). A recently published study based on data from 15 European countries observed associations between teenage pregnancies and gastroschisis, tricuspid atresia, anencephaly, and defects of the gastrointestinal and nervous systems (Loane et al., 2009). Interestingly, the maternal age pattern of risk for birth defects differed among European countries, suggesting that lifestyle factors or genetic background, rather than biologic age, contribute to the etiology for birth defects in younger mothers (Loane et al., 2009). Other studies have hypothesized that adverse pregnancy outcomes in younger mothers can be attributed to nonbiologic factors such as lower socioeconomic status, predictive lack of health insurance and appropriate prenatal care, including supplementation with folic acid-containing multivitamins (Reichman and Pagnini, 1997; Nilsen et al., 2006; Raatikainen et al., 2006; Wahn and Nissen, 2008).

Older Maternal Age

Older maternal age is associated with risks such as problems with fertility, multiple births, and chromosomal anomalies; however, more women are delaying childbearing (American Society for Reproductive Medicine, 2003; Tough et al., 2007), resulting in 14.9% of annual live births occurring in women aged 35 years or older (National Center for Health Statistics, 2010). It is widely recognized that older maternal age is strongly associated with chromosomal birth defects such as trisomies 13, 18, and 21 (Hagen et al., 2011). Several studies have also observed an association between older maternal age and nonchromosomal

birth defects such as neural tube defects, cleft lip or palate, congenital inguinal hernia, and cardiac defects (Baird et al., 1991; Czeizel, 1988; Khoshnood et al., 2008; Reefhuis and Honein, 2004). It has been proposed that the risk for nonchromosomal birth defects with older maternal age is negligible compared to the risk for chromosomal birth defects (Loane et al., 2009); however, the magnitude of risk for specific nonchromosomal defects is still unclear.

Rationale

Although a plethora of data exist regarding increased risks for chromosomal birth defects, debate still lingers over whether older maternal age increases the risk for nonchromosomal birth defects (Loane et al., 2009; Materna–Kiryluk et al., 2009). Similarly, limited data exist on the effects of younger maternal age on the potential for increased risks for birth defects. In a previous study conducted by Reefhuis and Honein, 2004, age-related increases in specific birth defects were observed. Data from that study, however, were collected between 1968 and 2000 from a single geographic region in the United States (the Metropolitan Atlanta Congenital Defects Program), and may not be representative of the United States (Reefhuis and Honein, 2004). Although certain risk factors, such as maternal race, were controlled for in that previous study, other risk factors, such as body mass index (BMI), were not included in the adjusted models (Reefhuis and Honein, 2004). An increase in public health awareness initiatives regarding smoking and alcohol use during pregnancy, prenatal care, and supplementation with folic acid-containing multivitamins may have also contributed to a potential reduction in these age-associated risk factors for certain birth defects since the time those data were published (Rasmussen et al., 2009). The objective of this study was to use more current data obtained across the United States to assess the association between maternal age and the risk for birth defects of unknown etiology.

METHODS

Design and Study Population

The National Birth Defects Prevention Study (NBDPS) is a population-based, case-control study that includes case infants identified through either statewide or regional birth defect surveillance systems in Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah. The study is described in detail elsewhere (Yoon et al., 2001).

Case infants include live born infants (all sites), fetal deaths, defined as 20 weeks gestation (all sites except New Jersey and New York before January 2000), and pregnancy terminations at any gestational age (all sites except Massachusetts, New Jersey, and New York before January 2000) with at least one of more than 30 types of major structural birth defects. Infants with recognized or strongly suspected chromosomal abnormalities or single-gene disorders are excluded from the NBDPS. To ensure the infant's birth defect meets the NBDPS case definition, experts in clinical genetics or pediatric cardiology review case records. Details of the clinical methods of the study have been published elsewhere (Rasmussen et al., 2003). Control infants include live born infants with no major birth

defects randomly selected from birth certificates or birth hospitals from the same source population and time period as case infants.

Mothers of any age, with the exception of those residing in New York (minimum maternal age of 18 years from 2004–2008), and Georgia and Iowa (minimum maternal age of 18 years for all study years) are contacted 6 weeks to 24 months after their estimated delivery date (EDD). Of eligible case and control mothers, 70% and 69% agreed to participate, respectively. After obtaining informed consent, a trained interviewer administers a standardized computer-assisted telephone interview in English or Spanish to ascertain exposures and behaviors 3 months before and during pregnancy, and to obtain information on maternal and paternal demographic and lifestyle factors and pregnancy history. The NBDPS is approved by the institutional review boards of participating study sites and the Centers for Disease Control and Prevention.

This analysis was limited to mothers who completed the interview and had an EDD from October 1, 1997, through December 31, 2007. Infants whose mothers reported having type 1 or type 2 diabetes were excluded because of the strong association between diabetes and birth defects (Verheijen et al., 2005). Only singleton pregnancies were included in the analyses as an association between birth defects and multiple pregnancies has been observed (Li et al., 2003, Zhang et al., 2011).

Maternal age at EDD was calculated from self-reported maternal birth date and date of the last menstrual period. To retain consistency and allow for comparisons with published literature, maternal age at EDD was categorized as follows: <20, 20 to 24, 25 to 29, 30 to 34, 35 to 39, and 40 years. Analyses were performed for birth defect categories containing 100 or more case infants in total, and three or more case infants per age category to avoid assessments with insufficient statistical power.

Statistical Analyses and Covariates

Univariate analyses were conducted using Pearson chi-square tests to estimate crude odds ratios (cORs) and 95% confidence intervals (CIs) relative to the 25 to 29 year age group for each birth defect. For cells with expected counts less than five, the Fisher exact test was used to calculate the cOR and 95% CI.

Separate multivariate logistic regression models for each birth defect were used to estimate maternal age-specific adjusted odds ratios (aORs) and 95% CIs relative to the 25 to 29 year age group. A priori selected covariates included in the models were maternal race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, all other races and ethnicities), maternal education (<12 years, 12 years), maternal BMI (<18.5 kg/m^2, 18.5–24.9 kg/m^2, 25 kg/m^2), maternal periconceptional folic acid use during the month before pregnancy to the end of the first trimester (no use, at least some use in each of the months from the month before pregnancy to the end of the first trimester, at least some use from the month before pregnancy to the end of the first trimester), gravidity (1, >1), maternal periconceptional smoking (yes, no), and parental age difference (0–5 years, father >5 years older, mother >5 years older).

Exploratory data analysis was conducted for each birth defect by dividing maternal age at EDD into quartiles, and determining the proportion of birth defect cases in each quartile. Based on the results from this exploratory data analysis, most birth defects examined suggested a linear or flat relationship with maternal age, with the exception of gastroschisis and perimembranous ventricular septal defect, both of which exhibited a quadratic relationship with maternal age. Maternal age at EDD was used as a linear, continuous variable in separate multivariate regression models using the same covariates listed above for each birth defect to estimate aORs and 95% CIs for each additional year of maternal age. For gastroschisis and perimembranous ventricular septal defect, maternal age at EDD was also assessed as a quadratic term in multivariable regression models; however, because these results were similar to the results when maternal age was used as a linear, continuous variable, the results using maternal age as a quadratic term are not presented.

Subanalysis was conducted after excluding for the use of illicit drugs, which is known to be more common in younger women, and the use of fertility treatment, which is more common in older women and has been shown to be associated with certain birth defects in previous studies (Hansen et al., 2005; Zhu et al., 2006; Reefhuis et al., 2009; Reefhuis et al., 2011). A single subanalysis was conducted in which mothers were excluded if they reported illicit drugs such as marijuana, crack-cocaine, or heroin, or fertility treatments such as introcytoplasmic sperm injection, in vitro fertilization, or fertility drugs such as clomiphene citrate. Because the number of women exposed to illicit drugs or fertility treatments was small, the subanalysis excluded women exposed to any of these substances.

All statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC).

RESULTS

In total, the NBDPS contains interviews from mothers of 23,333 case infants and 8494 control infants for 1997 to 2007. After applying the exclusion criteria, the final analytical sample size consisted of 20,377 case infants and 8169 control infants (Fig. 1).

The mean maternal age at EDD for case mothers and control mothers was the same at 27.5 years. The median maternal age at EDD was also the same for case mothers and control mothers at 27 years. For case mothers, the maternal age range was 12 to 53 years; for control mothers, the maternal age range was 13 to 50 years.

Case and control mothers were demographically similar within each age category (data not shown). Table 1 shows the characteristics of control mothers by age category. As maternal age increased, the proportion of non-Hispanic white mothers increased; conversely, as age increased, the proportion of Hispanic and non-Hispanic black mothers decreased (Table 1). The proportion of smokers was 2.5 times higher in mothers <20 years compared to mothers 40 years of age; alternatively, the use of folic acid-containing supplements increased with increasing maternal age (Table 1). As age increased, there were a greater proportion of women with at least a high school education, and with more than one previous pregnancy (Table 1).

Of 60 birth defect categories considered for these analyses, 51 defects had at least 100 cases; of these 51 defects, 8 defects had <3 case infants in the   40 years age category. The cORs, aORs, and 95% CIs were calculated; because there were minimal differences between the cORs and the aORs, only the aORs are presented.

We assessed the association between all birth defects categories and maternal age categories, adjusted for potential confounders (Table 2). For maternal age <20 years, positive associations with total anomalous pulmonary venous return (aOR, 2.3; 95% CI, 1.3–4.0), amniotic band sequence (aOR, 2.4; 95% CI, 1.5–3.8), and gastroschisis (aOR, 6.1; 95% CI, 4.8–8.0) were observed.

For the   40 years age group, positive associations with several cardiac defects were observed including Tetralogy of Fallot (aOR, 2.2; 95% CI, 1.4–3.3), perimembranous ventricular septal defect (aOR, 2.5; 95% CI, 1.8–3.5), atrial septal defect, not otherwise specified (aOR, 2.5; 95% CI, 1.5–4.1), and ventricular septal defect + atrial septal defect association (aOR, 2.9; 95% CI, 1.8–4.7). Non-cardiac defects observed to be associated with maternal age   40 years were esophageal atresia (aOR, 2.9; 95% CI, 1.7–4.9), hypospadias (aOR, 2.0; 95% CI, 1.4–3.0), and craniosynostosis (aOR, 1.6; 95% CI, 1.1–2.4).

Interestingly, for the <20 years age category, there were a few birth defects associated with reduced aORs including cataracts and lens defects (aOR, 0.5; 95% CI, 0.3–0.9), perimembranous ventricular septal defect (aOR, 0.7; 95% CI, 0.6–0.9), left ventricular outflow tract obstruction (aOR, 0.6; 95% CI, 0.5–0.8), coarctation of the aorta (aOR, 0.5; 95% CI, 0.4–0.8), hypospadias (aOR, 0.6; 95% CI, 0.5–0.8), and craniosynostosis (aOR, 0.6; 95% CI, 0.4–0.8). In comparison, the only birth defect with a reduced aOR observed with increasing maternal age was gastroschisis; for the 30 to 34 and 35 to 39 age categories, the aORs were 0.5 (95% CI, 0.3–0.6) and 0.2 (95% CI, 0.1–0.3), respectively, and no cases of gastroschisis were present in the   40 years age category.

When maternal age at EDD was used as a linear, continuous variable in the regression models, the results were consistent with those findings that used categorized maternal age (Table 3). Notably, however, the aORs for cleft palate (aOR, 1.04; 95% CI, 1.02–1.06) and duodenal atresia/stenosis (aOR, 1.05; 95% CI, 1.01–1.08) were observed to be significant. Some defects that showed associations for some age categories, such as total anomalous pulmonary venous return did not show a linear association; this could reflect a more u-shaped association.

After excluding for illicit drug use in both case (n = 365) and control (n = 143) mothers, and the use of fertility treatments in case (n = 1005) and control (n = 239) mothers, there were no substantial differences in the aORs for any specific birth defect as presented in Table 2.

DISCUSSION

Based on these findings, in the United States, younger maternal age, <20 years, is associated with gastroschisis, amniotic band sequence, and, perhaps, anomalous pulmonary venous return. On the other hand, older maternal age,   40 years, is associated with some atrial and

ventricular septal defects, Tetralogy of Fallot, esophageal atresia, craniosynostosis, and hypospadias.

Previous studies have also observed increased risks for gastroschisis with younger maternal age (Loane et al., 2009; Benjamin et al., 2010; Chabra et al., 2011). The increased risk for gastroschisis observed in the younger population has been hypothesized to be caused by risk factors disproportionately higher among adolescents (Rasmussen and Frias, 2008). These risk factors include low BMI, cigarette smoking, use of illicit drugs, genitourinary infections, sexually transmitted diseases, and Epstein–Barr virus (Loane et al., 2009; Werler, 2010). The increased risk for gastroschisis in younger mothers observed in this study is possibly associated with cigarette smoking because we observed higher proportions of teen mothers self-reporting smoking compared with older mothers (Table 2); however, in an earlier analysis of a subset of this data, cigarette smoking was not associated with young maternal age (Mac Bird et al., 2009, Werler et al., 2009).

Similar to the present findings, several studies have observed an association between amniotic band sequence and young maternal age (Garza et al., 1988; Mastroiacovo et al., 1992; Bower et al., 1993). A case-control study using data from Boston, Philadelphia, and Toronto observed a threefold increase in amniotic band sequence in mothers <25 years of age; however, this association was not found to be statistically significant (Werler et al., 2003). Interestingly, etiologic theories for both gastroschisis and amniotic band sequence include vascular disruptions, immune system involvement, or poor nutritional status associated with younger maternal age (Martínez–Frías et al., 2000; Werler et al., 2003; Rasmussen and Frias, 2008). This study could not assess these risk factors; however, a greater proportion of teenage mothers in the present study were underweight with a BMI of <18.5 kg/m^2 compared with older mothers, suggesting nutritional deficiencies may exist in this younger group (Table 2).

For total anomalous pulmonary venous return, we observed a statistically significant increased odds ratio for young maternal age, and although the odds ratio for older maternal age was elevated, it was not found to be statistically significant. A study using NBDPS data from 1997 through 2004 observed associations with young and old paternal age and anomalous pulmonary venous return; however, only the associations with young paternal age were observed to be statistically significant (Green et al., 2010). Loane et al. (2009) also observed elevated odds ratios for young and older maternal age pointing toward a possible u-shaped association with maternal age. However, when maternal age was used either as a linear or quadratic continuous variable in the regression models, this association was not observed.

Several studies propose that the association between young maternal age and poor pregnancy outcome, including birth defects, is related to biologic factors such as mother's gynecological immaturity and nutritional status (Scholl et al., 1990; Wallace et al., 2001; Raatikainen et al., 2006). Fetal growth and development is highly dependent on placental growth and transport of nutrients; in adolescent pregnancies, competition for nutrients between the developing adolescent and the placenta and fetus may result in adverse pregnancy outcomes (Wallace et al., 2001). Additionally, teenage mothers are more likely to

smoke, drink alcohol, and have poor diet resulting in greater nutritional deficits (Scholl et al., 1990; Raatikainen et al., 2006; Wahn and Nissen, 2008) compared with older mothers.

Compared to young maternal age, results from this study suggest that older maternal age may be a stronger risk factor for certain cardiac defects. Specifically, in mothers 40 years, increased risks for several cardiac defects were observed including ventricular septal defects, atrial septal defects, and Tetralogy of Fallot. Several other studies have observed an association between older maternal age and the risk for cardiac defects (Reefhuis and Honein, 2004; Reller et al., 2008; Materna–Kiryluk et al., 2009). A more recent study using data from the Metropolitan Atlanta Congenital Defects Program (one of the 10 birth defects surveillance systems contributing cases to the NBDPS) assessed the association between maternal age and the risk for isolated cardiac defects that excluded defects with syndromes; results from this study showed associations between maternal age 35 years and conotruncal defects, coarctation of the aorta, ventricular septal defects, and atrial septal defects (Miller et al., 2011). It is important to point out, however, that maternal age 35 years is a common reason for referral for fetal echocardiography, which can detect cardiac defects more reliably than a regular ultrasound (Davey et al., 2009). Because ventricular septal defects may close spontaneously up to 2 years after birth (Helgason and Jonsdottir, 1999; Mehta et al., 2000), it is possible that these defects are not detected if they occur and spontaneously close in infants born to younger mothers.

Consistent with previous research using data from the United States, we observed associations between older maternal age and noncardiac defects such as hypospadias (Reefhuis and Honein, 2004). A study using NBDPS data from 1997 to 2000 observed an association between maternal age 35 years and hypospadias (Carmichael et al., 2007). However, two studies using data from Europe did not observe an association between maternal age and hypospadias (Loane et al., 2009; Materna–Kiryluk et al., 2009). Hypospadias is the most common major genital birth defect among male infants, and although research is being conducted to identify the cause, the etiology is still unknown but it is thought to be multifactorial, with genetic and environmental factors playing a role (Kalfa et al., 2009; Kalfa et al., 2010).

Results from this study suggest an association between older maternal age and esophageal atresia. A study conducted using data from 1998 to 2002 from the Polish Registry of Congenital Malformations observed an elevated, but nonstatistically significant, odds ratio between esophageal atresia and maternal age (Materna–Kiryluk et al., 2009), and results from a large European study including 15 countries also observed an increased risk for esophageal atresia in older mothers (Loane et al., 2009). Loane et al. (2009) did not observe an increased risk for craniosynostosis in older mothers; whereas, results from the present study showed a twofold increased risk for craniosynostosis in older mothers consistent with previously published US data (Reefhuis and Honein, 2004). It is possible that certain risk factors may differ among countries and contribute more heavily to the susceptibility of certain birth defects; however, differences in study design, case definition, and potential confounders may play a role in the discrepancies observed.

In older mothers, biologic factors such as ovarian age are thought to contribute more to adverse pregnancy outcomes than nonbiologic factors (Raatikainen et al., 2006). Ovarian follicles established during fetal life exponentially decline in quantity and quality over the years, resulting in subfertility as early as 30 years of age (te Velde et al., 1998). In addition to decreased ova quality, age-related increases in comorbidities, such as hypertension and gestational diabetes, contribute to increased risks for pregnancy complications, and possibly birth defects (Raatikainen et al., 2006; Khoshnood et al., 2008; Schoen and Rosen, 2009; Yogev et al., 2010).

Compared to previous work, this study has several key strengths. Results from the data analysis were consistent when maternal age was either categorized or used as a continuous variable. Furthermore, data on demographics and risk factors such as BMI, smoking, and folic acid use are collected and have been incorporated into the logistic regression models; whereas, in other studies, these variables are not always available and accounted for in the analysis. Additionally, women with certain risk factors that have been consistently associated with birth defects, such as type 1 and type 2 diabetes and multiple pregnancies, were excluded from this analysis. Although the aforementioned data are based on self-report, the exposure of interest, maternal age calculated by date of birth, is unlikely to be affected by recall bias or misreported. Furthermore, misclassification of birth defect outcomes was minimized by case records being reviewed by experts in medical genetics or pediatric cardiology based on specific standardized inclusion criteria for each defect.

Results from this study are based on data collected from control mothers from the same source population and time period as case mothers, and have been shown to be representative of mothers across the United States (Cogswell et al., 2009). An important limitation; however, is that Iowa, Georgia, and New York (for some years) did not include mothers <18 years of age. The large sample size allows for the evaluation of individual birth defects with sufficient statistical power; however, the multiple testing conducted in this analysis may be responsible for some of the positive associations observed. Furthermore, this study did not assess the association between maternal age and isolated defects; all analyses conducted included both isolated and multiple defects. This study was not designed to assess the association between environmental risk factors specific to younger versus older mothers, although based on the exclusion criteria, in this analysis, preexisting diabetes and multiple births can be excluded as contributing to this etiologic pathway. Despite the aforementioned limitations, results obtained from these data can assist in making public health recommendations to help reduce the occurrence of specific birth defects that may be associated with certain risk factors in older or younger mothers.

The rate of live births among teenagers in the United States is one of the highest among industrialized countries, and this study shows that birth defects among teen-age mothers are a public health concern. Similarly, rates of live births among older mothers are increasing, and although there may be associations between biologic factors and certain birth defects that cannot be modified, modifications in lifestyle factors can help to improve infant outcomes. Regardless of age, women who optimize their health before conception, and are aware of information on all risks and potential prevention opportunities, such as smoking cessation and supplementation with folic acid, can reduce their risks for birth defects.

Acknowledgments

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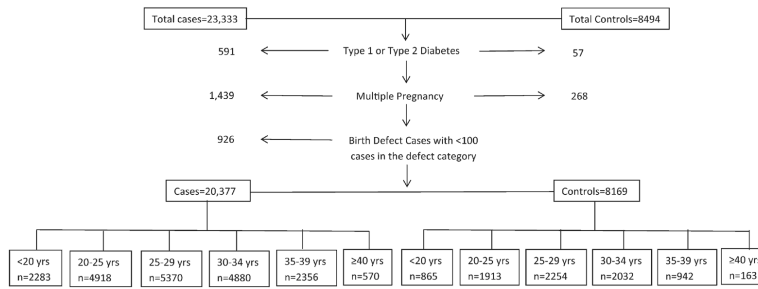
Figure 1.
Flowchart of Included Mothers of Cases and Controls, National Birth Defects Prevention Study, 1997 to 2007.

Table 1

Distribution of a Priori Selected Covariates by Maternal Age Category among Control Mothers, National Birth Defects Prevention Study, 1997 to 2007

Covariate[a]	Maternal Age, Years					
	<20, n (%)	20–24, n (%)	25–29, n (%)	30–34, n (%)	35–39, n (%)	40, n (%)
Race/ethnicity	n = 861	n = 1911	n = 2151	n = 2025	n = 935	n = 163
Non-Hispanic white	301 (35)	960 (50)	1231 (59)	1378 (68)	665 (71)	114 (70)
Non-Hispanic black	158 (18)	265 (14)	219 (10)	160 (8)	78 (8)	15 (9)
Hispanic	330 (38)	551 (29)	524 (23)	333 (16)	111 (12)	21 (13)
Other	72 (8)	135 (7)	177 (8)	154 (8)	81 (9)	13 (8)
BMI (kg/m^2)	n = 816	n = 1796	n = 2154	n = 1966	n = 924	n = 162
<18.5	90 (11)	136 (8)	89 (4)	76 (4)	27 (3)	7 (4)
18.5–24.9	497 (61)	919 (51)	1161 (54)	1126 (57)	542 (59)	77 (48)
25	229 (28)	741 (41)	904 (42)	764 (39)	355 (38)	78 (48)
Folic acid use[b]	n = 858	n = 1902	n = 2242	n = 2028	n = 940	n = 163
No	251 (29)	387 (20)	316 (14)	208 (10)	100 (11)	19 (12)
Yes[c]	55 (6)	284 (15)	709 (32)	829 (41)	421 (45)	82 (38)
Some use[d]	552 (64)	1231 (65)	1217 (54)	991 (49)	419 (44)	62 (50)
Gravidity	n = 862	n = 1907	n = 2249	n = 2029	n = 942	n = 163
1	602 (70)	687 (36)	614 (27)	367 (18)	104 (11)	17 (10)
>1	260 (30)	1220 (64)	1635 (73)	1662 (82)	838 (89)	146 (90)
Education, years	n = 834	n = 1875	n = 2215	n = 2008	n = 929	n = 163
<12	447 (54)	414 (22)	276 (13)	177 (9)	63 (7)	11 (7)
12	387 (46)	1461 (78)	1939 (87)	1831 (91)	866 (93)	152 (93)
Smoking[e]	n = 840	n = 1881	n = 2221	n = 2013	n = 932	n = 163
No	614 (73)	1362 (72)	1877 (85)	1742 (87)	827 (89)	145 (89)
Yes	226 (27)	519 (28)	344 (15)	271 (13)	105 (11)	18 (11)
Parental age difference, years	n = 865	n = 1913	n = 2254	n = 2032	n = 942	n = 163
0–5	614 (71)	1408 (73)	1732 (77)	1581 (78)	718 (76)	155 (71)
Father >5	251 (29)	502 (27)	486 (21)	368 (18)	140 (15)	25 (15)
Mother >5	0 (0)	3 (<1)	36 (2)	83 (4)	84 (9)	23 (14)

BMI, pre-pregnancy body mass index.

[a]Some covariates have missing data.

[b]Month before pregnancy to the end of the first trimester.

[c]At least some use in each of the months from the month before pregnancy to the end of the first trimester.

[d]At least some use anytime from the month before pregnancy to the end of the first trimester.

[e]Anytime during the periconceptional period.

Table 2

The aORs[a] and 95% CIs for Birth Defects among Maternal Age Groups, 25 to 29 years Is the Reference, National Birth Defects Prevention Study, 1997 to 2007

Birth Defect	Cases (Total No.)	aOR (95% CI)				
		<20	20–24	30–34	35–39	40
Anencephaly and craniorachischisis	377	1.2 (0.8–1.8)	0.9 (0.7–1.3)	0.8 (0.6–1.1)	0.8 (0.6–1.2)	1.5 (0.8–2.7)
Spina bifida	821	1.0 (0.8–1.4)	0.9 (0.7–1.1)	**0.7 (0.6–0.9)**	0.8 (0.6–1.0)	1.3 (0.9–2.1)
Hydrocephaly	318	1.1 (0.7–1.7)	1.2 (0.8–1.6)	1.0 (0.7–1.4)	0.9 (0.6–1.4)	1.1 (0.5–2.5)
Encephalocele	142	1.3 (0.7–2.1)	1.0 (0.6–1.7)	0.9 (0.6–1.5)	0.9 (0.5–1.7)	2.4 (1.0–5.6)
Holoprosencephaly	100	1.0 (0.5–2.1)	1.2 (0.7–2.1)	1.0 (0.6–1.8)	1.2 (0.6–2.5)	Insufficient
Dandy–Walker malformation	105	0.5 (0.4–1.6)	0.8 (0.5–1.5)	1.5 (0.9–2.5)	0.9 (0.4–2.0)	Insufficient
Anophthalmos/microphthalmos	151	0.8 (0.4–1.5)	0.8 (0.5–1.3)	0.9 (0.6–1.3)	0.6 (0.3–1.2)	1.3 (0.4–3.6)
Cataracts and other lens defects	232	**0.5 (0.3–0.9)**	0.7 (0.5–1.1)	0.9 (0.6–1.2)	1.0 (0.6–1.5)	0.9 (0.4–2.4)
Glaucoma and anterior segment defects	117	0.6 (0.2–1.4)	1.4 (0.9–2.4)	1.1 (0.6–1.8)	0.9 (0.5–1.9)	1.3 (0.4–4.3)
Anotia/microtia	404	0.9 (0.6–1.3)	0.9 (0.7–1.3)	1.0 (0.7–1.3)	1.3 (0.9–1.9)	1.0 (0.4–2.2)
Conotruncal defects	1651	0.8 (0.7–1.1)	1.0 (0.8–1.1)	1.2 (1.0–1.4)	1.2 (1.0–1.4)	**1.8 (1.3–2.5)**
D-Transposition of the great arteries	526	1.1 (0.8–1.6)	1.1 (0.8–1.4)	1.2 (0.9–1.5)	0.8 (0.6–1.1)	1.6 (1.0–2.7)
Double outlet right ventricular with transposition of the great arteries	101	2.1 (1.0–4.3)	1.0 (0.5–1.8)	1.0 (0.4–1.5)	0.6 (0.9–3.0)	Insufficient
Tetralogy of Fallot	750	0.6 (0.4–0.9)	0.9 (0.7–1.2)	1.2 (1.0–1.5)	1.4 (1.1–1.8)	**2.2 (1.4–3.3)**
Single ventricle/complex heart	218	0.8 (0.5–1.4)	0.7 (0.5–1.1)	0.8 (0.6–1.2)	1.0 (0.7–1.6)	0.8 (0.3–2.3)
Ventricular septal defects, muscular	167	0.8 (0.4–1.7)	0.9 (0.5–1.5)	1.0 (0.6–1.5)	1.0 (0.5–1.7)	1.5 (0.5–5.5)
Ventricular septal defects, perimembranous	1293	**0.7 (0.6–0.9)**	1.0 (0.8–1.2)	1.1 (1.0–1.3)	**1.4 (1.1–1.7)**	**2.5 (1.8–3.5)**
Ventricular septal defects, conoventricular	101	0.4 (0.2–1.1)	0.7 (0.4–1.2)	1.3 (0.8–2.2)	1.3 (0.6–2.2)	**3.1 (1.2–7.8)**
Atrial septal defect secundum	1493	0.7 (0.6–0.9)	1.0 (0.8–1.1)	0.9 (0.8–1.1)	0.9 (0.8–1.1)	1.5 (1.0–2.1)
Atrial septal defect, not otherwise specified	468	0.8 (0.6–1.2)	0.9 (0.7–1.2)	1.0 (0.7–1.3)	1.1 (0.8–1.5)	**2.5 (1.5–4.1)**
Ebstein malformation	112	0.7 (0.3–1.6)	1.0 (0.6–1.6)	1.0 (0.6–1.6)	0.8 (0.4–1.7)	2.2 (0.8–5.7)
Right ventricular outflow tract obstruction	1258	0.8 (0.6–1.0)	0.9 (0.8–1.1)	1.0 (0.8–1.2)	1.0 (0.8–1.3)	1.5 (1.0–2.2)
Pulmonary valve stenosis	923	0.8 (0.6–1.0)	0.9 (0.8–1.1)	1.0 (0.8–1.2)	1.0 (0.8–1.3)	1.5 (1.0–2.3)
Pulmonary atresia	159	1.2 (0.6–2.2)	0.9 (0.6–1.4)	1.0 (0.7–1.6)	0.9 (0.5–1.6)	1.8 (0.7–4.3)
Tricuspid atresia	106	0.9 (0.4–1.9)	0.9 (0.5–1.5)	0.6 (0.4–1.1)	1.0 (0.5–1.8)	1.0 (0.3–3.6)
Left ventricular outflow tract obstruction	1359	**0.6 (0.5–0.8)**	0.9 (0.8–1.1)	1.0 (0.9–1.3)	0.8 (0.7–1.1)	1.0 (0.7–1.6)
Coarctation of the aorta	710	**0.5 (0.4–0.8)**	0.8 (0.7–1.1)	1.2 (1.0–1.5)	0.9 (0.7–1.2)	1.5 (0.9–2.3)
Aortic stenosis	305	0.6 (0.4–1.1)	0.7 (0.5–1.0)	0.9 (0.7–1.2)	0.9 (0.6–1.4)	0.8 (0.3–1.8)
Hypoplastic left heart syndrome	409	0.9 (0.6–1.4)	1.0 (0.7–1.3)	1.0 (0.8–1.3)	0.8 (0.5–1.1)	1.0 (0.5–1.1)
Total anomalous pulmonary venous return	190	**2.3 (1.3–4.0)**	**1.8 (1.2–2.7)**	1.2 (0.7–1.8)	1.1 (0.6–2.0)	1.9 (0.8–4.6)
Heterotaxia with CHD	222	1.2 (0.7–1.9)	1.0 (0.7–1.5)	1.1 (0.7–1.6)	1.0 (0.6–1.6)	Insufficient
Association: coarctation + ventricular septal defect	191	**0.4 (0.2–0.8)**	1.1 (0.8–1.7)	1.1 (0.8–1.7)	1.0 (0.6–1.7)	1.5 (0.6–3.6)

Birth Defect	Cases (Total No.)	aOR (95% CI)				
		<20	20–24	30–34	35–39	40
Association: ventricular septal defects + atrial septal defects	519	0.7 (0.5–1.1)	0.9 (0.7–1.2)	1.2 (1.0–1.6)	1.3 (1.0–1.8)	**2.9 (1.8–4.7)**
Association: pulmonary valve stenosis + ventricular septal defect	105	1.2 (0.4–2.9)	**2.4 (1.3–4.5)**	1.9 (1.0–3.6)	**2.5 (1.2–5.1)**	2.3 (0.5–7.2)
Association: pulmonary valve stenosis + atrial septal defect	137	0.6 (0.3–1.1)	**0.6 (0.3–0.9)**	0.8 (0.5–1.3)	0.9 (0.5–1.7)	1.2 (0.4–3.5)
Cleft lip ± palate	1997	1.0 (0.8–1.2)	1.1 (1.0–1.3)	0.9 (0.8–1.0)	1.0 (0.9–1.2)	1.2 (0.9–1.7)
Cleft palate	1069	0.8 (0.6–1.0)	0.9 (0.8–1.1)	1.0 (0.9–1.2)	1.2 (1.0–1.5)	1.4 (1.0–2.2)
Esophageal atresia	437	1.1 (0.8–1.7)	1.0 (0.7–1.3)	**1.4 (1.1–1.9)**	**1.6 (1.2–2.3)**	**2.9 (1.7–4.9)**
Anorectal atresia/stenosis	661	0.9 (0.6–1.2)	1.2 (0.9–1.5)	1.1 (0.9–1.4)	1.2 (0.9–1.6)	1.1 (0.6–2.0)
Intestinal atresia/stenosis	300	1.1 (0.7–1.6)	0.9 (0.7–1.3)	0.9 (0.6–1.2)	1.4 (0.9–2.1)	1.8 (0.9–3.6)
Duodenal atresia/stenosis	142	0.7 (0.3–1.4)	1.2 (0.7–1.9)	1.6 (1.0–2.6)	1.6 (0.9–3.0)	2.3 (0.8–6.5)
Biliary atresia	120	1.2 (0.6–2.6)	1.2 (0.7–2.0)	1.2 (0.7–2.0)	0.9 (0.4–1.8)	1.3 (0.4–4.5)
Hypospadias	1466	**0.6 (0.5–0.8)**	0.9 (0.8–1.1)	**1.4 (1.2–1.7)**	**1.6 (1.3–1.9)**	**2.0 (1.4–3.0)**
Renal agenesis/hypoplasia	106	0.8 (0.4–1.6)	1.0 (0.6–1.6)	0.6 (0.4–1.1)	0.4 (0.2–1.0)	Insufficient
Limb deficiency	774	1.2 (0.8–1.5)	1.1 (0.9–1.3)	1.0 (0.8–1.3)	0.8 (0.6–1.1)	1.0 (0.6–1.7)
Longitudinal preaxial limb deficiency	176	1.1 (0.6–1.9)	1.1 (0.8–1.7)	0.7 (0.5–1.2)	1.0 (0.6–1.8)	Insufficient
Limb deficiency, transverse	459	1.2 (0.8–1.7)	1.1 (0.8–1.4)	1.2 (0.9–1.5)	0.9 (0.6–1.2)	0.7 (0.6–2.5)
Omphalocele	288	0.9 (0.6–1.6)	1.2 (0.9–1.6)	1.0 (0.7–1.4)	1.5 (1.0–2.7)	1.8 (0.9–3.6)
Gastroschisis	899	**6.1 (4.8–8.0)**	**3.1 (2.5–3.9)**	**0.5 (0.3–0.6)**	**0.2 (0.1–0.3)**	Insufficient
Amniotic band syndrome and limb body wall complex	219	**2.4 (1.5–3.8)**	1.7 (1.1–2.5)	0.8 (0.5–1.2)	0.8 (0.4–1.5)	Insufficient
Craniosynostosis	966	**0.6 (0.4–0.8)**	0.8 (0.6–1.0)	1.2 (1.0–1.4)	1.3 (1.1–1.6)	**1.6 (1.1–2.4)**
Diaphragmatic hernia	559	0.8 (0.6–1.2)	1.0 (0.8–1.2)	0.9 (0.7–1.2)	1.0 (0.8–1.4)	0.7 (0.3–1.5)

aORs, adjusted odds ratios; CIs, confidence intervals; CHD, coronary heart disease.

The numbers in boldface represent a statistically significant association.

[a]Adjusted for race/ethnicity, body mass index, folic acid use, gravidity, education, smoking, and parental age difference; mothers with missing covariate data are excluded from these analyses.

Table 3

Estimated aORs[a] for a 1-year Increase in Maternal Age, National Birth Defects Prevention Study, 1997 to 2007

Birth Defect	Cases (Total No.)	aOR (95% CI)
Anencephaly and craniorachischisis	377	0.99 (0.97–1.01)
Spina bifida	821	199 (0.98–1.01)
Hydrocephaly	318	0.99 (0.97–1.01)
Encephalocele	142	1.00 (0.99–1.03)
Holoprosencephaly	100	1.01 (0.97–1.04)
Dandy-Walker malformation	105	1.02 (0.98–1.06)
Anophthalmos/microphthalmos	151	1.00 (0.97–1.03)
Cataracts and other lens defects	232	1.02 (0.99–1.05)
Glaucoma and anterior segment defects	117	0.99 (0.95–1.03)
Anotia/microtia	404	1.01 (0.99–1.03)
Conotruncal defects	1651	**1.02 (1.01–1.03)**
D-Transposition of the great arteries	526	1.00 (0.98–1.02)
Double outlet right ventricular with transposition of the great arteries	101	0.98 (0.95–1.02)
Tetralogy of Fallot	750	**1.04 (1.02–1.05)**
Single ventricle/complex heart	218	1.01 (0.99–1.04)
Ventricular septal defects, muscular	167	1.01 (0.98–1.05)
Ventricular septal defects, perimembranous	1293	**1.03 (1.02–1.04)**
Ventricular septal defects, conoventricular	101	**1.06 (1.03–1.10)**
Atrial septal defect secundum	1493	1.01 (1.00–1.01)
Atrial septal defect, not otherwise specified	468	1.02 (1.00–1.04)
Ebstein malformation	112	1.02 (0.98–1.06)
Right ventricular outflow tract obstruction	1258	1.01 (1.00–1.03)
Pulmonary valve stenosis	923	1.01 (1.00–1.03)
Pulmonary atresia	159	1.00 (0.97–1.03)
Tricuspid atresia	106	0.99 (0.96–1.03)
Left ventricular outflow tract obstruction	1359	1.01 (1.00–1.02)
Coarctarion of the aorta	710	**1.02 (1.01–1.04)**
Aortic stenosis	305	1.01 (0.99–1.04)
Hypoplastic left heart syndrome	409	1.00 (0.98–1.02)
Total anomalous pulmonary venous return	190	0.97 (0.94–1.00)
Heterotaxia with CHD	222	0.99 (0.97–1.02)
Association: coarctarion + ventricular septal defect	191	1.02 (0.99–1.05)
Association: ventricular septal defects + atrial septal defects	519	**1.04 (1.03–1.06)**
Association: pulmonary valve stenosis + ventricular septal defect	105	1.01 (0.98–1.05)
Association: pulmonary valve stenosis + atrial septal defect	137	1.02 (0.99–1.06)
Cleft lip ± palate	1997	1.00 (0.99–1.01)
Cleft palate	1069	**1.04 (1.02–1.06)**
Esophageal atresia	437	**1.05 (1.03–1.07)**

Birth Defect	Cases (Total No.)	aOR (95% CI)
Anorectal atresia/stenosis	661	1.01 (0.99–1.02)
Intestinal atresia/stenosis	300	1.02 (0.99–1.04)
Duodenal atresia/stenosis	142	**1.05 (1.01–1.08)**
Biliary atresia	120	1.00 (0.96–1.04)
Hypospadias	1466	**1.05 (1.03–1.06)**
Renal agenesis/hypoplasia	106	0.98 (0.94–1.02)
Limb deficiency	774	0.99 (0.98–1.00)
Longitudinal preaxial limb deficiency	176	0.98 (0.95–1.01)
Limb deficiency, transverse	459	1.00 (0.98–1.02)
Omphalocele	288	1.01 (0.99–1.04)
Gastroschisis	899	**0.81 (0.80–0.83)**
Amniotic band syndrome and limb body wall complex	219	**0.93 (0.90–0.96)**
Craniosynostosis	966	**1.04 (1.02–1.04)**
Diaphragmatic hernia	559	1.01 (0.99–1.02)

aORs, adjusted odds ratios; CIs, confidence intervals; CHD, coronary heart disease.

The numbers in boldface represent a statistically significant association.

[a]Adjusted for race/ethnicity, body mass index, folic acid use, gravidity, education, smoking, parental age difference; mothers with missing covariate data are excluded from these analyses.