OBSTETRICS

Influence of periconception smoking behavior on birth defect risk

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BACKGROUND: Smoking is one of the most important modifiable risk factors for adverse maternal and neonatal outcomes. Smoking during pregnancy has been associated with fetal growth restriction, adverse pregnancy outcomes, and chronic adult diseases. Existing research has evaluated the risk of smoking on congenital defects. However, no studies have evaluated how periconception smoking affects birth defects.

OBJECTIVE: The purpose of this study was to assess the association of maternal smoking and the timing of periconception exposure with congenital birth defects.

STUDY DESIGN: This study was a population-based retrospective cohort of live births in Ohio from 2006–2015 with the use of data from birth certificates. Rates of cardiovascular, musculoskeletal, gastrointestinal, and neural tube birth defects were compared between a referent group of women who did not smoke and a group of women who smoked (1) during the preconception period of 3 months before conception only and not in the first trimester and (2) in the preconception period plus throughout the first trimester of pregnancy. Multivariate logistic regression was used to quantify the relationship between periconception smoking and the rate of birth defects after adjustment for maternal race, age, pregestational diabetes mellitus, and socioeconomic factors.

RESULTS: Of the 1,436,036 live births in the study period, 75% of mothers did not smoke during the preconception period or during pregnancy. There were 334,156 women (23.3%) who smoked during pregnancy; 6.0% of the population smoked preconception only, and 17.3% of the population smoked both during the preconception period and through the first trimester. Smoking during the preconception period only, even without first trimester exposure, was associated with a 40% increased risk of gastroschisis. Smoking that was limited to preconception only was not associated with any other individual birth defects. However, smoking through the first trimester was associated with a statistically significant increased risk of several defects that included gastroschisis and limb reduction and a composite outcome of any defect, even after adjustment for coexisting factors.

CONCLUSION: Smoking during the period of fetal organogenesis (during the first trimester of pregnancy) is associated with increased risk of some birth defects. In this study, we provide novel data that smoking during the few months before conception, even with cessation in the first trimester, may also pose a risk for fetal malformation such as gastroschisis. These findings highlight the importance of preconception women's public health education efforts and warrant further investigation.

Key words: birth defect, congenital anomaly, pregnancy, smoking

One of the most important modifiable risk factors for poor fetal and maternal outcomes in pregnancy is smoking.[1] Smoking has been associated with fetal growth restriction and other adverse outcomes, such as perinatal death and preterm birth.[2–4] Moreover, fetal growth restriction has been shown through animal and human models to be a factor in many chronic adult diseases, such as obesity, hypertension, and diabetes mellitus.[5] Overall, smoking during pregnancy contributes to neonatal morbidity and death.

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A potential consequence of smoking during or before pregnancy that has not been extensively studied is the effect of smoking on congenital birth defects. Past research has found that smoking during pregnancy could be a factor in a variety of congenital defects that include digit anomalies, cryptorchidism, heart defects, musculoskeletal defects, limb abnormalities, oral clefts, defects of the eyes, and abnormalities of the gastrointestinal system.[6] There is evidence of a dose-response relationship between the number of cigarettes smoked and the existence of some birth defects, such as oral clefts.[7] Furthermore, the association between periconception smoking and smoking during pregnancy and the occurrence of oral clefts and heart defects has been investigated more thoroughly and repeatedly supported.[7–9]

Although some studies have reported the relationship between birth defects and maternal smoking, there have been no population-based United States studies focused on the risk of maternal smoking before conception and overall birth defect risk. Previously published studies that have explored the association between maternal smoking and birth defects in the United States were completed before the 2003 revision in birth certificates.[1,10,11] For this reason, they could not analyze the potential differential effect of smoking before pregnancy vs smoking in the first trimester of pregnancy. The 2003 version of the birth certificate is used in all 50 states and is the version that was used in Ohio during the study period. Maternal cigarette smoking behavior is captured on the birth certificate during the 3 months before pregnancy, and first, second, and third trimester.[12] Smoking behavior is quantified by cigarettes or packs of cigarettes per day.[12] Because detailed maternal smoking data are

AJOG at a Glance

Why was this study conducted?

Smoking is one of the most important modifiable risk factors in pregnancy for adverse perinatal and maternal outcomes, and its effects on congenital anomalies have not been evaluated in the periconception period.

Key findings

Some birth defects, such as gastroschisis, are more likely to occur in women who smoke specifically in the preconception period.

What does this add to what is known?

Smoking during the preconception period has not been studied before. The association between smoking during this period and an increased risk of certain birth defects suggests that encouraging women to stop smoking at the time they find out they are pregnant may not be effective in the prevention of adverse outcomes that are associated with smoking.

captured for all births in the United States in a uniform way through vital statistics, the birth certificate is uniquely suited to estimate the association between birth defects and risk factors that are recorded on birth certificates, such as maternal smoking.[10] Past research has indicated that the magnitude of the effect of smoking on risk of birth defects is similar when data were collected from birth certificates in comparison with other surveillance methods.[10] Therefore, we performed a population-based cohort study using current birth certificate data to explore the relationship between maternal smoking before or during pregnancy and birth defects to provide information that may be beneficial for the counseling of women who are pregnant or considering becoming pregnant.

Materials and Methods

The Ohio Department of Health and Human Subjects Institutional Review Board approved the protocol for this study. The study was exempt from review at the University of Cincinnati. A data set generated from birth certificates of all live births that occurred in Ohio over a 10-year period (2006−2015) was provided for this analysis (n=1,463,506 live births). All Ohio birth records used the newest (2003) version of the national birth certificate beginning in 2006.[12,13]

We performed a population-based, retrospective cohort study to compare trimester-specific maternal self-reported smoking behaviors during pregnancy with congenital birth defect rates. The US birth certificate contains data on maternal tobacco smoking during 4 time periods: "3 months before pregnancy," "first 3 months of pregnancy," "second 3 months of pregnancy," and "third trimester of pregnancy." From these data, study subjects were categorized into 1 of 3 groups, based on their smoking behaviors. The referent group consisted of women who did not smoke in the 3 months leading up to pregnancy or any time in pregnancy. The 2 exposure groups included (1) those who smoked in the 3 months immediately preceding the pregnancy, but not at any time during the pregnancy and (2) those who smoked in the 3 months immediately preceding the pregnancy and through the first trimester. Data from women who smoked only in the second or third trimesters were excluded, as were data from women with missing smoking data (n=19,270; 1.3%). Women who smoked only during the latter part of pregnancy (0.8% of the population) were not included in analyses because they did not fit into the category of periconception smoking exposure nor were they nonsmokers appropriate to categorize in the referent group. Smoking >1 cigarette per day qualified women as being a smoker for the purpose of this study.

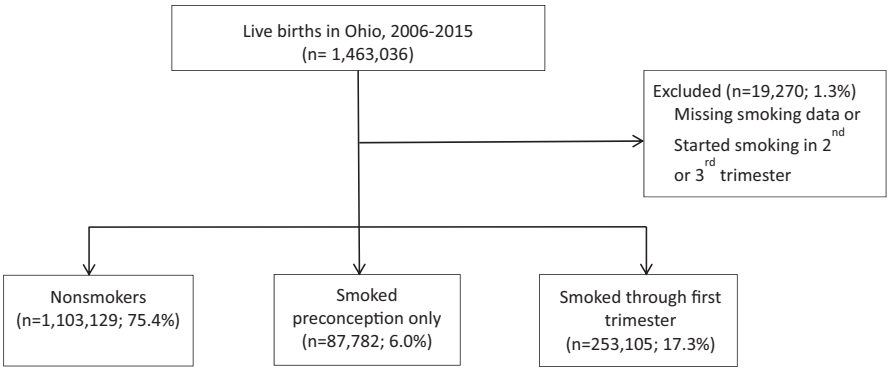
The outcome for this study was the presence of newborn infant congenital anomalies. Data regarding the existence of congenital malformation were obtained from birth certificates. The congenital anomalies that were evaluated in this study included heart defects, limb reduction, diaphragmatic hernia, oral cleft, cleft palate, gastroschisis, omphalocele, hypospadias, anencephaly, and neural tube defects.[12,13] We analyzed these anomalies as individual outcomes and also created a composite variable of any anomaly, which included any of the individual malformations. We chose to examine malformations that had been shown in existing literature to be associated with maternal smoking and were likely to be diagnosed prenatally or at the time of birth. The rates of these congenital anomalies were compared between the referent group of nonsmokers and the 2 exposure groups.

Multivariate logistic regression was used to quantify the relationship between periconception smoking and the presence of congenital birth defects. The results were adjusted for potential confounding variables that included maternal race, age, pregestational diabetes mellitus, and socioeconomic status. Relative risk ratios with 95% confidence intervals were calculated for each birth defect, which compared periconception smoking exposures with nonsmokers. A relative risk of >1.0, with associated 95% confidence interval noninclusive of the null value of 1.0, was defined as a statistically significant increase of overall risk for a birth defect. Additionally, to assess the existence of a dose-dependent relationship between periconceptual smoking and birth defect risk, the Spearman correlation was measured. Statistical analyses were performed with STATA software (release 12; StataCorp, College Station, TX).

Results

There were 1,463,036 live births in the state of Ohio from 2006−2015 that were included in this study. After the exclusion of births with missing maternal

FIGURE
Flow diagram of study population



Categories of maternal smoking status as indicated in the US Certificate of Live Birth.

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smoking data and those recorded as started smoking in the second or third trimester, there were 3 study groups (Figure). Women who did not smoke before or during pregnancy comprised 75.4% of the study population. Six percent of pregnant women smoked in the 3 months immediately preceding pregnancy but not anytime during pregnancy; 17.3% of pregnant women smoked in the 3 months immediately preceding pregnancy and in the first trimester.

Baseline maternal characteristics were compared between the nonsmoking referent group and the 2 periconception smoking exposure groups (Table 1). The maternal characteristics analyzed included demographic factors, socioeconomic factors, prenatal care, and maternal health indicators. Women in the nonsmoking group were generally older, had a higher socioeconomic status, used more prenatal care and initiated care earlier in pregnancy, and had indicators of improved maternal health, such as less obesity. Women who smoked during pregnancy were more likely to be younger and of a lower socioeconomic status. Although many of these differences were statistically significant, the absolute differences were small in most comparisons.

The frequency of congenital anomalies that were stratified by maternal smoking status is presented in Table 2. There was no significant increase in frequency or risk of the composite variable of any congenital anomaly for women who smoked only in the 3 months immediately preceding pregnancy but who did not smoke at any time during the pregnancy, when compared with nonsmokers. However, when we analyzed individual birth defects, gastroschisis occurred slightly more frequently in preconception smokers, even when they did not smoke in the first trimester or any time during pregnancy. The risk for gastroschisis with preconception-only smoking was 40% increased in comparison to the referent group, even after we accounted for the confounding effect of coexisting risk factors (adjusted relative risk [RR], 1.4; 95% confidence interval [CI], 1.1−1.9). Smoking that was limited to the preconception period was not associated with significant risk increases of any other individual malformations.

The frequency of the composite variable "any congenital anomaly" was significantly higher in women who smoked in the first 3 months of pregnancy compared with the nonsmoker referent group. Smoking in the first 3 months of pregnancy was associated with a small increased risk of any congenital birth anomaly (adjusted RR, 1.1; 95% CI, 1.1−1.2). Several individual congenital anomalies were also found to occur with increased frequency in newborn infants of women who smoked in the first 3 months of pregnancy. The largest risk increase was with gastroschisis, with a rate 3-fold higher (0.03% vs 0.09%) and a 90% increase in risk in fetuses born to women who smoked through the first 3 months of pregnancy (adjusted RR, 1.9; 95% CI, 1.6−2.3), compared with nonsmokers. There was an increased frequency of limb reduction, cleft palate, and diaphragmatic hernia associated with first-trimester smoking exposure; however, the adjusted risk was significant only for limb reduction after we accounted for the confounding influence of coexisting risk factors.

Because gastroschisis was found to be the most likely congenital anomaly in women who smoked in the 3 months leading up to pregnancy and through the first 3 months of pregnancy, the existence of a dose-dependent relationship was evaluated. Although there was a significant association between gastroschisis and smoking during the first trimester, with a Spearman's rho of 0.0093, there was no directionality for this relationship. Similarly, there was a significant association between any defect and smoking, but no directionality of this relationship.

Comment

We found that exposure to smoking in the periconception period is associated with a moderate increased risk of certain congenital malformations, even after adjustment for confounding influences of other factors associated with malformation risk. Similar to existing research, we found an increased risk of any birth defect and specific birth anomalies with maternal smoking in the first 3 months of pregnancy.[6-11,14] Embryonic development occurs in weeks 3−10 of gestational age or weeks 1−8 of embryonic age, and exposure to teratogenic agents at this time is thought to increase the risk of birth defects.

Our analysis adds depth to the existing body of literature because we provide novel data about the influence of smoking during the preconception period, even when smoking does not occur in the first trimester. This knowledge is useful when women of reproductive age are being counseled

TABLE 1
Baseline characteristics of study population

Factor	Nonsmokers (n=1,101,880)	Smoked preconception only (n=86,217)	Smoked through first trimester (n=247,939)
Demographic factors			
Maternal ethnicity/race, n (%)			
Non-Hispanic white	803,768 (73.0)	70,126 (81.2)	208,129 (83.9)
Non-Hispanic black	194,212 (17.6)	12,054 (14.0)	32,103 (13.0)
Hispanic	58,053 (5.3)	3,083 (3.6)	5,711 (2.3)
Other	45,847 (4.2)	922 (1.1)	1,926 (0.8)
Maternal age, y[a]	27.9±5.9	25.7±5.3	25.3±5.3
Age group, n (%)			
<18 Y	29,185 (2.7)	1,999 (2.3)	6,311 (2.6)
18–34 Y	919,341 (83.5)	78,352 (90.9)	224,797 (90.7)
≥35 Y	153,152 (13.9)	5,837 (6.8)	16,704 (6.7)
Socioeconomic factors, n (%)			
Less than high school diploma	141,239 (12.9)	11,843 (13.8)	71,205 (28.7)
Married	720,487 (65.3)	36,047 (41.8)	68,892 (27.8)
Women, Infants and Children enrollment	375,746 (34.1)	43,507 (50.5)	164,176 (66.2)
Medicaid	329,223 (29.9)	40,301 (46.7)	167,662 (67.7)
Prenatal care, n (%)			
Limited (≤5 visits)	81,363 (7.4)	5,768 (6.7)	31,342 (12.6)
Early initiation (≤12 weeks gestation)	320,816 (29.1)	24,739 (28.7)	58,902 (23.7)
Late initiation (>20 weeks gestation)	113,171 (12.7)	8,390 (11.9)	37,914 (15.3)
Maternal health indicators, n (%)			
Previous cesarean delivery	335,383 (30.5)	27,496 (32.0)	76,485 (30.9)
Obesity (pregnancy body mass index, ≥30 kg/m^2)	246,616 (23.5)	20,733 (24.8)	58,059 (24.4)
Pregestational hypertension	23,345 (2.1)	1,738 (2.0)	4,966 (2.0)
Pregestational diabetes mellitus	9,097 (0.8)	678 (0.8)	2,400 (1.0)
Gestational hypertension	60,057 (5.4)	5,071 (6.6)	10,249 (4.3)
Gestational diabetes mellitus	66,104 (6.1)	5,317 (6.2)	13,207 (5.3)

All comparisons, except pregestational diabetes mellitus (P=.24), are statistically significant at P≤.001 for the chi square statistic corresponding to the 3-smoking group comparison for each maternal characteristic in this table.

[a] Data are given as mean±standard deviation.

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because some women may presume that, if they quit smoking as soon as they find out they are pregnant, early cessation may mitigate pregnancy risks. However, our study findings suggest that maternal cigarette smoking, even when limited to the months leading up to pregnancy, influences birth defect risk because it demonstrates that smoking even before conception can be detrimental to a developing fetus. We present novel data because we evaluated birth defect risk with smoking before conception occurs.

The pathophysiologic evidence of these outcomes currently is speculative. Prenatal tobacco exposure is known to have detrimental effects to offspring.[15] Tobacco and smoking are associated with a number of dangerous and carcinogenic chemicals. Nicotine and carbon monoxide are often of increased interest because of their effect on blood flow and blood vessel contractility. Elements of cigarette smoke have been associated with vascular diseases because these elements can decrease angiogenesis, increase tissue destruction, and lead to thrombosis.[16,17] There is not a single chemical or component in cigarettes that has been linked directly to vascular disruption.

TABLE 2
Effect of periconception smoking on risk of congenital birth defect

Categories of defects	Nonsmokers (n=110,2890; 75.4%), n (%)	Smoked preconception only (n=86,217; 5.9%), n (%)	Relative risk (95% confidence interval)	Adjusted relative risk (95% confidence interval)[a]	Smoked through first trimester (n=247,939; 16.9%), n (%)	Relative risk (95% confidence interval)	Adjusted relative risk (95% confidence interval)[a]
Cardiovascular: heart	737 (0.07)	59 (0.07)	1.0 (0.8–1.3)	1.0 (0.7–1.3)	176 (0.07)	1.1 (0.9–1.3)	1.0 (0.8–1.2)
Musculoskeletal							
Limb reduction	194 (0.02)	16 (0.02)	1.0 (0.6–1.8)	1.0 (0.6–1.7)	76 (0.03)	1.8 (1.3–2.3)	1.6 (1.2–2.1)
Diaphragmatic hernia	222 (0.02)	15 (0.02)	0.9 (0.5–1.5)	0.9 (0.5–1.6)	16 (0.03)	1.2 (0.9–1.6)	1.4 (1.0–1.9)
All oral clefts	954 (0.09)	58 (0.07)	0.8 (0.6–1.0)	0.7 (0.5–0.9)	276 (0.11)	1.3 (1.1–1.5)	1.1 (1.0–1.3)
Cleft lip with or without cleft palate	663 (0.06)	39 (0.05)	0.8 (0.5–1.0)	0.7 (0.5–0.9)	190 (0.08)	1.3 (1.0–1.5)	1.1 (0.9–1.3)
Cleft palate	544 (0.05)	34 (0.04)	0.8 (0.6–1.1)	0.8 (0.6–1.1)	163 (0.07)	1.3 (1.1–1.6)	1.2 (1.0–1.4)
Gastrointestinal							
Gastroschisis	375 (0.03)	54 (0.06)	1.8 (1.4–2.5)	1.4 (1.1–1.9)	218 (0.09)	2.6 (2.2–3.1)	1.9 (1.6–2.3)
Omphalocele	159 (0.01)	13 (0.02)	1.0 (0.6–1.8)	1.1 (0.6–1.9)	47 (0.02)	1.3 (1.0–1.8)	1.2 (0.9–1.8)
Gastroschisis or omphalocele	532 (0.05)	67 (0.08)	1.6 (1.3–2.0)	1.4 (1.1–1.8)	262 (0.11)	2.2 (1.9–2.6)	1.7 (1.5–2.0)
Genitourinary: hypospadias	819 (0.07)	73 (0.08)	1.1 (0.9–1.5)	1.1 (0.8–1.4)	191 (0.08)	1.0 (0.9–1.2)	0.9 (0.8–1.1)
Central nervous system							
Anencephaly	322 (0.03)	25 (0.03)	1.0 (0.7–1.5)	0.9 (0.6–1.4)	79 (0.03)	1.1 (0.9–1.4)	0.9 (0.7–1.2)
Neural tube defects	312 (0.03)	25 (0.03)	1.0 (0.7–1.5)	1.0 (0.7–1.5)	76 (0.03)	1.1 (0.8–1.4)	1.0 (0.8–1.4)
Any defect	3984 (0.37)	328 (0.39)	1.0 (0.9–1.1)	1.0 (0.9–1.1)	1151 (0.48)	1.3 (1.2–1.4)	1.1 (1.1–1.2)

[a] Adjusted for maternal age, race, pregestational diabetes mellitus, and Medicaid.

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In this study, we found that gastroschisis is the congenital malformation most strongly associated with both preconception smoking and smoking in the first 3 months of pregnancy. The original hypothesis for the development of gastroschisis was vascular disruption of the omphalomesenteric artery that leads to herniation of the abdominal content most commonly ventrally and to the right of the umbilicus.[18,19] Smoking during pregnancy has been associated with vascular disruption and endothelial dysfunction in both maternal body and fetus, which may contribute to gastroschisis.[20-22] Research that suggests a relationship between periconceptual use of vasoconstricting drugs such as cocaine and gastroschisis further strengthens this association.[23] Additionally, associations between gastroschisis, previous miscarriages and increase in sex hormones during pregnancy again suggest a vascular, thrombotic cause to this congenital birth anomaly.[24]

Literature on the type of congenital malformations that are associated with smoking is variable. This is understandable, considering that the pathophysiologic basis of these defects has not been established completely. Multiple systematic reviews have found an association between maternal smoking and congenital heart defects.[6,25,26] However, this association was not found in the present study. This could be related to the underrepresentation of heart defects that are identifiable at the time of birth, because many heart defects may be diagnosed later after the birth certificate is generated. Congenital heart defects are thought to be more likely in fetuses of women who smoke because toxins from cigarette smoke exposure could cause alterations in blood pressure and fetal hypoxia that could predispose to these conditions.[25] Gastroschisis, limb defects, and cleft lip and palate previously have been found in literature to be associated with smoking during pregnancy.[6,7,25,27] Limb defects are associated with vascular disruption, and cleft lip and palate are midline defects.[27,28] Smoking has not been associated with diaphragmatic hernia in previous literature, and only a nonsignificant trend towards an increased frequency was found in this

study when smoking through the first trimester was included. Omphalocele, a birth defect secondary to incomplete closure of the umbilical ring, has not been associated with smoking and is not correlated in the current study. Smoking has been found to be protective against hypospadias in past studies and, in the current evaluation, was not associated significantly with cigarette use.[6] Evaluation of the relationship between neural tube defects, which includes anencephaly, and maternal smoking during pregnancy is inconclusive; in this evaluation, no relationship was found.[29]

Novel to this study is the evaluation of birth defect risk when mothers smoke in the preconception period, the months leading up to pregnancy. To our knowledge, this time frame has not been studied previously independent from the first trimester of pregnancy. The increased risk associated with gastroschisis when smoking is limited to only the preconception period and suggests that smoking may have lasting effects on maternal reproductive health that could influence fetal development even if smoking does not occur during the period of organogenesis. This finding supports further research and public health efforts to eliminate smoking in women of childbearing age.

Birth certificate data have been used in previous studies for the evaluation of the association between smoking and birth defect risk.[10] Although birth certificates may underrepresent birth defects that are not easily identifiable at the time of birth, such as congenital heart defects, most of the anomalies in this study are easy to characterize before the birth certificate is generated. The use of vital records for birth defect outcome studies presents the advantage of a large population for analysis, considering that the population incidence of congenital anomalies is overall low. Likewise, birth certificate data have been used to evaluate maternal smoking in the past.[1,2,4,12,13] Self-reported maternal smoking may be underestimated on the US certificate of live birth. However, kappa statistics that analyze the difference between reporting rates of maternal smoking on birth certificates and anonymous Pregnancy Risk Assessment Monitoring System surveys have shown "good" to "almost perfect" agreement between the 2.[30,31] Maternal smoking data from the birth certificate have been reported as a valid measure to evaluate reproductive smoking behavior, especially when timing of smoking exposure is significant.[31,32] Assuming that the frequency of smoking during pregnancy is slightly underreported in birth certificate data, this misclassification could underestimate the influence of periconception smoking exposure on birth defect risk because some smokers may have been classified in the referent "unexposed" group. Further, women who underreport smoking are more likely to have characteristics (such as being college educated, married, employed full-time, and planning to breast feed) that are associated with a lower risk for pregnancy complications.[33] As an additional limitation, birth certificates do not include a thorough list of all medical comorbid conditions of the mother nor all potentially teratogenic exposures that may have occurred during gestation. Therefore, we could not adjust for concomitant alcohol use, drug use, and second-hand smoke exposure during pregnancy in our analyses because these data were not available in our data source.

Previous methods for studying smoking and associated congenital birth defect risk have been varied. No existing studies have used birth certificate data from the United States to evaluate the risk of a variety of birth defects that may have a relationship with smoking preconception and first-trimester smoking. Many studies investigated birth defects individually, rather than a composite of any congenital anomaly as was done in this study.[7-9,25,27-29,34] Data on maternal smoking prevalence are collected from variable resources, which include birth certificate data, the Centers for Disease Control and Prevention's pregnancy risk assessment monitoring system and the National Birth Defects Prevention Study.[6,8,10,11,28,35,36] This variability in data collection make generalizability challenging. By using birth certificate data and analyzing a sample of congenital birth anomalies, we provide an analytic approach to overcome some of the variability of findings on this topic.

There are a number of inherent limitations to this type of study that is aimed at the evaluation of the risk of smoking on birth defect risk. Birth certificate records have a lower sensitivity for the identification of birth defects compared with review of medical records, because not all birth defects are readily identifiable within the first few days of birth when the birth certificate is generated. Therefore, some congenital anomalies that are not yet identified may be coded as no anomaly in the birth certificate, potentially biasing the results of our study and those of many studies that are similar in design toward the null. However, past research has indicated that the magnitude of effect of smoking on the risk of birth defects is similar when data were collected from birth certificates in comparison with other surveillance methods.[10] Furthermore, some congenital anomalies are recorded as a category within an organ system rather than the specific defect (ie, heart defect rather than Tetralogy of Fallot). Finally, some congenital anomalies may be recorded inappropriately, which leads to some misclassification of referent and case status. An additional inherent limitation to cohort studies is that they can demonstrate only associations but cannot infer causation.

Future investigations should address 2 aspects of smoking and congenital anomalies. First, investigation into the pathophysiologic cause of smoking-related congenital anomalies will bring clarity about how smoking and congenital anomalies are related. This is especially important in regards to gastroschisis, which is uniquely associated with smoking before conception occurs. Because we found that even preconception smoking may be detrimental to a fetus, future public health studies should evaluate how to reduce preconception smoking most effectively and better understand how nicotine replacement therapy, a common therapy to reduce smoking, affects the developing fetus. ■

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