Maternal Smoking and the Risk of Congenital Birth Defects: A Cohort Study

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Background: **The literature linking gestational smoking to congenital defects has been very inconsistent. The purpose of this study was to reinvestigate the relation between gestational smoking and congenital malformations.**

Methods: **This study was a retrospective cohort (N = 18,016) of live births in the TriHealth Hospital system from 1 January 1998 to 31 December 1999. The cohort included 1,943 mothers who were smokers. Congenital defects were grouped into 22 different categories. Multifactorial logistic regression was used to find any association between exposure and the possible outcomes.**

Results: **Mothers who smoked were significantly younger and had babies of lower birth weight and shorter gestational age ($P < .05$). Of the 22 categories of congenital defects, only cardiovascular system abnormalities showed a significant difference ($P < .01$) between the two groups. The remaining 21 categories of congenital defects showed no statistical difference.**

Conclusion: **Women who smoke during pregnancy have infants that are significantly smaller and of shorter gestational age compared with mothers who do not smoke. Based on these data and findings from most of the available literature, however, gestational smoking is unlikely to cause a large increase in congenital birth defects. (J Am Board Fam Pract 2001;14:330–4.)**

Gestational smoking has been associated with low-birth-weight infants and increased infant mortality.[1] Studies investigating any relation between congenital anomalies and maternal smoking, however, have been inconsistent in their findings.

The most studied congenital defect in association with maternal smoking has been cleft lip and cleft palate. Khoury et al[2] found that cigarette smoking during pregnancy was associated with cleft defects, with odds ratios of 2.56 and 2.39 for cleft lip and cleft palate, respectively. Their case-control study matched 107 cases of cleft palate and 238 cases of cleft lip and palate obtained from the 1968–1980 records of the Metropolitan Atlanta Congenital Defects Program to 2,809 controls. Kallen[3] confirmed this association with a more recent, larger study involving infants with cleft lip and palate or cleft palate between 1983 to 1992 in Sweden. Kallen's study included data collected for 1,834 infants born with cleft defects among 1,002,742 births occurring during that period and found a significant odds ratio of 1.16 for cleft lip and palate or cleft palate. In contrast, however, Lieff et al,[4] in a case-control study involving 3,774 mothers interviewed from 1976 to 1992, found no association with maternal smoking for any oral cleft group. Malloy et al,[5] while performing a retrospective cohort using the Missouri Birth Defects Registry data from 1980 to 1983 with 288,067 singleton births of which 10,223 had congenital malformations, disputed the association of cleft lip or palate with maternal smoking. They reported in their analysis that there was no link between maternal smoking during pregnancy and congenital malformations.

Other studies focusing on other specific congenital defects also are varied. Some studies do quote a positive relation of maternal smoking to congenital defects. In a case-control study Li et al[6] reviewed 187 singleton infants born from 1990 to 1991 that had a confirmed urinary tract anomaly and compared them with control infants. They found a twofold increased risk of congenital urinary tract anomalies with maternal smoking, and found the risk to be greater with lighter smokers than heavy smokers. Evans et al,[7] in reviewing 67,609 single-

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ton births, noted a small increase in neural tube defects associated with maternal smoking. In 1986 Shiono et al[8] reviewed and performed a comparative analysis of two large prospective studies – The Kaiser-Permanente Birth Defects Study (33,434 live births) and the Collaborative Perinatal Project (CPP) (53,512 live births). In the Kaiser-Permanete Study, there was a noted significant positive association of maternal smoking and infants with ventral hernias, hemangiomas, omphaloceles, and other "major gut abnormalities." When these malformations were analyzed and compared with the CPP data, only hemangiomas were significant in both studies. From this analysis Shiono's group concluded that these associations were likely due to chance and that smoking is "unlikely to be responsible to a large increase in malformations at birth."

Because the evidence on this clinical question has been very inconsistent, this subject requires further investigation. The purpose of this study was to investigate the relation between smoking during pregnancy and congenital malformations in a large private hospital population.

Methods

Study Design and Population

This gestational cohort study had a study population of all mothers who gave birth to a live infant at the TriHealth hospitals in Cincinnati during a specified 2-year period. The TriHealth hospital system consists of three private hospitals all in the greater Cincinnati area. Inclusion criteria for entering the cohort included admission to a TriHealth hospital between 1 January 1998 and 31 December 1999, delivery of a live infant, and having available maternal demographic data and infant congenital defects data. Maternal exclusion criteria included a history of drug abuse (marijuana, cocaine, barbiturates, amphetamines, opiates, or mixed) or use of these drugs during pregnancy, a history of or occurrence of epilepsy during pregnancy, a diagnosis of psychiatric disorders (depression, bipolar disorder, schizophrenia, psychosis), a history of alcohol abuse or use during pregnancy, and a history of diethylstilbestrol exposure or rubella. Individuals exited the cohort when both the mother and the infant were released from the hospital.

Table 1. Maternal Smoking and Congenital Birth Defects: Groupings of the Congenital Birth Defects.

1.	Congenital anomalies of skin
2.	Congenital anomalies of the kidney, urinary tract, and bladder
3.	Congenital anomalies of the cardiovascular system
4.	Congenital anomalies of the skeletal system
5.	Congenital anomalies of the tongue
6.	Congenital anomalies of the hematologic system
7.	Polydactyly of fingers and toes
8.	Congenital anomalies of the ear
9.	Congenital anomalies of the head, ear, nose, mouth, and throat
10.	Hernias (umbilical and inguinal)
11.	Periauricular sinus or fistula
12.	Congenital anomalies of the nervous system
13.	Congenital anomalies of the breast
14.	Congenital anomalies of the hand
15.	Congenital anomalies of the pulmonary system
16.	Congenital anomalies of the foot
17.	Congenital anomalies of the gastrointestinal system
18.	Congenital anomalies of the muscular system and diaphragm
19.	Congenital anomalies of the gallbladder
20.	Cleft palate and lip
21.	Congenital anomalies of the genitalia
22.	Spina bifida

Data Collection

Data were collected concurrently during admission on maternal smoking status, 1-minute Apgar, 5-minute Apgar, gestational age, and birth weight, as well as the three potential confounding variables of maternal age, race, and diabetes. More specifically, for smoking status women were asked whether they smoked during their pregnancy, and if they did, they were asked to quantify their use. The data were collected at hospital admission, before the infant was born. The personnel collecting the data had no knowledge of any infant congenital defects. All data on the congenital birth defects were collected at the time of the infant's discharge. The congenital defects were grouped into 22 potential outcomes (Table 1).

Analysis

Analysis was performed using STATA (STATA Corporation, College Station, Texas), statistical software. Uncontrolled univariate analysis using chi-square and *t* test was performed comparing maternal smoking status with the other background variables (1-minute Apgar, 5-minute Apgar, gesta-

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Table 2. Maternal Smoking and Congenital Birth Defects Cohort.

Characteristic	Smokers (n = 1,943)	Nonsmokers (n = 16,073)	*P* Value
Age, mean years	25.4	28.4	<.05
Diabetes, No. (%)	128 (6.6)	940 (5.8)	NS
Birth weight, g	3,093	3,351	<.05
Gestational age, weeks	38.6	38.9	<.05
Apgar, 1 minute	8.0	8.0	NS
Apgar, 5 minute	8.8	8.8	NS
Race, No. (%)			NS
White	1,478 (76)	1,580 (73)	
African-American	3,26 (17)	2,394 (15)	
Oriental	2 (0)	238 (1)	
Other	137 (7)	1,861 (11)	

NS—not significant.

tional age, birth weight), as well as the three potential confounding variables (age, race, and diabetes). Then, using multifactorial logistic regression, smoking status and each of the 22 congenital defect categories were analyzed while controlling for the three potential confounders. Given an α of 0.05, a β of 0.10, a smoking population of 1,943, and a nonsmoking population of 16,073, this study has 93% power to find a significant difference between the two populations on any category of congenital defects if they differ in prevalence by 1%.

Results

A total of 18,076 patients were entered into the study, with 1,943 reporting they were smokers and 16,073 saying they were nonsmokers. Baseline characteristics of both groups are displayed in Table 2. Smokers were significantly younger ($P < .05$), and their babies were of lower birth weight ($P < .05$) and shorter gestational age ($P < .05$). There was no significant difference between the two groups based on race, diabetes, 1-minute Apgar scores, and 5-minute Apgar scores.

Using uncontrolled univariate analysis, smokers and nonsmokers were compared in relation to the 22 groupings of congenital defects. The significance of each analysis was set at $P = .01$ based on the Bonferroni adjustment[9] for multiple comparisons and an overall $P = .05$. Only the congenital abnormalities of the cardiovascular system was significantly higher in the smoking population ($P < .01$). The remaining 21 congenital defects showed no significant difference in outcomes between the two groups.

We used multifactorial logistic regression to control for the three potential confounding variables (age, race, diabetes). Results for the logistic model (Table 3) were identical to the univariate analysis, with only the cardiovascular system abnormalities being significant ($P < .01$).

Discussion

For several decades now, the ill effects of cigarette smoking have been a focus of considerable research and concern. It is well known that mothers who smoke have infants that are smaller and of shorter gestational age. The data linking smoking to congenital defects, however, have been very inconsistent. This study was conducted with the hope that a large study population might help to understand better any relation that might exist.

Several limitations of this study need to be considered before contemplating the results. Most important is the exposure variable of smoking. A continuous distribution was not used for two main reasons. First, women smoking more than one pack per day were extremely rare. Second, being self-reported data, the reported quantity likely underrepresents the true quantity smoked. We classified women dichotomously as to gestational smoking. Another study limitation resulting from underreporting of exposure history is that there could be women who smoked who reported no exposure and were classified incorrectly. Also, smoking during the first trimester was not differentiated from smoking during the rest of the pregnancy. If smoking causes any congenital defects, the first-trimester exposure data would be most important. Additionally, any exposure history from cigars, pipes, chewing tobacco, or even second-hand smoke was not ascertained. Finally, although the exposure data were collected at admission, before delivery, some women could have been aware of a congenital defect found during an ultrasound examination. Had this knowledge influenced their reporting of smoking exposure, another potential source of bias would have resulted. All these limitations decrease the likelihood of finding a significant difference between the two groups.

Compared with other large studies investigating an association between gestational smoking and multiple possible congenital defects, the current

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Table 3. Adjusted Relative Risks and 95% Confidence Intervals for Maternal Smoking and the Risk of Congenital Birth Defects.

Congenital Anomalies	Relative Risk	No. of Smokers	No. of Nonsmokers	95% CI	*P* Value
General					
Skin	0.84	41	388	0.61–1.10	NS
Renal, urinary tract, and bladder	0.93	30	258	0.63–1.37	NS
Cardiovascular system	1.56	43	217	1.12–2.19	<.01
Skeletal system	1.11	19	139	0.68–1.82	NS
Tongue	1.04	10	86	0.53–2.03	NS
Hematologic system	1.39	20	121	0.86–2.25	NS
Ear	1.47	10	53	0.74–2.92	NS
Head, ear, nose, mouth, and throat	0.70	6	69	0.30–1.63	NS
Nervous system	1.30	36	228	0.91–1.86	NS
Breast	1.22	10	64	0.62–2.41	NS
Hand	1.30	4	25	0.44–3.79	NS
Pulmonary system	1.25	7	39	0.55–2.84	NS
Foot	0.56	1	15	0.07–4.30	NS
Gastrointestinal system	0.54	1	17	0.07–4.11	NS
Muscular system and diaphragm	2.22	1	4	0.24–20.50	NS
Gallbladder	1.96	5	23	0.73–5.20	NS
Genitalia	1.82	4	19	0.60–5.49	NS
Specific					
Spina bifida	0.83	1	10	0.10–6.70	NS
Cleft palate and lip	1.23	1	6	0.14–10.70	NS
Hernias (umbilical and inguinal)	2.58	3	11	0.70–9.51	NS
Polydactyly of fingers and toes	1.32	2	12	0.28–6.12	NS
Periauricular sinus or fistula	1.69	1	6	0.19–14.3	NS

Note: Data controlled for maternal age, race, and diabetes.
CI—confidence interval.
NS—not significant.

study produced similar general results. Many studies have found an association of smoking with typically a single defect of a possible 20 to 25 categories. For these previous studies, given a two-sided test of significance, a standard α of 0.05, and 20 possible outcomes, one or two outcomes could be significant based purely on chance. To support this possibility, there has been no congenital defect category that has been consistently found to be significant in even a preponderance of studies. Also, unlike these data, some authors have found in a single classification of defects a significant protective effect of smoking.[8] These results are also likely due to chance alone. In our study, which used multiple comparisons, we used the Bonferroni adjustment (significance at $P < .01$ for each outcome, for an overall significance of $P = .05$) to reduce the possibility of chance playing a significant role.

Consistent with many previous studies, the infants of smoking mothers in this study were significantly smaller and of shorter gestational age. The single category of congenital defects that was statistically significant between the two exposure groups was the cardiovascular system. The offspring of smokers had a 56 percent increase in the frequency of cardiovascular anomalies when compared with those born to nonsmokers. This cardiovascular category included infants with a patent ductus arteriosus, ventricular septal defect, atrial septal defect, congenital stenosis of any valve, tetralogy of Fallot, transposition of the great vessels, coarctation of the aorta, congenital atresia of any valve, or any other congenital anomaly of the heart or blood vessels. Including both the smokers and the nonsmokers, there were 260 defects in this category. Patent ductus arteriosus (n = 153) and ventricular septal defect (n = 48) were most common. There was no analysis performed on any of the individual defects in this large category. It is interesting to mention that Shiono et al, in the

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prospective Kaiser-Permanente Birth Defects Study, found a significant protective effect of smoking and ventricular septal defect.[8]

The powerful aspect of this cohort study is the large study population and the number of smoking mothers. As mentioned above, there was likely underreporting of exposure and misclassification bias; however, the mothers who were counted as smokers were likely classified correctly. The surprising aspect of these data was the small number of defects in several of the categories for the smoking mothers. There were six categories of congenital defects that had only a single occurrence in the smoking mothers, and in seven other categories there were fewer than 8 infants born with these defects to smoking mothers. The low prevalence of defects in these categories resulted in wide confidence intervals. In particular, there was only one cleft lip and palate in the smoking population of this study. This was unexpected given the popular belief of a possible association based on the case-control data by Khoury et al.

Conclusion

Women who smoke during pregnancy have significantly smaller infants and infants with a shorter gestational age compared with mothers who do not smoke. Although the current study found an association between maternal smoking and cardiovascular anomalies, the inconsistent findings in the literature suggest that gestational smoking is unlikely to cause a large increase in congenital birth defects.

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