Maternal Smoking during Pregnancy: No Association with Congenital Malformations in Missouri 1980–83

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Abstract: Using a multisource birth defects registry developed by the Missouri Center for Health Statistics for the years 1980–83, we examined the relation between maternal smoking during pregnancy and the occurrence of congenital malformations. There were 288,067 live singleton births in this data set of which 10,223 had one or more congenital malformations. When adjusted for potential confounders the odds ratio for congenital malformations in the infants of women who smoked during pregnancy was not increased (odds ratio = 0.98, 95% confidence interval = 0.94 – 1.03). We examined the relation between smoking and groups of malformations using the International Classification of Diseases, 9th Revision, as well as analyzing for certain specific malformations within each group and found no increased risk for infants of smokers. (*Am J Public Health* 1989; 79:1243–1246).

Introduction

Maternal cigarette smoking during pregnancy has been positively associated with low birthweight infants[1,2] and increased infant mortality.[3,4] The relation between smoking and the occurrence of congenital malformations is less certain. The biologic rationale for exploring the relation between smoking and congenital malformations is based on the results of experiments exposing animals to various teratogens that occur in cigarette smoke.[5–8] These teratogens include among others nicotine and cadmium which have been associated with cleft palate, anophthalmia, exencephaly, limb defects, and rib fusions.[7,8] Carbon monoxide, a major constituent of cigarette smoke has been associated with minor limb defects, but is considered more of an embryotoxic agent than a teratogen.[5,9] Clinical reports have suggested a higher prevalence of congenital heart disease in the infants of smokers[10] as well as a higher prevalence of oral clefts.[11] Other clinical reports have found no association between maternal smoking during pregnancy and congenital malformations.[12,13]

In order to examine the relation between maternal cigarette smoking and congenital malformations, we used a multisource birth defects file from Missouri. This file gives more complete ascertainment of birth defects than birth certificates alone and also contains information on maternal smoking during pregnancy.

Methods

The Missouri Birth Defects Registry for the years 1980 to 1983 is a linked file of birth certificates, hospital discharge diagnoses, neonatal intensive care unit diagnoses, Crippled Children Service diagnoses, and death certificates for children under two years of age. Linkage to the birth certificate was accomplished by matching last names and date of birth for death certificates, neonatal intensive care unit files, and Crippled Children Service files. Because names were not available on the hospital discharge file, matching was based on hospital of birth, date of birth, mother's zip code, and the child's sex and race. Match rates for the four files to the birth certificate approximated 90 percent.

This analysis was limited to singleton births. The total number of singleton births over the four-year period was 302,971. We excluded all records that were incomplete for the variables in our analysis. We were left with 288,067 records or 95 percent of the total singleton births. Variables used in this analysis and obtained from the birth certificate include race, the mother's martial status, educational attainment, age, and parity. Parity was defined as the number of live births plus abortions (induced and spontaneous) and stillbirths experienced by a woman. Information on the mother's smoking status during pregnancy was ascertained from the birth certificate as reported by the mother in terms of packs of cigarettes smoked per day. The categories recorded were nonsmoker, less than one pack per day, or one or more packs per day.

Malformations from this study were limited to those within the Version Nine - International Classification of Diseases (ICD-9) codes Congenital Malformation Chapter and to the ICD-9 Digestive System Chapter.[14] Malformations were analyzed as groups according to the 12 subchapters of the ICD-9 Congenital Malformation Chapter. These groupings attempt to categorize based on the anatomical relatedness of various specific defects (see Appendix). In addition, we analyzed several specific malformations that had been previously reported to be related to maternal smoking.

Multiple logistic regression was used to assess the effects of maternal smoking on congenital malformations, adjusting for maternal characteristics (age, marital status, educational attainment, and parity).[15] Separate models were fit for all malformations, for each group of malformations, and for each specific malformation. We ran separate models for Blacks and Whites for all malformations, groups of malformations, and specific malformations. The odds ratio for malformations for Black smokers, however, did not appear different from those of Whites.* The results presented thus combine both races with an adjustment for race within each model. Because parity had been observed to have significant interactions with maternal age in previous work done on infant mortality,[3] we fit models with two-way interactions between parity and maternal age. As in previous work, we also add a term to control for high parity (parity 3 or more for mothers under 25 years of age and parity 4 or more for those 25 or over).

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*Data available on request to authors.

Results

There were 10,223 infants (3.5 percent of live births) with one or more congenital malformations ascertained from the multisource file and 13,582 unique malformations (4.7 percent of live births). Only one-fifth of these were identified from the birth certificate portion of the file. The hospital discharge diagnosis file was the largest contributor of unique diagnoses, providing over 65 percent of them. The distribution of the number of malformations per infant was 79 percent with only one malformation, 14 percent with two malformations, and 7 percent with three or more malformations.

The prevalence of smoking and malformations by selected population characteristics is shown in Table 1. Blacks reported having smoked during pregnancy more than Whites, the women aged 18–19 years reported smoking more often than the women in the older aged strata, the least educated mothers reported smoking the most, single mothers smoked more than married mothers, and the high multiparity mothers had a higher prevalence of smoking than lower parity mothers.

The adjusted odds ratios (OR) for all malformations for smokers of less than a pack a day vs nonsmokers was 0.99 (95% confidence interval (CI) = 0.93, 1.04). For smokers of one or more packs per day vs nonsmokers, the OR = 0.98 (95% CI = 0.92, 1.05). Because no dose response relation was observed in this data set between the level of smoking and all malformations, we chose to report models with only two levels of smoking (nonsmokers vs smokers).** For certain specific malformations, however, we did examine for a dose response relation across the three levels of smoking and report these results in the text.

**Results of other models available on request to authors.

TABLE 1—Distribution of Population Characteristics, Prevalence of Smoking and Prevalence of One or More Congenital Malformations among 288,067 Singleton Births to Missouri Residents, 1980–83

Population Characteristics	Percent of Population	Percent of Smokers in Each Group	Percent with Malformations in Each Group
Total Population	100.0	30.3	3.7
Race			
White	85.2	29.4	3.5
Black	14.8	35.5	3.7
Maternal Age (years)			
<18	5.7	36.0	3.8
18–19	10.0	41.9	3.6
20–24	34.6	35.5	3.5
25–29	31.0	24.4	3.5
30–34	14.5	21.8	3.5
≥35	4.2	25.7	4.2
Maternal Education (years)			
<12	32.2	52.2	3.6
12	22.7	30.0	3.5
>12	45.1	15.4	3.5
Marital Status			
Married	81.4	26.5	3.8
Single	18.6	47.0	3.9
Parity			
Primipara	36.9	27.4	4.0
Low multipara	43.1	29.0	3.7
High multipara	20.0	38.6	4.3

No congenital malformations occurred significantly more frequently in the infants of smokers than nonsmokers following adjustment for other maternal risk factors (Table 2). Only for gastrointestinal malformations did maternal smoking suggest a trend toward being a risk factor (OR = 1.11, 95% CI = 0.96, 1.29). Several congenital malformations, however, did appear to occur less frequently in infants of smokers. The odds ratio for malformations of the integument was less than 1.0 for smokers (OR = 0.82, 95% CI = 0.70, 0.97). The odds ratio for eye/ear/nose/throat malformations (OR = 0.84), ventricular septal defects (OR = 0.87), valvular defects (OR = 0.74) and cleft lip/cleft palate (OR = 0.84) suggested a lower prevalence in smokers although the 95% confidence intervals included 1.00.

We analyzed for several specific malformations within major organ systems that had been reported previously as being associated the maternal smoking during pregnancy. For example, the adjusted odds ratio for anencephaly for smokers compared with nonsmokers was 0.77 with a 95 percent CI of 0.44, 1.36. The odds ratio for atrial septal defects was 1.04 (95% CI = 0.70, 1.55).

The large number of odds ratios near 1.00 might suggest the data or methods used are not capable of detecting an effect of smoking. As an example of the validity of our model, we examined the odds ratio for chromosome malformations for various age groups. It is widely accepted that women over 35 years of age are at higher risk for having an infant with a chromosome abnormality. In fact, our data show the adjusted odds ratio for a chromosome malformation for women age 35 years and older was 7.04 (95% CI = 4.82, 10.28). There was no significant age-parity interaction for chromosome malformations ($p > 0.5$).

Discussion

The reported incidence of congenital anomalies varies from a low of 0.8 percent of live births[16] to a high of 7.1 percent.[17] This variation in the reported incidence of malformations makes it extremely difficult to determine the

TABLE 2—Adjusted Odds Ratios[a] for Congenital Malformations for Smokers Among Singleton Births to Missouri Residents by Congenital Malformation, 1980–83

Congenital Malformation	Number of Malformations	Adjusted Odds Ratio	95 Percent CI
All Malformations	10,223	0.98	0.94,1.03
Central Nervous System	489	1.04	0.85,1.26
Anencephaly	67	0.77	0.44,1.36
Eye/Ear/Nose/Throat	533	0.84	0.68,1.02
Heart	1,341	0.92	0.82,1.05
Ventricular septal	447	0.87	0.70,1.09
Atrial septal	123	1.04	0.70,1.55
Valvular	151	0.74	0.50,1.09
Other cardiovascular	756	1.01	0.86,1.19
Respiratory	299	1.01	0.83,1.24
Cleft Lip and/or Palate	451	0.84	0.68,1.05
Gastrointestinal	961	1.11	0.96,1.29
Genitourinary	1,622	0.97	0.86,1.08
Musculoskeletal	3,705	0.99	0.92,1.06
Clubfoot	980	1.02	0.88,1.17
Integument	830	0.82	0.70,0.97
Chromosome	330	0.99	0.76,1.28
Residual	435	0.95	0.77,1.18
Umbilical hernia	80	1.09	0.62,1.65

[a]Odds ratios adjusted for maternal age, race, martial status, educational attainment and parity.

validity of reports of associations between congenital malformations and potential risk factors. Because the Missouri Birth Defect File uses several sources of information to obtain diagnoses of malformations, we feel this file comes close to accurately assessing the number of malformations in a birth cohort. In addition, ascertainment of malformations is more complete because two files, the Crippled Children Services file and the death certificate file, include diagnoses made up to two years after birth. The Missouri Birth Defects Registry's completeness is similar to the Centers for Disease Control Birth Defects Monitoring Program.[18] For many birth defects, the Missouri system appears to be more complete. However, the Missouri system is not as complete as the more comprehensive Metropolitan Atlanta Congenital Defects Program.[18]

In our analysis we did not find a relation between maternal smoking during pregnancy and the occurrence of congenital malformations. These findings merit attention because of the large sample size available for this analysis and the opportunity to adjust for variables that may confound the relation between smoking and malformations. For example, the positive associations with smoking reported by Shiono, *et al*,[19] for ventral hernias (OR = 10.1), omphaloceles (OR = 3.0), and other gut abnormalities (OR = 12.6) are based upon five, five, and six cases, respectively. Shiono's results may well be based on the chance distribution of a larger number of cases among smokers.

Other studies where positive associations have been reported between maternal smoking and congenital malformations may suffer from problems of failure to adjust for potential confounding variables.[20,21] Evans, *et al*,[21] reported an unadjusted association between maternal smoking and anencephaly (relative risk = 1.76 for smokers of more than 20 cigarettes per day). When the relation was examined by socioeconomic status the dose response relation between smoking and anencephaly was not apparent in the lowest socioeconomic strata and was inconsistent in the upper strata. Both socioeconomic status and race have been reported to be associated with congenital malformations as well as smoking.[17,22,23]

Several reports have suggested a lower rate of malformations in infants of smokers.[19,24,25] We did observe one group of malformations (malformations of the integument) for which maternal smoking during pregnancy did seem marginally protective (OR = 0.82, 95% CI = 0.70, 0.97). This observation was also reported by Shiono, *et al.*[19] Hook, *et al*,[25] reported a lower risk of Down Syndrome in infants of smokers. We observed no protective relation between smoking and chromosomal abnormalities (OR = 0.99).

Our analysis of the relation between maternal smoking during pregnancy and the occurrence of congenital malformations does not support a causal role for smoking. The validity of this observation may be questioned on the basis of an under-ascertainment of smoking using birth certificate data attenuating the relation between malformations and smoking. However, the prevalence of smoking in the Missouri data is similar to that reported in other populations.[3] In addition, we have no reason to believe there was differential reporting of smoking between women who had infants with malformations and those who did not have malformed infants (especially since many of the malformations were identified from sources other than the birth certificate). Secondly, the validity of our analyses might be questioned on the grounds of lumping specific malformations into groups of malformations within organ systems. However, the analysis of many more specific malformations with many fewer cases results in lower statistical power to find a relation and greater chances of finding spurious relations. We did analyze for several specific malformations that others had found to be related to maternal smoking and found no relation (e.g., anencephaly, ventricular septal defects, atrial septal defects, valvular defects, clubfoot, and umbilical hernias). It is interesting to note that the lumping of specific malformations did not mask the risk associated with age for certain malformations, e.g., Down Syndrome, within the chromosome malformation group. Within our model for chromosomal anomalies we did confirm the marked increased risk associated with age over 35 years for both multiparous women and primiparous women (OR = 7.04). This observation may lend support to the validity of analyzing the data across groups of malformations.

The lack of relation between smoking during pregnancy and congenital malformations in liveborn infants may be partially a result of a selection bias. Because smokers have twice as many abortions as nonsmokers[26] and 30 percent more fetal deaths,[3] fetuses with malformations among smoking mothers may be underrepresented in a study of live births. Despite the lack of a relation between maternal smoking during pregnancy and the occurrence of malformations in liveborn infants, the established relation between smoking and infant mortality and morbidity[3,4,27] argues against maternal smoking during pregnancy.

APPENDIX

International Classification of Diseases Ninth Revision (ICD-9) Codes Defining Malformation Categories

Cause of Death	ICD-9 Codes
Central Nervous System	7400-7429
Anencephaly	7400
Eye/Ear/Nose/Throat	7430-7449
Heart	7450-7469
Ventricular septal defects	7454
Atrial septal defects	7455
Valvular defects	7460-7467
Other Cardiovascular Defects	7470-7479
Respiratory	7480-7489
Cleft Lip and/or Palate	7490-7499
Gastrointestinal	7500-7519
Genitourinary	7520-7539
Musculoskeletal	7540-7569
Clubfoot	7545-7547
Integument	7570-7579
Chromosome	7580-7589
Residual*	7590-7599
Umbilical Hernia	5521, 5531

* Residual—remaining diagnoses in the ICD-9 Congenital Malformation Chapter (7400-7599).

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Conference on Health and Social Services for Elderly, Disabled Announces Call for Abstracts

The Department of Social Security of Regione Emilia Romagna is organizing an international scientific meeting, to be held in Bologna, Italy from April 17–21, 1990, to address the systems and science related to health and social services for the elderly and the disabled.

The objective of the conference is to focus on the problems of planning, organizing, and managing health and social services for this population, utilizing a multidisciplinary approach to solving the complex problems. Conference participants will be drawn from various groups, including systems analysts and scientists, professional health care providers, and policy-makers so that the final program will emphasize the interactions of the various interests and disciplines.

Interested program participants may submit an abstract (maximum one page, typed) representing an individual presentation, or proposals for an entire session, with subject matter and individual speakers identified. The deadline for submitting abstracts and session proposals is December 15, 1989. Papers accepted by the Scientific Committee will be published in the conference proceedings.

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