Maternal Cigarette Smoking during Pregnancy Increases the Risk of Having a Child with a Congenital Digital Anomaly

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Background: The U.S. Natality database from 2001 and 2002 was used to investigate the relationship between maternal cigarette smoking during pregnancy and the risk of having a child with polydactyly, syndactyly, or adactyly.
Methods: The records of 6,839,854 live births were examined to identify 5171 newborns with isolated polydactyly, syndactyly, or adactyly and 10,342 controls with no congenital anomalies.
Results: Maternal cigarette use during pregnancy was associated with a significantly elevated risk of having a child with a congenital digital anomaly (unadjusted odds ratio, 1.33; 95 percent confidence interval, 1.21 to 1.47; $p < 0.0001$). Univariate analysis indicated that maternal marital status and medical risk factors (anemia, cardiac disease, lung disease, diabetes, hydramnios/oligohydramnios, pregnancy-associated hypertension, incompetent cervix, previous preterm or small-for-gestational-age infant, and rhesus factor sensitization) were potential confounding factors. After adjustment for these variables, the odds ratio remained significant (adjusted odds ratio, 1.31; 95 percent confidence interval, 1.18 to 1.45; $p < 0.0001$). Cigarette consumption per day was divided into four groups: no smoking, 1 to 10 cigarettes per day, 11 to 20 cigarettes per day, and 21 or more cigarettes per day. A statistically significant dose–response relationship was found when comparing each smoking category with the no-smoking reference group: 1.29 (95 percent confidence interval, 1.15 to 1.46), 1.38 (95 percent confidence interval, 1.12 to 1.71), and 1.78 (95 percent confidence interval, 0.97 to 3.26), respectively. Increased cigarette smoking during pregnancy resulted in an elevated risk of having a child with polydactyly, syndactyly, or adactyly.
Conclusions: This is the largest study to date to investigate specifically the association between maternal cigarette smoking and the risk of having a newborn with a congenital digital anomaly. The elevated odds ratio for tobacco use and the significant trend in the dose–response relationship suggests smoking during pregnancy may be an important preventable risk factor for these common congenital differences. (*Plast. Reconstr. Surg.* 117: 301, 2006.)

Congenital differences of the digits are among the most common congenital limb abnormalities. Isolated syndactyly occurs in one per 2000 to 2500 live births,[1–3] and polydactyly has a reported incidence of up to one in every 600 live births.[4–6] Certain demographic differences in the incidence of these anomalies are well known. Syndactyly occurs twice as often in boys and is more common in whites than in blacks,[2,6] whereas polydactyly is 10 times more common in blacks and is only slightly predominant in boys.[6–8] Nevertheless, the majority of isolated congenital digital anomalies occur spontaneously without any family history. This has led researchers to search for environmental etiologic factors.

The association between several teratogenic medications taken during pregnancy and congenital limb anomalies is now well recognized. These include thalidomide,[9–12] warfarin,[13,14] phenytoin,[15–17] and valproic acid.[18,19] Procedures during pregnancy such as chorionic villus sampling also have been linked to terminal transverse limb defects.[20–23] There is growing evidence that prenatal exposures to common

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substances such as cocaine[24] and alcohol[25–27] may also produce congenital digital anomalies. The question of whether cigarette smoking during pregnancy increases the risk of having a child with a limb anomaly is more controversial. Although some studies have noted an increased risk of limb reduction defects,[28–30] others have not.[27,31,32] One surveillance study found a higher rate of smoking during pregnancy among mothers of children with polydactyly compared with those of children with other congenital anomalies.[33] A few epidemiologic studies have demonstrated an association between heavy smoking and polydactyly alone[32] or between any smoking with polydactyly and/or syndactyly.[34] Two studies that examined polydactyly and syndactyly separately, however, did not find an association with cigarette smoking.[35,36] Most of these studies, however, have been limited by small sample sizes and inadequate adjustment for potential confounding factors.

In this study, we used the 2001 and 2002 U.S. Natality database to investigate whether maternal cigarette smoking during pregnancy is a significant risk factor for having a child with polydactyly, syndactyly, or adactyly. A matched case-control design and conditional logistic regression were used to control for potential confounding factors. To our knowledge, this is the largest study to date to explore the relationship between cigarette smoking and congenital digital anomalies.

METHODS

Data were obtained from the U.S. Natality database for 2001 and 2002. This database is available from the National Center for Health Statistics and contains detailed information for all 8,058,907 recorded live births occurring in all 50 states and the District of Columbia during 2001 and 2002. More than 99 percent of births occurring in the United States were registered.[37,38] The database contains parental demographic information, maternal health risk factors, and newborn health characteristics recorded by a physician or nurse at the time of birth.

Maternal tobacco use during pregnancy was reported in all states except California, accounting for 87 percent of all U.S. births. Comparable information on the average number of cigarettes smoked per day was not available for Indiana, New York State (except for New York City), and South Dakota. Tobacco exposure information was available both as a dichotomous response to "tobacco use during pregnancy? yes/no" and as a continuous variable in "average number of cigarettes per day." Because tobacco use was the primary exposure studied, data from California were excluded from the analysis.

Congenital hand and foot anomaly data, including polydactyly, syndactyly, and adactyly, were reported in all states except New Mexico. The operational definitions for these conditions were "Polydactyly is the presence of more than five digits on either hands and/or feet; syndactyly is having fused or webbed fingers and/or toes; adactyly is the absence of fingers and/or toes." These definitions were adapted from a set of definitions compiled by a committee of state and federal health statistics officials for the National Association of Public Health Statistics and Information Systems. Other congenital anomalies included in the U.S. Natality database are anencephalus, spina bifida/meningocele, hydrocephalus, microcephalus, other central nervous system anomalies, heart malformations, other circulatory/respiratory anomalies, rectal atresia/stenosis, tracheoesophageal fistula/esophageal atresia, omphalocele/gastroschisis, other gastrointestinal anomalies, malformed genitalia, renal agenesis, other urogenital anomalies, cleft lip/palate, club foot, diaphragmatic hernia, other musculoskeletal/integumental anomalies, Down syndrome, and other chromosomal anomalies.

Cases consisted of all newborns with polydactyly, syndactyly, or adactyly but without any of the other listed congenital anomalies. A total of 5171 cases with nonsyndromic digit anomalies were identified. Two controls with no congenital anomalies were matched to each case (10,342 controls). Matching variables were mother's and father's race, child's sex, county of birth, and month of birth. When more than two controls were available for a case, the controls were randomly selected. When a control could not be matched to a case based on the exact matching criteria, the month of birth criterion was allowed to vary and controls were randomly selected from matched newborns born during the nearest months. Study subjects without smoking history were excluded. The study sample was obtained from a population of 6,839,854 live births in the United States in 2001 and 2002 from states that had smoking data available.

Analyses were conducted with Stata statistical software, version 8.2 (Stata Corp., College Station, Texas). Accounting for the matched data, Cochran-Mantel-Haenszel methods were used to test for statistically significant differences between cases and controls for demographic and clinical categorical variables of the parents and newborns.[39] These variables included mother's level of education (≤12 years versus >12 years), mother's marital status (married versus unmarried), mother's and father's Hispanic ethnicity (Hispanic versus non-Hispanic), mother's and father's age (<15 years, 15 to 24 years, 25 to 34 years, or ≥35 years), mother's number of previous pregnancies (none, one, two, or three or more pregnancies), lack of prenatal care (yes/no), month of pregnancy when prenatal care began, newborn gestational age (<37 weeks, 37 to 41 weeks, or ≥42 weeks), newborn birth weight (<2500 g, 2500 to 3999 g, or ≥4000 g), maternal alcohol use during pregnancy (yes/no), and maternal tobacco use during pregnancy (yes/no). Maternal medical risk factors included anemia, cardiac disease, acute or chronic lung disease, diabetes mellitus, genital herpes, hydramnios/oligohydramnios, hemoglobinopathy, chronic hypertension, pregnancy-associated hypertension, eclampsia, incompetent cervix, previous newborn weighing more than 4000 g, previous preterm or small-for-gestational-age infant, renal disease, rhesus factor sensitization, and uterine bleeding.

Crude odds ratios were calculated for maternal tobacco use during pregnancy and the risk of having a newborn with polydactyly, syndactyly, or adactyly using univariate conditional logistic regression models.[40] Cigarette use was stratified into four groups: no smoking during pregnancy, 1 to 10 cigarettes per day, 11 to 20 cigarettes per day, and 21 or more cigarettes smoked per day. The smoking groups were compared with the nonsmoking group to test for a dose–response relationship using a nonparametric test for trend.[41] Demographic and clinical variables with statistically significant differences between cases and controls were considered to be potential confounding factors. Multivariate conditional logistic regression modeling was used to adjust for potential confounding variables. Odds ratios and 95 percent confidence intervals were estimated from the coefficients of the conditional logistic regression models. Statistical significance was set at $p < 0.05$.

RESULTS

The U.S. Natality database for 2001 and 2002 contained information on 6522 newborns with polydactyly, syndactyly, or adactyly. A total of 1121 newborns were excluded because they had other associated congenital anomalies (Table 1). An additional 230 newborns were excluded because of the lack of information on maternal tobacco use. Thus, 5171 newborns with congenital digital anomalies were selected for the analysis.

Table 1. Anomalies Associated with Polydactyly, Syndactyly, or Adactyly in 1121 Newborns in the United States, 2001 to 2002

Condition	No.
Hydrocephalus	9
Spina bifida	16
Anencephaly	36
Microcephaly	35
Other central nervous system anomalies	43
Heart malformation	134
Other circulatory/respiratory anomalies	86
Rectal atresia/stenosis	24
Tracheoesophageal fistula/esophageal atresia	19
Omphalocele/gastroschisis	39
Other gastrointestinal anomalies	29
Malformed genitalia	118
Renal agenesis	25
Other urogenital anomalies	69
Club foot	180
Diaphragmatic hernia	116
Other musculoskeletal/integumental anomalies	13
Down syndrome	345
Other chromosomal anomalies	41
Other congenital anomalies	122

Newborn and maternal demographic characteristics are presented in Table 2. The proportions of black and male newborns in the cases and controls selected for this study were higher than in the general population as a whole. Black newborns represented 14.9 percent and male gender represented 51.1 percent of all live births in the United States in 2001 and 2002.[37,38] Within the study population, a slightly higher proportion of mothers of children with digital anomalies were unmarried compared with mothers of healthy children. There was no significant difference for any of the other paternal, maternal, or newborn demographic variables.

Maternal demographic and clinical variables that had statistically significant differences between case and control groups are listed in Table 3. In addition to unmarried marital status, mothers of children with digital anomalies were more likely to suffer from a number of medical conditions, including anemia, cardiac disease, lung disease, diabetes, hydramnios or oligohydramnios, pregnancy-associated hypertension, incompetent cervix, previous delivery of a preterm or small infant, and rhesus factor sensitization. There was no significant difference between cases and controls with regard to lack of prenatal care, time point when prenatal care began, maternal alcohol use during pregnancy, or any of the other medical risks not listed in Table 3. All of the significantly different maternal variables listed in Table 3 were considered potential confounders and were included in the multivariate analysis.

Table 2. Demographic Characteristics of Congenital Digital Anomaly Cases and Controls in the United States, 2001 to 2002*

	Cases (n = 5171)		Controls (n = 10,342)		
	No.	%	No.	%	p
Newborn gender†					1.00
Male	3091	59.78	6182	59.78	
Female	2080	40.22	4160	40.22	
Newborn gestational age					0.91
<37 weeks	695	13.46	1307	12.67	
37–41 weeks	4084	79.09	8255	80.04	
≥42 weeks	385	7.46	751	7.28	
Newborn birth weight					0.52
<2500 g	450	8.70	859	8.31	
2500–3999 g	4286	82.89	8652	83.73	
≥4000 g	435	8.41	822	7.95	
Mother's age					0.90
<15 years	19	0.37	42	0.41	
15–24 years	2293	44.34	4542	43.92	
25–34 years	2278	44.05	4618	44.65	
≥35 years	581	11.24	1140	11.02	
Mother's race†					1.00
White	2779	53.74	5558	53.74	
Black	2231	43.14	4462	43.14	
Native American	42	0.81	84	0.81	
Asian	119	2.30	238	2.30	
Mother's marital status					0.005
Married	2640	51.05	5469	52.88	
Unmarried	2531	48.95	4873	47.12	
Mother's education					0.37
≤12 years	3131	58.92	6191	58.30	
>12 years	2183	1.08	4428	41.70	

*Numbers do not always match totals because of missing responses.
†Matching variables.

Maternal tobacco use during pregnancy for cases and controls is shown in Table 4. The unadjusted odds ratio for any use of cigarette smoking compared with no smoking during pregnancy was 1.33 (95 percent CI, 1.21 to 1.47). Table 5 shows the number of cases and controls stratified by maternal smoking level (none, 1 to 10, 11 to 20, and 21 or more cigarettes per day). Compared with the reference (nonsmoking) group, the relative odds of having an infant with a digit anomaly increased from 1.29 (95 percent CI, 1.15 to 1.46) for 1 to 10 cigarettes smoked per day to 1.38 (95 percent CI, 1.12 to 1.71) for 11 to 20 cigarettes per day to 1.78 (95 percent CI, 0.97 to 3.26) for 21 or more cigarettes per day during pregnancy.

Multivariate conditional logistic regression analysis indicated the risk of having a child with a congenital digital anomaly in mothers who smoked during pregnancy compared with those who did not remained significantly higher (adjusted odds ratio, 1.31; 95 percent confidence interval, 1.18 to 1.45), even after adjusting for the variables in Table 3. The attributable risk percentage in the exposed was 23.7 percent, and the population-attributable fraction was 3.5 percent. In the stratified multivariate analysis, adjustment for the potential confounding factors also did not change the odds ratios significantly. The relative odds of having a child with a digit anomaly increased from 1.27 (95 percent confidence interval, 1.12 to 1.44) for 1 to 10 cigarettes per day, to 1.38 (95 percent confidence interval, 1.12 to 1.71) for 11 to 20 cigarettes per day, to 1.57 (95 percent confidence interval, 0.84 to 2.93) for 21 or more cigarettes per day.

DISCUSSION

This study found that cigarette smoking during pregnancy was significantly associated with an increased risk of having a newborn with polydactyly, syndactyly, or adactyly. The association remained significant even after adjusting for potential confounding variables. This finding is consistent with the results of a study by Honein et al.[34] that attempted to assess the validity of U.S. birth certificate data for estimating the association between maternal smoking and congenital anomalies. They reported an increased prevalence ratio of 1.33 (95 percent confidence interval, 1.23 to 1.43) for polydactyly, syndactyly, or adactyly but found no significant dose–response relationship.

Table 3. Distribution of Significant Maternal Demographic and Medical Risk Factors between Congenital Digital Anomaly Cases and Controls in the United States, 2001 to 2002*

	Cases (n = 5171)		Controls (n = 10,342)				
	No.	%	No.	%	OR	95% CI	p
Mother's marital status							
Married	2640	51.05	5469	52.88	1.00	Reference	
Unmarried	2531	48.95	4873	47.12	1.13	1.04–1.23	0.005
Maternal anemia							
No	4873	94.73	9916	96.18	1.00	Reference	
Yes	271	5.27	394	3.82	1.41	1.20–1.65	< 0.0001
Maternal cardiac disease							
No	5096	99.07	10,246	99.38	1.00	Reference	
Yes	48	0.93	64	0.62	1.52	1.04–2.23	0.031
Maternal lung disease							
No	4996	97.12	10,097	97.93	1.00	Reference	
Yes	148	2.88	213	2.07	1.42	1.14–1.76	0.001
Maternal diabetes							
No	4932	95.88	9960	96.61	1.00	Reference	
Yes	212	4.12	350	3.39	1.23	1.03–1.46	0.021
Hydramnios/oligohydramnios							
No	5018	97.55	10,134	98.29	1.00	Reference	
Yes	126	2.45	176	1.71	1.44	1.14–1.81	0.002
Pregnancy-associated hypertension							
No	4876	94.79	9860	95.64	1.00	Reference	
Yes	268	5.21	450	4.36	1.21	1.03–1.41	0.018
Incompetent cervix							
No	5113	99.40	10,273	99.64	1.00	Reference	
Yes	31	0.60	37	0.36	1.69	1.04–2.75	0.031
Previous preterm or small-for-gestational-age infant							
No	5003	97.26	10,170	98.64	1.00	Reference	
Yes	141	2.74	140	1.36	2.04	1.61–2.59	< 0.0001
Maternal Rh sensitization							
No	5045	99.00	10,149	99.32	1.00	Reference	
Yes	51	1.00	70	0.68	1.47	1.02–2.12	0.038

OR, odds ratio; CI, confidence interval.
*Numbers do not always match totals because of missing responses.

These results are not corroborated by other studies. Kelsey et al.[32] analyzed the risk of polydactyly and syndactyly by the amount of smoking and found the relative risk to be 0.6 and 1.6 in mothers who smoked 1 to 20 cigarettes per day and more than 20 cigarettes per day, respectively, when compared with nonsmoking mothers. These findings were based on a total of 50 isolated and syndromic cases identified primarily from Connecticut general hospitals, and no p values or confidence intervals were given. Shiono et al.[35] found no association in a large health maintenance organization study population for both polydactyly (odds ratio, 1.0; 95 percent confidence interval, 0.6 to 1.6) and syndactyly (odds ratio, 0.7; 95 percent confidence interval, 0.3 to 1.5). In a birth certificate–based study in Washington State, Van den Eeden et al.[36] found no association with maternal smoking for polydactyly (relative risk, 0.9; 95 percent confidence interval, 0.6 to 1.5), syndactyly (relative risk, 1.0; 95 percent confidence interval, 0.6 to 1.7), and adactyly (relative risk, 0.9; 95 percent confidence interval, 0.3 to 2.9). These two studies also included both isolated and syndromic cases, and in all instances results were based on less than 100 cases per group. The pur-

Table 4. Maternal Tobacco Use During Pregnancy in Congenital Digital Anomaly Cases and Controls in the United States, 2001 to 2002

	Cases		Controls		Crude*		Adjusted†	
	No.	%	No.	%	OR	95% CI	OR	95% CI
No smoking	4366	84.43	9062	87.62	1.00	Reference	1.00	Reference
Any smoking	805	15.57	1280	12.38	1.33	1.21–1.47	1.31	1.18–1.45

OR, odds ratio; CI, confidence interval.
*Mantel-Haenszel chi-square, 32.53 (1 df), $p < 0.0001$.
†Adjusted for variables listed in Table III, $p < 0.0001$.

Table 5. Maternal Smoking During Pregnancy by Cigarettes Used per Day in Congenital Digital Anomaly Cases and Controls in the United States, 2001 to 2002*

	Cases		Controls		Crude†		Adjusted‡	
Smoking Level	No.	%	No.	%	OR	95% CI	OR	95% CI
No smoking	4366	86.56	9062	89.36	1.00	Reference	1.00	Reference
1–10 cigarettes	507	10.05	824	8.13	1.29	1.15–1.46	1.27	1.12–1.44
11–20 cigarettes	151	2.99	231	2.28	1.38	1.12–1.71	1.38	1.12–1.71
≥21 cigarettes	20	0.40	24	0.24	1.78	0.97–3.26	1.57	0.84–2.93

OR, odds ratio; CI, confidence interval.
*Numbers do not always match totals because of missing responses.
†Trend $p < 0.001$.
‡Adjusted for variables listed in Table III.

pose of each of these studies was to examine congenital anomalies as a whole rather than specifically digital anomalies. Thus, when analyzed for congenital digital anomalies alone, they suffer from small sample size limitations[32,35,36] and incomplete adjustment for other known risk factors such as race,[32,36] child's sex,[32,34–36] and alcohol consumption.[32,34–36]

Although alcohol use is often associated with cigarette smoking and several case reports have found an association between alcohol use and congenital digital anomalies,[25,26] maternal alcohol consumption was not a risk factor in this analysis. Maternal alcohol use during pregnancy is substantially underreported in birth certificate data.[38,42] Increasing public awareness of the risks of alcohol consumption during pregnancy has probably contributed to this underreporting. This study also identified a number of maternal medical conditions as potential confounding variables. Although three of these variables—married status, lung disease, and having a previous preterm or small infant—were associated with maternal smoking, each of the variables listed in Table III was independently associated with having a child with a digital anomaly even after adjusting for tobacco use. Of these, only diabetes mellitus has been previously linked to an increased risk of digital anomalies,[43] but no systematic studies have corroborated these results. Several of the maternal medical risk factors, such as anemia and cardiac disease, could be markers for vascular compromise of a limb, a recognized mechanism for congenital limb deficiencies.[44] Unfortunately there is no information on the relative severity of the medical conditions in the data. The sensitivity of birth certificates to measure maternal medical risk factors is low, but the specificity is high.[45–47] Nevertheless, adjusting for these potential confounding factors did not affect the results substantially. Additional studies are needed to explore the association of these risk factor and congenital digital anomalies.

The demonstration of a dose-response relationship between an exposure and a disease is an important criterion toward establishing causation.[48] This study revealed a statistically significant dose–response effect with increased odds of having a newborn with a congenital digital anomaly with increased maternal cigarette smoking during pregnancy. This finding was generally consistent with the case-control study performed by Kelsey et al.,[32] which showed an increased risk of having a newborn with polydactyly or syndactyly in women who smoked more than 20 cigarettes per day. They, however, suggested that women who smoked 20 cigarettes or fewer per day were at no higher risk than those who did not smoke at all. In this study, smoking as few as 1 to 10 cigarettes per day during pregnancy was associated with a statistically significant increase in risk.

One of the major advantages of this study is that it is population-based, covering over 84 percent of U.S. births. The large sample size is well suited for epidemiologic studies involving rare diseases and low exposure rates. The system used to register birth certificates is standardized, and primary care physicians and nurses record the congenital anomalies. Because specialists do not diagnose the digital differences, perhaps only the more obvious cases are noted. It is possible that some controls may have subtle, unrecorded digital anomalies. Some cases may have unobserved associated anomalies at the time of birth, leading to improper inclusion in this study. Both of these situations would skew the estimated odds ratios toward the null hypothesis. Therefore, the estimated odds ratios may be an underestimate of the true risk.

The presence of polydactyly, syndactyly, or adactyly was coded as a single dichotomous variable in the database even though these conditions are etiologically distinct. There was no information recorded on the location (hands versus feet, unilateral versus bilateral, preaxial versus postaxial) or the severity, functional or cosmetic, of the congenital anomaly. Because only general, imprecise definitions of polydactyly, syndactyly, and adactyly are given in the guidelines for completing birth certificate forms, it is unclear how health care practitioners interpreted and coded these conditions. There may be differences in interpretation of the definitions between geographical regions, hospitals, or even individual health care providers throughout the United States. It was also difficult to determine whether only isolated digital anomalies were included in the analysis after excluding the 1121 newborns with concomitant anomalies listed in Table I. For example, it is likely that children with the VACTERL association were not included, as those listed as having heart malformations, rectal atresia/stenosis, tracheo-esophageal fistula/esophageal atresia, renal agenesis, other urogenital anomalies, and other musculoskeletal/integumental anomalies were excluded. In contrast, newborns with anomalies that are less likely to be diagnosed at birth, such as Poland syndrome, may not have been adequately excluded.

Although this study benefits from a large sample population, the complexities of classifying these digital anomalies cannot be captured. It is possible that many previous studies did not find an association between maternal smoking and congenital digital anomalies because of differing definitions and methods of case ascertainment. Most of the previous studies did not exclude syndromic cases.[32,35,36] Some studies[32,34] combined polydactyly and syndactyly, whereas the others separated these entities.[33,35,36] Kelsey et al.[32] selected cases based on diagnoses made up to 1 year after birth. The other studies selected cases based on diagnoses made during the perinatal period.[33–36] This study used birth certificate data and was therefore most directly comparable to the studies of Honein et al.[34] and Van den Eeden et al.[36]

The current standard U.S. birth certificate does not include information on the time of exposure to potential risk factors. It cannot capture detailed tobacco exposure data such as whether a woman smoked before pregnancy, smoked until she learned that she was pregnant, or reduced her cigarette use during pregnancy.[49] Estimates of the sensitivity and specificity of maternal smoking data recorded on birth certificates range from 53 to 89 percent and 92 to 99 percent, respectively.[42,45–47] Some researchers report the stigma associated with tobacco use may be exacerbated in cases of poor birth outcome, leading to the reduced sensitivity of the tobacco data.[37,38,49–52] Other authors have shown that maternal knowledge of the severity of the newborn's anomalies do not significantly affect recall of maternal cigarette exposure.[53–55] If case mothers who had smoked during pregnancy reported that they had not, the results of this study may underestimate the true risk. In the future, birth certificates will be able to report maternal tobacco data with greater precision. The 2003 revision of the U.S. Standard Certificate of Live Birth includes new questions on smoking behavior during the 3 months before pregnancy and for each trimester of pregnancy.[49,56]

CONCLUSIONS

This study indicates that maternal smoking during pregnancy is a statistically significant risk factor for having a newborn with polydactyly, syndactyly, or adactyly. Moreover, even smoking levels of one-half pack per day or less increased the risk of having a child with a congenital digital anomaly. Given the considerable number of women who report smoking during pregnancy (12.0 and 11.4 percent of women who gave birth in the United States in 2001 and 2002, respectively), even the moderate increase in risk posed by tobacco exposure has the potential to impact thousands of children. This study adds to the already substantial evidence that smoking during pregnancy has deleterious effects on newborns. Health professionals should make more efforts to increase awareness of the dangers of smoking to women.

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REFERENCES

1. Lamb, D. W., Wynne-Davies, R., and Soto, L. An estimate of the population frequency of congenital malformations of the upper limb. *J. Hand Surg. (Am.)* 7: 557, 1982.
2. Eaton, C. J., and Lister, G. D. Syndactyly. *Hand Clin.* 6: 555, 1990.
3. Waters, P. M. The upper limb. In R. T. Morrissy and S. L. Weinstein (Eds.), *Lovell and Winter's Pediatric Orthopaedics*, Vol. 2, 5th Ed. Philadelphia: Lippincott Williams & Wilkins, 2000.
4. Wynne-Davies, R., and Lamb, D. W. Congenital upper limb anomalies: An etiologic grouping of clinical, genetic, and epidemiologic data from 387 patients with "absence" defects, constriction bands, polydactylies, and syndactylies. *J. Hand Surg. (Am.)* 10: 958, 1985.
5. Perez-Molina, J. J., Alfaro-Alfaro, N., Lopez-Zermeno, M. C., and Garcia-Calderon, M. A. Polydactyly in 26,670 consecutive births: The clinical characteristics, prevalence and risk factors (in Spanish). *Bol. Med. Hosp. Infant Mex.* 50: 803, 1993.
6. Herring, J. A. (Ed.). *Tachdjian's Pediatric Orthopaedics*, 3rd Ed. Philadelphia: Saunders, 2001. Pp. 422, 1021.
7. Woolf, C. M., and Myrianthopoulos, N. C. Polydactyly in American Negroes and whites. *Am. J. Hum. Genet.* 25: 397, 1973.
8. Aro, T., Heinonen, O. P., and Saxen, L. Incidence and secular trends of congenital limb defects in Finland. *Int. J. Epidemiol.* 11: 239, 1982.
9. Lenz, W. Malformations caused by drugs in pregnancy. *Am. J. Dis. Child.* 112: 99, 1966.
10. Lenz, W. How can the teratogenic action of a factor be established in man? *South. Med. J.* 64 (Suppl. 1): 41, 1971.

11. Smithells, R. W. Defects and disabilities of thalidomide children. *Br. Med. J.* 1: 269, 1973.
12. Smithells, R. W., and Newman, C. G. Recognition of thalidomide defects. *J. Med. Genet.* 29: 716, 1992.
13. Shaul, W. L., and Hall, J. G. Multiple congenital anomalies associated with oral anticoagulants. *Am. J. Obstet. Gynecol.* 127: 191, 1977.
14. Hall, J. G., Pauli, R. M., and Wilson, K. M. Maternal and fetal sequelae of anticoagulation during pregnancy. *Am. J. Med.* 68: 122, 1980.
15. Lu, M. C., Sammel, M. D., Cleveland, R. H., Ryan, L. M., and Holmes, L. B. Digit effects produced by prenatal exposure to antiepileptic drugs. *Teratology* 61: 277, 2000.
16. Holmes, L. B., Harvey, E. A., Coull, B. A., et al. The teratogenicity of anticonvulsant drugs. *N. Engl. J. Med.* 344: 1132, 2001.
17. Bokhari, A., Coull, B. A., and Holmes, L. B. Effect of prenatal exposure to anticonvulsant drugs on dermal ridge patterns of fingers. *Teratology* 66: 19, 2002.
18. Sharony, R., Garber, A., Viskochil, D., et al. Preaxial ray reduction defects as part of valproic acid embryofetopathy. *Prenat. Diagn.* 13: 909, 1993.
19. Rodriguez-Pinilla, E., Arroyo, I., Fondevilla, J., Garcia, M. J., and Martinez-Frias, M. L. Prenatal exposure to valproic acid during pregnancy and limb deficiencies: A case-control study. *Am. J. Med. Genet.* 90: 376, 2000.
20. Firth, H. V., Boyd, P. A., Chamberlain, P., MacKenzie, I. Z., Lindenbaum, R. H., and Huson, S. M. Severe limb abnormalities after chorion villus sampling at 56-66 days' gestation. *Lancet* 337: 762, 1991.
21. Burton, B. K., Schulz, C. J., and Burd, L. I. Limb anomalies associated with chorionic villus sampling. *Obstet. Gynecol.* 79: 726, 1992.
22. Olney, R. S., Khoury, M. J., Alo, C. J., et al. Increased risk for transverse digital deficiency after chorionic villus sampling: Results of the United States Multistate Case-Control Study, 1988-1992. *Teratology* 51: 20, 1995.
23. Stoler, J. M., McGuirk, C. K., Lieberman, E., Ryan, L., and Holmes, L. B. Malformations reported in chorionic villus sampling exposed children: A review and analytic synthesis of the literature. *Genet. Med.* 1: 315, 1999.
24. Hoyme, H. E., Jones, K. L., Dixon, S. D., et al. Prenatal cocaine exposure and fetal vascular disruption. *Pediatrics* 85: 743, 1990.
25. West, J. R., Black, A. C., Jr., Reimann, P. C., and Alkana, R. L. Polydactyly and polysyndactyly induced by prenatal exposure to ethanol. *Teratology* 24: 13, 1981.
26. Pauli, R. M., and Feldman, P. F. Major limb malformations following intrauterine exposure to ethanol: Two additional cases and literature review. *Teratology* 33: 273, 1986.
27. Aro, T., Haapakoski, J., and Heinonen, O. P. A multivariate analysis of the risk indicators of reduction limb defects. *Int. J. Epidemiol.* 13: 459, 1984.
28. Czeizel, A. E., Kodaj, I., and Lenz, W. Smoking during pregnancy and congenital limb deficiency. *B.M.J.* 308: 1473, 1994.
29. Wasserman, C. R., Shaw, G. M., O'Malley, C. D., Tolarova, M. M., and Lammer, E. J. Parental cigarette smoking and risk for congenital anomalies of the heart, neural tube, or limb. *Teratology* 53: 261, 1996.
30. Kallen, K. Maternal smoking during pregnancy and limb reduction malformations in Sweden. *Am. J. Public Health* 87: 29, 1997.
31. Kallen, B. A prospective study of some aetiological factors in limb reduction defects in Sweden. *J. Epidemiol. Community Health* 43: 86, 1989.
32. Kelsey, J. L., Dwyer, T., Holford, T. R., and Bracken, M. B. Maternal smoking and congenital malformations: An epidemiological study. *J. Epidemiol. Community Health* 32: 102, 1978.
33. Seto, T., Nakagawa, H., Morikawa, Y., Nishijo, M., Miura, K., and Kadoshima, Y. Trend of congenital anomalies over 20 years ascertained by population-based monitoring in Ishikawa Prefecture, Japan. *Congenit. Anom. (Kyoto)* 43: 286, 2003.
34. Honein, M. A., Paulozzi, L. J., and Watkins, M. L. Maternal smoking and birth defects: Validity of birth certificate data for effect estimation. *Public Health Rep.* 116: 327, 2001.
35. Shiono, P. H., Klebanoff, M. A., and Berendes, H. W. Congenital malformations and maternal smoking during pregnancy. *Teratology* 34: 65, 1986.
36. Van den Eeden, S. K., Karagas, M. R., Daling, J. R., and Vaughan, T. L. A case-control study of maternal smoking and congenital malformations. *Paediatr. Perinat. Epidemiol.* 4: 147, 1990.
37. Martin, J. A., Hamilton, B. E., Ventura, S. J., Menacker, F., Park, M. M., and Sutton, P. D. Births: Final data for 2001. *Natl. Vital Stat. Rep.* 51: 1, 2002.
38. Martin, J. A., Hamilton, B. E., Sutton, P. D., Ventura, S. J., Menacker, F., and Munson, M. L. Births: Final data for 2002. *Natl. Vital Stat. Rep.* 52: 1, 2003.
39. Fleiss, J. L., Levin, B. A., and Paik, M. C. *Statistical Methods for Rates and Proportions: Wiley Series in Probability and Statistics*, 3rd Ed. Hoboken, N.J.: Wiley-Interscience, 2003. Pp. 384–387.
40. Hosmer, D. W., and Lemeshow, S. Logistic regression for matched case-control studies. In D. W. Hosmer and S. Lemeshow (Eds.), *Applied Logistic Regression: Wiley Series in Probability and Statistics*, 2nd Ed. New York: Wiley-Interscience, 2000.
41. Cuzick, J. A. method for analysing case-control studies with ordinal exposure variables. *Biometrics* 41: 609, 1985.
42. Buescher, P. A., Taylor, K. P., Davis, M. H., and Bowling, J. M. The quality of the new birth certificate data: A validation study in North Carolina. *Am. J. Public Health* 83: 1163, 1993.
43. Martinez-Frias, M. L. Epidemiological analysis of outcomes of pregnancy in diabetic mothers: Identification of the most characteristic and most frequent congenital anomalies. *Am. J. Med. Genet.* 51: 108, 1994.
44. Holmes, L. B. Teratogen-induced limb defects. *Am. J. Med. Genet.* 112: 297, 2002.
45. Piper, J. M., Mitchel, E. F., Jr., Snowden, M., Hall, C., Adams, M., and Taylor, P. Validation of 1989 Tennessee birth certificates using maternal and newborn hospital records. *Am. J. Epidemiol.* 137: 758, 1993.
46. Reichman, N. E., and Hade, E. M. Validation of birth certificate data: A study of women in New Jersey's HealthStart program. *Ann. Epidemiol.* 11: 186, 2001.
47. Roohan, P. J., Josberger, R. E., Acar, J., Dabir, P., Feder, H. M., and Gagliano, P. J. Validation of birth certificate data in New York State. *J. Community Health* 28: 335, 2003.
48. Hill, A. B. The environment and disease: Association or causation? *Proc. R. Soc. Med.* 58: 295, 1965.
49. Ventura, S. J., Hamilton, B. E., Mathews, T. J., and Chandra, A. Trends and variations in smoking during pregnancy and low birth weight: Evidence from the birth certificate, 1990-2000. *Pediatrics* 111: 1176, 2003.
50. Kharrazi, M., Epstein, D., Hopkins, B., et al. Evaluation of four maternal smoking questions. *Public Health Rep.* 114: 60, 1999.
51. Ventura, S. J. Using the birth certificate to monitor smoking during pregnancy. *Public Health Rep.* 114: 71, 1999.
52. Wong, M., and Koren, G. Bias in maternal reports of smoking during pregnancy associated with fetal distress. *Can. J. Public Health* 92: 109, 2001.
53. Werler, M. M., Lammer, E. J., Rosenberg, L., and Mitchell, A. A. Maternal cigarette smoking during pregnancy in relation to oral clefts. *Am. J. Epidemiol.* 132: 926, 1990.
54. Verkerk, P. H., Buitendijk, S. E., and Verloove-Vanhorick, S. P. Differential misclassification of alcohol and cigarette consumption by pregnancy outcome. *Int. J. Epidemiol.* 23: 1218, 1994.
55. Chung, K. C., Kowalski, C. P., Kim, H. M., and Buchman, S. R. Maternal cigarette smoking during pregnancy and the risk of having a child with cleft lip/palate. *Plast. Reconstr. Surg.* 105: 485, 2000.
56. National Center for Health Statistics. Report of the Panel to Evaluate the U.S. Standard Certificates and Reports. Hyattsville, Md.: National Center for Health Statistics, 2002. Available at: www.cdc.gov/nchs/vital_certs_rev.htm. Accessed on July 10, 2004.