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Self-Reported Maternal Cigarette Smoke Exposure during the Periconceptional Period and the Risk for Omphalocoele

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Abstract

Background—We investigated whether maternal exposure to cigarette smoke was associated with omphalocoele and whether periconceptional folic acid modified the association.

Methods—We analysed data from the National Birth Defects Prevention Study on omphalocoele case (n = 301) and control (n = 8135) mothers for infants born from 1997 through 2007. Mothers who reported active smoking or exposure to second-hand smoke during the periconceptional period (1 month before conception to 3 months after) were considered exposed. Those who reported use of folic acid supplements during the same period were considered supplement users. Odds ratios and 95% confidence intervals were estimated using multivariable logistic regression adjusted for alcohol use, preconception body mass index, and race/ethnicity.

Results—One hundred fifteen (38.2%) case and 2592 (31.9%) control mothers reported exposure to cigarette smoke during the periconceptional period. Adjusted odds ratios [95% confidence intervals] were 1.19 [0.94, 1.53] for any smoke exposure, 0.87 [0.54, 1.40] for active smoking, 1.38 [1.00, 1.90] for second-hand smoke exposure, and 1.16 [0.80, 1.67] for both exposures combined. No dose-response relationship was observed. Folic acid-containing supplements did not reduce the risk for omphalocoele among women with active or second-hand smoke exposure.

Conclusions—Self-reported active maternal smoking, with or without exposure to second-hand smoke, during the periconceptional period was not associated with omphalocoele. In contrast, there was a possible association with periconceptional exposure to second-hand smoke.

Keywords

cigarette smoke; maternal smoking; omphalocoele; second-hand smoke

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Omphalocoele is a midline abdominal wall defect consisting of a membrane-covered herniation of abdominal organs through a widened umbilical ring.[1] Omphalocoele may develop in the embryo before[1] or after[2] normal physiologic herniation (6 to 10 weeks post-conception) making it more challenging to assess its relation to environmental exposures. Though the aetiology of non-syndromic omphalocoele is not known, associations have been reported with young as well as advanced maternal age,[4] alcohol consumption,[5] US born Hispanic mothers,[4] obesity,[6] clomiphene citrate,[7] hot tub use,[8] asthma medication,[9] and heavy smoking.[5] Maternal cigarette smoking during pregnancy is known to cause adverse pregnancy outcomes[10-12] including birth defects.[13-17] We used data from the National Birth Defects Prevention Study (NBDPS) to investigate whether non-syndromic omphalocoele was associated with self-reported active maternal cigarette smoking and/ or exposure to second-hand smoke. We also examined whether such association was modified by periconceptional folic acid.

Methods

The NBDPS is the largest population-based case-control study of birth defects in the US. Nine sites (Arkansas, California, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah) and the Centers for Disease Control and Prevention (CDC) followed a common protocol for enrolment, classification, and maternal interview.[18] All pregnancy outcomes (liveborn, stillborn ≥20 weeks, or termination at any gestation) were eligible; however, not all sites were able to ascertain stillbirths and terminations.[19] One geneticist (RSO) reviewed all case records of omphalocoele to confirm eligibility and classify cases as isolated (without another major birth defect) or multiple (with one or more additional major birth defects, such as cleft lip). Unaffected live births (controls) were randomly selected from birth certificates or hospital logs in the same catchment area.[19] Trained interviewers administered a telephone interview to mothers 6 weeks to 24 months after the estimated date of delivery (EDD) of their pregnancy.[19] All sites maintained institutional review board approvals for the NBDPS.

Exposure assessment

Case and control mothers were queried about their smoking and exposure to second-hand (home, work, or school) smoke during the 3 months before conception and throughout the pregnancy. Those reporting having smoked were queried about the average number of cigarettes smoked per day. We created four groups (any exposure; active smoking only; exposure to second-hand smoke only; and active smoking with exposure to second-hand smoke) based on the exposure from 1 month before conception to 3 months after.

Inclusion criteria

Eligible case (n = 376) and control (n = 8494) infants were delivered on or after 1 October 1997 and had an EDD prior to 1 January 2008. We excluded 54 cases associated with OEIS complex (Omphalocoele, bladder Exstrophy, Imperforate anus, and Spina bifida), cloacal exstrophy, limb–body wall complex, conjoined twins, Pentalogy of Cantrell, prune belly or urethral obstruction sequence, or Beckwith–Wiedemann syndrome. We also excluded mothers with or missing information on pre-gestational diabetes (16 cases; 245 controls) or

who did not complete all interview sections (i.e. break-off) (5 cases; 114 controls). After exclusions, 301 omphalocoele cases (181 isolated; 120 multiple), and 8135 controls were available for analysis.

Statistical analysis

We used unconditional logistic regression to calculate adjusted (aOR) odds ratios with 95% confidence intervals [95% CI]. The final logistic regression models controlled for maternal alcohol use (yes, no), preconception body mass index (BMI, kg/m^2: <18.5, 18.5–24.9, ≥25), and race/etimicity (non-Hispanic White, non-Hispanic Black, Hispanic, other). We used the Mantel–Haenszel chi-square test to evaluate the dose relationship based on average number of cigarettes smoked per day. We used the relative excess risk due to interaction[20] to evaluate whether periconceptional folic acid (with or without other prenatal or multivitamins or minerals) modified the association with cigarette smoke exposure.

Results

Compared to control mothers, case mothers were more likely to report a higher preconception BMI, periconceptional alcohol use, be interviewed more than 12 months after delivery, and be exposed to second-hand smoke (Table 1).

Among all cases, no statistically significant increased risks were observed for active smoking only or with exposure to second-hand smoke (Table 2). However, second-hand smoke produced a significant positive association with multiple cases.

No dose–response relationships were observed (Mantel–Haenszel chi-square test $P = 0.67$) in any of the groups (data for all omphalocoele cases based on the average number of cigarettes smoked per day: <15 aOR= 1.02 [95% Cl 0.72, 1.45]; 15–24 aOR = 0.82 [95% CI 0.43, 1.53]; >24 aOR = 2.05 [95% CI 0.87, 4.82]). Folic acid supplementation did not modify the association between active smoking with or without exposure to second-hand smoke or for second-hand smoke exposure alone (data not shown).

Discussion

Active smoking during the periconceptional period was not associated with omphalocoele; second-hand smoke exposure only was weakly associated with omphalocoele. There was not a dose–response pattern among women who reported active smoking. Our results among the heaviest smokers (>24 cigarettes per day) (aOR 2.05 [95% CI 0.87, 4.82]) differed from those reported by Bird *et al*[5] (a OR= 4.26 [95% CI 1.58, 11.52]) using an earlier NBDPS data set with similar dose categories. Our lower observed association may reflect the change in the proportion of non-smokers among control (81% to 68%) and case (75% to 80%) mothers during the two time periods.

Periconceptional folic acid-containing supplement use did not statistically reduce the risk for smoke-associated omphalocoele. In this study, maternal self-report of periconceptional use of folic acid included folic acid alone or folic acid contained in a multivita min (either prenatal vitamins or multivitamins). Reported use was very similar in case and control

mothers (cases 86.7%, controls 86.2%). Because of diminishing sample sizes, it was not possible to analyse separately multivitamin use with and without folic acid supplementation.

The biologic mechanisms linking cigarette smoking to alteration in early fetal development are likely complex. Mainstream cigarette smoke (exhaled smoke) creates a complex aerosol containing thousands of chemicals,[21] whose impact, individually or synergistically, on the developing fetus is largely unknown. Cigarette smoking during pregnancy exposes both mother and the developing fetus to carbon monoxide, nicotine, and cadmium,[22] as well as several thousand additional chemicals.[23] Tobacco combustion also generates high levels of carbon monoxide[24] contributing to reduced oxygen levels in the mother and fetus. These exposures also decrease both serum and red blood cell folate levels.[25] Maternal cigarette smoking during pregnancy has been associated with several types of birth defects[17,26,27] and mothers are strongly encouraged to discontinue smoking before becoming pregnant.

Interestingly, we observed an increased risk for omphalocoele among mothers with second-hand exposure only. Second-hand smoke is becoming an increasing source of concern for several reasons. Second-hand smoke is a mixture of both mainstream and side-stream smoke. Side-stream smoke has been found to contain nicotine as well as toxic chemicals and several particulates that, because they are smaller than in mainstream smoke, are capable of entering the body more readily. Compared to active smoking, second-hand exposure introduces higher concentrations of some toxic constituents due to incomplete combustion of tobacco products.[28] Immediate side-stream smoke is estimated to be four times more toxic than mainstream smoke.[29] Maternal exposure to second-hand smoke during pregnancy is less studied, but evidence is accumulating suggesting that this exposure may increase the risk for several birth defects.[30-32]

Our findings were observed in a large and well-characterised group of non-syndromic omphalocoele cases identified from 10 population-based, US surveillance systems. Self-reported smoking prior to and during pregnancy was ascertained systematically from both case and control mothers using trained interviewers and a structured telephone interview. Questions were specific to assess whether their monthly exposure prior to and during pregnancy was for maternal smoking and/ or exposure to second-hand smoke in the home, work, or school.

Use of maternal self-reports of pregnancy exposures, especially for behaviours that may not be socially acceptable, may limit interpretation of study findings. We relied on maternal self-reports for cigarette smoking anytime during the 3 months before pregnancy throughout the pregnancy. Mothers may not have reported their smoking or stated they discontinued smoking before pregnancy, when in fact they were still smoking. However, a recent study compared maternal self-reports for cigarette smoking from three data sources for Utah case and control mothers in the NBDPS; interview reports had the highest prevalence of maternal cigarette smoking during the periconceptional period compared to the prenatal medical records or the birth certificate.[33] Another limitation is the embryologic timing of omphalocoele relative to any environmental exposure. An omphalocoele may occur either before six weeks or after 10 weeks post-conception. This lack of precision in the timing of

omphalocoele requires a broader exposure window, which may lead to some exposure misclassification.

In summary, we found that maternal periconceptional exposure to second-hand smoke may be a greater concern than exposure only to active smoking. Because of the limited power of these stratified analyses and novelty of the findings, replication is needed. Substantiating the risks associated with second-hand smoke is of crucial importance as it constitutes an important primary prevention message to disseminate among providers and the general public.

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Table 1

Crude odds ratios (cOR) for maternal characteristics and exposures among case and control mothers, National Birth Defects Prevention Study, 1997–2007

	Cases (n = 301)		Controls (n = 8135)		
Maternal characteristics	**N**	**%**	**N**	**%**	**cOR [95%CI]**
Age (years)					
<20	30	(10.0)	848	(10.4)	1.09 [0.71, 1.68)
20–24	76	(25.3)	1876	(23.1)	1.25 [0.90, 1.73]
25–29	73	(24.3)	2246	(27.6)	1.00 [Reference]
≥30	122	(40.5)	3165	(38.9)	1.19 [0.88, 1.59]
Race/ethnicity					
White, non-Hispanic	172	(57.1)	4841	(59.5)	1.00 [Reference]
Black, non-Hispanic	46	(15.3)	910	(11.2)	1,42 [1.02, 1.98]
Hispanic	60	(19.9)	1862	(22.9)	0.91 [0.67, 1.22]
Other	23	(7.6)	519	(6.4)	1.25 [0.80, 1.95]
Missing	0		3	(0.1)	–
Education (years)					
<12	43	(14.3)	1383	(17.0)	1.00 [Reference]
≥12	258	(85.7)	6722	(82.6)	1.23 [0.89, 1.71]
Missing	0		30	(0.4)	–
Preconception BMI[a]					
<18.5	17	(5.7)	433	(5.3)	1.30 [0.78, 2.17]
18.5–24.9	131	(43.5)	4325	(53.2)	1.00 [Reference]
≥25.0	142	(47.2)	3044	(37.4)	1.54 [1.21, 1.96]
Missing	11	(3.7)	333	(4.1)	–
Previous pregnancy					
0	103	(34.2)	2434	(29.9)	1.00 [Reference]
>1	198	(65.8)	5700	(70.1)	0.82 [0.64, 1.05]
Missing	0		1	(0.01)	–
Fever					
No	296	(98.3)	8000	(98.3)	1.00 [Reference]
Yes	4	(1.3)	94	(1.2)	1.15 [0.42, 3.15]
Missing	1	(0.3)	41	(0.5)	–
Substance abuse					
No	237	(78.7)	6240	(76.7)	1.00 [Reference]
Yes	14	(4.7)	331	(4.1)	1.11 [0.64, 1.93]
Missing	50	(16.6)	1564	(19.2)	–
Alcohol Use					
No	161	(53.5)	5095	(62.6)	1.00 [Reference]
Yes	140	(46.5)	3004	(36.9)	1.48 [1.17, 1.86]
Missing	0		36	(0.4)	–
Folic acid supplements					

	Cases (n = 301)		Controls (n = 8135)		
Maternal characteristics	**N**	**%**	**N**	**%**	**cOR [95%CI]**
None	39	(13.0)	1016	(12.5)	1.00 [Reference]
Periconception[b]	261	(86.7)	7013	(86.2)	0.97 [0.69, 1.37]
Missing	1	(0.3)	106	(1.3)	–
Gestational diabetes					
No	284	(94.4)	7746	(95.2)	1.00 [Reference]
Yes	16	(5.3)	341	(4.2)	1.28 [0.77, 2.14]
Missing	1	(0.3)	48	(0.6)	–
Paternal age (years)					
<20	10	(3.3)	378	(4.7)	0.69 [0.35, 1.33]
20–24	50	(16.6)	1401	(17.2)	0.92 [0.64, 1.32]
25–29	80	(26.6)	2070	(25.5)	1.00 [Reference]
≥30	149	(49.5)	3971	(48.8)	0.97 [0.74, 1.28]
Missing	12	(4.0)	315	(3.9).	–
Time to interview (months)					
<12	196	(65.1)	6054	(74.4)	1.00 [Reference]
≥12	104	(34.6)	2054	(25.3)	1.56 [1.23, 1.99]
Missing	1	(0.3)	27	(0.3)	–
Centre					
Arkansas	38	(12.6)	1039	(12.8)	1.00 [Reference]
California	45	(15.0)	985	(12.1)	1.25 [0.80, 1.94]
Georgia	42	(14.0)	853	(10.5)	1.35 [0.86, 2.11]
Iowa	25	(8.3)	900	(11.1)	0.76 [0.46, 1.27]
Massachusetts	36	(12.0)	1003	(12.3)	0.98 [0.62, 1.56]
New Jersey	27	(9.0)	568	(7.0)	1.30 [0.79, 2.15]
New York	20	(6.6)	704	(8.7)	0.78 [0.45, 1.35]
North Carolina	10	(3.3)	553	(6.8)	0.50 [0.25, 1.00]
Texas	37	(12.3)	935	(11.5)	1.08 [0.68, 1.72]
Utah	21	(7.0)	595	(7.3)	0.97 [0.56, 1.66]
Cigarette smoke exposure					
None	186	(61.8)	5528	(68.0)	1.00 [Reference]
Maternal only	21	(7.0)	609	(7.5)	1.03 [0.65, 1.62]
Second-hand smoke only	56	(18.6)	1103	(13.6)	1,51 [1.11, 2.05]
Maternal and second-hand	38	(12.6)	880	(10.8)	1.28 [0.90, 1.83]
Missing	0		15	(0.2)	–

[a] BMI = body mass index in kg/m^2.

[b] Includes women reporting multivitamins or prenatal vitamins with folic acid or folic acid alone.

Table 2

Frequency and adjusted odds ratios (aOR) and 95% confidence intervals [95%CI] for maternal smoking exposures and stratified by all, isolated, and multiple cases of omphalocoele, National Birth Defects Prevention Study, 1997–2007

Smoking exposure	Controls *n* = 8135 (%)	Cases *n* = 301 (%)	All	Isolated		Multiple	
			aOR [95% CI]	(*n* = 181)	aOR [95% CI]	(*n* = 120)	aOR [95% CI]
None	5528	186	1.00 [Reference]	120	1.00 [Reference]	66	1.00 [Reference]
Any	2592 (31.9)	115 (38.2)	1.19 [0.94, 1.53]	61	0.99 [0.72, 1.36]	54	1.58 [1.08, 2.30]
Maternal only	609 (23.5)	21 (18.3)	0.87 [0.54, 1.40]	11	0,73 [0.39, 1.37]	10	1.15 [0.56, 2.36
Second-hand	1103 (42.6)	56 (48.7)	1.38 [1.00, 1.90]	30	1.22 [0.80, 1.85]	26	1.65 [1.02, 2.66]
Maternal with second-hand	880 (34.0)	38 (33.0)	1.16 [0.80, 1.67]	20	0.89 [0.55, 1.46]	18	1.70 [0.98, 2.95]

Odds ratios adjusted for race/ethnicity, preconception BMI, and alcohol use.