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Maternal Cigarette Smoking During Pregnancy Is an Independent Predictor for Symptoms of Middle Ear Disease at Five Years' Postdelivery

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ABSTRACT. Although an increasing body of literature has demonstrated a link between in utero exposure to cigarette smoke and childhood morbidity, the extent to which such exposure is associated with middle ear disease (MED) is less certain. We hypothesized that in utero exposure to cigarette smoke was associated with an increased risk of MED and aimed to calculate the proportion of disease at 5 years' postdelivery attributable to cigarette exposure during pregnancy.

Methods. **At their first antenatal session, 8556 women were enrolled in a prospective study of pregnancy. Mothers were followed during pregnancy, at birth, at 6 months' and at 5 years' postdelivery and completed a detailed questionnaire aimed at assessing the frequency of acute (<1 month) and subacute (1–3 months) symptoms of MED and ear surgery. The relationship between MED and smoking status during pregnancy was then examined and subsequently adjusted simultaneously for smoking status at other times and for other potentially confounding variables.**

Results. **In the adjusted analyses, acute ear infections were associated with consumption of 1 to 9 cigarettes (OR: 1.6; 95% CI: 1.1–2.5), 10 to 19 cigarettes (OR: 2.6; 95% CI: 1.6–4.2) and 20+ cigarettes (OR: 3.3; 95% CI: 1.9–5.9) per day at the first clinic visit. For subacute ear infections, an association was present with consumption of 10 to 19 cigarettes (OR: 2.6; 95% CI: 1.4–5.0) and 20+ cigarettes (OR: 2.8; 95% CI: 1.3–6.0) at the first clinic visit. In utero exposure to 20+ cigarettes per day at the first clinic visit was also associated with an increased risk of ear surgery by 5 years' postdelivery (OR: 2.9; 95% CI: 1.3–6.6). These associations were independent of smoking at 6 months and at 5 years, age and gender of the child, breastfeeding history, maternal age, maternal education, maternal employment at 5 years, marital status at 5 years, socioeconomic status, use of day care, and the number of siblings or children in the household. A population attributable risk percent at 5 years of 39.4% for acute ear infections, 37.9% for subacute ear infections, and 30.0% for previous ear surgery was found for in utero exposure to cigarette smoke at the first clinic visit.**

Conclusions. **Smoking at the first clinic visit was associated with an increased risk of MED and ear surgery at 5 years of age. The frequency of maternal smoking in the general population gives rise to a high population attributable risk percent for MED. Therefore, it is a significant contributor to childhood morbidity and provides another reason why women should be encouraged to avoid smoking during pregnancy.** ***Pediatrics*** **1999;104(2). URL: http://www.pediatrics.org/cgi/content/full/104/2/e16;** ***maternal smoking, pregnancy, fetus, otitis media, middle ear disease.***

ABBREVIATIONS. MED, middle ear disease; PAR%, population attributable risk percent; RR, relative risk.

An increasing body of literature has demonstrated an association between in utero exposure to cigarette smoke and adverse neonatal events and childhood morbidity. These include increased risks of premature delivery and the birth of small-for-gestational-age or low birth weight infants,[1–3] cognitive and learning difficulties,[4,5] and behavior and attention problems.[6–8] Decreased neonatal respiratory function[9–11] and a greater prevalence of childhood asthma[12–14] also have been reported.

Exposure to passive smoke during early childhood has been associated with an increased prevalence of hospitalization[15] and symptoms of chronic respiratory tract infections.[16,17] The prevalence of otitis media also is reportedly increased in children from smoking families.[18] Otitis media is of recognized importance during early childhood not only because of its acute symptoms, morbidity, and direct complications at that time, but also because it is associated with a subsequent increased prevalence of speech and language difficulties, attention disorders, and learning difficulty.[19,20]

Because of the high concordance in maternal smoking between pregnancy and the postpartum period, it is difficult to separate the effects of smoking during pregnancy on the child's health from those of subsequent exposure to passive smoke. Because the prevalence of smoking during pregnancy is high, the attributable risk of even a weak association with later disease may be substantial. Large cohort studies that identify groups of mothers whose smoking status changes during or after pregnancy allows the effects of maternal smoking at different times on the child's health to be evaluated.

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We hypothesized that smoking during pregnancy would increase the prevalence of otitis media at 5 years' follow-up independent of maternal smoking status at 5 years' postdelivery and other confounding factors. We also aimed to identify whether in utero cigarette exposure at the first clinic visit or during the third trimester had the greater risk of otitis media and to calculate the proportion of disease that could be attributed to fetal cigarette exposure in children at 5 years' postdelivery.

METHODS

Between 1981 and 1984, 8556 women attending their first antenatal session at the Mater Mothers' Hospital (Brisbane, Australia) were enrolled in the Mater-University Study of Pregnancy. Of the subsequent 7785 singleton deliveries, 7357 children remained for consideration. Reasons for the exclusion of the other 428 infants included delivery at another hospital, perinatal deaths, and adoptions.[21]

Mothers completed detailed health and psychosocial questionnaires at their first clinic visit (mean gestational age = 19.8 ± 6.0 weeks; 80% seen by 24 weeks' gestation), within 2 to 4 days after birth and at 6 months' and at 5 years' postdelivery. At the first clinic visit, mothers were asked to quantify their smoking over the past week. After giving birth, mothers quantified their smoking over the past trimester of pregnancy. At 6 months and at 5 years' postdelivery, smoking was quantified over the previous week. Then mothers were categorized either as nonsmokers or as those who on average smoked 1 to 9 cigarettes, 10 to 19 cigarettes, or 20+ cigarettes per day during these periods.

Details concerning the child's health at 5 years' postdelivery were obtained from 5627 mothers, although numbers did change slightly for different outcomes because of missing data. Mothers lost to follow-up at 5 years' postdelivery tended to be younger, single, less well educated, and more likely to have been smokers than were those who continued to participate. In a separate report on this cohort, loss to follow-up between smokers and nonsmokers was examined. Smoking status was unrelated to loss to follow-up in a logistic model.[22] Change in smoking status of the cohort during and after pregnancy also has been described.[23] The average age of the children was 66 months. Mothers were asked to complete a detailed questionnaire concerning general and specific health issues of their child at 5 years' postdelivery. A series of questions assessed the frequency of acute (<1 month's duration) and subacute (1–3 months' duration) symptoms of ear infection. Mothers also were asked whether their child had required ear surgery or had seen a doctor for hearing problems over the past 5 years. Parents in a consecutive sample of 61 children who underwent ear surgery were contacted to determine the type of surgery performed, and 93% reported that their children had had ventilation tubes inserted.

Using the χ^2 test for statistical significance, frequency counts in smoking categories at the first clinic visit, at the third trimester of pregnancy and at 6 months' and at 5 years' postdelivery were compared with responses in the questionnaire for acute and subacute symptoms of middle ear disease (MED), history of ear surgery, and past medical consultation for the child's hearing. Logistic regression analysis was used to assess the independent effect of smoking at the first clinic visit, in the third trimester, and at 6 months' and at 5 years' postdelivery with MED and hearing problems at 5 years' follow-up. The initial model adjusted simultaneously for smoking on each of these occasions. The second model included the child's age and gender, maternal age, maternal education, and socioeconomic status, breastfeeding history, maternal employment status at 5 years' postdelivery, marital status at 5 years' follow-up; history of day care use at 0 to 6 months', >6 to 12 months', >1 to 2 years', and >2 years' postdelivery; and the number of siblings or children in the household at 5 years' postdelivery. All were entered simultaneously into the model as possible confounders. Socioeconomic status was measured as an average of family income over 5 years from the first clinic visit to the 5-year follow-up.

The population attributable risk percent (PAR%)[24] was calculated using the formula:

$$\text{PAR\%} = \frac{\text{P(RR} - 1)}{1 + \text{P(RR} - 1)},$$

where P was the prevalence of the risk factor and relative risk (RR) was the stratum RR of the outcome for each level of smoking. For each outcome the PAR proportions for each level of smoking were summed, and PAR% was used to assess the proportion of disease at 5 years of age attributed to fetal cigarette exposure.

Analysis was performed using the *Statistic Package for the Social Sciences (Version 7)*[25] and the *SAS Institutes Statistic Package*.[26]

RESULTS

Acute ear infections were associated significantly with a history of maternal smoking at the first clinic visit ($P = .01$) (Table 1), and the association was dose related. A history of subacute ear infections at 5 years' postdelivery was significantly associated with a maternal history of smoking at the first clinic visit ($P = .001$), during the third trimester of pregnancy ($P = .008$), and at 6 months' ($P = .04$) and at 5 years' postdelivery ($P = .02$) (Table 1). Although children of nonsmokers generally had the lowest prevalence of subacute ear infections, the risk did not increase progressively with higher maternal cigarette consumption. A history of previous ear surgery was related to cigarette exposure at the first clinic visit ($P = .001$), during the third trimester of pregnancy ($P = .002$), and at 6 months' ($P = .001$) and at 5 years'

TABLE 1. Prevalence of Children With a History of Ear Infections Versus History of Maternal Smoking

	Smoking (Cigarettes/Day)	First Clinic Visit		Third Trimester		6 Months		5 Years	
		No.	%*	No.	%	No.	%	No.	%
Acute†		(n = 5210)		(n = 5154)		(n = 5046)		(n = 5170)	
	Nil	439	13.0	446	13.6	406	13.5	431	13.3
	1–9	114	13.5	88	12.6	68	11.5	55	12.8
	10–19	100	16.6	99	16.1	92	14.2	99	15.6
	20+	69	17.7	76	13.8	122	15.3	134	15.5
	P‡	.01		.3		.2		.2	
Subacute†		(n = 5212)		(n = 5156)		(n = 5047)		(n = 5172)	
	Nil	199	5.9	197	6.0	188	6.3	199	6.2
	1–9	68	8.1	53	7.6	33	5.5	34	7.9
	10–19	59	9.8	59	9.6	56	8.6	59	9.3
	20+	34	8.7	36	6.5	65	8.1	67	7.7
	P	.001		.008		.04		.02	

* Number and percentage of children in each smoking category with a history of ear infections.
† Acute, <1 month; subacute, 1 to 3 months.
‡ χ^2 test.

follow-up ($P = .01$) (Table 2). There was a dose–response curve between in utero cigarette exposure and the risk of requiring ear surgery. Children exposed in utero to 20+ cigarettes per day at the first clinic visit had a prevalence of ear surgery that was 6% higher (or an overall increased risk of 250%) than did children of nonsmoking mothers. History of medical consultation for concerns about the child's hearing was significantly associated with maternal cigarette consumption at the first clinic visit ($P = .009$), during the third trimester ($P = .001$), and at 6 months' ($P = .01$) and at 5 years' follow-up ($P = .03$; Table 3).

For each outcome, a logistic regression analysis was performed to test for independent associations between smoking at different times and MED at 5 years' postdelivery. Model 1 included smoking at the first clinic visit, during the third trimester of pregnancy, and at 6 months' and at 5 years' postdelivery with risk of MED as the dependent variable using nonsmoking mothers as the reference category. In model 2, the child's age and gender, maternal age, maternal education and socioeconomic status, breastfeeding history, maternal employment at 5 years' postdelivery, marital status at 5 years' follow-up, history of day care use, and the number of siblings or children in the household at specific years were added simultaneously to model 1 to identify possible confounding. Smoking was coded as a categoric variable to not prompt a trend, with nonsmoking being the reference category for each level of smoking. For both acute and subacute ear infection and ear surgery, the predominant association between smoking and MED was only for relationship with smoking at the first clinic visit.

For acute ear infections, an association was present with consumption of 1 to 9 cigarettes (OR: 1.6; 95% CI: 1.1–2.5), 10 to 19 cigarettes (OR: 2.6; 95% CI: 1.6–4.2) and 20+ cigarettes (OR: 3.3; 95% CI: 1.9–5.9) per day at the first clinic visit (Table 4). For subacute ear infections, an association was present with consumption of 10 to 19 cigarettes (OR: 2.6; 95% CI: 1.4–5.0) and 20+ cigarettes (OR: 2.8; 95% CI: 1.3–6.0) per day at the first clinic visit (Table 5). An independent association was also found between a history of previous ear surgery and consumption of 20+ cigarettes per day at the first clinic visit (OR: 2.9; 95% CI: 1.0–6.6) (Table 6). No independent association was found between smoking past and medical consultation for the child's hearing. Similarly, no independent association was found between smoking during the third trimester or at 6 months' or at 5 years' postdelivery and increased risk of subacute MED or ear surgery, although for acute ear infections smoking >20+ cigarettes per day was associated with a lower risk of MED (OR: 0.4; 95% CI: 0.2–0.8).

PAR% was calculated on acute and subacute MED to assess the proportion of disease at 5 years' follow-up in the study population that could be attributed to cigarette exposure at the first clinic visit. A PAR% of 39.4% for acute ear infections and a PAR% of 37.9% for subacute ear infections were found at 5 years of age for a history of maternal smoking at the first clinic visit. A PAR% of 30.0% also was demonstrated between a history of previous ear surgery at 5 years of age and maternal smoking at the first clinic visit. These calculations of PAR% are substantially higher than are those that would have been obtained using the unadjusted RR because of the increase in RR obtained from the logistic model.

DISCUSSION

This study demonstrates an independent association between in utero cigarette exposure and an increased risk of subsequent otitis media. There was a significant relationship between smoking at the first clinic visit and the risk of otitis media and complications of MED, such as risk of ear surgery, at 5 years

TABLE 2. Prevalence of Children With a History of Ear Surgery Versus History of Maternal Smoking

Smoking (Cigarettes/Day)	First Clinic Visit		Third Trimester		6 Months		5 Years	
	No.	%*	No.	%	No.	%	No.	%
	($n = 5261$)		($n = 5203$)		($n = 5094$)		($n = 5218$)	
Nil	152	4.5	157	4.7	137	4.5	153	4.7
1–9	59	7.0	37	5.3	26	4.3	26	5.9
10–19	40	6.6	43	6.9	47	7.2	44	6.9
20+	39	9.8	46	8.2	60	7.4	62	7.1
P‡	.001		.002		.001		.01	

* Number and percentage of children in each smoking category with a history of ear surgery.
‡ χ^2 test.

TABLE 3. Prevalence of Children With a History of Seeing a Doctor for Hearing Problems Versus History of Maternal Smoking

Smoking (Cigarettes/Day)	First Clinic Visit		Third Trimester		6 Months		5 Years	
	No.	%*	No.	%	No.	%	No.	%
	($n = 5267$)		($n = 5208$)		($n = 5100$)		($n = 5226$)	
Nil	310	9.1	298	9.0	279	9.2	298	9.1
1–9	94	11.1	71	10.1	53	8.8	47	10.8
10–19	76	12.4	89	14.3	81	12.4	78	12.2
20+	51	12.9	63	11.3	98	12.1	101	11.5
P‡	.009		.001		.01		.03	

* Number and percentage of children in each smoking category who saw a doctor for hearing problems.
‡ χ^2 test.

TABLE 4. Strength of Association: History of Acute Ear Infections by 5 Years Versus Time of Smoking and History of Maternal Smoking

	Smoking (Cigarettes/Day)	Model 1*		Model 2†	
		OR	95% CI	OR	95% CI
First clinic visit	1–9	1.5	1.0–2.2	1.6	1.1–2.5
	10–19	2.3	1.4–3.7	2.6	1.6–4.2
	20+	2.8	1.6–4.9	3.3	1.9–5.9
Third trimester	1–9	0.6	0.4–1.0	0.6	0.4–1.0
	10–19	0.7	0.4–1.1	0.6	0.3–1.0
	20+	0.5	0.3–0.8	0.4	0.2–0.8
6 mo	1–9	0.8	0.6–1.2	0.8	0.6–1.2
	10–19	0.8	0.5–1.3	0.8	0.5–1.2
	20+	0.9	0.5–1.4	0.9	0.2–1.4
5 y	1–9	1.0	0.7–1.5	1.0	0.7–1.4
	10–19	1.1	0.8–1.7	1.1	0.8–1.6
	20+	1.0	0.7–1.4	1.0	0.7–1.4

* Smoking at different times compared with nonsmoking mothers as baseline.
† Smoking at each phase similar to model 1. In addition to confounders, including child's age and gender, maternal age and education, maternal employment at 5 years, marital status at 5 years, socioeconomic status, breastfeeding history, use of day care, and number of siblings or children in the household. Nonsmoking mothers used as baseline.

TABLE 5. Strength of Association: History of Subacute Ear Infections by 5 Years Versus Time of Smoking and History of Maternal Smoking

	Smoking (Cigarettes/Day)	Model 1*		Model 2†	
		OR	95% CI	OR	95% CI
First clinic visit	1–9	1.6	0.9–2.3	1.7	1.0–3.0
	10–19	2.4	1.3–4.4	2.6	1.4–5.0
	20+	2.6	1.2–5.3	2.8	1.3–6.0
Third trimester	1–9	1.1	0.6–1.9	1.0	0.6–1.9
	10–19	1.0	0.5–2.0	0.9	0.5–1.8
	20+	0.7	0.3–1.5	0.5	0.2–1.2
6 mo	1–9	0.6	0.4–1.1	0.6	0.4–1.1
	10–19	0.8	0.5–1.5	0.8	0.4–1.4
	20+	0.8	0.4–1.6	0.9	0.4–1.7
5 y	1–9	1.1	0.7–1.9	1.1	0.7–1.7
	10–19	1.0	0.6–1.6	0.9	0.6–1.5
	20+	0.8	0.5–1.3	0.7	0.4–1.2

* Smoking at different times compared with nonsmoking mothers as baseline.
† Smoking at each phase similar to model 1. In addition to confounders including child's age and gender, maternal age and education, maternal employment at 5 years, marital status at 5 years, socioeconomic status, breastfeeding history, use of day care, and number of siblings or children in the household. Nonsmoking mothers used as baseline.

of age. Because of the high prevalence of maternal smoking during pregnancy, we found in utero cigarette exposure to be associated with significant childhood morbidity in the cohort studied, as demonstrated by the high PAR% values.

Ey et al[18] in the Tucson Children's Respiratory Study, prospectively followed 1013 infants to 1 year of age, and reported an increased risk of recurrent otitis media in infants of mothers who smoked ≥11 cigarettes during pregnancy. Because of the high concordance of smoking during pregnancy and early infancy, it was difficult to assess the effects of smoking during pregnancy, independent of smoking after delivery, on the occurrence of recurrent otitis media. The authors concluded that smoking during pregnancy was not a significant risk factor for recurrent otitis media when included in a multivariate logistic regression. Smoking during pregnancy was assessed by maternal report, and although reports correlated closely to cord serum cotinine measurements in a subset of infants, only the average number of cigarettes consumed, instead of changing rates of cigarette consumption throughout pregnancy as examined in our study, was investigated.

The mechanism linking in utero cigarette exposure with the development of later MED is unknown. There is speculation that fetal cigarette exposure may affect lung development adversely in utero.[9] Maternal smoking during pregnancy has been reported to cause histologic changes in fetal alveolar and bronchial epithelium.[27] This also may apply to the epithelium of the middle ear and the eustachian tube. An alternative explanation is that in utero smoke exposure may interfere with the immune system, predisposing the child to otitis media. Although the majority of individual relationships were not statistically significant and are likely to be caused by chance, there was a trend in the adjusted analysis for heavy smoking in late pregnancy to be associated with a lower risk of acute MED and a history of previous ear surgery. However, a biological explanation is not implausible, because infants of smoking mothers are at reduced risk of neonatal respiratory distress syndrome, and there is associated evidence of enhanced fetal lung maturation and alteration in surfactant.[28] The latter also is found in eustachian tubes and is important for eustachian tube function and possible risk of MED.[29] The trend for lowered risk associated

TABLE 6. Strength of Association: History of Previous Ear Surgery by 5 Years Versus Time of Smoking and History of Maternal Smoking

	Smoking (Cigarettes/Day)	Model 1*		Model 2†	
		OR	95% CI	OR	95% CI
First clinic visit	1–9	1.6	0.9–2.8	1.7	0.9–3.1
	10–19	1.4	0.7–2.9	1.7	0.8–3.5
	20+	2.2	1.0–4.8	2.9	1.3–6.6
Third trimester	1–9	0.6	0.3–1.1	0.6	0.3–1.1
	10–19	0.7	0.3–1.4	0.6	0.3–1.3
	20+	0.7	0.3–1.6	0.6	0.3–1.4
6 mo	1–9	0.9	0.5–1.7	1.0	0.5–1.8
	10–19	1.7	0.9–3.2	1.7	0.9–3.4
	20+	1.6	0.8–3.2	1.6	0.8–3.3
5 y	1–9	1.2	0.7–2.1	1.2	0.7–2.0
	10–19	1.0	0.6–1.6	0.9	0.5–1.5
	20+	0.8	0.5–1.3	0.8	0.5–1.3

* Smoking at different times compared with nonsmoking mothers as baseline.
† Smoking at each phase similar to model 1. In addition of confounders including child's age and gender, maternal age and education, maternal employment at 5 years, marital status at 5 years, socioeconomic status, breastfeeding history, use of day care, and number of siblings or children in the household. Nonsmoking mothers used as baseline.

with smoking during late pregnancy influences the relationship in the adjusted analysis between smoking in early pregnancy and the risk of MED. This increased RR for smoking in early pregnancy in the adjusted analysis compared with the unadjusted analysis, results in the PAR% being higher than those that would have been calculated from the unadjusted risk and should be interpreted cautiously.

This study has a number of potential weaknesses. There was ~30% attrition, with single, young mothers more likely to be lost to follow-up at 5 years' postdelivery. The higher rates of attrition for smokers during pregnancy were shown by multivariate analysis to be a consequence of smokers being younger and less well educated, rather than an independent effect of smoking itself.[22] If mothers who failed to attend did not attend because their child has less illness, this would exaggerate the reported association between smoking and MED. However, this explanation is unlikely, because families who failed to attend follow-up in cohort studies usually are more disadvantaged on a range of health and social factors than are those who attend. For these reasons, we believe that attrition is unlikely to bias our findings substantially. Mothers were asked to estimate the degree of childhood respiratory morbidity, and children were not examined medically. The categories (acute, subacute, and chronic) do not follow recognized medical criteria for the diseases investigated but were categorized this way for ease of maternal recognition. Although we relied on maternal reports of cigarette consumption, such self-reports are a valid indicator of actual smoking levels,[30] although no independent confirmation was obtained nor cotinine levels determined in our study. A history of paternal smoking was not measured, therefore its effects could not be investigated. Paternal smoking has been associated with an increased risk of childhood respiratory disease,[31] although results are inconclusive.[32,33] Taylor and Wadsworth[34] reported no association between paternal smoking during pregnancy and lower respiratory tract disease at 5 years' follow-up. Whether these findings can be extrapolated to upper respiratory tract and MED is unknown.

CONCLUSION

We conclude that smoking at the first clinic visit is associated independently with an increased risk of MED and ear surgery by 5 years of age. The frequency of maternal smoking in the general population gives rise to a high PAR% for MED and therefore is a significant contributor to childhood morbidity. This study provides yet another reason why women should be encouraged to avoid smoking during pregnancy.

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