ARTICLE

Maternal Smoking During Pregnancy, Other Prenatal and Perinatal Factors, and the Risk of Legg-Calvé-Perthes Disease

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What's Known on This Subject

The causes of LCP disease are largely unknown, but this pediatric disease seems to result from interruption of the blood supply to the proximal femur and is considered a vascular disease.

What This Study Adds

This study identified associations with LCP disease for maternal smoking during pregnancy and low birth weight, which suggests that exposures associated with impaired fetal development, such as maternal smoking, may restrict the vasculature of the femoral head, increasing LCP disease risk.

ABSTRACT

OBJECTIVE. The causes of Legg-Calvé-Perthes disease are largely unknown, but this pediatric disease seems to result from interruption of the blood supply to the proximal femur and is considered a vascular disease. Because maternal smoking during pregnancy influences fetal development and is associated with cardiovascular diseases in offspring, we hypothesized that this exposure is a risk for Legg-Calvé-Perthes disease and also investigated other markers of impaired fetal development and early-life exposures.

MATERIALS AND METHODS. The Swedish Inpatient Register identified 852 individuals with a diagnosis of Legg-Calvé-Perthes disease from 1983 to 2005, individually matched by year of birth, age, sex, and region of residence with 4432 randomly selected control subjects. Linkage with the Swedish Medical Birth Register provided information on prenatal factors, including maternal smoking. Conditional logistic regression examined associations of maternal smoking during pregnancy and the other measures with the risk of Legg-Calvé-Perthes disease in offspring, adjusted for socioeconomic index and other potential confounding factors.

RESULTS. Maternal smoking during pregnancy was associated with an increased Legg-Calvé-Perthes disease risk, and heavy smoking was associated with a risk increase of almost 100%. Very low birth weight and cesarean section were independently associated with ~240% and 36% increases in the risk of Legg-Calvé-Perthes disease, respectively.

CONCLUSION. Maternal smoking during pregnancy and other factors indicated by impaired fetal development may be associated with an increased risk of Legg-Calvé-Perthes disease. *Pediatrics* 2008;122:e459–e464

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Key Words
Legg-Perthes disease, maternal smoking, passive smoking, risk factors

Abbreviations
LCP—Legg-Calvé-Perthes
ICD—*International Classification of Diseases*
OR— odds ratio
CI— confidence interval

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LEGG-CALVÉ-PERTHES (LCP) DISEASE is defined as ischemic necrosis of the femoral head among children <15 years old.[1–3] It occurs mostly between ages 4 and 8 years with a male/female ratio of 3 to 5:1.[4–6] The prevalence range has been estimated at 0.2 to 29.0 per 100 000 in children <14 years old,[7,8] and among Swedish children a prevalence of 8.5 per 100 000 has been identified.[9] Although the precise cause of LCP is unknown, this disease is considered a vascular condition involving interruption of the blood supply to the proximal femur.[1–3,10–12] The medial femoral circumflex artery is the principal source of blood supply to the femoral head. Several possible risk factors for the disease have been suggested, including impaired and disproportionate growth,[13] low birth weight,[14,15] delayed skeletal maturity,[16] short stature,[13,17] systemic hormonal changes,[18–22] and low socioeconomic index.[23–27] Several of these factors are consistent with the hypothesis that some form of developmental impairment is implicated in the etiology of LCP disease, possibly because of restricted development of the vasculature to the proximal femur. Associations with low birth weight and impaired fetal growth[14,15] suggest that prenatal and other early-life factors may be important in determining disease risk.

A small number of earlier studies reported associations between exposure to environmental tobacco smoke and

LCP disease.[28–30] Although it is particularly difficult to draw firm conclusions about causation from these studies, they reported a positive association; the findings suggest that parental smoking may represent a risk factor. We hypothesized that maternal smoking during pregnancy may be a specific risk, because this has been associated with cardiovascular disease risk and intima-media thickness in offspring during early life,[31] which indicates early damage to blood vessels. Smoking during pregnancy has been linked with low birth weight and impaired fetal growth,[32,33] providing evidence that it may be relevant to LCP disease risk. Thus, because both LCP disease and smoking during pregnancy are associated with impaired fetal development and vascular abnormalities, it is feasible that smoking during pregnancy is associated with a raised risk of LCP disease among offspring.

This case-control study using material from Swedish general population-based registers was designed specifically to examine the hypothesis that maternal smoking during pregnancy is associated with an increased risk of LCP disease among offspring; we know of no other studies that have investigated this hypothesis to date. We also evaluated the risk associated with birth weight, body size at birth, gestational age, presentation of the infant, delivery mode, Apgar score, maternal age, birth order, and history of earlier pregnancies. These measures were selected as relevant to fetal development and early trauma.

MATERIALS AND METHODS

We identified all of the patients in the Swedish Inpatient Register with a diagnosis of LCP disease (*International Classification of Diseases* [ICD]-8 codes 722.10, 722.11, and 722.19; ICD-9 code 732B; and ICD-10 codes M91.1, M91.2, and M91.3) between 1982 and 2005. The Swedish Inpatient Register includes data on individual hospital admissions collected by the Swedish National Board of Health and Welfare since 1964. Each record contains the national registration number, a unique personal identifier assigned to every Swedish resident from birth or immigration, as well as medical data, including discharge diagnoses. Subjects with LCP disease were individually matched with ≤5 individuals without the disease by Statistics Sweden, the government agency responsible for population statistics. The matching criteria were year of birth, age, sex, and region of residence at the time of diagnosis in the case subjects.

The Swedish Medical Birth Register includes information collected prospectively during pregnancy, delivery, and the neonatal period on virtually all births in Sweden since 1973. From 1982, women were asked about smoking during their first prenatal visit, which occurs before the 15th week of gestation in >95% of pregnancies in Sweden.[34] In this register, gestational age is based largely on early second-trimester ultrasound examination, when available, or is estimated from the date of the last menstrual period. The national registration number enables linkage between mothers and their offspring. Through linkage with the Total Population Register, we identified participants' date of birth, sex, region of residence at diagnosis, dates of death, and emigration. Census data provided the socioeconomic index of parents on the basis of occupation (manual workers, nonmanual workers, self-employed, farmers, and others). In total we identified 924 case subjects and 4550 matched control subjects born after 1982. We excluded 14 case subjects because of lack of matched control subjects, as well as 72 case subjects and 118 control subjects because we could not link them with their mothers in the Swedish Medical Birth Register. The analysis was, thus, based on 852 case subjects and 4432 matched control subjects. The distribution of missing data for the putative risk factors (including 84 case subjects and 397 control subjects for smoking during pregnancy, 3 case subjects and 16 control subjects for birth weight, and 10 case subjects and 54 control subjects for birth length) did not vary notably between case subjects and control subjects, indicating that differential selection bias is unlikely to represent a problem. The study was approved by the ethics research committee at the Karolinska Institutet.

Statistical Analysis

We used conditional logistic regression to evaluate associations between maternal smoking during pregnancy and risk of LCP disease among offspring. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to approximate relative risks. Associations between maternal smoking and the risk of LCP disease among offspring were evaluated using smoking as both a dichotomous measure (smoker or nonsmoker) and an ordinal factor categorized as nonsmoker, moderate smoker (1–9 cigarettes per day), and heavy smoker (≥10 cigarettes per day). First we used univariate conditional logistic regression models to evaluate the OR for each potential risk or confounding factor. The variables were maternal smoking during pregnancy, maternal age categorized into tertiles (<25, 25–29, or ≥30 years), malpresentation of the infant at the time of delivery, breech birth, birth weight (<1500, 1500–2499, 2500–4499, or ≥4500 g), birth length categorized into tertiles (<49, 49–51, or >51 cm), head circumference categorized into tertiles (<34, 34–36, or >36 cm), small for gestational age standardized by gestational week, gestational age (<32, 32–36, 37–42, or >42 weeks), any infection in the infant registered in the birth records, any trauma during delivery, any complication during delivery, cesarean section, Apgar score at the first minute after delivery (<4, 4–6, or >6), birth order (first born, second, third, or fourth or later), previous stillbirth, and previous spontaneous abortions. Then we used multivariate conditional logistic regression models to estimate adjusted ORs. In the univariate analysis we excluded observations with missing values, so the total number of subjects varied by variable.

Another model included the a priori putative risk factors, maternal smoking and fetal growth restriction, as well as variables that had statistically significant univariate associations, gestational age and socioeconomic index. In the multivariate analysis, subjects with missing values for any of the included variables were excluded. Only 1 of the measures of fetal growth was included, to

TABLE 1 **Characteristics of Case and Control Subjects**

	Case Subjects	Control Subjects
Total No.	852	4432
Male, %	79.7	79.4
Age at diagnosis, *n*		
<3 y	16	90
3–5 y	187	978
6–8 y	401	2066
9–12 y	180	934
>12 y	68	364
Gestational duration, *n*		
<32 wk	9	41
32–36 wk	65	240
37–42 wk	773	4114
>42 wk	5	37
Maternal smoking in the pregnancy, *n*		
None	501	3066
<10 cigarettes per d	149	625
≥10 cigarettes per d	118	344
Missing	85	397

avoid colinearity. Although it is possible that low birth weight could be intermediate in a causal pathway between maternal smoking and LCP disease, we included both of these measures in the same model to estimate their independence from each other. Another model excluded birth weight to assess whether its inclusion in the model masked an association with maternal smoking.

A test for trend of relative risks for smoking during pregnancy was performed by calculating the difference in deviance derived from the models, including and excluding the explanatory variable treated semicontinuously, and interpreting the difference as a χ^2 statistic with 1 degree of freedom. We also examined whether there was evidence of differences in association by performing analyses stratified by gender and age of diagnosis categorized into tertiles (<6, 6–8, and >8 years). All of the statistical analyses were performed by using SAS 9.1 (SAS Institute, Inc, Cary, NC).

RESULTS

Table 1 shows the characteristics of the case and control subjects. Some 79% of the case subjects were male. In the univariate model, smoking during pregnancy was a risk factor associated with a 67% increase in the risk of LCP disease (OR: 1.67 [95% CI: 1.41–1.97]), and there was a dose-dependent trend (Table 2). Low birth weight, being in the lowest tertile of height or head circumference, being small for gestational age, preterm birth, any complication during delivery, and cesarean section were associated with a raised risk of LCP disease.

Table 3 shows the crude and adjusted ORs for smoking during pregnancy, birth weight, gestational age, and cesarean section after excluding all of the observations with missing values for any of these measures and socioeconomic index. In multivariate conditional logistic regression analysis, the associations of maternal smoking during pregnancy, very low birth weight, and cesarean section with the risk of LCP disease remained statistically

TABLE 2 **Risk of LCP Disease Associated With Some Early-Life Factors**

Parameter	Case Subjects, *n*	Control Subjects, *n*	OR (95% CI)
Smoking during pregnancy			
No	501	3066	Reference
<10 cigarettes per d	149	625	1.44 (1.18–1.77)
≥10 cigarette per d	118	344	2.07 (1.64–2.61)
Mother's age			
<25 y	202	982	1.02 (0.85 –1.24)
25–29 y	326	1608	Reference
≥30 y	324	1842	0.87 (0.74–1.03)
Birth weight			
<1500 g	11	22	2.36 (1.29–4.33)
1500–2499 g	37	146	1.35 (1.04–1.75)
2500–4499 g	773	4079	Reference
≥4500 g	28	169	0.97 (0.72–1.30)
Birth length, tertile			
<49 cm	321	1278	1.24 (1.01–1.52)
49–51 cm	167	822	Reference
>51 cm	354	2278	0.76 (0.62–0.93)
Head circumference, tertile			
<34 cm	185	775	1.28 (1.06–1.56)
34–36 cm	391	2044	Reference
>36 cm	251	1473	0.90 (0.76–1.07)
Small for gestational age			
No	791	4183	Reference
Yes			
<32 wk	3	4	4.44 (1.03–19.09)
32–36 wk	6	19	1.77 (0.70–3.27)
37–42 wk	24	91	1.38 (1.09–1.91)
≥43 wk	1	1	5.00 (0.31–79.95)
Gestational age			
<32 wk	9	41	1.13 (0.56–2.31)
32–36 wk	65	240	1.41 (1.07–1.87)
37–42 wk	773	4114	Reference
>42 wk	5	37	0.71 (0.28–1.79)
cesarean section			
No	673	3698	Reference
Yes	179	734	1.32 (1.10–1.58)
Apgar score 1			
<4	11	55	1.07 (0.56–2.03)
4–6	30	145	1.07 (0.72–1.58)
>6	800	4187	Reference
Malpresentation			
No	779	4216	Reference
Yes	53	216	1.28 (0.94–1.74)
Breech birth			
No	841	4350	Reference
Yes	11	82	0.73 (0.39–1.37)
Any complication during delivery			
No	684	3685	Reference
Yes	168	747	1.20 (1.00–1.45)
Trauma during delivery, general			
No	823	4278	Reference
Yes	29	154	1.01 (0.67–1.50)
Trauma during delivery, skeletal			
No	837	4337	Reference
Yes	15	95	0.84 (0.49–1.46)
Infection in child			
No	833	4361	Reference
Yes	19	71	1.38 (0.83–2.29)
Child order			
First	323	1742	Reference
Second	321	1645	1.06 (0.89–1.25)

TABLE 2 **Continued**

Parameter	Case Subjects, *n*	Control Subjects, *n*	OR (95% CI)
Third	148	743	1.08 (0.87–1.33)
Fourth or later	60	302	1.06 (0.79–1.43)
Previous stillbirth			
No	755	3929	Reference
Yes	9	45	0.75 (0.30–1.89)
Previous abortion			
No	364	1978	Reference
Yes			
1	121	549	1.18 (0.89–1.56)
2	20	92	1.20 (0.71–2.01)
>2	8	37	1.18 (0.54–2.59)

significant after adjustment for all of these measures and the socioeconomic index. The statistically significant positive trend, indicating a dose response, for smoking during pregnancy (P for trend $< .0001$) was observed in the results from in the adjusted model. In the same model, the point estimate was 0.93 (95% CI: 0.77–1.11), comparing nonmanual workers with manual workers, after adjustment for all of the aforementioned measures.

When we excluded maternal smoking from the multivariate conditional logistic regression model, the results for the other covariates (birth weight, gestational age, and cesarean section) remained stable (data not shown). Removing birth weight from the adjusted model did not change the point estimates for maternal smoking and the other covariates (data not shown).

Stratified analyses showed that the association between LCP disease and maternal smoking during pregnancy was consistent, with a dose-dependent trend, for both male subjects (OR for moderate smoker: 1.42 [95% CI: 1.12–1.81]; OR for heavy smoker: 1.92 [95% CI: 1.45–2.53]) and female subjects (OR for moderate smoker: 1.17 [95% CI: 0.73–1.86]; OR for heavy smoker: 2.47 [95% CI: 1.47–4.15]). The point estimates for birth weight, gestational age, and cesarean section were stable in the stratified analyses, although they were based on small numbers, especially for female subjects. No conspicuous variation in the ORs was observed in analyses stratified by age of onset (data not shown).

DISCUSSION

This study found a statistically significant dose-dependant association between maternal smoking during pregnancy and an increased risk of LCP disease among offspring. We also found that low birth weight adjusted for gestational age was associated with LCP disease and that delivery by cesarean section represented a modestly increased risk.

Although this study cannot identify causation, it is plausible that maternal smoking during pregnancy could influence the risk of LCP disease, because it is known that smoking has direct effects on the fetus. A direct effect has been shown for other diseases and adverse pregnancy outcomes, such as low birth weight.[32,33] It has been suggested that impaired placental function,[35] reduced uteroplacental blood flow,[36] or influences on fetal oxygen supply could be responsible for the harmful effects on the fetus of maternal smoking during pregnancy. The apparently large effect on femoral development associated with maternal smoking during pregnancy[32] also suggests that this exposure may be relevant to LCP disease risk. The mechanism underlying the putative associations with LCP for maternal smoking and other risk factors could be through impaired in utero growth and development, particularly where this results in inadequate development of the femur[32] or associated blood vessels.[31] It has been shown that maternal smoking in utero exposes the fetus to oxidative stress,[37] which has been implicated in the pathogenesis of atherosclerosis. Additional evidence that impaired fetal development or associated exposures are implicated in LCP disease etiology comes from the consistent associations with

TABLE 3 **Risk of LCP Disease Associated With Some Early-Life Factors: Multivariate Model**

Parameter	Case Subjects, *n*	Control Subjects, *n*	Unadjusted, OR (95% CI)	Adjusted, OR (95% CI)[a]
Smoking during pregnancy				
No	483	2880	Reference	Reference
1–9 cigarettes per d	141	594	1.38 (1.12–1.70)	1.36 (1.10–1.68)
≥10 cigarettes per d	114	323	2.08 (1.64–2.64)	2.02 (1.59–2.58)
Birth weight				
<1500 g	9	18	2.34 (1.05–5.19)	3.46 (1.11–10.84)
1500–2499 g	33	121	1.41 (0.95–2.08)	1.14 (0.72–1.81)
2500–4499 g	671	3513	Reference	Reference
≥4500 g	25	145	0.94 (0.61–1.46)	0.99 (0.64–1.54)
Gestational age				
<32 wk	5	27	0.91 (0.35–2.35)	0.29 (0.08–1.07)
32–36 wk	58	202	1.46 (1.08–1.98)	1.21 (0.84–1.73)
37–42 wk	672	3536	Reference	Reference
>42 wk	3	32	0.51 (0.16–1.66)	0.47 (0.14–1.53)
Cesarean section				
No	582	3196	Reference	Reference
Yes	156	601	1.40 (1.14–1.70)	1.36 (1.11–1.67)

[a] Data were adjusted for all of the variables in the table and socioeconomic index.

birth weight, recumbent length, head circumference, and being small for gestational age. The association of these measures with LCP risk is of lower magnitude than for maternal smoking, and the association with maternal smoking is independent of the measures of growth. A range of factors influence birth weight, but different exposures may result in different aspects of developmental impairment, suggesting a more important role in the etiology of LCP disease for some exposures that influence early development. It is also possible that maternal smoking is a proxy indicator of other factors, which might be causally associated with LCP, for example, other hazardous health behaviors, nutrition, and fetal micronutrient supply. In this study it was not possible to obtain information on smoking before pregnancy or a wealth of other potential confounding factors associated with maternal smoking, so the nature of causality in this association must remain speculative. The small effect of adjustment for available potential confounding factors and the dose-dependent association does no rule out a more direct association between maternal smoking during pregnancy and LCP disease.

We observed that the association between cesarean section and LCP disease remains statistically significant after adjustment for other risk factors. The reason for cesarean section is not recorded in the register data, so it is not possible to explore fully the reasons underlying this association. It is conceivable that some conditions associated with impaired fetal development, which also increased LCP disease risk, resulted in delivery by cesarean section. Measures such as breech birth and trauma were not associated with LCP disease risk, suggesting that influences on earlier development, rather than perinatal trauma, are involved in the etiology of the disease. Although we identified associations with smoking during pregnancy, earlier maternal smoking could theoretically influence fetal development through epigenetic mechanisms, altering gene expression through the placenta or the cytoplasm of the egg.

To our knowledge, this is the first study to date that has investigated maternal cigarette smoking specifically during pregnancy and the risk of LCP disease. Three previous studies showed an association between passive smoking and LCP disease.[28–30] However, methodologic limitations, such as small numbers of case subjects, prevent any firm conclusions being drawn from these studies. If there was an association between maternal smoking during pregnancy and the risk of LCP disease, it would be unsurprising to find an association with passive smoking after birth, because women rarely give up smoking completely.[38,39] Men with a spouse who smoke are also more likely to smoke,[40] so associations of LCP disease with paternal smoking may be confounded by maternal smoking, including during pregnancy. Additional evidence that exposure to environmental tobacco smoke after birth is not a substantial risk comes from our stratified analysis of age at diagnosis: there was no pattern for the risk of LCP disease by age of onset. Because onset age also indicates duration of previous exposure, this suggests that environmental tobacco smoke is not associated with disease risk. Although passive smoking after birth is a less plausible risk for LCP disease than smoking during pregnancy, we cannot rule out the possible additive effect of this exposure after birth. It has been shown that exposure to environmental tobacco smoke may be associated with arterial abnormalities in children,[41] and it is conceivable that children who were exposed to smoking in utero could also be more susceptible to endothelial dysfunction caused by passive smoking after birth. This may also influence susceptibility to infections, but because we found no notable association of infections with LCP disease, we do not believe that this explains the association with maternal smoking during pregnancy. One of the strengths of this study is its large sample size. The general population-based nature of the sample is another strength, indicating that the findings are not limited to a subset of the population. More than 95% of pregnancies would have been recorded in the registers used here.[34] The unique national registration number permits virtually complete linkage of individual information in the inpatient register with data on mothers receiving prenatal care and their infants. Information on cigarette smoking during pregnancy was recorded prospectively, thus limiting the possibility of recall or reporting bias and selection bias. One of the limitations of the present study is that the details of cigarette smoking were based on self-reported information in the first visit after pregnancy, and it is possible that women underreported smoking.[42] However, the measurement of cigarette smoking in the Swedish Medical Birth Register is reported to be reasonably accurate.[43,44] As pregnant women receive information about the harmful effects of smoking, it is also probable that some smokers gave up after the first visit. This may have resulted in an underestimation of the magnitude of the association between smoking and LCP disease. Like most other register-based studies, we lack information on some potentially important measures, such as maternal nutrition, other lifestyle factors, and smoking behavior before and after pregnancy. However, we adjusted the model for socioeconomic index on the basis of occupation, which is associated with smoking and many other important lifestyle factors.

CONCLUSIONS

This study identified associations with LCP disease for maternal smoking during pregnancy and low birth weight. This suggests that exposures associated with impaired fetal development, such as maternal smoking, may restrict the vasculature of the femoral head, increasing LCP disease risk.

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