

## OBSTETRICS

# Congenital cerebral palsy and prenatal exposure to self-reported maternal infections, fever, or smoking

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**OBJECTIVE:** The objective of the study was to investigate the association between maternal self-reported infections, fever, and smoking in the prenatal period and the subsequent risk for congenital cerebral palsy (CP).

**STUDY DESIGN:** We included the 81,066 mothers of singletons born between 1996 and 2003 who participated in the Danish National Birth Cohort. Children were followed up through December 2008. Information on maternal infections, fever, smoking, and other demographic and lifestyle factors during pregnancy were reported by mothers in computer-assisted telephone interviews in early and midgestation. We identified 139 CP cases including 121 cases of spastic CP (sCP) as confirmed by the Danish National Cerebral Palsy Register. Cox proportional hazards regression models were used to estimate adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs).

**RESULTS:** Self-reported vaginal infections were associated with an increased risk of CP and sCP (aHR, 1.52; 95% CI, 1.04–2.24; and

aHR, 1.73; 95% CI, 1.16–2.60, respectively) and particularly untreated vaginal infections were associated with an increased risk of sCP (aHR, 1.95; 95% CI, 1.16–3.26). Fever was associated with the risk of CP (aHR, 1.53; 95% CI, 1.06–2.21). Smoking 10 or more cigarettes per day during pregnancy was also associated with sCP (aHR, 1.80; 95% CI, 1.10–2.94). There was a modest excess in risk for children exposed to both heavy smoking and vaginal infections. No other self-reported infections were significantly associated with CP.

**CONCLUSION:** Self-reported vaginal infections, fever, and smoking 10 or more cigarettes per day during pregnancy were associated with a higher risk of overall CP and/or sCP.

**Key words:** congenital cerebral palsy, maternal infections, pregnancy, smoking

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Congenital cerebral palsy (CP) constitutes a group of permanent disorders of movement and posture causing activity limitation attributed to non-progressive disturbances that occurred in the developing fetal or infant brain.<sup>1</sup> CP is the most common physical developmental disability in childhood with a birth prevalence of 2 per 1000 live births

in Denmark.<sup>2,3</sup> The incidence of CP increases with lower gestational age, up to 100 cases per 1000 births in extreme preterm cases (<28 weeks).<sup>4,5</sup> Improvements in perinatal care and neonatal survival in recent decades have increased the survival of children born preterm and therefore the number of CP cases.<sup>4,6</sup>

Maternal fever<sup>7,8</sup> and maternal infections<sup>9-11</sup> have been associated with an increased risk of CP, irrespective of gestational age. Infections of the vagina or urinary tract during pregnancy have been of special interest because of their proximity to the fetus, but most studies have not clearly separated these infections. Self-reported data from questionnaires

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administered during pregnancy provide separation of each type of infection and more importantly include infections that did not receive medical attention. The proposed mechanism of action for maternal infections increasing risk of CP is by triggering a fetal inflammatory response, which results in fetal brain damage, particularly if added to fetal hypoxia.<sup>12</sup>

Smoking 10 or more cigarettes during pregnancy has also been associated with CP.<sup>13</sup> The possible mechanism of action of this association is by the creation of a pathological hypoxic environment for the fetus.<sup>13</sup> Moreover, smoking has also been associated with vaginal infections.<sup>14</sup> We therefore hypothesize that exposure both maternal infection and maternal smoking may result in excess risk of CP in comparison with either exposure alone.

Maternal age,<sup>15-17</sup> smoking during pregnancy,<sup>14,18</sup> alcohol consumption,<sup>14,19</sup> socioeconomic status,<sup>20-22</sup> household size during pregnancy,<sup>14,22</sup> season of pregnancy start,<sup>23,24</sup> and calendar year of birth<sup>2,25</sup> may confound the association between infection and CP. These factors have been shown to be associated with an increased risk of CP as well as being associated with increased risk of infections.

This study explores the association between CP and self-reported maternal infections during pregnancy, using the Danish National Birth Cohort and the Danish National Cerebral Palsy Registry. We analyzed all infections combined and separately as well as fever (a marker of infection). We specifically focused on the association between CP and self-reported vaginal infections, urinary tract infections, or smoking, adjusting for available confounders. Because there might be specific etiological links between infection and spastic CP (sCP),<sup>26</sup> we analyzed this group separately.

## MATERIALS AND METHODS

The Danish National Birth Cohort is a nationwide population-based cohort of pregnancies and their offspring designed to provide questionnaires for collecting self-reported data for epidemiological studies of short-term and long-term

consequences of intrauterine exposures. Details on the Danish National Birth Cohort study design and recruitment procedures have been published elsewhere,<sup>27</sup> and the translated questionnaires are available ([www.dnbc.dk](http://www.dnbc.dk)).

We included women in our study only if they participated in both of the 2 interviews during pregnancy ( $n = 83,935$ ). We additionally excluded 2447 non-singleton children, 261 children who died, and 118 children who emigrated prior to their first birthday, and 43 children who were not in the Danish Medical Birth Registry. Of the 261 children who died, 186 died neonatally (within the first 30 days after delivery). This study was approved by the Danish Data Protection Agency. The study was also approved and by the Research Ethic Committee and University of California, Los Angeles, Institutional Review Boards.

Danish National Birth Cohort participants were identified as having validated CP if they were alive after the first year of life and included in the Danish Cerebral Palsy Registry. Validation of CP cases and inclusion in the register has been previously described.<sup>28</sup> Time of CP onset for the analysis was defined as age 1 year or first recorded date of diagnosis in the Danish Cerebral Palsy Registry. If a child's date of diagnosis was prior to the age of 1 year ( $n = 76$ ), the child's date of diagnosis was recentered to the date of child's first birthday (date of birth plus 365 days) and coded as a CP child if included in the CP registry. All children were followed up from 1 year of age until a reported diagnosis of CP in the Danish Cerebral Palsy Registry, death, or Dec. 31, 2008, whichever occurred first.

Information on urinary tract infections (cystitis, pyelonephritis), vaginal infections, diarrhea, cough, genital herpes, venereal warts, herpes labialis, fever, and smoking was collected from participants as part of the Danish National Birth Cohort interviews.

Because the etiology of CP is largely unknown, confounding adjustment is based on availability of data and previous findings. Information on maternal age at birth and calendar year of birth was obtained from the Danish Medical Birth Registry, whereas information on

other confounders (smoking during pregnancy, alcohol consumption, socioeconomic status, household size during pregnancy) was available from interviews.

Coding of social status was based on highest self-reported education and job titles between both parents at the time of recruitment. Parents who had a completed education 4 years beyond secondary school education or were in management were classified as high social status. Parents with middle-range training and skilled workers were classified as middle social status, and unskilled workers and unemployed were classified as low social status. If unemployed more than 12 months, parents were categorized in the lowest category, if unemployed less than 12 months, parents' completed education and or training were used to determine status.

Women were classified into alcohol consumption categories based on the maximum consumption at any point in time during their pregnancy, as described in either of the 2 interviews. Binge drinking was having at least 1 episode of intake of 5 drinks or more in 1 night during pregnancy. In addition to potential confounders, we collected information concerning gestational age (in weeks) at birth, and Apgar score at 5 minutes from the Danish Medical Birth Registry.

Characteristics of maternal cohort across maternal infection and smoking groups were summarized as proportions and analyzed using  $\chi^2$  tests. For each infectious exposure group, we modeled the risk of CP and the risk of sCP. Hazard ratios and 95% confidence intervals (CIs) were estimated by Cox proportional hazard regression models with person-years as the time-to-event variable using robust sandwich covariance estimates to take into account interdependency among women who had more than 1 child during the cohort recruitment time and therefore participated more than once in the cohort (4997 women participated in the cohort twice and 56 women participated 3 times). Adjusted hazard ratios included all potential confounders listed above. Confounders were selected for adjustment in

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