Risk of Cerebral Palsy and Childhood Epilepsy Related to Infections before or during Pregnancy

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Abstract

Background and Aim: Maternal infections during pregnancy have been associated with several neurological disorders in the offspring. However, given the lack of specificity for both the exposures and the outcomes, other factors related to infection such as impaired maternal immune function may be involved in the causal pathway. If impaired maternal immune function plays a role, we would expect infection before pregnancy to be associated with these neurological outcomes.

Methods/Principal Findings: The study population included all first-born singletons in Denmark between January 1 1982 and December 31 2004. We identified women who had hospital-recorded infections within the 5 year period before pregnancy, and women who had hospital-recorded infections during pregnancy. We grouped infections into either infections of the genitourinary system, or any other infections. Cox models were used to estimate adjusted hazard ratios (aHRs) with 95% confidence interval (CI). Maternal infection of the genitourinary system during pregnancy was associated with an increased risk of cerebral palsy (aHR = 1.63, 95% CI: 1.34–1.98) and epilepsy (aHR = 1.27, 95% CI: 1.13–1.42) in the children, compared to children of women without infections during pregnancy. Among women without hospital-recorded infections during pregnancy, maternal infection before pregnancy was associated with an increased risk of epilepsy (aHR = 1.35, 95% CI: 1.21–1.50 for infections of the genitourinary system, and HR = 1.12, 95% CI: 1.03–1.22 for any other infections) and a slightly higher risk of cerebral palsy (aHR = 1.20, 95% CI: 0.96–1.49 for infections of the genitourinary system, and HR = 1.23, 95% CI: 1.06–1.43 for any other infections) in the children, compared to children of women without infections before (and during) pregnancy.

Conclusions: These findings indicate that the maternal immune system, maternal infections, or factors related to maternal immune function play a role in the observed associations between maternal infections before pregnancy and cerebral diseases in the offspring.

Introduction

Maternal infections during pregnancy have been associated with a wide variety of neurological and psychiatric disorders in the offspring, such as cerebral palsy [1–3], epilepsy [4–6] autism [7–10] and schizophrenia [11], respectively. These associations have also been observed in animal studies. [12,13] However, the lack of specificity related to both the exposures and the outcomes suggests that underlying factors correlated with maternal infections may play a role. Considering a family history of autoimmune disease is associated with autism in the offspring [14], underlying factors with other outcomes could also be related to impaired maternal immune function. If so, we would expect to see associations between maternal infections occurring before pregnancy, as an indicator of impaired immune function, and the risk of childhood neurological disorders, even in mothers without reported infections during pregnancy. In regards to genetic causation, paternal infection may also be associated with an increased risk of these outcomes in the offspring.

We conducted a population-based cohort study to examine whether the risk of cerebral palsy and epilepsy in the offspring is related to maternal (or paternal) infections occurring either during pregnancy or within the five year period before pregnancy. The underlying hypothesis is that maternal infections occurring before pregnancy increases the risk of cerebral palsy and epilepsy in the offspring. Under the hypothesis we would expect no associations between paternal infections and the outcomes under study.
Table 1. Characteristics of the study population according to hospitalized infections during pregnancy.

| Maternal infections during pregnancy | No   | %    | Infection related to the genitourinary system | Number | %    | Any other infections | Number | %    |
|-------------------------------------|------|------|-----------------------------------------------|--------|------|----------------------|--------|------|
|                                     | 565,343 | 95.99 | 14,037                                        | 2.38   | 9,556 | 1.62                 |

Maternal infection before pregnancy

|                                     | Number | %    |
|-------------------------------------|--------|------|
| No infection                        | 518,173 | 91.66 |
| Infection related to the genitourinary system | 15,425 | 2.73  |
| Any other infections                | 31,745 | 5.62  |

Gender

|                  | Number | %    |
|------------------|--------|------|
| Male             | 290,006 | 51.30 |
| Female           | 275,337 | 48.70 |

Maternal age

|                  | Number | %    |
|------------------|--------|------|
| <20              | 24,137 | 4.27  |
| 20               | 164,640 | 29.12 |
| 25               | 244,944 | 43.33 |
| 30               | 101,734 | 18.00 |
| 35               | 25,826 | 4.57  |
| 40               | 4,062 | 0.72  |

Maternal education

|                  | Number | %    |
|------------------|--------|------|
| Low              | 199,378 | 35.27 |
| Middle           | 200,248 | 35.42 |
| High             | 165,717 | 29.31 |

Marital status

|                  | Number | %    |
|------------------|--------|------|
| Married          | 264,097 | 46.71 |
| Others           | 301,246 | 53.29 |

Gestational week

|                  | Number | %    |
|------------------|--------|------|
| <33              | 5,880 | 1.04  |
| 33               | 23,974 | 4.24  |
| 37               | 23,745 | 4.20  |
| 38               | 54,936 | 9.72  |
| 39               | 110,313 | 19.51 |
| 40               | 179,803 | 31.80 |
| 41               | 109,162 | 19.31 |
| 42               | 57,530 | 10.18 |

Calendar year

|                  | Number | %    |
|------------------|--------|------|
| 1982             | 111,801 | 19.78 |
| 1987             | 100,333 | 17.75 |
| 1991             | 79,537 | 14.07 |
| 1994             | 127,658 | 22.58 |
| 1999             | 122,200 | 21.62 |
| 2004             | 23,814 | 4.21  |

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Methods

Ethic Statement

According to Danish law, register-based studies do not require consent from individuals when personal identifiers are encrypted and stored by a trusted third party (Statistic Denmark). This study was approved by the Danish Data Protection Agency (J.nr.2008-41-2680).

Study Population

All live-born children and new residents in Denmark are assigned a unique civil registration number, which we used to link...
individual information from several national registries. We identified all first live-born singletons born in Denmark between January 1 1982 and December 31 2004 (N = 624,620) from the Danish Medical Birth Register, which has included all births in Denmark since 1973. [15] Children were linked to their biological parents as recorded in the register. We excluded children who were adopted (N = 4320), could not be linked to their mothers (N = 1), or had missing data on gestational age (N = 4,132), leaving 616,167 singletons. We further excluded children with missing values for maternal education (9,936), maternal marital status (N = 29), maternal income (N = 1,454), or paternal income (15,818), leaving 588,936 singletons in the final analyses.

Maternal Infection

Information on maternal infections was extracted from the Danish National Hospital Register, which holds nationwide data on all admissions to any Danish hospital since 1977, and on all outpatient visits since 1995. Diagnostic information is based on the Danish version of the 8th revision of the International Classification of Diseases (ICD-8) from 1977 to 1993, and the 10th revision (ICD-10) from 1994 onwards. [16] Repeated hospitalizations due to infections within 4 days of each other were grouped together and considered a single admission.

We identified all mothers diagnosed with any type of infections within the five year period before pregnancy and during pregnancy. Mothers were classified as having infection before pregnancy if they had at least one hospital-recorded infection within the five year period prior to the onset of pregnancy. Mothers were classified as having infection during pregnancy if they had at least one hospital-recorded infection during pregnancy. We divided hospital-recorded infections into two groups: those of the genitourinary system, which have been associated with an increased risk of neurological disorders in the offspring [1,17,18]; and any other infections (Table S1 and S2).

Paternal Infection

We also identified fathers diagnosed with any type of infections within the five year period before or during the partner’s pregnancy. Fathers were classified as having infection before the partner’s pregnancy if they had at least one hospital-recorded infection within the five year period before the onset of the partner’s pregnancy. Fathers were classified as having infection during the partner’s pregnancy if they had at least one hospital-recorded infection during the partner’s pregnancy.

Outcomes

Children were identified as having epilepsy if they were recorded in the Danish National Hospital Register with an ICD-8 code (345) or ICD-10 codes (G40-G41).

For the main analyses, children were identified as having cerebral palsy from two different data sources: the Danish National Hospital Register (from 1982 to 2004) and the Danish Cerebral Palsy Register (from 1996 to 2002). [19] Children were identified as having cerebral palsy if they were recorded in the Danish Hospital Register with ICD-8 codes (343 and 344) or ICD-10 codes (G80–G83) from 1982 until 2004. The Danish Cerebral Palsy Register includes children with a diagnosis of cerebral palsy in eastern Denmark from birth year 1979, and only for the entire country since 1996. [19] Children identified from the Danish Cerebral Palsy Registered were used in a subgroup analysis, described below.

Covariates

Information on gestational age, birth weight, maternal age at birth, and parity was obtained from the Danish Medical Birth Registry. [15] Information on maternal education, marital status at birth, and family income at birth was obtained from the Statistics Denmark, available since 1979. Missing values for maternal education were replaced by available information from the preceding or following five years and missing values for marital status were replaced by available information from the preceding or following three years, whichever was closest to the date of delivery.

Statistical Analyses

Children were followed from the day of birth until the first hospitalization or first outpatient visit for the outcomes under study, death, emigration, or December 31, 2009, whichever came first. We used Cox proportional hazards models to estimate hazard ratios (HRs) with 95% confidence interval (95% CI) for both cerebral palsy and epilepsy in the children.

| Maternal infections during pregnancy | Total | Cases | IR/year (*10^-3) | HR (95% CI) 1 | Crude HR | HR (model 1) 2 | HR (model 2) 3 |
|------------------------------------|-------|-------|----------------|-------------|---------|--------------|--------------|
| Cerebral palsy                     |       |       |                |             |         |              |              |
| No infections (ref)                | 565,343 | 2,607 | 0.29           | 1.00        | 1.00    | 1.00         |              |
| Infections of the genitourinary system | 14,037 | 291  | 0.46           | 1.27        | 1.05–1.42 |              |              |
| Any other infections               | 9,556  | 53    | 0.34           | 1.15        | 0.88–1.51 | 1.13         | 0.86–1.49    |
| Epilepsy                           |       |       |                |             |         |              |              |
| No infections (ref)                | 565,343 | 9,411 | 1.08           | 1.00        | 1.00    | 1.00         |              |
| Infections of the genitourinary system | 14,037 | 291  | 1.49           | 1.27        | 1.05–1.42 |              |              |
| Any other infections               | 9,556  | 197   | 1.30           | 1.22        | 0.98–1.30 | 1.12         | 0.91–1.38    |

1The analyses were done in the entire study population (N = 588,936).
2Model 1 adjusted for sex, maternal age (five years intervals), maternal education (low, middle, and high), maternal marital status (married, other), family income (1st, 2nd, 3rd, and 4th quartile), and birth year (1982–1986, 1987–1990, 1991–1993, 1994–1998, 1999–2004).
3Model 2 adjusted for maternal infections before pregnancy (no infection, infections of the genitourinary system, and any other infections) in addition to the covariates in model 1.

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Table 3. Hazard Ratios (HRs) for cerebral palsy or epilepsy according to maternal infections before pregnancy.

| Maternal infections before pregnancy | Total Cases HR with 95% CI | Adjusted analyses* |
|-------------------------------------|---------------------------|-------------------|
|                                     | IR/year (*10^3) | Crude HR | Adjusted HR |
| Cerebral palsy                      |                           |               |             |
| No infections (ref)                 | 518,173 2,347 0.29 | 1.00 | 1.00 |
| Infections of the genitourinary system | 15,425 84 0.36 | 1.31 | 1.20 (0.96–1.49) |
| Any other infections                | 31,745 176 0.36 | 1.26 | 1.23 (1.06–1.43) |
| Epilepsy                            |                           |               |             |
| No infections (ref)                 | 518,173 8,480 0.06 | 1.00 | 1.00 |
| Infections of the genitourinary system | 15,425 336 1.47 | 1.37 | 1.35 (1.21–1.50) |
| Any other infections                | 31,745 595 1.24 | 1.17 | 1.03 (1.03–1.04) |

*The analyses were done in a restricted population (N = 588,936) of children of mothers without hospital-reported infections during pregnancy.

All multivariate analyses included the pre-specified covariates of maternal age (five year intervals), sex (boy, girl), maternal education (low, middle, and high), maternal marital status at birth (married, other), birth year (1982–1986, 1987–1990, 1991–1993, 1994–1998, 1999–2004), and family income at birth (1st, 2nd, 3rd, and 4th quartile).

The statistical analyses were done using Stata version 11 (StataCorp, College station, TX, USA).

Maternal infection during pregnancy. Children of mothers with infections of the genitourinary system or any other infection during pregnancy were compared to the reference group of children of mothers without infections during pregnancy. Two adjusted models were used for these analyses. Model 1 adjusted for the aforementioned covariates; model 2 adjusted for the aforementioned covariates in addition to maternal infections before pregnancy (no infection, infections of the genitourinary system, and any other infections) in order to control for maternal infections before pregnancy. All analyses were done in the entire study population (N = 588,936).

Maternal infection before pregnancy. Children of mothers with infections of the genitourinary system or any other infections before pregnancy were compared to the reference group of children of mothers without infections before pregnancy. Two approaches were used to estimate associations between maternal infections before pregnancy and our outcomes. In the first approach, we ran analyses in a restricted population of children whose mothers did not have any hospital-reported infections during pregnancy (N = 565,343). In the second approach, we ran analyses in the entire study population (N = 588,936) but adjusted for maternal infection during pregnancy (no infection, infections of the genitourinary system, and any other infections) in the model. Both approaches adjusted for the aforementioned pre-specified covariates.

We used a similar strategy when analysing associations between paternal infections and the outcomes under study.

Sensitivity analyses. Gestational age at birth was not included in the main analyses because gestational age may be an intermediate variable in the maternal infection and cerebral palsy or epilepsy causal pathways. Maternal infection is a strong risk factor for decreased gestational age [20–22], which in turn is a powerful risk indicator for cerebral palsy and epilepsy. [23–25] In addition, unmeasured and unknown confounders most likely confound the gestational age and outcome association. If gestational age is adjusted for or stratified on, collider bias may occur by inducing associations along otherwise controlled pathways. The extent and direction of the bias can be strong and unpredictable. [26,27] We did, however, perform sensitivity analyses where we included gestational week as a categorical variable (<33, 33-36, 37, 38, 39, 40, 41, and > = 42) in our model and repeated all analyses for associations between maternal infections and the outcomes under study.

Sub-group analyses for cerebral palsy. Since nationwide information on verified cases of cerebral palsy in the Danish Cerebral Palsy Register has only been available since 1996, [19]...
we performed a sub-group analysis and restricted the study population to children born between 1996 and 2002 (N = 180,238). Children were identified as having cerebral palsy if they were recorded in the Danish Cerebral Palsy Register. We repeated analyses to estimate hazard ratios between maternal infections and cerebral palsy.

**Results**

In the study population of first-born singletons (N = 588,936), 14,037 (2.38%) children were born to mothers who had infections of the genitourinary system or any other infections during pregnancy, respectively. The number of children born to mothers without any hospital-recorded infections during pregnancy was 565,343 (95.99%). Among children born to mothers without infections during pregnancy, 15,425 (2.73%) and 31,745 (5.62%) children had mothers with infections of the genitourinary system or any other infections before pregnancy, respectively. The singletons were followed from 0.45 to 27.7 years of age (median 15.4 years with an interquartile range of 9.6 to 21.0 years). Hospital-recorded infections occurred more frequently in women with lower education and in women who were not married when pregnant (Table 1).

**Maternal Infection during Pregnancy**

Maternal infections during pregnancy of the genitourinary system were associated with a significantly increased risk of cerebral palsy (HR = 1.63, 95% CI 1.34–1.98) and epilepsy (HR = 1.27, 1.13–1.42) in children when compared to women without maternal infections during pregnancy (Table 2). The increased risk remained when we further adjusted for maternal infection before pregnancy (Table 2).

**Maternal Infection before Pregnancy**

In the restricted analyses in women without infections during pregnancy, maternal infections before pregnancy of the genitourinary system and any other infections were associated with an increased risk of cerebral palsy (HR = 1.20, 95% CI: 0.96–1.49 and HR = 1.23, 95% CI: 1.06–1.43, respectively), and epilepsy in the offspring (HR = 1.35, 95% CI: 1.21–1.50 and HR = 1.12, 95% CI: 1.03–1.22, respectively) when compared to children born to mothers without infections before (and during) pregnancy (Table 3).

The patterns of association between maternal infection before pregnancy and our outcomes were very similar when we ran our analyses in the entire population, adjusting for maternal infection during pregnancy (Table 3).

The associations were similar when gestational age was included as a categorical variable in the analyses (data not shown).

When we restricted our analyses to children born between 1996 and 2002, and used cases of cerebral palsy identified by the Danish Cerebral Palsy Register [19], the patterns of association between maternal infections either before or during pregnancy and the risk of cerebral palsy remained similar, except that cerebral palsy was no longer significantly associated with infections of the genitourinary system during pregnancy (HR = 1.35, 95% CI: 0.86–2.11).

None of the associations between paternal infection and cerebral palsy or epilepsy in the offspring reached statistical significance (Table 4 and 5).

**Discussion**

Children born to mothers with hospital-recorded infections during pregnancy had an increased risk of cerebral palsy and epilepsy as well as children born to mothers with infections before pregnancy, even among mothers who did not have recorded hospitalized infections during pregnancy. This suggests that factors other than infection play a role in the observed associations. The maternal immune system could be a more distal factor in a causal pathway including infections, or as part of a different causal pathway, for example by modifying the immune response. Paternal infections had no associations with onset of cerebral palsy or epilepsy in the children, indicating that the increased risk is probably not due to genetic factors related to susceptibility to infections. The lack of an association between paternal infection and our outcomes suggests residual social confounding to be unlikely, however other confounders could play a role.

Several studies have explored the association between prenatal infection and the risk of neurological and psychiatric disorders. Intrauterine exposures to maternal infections, chorioamnionitis, and modest maternal fever during labour have been associated with an increased risk of cerebral palsy. [2,28–30] Furthermore, maternal infection during pregnancy has been associated with an increased risk of epilepsy, [4–6,31] schizophrenia, [32,33] autism, [34,35] and even multiple sclerosis, [36] but the causal mechanism(s) still remain undetermined. The link may be directly

| Table 5. Hazard Ratios (HRs) with 95% CI (confidence interval) of cerebral palsy and epilepsy according to paternal infections before partners’ pregnancy. |
|-----------------------------------------------|
| **Restricted analyses**  | **Adjusted analyses**  |
| **Cerebral palsy**        | **Total** | **Cases** | **Crude HR** | **Adjusted HR** | **Total** | **Cases** | **Adjusted HR** |
| ---                      |          |          |         |             |          |          |             |
| No (ref)                 | 550,826  | 2,576    | 1.00    |             | 552,934  | 2,599    | 1.00        |
| Yes                      | 32,339   | 164      | 1.09    | 1.09 (0.93–1.28) | 33,237   | 166      | 1.07 (0.92–1.26) |
| **Epilepsy**             |          |          |         |             |          |          |             |
| No (ref)                 | 550,826  | 9,234    | 1.00    |             | 546,218  | 9,315    | 1.00        |
| Yes                      | 32,339   | 564      | 1.09    | 1.08 (0.99–1.17) | 32,819   | 584      | 1.08 (0.99–1.17) |

1The analyses were done in a restricted population (N = 583,165) of children whose fathers did not have hospitalized infections during their partner’s index pregnancy.
2Adjusted for sex, maternal age (five years intervals), maternal education (low, middle, and high), paternal marital status (married, other), family income (1st, 2nd, 3rd, 4th quartile), and birth year (1982–1986, 1987–1990, 1991–1993, 1994–1996, 1999–2004).
3The analyses were done in the entire study population (N = 588,936).
4Adjusted for paternal infections during the partner’s pregnancy (yes or no) in addition to the covariates in the restricted analyses.

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mediated through an infection of the fetal brain; an indirect mechanism such as fever, cytokine exposure, dietary changes; or, confounding by subclinical impaired maternal immune function. The former mechanisms have been comprehensively reviewed. If maternal infections only play a direct causal role during pregnancy, then an association should not be observed for maternal infection occurring before pregnancy, as we found. These results could be confounded by factors causally related to brain exposures and risk of infection not controlled for in our adjustments. Dietary factors, occupational or environmental exposures, or even side effects of antibiotics could play a role.

Recent studies suggest that the maternal innate immune system, which represents the immunological first line defense against pathogens, plays a key role in pregnancy complications related to infections. [37–39] Variation in immune-regulatory genes may also influence host immune response to an altered vaginal flora. [40,41] A dysfunction of the maternal immune system may lead to an insufficient response to an infectious agent or reduce the ability to prevent an infectious agent from crossing the maternal-fetal barrier [42,43].

Women with a history of infection before pregnancy have significantly more infections during pregnancy than those without a history of infection. Since only infections resulting in a hospital visit were included in this study, it is possible that more mild infections not requiring a hospital visit play a role in the observed associations. Unfortunately we did not have information on these infections. We categorized infections in a broad way which could mask strong associations for specific infections. Infections of similar severity may be more likely to result in a hospital visit if occurring during pregnancy rather than before or after pregnancy, which would underestimate the associations between maternal infection before pregnancy and the outcomes under study. We were able to adjust for a number of variables in the analyses but we did not have data on lifestyle factors such as maternal smoking, pre-pregnancy body mass index, or dietary factors, which may be potential confounders.

Conclusions
An increased risk of cerebral palsy and epilepsy was found in children born to mothers who had hospital-recorded infection either before or during pregnancy. Even in mothers without hospital-recorded infection during pregnancy, we found an association between infections before pregnancy and the outcomes under study. These findings indicate that other non-genetic factors play a role. Genetic confounding is a less likely cause of these associations unless susceptible genes are inherited only through the maternal cell lines.

Supporting Information
Table S1 ICD-8 and 10 codes for infectious related to genitourinary system.
(DOC)
Table S2 ICD-8 and 10 codes for any other infections.
(DOC)

Author Contributions
Conceptualized the study: JO. Contributed to the study design: CSW LHP JEM YS ES PU JO. Drafted the manuscript: CSW. Contributed to the interpretation of the study: CSW LHP JEM YS ES PU JO. Analyzed the data: CSW. Wrote the paper: CSW LHP JEM YS ES PU JO.

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