

Contents lists available at [ScienceDirect](http://www.sciencedirect.com)

Annals of Epidemiology

journal homepage: www.annalsofepidemiology.org

Brief communication

Fever in pregnancy and offspring head circumference

Julie Werenberg Dreier PhD^{a,b,*}, Katrine Strandberg-Larsen PhD^a, Peter Vilhelm Uldall MD, PhD^c, Anne-Marie Nybo Andersen MD, PhD^a^a Section of Social Medicine, Department of Public Health, University of Copenhagen, Copenhagen, K, Denmark^b National Centre for Register-Based Research, Aarhus University, Aarhus V, Denmark^c Department of Pediatrics and Adolescent Medicine, Neuropediatric Unit, Copenhagen University Hospital, Copenhagen Ø, Denmark

ARTICLE INFO

Article history:

Received 20 June 2017

Accepted 29 November 2017

Available online xxx

Keywords:

Fever

Pregnancy

Microcephaly

Cohort studies

ABSTRACT

Purpose: To examine whether maternal fever during pregnancy is associated with reduced head circumference and risk of microcephaly at birth.**Methods:** A prospective study of 86,980 live-born singletons within the Danish National Birth Cohort was carried out. Self-reported maternal fever exposure was ascertained in two interviews during pregnancy and information on head circumference at birth was extracted from the Danish Medical Birth Registry.**Results:** Fever in pregnancy was reported by 27% of the mothers, and we identified 3370 cases of microcephaly (head circumference less than or equal to third percentile for sex and gestational age) and 1140 cases of severe microcephaly (head circumference less than or equal to first percentile for sex and gestational age). In this study, maternal fever exposure was not associated with reduced head circumference (adjusted $\beta = 0.03$, 95% confidence intervals [CI]: 0.01–0.05), increased risk of microcephaly (odds ratio: 0.95, 95% CI: 0.88–1.03) nor severe microcephaly (odds ratio: 1.01, 95% CI: 0.88–1.15) in the offspring. These findings were consistent for increasing numbers of fever episodes, for increasing fever severity, and for exposure in both early pregnancy and midpregnancy.**Conclusions:** In this most comprehensive study to date, we found no indication that maternal fever in pregnancy is associated with small head size in the offspring.

© 2017 Elsevier Inc. All rights reserved.

Introduction

Maternal fever during pregnancy has been hypothesized to interfere with fetal development and has been linked to a range of congenital malformations, such as heart defects, oral clefts, and neural tube defects [1–3]. Animal studies suggest that the brain is particularly susceptible to hyperthermia-induced defects [4], and among brain anomalies, microcephaly is the most common [5]. Head circumference at birth reflects brain volume and thus serves as an indicator of in utero brain development [6]. Nevertheless, in humans little is known about the relationship between maternal fever and offspring head size. In a small U.S. study, they found no excess prevalence of microcephaly among 54 women who had reported fever during the first trimester [7], but large-scale studies examining whether maternal fever in pregnancy affects offspring head circumference in general or risk of microcephaly in particular

are lacking. The aim of this study was therefore to examine whether maternal fever during pregnancy was associated with small head size at birth, in a large sample of Danish children.

Materials and methods

This study was based on the children in the Danish National Birth Cohort [8]. Pregnant women were enrolled into the cohort by their general practitioner between 1996 and 2002 and were invited to participate in two interviews during pregnancy concerning their lifestyle and health (at approximately gestational week 12 and 30 [range: week 7–40]). Maternal episodes of fever were recorded in each interview, along with specific details of each episode, such as timing (gestational week) and highest recorded temperature (°C). A woman was considered as exposed to fever if she in any of the two interviews reported a fever episode. Fever episodes were additionally divided into severity with a no fever group (temperature less than or equal to 37.6°C), low-grade fevers (greater than or equal to 37.7°C and less than 39°C), high-grade fevers (greater than or equal to 39°C), and fevers of unknown temperature (~49% of all women with fevers did not measure their temperature or were

The authors have no conflicts of interest to disclose.

* Corresponding author. National Centre for Register-Based Research, Aarhus University, Fuglesangs Allé 26, 8210 Aarhus V, Denmark. Tel.: +4525621178; fax: +4587164601.

E-mail address: jwdreier@econ.au.dk (J.W. Dreier).<https://doi.org/10.1016/j.annepidem.2017.11.011>

1047-2797/© 2017 Elsevier Inc. All rights reserved.

unable to recall the exact temperature). Written informed consent was obtained from all cohort participants before entering the study, and the study was approved by the Danish Data Protection Agency (journal number: 2013-41-1431).

Head circumference at birth (in centimeters, integer values) was extracted from the Danish Medical Birth Registry, by linkage using the child's unique personal identification number. Microcephaly and severe microcephaly at birth were defined as head circumference below the third and first percentile for sex and gestational age, respectively, using a Swedish reference population [9]. In the registry, gestational age at birth is based on the best clinical estimate at birth, based on the last menstrual period, ultrasound estimation, and the maturation of the child. A total of 90,508 pregnancies with information from either or both pregnancy interviews and resulting in live-born singletons were eligible for inclusion in this study. Missing information on head circumference ($n = 2620$), maternal fever exposure ($n = 186$), or covariates ($n = 722$) resulted in a sample of $n = 86,980$ children.

Linear and logistic regression models were used to examine the associations between maternal fever and, respectively, head circumference and microcephaly. Analyses were conducted to examine the association with fever in pregnancy (yes/no), number of fever episodes (none, 1, 2, and greater than or equal to 3), fever of varying severity (no fever, low-grade fever, high-grade fever, and unknown temperature), and exposure during different gestational periods (first trimester, second trimester). All analyses were adjusted for maternal age at birth, maternal education, and household income in the year before birth, which were all retrieved from the registers, and for maternal smoking in pregnancy, reported in the first interview (never smoked in pregnancy [non-smokers], smoked initially but stopped before being interviewed [former smokers], and current smokers [light: 1–9 cigarettes per day and heavy: greater than or equal to 10 per day]). Analyses of head circumference were additionally adjusted for completed gestational weeks at birth. The analyses were conducted using Stata (StataCorp, College Station, TX) and robust standard errors were used to correct for the dependency between siblings in the sample ($n = 6126$ sibships).

Results

Fever in pregnancy was reported in approximately 27% of pregnancies. Women who reported fever episodes tended to have higher levels of education and to smoke more, and their children were born closer to term, when compared to unexposed mothers and children, see [Table 1](#). The mean head circumference at birth in this sample was 35.3 cm. (SD: 1.75), and 3370 (3.9%) cases of microcephaly (head circumference less than or equal to third percentile for sex and gestational age) as well as 1140 (1.3%) cases of severe microcephaly (head circumference less than or equal to first percentile for sex and gestational age) were identified.

We did not find any evidence to support that maternal fever during pregnancy was associated with small head size in the child, when measured at birth ([Table 2](#)). The absence of any negative effect was evident for various measures of head size (head circumference, microcephaly, and severe microcephaly), and for increasing numbers of fever episodes, for increasing fever severity, and for exposure in both early pregnancy and midpregnancy. In some of the analyses, however, maternal fever did seem to be associated with a marginally larger head circumference (approximately 0.3–0.8 mm). Sensitivity analyses revealed that this slight increase was not explained by an elevated risk of the child having macrocephaly or severe macrocephaly defined as head circumference above the 97th and 99th percentile for sex and gestational age, respectively (data not shown).

Table 1

Characteristics of the study population ($n = 86,980$), according to maternal fever episodes in pregnancy

Characteristic	Fever, N = 23,962, n (%)	No fever, N = 63,018, n (%)	P-value*
Maternal age at birth			<.001
<24 y	3051 (12.7)	8186 (13.0)	
25–29 y	9871 (41.2)	26,288 (41.7)	
30–34 y	8429 (35.2)	21,204 (33.7)	
≥35 y	2611 (10.9)	7340 (11.7)	
Maternal education at birth			<.001
Primary education	2697 (11.3)	7140 (11.3)	
Secondary education	9779 (40.8)	27,486 (43.6)	
Higher education	11,486 (47.9)	28,392 (45.1)	
Household income in year before birth			.162
Lowest quintile	4752 (19.8)	12,706 (20.2)	
Second quintile	4806 (20.1)	12,657 (20.1)	
Medium	4717 (19.7)	12,630 (20.0)	
Fourth quintile	4809 (20.1)	12,647 (20.1)	
Highest quintile	4878 (20.4)	12,378 (19.6)	
Maternal smoking in pregnancy			<.001
Nonsmokers	17,483 (73.0)	47,212 (74.9)	
Former smokers	2340 (9.8)	5594 (8.9)	
Light smokers (1–9 cigarettes/d)	2251 (9.4)	5690 (9.0)	
Heavy smokers (≥10 cigarettes/d)	1888 (7.9)	4522 (7.2)	
Completed gestational weeks at birth			<.001
<37	854 (3.6)	2614 (4.2)	
37–41	21,044 (87.8)	54,739 (86.9)	
≥42	2064 (8.6)	5665 (9.0)	

* Pearson's χ^2 test for categorical data and two-sample t test for numerical variables.

Discussion

In this large prospective study, we did not find any evidence to suggest that maternal fever in pregnancy causes reduced head size in the offspring. We had access to detailed information on maternal fever exposure, which allowed us to examine for dose-response and timing-specific effects, and none of these analyses were indicative that maternal fever at any time or to any extent was associated with small head size in the child.

Minor positive associations were found in some of the analyses, suggesting that children born to mothers who experienced fevers in pregnancy had slightly larger heads. Although prenatal infections are known risk factors of hydrocephalus [10], which leads to enlarged head circumference, our analyses did not suggest that prenatal fever exposure was associated with macrocephaly. Given that women who reported fevers tended to have higher education and income, this could indicate that these results could (at least partly) be attributable to residual confounding by factors related to socioeconomic position. Furthermore, as many analyses were conducted, we cannot exclude that it was a chance finding.

Until now, little evidence from human studies exists on the association between maternal fever in pregnancy and head circumference at birth. Our results are, however, in line with the study by Little et al., finding no excess prevalence of microcephaly in the offspring born to fever-exposed mothers [7]. In addition, in a large U.S.-based study of 109,015 pregnancies, maternal seasonal influenza in pregnancy (which is frequently accompanied by high fever) was not associated with a head circumference below the 10th percentile in the offspring (odds ratio: 1.14, 95% confidence interval: 0.76–1.67) [11].

Our findings do, however, stand in contrast to the growing evidence that maternal hyperthermia in pregnancy (either by fever or

Download English Version:

<https://daneshyari.com/en/article/8753296>

Download Persian Version:

<https://daneshyari.com/article/8753296>

[Daneshyari.com](https://daneshyari.com)