

W Fever in pregnancy and risk of fetal death: a cohort study

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Summary

Background Hyperthermia acts as a teratogen in some animals where it can induce resorption of the fetus and fetal death. Fever during pregnancy, especially in the period of embryogenesis, is also suspected as being a risk factor for fetal death in human beings. We did a large cohort study in Denmark to investigate this possibility.

Methods We interviewed 24 040 women who were recruited in the first half of pregnancy to the Danish National Birth Cohort Study, and obtained information on the number of fever incidents during the first 16 weeks of pregnancy. For each fever episode, the highest measured body temperature, duration of incident, and gestational age were recorded. Outcomes of pregnancies were identified through linkage with the Civil Registration System and the National Discharge Registry. Cox's regression with time-dependent variables was used to estimate the relative risk of fetal death, taking delayed entry into account.

Findings 1145 pregnancies resulted in a miscarriage or stillbirth (4.8%). During the first 16 pregnancy weeks 18.5% of the women experienced at least one episode of fever. However, we found no association between fever in pregnancy and fetal death before or after adjustment for known risk factors of fetal death (relative risk 0.95 [95% CI 0.80–1.13]). This finding was consistent irrespective of measured maximum temperature, duration and number of fever incidents, or the gestational time of the fever incident, and was observed for fetal death in all three trimesters of pregnancy.

Interpretation We found no evidence that fever in the first 16 weeks of pregnancy is associated with the risk of fetal death in clinically recognised pregnancies.

Lancet 2002; **360**: 1552–56. Published online Oct 22, 2002
<http://image.thelancet.com/extras/01art12058web.pdf>

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Introduction

Results of several studies in guineapigs, rats, mice, sheep, and monkeys have shown that hyperthermia in pregnancy is associated with resorption of the embryo, fetal deaths, and potentially lethal malformations such as central-nervous-system defects, abdominal-wall defects, and cardiovascular malformations.^{1–6} Hyperthermia interferes with protein synthesis via heat-shock proteins, inducing cell death in the S-phase of the cell cycle by apoptosis and delay of mitotic activity in M-phase cells, and causing vascular disruption and placental infarction. All these mechanisms can lead directly to death of the embryo or to severe and lethal malformations. Furthermore, heat-induced increased uterine contractility can lead to expulsion of the fetus at a non-viable stage of gestation. The possible mechanisms of hyperthermia-induced fetal loss differ according to gestational time of exposure.⁷

The results of animal experiments suggest that a similar effect might occur in human beings.^{7–9} Some researchers have found maternal exposure to heat (endogenous [eg, fever] and exogenous [eg, hot tubs and saunas]) to be associated with neural-tube defects,^{10–14} whereas others have reported no such association.^{15,16} Fever and upper-respiratory-tract infection, but not sauna bathing or high workplace temperature, were found to be associated with cardiovascular malformations in a case-control study.¹⁷ However, few studies in human beings have addressed fever as a risk factor for fetal death. In a case-control study by Kline and colleagues, fever was associated with miscarriage of normal-karyotype fetuses (odds ratio 2.96 [95% CI 1.99–4.41]), but not of abnormal-karyotype fetuses.¹⁸ This finding was taken as evidence that fever was a risk factor for miscarriage rather than a consequence of it.

A recent study, based on women who made inquiries to a teratology information programme, showed no association between maternal fever and miscarriage, but women with fever had a significantly increased risk of stillbirth.¹⁹ A study from the Collaborative Perinatal Project found no association between fever in the first trimester and late intrauterine death, but no data were available from which to address fetal deaths in the first half of pregnancy.¹⁶

The purpose of this study was to investigate the association between fever incidents and fetal death in a large population-based cohort. We expected fever, especially fever early in pregnancy, high fever, and fever of long duration, to be associated with fetal death. We focused on fever in the first 16 weeks of pregnancy when an adverse effect on the fetus is most likely to occur.

Methods

Participants

The study was done within the Danish National Birth Cohort, which is an ongoing nationwide study of pregnant women and their offspring. For this study, we used data

from all pregnant women recruited to the Danish National Birth Cohort from Oct 1, 1997, to Mar 31, 1999. Recruitment to the cohort took place after the first antenatal visit to the general practitioner, which is scheduled as early as possible after recognition of pregnancy. The pregnant woman received written information about the Danish National Birth Cohort at the antenatal visit, and was included in the cohort if we received an informed consent form.

Participants provided information on exposures during the first part of pregnancy by means of a computer-assisted telephone interview, scheduled to take place in pregnancy weeks 12–16. In case of fetal death before completion of this interview, participants were offered a similar interview. However, a few questions were omitted from the retrospective interview; namely those that were considered to be sensitive to recall bias, eg, general statements about psychological wellbeing in pregnancy. The interviews covered questions on events during the first 16 weeks of pregnancy (including fever), reproductive history, occupation, smoking status, alcohol consumption, and coffee intake. All women were asked about incidents of fever during pregnancy. Number of fever episodes was recorded, and for each episode details such as duration, highest body temperature, and gestational weeks in which fever was present were noted.

The outcome measure of interest was fetal death—ie, miscarriage and stillbirth. According to national standards, a stillbirth is defined as the birth of a child showing no signs of life and with a gestational age of 28 weeks or more. Miscarriage is defined as a non-deliberate fetal death of an intrauterine pregnancy before 28 completed weeks of gestation. The pregnancy outcomes were identified from the Civil Registration System, the National Discharge Registry, and the participating mothers. All citizens in Denmark, including liveborn children, are registered in the Civil Registration System and given a unique number which is used in all national registers to identify that person. Linkage between registers can be made on the basis of this number. In the Civil Registration System there is a link between mother and child. By record linkage with the Civil Registration System, we identified liveborn offspring from all pregnancies in the cohort. From the National Discharge Registry, which contains information about all citizens diagnosed or treated in a hospital setting, we obtained information about other pregnancy outcomes: ectopic pregnancy, induced abortion, hydatidiform mole, and miscarriage and stillbirth. In case we could not identify outcome of pregnancy by these two procedures, we used information about outcome of pregnancy obtained from the mother and registered in the Danish National Birth Cohort Study. Gestational age at fetal loss or birth was calculated from the last menstrual period, which was reported in the informed consent form. Gestational age was reported in initiated gestational weeks, termed pregnancy weeks.

Permission from the Danish Data Protection Board and the National Scientific Ethics Committees were obtained before the start of the study.

Statistical analysis

The relative risk of fetal death after recruitment according to history of fever during pregnancy was calculated by Cox's regression. Women entered the cohort on the day of signing the informed consent form (delayed entry).²⁰ Gestational days (days since last menstrual period) were used as the underlying time variable. Follow-up ended at the time of fetal death, livebirth, induced abortion, hydatidiform mole, or ectopic pregnancy.

In the analyses of the association with fever in three specific gestational periods (pregnancy weeks 1–8, 9–12, and 13–16), the women entered the cohort at the beginning of the specific gestational period, or at the time of signing the informed consent form if this was later than the beginning of the specific gestational period. Only women who were interviewed in the specific gestational period or later were included in these analyses. In the analyses of the subcohort restricted to women interviewed during pregnancy, follow-up started from time of interview.

In the analyses of intensity of fever exposure, the maximum temperature was categorised as less than 39.0°C, 39.0°C or more, or temperature unknown. Duration of fever was calculated as total number of days with fever during pregnancy (1 day, 2–3 days, or 4 days or more); and number of fever incidents was recorded as either as one, or more than one.

All fever variables were treated as time-dependent variables, the variable thus reflecting the status at a given time of follow-up. For example, if a woman had two episodes of fever with measured maximum temperatures of 38.0°C and 39.5°C, respectively, she would be included in the “no fever” group during follow-up before the first incident, in the “below 39.0°C” group in the period of follow-up between the two incidents, and in the “39.0°C or more” group in the period of follow-up after the second fever incident.

All estimates were adjusted for maternal age (≤ 19 years, 20–24 years, 25–29 years, 30–34 years, or ≥ 35 years); number of previous miscarriages (0, 1, 2, or ≥ 3); parity (0 or ≥ 1), average daily number of cigarettes during pregnancy (0, < 10 , or ≥ 10); average weekly alcohol intake during pregnancy (0 drinks, 0.5–2 drinks, 2.5–7 drinks, or ≥ 7.5 drinks); average daily coffee consumption during pregnancy (0 cups, 1–7 cups, or ≥ 8 cups); and employment in daycare facilities (yes or no). Work in day-care facilities includes other suspected risk factors, eg heavy lifting, and there might also be an association between day-care work and infections (fever).

Likelihood ratio tests were used to test for homogeneity. The frequency of fever according to gestational age in the cohort was described by the Kaplan-Meier estimator. In this analysis, women were followed up from the beginning of pregnancy week 1 to the date of fetal death, pregnancy interview, or end of pregnancy week 16, whichever came first.

Cox's regression models were analysed with the SAS procedures software package PROC PHREG.²¹

Role of the funding source

The sources of funding had no involvement in the study design, data collection, data analysis, data interpretation, or reporting of the results.

Results

During the study period, 27 432 pregnant women were recruited to the Danish National Birth Cohort Study. Interviews were obtained from 24 040 women. Of these, 1145 (4.8%) had miscarriages or stillbirths. Table 1 shows the outcome of pregnancy, gestational age at enrolment and at interview, and the mode of collection of exposure data in the cohort.

Overall, 3752 of the women reported at least one episode of fever within the first 16 weeks of pregnancy. This corresponds to 18.5% of the women having experienced fever during the first 16 weeks of pregnancy, based on the Kaplan-Meier estimator (figure).

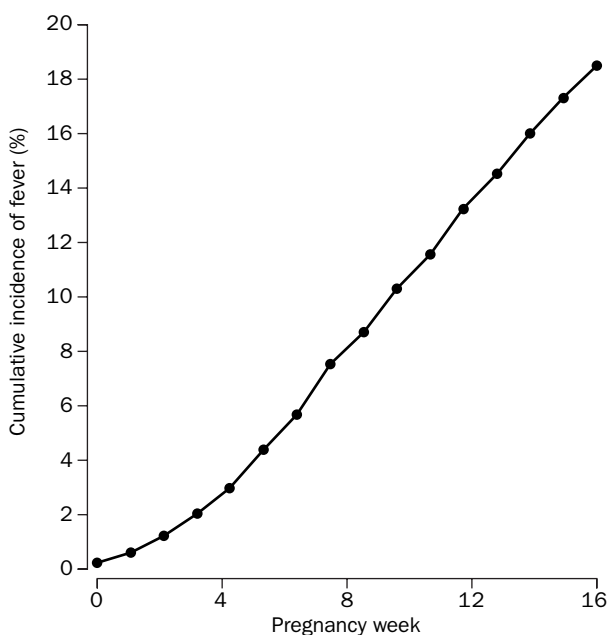
	Total cohort (n=24 040)	Prospectively collected data (n=23 262)	Retrospectively collected data (n=778)
Outcome of pregnancy			
Livebirth	22 795	22 794	1*
Fetal death	1145	390	755
First trimester	557	41	516
Second trimester	474	236	238
Third trimester	112	111	1
Trimester at event missing	2	2	0
Induced abortion on indication	65	50	15
Other pregnancy outcomes†	9	2	7
Loss to follow-up‡	26	26	0
Pregnancy week at recruitment			
≤6	902	816	86
7–8	3495	3255	240
9–10	6136	5892	244
11–12	5622	5473	149
13–16	5771	5724	47
17–20	1653	1644	9
21–28	460	458	2
≥29	1	0	1
Pregnancy week at interview			
6–8	..	3	..
9–12	..	3016	..
13–16	..	9173	..
≥17	..	11 070	..

*Representing a woman with an extremely preterm livebirth. †Including seven ectopic pregnancies and two cases of hydatidiform mole. ‡Including 15 women who emigrated during pregnancy.

Table 1: Pregnancies included in the study

Of those with fever, 2187 women (58.3%) provided a maximum temperature, and of these 974 (44.5%) reported incidents of 39.0°C or above. 3703 women (98.7%) reported the length of their fever incidents, which was distributed as follows: 1 day 827 (22.3%), 2–3 days 1999 (54.0%), and 4 days or more 877 (23.7%). 341 women (9.1%) reported more than one episode with fever.

Table 2 shows the association between fever in pregnancy and risk of fetal death. Overall, the risk of fetal death in women reporting fever in the first 16 weeks of



Cumulative incidence of fever according to pregnancy week based on Kaplan-Meier estimator

	Total cohort*			Subcohort† relative risk (95% CI)‡
	Fetal deaths	Fetus- weeks at risk	Relative risk (95% CI)‡	
Overall risk of fetal death				
No fever	986	545 292	1.00	1.00
episodes				
Fever in pregnancy week 1–16	147	103 191	0.95 (0.80–1.13)	0.96 (0.72–1.26)
Trimester-specific risk of fetal death				
First-trimester fetal loss	76	7064	0.92 (0.72–1.16)	0.97 (0.51–1.84)
Second-trimester fetal loss	54	55 222	0.95 (0.71–1.27)	0.87 (0.59–1.26)
Third-trimester fetal loss (stillbirth)	17	40 905	1.16 (0.69–1.97)	1.19 (0.70–2.02)

*Exposure data collected prospectively and retrospectively. †Exposure data collected prospectively. ‡Adjusted for maternal age, number of previous miscarriages, parity, occupation in daycare, and smoking, alcohol consumption, and coffee consumption during pregnancy.

Table 2: Adjusted relative risks of fetal death according to fever in pregnancy week 1–16

pregnancy did not differ from that in women who did not report fever. This estimate did not change when adjusted for maternal age, number of previous miscarriages, parity, work in children's daycare (nursery, kindergarten), and consumption of tobacco, alcohol, and coffee during pregnancy. Inclusion of pregnancies that ended in induced abortion on indication in the fetal death group did not change this result. When pregnancies that ended in induced abortion on indication were included, the adjusted relative risk of fetal death in women who did report fever was 0.99 (95% CI 0.84–1.16) compared with those who did not report fever (data not shown).

To estimate the specific risk of fetal death in the first and second trimester (ie, miscarriage) and in the third trimester (ie, stillbirth), we calculated the risks of fetal death according to fever for the three trimesters of

	Total cohort*			Subcohort† relative risk (95% CI)‡
	Fetal deaths	Fetus- weeks at risk	Relative risk (95% CI)‡	
Gestational age at fever incident§				
Pregnancy week 1–8	93	49 220	1.03 (0.83–1.27)	0.88 (0.60–1.30)
Pregnancy week 9–12	49	37 204	0.91 (0.69–1.22)	1.17 (0.80–1.73)
Pregnancy week 13–16	14	23 558	0.95 (0.56–1.62)	0.84 (0.41–1.71)
Maximum temperature¶				
≤38.9°C	37	33 762	0.74 (0.53–1.02)	0.79 (0.49–1.29)
>39.0°C	34	26 912	0.88 (0.62–1.23)	1.21 (0.75–1.95)
Unknown	76	42 517	1.16 (0.92–1.47)	0.99 (0.66–1.48)
Number of days with fever¶				
1	33	22 704	1.05 (0.74–1.49)	0.85 (0.48–1.51)
2–3	76	55 081	0.91 (0.72–1.15)	0.95 (0.66–1.37)
>4	36	24 097	0.95 (0.68–1.33)	1.13 (0.68–1.86)
Unknown	2	1 309	1.14 (0.28–4.56)	..
Number of fever incidents¶				
1	137	92 858	0.97 (0.81–1.16)	0.93 (0.70–1.25)
>2	10	9 336	0.88 (0.47–1.64)	1.30 (0.61–2.74)
Unknown	0	998

*Exposure data collected prospectively and retrospectively. †Exposure data collected prospectively. ‡Adjusted for maternal age, number of previous miscarriages, parity, occupation in daycare, and smoking, alcohol consumption, and coffee consumption during pregnancy. §Relative risks calculated with no fever in the specific pregnancy weeks as reference group. Number of fetal deaths add up to more than 147 because some women had fever episodes in more than one gestational period. ¶Relative risks calculated with women with no fever episodes as reference group.

Table 3: Adjusted relative risks of fetal death according to characteristics of fever in pregnancy week 1–16

pregnancy separately (table 2). Test for homogeneity (proportional hazards) showed no difference between these estimates ($p=0.72$).

The risks of fetal death according to several characteristics of the fever incident are presented in table 3. We estimated the risk of fetal death according to gestational period of the exposure (fever in pregnancy week 1–8, 9–12, or 13–16). All these estimates were around 1 and not significantly different from each other ($p=0.73$). The risk of fetal death was not influenced by level of maximum temperature, and homogeneity test showed no significant difference between the risk estimates in the two groups with measured temperature ($p=0.46$). Furthermore, the risk of fetal death was not affected by temperature level according to gestational age at exposure (data not shown). Finally, neither the number of days with fever nor the number of fever episodes was associated with risk of fetal death. A test for interaction between temperature level and duration of fever incident showed no significant interaction ($p=0.41$).

We repeated all analyses in the subcohort of women who were interviewed during pregnancy and followed up from the pregnancy interview and onwards—ie, restricted to prospectively collected exposure information. These analyses gave a similar overall relative risk of fetal death according to fever in the first 16 weeks of pregnancy (table 2). The risk estimates according to gestational age at fever incident, measured maximum temperature, duration, and number of fever incidents were also close to the findings in the total cohort (table 3).

Discussion

In this cohort study of more than 24 000 women, we found fever to be a common phenomenon during pregnancy with 18.5% having experienced at least one episode of fever within the first 16 weeks of pregnancy. However, fever did not influence the risk of fetal death after pregnancy week 6—ie, the period when a pregnancy becomes clinically apparent. This lack of association was consistent when the effect of fever during specific gestational periods of pregnancy, the maximum temperature, number of days with fever, and number of fever episodes were taken into account. The CIs for the relative risks associated with fetal death were narrow, which indicates a high credibility of this negative finding.

The most frequently reported suspected teratogenic effects of hyperthermia in human beings are neural-tube defects and cardiac malformations. Since most embryos with serious malformations are miscarried, we examined whether fever in pregnancy weeks 1–8 (the gestational period of neural-tube closure and heart development) was associated with fetal death. We found no such indication. In fact, fever was not associated with fetal death at any gestational age.

Fever is a response to an underlying disease, usually an infection. Febrile diseases such as fifth disease,²² listeriosis,²³ and psittacosis²⁴ during pregnancy have been associated with fetal death. Since these infections are rare events, and thus account for only a small proportion of all infections, our results do not necessarily contradict such findings. This study shows that fever per se is not a risk factor for fetal death, and furthermore lends support to the suggestion that common febrile infections are infrequent causes of miscarriage.^{25,26}

Animal experiments indicate that a temperature increase of 2°C above normal body temperature serves as a threshold for teratogenesis, irrespective of the normal body temperature of the species.⁷ We found no indication of this finding with respect to fetal death in human beings. In

Denmark, fever is usually measured as rectal temperature. The given temperature in our study is therefore likely to be taken as a measure of core temperature. The indicated maximum temperature is not necessarily the real maximum temperature for the event, but only the measured one. However, measured values are likely to correlate closely with the real maximum temperature. Experiments in rats have indicated that temperature could modify the effect of the duration of fever on teratogenesis,²⁷ but we found no support for this finding on the basis of an analysis of interaction between temperature and duration of fever episode. However, the number of women with high level of fever and a long duration of the episode was limited even in a large study like ours.

In human beings, prospective study of the association between fever early in pregnancy and fetal death is difficult. We are aware of only one study that addressed fever and fetal death in a population-based cohort design, and this study had no data from the first part of pregnancy because recruitment took place in midgestation.¹⁶ An ideal study that uses exclusively prospectively collected data on fever in pregnancy should begin at conception and collect exposure information frequently, ideally on a daily basis.

The overall risk of fetal loss from the beginning of pregnancy week 6 has been estimated at 11.5% in a fetal life-table analysis of these data.²⁸ The stillbirth rate in our cohort (4.9 per 1000 births) is similar to the national stillbirth rate in Denmark during 1980–95. These figures indicate that selection bias according to outcome in the cohort was negligible.

The main limitation of this study is that risk of fetal death before pregnancy week 6 could not be assessed. We have no data on very early pregnancy losses and cannot rule out that fever is associated with fetal losses in the preclinical phase of pregnancy. We took advantage of the cohort design and thus avoided the problems associated with selection of an appropriate control group. However, recall bias can be a problem in retrospectively collected data. Findings from other reports indicate that recall bias in studies of reproductive outcomes tends to account for higher reporting of potentially hazardous exposures after an adverse pregnancy outcome.²⁹ However, a study of recall bias after miscarriage in a cohort study with a design similar to ours showed a small and consistent pattern of reporting exposures less frequently after miscarriage.³⁰ Furthermore, we were reassured by our finding of similar risk estimates in the whole cohort and in the subcohort in which all exposure data were obtained before the outcome of pregnancy was known. This similarity indicated that recall bias was not a serious problem for this exposure.

In conclusion, fever in the first 16 weeks of pregnancy does not increase risk of fetal death. The size and prospective design of this study give high credibility to these results. Therefore, pregnant women need not fear a fetal death after an episode of fever.

Contributors

The study idea was conceived by M Melbye and A-M Nybo Andersen. The study design and analytical strategy were developed by A-M Nybo Andersen, J Wohlfahrt, M Melbye, J Olsen, and P Kragh Andersen. P Vastrup and J Wohlfahrt managed data and did the statistical analyses. A-M Nybo Andersen wrote the first version of the paper and all authors took part in the revision.

Conflict of interest statement

None declared.

Acknowledgments

The study was supported by the Danish Ministry of Health Research Centre for Environmental Health Fund. The Danish National Research Foundation established the Danish Epidemiology Science Centre that

initiated and created the Danish National Birth Cohort. The Cohort is furthermore a result of a major grant from this foundation. Additional support for the Danish National Birth Cohort is obtained from the Pharmacy Foundation, the Egmont Foundation, the March of Dimes Birth Defects Foundation, and the Augustinus Foundation.

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