SHORT REPORT

Pre-eclampsia and febrile convulsions

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Arch Dis Child 2003;88:726–727

An association between pre-eclampsia and febrile convulsions has been reported, but the association may not be causal. We compared the risk of febrile convulsions in 14 974 children who had been exposed to pre-eclampsia in fetal life with that of 39 210 unexposed children. Children exposed to pre-eclampsia had a slightly increased risk of febrile convulsions, but the association was apparently caused by a shorter gestation in pre-eclamptic women.

Pre-eclampsia occurs in approximately 3% of all pregnancies, and is characterised by pregnancy induced hypertension and proteinuria. Children of pre-eclamptic women have an increased risk of preterm birth, intrauterine growth retardation, and perinatal death,^{1,2} but little is known about the impact of pre-eclampsia on childhood morbidity. Two studies have found an increased risk of febrile convulsions in children exposed to pre-eclampsia,^{3,4} but these findings are in conflict with earlier studies.^{5,6} A positive association could suggest that either pre-eclampsia or its treatment may have an adverse effect on the developing brain, or that the association is an epiphenomenon to the well known link between pre-eclampsia and preterm birth.

We evaluated the association between pre-eclampsia and febrile seizures in a large population based cohort study of children born to primiparous women.

METHODS

We performed a follow up study based on information from three population based registries in Denmark. The National Hospital Register contains information on almost all (99.4%) patients admitted to Danish hospitals. Diagnostic information is classified according to a Danish version of the International Classification of Diseases (ICD); ICD8 from 1980 to 1993 and ICD10 from 1994 to 1998. Using the National Hospital Register, we identified all pregnancies complicated by mild pre-eclampsia (ICD8: 63703; or ICD10: O140), severe pre-eclampsia (63704 or O141), or eclampsia (63719 or O15). We omitted all diagnoses with modification code "suspected" and

"not found". The information from the National Hospital Register was linked to the Medical Birth Registry by means of the civil registration number assigned to all Danish citizens at birth. We then identified singleton children of primiparous women who had been hospitalised with pre-eclampsia ($n = 14\,974$), and a random sample of single born children of primiparous women who had not been hospitalised with pre-eclampsia ($n = 39\,210$). All the children were born between 1 January 1980 and 31 December 1994. Information about the social status of the family and residence at birth was obtained from Statistics Denmark's Fertility database. We included children with febrile convulsions (ICD8: 780.21; or ICD10: R56.0) if they were between 3 and 60 months old at the day of discharge and had no recorded history of epilepsy, cerebral palsy, severe head trauma, intracranial tumours, meningitis, or encephalitis.

We used a Cox proportional hazards model to assess hazard ratios (HR) and 95% confidence intervals (95% CI) for febrile convulsions. The follow up period for febrile convulsions began at the age of 3 months and ended on the day of admission for febrile convulsions, day of death, on the child's fifth birthday, or 31 December 1998, whichever came first.

RESULTS

We followed 54 184 children (14 974 exposed and 39 210 unexposed) for 247 927 person-years (median 4.748; range 0.01 to 4.75 years), and identified 2066 children who had been hospitalised with febrile convulsions at least once.

Children exposed to pre-eclampsia in fetal life had a small, but statistically significant, increased risk of febrile convulsions (HR: 1.12; 95% CI: 1.02 to 1.23) compared with unexposed children. The risks increased from mild (HR: 1.09; 95% CI: 0.98 to 1.21) to severe pre-eclampsia (HR: 1.28; 95% CI: 1.07 to 1.53), but we found no association between exposure to eclampsia and febrile convulsions. However, the statistical precision of the latter estimate was limited as shown by the wide confidence interval. Adjustment for maternal age (<25, 25–34, >34 years), citizenship of the mother (Danish, not Danish), social class of the family (low, middle, high), year at birth (1980–84, 1985–89, 1990–94), residence at time of birth (large city, small city, rural), and gender of the child did not change the results (table 1).

The risk of preterm birth (<37 completed weeks of gestation) was 4.4%, 6.5%, 42.1%, and 26.9% for women with

Table 1 Risk of febrile convulsions in children exposed to pre-eclampsia

Pre-eclampsia	Person-years	No. of febrile convulsions	HR	(95% CI)	HR*	(95% CI)
No	179596	1447	1.00	Reference	1.00	Reference
Yes	68331	619	1.12	(1.02 to 1.23)	1.13	(1.03 to 1.25)
Mild	54446	478	1.09	(0.98 to 1.21)	1.10	(1.00 to 1.22)
Severe	12873	133	1.28	(1.07 to 1.53)	1.27	(1.07 to 1.52)
Eclampsia	1012	8	0.97	(0.49 to 1.95)	0.98	(0.49 to 1.96)

*Adjusted for maternal age and citizenship, social status of the family, year of birth, residence at time of birth, and gender of the child.

Table 2 Febrile convulsions according to pre-eclampsia and gestational age at birth in Denmark 1980–94

Gestational age at birth	Pre-eclampsia	Person-years at risk	No. of febrile convulsions	HR	95% CI
37–42 weeks	No	148841	1179	1.00	Reference
	Mild	44841	375	1.06	(0.95 to 1.19)
	Severe*	7502	63	1.07	(0.83 to 1.36)
34–36 weeks	No	5947	70	1.00	Reference
	Mild	2804	34	1.03	(0.68 to 1.55)
	Severe*	3167	37	0.99	(0.67 to 1.48)
<34 weeks	No	1763	22	1.00	Reference
	Mild	690	11	1.27	(0.62 to 2.62)
	Severe*	2471	33	1.07	(0.62 to 1.83)

*Including severe pre-eclampsia and eclampsia.

no pre-eclampsia, mild pre-eclampsia, severe pre-eclampsia, and eclampsia, respectively. As shown in table 2, the association between pre-eclampsia and febrile convulsions disappeared after stratifying the data by gestational age at birth. Stratification for “birth weight for gestational age” did not change the results (data not shown).

DISCUSSION

Children exposed to pre-eclampsia in fetal life had a slightly increased risk of febrile convulsions, but this was apparently caused by a higher incidence of preterm birth in women with pre-eclampsia.

Our study has strengths and limitations. It was based on information from nationwide registers with complete follow up, which eliminates bias caused by selection of study subjects. The registers gave us substantially more statistical precision than previous studies. The information was furthermore collected prospectively—that is, independently of parental recall. The National Hospital Register depends on routinely collected data, and some cases may not have fulfilled the criteria for pre-eclampsia, while others were probably missed. Non-differential misclassification will bias the results towards no association, but does not explain why stratification by gestational age eliminated the association between pre-eclampsia and febrile seizures. The results remained unchanged when the analyses were restricted to women living in cities with highly specialised obstetric departments. Some children may not be hospitalised for febrile convulsions, but we expect the number to be small since febrile convulsions are a frightening experience for most parents, especially for first-time parents. Furthermore, all health services, including hospitalisation, are free of charge in Denmark. We therefore find it unlikely that bias can explain our finding. Based on our estimates, we believe that the association between pre-eclampsia and febrile convulsions is mediated by gestational age.

ACKNOWLEDGEMENTS

The study was supported by grants from the Danish Medical Research Council (j.nr 9802019), The Danish Epilepsy Society, and Ronald McDonald House Charities. The activities of the Danish Epidemiology Science Centre are financed by a grant from the National Danish Research Foundation.

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Accepted 16 November 2002

REFERENCES

- 1 Churchill D, Perry IJ, Beevers DG. Ambulatory blood pressure in pregnancy and fetal growth. *Lancet* 1997;**349**:7–10.
- 2 Cnattingius S, Haglund B, Kramer MS. Differences in late fetal death rates in association with determinants of small for gestational age fetuses: population based cohort study. *BMJ* 1998;**316**:1483–7.
- 3 Greenwood R, Golding J, Ross E, *et al.* Prenatal and perinatal antecedents of febrile convulsions and afebrile seizures: data from a national cohort study. *Paediatr Perinat Epidemiol* 1998;**12**(suppl 1):76–95.
- 4 Forsgren L, Sidenvall R, Blomquist HK, *et al.* Pre- and perinatal factors in febrile convulsions. *Acta Paediatr Scand* 1991;**80**:218–25.
- 5 Tsuboi T, Okada S. Exogenous causes of seizures in children: a population study. *Acta Neurol Scand* 1985;**71**:107–13.
- 6 Wallace SJ. Aetiological aspects of febrile convulsions. *Arch Dis Child* 1972;**47**:171–8.