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Historical cohort study of in utero exposure to uterotonic drugs and cognitive function in young adult life

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Oxytocin has potent uterotonic properties which can induce tetany, rupture, and water intoxication. Inappropriately high doses can affect the fetus by inducing abnormal heart rhythms, circulatory collapse, and pre-term delivery accompanied by an increased risk of respiratory distress and damage to the central nervous system.¹ Several studies have reported an association between oxytocic drugs and neonatal hyperbilirubinemia,² which might influence long term cognitive function.³ Little is known, however, of the long term consequences of exposure to uterotonic drugs. We investigated whether in utero exposure to uterotonic drugs affects cognitive performance in draft age men.

Subjects, methods, and results

Nearly all Danish men have to register with the draft board at around the age of 18 years, at which time they undergo physical and mental examinations. We studied all men who were born in Denmark after 1 January 1973 and who were drafted while residing in North Jutland and Viborg counties from 1 August 1993 to 31 July 1994.

All draftees took a 45 minute intelligence test, the Boerge Prien test, developed in 1957 for the Danish draft board.⁴ The test includes four time limited subtests covering four categories: letter matrices, verbal analogies, number series, and geometric figures. The test shows high correlations with the Weschler adult intelligence scale verbal intelligence quotient (0.78), the performance intelligence quotient (0.71), and the full scale intelligence quotient (0.82). In the validation study the mean full scale intelligence quotient was 106, equivalent to a mean Boerge Prien test score of 44.2.⁴

We linked data from the draft examination with the Danish Medical Birth Registry by means of a 10 digit unique personal identification number. The registry contains information relating to all births in Denmark since 1973. Oxytocin was the most commonly used uterotonic drug in that period. We examined the mean Boerge Prien test score according to in utero exposure to uterotonic drugs, taking account of possible confounding variables (table).

We identified 4805 conscripts during the study period. We had complete draft medical data on 4300;

of the remainder, 495 were exempt from the examination mainly because of asthma, osteochondrosis, and epilepsy, and 10 had incomplete data in the birth registry. Of the 4300 men, 22.8% had been exposed to uterotonic drugs; among those who were exempt from the examination 23.5% had been exposed to uterotonic drugs.

The mean Boerge Prien score was similar for those exposed and not exposed to uterotonic drugs (43.1 v 42.9). We also stratified the subjects by mode of delivery; in subjects born by vaginal delivery the mean Boerge Prien score was 43.0 among those exposed to

Descriptive data on 4300 Danish draftees* according to exposure to uterotonic drugs during their delivery. Figures are numbers (percentages) of subjects unless stated otherwise

Detail	Not exposed (n=3289)	Exposed (n=1011)
Draftees		
Boerge Prien test score:		
Median (range)	44 (5-69)	44 (9-68)
Mean (95% CI)	43.1 (42.8 to 43.4)	42.9 (42.3 to 43.5)
Quartiles (1-3)	37-50	37-49
Median (range) birth weight (g)	3380 (1130-5380)	3630 (1630-5380)
Quartiles of birth weight (1-3)	3130-3800	3130-3880
Median (range) birth length (cm)	52 (39-62)	53 (40-61)
Quartiles of birth length (1-3)	51-54	51-54
Gestational age (weeks):		
≥ 37	2974 (90.5)	926 (91.6)
34-36	222 (6.8)	62 (6.1)
≤ 33	92 (2.8)	23 (2.3)
No of caesarean sections	188 (5.7)	76 (7.5)
Mother		
Median (range) age (years) at delivery	26 (15-43)	26 (16-43)
Quartiles of age (1-3) at delivery	23-29	23-29
Parity:		
0-1	2261 (68.7)	724 (71.6)
2	638 (19.4)	172 (17.0)
≥3	390 (11.9)	115 (11.4)
Employment:		
Unemployed, housewife, retired	869 (26.6)	222 (22.1)
Employed	2219 (67.9)	737 (73.5)
Self employed, assisting spouse	179 (5.5)	44 (4.4)

*Total number of subjects for each variable is not always 4300 because of missing data.

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uterotonic drugs compared with 43.1 among those not exposed. From a multiple linear regression with all above mentioned confounders included we estimated the difference in Boerge Prien score to be -0.58 (95% confidence interval -1.25 to 0.08) between those exposed and not exposed to uterotonic drugs.

Comment

Friedman et al examined 156 children 23 to 62 months after births associated with spontaneous labour, labour induced with oxytocin, or labour induced with dinoprostone. The prevalence of neurological or developmental abnormalities not attributable to events after delivery was the same overall in induced and spontaneous labours, but those abnormalities occurring after induction of labour all followed use of oxytocin.⁵ Our data indicate that exposure to uterotonic drugs does not substantially affect cognitive function 20 years later. A small difference due to non-differential misclassification, however, cannot be ruled out. A strength of our study is the large size, the population based design, and complete ascertainment. It is unlikely that selection bias and confounding explain the lack of association.

Contributors: HTS, KJR, and MWG in collaboration with SS initiated the establishment and design of the cohort. HTS initiated this study and discussed the hypothesis with KJR. HTS and FHS analysed the data. PF collected the outcome data. SS linked the data to the birth registry. All authors participated in the interpretation of the findings. HTS, KJR and FHS wrote the first draft of the paper. All participated in editing the paper. HTS is guarantor of the paper.

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Giant cell arteritis and thyroid dysfunction: multicentre case-control study

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The association between giant cell arteritis and thyroid dysfunction remains controversial, but as giant cells are a possible feature of Graves' disease, a common pathway has been suggested. In two series of 101 and 98 patients, the prevalence of hyperthyroidism was reported to be six times higher in cases of giant cell arteritis than in controls.^{1,2} This was not confirmed on smaller series,^{3,4} but 15 cases of hypothyroidism were reported in 31 patients with giant cell arteritis.⁵

We conducted a multicentre case-control study on cases of giant cell arteritis to investigate this relation.

Subjects, methods, and results

Assuming a prevalence of thyroid dysfunction of 1% in the general population and an odds ratio of 6 for hyperthyroidism in the patient group, the sample size requested, with $\alpha=0.05$ and $\beta=0.2$, had been estimated to be 269 cases and controls.²

We prospectively studied 285 cases of giant cell arteritis (205 women, mean age 74.7 ± 8.2 years; 80 men, 72.7 ± 8.2) newly diagnosed during 1991-96. An experienced pathologist reviewed 262 (92%) of the biopsies: temporal arteritis was confirmed in 145-68 were classed as negative (eight did not have a biopsy), and 72 were classed as having polymyalgia rheumatica alone (22 did not have a biopsy). Blood samples taken up to 48 hours after diagnosis were sent to a reference laboratory.

Controls, randomly selected by computer from residents of Saint-Etienne affiliated to a health insurance company, were matched to cases for age and sex. Of the 222 controls participating, 208 (94%) agreed to have a blood sample taken (140 women, mean age 74.9 ± 8.7 years; 68 men, 71.7 ± 8.0) (table). Neither cases nor controls had clinical signs or symptoms of thyroid dysfunction.

We measured concentrations of free thyroxine, thyroid stimulating hormone, and antithyroid peroxidase antibodies by standard radioimmunoassays. Antithyroglobulin antibodies were measured as follows: sera were incubated at room temperature with thyroglobulin labelled with 125-iodine, and the immune complexes were precipitated in fetal veal buffer with polyethylene glycol. A positivity threshold of 50 U/l for a population free of thyroid disease was determined.

We performed multiple logistic regression. Dependent variables were high and low concentrations of thyroid stimulating hormone, high and low concentrations of free thyroxine, and concentrations of positive or negative antiperoxidase antibodies, positive or negative antithyroglobulin antibodies, or positive or negative antithyroid antibodies (antiperoxidase or antithyroglobulin). Independent variables were case or control, geographical origin (north or south), age, sex, and clinical subgroup of patients.

When we took potential confounders into account, we found no difference between cases and controls.

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