Birth outcome following maternal use of metoclopramide

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Aims Metoclopramide is an antiemetic drug used widely during pregnancy for nausea and vomiting. Because of its frequent use any adverse effects on infant health would have major public health implications. We therefore examined the safety of metoclopramide during pregnancy.

Methods Using the Pharmaco-Epidemiological Prescription Database of North Jutland County, we identified 309 women with singleton pregnancies who had prescriptions for metoclopramide from 1 January 1991 to 31 December 1996. Information on malformations, birth weight, preterm deliveries and stillbirth were compared with 13 327 references who did not receive prescriptions of any kind during pregnancy.

Results Mean birth weight among exposed women was 3480 g compared with 3470 g among nonexposed. Based on logistic regression models no major differences in the risk were found concerning malformations (OR = 1.11; 95% confidence interval (CI): 0.6–2.1); low birth weight (OR = 1.79; 95% CI: 0.8–3.9) or preterm delivery (OR = 1.02; 95% CI: 0.6–1.7).

Conclusions We could not document any association between the use of metoclopramide during pregnancy and adverse pregnancy outcome. Because of the limited power of our study further research is required.

Keywords: metoclopramide, birth outcome, pregnancy

Introduction

Nausea and vomiting are frequent during pregnancy. Metoclopramide is an antiemetic drug that increases gastric motility and is widely used for nausea and vomiting in pregnancy [1–4]. The drug crosses the placenta at term, but placental transfer during other stages of pregnancy has not been investigated [5]. Since metoclopramide is widely used, even a small excess risk for adverse pregnancy

outcome would have major clinical and public health implications. Nonetheless, there is a paucity of information on the safety of metoclopramide during human pregnancy.

Anecdotal reports regarding toxicity in pregnancy preclude formal estimates of fetal risk and animal toxicological studies have limited predictive value for teratogenicity in humans. There has been only one formal study of the effect of metoclopramide on birth defects and this study was confined to 192 newborns who had been exposed during the first trimester. The results did not support any substantial association between metoclopramide and birth defects [6].

In order to assess whether the exposure to metoclopramide during pregnancy is associated with adverse birth outcome such as malformations, low birth weight and preterm delivery, we used data from the population-based Pharmaco-Epidemiological Prescription Database of North Jutland, the Danish Medical Birth Registry and

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the Danish Hospital Discharge Registry. The proportion of malformations, low birthweight and preterm delivery among women exposed and unexposed to metoclopramide were compared in a follow-up design.

Methods

North Jutland County has approximately 490 000 inhabitants constituting 9% of the total Danish population. The actual study population consisted of all women delivering a child (approximately 36 000 births) in the county from 1991 to 1996, identified from the Danish Medical Birth Registry.

Exposure data

The Pharmaco-Epidemiological Prescription Database of North Jutland The National Health Service in Denmark offers free, tax-financed primary health care and a 50% reimbursement of all expenditures on a wide range of prescribed drugs, including metoclopramide. North Jutland County is served by 33 pharmacies, each equipped with an electronic accounting system used primarily to secure reimbursement from the National Health Service. This computerized accounting system includes the Anatomical Therapeutic Classification (ATC) code [7], the commodity number, the daily dose, date of issue and the civil registration number (CPR-number) of the patient (incorporating gender and date of birth).

From the Regional Health Service, all data are transferred to the research Pharmaco-Epidemiological Prescription Database of North Jutland which thus retains key information on all prescribed and reimbursed drugs sold at pharmacies in the county since 1 January 1991 [8].

We linked the data to the Danish Medical Birth Registry, which contains information on all births in Denmark since 1 January 1973 by means of the personal identification number [9]. Data on all births are recorded by midwives and doctors responsible for the deliveries. The main variables in the registry are maternal age, birth weight, length at birth, birth order, gestational age and self reported smoking status of the mother during pregnancy and the CPR-number of the parents and child.

From these databases, we identified a total of 443 prescriptions for metoclopramide (ATC code A03FA01) obtained at the pharmacies between 1991 and 1996 by 309 women, who had a singleton pregnancy in which they had taken up a prescription for metoclopramide. We have recently reported data on overall drug consumption in the cohort [10]. To address more specifically the total consumption of prescribed drugs in the actual cohorts, we compared the number of prescriptions issued in the metoclopramide-exposed group with the remaining cohort who had taken up at least one other prescription

during pregnancy ($n =$ approximately 22 000). To look at more specific indicators of exposure to potentially teratogenic drugs, we also compared the consumption of insulin (ATC A10A) and antiepileptic medications (ATC N03A) in both of the above referenced cohorts.

Outcome data

The Danish Hospital Discharge Registry We used the Danish Hospital Discharge Registry to assess malformations. This register, which was established in 1977, records 99.4% of all discharges from Danish acute care hospitals [11]. The dataset includes civil registration number (CPR), the dates of admission and discharge, the surgical procedures performed, and up to 20 discharge diagnoses, classified according to the Danish versions of the International Classification of Diseases (8th revision until the end of 1993 and from then on the 10th revision). The children were followed in the registry until the end of 1997. The codes for congenital malformations were 740.00–759.99 (ICD 8) and Q0.0 – Q99.9 (ICD 10).

Unexposed reference pregnancies

As reference, we used all 13 327 pregnancies in the county from 1991 to 1996 in which the mothers had obtained no prescriptions for any reimbursed drugs in any of the referenced time windows (see below). Outcome data were likewise collected from the Danish Birth and Hospital Discharge Registry.

Statistical analyses

For all pregnancies, time windows up to the time of birth were calculated based on gestational age as reported to the Medical Birth Registry. The time windows were defined as follows:

Interval 1: 0–30 days before conception to the end of 12th gestational week;

Interval 2: Second and third trimester.

All prescriptions for metoclopramide during pregnancy were classified in these two time windows. Multiple regression analyses were used to analyse differences in birth weight among infants of women exposed to metoclopramide compared with babies born to the reference group of women not exposed to any prescription drugs during pregnancy. The analysis included the following potential confounders: maternal age, birth order and smoking. The model fit was evaluated by plot of the residuals (observed value minus expected) against the predicted value of birth weight. Logistic regression models were applied to evaluate the influence of exposure to metoclopramide on the risk of malformations, low birth weight (defined as less than 2500 g) and preterm delivery (less than 37 weeks).

We used data from interval 1 to estimate the risk of malformations, and based on interval 2, we estimated the risk of preterm delivery and low birth weight. This analysis was restricted to full term deliveries. Gestational age was not included in these models, since it is not a confounder in this context.

Results

A total of 309 women with singleton pregnancies who had a prescription issued for metoclopramide at pharmacies around the time of conception and/or in pregnancy were identified. The reference group consisted of 13 327 women not registered as having been exposed to any reimbursed prescriptions during their pregnancies. The characteristics of women in the two groups are summarized in Table 1.

No substantial differences were found between the exposed and nonexposed groups with respect to birth outcomes. The proportion of malformed babies was 5.8% and 5.2% respectively, in women exposed to metoclopramide around conception or in the first trimester and in the reference group. The corresponding adjusted odds ratio (OR) of any malformation was of 1.11 (95% CI 0.6–2.1) (Table 2). The recorded malformations among the exposed included: 1) unilateral undescended testis; 2) contracture of a hand; 3) obstructive hydrocephalus in a baby born in 27th gestational week; 4) valvular pulmonary

stenosis; 5) lacrimal duct stenosis; 6) hypospadias; 7) spina bifida and myelomeningocele; 8) malformed hand; 9) valgus deformity of foot; 10) defect of atrial septum with pulmonary artery stenosis and 11) nonspecific malformation of the locomotor apparatus.

The proportion of preterm deliveries (5.8%) in the exposed women was not significantly higher than in the reference group (6.0%); the adjusted OR was 1.02 (95% CI 0.6–1.7). When restricted to full-term infants, the proportion of low birth weight babies was 6.1% among women exposed in the second or third trimester compared with 4.9% among the reference groups. Using logistic regression analysis, the adjusted OR for low birth weight was 1.79 (95% CI 0.8–3.9) (Table 2). The mean difference in birth weight was 5 g after adjustment for maternal age, birth order, gestational age and smoking.

To focus on women who had common hyperemesis, defined as pregnant women exposed to metoclopramide in the first trimester only as opposed to exposure throughout pregnancy we also restricted the analyses to women who obtained a prescription of metoclopramide during the first trimester. This yielded an OR of 1.17 (95% CI: 0.6–2.2) for malformations, 1.47 (95% CI: 0.5–4.7) for low birth weight and 1.46 (95% CI: 0.8–2.5) for preterm delivery.

If the total consumption of prescribed drugs is considered, the metoclopramide-exposed group had been issued a median of 5.6 prescriptions compared with 3.1 in the group of 22 000 having bought any other

Table 1 Characteristics of pregnant women having obtained a prescription for metoclopramide at the pharmacy and women without exposure to any reimbursed, prescribed medications and outcome of birth.

Variable	Exposure only in interval 1 ¹	Exposure only in interval 2 ²	Exposure at any time in interval 1 or 2 ³	References not exposed ⁴
Number of pregnancies	190	295	309	13327
Number of prescriptions	239	428	443	-
Maternal mean age, years	27.9	27.5	27.5	27.8
Range, years	18–41	17–41	17–41	13–47
Smokers, %	19.4	24.1	24.6	28.9
Birth order, no. 1	79	130	136	7472
Birth order, > no. 1	111	165	173	5855
Gestational age (weeks)				
≥ 37 weeks	176	278	292	12534
34–36 weeks	9	10	10	540
< 34 weeks	5	7	7	253
Mean birth weight, g	3489	3480	3483	3470
Range, g	883–5530	883–5530	883–5530	500–5520
Number of malformations	11	15	16	697
Number of low birth weight	11	18/7**	18	657/209**
Number of preterm deliveries	14	17	17	793
Number of stillborn (before birth)	0	1	1	31
Number of stillborn (during birth)	1	1	1	15

** restricted to full-term deliveries.

¹Exposed to metoclopramide 30 days before conception to end of 1st trimester.

²Exposed to metoclopramide in 2nd or 3rd trimester.

³Exposed to metoclopramide at any time from 30 days before conception to delivery.

⁴Reference pregnancies not exposed to any prescribed, reimbursed drugs at any time during pregnancy.

Table 2 Risk of adverse pregnancy outcomes according to exposure to metoclopramide and maternal characteristics.

Variable	Malformations				Outcome Low birth weight				Preterm delivery			
	Crude analysis	95% CI	Adjusted	95% CI	Crude analysis	95% CI	Adjusted	95% CI	Crude analysis	95% CI	Adjusted	95% CI
No exposures to metoclopramide	1		1		1		1		1		1	
Exposure to metoclopramide	1.18	0.64–2.19	1.11	0.60–2.06	1.52	0.71–3.28	1.79	0.83–3.86	0.97	0.59–1.59	1.02	0.62–1.67
Birth order, number												
1	1		1		1		1		1		1	
>1	0.84	0.71–1.0	0.85	0.73–0.99	0.62	0.47–0.82	0.55	0.40–0.75	0.82	0.71–0.95	0.77	0.66–0.90
Non-smoking	1		1		1		1		1		1	
Smoking	1.17	1.0–1.38	1.18	1.0–1.38	3.68	2.80–4.84	3.7	2.81–4.87	1.27	1.09–1.48	1.28	1.10–1.49
Maternal age, years												
<25 years	1		1		1		1		1		1	
25–30 years	0.86	0.71–1.04	0.82	0.68–0.99	0.6	0.43–0.82	0.79	0.57–1.09	0.85	0.71–1.01	0.92	0.77–1.10
>30 year	1	0.8–1.25	0.9	0.73–1.11	0.79	0.56–1.12	1.19	0.81–1.75	1	0.82–1.21	1.16	0.94–1.44

kind of medicine ($P=0.001$). In relation to concomitant use of antiepileptic drugs the number of women exposed was 1.9% (6/309) and 0.9% (176/22 000) ($P=0.05$) in the two groups; the corresponding figures for insulin were 0 and 0.7% ($P=0.23$).

Discussion

Based on data from 309 pregnancies in which the mothers had taken up a prescription for metoclopramide, we did not detect any significant increase in risk of malformations, preterm delivery or low birth weight among women exposed to metoclopramide during pregnancy.

The major strength of the present study is the complete assessment of both exposure and outcome thereby preventing selection bias. The proportion of coding errors in the prescription databases is approximately 0.2% [12]. Moreover, we were able to control for gestational age which is important when studying the risk of malformations, and had access to data on major confounding factors, i.e. maternal age, smoking habits and birth order. As in other studies regarding drug exposure we did not have information about compliance, i.e. whether the prescribed drug had actually been taken by the patient. Although we have not been able to find specific documentation we find it reasonable to believe that a higher degree of compliance is likely in cases where the medicine has actually been paid for by the patient, compared with studies dealing with information based on recordings from hospital or GP office records. We therefore find it unlikely that noncompliance could seriously invalidate our results. The outcome data have been validated [13] and were obtained independently of exposure information. It is well known that discharge diagnoses can vary in quality, but it seems unlikely that

there was any differential misclassification [14]. Our use of routine data might be a strength since the study itself did not affect the diagnostic process, thereby introducing bias due to more surveillance of the exposed children [14]. Furthermore, to ensure data quality regarding malformations, all hospital records of both mothers and children in the exposed group with malformations were reviewed by one of the study group members.

The prevalence of malformations in our study was higher than the prevalence in a British registry study [15] which investigated the safety of anticonvulsants in pregnancy. However, the prevalence of 5.2% in our control group is close to the prevalence reported in a Hungarian study based on a nationwide registry [16].

From an epidemiological point of view, it is of interest to study foetal outcome associated with exposure to metoclopramide since the drug should be a marker for more severe nausea and vomiting during pregnancy. Consequently, our observations indicate that nausea and vomiting of pregnancy does not imply an excess risk of malformations, preterm birth or low birth weight.

Although this cohort represents the largest published study to date assessing the potential association between metoclopramide use in pregnancy and adverse fetal outcome, the size of the study still remains a limiting factor. The sample size had statistical power to detect only a threefold increase in malformations above the baseline rate.

Our register-based design does not permit interpretation of more narrow time-windows of exposure than in one of the three trimesters partly due to increasing uncertainty about potential overlap between the time-windows and partly due to a very low number of cases in each interval.

The frequent use of metoclopramide during pregnancy implies that any associated increase in adverse outcome

could have major public health impact. It is therefore important to rule out any such effects. The Pharmaco-Epidemiological Prescription Database of North Jutland represents a valuable and unique source for postmarketing assessment of adverse effects for any reimbursed pharmacological compound on prescription. This study is a good illustration of how to utilize this database and to explore adverse outcomes through record linkage with other regional or national administrative registries.

In conclusion, based on a cohort comprising 309 pregnant women who used metoclopramide during pregnancy and a large number of references, we could not detect any increased risk of adverse pregnancy outcome among exposed women compared with a reference population of women not exposed to any prescribed drugs.

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