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MATERNAL-FETAL MEDICINE

Diclofenac/misoprostol during early pregnancy and the risk of miscarriage: a Danish nationwide cohort study

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Abstract
Introduction Misoprostol can be used in the prevention of gastric ulcer in treatment with diclofenac and is used in rheumatic diseases. Since misoprostol causes contractions of the uterus, it can also be used to induce abortions when administrated vaginally. The aim of the study was to investigate if early pregnancy exposure to oral diclofenac/misoprostol was associated with miscarriage.
Method We conducted a nationwide cohort study identifying all registered pregnancies in Denmark from 1997 to 2011. All births were identified using the Medical Birth Registry, and all records of induced abortion and miscarriage were from the National Hospital Register. Data on drug use were from the National Prescription Register. Cox proportional hazard regression models were used to calculate the hazard of miscarriage in women exposed to diclofenac/misoprostol in early pregnancy.
Result We identified 1,338,824 pregnancies (970,491 births, 142,147 miscarriages, 226,145 induced abortions). One hundred sixty-six were exposed to diclofenac/misoprostol in the early pregnancy of which 28.3 % (47) ended up in a miscarriage compared to 10.6 % among unexposed. The adjusted hazard ratio of having a miscarriage after exposure to diclofenac/misoprostol in the first trimester was 3.6 (CI 95 % 2.6–4.9).
Conclusion We found an increased risk of miscarriage after exposure to diclofenac/misoprostol during the early pregnancy. Women in the fertile age should not be treated with the combination of diclofenac/misoprostol if other options were available.

Keywords Maternal fetal medicine · Miscarriage · Misoprostol · Arthrotec · Rhematology · Spontaneous abortion · Drug during pregnancy

Introduction

Misoprostol is a synthetic 15-deoxy-16-hydroxy-16-methyl prostaglandin E1 analog that prevents gastric ulcer by decreasing the proton pump activity and thereby decreasing the gastric acid secretion [1, 2]. Misoprostol is, therefore, often used in combination with diclofenac to prevent gastric ulcer caused by the NSAID in rheumatic diseases and other inflammatory disorders. As a side effect, misoprostol also causes the smooth muscles in uterus to contract and can thereby cause abortion [3]. Therefore, it is also used for medically induced abortions in combination with mifepristone or alternatively methotrexate [4]. When used for medical abortion misoprostol is often administrated vaginally in doses from 400–800 μg, which has been proven more effective than oral administration [5] although buccal and sublingual formulations can be used [6, 7]. When used in preventing gastric ulcer, it is administrated orally and in a lower dose, typically 200 μg three times a day [8].

It is not recommended to use diclofenac in combination with misoprostol orally during pregnancy due to the theoretical risk of miscarriage [8]. Furthermore, misoprostol has

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repeatedly been associated with an increased risk of congenital malformations among others limb defects and Moebius sequence [9–11]. Several studies have found an increased risk of miscarriage in women exposed to misoprostol, both orally and vaginally [12–14]. In these studies the intent of the treatment has predominantly been to induce abortion. No studies have assessed the risk of miscarriage in women treated with the combination of misoprostol and diclofenac in a lower oral dose to prevent gastric ulcer. Only one case report has addressed the issue, in which a man deliberately poisoned a woman with diclofenac/misoprostol with the purpose of inducing an abortion. The man was convicted of poisoning the woman but was not convicted of inducing the subsequent abortion [15].

We, therefore, conducted a cohort study investigating whether exposure to diclofenac/misoprostol in early pregnancy is associated with miscarriage.

Methods

All registered pregnancies in Denmark from 1997 to 2011 were identified ($n = 1{,}348{,}507$). We used the Medical Birth Registry to identify all pregnancies ending in a birth [16]. The National Hospital Register was used to identify all records of induced abortion [O04, O05 and O06 according to the International Classification of Diseases 10th edition Danish revision (ICD10)] and all records of miscarriage (ICD10-codes O021 and O03) [17]. We excluded 9683 records because of coding errors in information on gestational length, identification number and missing information on the identity of the mother.

The Medical Birth Registry holds information on all births in Denmark since 1978 including a unique identification number of the child, mother, and claimed father. The registry also includes information on time of conception based on ultrasound measures and information on last menstrual period, parental age, the number of previous births and abortions as well as weight and length at birth, death and cause of death, sex and gestational age of the offspring [16]. More than 99 % of all births in Denmark since 1978 are recorded in the register [18]. The National Hospital Register contains detailed information, including admittance data and discharge diagnoses, on all hospitalizations since 1978 and outpatient visits since 1995 [17]. It holds more than 99 % of all discharge records from Danish hospitals [19]. Since 1st January 1997, information on gestational age has been added to the diagnoses of miscarriage and induced abortion. In Denmark before April 1, 2004 a miscarriage was defined as rejection of the fetus before the end of week 28 of pregnancy. After this date, the definition changed to be a rejection of the fetus before the end of week 22 of pregnancy [20, 21].

Information on drug use was acquired from the National Prescription Register (Register of Medicinal Product Statistics) [22]. The register holds information on all redeemed prescriptions in Denmark since 1995. Pharmacies are required to register all redeemed prescriptions which is coupled with the reimbursement of expenses from the state. This ensures highly accurate prescription data and completeness has been estimated to be 97.5 % [23]. The register contains no information concerning over-the-counter drugs or indication of treatment, but in Denmark diclofenac/misoprostol cannot be dispensed over-the-counter. Furthermore, the register contains no information on prescribed dose; therefore, all analyses were limited to treatment or no treatment. Exposure was defined as redemption of a prescription of diclofenac/misoprostol [Anatomical Therapeutic Chemical Classification (ATC) M01AB55] between conception and the 84th day of pregnancy or if the pregnancy was shorter than 84 days to the end of the pregnancy. Exposure after miscarriage, induced abortion or birth was not included. In Denmark diclofenac/misoprostol is the only available combination of NSAID and misoprostol and exists in two strengths: 75 mg diclofenac in combination with 200 μg misoprostol or 50 mg diclofenac in combination with 200 μg misoprostol.

Information on income was acquired from the Income Statistics Register which contains information on, e.g., taxes, private pension contributions, entrepreneurial income, capital income, salaries, public transfer payments, and payouts [24]. Information on educational length was from the Populations Education Register which holds detailed individual educational history and standardized educational length on the highest completed education [25].

To determine whether a possible association between diclofenac/misoprostol and miscarriage is due to the effect of diclofenac or misoprostol, we analyzed the hazard of miscarriage in women exposed to diclofenac/misoprostol compared directly to women exposed only to diclofenac (ATC M01AB05) in the early pregnancy.

To test for confounding by indication we compared the hazard of miscarriage in women exposed to diclofenac/misoprostol in early pregnancy with the hazard of women exposed in the 12 week period before conception and not during pregnancy.

Statistics

Cox proportional hazard regression models with first trimester exposure to diclofenac/misoprostol as a time-dependent variable and time from conception to miscarriage as outcome were used to analyze the hazard of miscarriage. Time to induced abortion or birth was considered as

censoring variables. The method has been used before [26]. Time of start of exposure was defined as the day of redemption of a prescription of diclofenac/misoprostol. The assumption of proportional hazards in both univariate and multivariate Cox proportional hazard regression models is met. Time of conception was defined as 14 days after the first day of the last menstrual period based on either ultrasound or menstrual information. An unadjusted model is presented as well as a model adjusted for maternal age (five categories: <20, 20–24, 25–29, 30–34, ≥35 years), household income (as quartiles), educational length in months (four categories: ≤143, 144–155, 156–179, ≥180 months), number of previous miscarriages (four categories: 0, 1, 2, ≥3) and year of outcome (three categories: 1997–2001, 2002–2006, 2007–2010). Data on maternal age, household income, number of previous miscarriages and year of outcome had less than 1 % missing values. Information on educational length had 3.9 % missing values. All co-variables were selected á priori.

All analyses and data management were performed using SAS statistical software version 9.2 (SAS Institute Inc., Cary, NC, USA). Hazard ratios are presented with 95 % confidence intervals. For all analyses a two-sided p value less than 0.05 was considered statistically significant.

Ethics

In Denmark, the Act on Processing of Personal Data does not require ethical permission or obtained consent for anonymized retrospective register studies. The Danish Data Protection Agency approved the study (no. 2008-41-2517).

We report our findings according to strengthening the reporting of observational studies in epidemiology (STROBE) [27].

Results

We identified 1,338,824 registered pregnancies in the study period of which 970,491 (72.5 %) ended up in birth, 142,147 (10.6 %) in miscarriage and 226,145 (16.9 %) in induced abortion. 166 women were exposed to diclofenac/misoprostol in the first trimester. Exposed women were more likely to be older ($p < 0.003$), and have lower educational length ($p < 0.003$). There were no difference in household income ($p < 0.10$) or the number of previous miscarriages ($p < 0.15$) among exposed women compared to unexposed (Table 1).

Of 166 pregnancies exposed to diclofenac/misoprostol, 47 (28.3 %) ended up in a miscarriage compared to 142,100 (10.6 %) of unexposed pregnancies. The mean

Table 1 Patient characteristics

	First trimester exposure to diclofenac/misoprostol ($n = 166$)	No first trimester exposure to diclofenac/misoprostol ($n = 1{,}338{,}658$)	p value
Age (years)			0.003
<20	3 (1.9 %)	54,491 (4.1 %)	
20–24	14 (8.4 %)	176,999 (13.2 %)	
25–29	45 (27.1 %)	408,864 (30.5 %)	
30–34	53 (31.9 %)	436,871 (32.6 %)	
≥35	51 (30.7 %)	261,433 (19.5 %)	
Educational length (month)			0.003
0–143	63 (39.9 %)	370,177 (28.8 %)	
144–155	14 (8.9 %)	205,562 (16.0 %)	
156–179	46 (29.1 %)	351,766 (27.4 %)	
≥180	35 (22.2 %)	357,972 (27.9 %)	
Household income			0.10
Lowest quartile	53 (32.0 %)	333,622 (25.0 %)	
Low quartile	45 (27.1 %)	333,630 (25.0 %)	
Middle quartile	35 (21.1 %)	333,640 (25.0 %)	
High quartile	33 (19.9 %)	333,642 (25.0 %)	
Number of previous miscarriages			0.15
0	138 (83.1 %)	1,137,274 (85.0 %)	
1	21 (12.7 %)	166,123 (12.4 %)	
2	5 (2.4 %)	28,226 (2.1 %)	
≥3	3 (1.8 %)	7035 (0.5 %)	

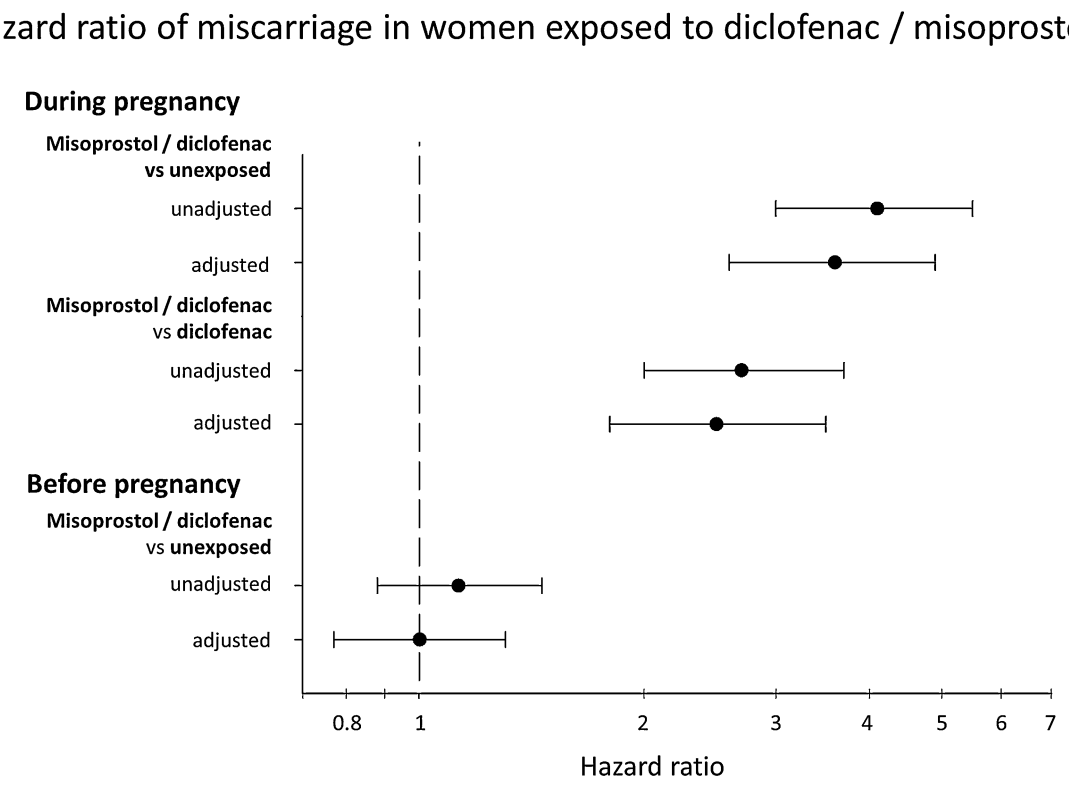

Fig. 1 Hazard ratio of miscarriage in women exposed to diclofenac/misoprostol during the early pregnancy. Adjusted models were adjusted for maternal age, household income, educational length in months, number of previous miscarriages and year of outcome. *Black dots* represent hazard ratio and *whiskers* represents 95 % confidence intervals

time of start of exposure was at gestational day 36.3. We found an unadjusted hazard ratio (HR) of 4.1 (95 % confidence intervals (CI 95 % 3.0–5.5) for miscarriage. When adjusting for maternal age, educational length, household income, number of previous miscarriages and year of outcome, the HR was 3.6 (CI 95 % 2.6–4.9) (Fig. 1).

Other analyses

Women ($n = 509$) exposed to diclofenac/misoprostol in the three months before pregnancy, but not during pregnancy, had an unadjusted HR of 1.1 (CI 95 % 0.9–1.5) compared to unexposed women. When adjusting for age, educational length, household income, number of previous miscarriages, marital status and year, the HR was 1.0 (CI 95 % 0.8–1.3) (Fig. 1).

To exclude the possibility that it was the diclofenac component of the treatment that was associated with miscarriage, we analyzed the hazard of miscarriage among women exposed to diclofenac/misoprostol compared directly to women exposed to diclofenac ($n = 5911$) only. We found that women exposed to diclofenac/misoprostol had an unadjusted hazard of 2.7 (CI 95 % 2.0–3.7) of having a miscarriage compared directly with women exposed to diclofenac only. When adjusting for age, educational length, household income, number of previous miscarriages, marital status and year, the HR was 2.5 (CI 95 % 1.8–3.5) (Fig. 1).

Discussion

In the present study, we found an increased hazard of having a miscarriage in women exposed to diclofenac/misoprostol. This has not been reported previously.

Misoprostol is a well-known abortogenic agent and is used in the treatment of unwanted pregnancy. It increases the uterine tonus and when administrated vaginally it induces regular contractions and softens the cervix [3]. Since it undergoes extensive and rapid first pass-metabolism when given orally [3], the drug is significantly more effective in medical-induced abortions when given vaginally [5]. Despite of diclofenac/misoprostol in the present study is administrated orally and not vaginally we believe that our findings can been explained by the uterus contracting effect of misoprostol. Furthermore, one would expect more miscarriages among women exposed to a drug like misoprostol which has been associated with an increased risk of congenital malformations [28, 29].

To address unaccounted confounders, we analyzed the hazard of having a miscarriage in women exposed to diclofenac/misoprostol in the 3 months before pregnancy but not during pregnancy. This group of women did not have an increased hazard of having a miscarriage. This suggests that the increased risk seen in women exposed during pregnancy is not due to unaccounted characteristics of women exposed to diclofenac/misoprostol but more likely due to the effect of diclofenac/misoprostol. Furthermore, we analyzed the hazard of miscarriage in women exposed to diclofenac/misoprostol using women exposed to diclofenac as reference instead of unexposed and found the same increased hazard. This indicates that the increased risk of miscarriage is due to misoprostol and not diclofenac. Even though diclofenac/misoprostol in the present study most probably was administrated orally and in a lower dose than recommended in induced abortion, the exposure period of diclofenac/misoprostol was likely to be longer than when used in medically induced abortion.

When considering possible explanations for the observed association between diclofenac/misoprostol in early pregnancy and miscarriage, it is important to remember that the present study is a retrospective and epidemiological study where no causality can be concluded. But if the association between diclofenac/misoprostol and miscarriage is causal, it could be explained by an increased muscular contraction of the uterus. Misoprostol stimulates the smooth muscles of the uterus to contraction and could thereby increases the risk of miscarriage directly or indirectly by increasing the rate of malformations possibly caused by vascular disruption due to uterine contractions [11, 30, 31].

Strength and limitations

The study has some limitations which are important to consider when interpreting the results. Even though a prescription of diclofenac/misoprostol was redeemed, collected at the pharmacy and paid for, we do not have any information on whether the drug was used or not. Furthermore we do not have any information on why the drug was prescribed, so we cannot completely rule out unaccounted confounding by indication. It would significantly have strengthened the study if a potential dose–effect relation could have been analyzed but unfortunately the prescription register holds no information on the prescribed dose. Therefore, the analyses are limited to treatment or no treatment. We only have information on registered pregnancies, and very early miscarriages not even recognized by the pregnant woman will not be included in the cohort. Lack of information on very early miscarriages could result in underestimation of the hazard of miscarriage.

The study is based on nationwide registers which ensure high completeness of data and minimize selection bias. The registers have been validated and found to be accurate. More than 99 % of all births are registered in the Medical Birth Registry [18]. The diagnosis of miscarriage has been found to have positive predictive value of 99 % [32] and more than 99 % of all discharge diagnoses have been registered in the National Hospital Register [19]. Exposure to misoprostol and diclofenac is based on information from the National Prescription Register. Due to the national health care reimbursement scheme, the register covers by law all redeemed prescription at all Danish pharmacies. This means that the drug was collected at the pharmacy and paid for. Completeness has previously been estimated to be 98 % [23].

Only 166 women were exposed to diclofenac/misoprostol in Denmark during the early pregnancy. Since diclofenac/misoprostol is contraindicated during pregnancy, the treatment is most probably initiated without the knowledge of the patient being pregnant. Caution is, therefore, extra necessary when treating women of childbearing age with diclofenac/misoprostol especially when considering that only 50 % of pregnancies are planned. [30].

In conclusion, we found an increased risk of miscarriage in women exposed to diclofenac/misoprostol in the early pregnancy compared to unexposed. This finding supports the theoretical concern associated with the use of diclofenac/misoprostol in pregnancy and should lead to that women in the fertile age never should be treated with the combination of diclofenac and misoprostol when alternatives are available.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

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