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Birth outcomes after preconception paternal exposure to methotrexate: A nationwide cohort study

Rachel W. Winter[a,*], Michael Due Larsen[b], Bjarne Magnussen[b], Sonia Friedman[a,b], Heidi Kammerlander[b], Bente Mertz Nørgård[a,b]

[a] Center for Crohn's and Colitis, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, 02115, USA
[b] Center for Clinical Epidemiology, Odense University Hospital, and Research Unit of Clinical Epidemiology, University of Southern Denmark, Odense, Denmark

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ABSTRACT

Background: Methotrexate (MTX), a folic acid antagonist, is often prescribed for moderate to severe inflammatory related diseases. The safety of paternal MTX use prior to conception is unknown. This study, using the National Danish Registries, aimed to examine the association between paternal MTX use three months before conception and adverse birth outcomes.
Results: Children fathered by men treated with MTX within three months before conception constituted the exposed cohort (N = 193), and children fathered by men not treated with MTX constituted the unexposed cohort (N = 1,013,801). The adjusted odds ratio (OR) for preterm birth was 1.38 (95% CI:0.68–2.81). The adjusted ORs of congenital anomalies (CAs) and small for gestational age (SGA) were 1.10 (95% CI:0.57–2.13) and 0.98 (95% CI:0.39–2.50), respectively.
Conclusion: Our results regarding the effect of paternal use of MTX within 3 months before conception on birth outcomes of CAs, preterm birth and SGA are overall reassuring.

1. Introduction

There has been a recent focus on fertility, pregnancy course and birth outcomes among women with chronic diseases, including inflammatory bowel disease (IBD), but there is little published regarding adverse pregnancy outcomes and congenital anomalies (CAs) of children fathered by men with chronic diseases. While many of the medications used to treat IBD and other rheumatologic conditions have recently been shown to be low risk among women during pregnancy [1], there have been fewer studies following men exposed to immunosuppressive medications and the effects of these medications on their offspring. Methotrexate (MTX) is a folic acid antagonist with known teratogenicity and is associated with an increased risk of CAs among children born to exposed mothers. Intrauterine exposure to MTX is associated with craniofacial and limb anomalies and developmental delay [1,2]. Folic acid antagonists may also increase the risk of cardiovascular, neural-tube and urinary tract defects, in addition to oral clefts [3]. Thus, current recommendations suggest that mothers discontinue use of MTX at least 3 months prior to conception [4]. Prior studies have also raised a number of concerns about MTX use and a possible genotoxic effect on sperm resulting in chronic illness or CAs from rearrangement of chromosomes [5].

Recommendations regarding medical management of men taking MTX while trying to conceive are less clear. Case reports and one small study of men who fathered children while on MTX have not demonstrated convincing evidence that men must discontinue the medication prior to conception [5,6]. Prior literature has not reported a negative impact on fertility among men taking MTX while trying to conceive, although one report described transient oligospermia in a man taking MTX, which resolved after discontinuation of the medication [7–9]. Published studies, including a recent review of 53 papers evaluating the effect of MTX on male fertility and pregnancy outcomes in both human and animal studies, have not shown increased rates of birth defects or adverse birth outcomes of children fathered by men on MTX, and larger prospective studies have been recommended [5,6,10]. Because there are limited data regarding the birth outcomes of children born to fathers

* Corresponding author at: Brigham and Women's Hospital, Division of Gastroenterology and Hepatology, 75 Francis Street, Boston, MA 02115, USA.
E-mail addresses: rwinter1@partners.org (R.W. Winter), Michael.due.larsen@rsyd.dk (M.D. Larsen), Bjarne.magnussen@rsyd.dk (B. Magnussen), sfriedman1@partners.org (S. Friedman), Heidi.Kammerlander@rsyd.dk (H. Kammerlander), Bente.Noergaard@rsyd.dk (B.M. Nørgård).

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on MTX, there are not standardized guidelines. Current recommendations include discontinuing the medication at least three-four months prior to conception [11], though some authors have proposed continuation of MTX at the time of conception [12].

Given the limited information regarding birth outcomes of children conceived by fathers on MTX, we conducted a nationwide cohort study to determine the risks of CAs, small for gestational age (SGA) and preterm birth on offspring after paternal exposure to MTX.

2. Materials and methods

2.1. Study population

This register-based cohort study included data from all live born singleton children in Denmark (population approximately 5.5 million people, >90% Caucasians) from January 1, 1997 through 2013. Study information was collected from four nationwide Danish health registries: the Danish National Patient Registry (DNPR) [13], the Danish Medical Birth Registry (MBR) [14,15], the Central Personal Registration system (CPR) [16] and the nationwide prescription database (NPD) [17]. Data were linked by using the unique civil registration number. Since 1968, this system has been utilized to assign a unique number to all Danish residents at birth from the CPR [16], and data from all sources were unambiguously linked on an individual level using the civil registration number.

The data set has also previously been used to study other paternal medical exposures [18].

2.2. Data

The uniform organization of the registries in Denmark, where all citizens have free and equal access to a tax supported health care system, allowed us to use a population-based study setting [16,19]. The MBR contains information on all births in Denmark since 1973 (55,000–70,000 annual births), including data on the mother and father, pre-pregnancy related information and birth outcomes. Children are linked to their father at birth; it is not routine practice to confirm paternity with a test for all children born in Denmark and it was unknown if children were conceived after fertility treatments. The DNPR includes records of all discharges from Danish hospitals since 1977 and all outpatient visits since 1994. Information in the DNPR includes patients' civil registration numbers, hospital, department, date of admission and discharge, procedures performed and up to 20 discharge diagnoses based on the International Classification of Diseases (ICD-8 before 1994 and ICD-10 from 1994 onward; ICD-9 was never used in Denmark); the DNPR also provided information on type of paternal underlying diseases.

All outpatient medication prescriptions filled since January 1, 1995 have been recorded in the NPD, which is maintained by the Danish Medicine Agency. All pharmacies in Denmark have a computerized system which sends data on outpatient drug prescriptions to the national database; the information transmitted includes the patient's civil registration number, the type of medication prescribed according to the anatomical therapeutic chemical (ATC) classification system and the date of the filled prescription.

2.3. Exposed cohort, children fathered by men exposed to methotrexate prior to conception

Since the MBR identifies fathers of children, we were able to obtain additional information about paternal medication use using the father's civil registration number. We linked information on prescriptions of MTX (ATC codes L04AX03 and L01BA01 for oral and subcutaneous MTX) filled by the father in the three months prior to conception. Because each person has a unique civil registration number, it was possible to identify patients who had filled MTX prescriptions within the defined time period. The NPD does not include data on over the counter medications, but MTX is only available by prescription in Denmark.

2.4. Unexposed cohort, children fathered by men not exposed to methotrexate prior to conception

The unexposed cohort consisted of all live born singleton children from the study population who were fathered by men who did not fill a prescription for MTX three months prior to conception.

2.5. Birth outcomes

Birth outcomes were identified in the MBR. They included CAs (within the first year of life), preterm birth and SGA. Preterm birth was defined as birth before or equal to 37 weeks gestation. Babies met criteria for SGA if, according to gestational age and sex, their birth weight was below two standard deviations of the mean [20]. Date of conception was based on ultrasound dating of gestational age. Since 2005, all Danish pregnant women were provided ultrasounds. Ultrasounds have been available since 2001; if unavailable, or prior to 2001, time of conception was estimated by clinical assessment. Congenital anomalies up to one year of age are included in the MBR. Possible ICD-10 codes for congenital anomalies include Q00–Q07; Q10–Q18; Q20–Q28; Q30–Q39; Q40–Q45; Q50–Q54; Q55.0–Q55.1; Q55.3–Q55.9; Q56; Q60–Q64; Q66–Q69; Q70–Q79; Q80–Q89; Q90–Q99.

2.6. Information on possible confounders

From the MBR, we obtained information on the age of the mother and father at the time of delivery, maternal parity and maternal lifestyle factors, including body mass index and smoking in early pregnancy.

We also obtained international classification of disease (ICD-8 codes before 1994 and ICD-10 codes from 1994 to 2013; ICD-9 codes were never used in Denmark) for the fathers who were prescribed MTX in order to try to determine the main indication for the medication prescription, including gastrointestinal, rheumatologic, dermatologic, oncologic and neurologic diseases. Regarding paternal underlying diseases we specifically looked for the following: (1) Inflammatory bowel diseases with history of ulcerative colitis (ICD-10 code: DK51.* (* indicating all subgroups)/ICD-8 codes: 563.19, 569.04), Crohn's disease (ICD-10 code: DK50.*/ICD-8 code: 563.01) or indeterminate colitis (ICD-10 codes: DK52.3, DK 52.8, DK52.9); (2) Rheumatologic group, including inflammatory polyarthritis (ICD-10 codes: DM05.*-DM14.*/ICD-8 codes: 696.09, 723.09, 274.0*, 711.*, 712.09, 712.19, 712.39, 714.*-718.*), spondyloarthropathies (ICD-10 codes: DM45.*-49.*/ICD-8 code: 712.4*), and other rheumatologic disorders (ICD-10 codes DD69.*, DD86.*, DL95.*, DM02.*, DM7*, DM30.*, DM31.*/ICD-8 code: 135.*); (3) Dermatologic group, including psoriasis (ICD-10 code: DL1*, DL2*, DL30.*, DL40.*, DL73.*/ICD-8 codes 692.*, 694.*, 696.10, 696.19), (4) Oncologic (ICD-10 code: DC*, DD0*, DD4*/ICD-8 codes: 14*-20*, 23*); (5) Neurologic, including multiple sclerosis (ICD-10 code: DG35/ICD-8 code: 340.*).

2.7. Statistical analysis

Contingency tables were constructed for the main study variables comparing the exposed and unexposed cohorts. Mixed-effect multilevel logistic regression analyses accounting for the random effects from multiple children born by the same woman was used to calculate crude and adjusted odds ratios (OR) with 95% confidence