Paternal antidepressant use as a negative control for maternal use: assessing familial confounding on gestational length and anxiety traits in offspring

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Parts of this work were presented as a poster at the 30th Annual Meeting of the Society for Pediatric and Perinatal Epidemiologic Research, Seattle, WA, June 20-21, 2017 and 50th Annual Meeting of the Society for Epidemiologic Research, Seattle, WA; June 21-23, 2017 and as an oral presentation at the 33rd International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Montreal, Canada; August 26-30, 2017.

Running Head: Paternal antidepressant use as a negative control

Abstract

Background: Maternal antidepressant use in pregnancy has been associated with both shorter gestational length and child anxiety. We employed paternal antidepressant use as a negative control exposure to indirectly assess whether confounding by genetic or shared familial environmental factors associated with depression may explain these associations.

Methods: The study sample came from the population-based Norwegian Mother and Child Cohort Study (MoBa) that recruited participants from 1999-2008. We included 70 959 families where the father completed a questionnaire about medication use in the 6 months prior to pregnancy. In 42 511 infants who completed the 3-year follow-up, we computed Z-scores for the anxiety domain of the Child Behavior Checklist. We used linear and logistic regression to assess the association between paternal antidepressant use, gestational age at birth, and child anxiety.

Results: 1.1% of fathers used antidepressants (n=755). Paternal antidepressant use was not associated with gestational age at birth (β=0.63 days, 95% CI -1.56, 0.31) whereas it was positively associated with child anxiety symptom Z-score and high anxiety symptoms (OR 1.33, 95% CI 0.90, 1.97) in unadjusted analyses. This association was attenuated when controlling for maternal and paternal history of depression and other measured factors (OR 1.14, 95% CI 0.76, 1.69).

Conclusions: These results support the suggested effect of maternal use of antidepressants in pregnancy on shorter gestation; however, they suggest familial confounding could explain the association between maternal use of antidepressants and anxiety traits in the offspring.

Keywords: Antidepressants; drug safety; negative controls; paternal exposure; pregnancy; pharmacoepidemiology; The Norwegian Mother and Child Cohort Study; MoBa

Key Messages

- Paternal antidepressant use may be an appropriate negative control exposure for maternal antidepressant use and offspring outcomes
- The null association between paternal antidepressant use and gestational age at birth supports the suggested effect of maternal use of antidepressants in pregnancy on shorter gestation
- The finding of a positive association between paternal antidepressant use and offspring anxiety suggests familial confounding could explain the association between maternal use of antidepressants and anxiety traits in the offspring

Introduction

Multiple studies have reported that maternal antidepressant use in pregnancy is associated with short and long-term adverse pregnancy outcomes including shorter duration of pregnancy[1,2] and neurodevelopmental problems in children.[3-5] Whether such associations are due to the effects of *in utero* exposure to the drugs, or to confounding by maternal characteristics, genetic predisposition, or family environment is difficult to disentangle. Confounding control is particularly challenging when studying the effects of prenatal exposures on outcomes that occur in childhood. In this setting, where unmeasured genetic and family environment characteristics may be strong confounders, the sibling design may have unique advantages over a traditional cohort design.[6,7] Associations between antidepressants and gestational length remained and between antidepressants and anxiety at three years strengthened after restriction to siblings that were discordant with respect to maternal use of antidepressants in pregnancy.[1-3] While this may suggest robust effects, the unique limitations inherent in sibling-controlled studies including an increased risk of exposure misclassification bias and potential amplification of the effects of non-shared confounders might also explain these associations.

Therefore, to assess the likelihood that observed associations between maternal use of medications during pregnancy and neurodevelopmental outcomes reflect true causal effects, rather than confounding, other approaches should be considered. The robustness of results in observational studies can be assessed by conducting multiple sensitivity analyses with different limitations and potential biases to corroborate or refute the evidence for a causal effect.[8] One of these approaches is the use of negative control exposures.[9,10]

We assessed the likelihood of residual confounding in observational studies on the effect of maternal use of antidepressants during pregnancy on the risk of shorter gestational length and child anxiety using paternal exposures as a negative control.[11,12] The rationale was that an association between paternal use of antidepressants in the 6-months before pregnancy with these adverse outcomes in the children would suggest residual confounding, assuming paternal use of antidepressants does not have a direct biological effect on offspring.

Methods

We used data from the Norwegian Mother and Child Cohort Study (MoBa), a prospective population-based study carried out by the Norwegian Institute of Public Health.[13] Participants from all over Norway were recruited via postal invitation from 1999-2008 around the 17-week ultrasound. Women consented to participate in 41% of pregnancies. The cohort includes children from over 112,000 pregnancies in 95,200 mothers with 75,200 participating fathers. The current study is based on quality-assured data from self-reported questionnaires (Q) (version 9, released for research October 2015) as well as from the Medical Birth Registry of Norway (MBRN). We included singleton, liveborn pregnancies where information from the father, mother, and child was available at baseline (Q1, QF), at delivery (MBRN), and in a sub-sample, where information about child outcomes at 3 years was available (Q6).

Information on paternal antidepressant use was collected in the fathers' questionnaire (QF) that included assessment of medication use in the 6 months prior to pregnancy. Our primary exposure of interest was paternal self-reported use of antidepressants at any time in the 6 months prior to pregnancy, coded according to the Anatomical Therapeutic Chemical (ATC) classification system (ATC N06A). A previous comparison of data from the Norwegian

Prescription Registry with paternal self-reported medication use in MoBa found that agreement between self-report and prescription data on antidepressant use among fathers (κ=0.74) was similar to what was previously reported among mothers (κ=0.72).[14,15] We also considered paternal use of selective serotonin reuptake inhibitor (SSRI) antidepressants (N06AB) as a secondary exposure of interest.

The outcome gestational age at birth was obtained from MBRN data. For this outcome, we excluded multiples (twins, triplets, quadruplets) and pregnancies with congenital malformations as we would expect a shorter duration of pregnancy to be driven by these conditions.

The outcome child anxiety was assessed by the anxiety domain of the Child Behavior Checklist (CBCL), completed by mothers when the child was approximately 36 months of age. The CBCL has been validated in Norway,[16] and the internalizing domain of the short version administered in MoBa at 36-months was validated against the full scale administered in a sample at 6 years (correlation 0.79), and other short scale time points (correlations 0.90 for 18 months and 0.86 for 5 years).[17] The anxiety domain was based on three items in the CBCL ("Clings to adults or too dependent," "Gets too upset when separated from parents," and "Too fearful or anxious"), scored as 1=not true, 2=somewhat or sometime true, or 3=very true or often true. We computed the average across the three domains, and allowed for subjects missing one item to be included. Thus, for this analysis, we excluded subjects who were missing the 3-year follow-up questionnaire or >1 item of the CBCL anxiety domain. We computed standardized Z-scores (mean=0, standard deviation, SD=1) and T-scores (mean=50, SD=10) based on the distribution of scores in all subjects who completed a 3-year follow-up (i.e. not restricted to those with father's participation) (mean 1.2, SD 0.3). Our primary outcome was the continuous Z-score. In

sensitivity analyses, we considered a dichotomous outcome of high anxiety symptoms, T-score≥70 (which corresponded to a report of 2 or 3 on each CBCL anxiety sub-domain item), used in psychology research to classify the outcome of clinical importance.[18]

Relevant confounders were selected a priori and informed by a directed acyclic graph (DAG) (**Figure 1**), and were similar to those previously used for the maternal exposure. The structure and notation of the DAG were modeled after the causal diagram proposed by Lipsitch et al. for an ideal negative-control exposure.[9] Data on confounders came from MoBa questionnaires (maternal and paternal) and MBRN data. Maternal self-reported antidepressant use in pregnancy was based on any use reported in questionnaires at approximately 17 and 30 gestational weeks, and 6 months post-partum.[15] Measured confounders included the maternal factors, maternal age (continuous), parity (0, 1, 2, 3, ≥4), maternal depression before or during pregnancy (yes, no), maternal anxiety before or during pregnancy (yes, no), maternal lifetime history of major depression (yes, no), maternal education (less than university, completed university or higher), any maternal smoking in pregnancy (yes, no), any maternal alcohol use in pregnancy (yes, no), and paternal factors, paternal age (<30, 30-34, ≥35) and paternal lifetime history of major depression (yes, no), and symptoms of anxiety and depression (Z-score of the 8-item version of the Hopkins Symptom Checklist; SCL-8).

Statistical Analysis

We used linear regression to assess the association between paternal antidepressant use and both gestational age at birth in days (unstandardized) and child anxiety at 3 years in units of SD (Z-scores), respectively. For all analyses, the comparison group is children of unexposed fathers. In sensitivity analyses, we used logistic models to estimate the association between

exposure and high symptoms of anxiety, T-score≥70. We used robust standard errors to account for the potential for fathers with more than one child. We used multiple imputation with chained equations to impute 20 complete datasets to address missing confounder information,[19] and censoring weights to address possible selection bias from incomplete follow-up of children at 3-years.[20] We computed censoring weights in each imputed dataset, and then weighted subjects according to the inverse probability of censoring, based on measured covariates (see **Supplementary Material** for additional details on missing data, imputation, weighting, and complete case analysis). We carried out corresponding analyses for maternal antidepressant use to compare the magnitude of the associations for maternal and paternal antidepressant use in this study sample.

Ethics

The establishment and data collection in MoBa has obtained a license from the Norwegian Data Inspectorate and approval from The Regional Committee for Medical Research Ethics. The current study (application 2015/2103) was approved on December 12, 2015 by The Regional Committee for Medical Research Ethics (Region South-East). The study was pre-approved by the MoBa steering committee.

Results

There were 70 959 pregnancies among 62 276 fathers available for the analysis of gestational length and 42 511 children among 37 719 fathers for the analysis of child anxiety at 3-years (**Figure 2**). Among the 70 959 pregnancies, 1.1% of fathers used antidepressants in the

six months before pregnancy (n=755 of which 553 used SSRIs), and 1.0% of mothers used antidepressants in pregnancy (n=686 of which 553 used SSRIs). In 37 pregnancies, both the father and mother were exposed to antidepressants, suggesting that having a partner who used an antidepressant increased the likelihood of using an antidepressant approximately five-fold. The mean gestational age at birth was 279.5 days (SD 12.2).

Compared to non-users, the crude association between paternal antidepressant use and gestational age at birth was -0.63 days (95% confidence interval -1.65, 0.31) (**Table 1**). When we adjusted for maternal antidepressant use and confounders related to it, the estimate was -0.45 days (95% CI -1.39, 0.49), and when we further adjusted for confounders that may be unique to the association with paternal antidepressant use (paternal factors), the estimate was -0.18 days (95% CI -1.13, 0.78). The associations were similarly null for paternal SSRI exposure. Adjusted estimates suggested pregnancies exposed to maternal antidepressant use were on average approximately 2 days shorter (**Supplementary Material**).

(Table 1 Here)

Among the 42 511 children included in the neurodevelopmental outcome analysis, 303 (0.7%) had one missing item from the CBCL anxiety domain questions. One percent of children had a father who used an antidepressant medication before pregnancy (n=418 of which 309 used SSRIs), while 0.9% had a mother used an antidepressant during pregnancy (n=381 of which 303 used SSRIs), and 19 had two parents who used antidepressants. The mean Z-score was -0.02 (SD 0.98) and 2,178 (5.1%) of children had high anxiety scores corresponding to T-scores ≥70. The crude association between paternal antidepressant use and child anxiety Z-score indicated that the anxiety scores were 0.14 SD (95% CI 0.04, 0.25) higher among children of exposed compared to unexposed fathers (**Table 1**), and 0.27 SD (95% CI 0.16, 0.39) higher for exposed

mothers. After adjusting for maternal exposure and confounders, the association for paternal use moved to 0.10 SD (95% CI 0.00, 0.22), and after additional adjustment for paternal factors, the difference attenuated further to 0.06 SD (95% CI -0.02, 0.23). The estimates for maternal exposure in these cohort-based analyses were also attenuated after adjustment for maternal factors. In particular, maternal self-reported anxiety, lifetime history of major depression, and lower education, and paternal lifetime history of major depression had the strongest associations with the anxiety score. The paternal exposure association was somewhat stronger for SSRIs and especially with the dichotomous outcome high symptoms of anxiety where the OR remained elevated for the fully adjusted model, OR 1.49 (95% CI 0.99, 2.25). In a sensitivity analysis with further adjustment for the Z-scores of the anxiety and depression domains of the paternal SCL-8, the OR was further attenuated, but remained elevated, OR 1.36 (95% CI 0.90, 2.07). The maternal estimates went from OR≥2 in the crude to approximately 1.2 after adjustment.

Discussion

We investigated the relationship between paternal pre-conceptional antidepressant use and both gestational length and child anxiety, considering the paternal exposure as a negative control for maternal exposure. We hypothesized that there may be an association with paternal exposure due to the presence of shared confounders, including unmeasured factors like genetic predisposition to anxiety and depression, and economic and other household environmental factors that can be difficult to measure and could influence both maternal and paternal exposures. Some examples could include parental behaviors and attitudes towards parenting in a household where one parent has a mental health disorder. We found no association between paternal antidepressant use and gestational age at birth, which we might expect to be less affected by

paternal depression. However, we did find that paternal exposure was associated with anxiety in the child at three years of age. After accounting for measured shared confounders (maternal factors), the association was attenuated, and with further adjustment for paternal age and lifetime history of depression, the association was close to null. These findings suggest that depression or anxiety in one of the parents can induce a positive association between use of antidepressants around the time of pregnancy and child anxiety. Given that adjustment for measured confounders tend to move the estimate downwards for the association between paternal antidepressant use and child anxiety, we expect further adjustment to move the estimate further towards the null. However, for the paternal association, since the fetus was not exposed to the drug, we believe the association must be due to confounding, thus supporting that the observed association in the mother is also due to residual confounding. Moreover, the adjusted OR of 1.36 for paternal SSRI use for potentially clinically-relevant child anxiety symptoms suggests that we should be cautious in interpreting associations between maternal antidepressant use in pregnancy and offspring internalizing mental health outcomes since this 36% increased risk reflects residual confounding that could also affect maternal estimates. The stronger associations for SSRIs could be due to chance or somewhat different indications for SSRIs and non-SSRI antidepressants.

The association between maternal antidepressant use and gestational length quantified here was consistent with prior studies suggesting an effect size of approximately 2-3 days shorter gestation.[1,2] However, while we found a similar crude association in this MoBa sample as the previous sibling-based study, we found no association between maternal antidepressant use and child anxiety after control for confounding. In a prior report from MoBa, the adjusted estimate from a sibling-controlled analysis of maternal antidepressant and use 3-year anxiety CBCL score was β=0.64 SD whereas the crude was β=0.44 SD. The crude estimate for the cohort-based

analysis of the sibling sample was β=0.22 (no adjusted reported), so our results are generally consistent with that study, but emphasize the need to for cautious interpretation.[3]

MoBa is a unique resource in which to explore the use of paternal medications as negative controls because fathers have actively participated in the study to report exposures in the period surrounding conception including prospective medication use. Furthermore, follow-up of children continues for years after birth and detailed child development and behavioral screening instruments are administered over time. When we assess the association between paternal medication use and child outcome, then we can confidently assume that any association identified is not due to a causal effect of in utero exposure to the medication, i.e. crossing the placenta to affect the developing fetus. Therefore, this approach may complement the traditional sibling design to control for genetic and family environment confounding. Other data that may be useful for this approach include other pregnancy and birth cohorts that enrolled fathers, population registries where information from both parents may be available from linked prescription databases, or insurance healthcare claims databases where members of the same family on a single plan share a common family enrolment identifier.

There is increasing interest in using paternal medication exposures as negative controls, when they are available. A study within the Swedish health registries assessed paternal exposure to antidepressant in the first trimester as a negative control exposure for maternal use.[21] They found a modest association between paternal antidepressant use and preterm birth and stronger associations with autism and ADHD. This combined with the results from a sibling analysis, which found no association for maternal use and autism or ADHD, strongly suggest that first trimester antidepressant use does not cause autism or ADHD, but may result in preterm birth.

Differences in the strength of association for the index exposure and the negative control could be seen because of differences in the validity of self-reported medication use between mothers and fathers.[22,23] If there were more misclassification among fathers, then we would expect a greater bias toward the null, which could spuriously produce the expected null risk estimates. One of the key strengths of this study was that both maternal and paternal antidepressant use had been validated, and agreement between self-reported and prescription records was similar for both.[14,15] This gives us more confidence that the null association for gestational length is not attributable to more exposure misclassification in the negative control. We benefited from several strengths of the MoBa study, including large sample size which allowed us to investigate a rare exposure, high quality of gestational age data, which is ultrasound based and available in days (rather than weeks or dichotomized), and long term follow up of children, which allowed us to investigate later neurodevelopmental outcomes. We had high quality data on important confounders including multiple measures of maternal and paternal depression and anxiety, including lifetime history of major depression, and standardized developmental assessments of the children.

The study may have limitations in its generalizability since the participation in MoBa was only 41% at baseline and lower at three years. However, prior work has demonstrated an absence of selection bias for known exposure-outcome relationships,[20] and the selection-weighted and unweighted estimates for anxiety at 3-years were similar. Since the prior results came from the MoBa study and other cohorts in similar populations, the results should be a valid check for the presence of confounding bias in prior studies. Unfortunately we cannot determine the magnitude of the residual confounding bias for maternal exposure estimates, but instead provide a qualitative assessment of confounding.[9] However, a recent study in MoBa found that genetic

transmission plays an important role in the association between maternal prenatal depression and offspring internalizing behavior, which supports our interpretation of these findings.[24] Furthermore, we have to assume that there is no direct effect of paternal exposure through, for example, epigenetic influence of paternal genetic material in sperm or carrying drug in semen. Although we cannot rule this out as a possibility, no current literature supports a direct causal effect of paternal exposure, and so we believe this assumption is plausible.[25] However, even if this assumption did not hold, imperfect negative control exposures may still be useful for causal inference,[26] especially as part of a series of sensitivity analyses aimed at assessing the robustness of the findings.

In conclusion, these results increase our confidence in the suggested effect of maternal use of antidepressants in pregnancy on shorter gestation. However, our results suggest familial confounding for the effect of prenatal exposure to antidepressants on offspring internalizing mental health outcomes may bias estimates in the positive direction. Care givers and health care personnel should support parents with mental health problems and their children as these families may have extra challenges. Future medication safety studies should address causal questions by integrating results from several different approaches with different and unrelated key sources of potential bias. Paternal negative controls could be one of these approaches.

Acknowledgements

We are grateful to all the participating families in Norway who take part in this on-going cohort study.

Funding

This work was supported by funding from the European Research Council starting grant ERC-STG-2014 DrugsInPregnancy (Grant Number 639377). Dr. Jacqueline Cohen and Dr. Sonia Hernández-Díaz were supported by the National Institute of Mental Health (R01 MH100216). Dr. Eivind Ystrom was supported by The Research Council of Norway (grant number 262177). The Norwegian Mother and Child Cohort Study are supported by the Norwegian Ministry of Health and Care Services and the Ministry of Education and Research, NIH/NIEHS (contract no N01-ES-75558), NIH/NINDS (grant no.1 UO1 NS 047537-01 and grant no.2 UO1 NS 047537-06A1).

Conflicts of interest

Dr Cohen has received salary support from a research grant from GSK for unrelated work. Dr Hernández-Díaz's institution has received research funding from GSK and Lilly for unrelated work, and salary support from the North American AED Pregnancy Registry; she has consulted for Roche. Drs Wood, Ystrom, and Nordeng have no potential conflicts to declare.

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Figures

Figure 1. Causal diagram

Figure 2. Flow diagram of study sample selection

Abbreviations: CBCL, child behavior checklist; MBRN, Medical Birth Registry of Norway

Supplemental Material

Online-Only Supplement:

- Additional details on missing data
    - Web Table 1: Description of missing covariate information
    - Web Table 2. Complete cases analyses
- Additional details on multiple imputation for missing covariate data
- Additional details on censoring weights for missing follow-up
    - Web Table 3. Model results for 36-month anxiety without applying censoring weights
- Additional description of study sample
    - Web Table 4: Characteristics of the cohort of fathers included in the study (before any further restrictions based on the pregnancy outcome and or follow up), N=76,345
    - Web Table 5: Characteristics of study samples
    - Web Table 6: Association between maternal antidepressant use and gestational age and child anxiety