



Discontinuation of antipsychotic medication in pregnancy: A cohort study



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ABSTRACT

Background: Women prescribed antipsychotics face the dilemma on whether to continue medication in pregnancy in terms of balancing risks and benefits. Previous research on other psychotropic medications suggests that many women discontinue treatment in early pregnancy. However, very limited evidence exists on discontinuation of antipsychotic medication.

Methods: We identified 495,953 pregnant women from THIN primary care database. Kaplan–Meier plots were used to examine time to last antipsychotic prescription. Poisson regression was used to examine characteristics of those who stopped treatment during pregnancy.

Results: There has been an overall increase in prevalence of antipsychotic prescribing since 2007. However, antipsychotics were more likely to be stopped in pregnant than non-pregnant women. Only 107/279 (38%) of women on atypical antipsychotics and 39/207 (19%) of women on typical antipsychotics before pregnancy still received treatment at the start of third trimester. Older women were more likely to continue typical antipsychotic treatment in pregnancy (35+ versus <25 years risk ratio: 3.09 [95% CI 1.76, 5.44]). Likewise, those who received typical antipsychotics for longer periods before were most likely to continue treatment in pregnancy (12+ versus <6 months: RR: 3.12 [95% CI 1.97, 4.95]). For atypical antipsychotics length and dose of prior prescribing were also associated with continuation in pregnancy.

Conclusions: Pregnancy was a major determinant of cessation of antipsychotics. Only 38% of women on atypical and 19% on typical antipsychotics were still prescribed the drug in the third trimester. Duration of prior treatment, maternal age as well as dose was significantly associated with continued treatment of antipsychotics in pregnancy.

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1. Introduction

The onset of schizophrenia and bipolar disorder in women usually occurs within childbearing age (Yonkers et al., 2004; Einarson and Boskovic, 2009; Hardoon et al., 2013) and many women with these illnesses are prescribed psychotropic medication including antipsychotics (Einarson and Boskovic, 2009; Hayes et al., 2011; Prah et al., 2012). Some women are prescribed antipsychotics either before they get a diagnosis of refractory mood and anxiety disorders. Women prescribed antipsychotics face the dilemma at the time of pregnancy or when

planning a pregnancy on whether to continue psychotropic medication in terms of balancing the potential teratogenic effects and other adverse effects of the medication against the consequences of a relapse of their illness (Galbally et al., 2011). However, limited information is available on the risks and benefits of antipsychotic treatment in pregnancy (Einarson and Boskovic, 2009).

Webb et al. conducted a systematic review in 2004 (updated in 2009) to establish whether the benefits of taking antipsychotic drugs outweigh the risks for pregnant or postpartum women and found no randomised controlled trials (Webb et al., 2004). A Swedish population registry study identified 570 women being prescribed antipsychotics in pregnancy and found that this was associated with increased risk of gestational diabetes (OR 1.78 95% CI 1.04–3.01) (Reis and Källén, 2008) and congenital malformations (OR 1.52 (95% CI 1.05–2.19)) in comparison

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to women not prescribed antipsychotics. This association was not specific to certain drugs suggesting that the underlying pathology or unidentified confounding could explain the excess risk of congenital malformations (Reis and Källén, 2008). A recent Canadian study assessed 133 pregnant women exposed to second generation antipsychotics against healthy women (Sadowski et al., 2013). Exposed neonates were more likely to be born prematurely and had higher rates of congenital malformations and this was particularly the case for those subject to poly-therapy (atypical antipsychotics as well as other psychotropic medication). In this study a relatively high proportion (72%) of women were on poly-therapy and 101/133 (76%) continued treatment throughout pregnancy (Sadowski et al., 2013).

Advice on treatment varies across countries and in some places standard psychiatric advice is that women maintain pharmacological treatment across the perinatal period (Galbally et al., 2011). The National Institute for Health and Clinical Excellence (NICE) guideline on antenatal and postnatal mental health raises specific issues with certain antipsychotics, but does not provide general recommendations on whether to stop or continue antipsychotic treatment in this period (National Institute for Health and Clinical Excellence, 2007). Previous research on other psychotropic medications including antidepressants and antiepileptic drugs suggests that many women discontinue treatment in early pregnancy (Petersen et al., 2011; Man et al., 2012). However, very limited evidence exists on extent of antipsychotic prescribing in pregnancy and whether pregnancy is associated with discontinuation of antipsychotic medication.

We investigated prescribing of antipsychotic medication in the United Kingdom primary care before and during pregnancy using data from The Health Improvement Network (THIN), a large primary care database. The aim of our study was to examine whether pregnancy was a determinant for discontinuation of antipsychotics and if so, to identify factors associated with discontinuation.

2. Methods

2.1. Data source

We used data from The Health Improvement Network (THIN) primary care database (<http://csdmruk.cegedim.com/>), one of the largest primary care databases that provide longitudinal health records. The database currently holds data from 578 practices and is approximately representative of the United Kingdom population (Blak et al., 2011). Over 98% of the UK population are registered with a general practitioner (family doctor) (Lis and Mann, 1995). Diagnoses and symptoms are recorded by practice staff using Read codes, a hierarchical coding system (Chisholm, 1990). In addition, THIN holds individual patient level information about year of birth, date of registration, and death or transfer out of the practice. Social deprivation is recorded for each individual by quintiles of Townsend scores, which is based on information from the 2001 census.

While antenatal care is often shared between general practice staff and midwives, the general practitioner remains responsible for women's general medical care during pregnancy including prescribing of medicines. Some women with psychosis also receive care from local National Health Service (NHS) mental health trusts, but most mental health trusts have limited prescribing budgets and for most women the continuing prescription of psychotropic medication will still remain with the general practitioners.

2.2. Participants

We identified women who were permanently registered with one of the general practices that contributed data to THIN for the period between 1 January 1995 and 31 December 2012 for at least six months before the pregnancy and throughout their pregnancy. We included women who received continuous antipsychotic medication before they became pregnant i.e. women were selected if they received prescriptions

between 6 and 4 months (inclusive) before they became pregnant and received at least one further prescription in the three months before the start of pregnancy. Thus, we focused on women who received two or more prescriptions of antipsychotics in the six months leading up to pregnancy. In accordance with clinical practice in the United Kingdom, the first day of the last menstrual period was considered as the start of pregnancy. The duration of the pregnancy was estimated from information on the date of the last menstrual period, antenatal records, delivery information, dates of postnatal examinations and gestational age at birth. Pregnancies that ended in miscarriage or termination were not included in the study. We conducted separate analyses for women in receipt of typical and atypical antipsychotics prior to pregnancy and for each of these groups we identified comparison groups of twice as many women also in receipt of antipsychotic prescriptions, but not being pregnant for at least 12 months before and 24 months after a randomly selected index date. We stratified this group such that the age distribution was similar in the pregnant and non-pregnant sample.

A few women treated with antipsychotics ($n = 19$) had records of more than one eligible pregnancy; in these situations we randomly selected one of the pregnancies.

Antipsychotic prescribing was most commonly prescribed at monthly intervals, although there was substantial variation. Therefore, we considered women to have discontinued antipsychotic medication if they had received no further prescriptions after three months.

We also calculated the average daily dose of antipsychotic medication during the period from six to four months before the start of pregnancy by dividing the total mass of drug prescribed over the period by the expected total duration of the relevant prescriptions. Durations were estimated with the help of the Enhanced Dosage Determination method developed by the University of Nottingham Division of Epidemiology and Public Health (Gibson, 2012). The mass of each antipsychotic drug was standardised into units of the Defined Daily Dose (DDD) for maintenance treatment of psychosis (WHO Collaborating Centre for Drug Statistics Methodology, 2013).

2.3. Data analysis

2.3.1. Secular trends

We estimated annual prevalence of antipsychotic prescribing before and during pregnancy for every two calendar years between 1995 and 2012, stratified by typical and atypical antipsychotics. Subsequently, we followed pregnant and non-pregnant women who were prescribed antipsychotics from 3 months before the pregnancy (or the index date for the non-pregnant women) and identified when they had their last consecutive prescription. We ended the follow-up after 220 days (two months before delivery). In the case of a premature delivery earlier than 220 days, follow-up was terminated at delivery. Although we defined stopping of antipsychotics as the date of issue of the last prescription, some women would continue taking the drug beyond this point.

2.3.2. Factors determining continuation of antipsychotic prescribing in pregnant women

For pregnant women we further examined whether continuation of antipsychotic prescribing beyond six weeks of pregnancy was associated with age, the average daily dosage, length of time the antipsychotic had been prescribed prior to pregnancy, prescription of antidepressants and/or mood stabilisers, records of illicit drug or alcohol problems, obesity, parity, social deprivation and ethnicity using a Poisson regression model with robust variance estimates to account for clustering within general practice. We estimated the univariate relative risk ratios for each of the variables as well as relative risk ratios adjusted for age and average daily dose.

Many factors may impact the decisions to continue or discontinue antipsychotic medication in pregnancy. However, we chose to examine the variables described above as they were available from primary care electronic health records. While there is no direct measurement of

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