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Prenatal exposure to anxiolytic and hypnotic medication in relation to behavioral problems in childhood: A population-based cohort study

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ABSTRACT

Benzodiazepines and benzodiazepine-related medications (BBRMs) are anxiolytics and hypnotics acting on γ-amino butyric acid $(GABA)_A$ receptors. BBRMs are assumed to have a low potential for major congenital malformations, but research on more subtle and protracted developing symptoms of these medications is lacking. Therefore, we prospectively investigated the association between BBRM use in pregnancy and long-term effects on child behavior in a large population-based cohort study. The study population consisted of 104 children prenatally exposed to BBRM, 527 children exposed to maternal prenatal anxiety or phobic anxiety symptoms (without exposure to BBRM), and 5609 control children. At child age, 6 years, Oppositional Defiant Disorder (ODD), Aggressive Behavior and Anxiety Problems were assessed by the Child Behavior Checklist (CBCL) reported by the mother and the Teacher Report Form (TRF). Children prenatally exposed to BBRM had higher scores of ODD and aggressive behavior, but not of anxiety. However, these associations were explained by maternal anxiety symptoms during pregnancy. Moreover, prenatal exposure to anxiety (without exposure to BBRM) was associated with increased scores of child ODD, aggressive behavior, and anxiety. In conclusion, the current study demonstrates that prenatal BBRM exposure was not independently associated with ODD and aggressive behavior in childhood when prenatal anxiety symptoms were taken into account.

1. Introduction

Pregnancy is commonly associated with emotional changes, anxiety, and sleep problems (Goodman et al., 2014; Cai et al., 2013; Mindell et al., 2015). The prevalence of any anxiety disorder during pregnancy varies between 4.4 and 39% (Goodman et al., 2014). Anxiety during pregnancy has been associated with adverse obstetric and neonatal outcomes (Dayan et al., 2002; Hedegaard et al., 1993; van Batenburg-Eddes et al., 2009; Monk et al., 2000). It is important to treat anxiety during pregnancy, but the use of medications in pregnancy could also have potential risks for a mother and her developing child. Therefore, clinicians need to carefully weigh the balance between maternal well-being and child safety in their treatment decisions. This is difficult as information about the potential long-term consequences of anxiolytic and hypnotic medication is limited.

Benzodiazepines and benzodiazepine-related medications (BBRMs) are anxiolytics and hypnotics with the same mechanism of action; they are positive allosteric modulators of the γ-amino butyric acid $(GABA)_A$ receptor. Benzodiazepines may be prescribed in pregnancy to treat anxiety, insomnia, epileptic seizures, hyperemesis gravidarum, eclampsia or the risk of preterm birth (Buhimschi and Weiner, 2009; Baldwin et al., 2013). Further, benzodiazepines are commonly combined with Selective Serotonin Reuptake Inhibitors (SSRIs) in treating comorbid anxiety and depressive disorders (Riska et al., 2014), and for the treatment of excitement and sleep disturbances that frequently occur at the beginning of SSRI treatment. Benzodiazepine-related medications or z-drugs (e.g. zolpidem, zopiclone and zaleplon) are only used for insomnia treatment as they produce fewer anxiolytic and anticonvulsant effects. The prevalence of BBRMs use during pregnancy varies from 1.5–3.9% (Riska et al., 2014; Hanley and Mintzes, 2014). BBRMs are lipophilic, un-ionized compounds that easily penetrate the placental

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barrier. Newborns can have three to four times higher levels of BBRM in their plasma compared to their mothers (Kanto, 1982; Juric et al., 2009), because maternal serum binding capacity for benzodiazepines is lower during pregnancy and negatively correlated with gestational age (Lee et al., 1982). These high BBRM levels in the fetal circulation may negatively affect offspring development in short and long term.

Several studies have demonstrated associations between prenatal exposure to BBRM and birth and infant outcomes. For example, the risk of major congenital malformations tends to be small (Dolovich et al., 1998; Wikner and Kallen, 2011), but poor neonatal outcomes related to BBRM are more evident (Wikner et al., 2007a; Wang et al., 2010), and benzodiazepine use in late pregnancy or during labor has been associated with withdrawal symptoms and hypotonia in newborns (Cree et al., 1973; McElhatton, 1994).

Associations of prenatal BBRM exposure with longer-term child outcomes are less clear. Relatively few studies focused on the potential behavioral consequences of prenatal exposure to BBRM (reviewed in El Marroun et al., 2014a). A clinical trial investigated the use of lorazepam as a premedication for caesarean section and showed that exposed neonates had reduced scores on the Brazelton Neonatal Behavior Assessment Scale (Houghton, 1983). Several studies have reported an association between prenatal exposure to benzodiazepines and short-term effects; such as delays in psychomotor development (Mortensen et al., 2003; Laegreid et al., 1992), social problems, and hearing and speech impairments (Viggedal et al., 1993). Additionally, hyperactivity and attention deficit symptoms in childhood after prenatal exposure to benzodiazepines have been described (Laegreid et al., 1989). No association between prenatal benzodiazepine exposure and child behavior was observed in children whose mothers attempted suicide during pregnancy with high benzodiazepine doses (Gidai et al., 2008a; Gidai et al., 2008b). Likewise, a study investigating teacher-reported child behavior found no differences between children prenatally exposed to benzodiazepine compared to non-exposed children (Stika et al., 1990).

The primary concern in studies examining prenatal exposure to BBRMs is confounding by indication, which is a specific type of confounding that can occur in observational (non-experimental) pharmacoepidemiological studies of the effects or side effects of medications. As none of the studies described above are experimental, all of the studies were prone to some level of confounding by indication. This type of confounding arises from the fact that individuals who are prescribed or who take a given medication may be inherently different from those individuals who are not treated by medication. Other limitations of the previous studies are that the studies are relatively small, and have a relatively short follow up as most of the studies focused on children younger than 18 months of age. In the current study, we attempted to address these limitations by taking into account maternal anxiety during pregnancy and the child's age of 3 to address confounding by indication and other factors that may confound the association such maternal smoking, drinking and socioeconomic indicators.

Since the long-term effects of prenatal BBRM exposure on childhood behavioral problems are unclear, the goal of this study was to prospectively investigate the association between BBRM (GABAergic anxiolytic and hypnotic medications) use in pregnancy and child behavioral problems in a large cohort study. Based on the studies described above, we hypothesized that children prenatally exposed to BBRMs will have increased behavioral problems as compared to non-exposed children.

2. Methods

2.1. Participants

This study was embedded in the Generation R Study, a population-based prospective birth cohort, designed to identify early environmental and genetic causes of growth, development and health during fetal life and childhood (Jaddoe et al., 2012). The Medical Ethics Committee of Erasmus MC in Rotterdam, the Netherlands, has approved the study in accordance with the Declaration of Helsinki of the World Medical Association. Written informed consent was obtained from all the participants.

All pregnant women resident in Rotterdam and whose delivery date was from April 2002 to January 2006 were eligible for enrollment in the study. The present study only included children who participated in the prenatal and postnatal follow-up (n = 8101). Of these, 685 (8.5%) were excluded because of unavailable information on maternal medication use. Further, 465 (6.3%) children whose mothers used BBRM but 'not in pregnancy' were excluded, as a spillover effect cannot be ruled out. Information on child emotional and behavioral problems was not obtained in 711 (10.2%) children during follow-up. Finally, 6240 children formed the study population.

2.2. Maternal use of BBRM and anxiety during pregnancy

In this study, we assessed two exposures: (a) BBRM use during pregnancy, and as a contrasting exposure, (b) maternal anxiety symptoms in pregnancy, not treated by benzodiazepines. It is important to contrast long-term child developmental effects of medications used in pregnancy with the common indication of those medications.

In order to optimize ascertainment of medication use, we used two sources of information, which were combined into one exposure variable: (1) self-reports assessed with questionnaires and (2) prescription records from pharmacies. This approach of combining self-reported information and data from prescription records has been described previously (El Marroun et al., 2012; El Marroun et al., 2014b). In each trimester, pregnant women reported whether and when they had used any medications. Using these questionnaires, BBRM exposure and relatively crude timing (first, second or third trimester) were assessed. To validate the use of filled prescriptions, we asked women for permission to contact their pharmacy. These records provided information on the type of medication, duration, dose and specific timing (Table 1). Any use of BBRM during pregnancy, as assessed by self-reports and prescription records, was defined as exposure. The agreement between self-reports and prescription records (BBRM use versus non-use during pregnancy), measured by Cohen's kappa of the agreement, was fair ($\kappa = 0.34$).

Of the 104 women who used BBRM during pregnancy, 50 women used them in the first trimester only and 54 women used them in the first and also in one or two additional trimesters. Prescription records were obtained for 67 (64.4%) participants. Information obtained from these pharmacy records is presented in Table 1 for illustrative purposes. According to the prescription records, 81.2% used BBRMs <30 days and doses were therapeutic; there was no case of BBRM use above the maximum daily dose. Using questionnaires, the pregnant women reported the use of brotizolam, clobazam, clonazepam and clorazepate additionally to data from prescription records. Reasons for using BBRMs were not systematically collected (open text fields) and were often left open. Most commonly BBRMs were used because of anxiety and stress symptoms, sleep problems, muscle relaxation, nervousness and panic.

Anxiety and phobic anxiety symptoms were assessed with the Brief Symptom Inventory (BSI) (Derogatis and Melisaratos, 1983) at the 20 weeks of pregnancy. The BSI is a validated questionnaire with 53 items on a 5-point scale, ranging from 0 = 'not at all' to 4 = 'extremely'. We used the anxiety scale with six items and the phobic anxiety scale with five items. According to the Dutch norm data, a score higher than 0.75 indicates clinically relevant anxiety symptoms and a score higher than 0.70 indicates clinically relevant phobic anxiety symptoms (de Beurs, 2004). Based on the reported maternal anxiety symptoms and BBRM use during pregnancy, children were classified into three groups:

(a). Controls - no exposure to BBRM and exposure to a low score of maternal anxiety or phobic anxiety symptoms (n = 5609, 89.9%)
(b). Exposed to anxiety - exposure to clinically relevant anxiety or phobic anxiety symptoms without exposure to benzodiazepines (n = 527, 8.4%)