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# Psychotropics in pregnancy: Safety and other considerations

Femi Oyebode *, Abhinav Rastogi, Giles Berrisford, Floriana Coccia

*National Centre for Mental Health, 25 Vincent Drive, Edgbaston, Birmingham B15 2FG, United Kingdom*

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ABSTRACT

*Introduction:* Perinatal psychiatric disorders are important because of their adverse effects on pregnancy outcomes. The aim of this review is investigate psychotropic drugs in the management of antenatal psychiatric disorders with emphasis on the risk of harmful effects.

*Method:* A systematic review of published electronic literature between January 2000 and August 2011 was conducted using the following keywords: pregnancy, pregnancy complications, neonatal complications, congenital anomalies, infant/child development, antidepressants, antipsychotics, and lithium. The search was conducted for each class of psychotropic agents. Further hand searches were conducted. Anticonvulsants were excluded.

*Results:* Antidepressants are associated with increased risk of spontaneous abortions, stillbirths, preterm deliveries, respiratory distress, endocrine and metabolic disturbance. There is evidence of discontinuation syndrome and of increased risk of cardiac defects. Antipsychotics are associated with increased gestational weight and diabetes and with increased risk of preterm birth. The effects of antipsychotics on birth weight are inconclusive. In addition, the findings in relation to malformations are inconclusive. Lithium is associated with increased birth complications such as polyhydramnios, pre-eclampsia, respiratory distress syndrome, hypotonia, and preterm birth. Lithium has previously been associated with markedly increased risk of Ebstein's anomaly. However, recent re-evaluation of the data casts doubt on the previous estimates. There is evidence that lithium is associated with cardiac septal defects.

*Conclusion:* Psychotropic drugs remain an important treatment option during pregnancy to properly manage symptoms of psychiatric diseases. Clinicians need to remain aware of the potential risk of adverse effects associated with psychotropic drug treatment.



**Contents**



## 1. Introduction

The principal psychiatric disorders of pregnancy are antenatal depression, recurrence of depressive or manic episodes as part of bipolar affective disorder, and schizophrenia. Puerperal psychosis is important because there is often the need to commence treatment before the end of pregnancy as a precautionary measure. The treatment of these conditions during pregnancy require the use of psychotropic agents and this raises questions about the safety of these drugs, their likely impact on the health of the pregnant woman, on pregnancy outcomes, on fetal development and neonatal health, the potential for major and minor malformations, and on the long term development and health of the child. Despite these matters of concern, it is often imperative to institute treatment.

Antenatal depression is recognized as a common condition affecting pregnant women with point prevalence estimates ranging from 6.5% to 12.9% at different trimesters of pregnancy and a combined

*Abbreviations:* SSRI, Selective serotonergic reuptake inhibitor; SNRI, Serotonergic noradrenergic reuptake inhibitor; FGA, First generation antipsychotic; SGA, Second generation antipsychotic.

* Corresponding author. Tel.: +44 121 301 2354.
*E-mail address:* Femi_Oyebode@msn.com (F. Oyebode).

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point prevalence of 19.2% of pregnant women (Gavin et al., 2005). There is now considerable evidence that perinatal depression, including antenatal depression is a global disorder and often affecting women in the developing world at disproportionately higher prevalence rates than in the developed world (Lee et al., 2004; Kitamura et al., 2006; Adewuya et al., 2007; Felice et al., 2007; Lau & Keung, 2007; Shakya et al., 2008; Gausia et al., 2009; Karmaliani et al., 2009; Pottinger et al., 2009; Golbasi et al., 2010; Silva et al., 2010; Hartley et al., 2011; Mohammad et al., 2010; Rochat et al., 2011; Senturk et al., 2011; Shah et al., 2011). Although the pathogenesis is unclear, a number of factors have consistently been shown to be associated with the development of antenatal depression: young maternal age; low social support; unsupportive family; low income; history of domestic, physical or sexual abuse; primiparity; past history of abortion; and negative attitude towards the pregnancy; (Kitamura et al., 1996; Edwards et al., 2008; Leigh & Milgrom, 2008; Gausia et al., 2009; Karmaliani et al., 2009; Luke et al., 2009; Golbasi et al., 2010; Hartley et al., 2011; Mohammad et al., 2010). The importance and need for treatment of antenatal depression is underlined by the associated risk of preterm delivery, low birth weight and intrauterine growth retardation (Grote et al., 2010a) but these effects are more prevalent in developing countries (Grote et al., 2010b). In addition, antenatal depression is a risk factor for postpartum depression (Leigh & Milgrom, 2008). The role of antenatal depression in the development of post partum depression is important because of the established risks associated with postpartum depression namely suicide in mothers (Gentile, 2011), cognitive and language delay in the child (Beck, 1998; Grace et al., 2003; Hollins, 2007; Talge et al., 2007; Stein et al., 2008; Barker et al., 2011), developmental delay and poorer motor skills in the child (Deave et al., 2008; Gerardin et al., 2011), and impairments of mother–child interaction (Breznitz & Sherman, 1987; Zekoski et al., 1987; Bettes, 1988; Lovejoy, 1991; Stein et al., 1991; Tronick & Reck, 2009). There is growing evidence that the intrauterine exposure of the fetus to psychological distress in the mother such as occurs during antenatal depression itself has sustained effects on the child over the lifespan (Kinsella & Monk, 2009) and this effect is thought to be mediated by abnormal cortisol response patterns in the infant, the so-called fetal programming hypotheses (de Bruijn et al., 2009) that influences the child's adrenocortical and cardiovascular responses to acute stress (Gump et al., 2009). In summary, antenatal depression is a common disorder with potential adverse long-term consequences both for the mother and the fetus. This means that effective treatment is important yet there is potential harm deriving from the use of psychotropic agents during pregnancy. The treatment of antenatal depression exemplifies the complexity of clinical medicine as it demonstrates that despite incomplete evidence and uncertainty about the risk–benefit quotient, clinical decision still needs to be made.

Bipolar affective disorder and schizophrenia are not as common as antenatal depression during pregnancy. Nonetheless, these two conditions are also associated with markedly elevated risks of pregnancy, birth and neonatal complications including antepartum hemorrhage, placental abnormalities, fetal distress, preterm birth, low birth weight, and small for gestational age babies (Jablensky et al., 2005; Lee & Lin, 2010). Schizophrenia is particularly associated with low birth weight and cardiovascular anomalies in neonates (Jablensky et al., 2005). Puerperal psychosis occurs following 1–2 births per 1000 and it is now well established that it has a close relationship to bipolar affective disorder. Puerperal psychosis often occurs in mothers with a past history of bipolar disorder and the diathesis to puerperal psychosis appears to be familial, as women with a history of bipolar affective disorder, were more likely to have puerperal psychosis if they also had a family history of puerperal psychosis (Jones & Craddock, 2001). In addition, there is evidence of postpartum recurrence, with childbirth acting as the trigger, of bipolar disorder (Harlow et al., 2007; Munk-Olsen et al., 2009) and of strong continuities between puerperal illnesses and non-puerperal illnesses (Robling et al., 2000).

In summary, although bipolar affective disorder, schizophrenia, and puerperal psychosis are infrequent in the perinatal period, there is good reason as described above to ensure that these conditions are effectively managed in order to ameliorate their adverse consequences on maternal and child wellbeing.

## 2. Aims

In this paper we will review, in detail, the most common psychotropic drugs used in the management of psychiatric disorders during pregnancy, paying particular attention to the actual risk of harmful effects during pregnancy, the potential for teratogenic effects, and the adverse effects on development including cognitive functions, language, and acquisition of motor skills.

## 3. Method

A systematic review of published literature between January 2000 and August 2011 was conducted using the following keywords: pregnancy, pregnancy complications, neonatal complications, congenital anomalies, infant/child development, antidepressants, antipsychotics, and lithium. The search was conducted for each class of psychotropic agents separately. Further hand searches were conducted to augment the electronic search results. We excluded anticonvulsants from this review since the literature in this area is substantial and exceeds that for other psychotropic drugs.

## 4. Results

### 4.1. Antidepressants

In the United Kingdom, in the period 1992–2006, the number of pregnant women receiving antidepressants increased 4-fold, and by 2001 3% of pregnant women were receiving antidepressant medication. Selective serotonergic reuptake inhibitors (SSRIs) constituted 80% of this increase (Petersen et al., 2011). There are now a number of large cohort studies investigating the effects of antidepressants on pregnancy outcomes, fetal development, malformations, neonatal problems, and child development (Einarson et al., 2001; Nulman et al., 2002; Djulus et al., 2006; Maschi et al., 2008; Einarson et al., 2009; Galbally et al., 2009; Pedersen et al., 2009; Suri et al., 2011). Despite the improvements in the overall quality of studies, particularly in sample size, there remain problems with multiple publications on the same cohort, with the added risk of double counting and bias. In addition, not all studies focus on the same outcome measures and for some outcome measures such as miscarriages, stillbirths, and neonatal complications, only the smaller, less rigorous studies have reported on these. There are other confounding factors such as smoking, alcohol and drug misuse which are often not taken into account even though the adverse effects include spontaneous abortion, placental insufficiency, low birth weight, fetal growth restriction, etc. (Einarson & Riordan, 2009). Finally, the role of polypharmacy in the reported adverse effects of psychotropic drugs has yet to be fully examined and determined.

#### 4.1.1. Pregnancy outcomes

There is consensus that pregnant mothers exposed to antidepressants are more likely to have spontaneous abortions, stillbirths and preterm deliveries (Simon et al., 2002; Källén, 2004; Hemels et al., 2005; Djulus et al., 2006; Davis et al., 2007; Maschi et al., 2008; Lund et al., 2009; Toh et al., 2009; Wisner et al., 2009; Einarson et al., 2010; Lewis et al., 2010; Nakhai-Pour et al., 2010). The risk of spontaneous abortions appears to be greatest with exposure to combined antidepressants: Odds ratio 1.68 for all antidepressants; 1.61 SSRI; 2.11 serotonergic noradrenergic reuptake inhibitors (SNRIs); and 3.51 combination of two or more antidepressants from different classes. As for individual