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Pregnancy

Critical review

Atypical antipsychotics, maternal and child outcomes: A critical review

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Abstract

Introduction

Atypical antipsychotics are increasingly prescribed for women suffering affective and non-affective psychoses during the antenatal and postnatal period. The level of evidence for psychopharmacological treatment during pregnancy with these agents is generally poor, especially on maternal, foetal and infant outcomes.

The aim is to summarize the current evidence on the use of atypical antipsychotics during pregnancy, and to evaluate the known maternal, foetal and neonatal outcomes related to maternal treatment with atypical antipsychotic during the antenatal period.

Materials and methods

A comprehensive literature search was undertaken by using various electronic databases to identify published studies reporting on safety of atypical antipsychotics in human pregnancy up to March 2014. We inspected all references of all identified studies and hand searched for key journals. The selected studies were reviewed, summarised, and synthesised.

Results

Atypical antipsychotics are known to be associated with maternal weight gain, which can increase risks of maternal gestational diabetes, metabolic syndrome, and foetal neural tube defects. Single cases of obstetrical complications and perinatal adverse reactions associated with exposure to atypical agents during pregnancy have also been reported. Conversely, there is no conclusive evidence of their structural teratogenicity.

Conclusion

The rapid development in pharmacotherapy has resulted in a growing number of women of childbearing age being treated with atypical antipsychotic drugs. The major challenge for healthcare professionals is to achieve an optimal balance between minimizing foetal and neonatal exposure whilst avoiding the potentially harmful consequences of maternal mental illnesses. Due to the limitation of the research and the potential public health implications, further evidence on maternal, obstetric and infant outcomes of mother treated with atypical antipsychotics is urgently needed.

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Introduction

Over the past ten years the importance of maternal mental health has become clear. In the sixth report of the UK Confidential Enquiry into Maternal and Child Health (CEMACH), mental illness was the leading cause of maternal death[1]. The numbers of maternal deaths from indirect psychiatric causes in the UK continues to outnumber direct deaths and has been demonstrated in the past four CEMACH reports where the mortality rate for mothers' deaths with either pre-existing or new major mental illnesses precipitated by pregnancy remains largely unchanged[2]. Typically mothers with a mental illness who die in the postpartum period are suffering from a severe psychotic illness.

The global prevalence of non-affective psychotic illnesses, such as Schizophrenia, is relatively rare. Epidemiological data indicates that their lifetime prevalence and incidence are 0.30–0.66% and 10.2–22.0 per 100.000 person-years, respectively[3]. Literature evidence shows higher prevalence and incidence rates in general population[4,5] for affective psychosis, such as Bipolar Affective Disorder which has an estimated lifetime prevalence of approximately about 2–4%[6]. The prevalence of Puerperal Psychosis (a psychotic episode precipitated by childbirth) is approximately 1-2 case per 1000 deliveries in the general population[7]. BPAD and, to a lesser extent, Schizophrenia have elevated prevalence in Puerperal Psychosis[8]. Women with a history of Puerperal Psychosis are at extremely high risk of relapse in new pregnancies and postpartum is the time of major risk for exacerbation of a psychotic episode[9,10].

The risk–benefit weighting of treatment versus no treatment in the puerperium for women who have had a prior episode of Puerperal Psychosis falls down very convincingly on the side of active prophylactic treatment[8,11].

However, there is no conclusive consensus regarding the most suitable time to reintroduce prophylaxis. Some authors suggest starting prophylaxis during the second or third trimester of pregnancy[12] when the teratogenesis risk is thought to be lower, while other authors suggest deferring prophylactic treatment immediately after delivery[11].

Other particularly vulnerable women, on the other hand, may require medication throughout pregnancy[8], and antipsychotic drugs remain an important treatment option during pregnancy to properly manage a psychotic illness[13]. In evaluating any negative effects of taking medication during pregnancy concerns include: whether there is an increased risk of miscarriage; the risks of major malformations in the baby; any obstetric and neonatal complication; safety during breastfeeding and the occurrence of long-term problems in the offspring. Any of these concerns must be weighed against the risks of

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relapse of the mental illness. Thus, although foetal medication exposure is identified as a risk to pregnancy outcome, maternal mental illness and its risks to the foetus must also be clearly evaluated when considering treatment during pregnancy[14,15,16].

In May 2008, the American Food and Drug Administration (FDA) proposed major revisions to prescription drug labelling during pregnancy and breastfeeding. The proposed regulations eliminate the current pregnancy categories of risk A, B, C, D, and X due to limitations in their ability to accurately and consistently convey risks and benefits, and the ultimate regulation is still in the writing and clearance process at present [17].

The atypical antipsychotics are now gradually replacing typical antipsychotics, as approved by the Medicines and Healthcare Products Regulatory Agency (MHRA) and the FDA, and are recommended as first-line agents for non-affective psychotic disorders, such as Schizophrenia, as well as other disorders such as the treatment of acute mania and bipolar depression, and the maintenance treatment for bipolar disorder.

Women treated with these prolactin-sparing agents, with the exception of risperidone, theoretically will have normal fertility rates (as the increased prolactin levels inhibited ovulation in typical antipsychotic use), thus being more likely to become pregnant than those receiving typical antipsychotics. Due to these potential changes in fertility rates in women using atypical antipsychotics, there is reason to believe that more women with psychotic disorders prescribed these medications will become pregnant in the future[18]. Consequently, data regarding the reproductive safety of these compounds bear tremendous public health implications[19].

The aim of this critical review is to summarize the current evidence on the use of atypical antipsychotics during pregnancy, and to evaluate the known maternal, foetal and neonatal outcomes related to maternal treatment with atypical antipsychotic during the antenatal period.

Materials and methods

A comprehensive literature search was undertaken by using various electronic databases to identify published studies reporting on safety of atypical antipsychotics in human pregnancy up to March 2014. Five databases (no language restriction) have been used which include: Medline, Embase, Cochrane Library, PsychINFO and CINAHL. Initial search terms included antipsychotics (including specific searches for each currently used atypical antipsychotic), drug, atypical in combination with pregnancy, maternal, foetal and neonatal outcome, puerperium, and puerperal psychosis.

All papers available were accessed. We inspected all references of all identified studies and hand searched for key journals. Due to the paucity of well-designed prospective studies, a formal appraisal of evidence was not conducted. Where case reports, manufacturers' data and other smaller studies have been included, the limitation of this evidence has been noted.

Results

Current use of atypical antipsychotics during pregnancy

In the UK the proportion of time patients spent on typical antipsychotics for Bipolar Affective Disorder in 1995 was 14.2%. By 2009 this had reduced to 6.9%. In contrast, the proportion of time spent on atypical antipsychotics had increased from zero to 35.0%[20]. The annual proportion of time patients spent in atypical antipsychotic treatment for Schizophrenia increased from 16.6% to 51.2% between 1998-2007, whereas time spent in typical antipsychotic treatment reduced from 37.1% to 15.0% during the same period[21].

According to literature evidence approximately 0.053% of the women took an atypical antipsychotic at some point during the antenatal period[22], while other authors recently showed a 2.5-fold increase in atypical antipsychotic use during pregnancy up until 0.82 %[23].

Pregnancy and obstetric outcomes

Most existing studies of pregnancy/ obstetric outcome in association with maternal psychotropic treatment during pregnancy have relied on maternal self-reports, assuming 100% maternal compliance. To date to our knowledge, there have been no blinded or randomized studies examining birth outcomes in women taking atypical antipsychotics. There are two prospective study[24,25], one descriptive cohort study[26] and the remainder of the data come from case reports and manufacturers' data collections[18]. Both case reports and manufacturers' data may show a reporting bias that could over represent the rate of adverse outcomes.

Atypical antipsychotics are known to be associated with weight gain[24], which can increase risks to both mother and baby, such as the risk of maternal obesity, gestational diabetes, metabolic syndrome and the baby being at higher risk for neural tube defects[27].

Weight gain and related metabolic syndrome have been reported in association with olanzapine, as well as other atypical antipsychotics including clozapine and quetiapine[28]. Women exposed to these agents have generally higher BMI compared to not exposed women[25]. There are also reports on the association between atypical anti-psychotics and increased risk of gestational diabetes[29,30]. Similar risks occur for the more obesogenic and diabetogenic antipsychotics clozapine and olanzapine as for other antipsychotics, which suggest similar effects[30].

In addition, women with excessive weight gain are more likely to have pre-existing hypertension or to develop this condition during pregnancy[26,31], while other authors found an increased risk of hypothyroidism in women exposed to atypical agents[26].

Literature research has shown that gestational diabetes can leads to higher risk of low for gestational age (LGA) babies[30].

Newham et al. found that infant exposed to atypical antipsychotics had a significantly higher incidence of being LGA[32], while other authors found that atypical antipsychotics exposure during

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pregnancy is not significantly associated with LGA babies, with the exception of olanzapine and/or clozapine exposure being related to macrocephaly[30]. A small, Australian database has shown two cases of high neural tube defects resulting in early second trimester miscarriages in women receiving aripiprazole in pregnancy[33], while other authors did not detect a significantly increased risk of miscarriage (<20 weeks)[25,26] and foetal death (≥20 weeks)[26] after exposure to antipsychotics which is in line with the findings of other investigators[25,34]. Single cases of poor pregnancy outcome, and perinatal adverse reactions associated with exposure to clozapine during pregnancy have been reported, though they have been shown only in case reports and/or small case series.

A report from the Lilly Worldwide Pharmacovigilance Safety Database identified some cases of complicated pregnancy outcome in women under olanzapine treatment. In contrast, there are a number of other reports describing healthy outcomes in babies exposed to olanzapine throughout pregnancy[18].

Only sporadic clinical observations have described complicated pregnancy outcomes following in utero exposure to risperidone that were consistent with rates in the general population[34]. Overall, the obstetrical complications found in literature include preterm deliveries (26), increased rate of instrumental deliveries[26], low birth weight babies[24], greater mean birth weight[25,32], increased neonatal intensive care unit admissions[19,26], and poor neonatal adaptation signs (central nervous system, respiratory and gastrointestinal problems)[26,35].

Several studies have described an increased risk of preterm birth in women treated with atypical agents, but it is not clear if it is a specific effect of treatment or a consequence of the mental illness itself.

Foetal, neonatal and child outcomes

There is no conclusive evidence of the structural teratogenicity of atypical antipsychotics. Manufacturers' data collections report that prevalence of major malformations does not differ from that detected in general population[18]. Most prospective and retrospective studies have not been found related to increased risk of major malformations in infant exposed to these agents[7,18,24,25,29,34,36,37], while a recent prospective observational cohort study from Habermann et al.[25] showed an increased rate of cardiovascular defects in offspring of mothers treated with atypical antipsychotics during pregnancy. Newport et al. found placental passage ratio for quetiapine and olanzapine being respectively the lowest (24.1%) and the highest (72.1%) compared to other atypical agents[19]. Knowledge concerning placental passage of clozapine is limited, with only one case report documenting foetal accumulation[30].

Sporadic cases of olanzapine-associated neonatal adverse reactions, self-remitted neuro-developmental impairment are now being recorded. An increased risk of hypoglycaemia has been seen in newborns of mothers treated with atypical agents[24,32].

Several authors report cases of neonatal convulsion and floppy baby syndrome in women taking clozapine during pregnancy[29], while clozapine overdose during pregnancy may lead to fatal poisoning of the newborn[18]. Other authors found speech problems in children of mother exposed to clozapine[38]. Self-limiting extra-pyramidal or possible withdrawal symptoms have also been described in infant exposed to risperidone in the third trimester[34].

Other atypical antipsychotic drugs, asenapine, paliperidone, ziprasidone and sertindole have not been used adequately to meaningfully discuss risks of treatment during pregnancy[18,29,31].

Discussion

The rapid development in pharmacotherapy has resulted in a growing number of women of childbearing age being treated with atypical antipsychotic medications[39].

While there have been many literature reviews related to this topic, for the clinician there remains insufficient evidence relating to best practice in using antipsychotic medication during pregnancy. Moreover, current clinical practice varies. This variation is attributable to clinician's awareness of the lack of substantial evidence and their uncertainty that treatment will work and, at the same time, will cause no harm to either mother or baby.

While long-term studies gathering controlled prospective data from large numbers of women are required, due to ethical issues no studies of medication during pregnancy meet the gold standard of randomized, placebo-controlled, double-blind, crossover trials. Despite the limitations of the research, it is still necessary to make recommendations based on the accumulated information of the best available studies on the safety of antipsychotic medication during pregnancy or breastfeeding.

Obstetricians, psychiatrists, and general practitioners need strong evidence on which to base prescribing of atypical antipsychotic drugs for pregnant and breastfeeding women, and women must be provided with reliable information to support them in decisions about medication during pregnancy and after childbirth.

The use of atypical antipsychotics during pregnancy is described as appropriate in clinical situations where the risk of prenatal exposure is outweighed by the risk of relapse if the drug were to be discontinued[39]. Current literature evidence provide no conclusive information about the best treatment option with antipsychotics (typical or atypical) during pregnancy. Although atypical antipsychotics are thought to be safer than typical antipsychotics[18], they still have side effects[40], that all confer significant risks for pregnancy. A recent systematic review from Gentile et al.[18] suggest using typical antipsychotics, especially chlorpromazine, instead of atypical agents for the management of psychotic symptoms in pregnant drug-naïve women, while when an unplanned pregnancy occurs during antipsychotic

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treatment with either typical or atypical agents, the choice to continue the previous therapy (if known as effective) should be preferred.

Clinical outcome studies following antenatal atypical antipsychotic administration are limited to analyses using small sample sizes of placental passage rates, neonatal outcomes and the risk for delivery complications and congenital malformations.

Thus, further investigation on the outcomes of women treated with atypical antipsychotic medications in pregnancy for any psychotic disorder and the consequences of this treatment on maternal, obstetric and infant outcomes urgently need to be characterised to inform the global evidence base for the management of these women in pregnancy.

Conclusion

The management of expectant mothers with psychotic illness poses a challenge for patients, their families, and obstetricians. The major goal is to achieve an optimal balance between minimizing foetal and neonatal exposure to drugs whilst avoiding the potentially serious consequences of a mother developing psychosis.

Literature evidence have highlighted the importance to start or continue antipsychotic therapy in vulnerable women due to the risk of relapse of their mental illness, which in some case represents a medical and obstetrical emergency.

The majority of studies on the reproductive safety of antipsychotic drugs are based on a single-dimension experimental design, which could underestimate all the possible factors related to the increased risk of poor pregnancy, obstetrical and neonatal outcomes independent of the medication itself. At present, the best available data on antipsychotic treatment during pregnancy come from non-randomized, prospective/ observational studies, case reports or manufacturers' data. Further evidence is required from large pragmatic studies that reflect routine clinical practice, examine a broad range of outcomes and accurately quantify risks and benefits to both mothers and their offspring, so that comparison between different treatment options can be made.

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