The Effects of Antipsychotic Medication in Pregnancy and Outcomes for Mothers and their Babies. A Review

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Abstract:

Objectives: To review studies examining whether the use of antipsychotics during pregnancy would have effects on the outcomes of the pregnancy for the mothers and their babies.

Method: Results of four journal articles published between 2008 and 2018 that satisfied the inclusion and exclusion criteria, retrieved from Medline and PubMed databases were summarised and analysed.

Results: Mentally ill pregnant women on antipsychotic medications and their babies are at higher risk of obstetric and gynaecological outcomes such as gestational diabetes, hypertension, premature delivery, babies small for gestational age and low birth weight. Other problems include congenital anomalies like arterial defects, cleft lip/palate and hydrocephalus and abnormal renal collecting tubule.

Conclusion: Further research is needed to gain knowledge of the relative risk of antipsychotics on pregnant mother and their babies so that clinicians would provide mentally ill pregnant patients with adequate information on the effects of these drugs on their body systems and their developing babies. Adequate knowledge of the effects of antipsychotics will limit clinicians to administer such medications only to those patients more at risk of relapse if not administered such drugs than the current practice of administering them to those with mild or moderate mental illness.

I. INTRODUCTION

Naturally pregnancy brings changes in actions and mood which in the end affect the general functioning of the pregnant woman. The condition is worse for women with history of mental illness because of the combined effects of bodily changes as a result of the pregnancy and issues resulting from the mental illness. To decrease the various effects pregnancy has in addition to those brought by the psychiatric illness, antipsychotic medications are prescribed to treat the mental illness.

Peter Haddad (2016) defined 'antipsychotics' as group of medicines primarily used to treat mental health or psychiatric conditions such as schizophrenia and bipolar disorder. Some antipsychotics are also used to treat other mental health conditions like severe depression (Peter Haddad 2016). Antipsychotics, also known as psychotropic or neuroleptic medications are effective for the treatment or controlling psychotic symptoms like delusions, hallucinations, or symptoms of mania (Mark 2010; Philip Timms and Lacey 2018). Antipsychotic drugs help regularize the operation of brain circuits that govern mood, thinking, and perception. They help to enhance or reduce the actions of neurotransmitters in the brain thus affecting its functions.

Antipsychotics have been generally categorized into classical or typical antipsychotics, which comprise phenothiazines and butyrophenones, and modern or atypical antipsychotics, which include benzamides. The initial usage of antipsychotics started in the 1950s, when new brands of medication including antipsychotics were introduced into psychiatric practice (Peter Haddad 2016).

Antipsychotic medications, though frequently used in treating psychotic conditions, have adverse effects on the pregnant mother and the baby at both prenatal and postnatal stages (Bellet et al. 2015). In recent years, there has been significant increase in women presenting with one form of psychiatric disorder or the other. Depression and anxiety disorders are the common psychiatric problems affecting pregnant women with about 12% of pregnant women experiencing depression and about 13% experiencing anxiety disorders; many women will suffer both. Fifteen to twenty percent of women also experience depression and anxiety disorders in the first 12 months after birth (NICE 2014). A recent UK study reported that, one in every four pregnant women have mental health problem (Kings College, London, 2018). Also, the World Health Organisation's report on maternal mental health 2013-2020 reported that, across the world, about ten per cent of pregnant women and thirteen percent of women who have just delivered suffer from mental health problem, primarily depression. The situation is even poorer in under developed countries who have a record of fifteen per cent cases of depression during pregnancy and nineteen percent cases of postpartum depression which in some cases lead to maternal suicide (World Health Organization 2018). Therefore, mothers affected by mental health problems cannot function effectively, as a result, the growth and development of their children may also be affected.

Maternal mental health problems are treatable. Effective treatments are available and delivered at different health care delivery settings. In the United Kingdom, maternal mental

health problems are managed at primary health care settings, obstetric and gynaecological trusts, general mental health services as well as specialists' health services. Given the fact that no drug is without side effects, there are obvious risks associated with the use of antipsychotic medications during pregnancy. These include high rate of neonatal death, stunted foetal development and growth and malformation of body parts (Galbally et al. 2014). Thus, general practitioners, obstetricians, and psychiatrists are confronted with hard decisions to judge whether to administer and treat mentally ill pregnant patients with antipsychotics or not. Whichever decision they take, they will need to look at the possible risks of the medication on the unborn baby against the likely effects of not administering the medication which may endanger their pregnant mentally ill patients to relapse. The consequences of not treating the pregnant mentally ill patient, according to (Yassar I Odhejo 2017) may lead to poor relations between the mother and her baby**.**

At present, clinicians are prescribing antipsychotics to mentally ill pregnant women mainly because of lack of availability of negative data rather than the availability of positive data about their effects on during pregnancy (Galbally et al. 2010). Thus, the widespread use of antipsychotics medications makes understanding their effects on pregnant women necessary so that clinicians treating mentally ill pregnant patients will not be in dilemma when prescribing antipsychotic medications.

This review is carried out to report the relevant and current findings of antipsychotic medication used to treat mentally ill pregnant women, so that clinicians may have more knowledge and understanding about these medications and also to give their mentally ill pregnant patients information about the benefits and risks of antipsychotic medications during pregnancy.

II. LITERATURE REVIEW

Mental health problems such as anxiety disorders, bipolar disorders and schizophrenia are very common. They affect both men and women. Among women, approximately 500,000 pregnancies every year get complicated by psychiatric illnesses occurring before or after the pregnancy (Levey et al. 2004). When affected, patients are treated with antipsychotic medications. These medications, like other medications have some negative effects. Generally, the effects of antipsychotics include neurological, problems such as tardive dyskinesia, ocular gyration, and neuroleptic malignant syndrome. Others are metabolic side effects such as weight gain, dyslipidemia and diabetes/glucose intolerance and hypothalamic and pituitary related side problems such as hyperprolactenemia (DOLDER 2008). For the mentally ill pregnant women, the effects are two-fold. Beside the effects of the medication on the women, their babies are also affected. Yet, the literature is lacking effective information on the safety of antipsychotics and their effects on the pregnant women and their babies. The physiological processes occurring during pregnancy, the pharmacokinetics and pharmacodynamics that result from pregnancy as well as delayed gastric emptying, reduced drug-protein binding, enhanced vascular volume leading to decreased drugs serum levels, improved hepatic absorption and increased renal clearance can greatly influence the concentration of the drug in the body (Stowe and Nemeroff 1998). The fetus on the other hand has low drug binding to plasma proteins, unformed hepatic metabolism, a rather penetrable blood brain barrier and difficulties in moving drug metabolites to the mother's circulation. These, coupled with the fetus's low ability to digest drugs results in excessive drug concentrations in the fetus than in the mother. Therefore, adequate levels of medication have to be maintained in the maternal serum while keeping it less in the circulation of the fetus (Stowe and Nemeroff 1998). Hence, clinicians must be careful with drug dosing, since sub-therapeutic levels of drugs have the possibility for relapse, whilst the opposite can predispose toxicity in the baby.

With the increasing number of antipsychotic drugs used daily to treat mentally ill pregnant women, studies on the efficacy and safety of these drugs produce mixed results (Menon 2008). For example, a study examining exposure to benzodiazepines in pregnant women have shown that, the drugs have led to the delivery of some children with facial clefts, cardiac malformations, and other range of deformities, but no syndrome of defects (Yonkers et al. 2004). Similarly, (Menon 2008) reported that maternal exposure to lithium throughout the first trimester is connected with an higher risk of cardiac abnormalities on the babies but no effects were observed on the mother. High potency typical antipsychotic drugs like haloperidol do not have the risk of teratogenicity (Koren et al. 2005). However, low potency antipsychotic medications such as chlorpromazine were reported to have minor but statistically significant higher risk of unspecified teratogenic effects when administered during the first trimester of the pregnancy. Studies have confirmed that, the use of atypical antipsychotics can change body weight homeostasis in humans, which may lead to major drug-induced increase in weight and high rate of visceral fat accumulation in women (Peindl et al. 2007; Seeman 2009; Boyda et al. 2010; Coccurello and Moles 2010). The increase in weight however, differs among the atypical antipsychotics, ranging from 2kg to 25 kg (Coccurello and Moles 2010), and these effect can be seen in up to 60% of patients after 3 to 12 months of medication (Seeman 2009).

While some studies reported proof that the danger of increased obstetric complications in women with severe mental illness is not related to any antipsychotic exposure during pregnancy (McKenna et al. 2004), other studies have reported potential risks linked precisely with antipsychotic medication in pregnancy including gestational diabetes, linked with Second Generation Antipsychotics (SGAs). These drugs have also been reported as causing premature birth, low and high birth weight, gestational diabetes and caesarean delivery (Galbally et al. 2010; Galbally et al. 2014). According to

(Newport et al. 2007), all antipsychotics medications pass through the placenta. Therefore, attention must to be given to their likelihood of physical or functional malformations of foetal vital organs or the skeletal system structures when administering them during the first trimester. High incidence of malformations, higher rates of postnatal disorders, preterm delivery and low birth weight are very common in neonates whose mothers were administered atypical antipsychotics during pregnancy. According to (Gentile 2008) there is higher risk of neonatal withdrawal, extra-pyramidal symptoms (EPS) as well as sedation in children of mothers exposed to antipsychotics during pregnancy (Gentile 2008)

The frequent and persistent use of antipsychotic medications in pregnant mentally ill women without scientific evidence regarding their efficacy and risks on both the pregnant mother and her baby raises a number of clinical and ethical dilemmas among clinicians. The same ethical reasons stop the generation of scientific knowledge on the efficacy and dangers of antipsychotic drugs on pregnant patients as this group of patients are restricted from participating in randomised drug trials. Without such knowledge, the provision of evidence based intervention is impossible (Unger et al. 2011) . Therefore clinicians are left to decide what to administer to their pregnant mentally ill patients based on their experience and comfort with the use of certain antipsychotics.

III. METHODOLOGY I

PICOS for the review

Population- The studies included in this review are those that are related to pregnant women diagnosed with mental disorders whose age ranged between 18 to 45 years, whose mental illnesses are managed with antipsychotic medication up to the first year of their baby's life.

Intervention- Antipsychotic medications

Comparison- pregnant women not on antipsychotic medication

Outcome- Morbidity, mortality observed in both mothers and their babies.

Studies- The studies reviewed include cohort studies, clinical studies and case control studies.

Search strategy

A systematic search of journal articles to retrieve publications from academic journals on the Cochrane library was conducted using key word and phrase searches.

The key words searched – antipsychotic, psychotropic, medication, pregnancy, mental illness, lactation, effects, and teratogenic.

Phrase search-

The phrase search include **-** mentally ill women, antipsychotic drugs, antipsychotic medications, side effects, pregnant women, effects on babies. These keywords and phrases were entered into PubMed and MedLINE, on the EBSCO interface. The search terms were combined with OR & AND commands. Other sources like Google and Google Scholar were also searched. Hand searching of the reference lists of some articles was also made.

Inclusion/exclusion criteria: Only studies reported in the English language, conducted with human participanta aged 18-45 years with diagnosis of mental illness, taking antipsychotic medications and conducted within 2008–2018 were included. Exclusion Criteria include studies conducted with children as participants, patients not on antipsychotic medication, not on pregnant women and without diagnosis of mental illness.

The initial search produced a total of 362 references. The references were all imported into the bibliographic software-endnote. Find duplicate function of the endnote was used to identify and delete 127 duplicates. Another 194 articles were removed as they are not related to the topic under investigation or not conducted with pregnant mentally ill patients or used animals as participants. Twenty seven (27) studies were also excluded for no full text or not written in English language, not published within the review period. The remaining 14 fourteen articles were appraised on Critical Appraisal Programme Checklist (CASP)(CASP UK 2013) to check for their validity.

IV. METHODOLOGY II

Title of the article	Authors	Methodology	Methods	Participants	Results/findings	Strengths and weaknesses of the studies
Study 1 A Prospective Cohort Study of Antipsychotic Medications in Pregnancy: The First 147 Pregnancies and 100 One Year Old Babies.	Jayashri Kulkami, Roisin Worsley, Heater Gilbert, Emorfia Gavrilidis, Tamsyn E Van Rheenen, Wei Wang, Kay McCauley and Paul Fitzgerald.	Qualitative-prospective cohort study.	Mixed method (Quantitative/Qualitative study)	147 pregnant women with moderate to severe mental disorders and on antipsychotic medication.	The study found that, there was a significant difference in antipsychotic dose at 12 weeks between babies born at term and babies born prematurely. There was 37% incidence of respiratory distress among children exposed to antipsychotics More than 40% of exposed babies needed support in a special care nursery or neonatal intensive care unit	**Strength** Data collection started from pregnancy up to one year after delivery. Ethical approval by 17 committees. Use of standardised tools to assess mental illness. The effects of antipsychotics were monitored on babies until one year after delivery. **Weaknesses-**

					There was incidence of medication withdrawal syndrome seen in 15% of babies exposed to higher doses of antipsychotics at week 12 of gestation Congenital anomalies like arterial septal defect, cleft lip/palate and hydrocephalus in a baby, abnormal renal collecting tubule, hypospadias and hypertelorism, gastroschisis and horseshoe kidney, bilateral hip dysplasia and CHARGE syndrome were noticed in eight exposed babies	Lack of control group. The study was funded by a pharmaceutical company.
Study 3 Antipsychotics during pregnancy: Relation to foetal and maternal metabolic effects	Robert Boden, Maria Lundgren, Lena Brandt, Johan Reutfors, Helle Kieler, (2012)	Population-based comparative cohort study of women exposed and those not exposed to antipsychotics during pregnancy.	Quantitative study	357, 696 Swedish women giving birth from 1st July, 2015 to 31st December 2009, who are under filled prescriptions for antipsychotics.	Women exposed to antipsychotics have twice the risk for gestational diabetes. The risk is even higher with olanzapine and clozapine. Infants exposed to any type of antipsychotics had higher risks of small for gestational age (SGA) on birth weight. Only exposure to other antipsychotics resulted in higher risks of being. SGA for length of birth and head circumference.	The study used large number of participants. Also the researchers use a control group, group as comparison. **Weakness** The use of data from national register instead of directly from the patients and their babies.
Study 3 Antipsychotic drug use in pregnancy: high dimensional, propensity matched, population based cohort study	Simone N Vigod, Tara Gomes, Andrew S Wilton, Valerie H Taylor, Joel G Ray (2015)	Quantitative population based cohort study		1) 1209 Women who delivered between 2003 and 2012, with ≥2 repeated prescriptions for an antipsychotic drugs in first or second trimester. 2) Non-antipsychotic users-women without exposure to antipsychotic medication during pregnancy	**Maternal outcome**: gestational diabetes, gestational hypertension, preeclampsia, eclampsia, and venous thromboembolism, occurring in the period of pregnancy, delivery or period of hospital admission, or within 42 days after delivery. There was 7.7% gestational diabetes in psychotic users as opposed to 6.2% non-antipsychotic users. There was 5.2% as opposed to 3.5% rate of hypertension in antipsychotic users compared to non-antipsychotic users. **Perinatal outcome**- Problems were higher among antipsychotic users than the non-antipsychotic user groups. Premature birth was 14.8% vs 10.3% ; baby weight at birth was >97th centile was 3.7% for antipsychotic users against 2.6% for non- antipsychotic users Higher incidence of placental abruption, labour induction, caesarean section, operative vaginal delivery and frequent hospital readmission among antipsychotic users.	The study used a matched control of non-antipsychotic user pregnant women as comparison. Effects of antipsychotics were assessed on the bases of trimester exposure. Ethical approval was obtained to conduct the study. The researchers used standardised tools and algorithms to minimise bias. **Weaknesses-** use of patients with worse health states, low socio-economic status and on provincially covered drug plan. This makes generalisability of the findings to other antipsychotic users difficult.

Study 4 Prenatal antipsychotic exposure and neuro-motor performance during infancy	KatrinaC. Johnson, Jamie L. LaPrairie, Patricia A. Brennan, Zachary N. Stowe, and D. and Jeffrey Newport (2012)	Prospective case control study	Quantitative method: involving descriptive analyses of sample characteristics such as demographics, obstetrical and psychiatric diagnoses, and medication exposure	309 women and infants were used as study participants	Women with history of in-utero antipsychotic exposure scored lower on a standardized test of neuro-motor performance in 6 month old children as opposed to those exposed to antidepressant or those with no exposer to antipsychotic or psychotropic medication	**Strengths of the study are:** Prospective recruitment of participants with prenatal use of antipsychotic medication. The use of a standardized assessment tools and interview schedule for neuro-motor assessment of infants and maternal psychiatric disorder. The use of comparator groups of women with and those without mental disorder and those with and without prenatal exposure to other classes of antipsychotic agents **Weakness:** Demographic sameness of the participants would limit the generalizability of the findings. Use of small sample size-22 participants. Symptoms of depressive disorder were assessed prenatally.

V. RESULTS

Generally, all the studies reviewed indicated that there are risks for antipsychotics use during pregnancy on both the mothers and their babies.

Risks on mothers:

The studies reviewed have shown that, pregnant women exposed to antipsychotics present with high incidence of gestational diabetes, hypertension during pregnancy and venous thromboembolism compared to pregnant women in control not exposed to antipsychotic medication during their pregnancies. Suggesting that these abnormalities were attributed to the use of antipsychotics during pregnancy.

Risks on the babies:

Study 1 and 4 used interview and standardised tools to collect data. The findings for study 1 reveal that babies exposed to antipsychotics are prematurely born, have respiratory distress (37%), needs special ICU care and have medication withdrawal syndrome. Study 4 reported that only 19% of babies exposed to antipsychotics showed normal neuromotor performance and that, 6 month old babies of women with history of in-utero antipsychotic exposure scored lower on a standardized tests of neuro-motor performance as opposed to babies of mothers exposed to antidepressant or those with no exposer to antipsychotic or psychotropic medication. Study 1 linked infant medication withdrawal syndrome to high dose of antipsychotic exposure at 12 weeks of gestation. However, study 3 on the other -hand proposed that neonatal adaptation syndrome is not only the result of antipsychotic use but other factors such as the use of other medications; maternal smoking alcohol intake and substance abuse play a significant role. Study 3 also found that exposure to antipsychotics during the first trimester is not associated with congenital abnormalities. Conversely, study 2 reported that, antipsychotic exposure may result in abnormal birth weight, though the state of pregnancy at which such abnormality may occur has not been stated.

Studies 2 and 3 pointed problems such as high risk of small gestational age on birth weight, premature birth (14.8% vs 10.3 %;) 3.7% of babies with birth weight > 97^{th} centile were born by antipsychotic users as opposed to 2.6% for non-antipsychotic users. There are also problems of placental abruption, induced labour, caesarean section, operative vaginal delivery and frequent hospital readmission among antipsychotic users.

VI. DISCUSSION

All the articles reviewed showed that there are risks associated antipsychotic drugs on the pregnant on women and their babies. Other published literatures also support these findings. But information is limited about the safety of these drugs on the pregnant mentally ill woman and of course the baby she is carrying. This causes dilemma among clinicians as to whether to discontinue administering antipsychotics to the pregnant mentally ill women for fear of adverse effects on babies, or, continue with the drugs to avoid relapse. What has been found in the reviewed articles shows that, the extent

of adverse effects of antipsychotics on the mother and the baby is sufficient enough for clinicians to strike a balance between the mother's psychiatric illness and the foetal toxicity (Raha et al. 2012) Iqbal et al. (2005) reported that, antipsychotic exposure during pregnancy is associated with toxicities leading to skeletal malformations, defects in central nervous system, cleft palate, cardiac abnormalities, stunted foetal growth and foetal death. Antipsychotic medications used during pregnancy have been reported to cause neonatal withdrawal and abnormal muscles movements (Galbally et al. 2014) However, (Vigod et al. 2015) reported that early exposure to atypical antipsychotics is not associated with congenital abnormalities and the risk of neonatal adaptation syndrome. According to Rahna et al., the effects of antipsychotics may be caused by changes in the maternal metabolism which then, affect the functions of the placenta making drug penetration easier and producing high concentration of toxic substances in the foetus (Raha et al. 2012). Other studies have reported other metabolic effects of antipsychotic medications that causes increased weight gain (Alvarez-Jimenez et al. 2008; Simon and De 2009). However, it was not clear whether the resultant weight gain following antipsychotic use is dose dependent. Atypical antipsychotics are the most widely prescribed for mentally ill women during pregnancy. However, it was difficult to analyze the possible teratogenicity of the drug because of the fact that pregnant mothers were exposed concomitantly to other psychotropic medications.

VII. CONCLUSION

Pregnant mentally ill patients are at risks of poor maternal and perinatal outcomes. Administering antipsychotics to such patients has to be done with caution, bearing in mind the affects of these drugs on both the patient and the child. As antipsychotic medication is recommended to avoid the risk of relapse, regular antenatal and postnatal care must be put in place to monitor the health conditions of the mother and the child so as to monitor problems such as congenital abnormalities, hypertension, premature birth and abnormal foetal development. This will help mentally ill pregnant patients to achieve reasonable mental health during pregnancy and beyond.

VIII. RECOMMENDATIONS

There is need for further research, preferably randomised controlled trials (RCTs) to ascertain the safety of antipsychotics on pregnant patients. It is also recommended those obstetricians, psychiatrists GPs and other clinicians treating mentally ill pregnant patients to prescribe antipsychotics with least side effects to their patients so as to avoid relapse and safeguard the foetus. Maternal antenatal and postnatal visits must be regular to monitor the conditions of the pregnant patient and check for any changes in the development of the foetus and the baby after birth.

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Appendix 1
PRISMA 2009 Flow Diagram