THE EFFECTS OF THE NEW ANTIPSYCHOTIC MEDICATIONS ON MOTHERS AND BABIES

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ABSTRACT

Second generation antipsychotics are widely used by thousands of pregnant women worldwide in order to control their psychiatric disorders. The clinical profiles of these drugs have improved, specifically the decreased risk of hyperprolactinemia, which has increased fertility in female patients. However, the reproductive safety of second generation antipsychotics remains undefined and controversial. The aim of this presentation is to synthesize the available evidence-based information into a systematic review of the safety in pregnancy of this group of drugs (in mono-and polytherapy).

Key Words: *Pregnancy, pregnancy outcome, malformations, second generation antipsychotics, atypical antipsychotics*

INTRODUCTION

From Neolithic times, when trephining (or trepanning) was used to release evil spirits, through to mental asylums, lobotomies and electroconvulsive therapy (ECT), many treatment modalities have been used for managing mental illness. This is the most common morbidity affecting individuals from all walks of life. It is still a puzzling and a devastating physical and emotional affliction on individuals and is a public health burden. Thanks to the development of psychopharmacology, patients with psychiatric disorders can now function productively in society.

The World Health Organization (WHO) has noted that almost 50% of the population will have some psychological disorder in their lifetime.[1] First onset commonly occurs between the ages of 14 and 24,[2] coinciding with childbearing age in women. According to the WHO, the prevalence of mental disorders in pregnancy is higher in developing countries.[1] Studies from the Sweden and the US have reported that 14 to 28% of pregnancies are affected by psychiatric disorders.[3,4] Furthermore, 67% of women with mental disorders give birth.[5]

Antipsychotic Drugs

The first generation of antipsychotic drugs was developed in the 1950s. They have also been called 'typical' antipsychotics and bind to dopamine D2 receptors in the brain. Although effective, they can have serious adverse effects, including extrapyramidal symptoms and hyperprolactinemia. Table 1 provides a list of such agents.

Second generation, (Atypical), antipsychotics first came on the market in the 1990s. They also bind to the dopamine D2 receptor, but have faster dissociation from the receptor than first generation drugs.[6] This transience in receptor binding may explain the lower incidence of hyperprolactinemia and extrapyramidal symptoms with these drugs.[6] There is no evidence regarding differences in efficacy between the two categories,[7] but there has been a shift towards higher use of atypical vs. typical antipsychotics in the US.[8]

TABLE 1 First Generation (Typical) Antipsychotic Agents

Class	Drug (trade name)
Butyrophenone	haloperidol (Haldol, Serenace)
Phenothiazine	levomepromazine, methotrimeprazine (Levinan, Nozinan) perphenazine (Trilafon) prochlorperazine (Compazine, Stemetil) promethazine (Avomine, Phenergan) trifluoperazine (Stelazine)
Diphenylbutylpiperidine	penfluridol (Semap) pimozide (Orap)
Thioxanthenes	chlorprothixene (Cloxan, Taractan, Truxal) flupenthixol (Depixol, Fluanxol) thiothixene (Navane) zuclopenthixol (Acuphase, Clopixol)

TABLE 2 Second Generation (Atypical) Antipsychotic Agents

Drug (trade name)	Drug (trade name)
amilsulpiride (Solian)	olanzapine (Zyprexa)
aripiprazole (Abilify)	paliperidone (Invega)
asenapine (Saphris)	quetiapine (Seroquel)
clozapine (Clozaril)	risperidone (Risperdal)
iloperidone (Fanapt)	ziprasidone (Geodon, Zeldox)
lurasidone (Latuda)	zotepine (Lodopin, Losizopilon)

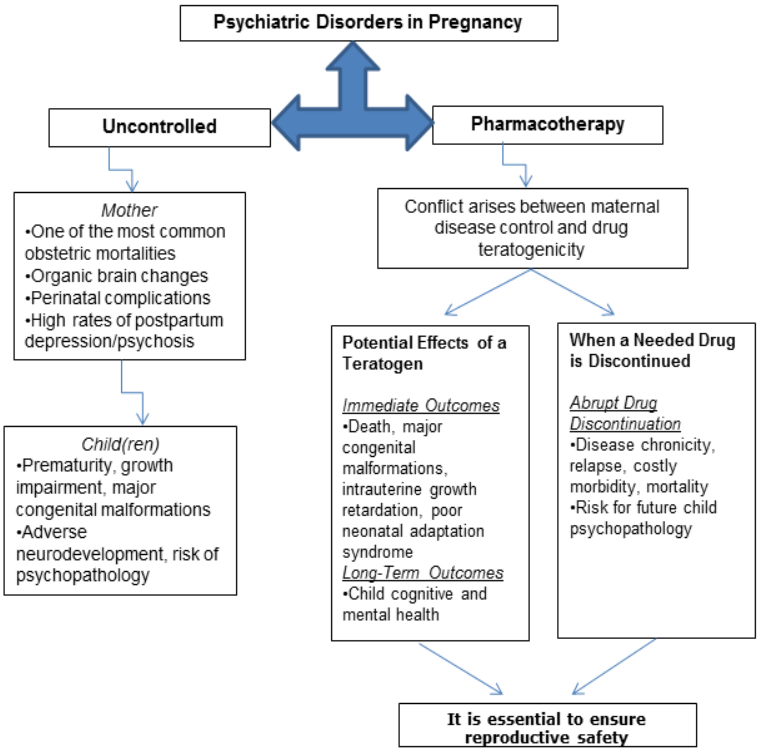
Psychiatric Disorders in Pregnancy

In the current social climate, we have seen the deinstitutionalisation and destigmatisation of mental health resulting in more women of reproductive age being treated for mental disorders, including psychoses. Moreover, the reduced incidence of hyperprolactinemia with second generation antipsychotics, means that these women have increased opportunities to conceive.

Both first and second generation antipsychotics have shown efficacy and effectiveness in schizophrenia, bipolar disorder, depression, and anxiety disorders, and are commonly used in pregnancy. It is estimated that about 80% of women treated for psychotic disorders are on multiple psychotropic drugs, which may represent a concern for reproductive safety.[9-11]

Figure 1 outlines the scenarios for treated and untreated mental disorder with psychosis during pregnancy. Although perinatal and postnatal control of mental disorders is the standard of care, it may create a conflict between optimal maternal treatment and fetal safety (i.e., potential teratogenicity). Psychotropic drugs have been shown to cross the human placenta, and may adversely affect fetal development. Establishing the reproductive safety of this group of drugs is essential and is most effectively done through controlled research.

FIG. 1 Untreated vs. Treated Mental Disorder with Psychosis During Pregnancy



Studying the Effects of Antipsychotic Therapy in Pregnancy - Research Challenges

A number of methodological challenges arise when wishing to conduct research on mental disorders. Although randomized placebo-controlled designs are the gold standard and a preferred approach, it can be ethically challenging. Researchers should choose appropriate comparison groups, control for biases and multiple confounders. Among the confounders are maternal socio-economic status, genetic matrix, the severity of the mental disorder, co-morbidities, and issues arising from pharmacotherapy with psychotropic drugs around pregnancy. These latter include the drug dose, treatment duration and time during pregnancy, whether mono-or polytherapy is used, concomitant use of drugs of abuse, genetic differences in drug disposition/metabolism, and perinatal complications (obstetric and paediatric). Study design plays a significant role in seeking for high validity and powerful statistical significance.

Pregnancy, Delivery, and Neonatal Outcomes with Maternal Exposure to Antipsychotic Drugs

Second Generation Antipsychotic Monotherapy

Information on the effects of antipsychotic treatment spans from the case report to the controlled randomized trial. Research in pregnancy is usually a consolidation and analysis of reports of women's exposure to drugs during pregnancy.[12] We recently prepared a systematic

review and meta-analysis on pregnancy outcomes and risks associated with *in utero* exposure to second generation antipsychotics. (The findings were presented at the 17th World Congress of Basic and Clinical Pharmacology, Cape Town, South Africa.)

For our analysis, studies were included if they reported on women exposed to antipsychotics during their pregnancy or at least the first trimester, if they followed a healthy comparator group, and if they reported data on pregnancy outcomes. The main outcomes analyzed were miscarriages, stillbirths, preterm births, small or large for gestational age neonates, gestational age, birth weight, and major congenital malformations. Forest plots were generated for each outcome and odds ratios with 95% confidence intervals were calculated. Continuous outcomes were evaluated using the standard mean difference.

Twelve high quality cohort studies were included, comprising 1783 case subjects and 1,322,746 controls. The drugs included olanzapine, quetiapine, risperidone, aripiprazole, clozapine, ziprasidone, amisulpiride, and zotepine. There were no reports for asenapine or paliperidone. The data summary is presented in Table 1. Our meta-analysis shows that the prenatal use of second generation antipsychotics may present an increased risk for major malformations and preterm delivery. The results are consistent with previous publications.[13-15]

TABLE 3 Findings of Meta-analysis on Second Generation Antipsychotic Exposure During Pregnancy

Outcome	Number of Studies Analyzed	Data Homogeneity	Odds Ratio (95% Confidence Interval) p-Value	Comments
Major congenital malformations	8	homogenous	OR = 2.03 (95% CI 1.41-2.93) p < 0.001	No specific pattern of malformations was identified Analysis for publication bias: no effect
Preterm births	7	homogeneous	OR = 1.85 (95% CI 1.2-2.86) p = 0.006	Analysis for publication bias: possible effect; adjusted OR=1.67 (95% CI 0.38-7.33)
Miscarriage	6	homogeneous	OR = 1.10 p = 0.6	No significant increased risk
Small for gestational age	3	homogeneous	OR = 1.58 p = 0.1	No significant increased risk
Large for gestational age neonates	3	heterogeneous	OR = 2.68 p = 0.2	No significant increased risk
Stillbirths	2	homogeneous	OR = 0.79 p = 0.7	No significant increased risk
Birth weight		homogeneous		No significant increased risk
Gestational age		heterogeneous		No significant increased risk

Second Generation Antipsychotics - Polytherapy with other Psychotropics

In the past few years no studies have compared monotherapy with polytherapy (involving other psychotropic medications). As a result, we decided to undertake a descriptive cohort study using the Motherisk prospectively collected database.[16] The database provided 133 women exposed to second generation antipsychotics and other psychotropic drugs and 133 matched healthy controls. There were 37 mother-child pairs exposed to monotherapy, 96 (72%) mother-child pairs exposed to polytherapy, and 133 healthy controls. One hundred and one women took their

medications throughout pregnancy, with quetiapine being the most commonly used drug.

We found that exposed mothers had a higher pre-pregnancy weight, had more comorbidities, were exposed to smoking, had more instrumental deliveries, and fewer took prenatal vitamins and fewer breastfed. The differences in all these parameters reached statistical significance. Of their infants, there were more with malformations, more admissions to NICU ($p = 0.002$), and more had poor neonatal adaptation ($p = 0.007$). No differences in maternal weight gain during pregnancy were found between the exposed and control groups nor between the monotherapy and polytherapy groups.

Most of the polytherapy women took a concomitant antidepressant. The polytherapy group of women, compared to the monotherapy group, had shorter gestation times ($p = 0.005$), more preterm deliveries, and more instrumental deliveries. Their infants had more admissions to NICU (28% vs. 16%), more malformations (8.2% vs. 0%), more were large for gestational age neonates (>90% centile) (13% vs. 6%), had comorbidities, and had poor neonatal adaptation (21% vs. 4%); however, none of these differences reached statistical significance. Overall, the listed outcomes may all confound the children's long-term neurodevelopment. The only significant predictor for the outcomes was the group affiliation.

We concluded that the use of second generation antipsychotics in polytherapy was prevalent and associated with adverse pregnancy outcome for both mother and neonate. Exposure to second generation antipsychotic monotherapy represented lower risk to the fetus. Given these findings, future research should focus on defining the reproductive safety of polytherapy. There is a need to separate the effects of medication exposure from the effects of the mother's underlying psychopathology and from its associated comorbidities. We must also keep in mind that antipsychotic medications can change the quality of someone's life. Moreover, there is a need to address exposed children's long-term neurodevelopment and psychopathology.

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