Use of psychotropic drugs during pregnancy: necessity vs Safety

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Abstract:

The safety of psychotropic drugs during pregnancy is a crucial issue in clinical practice. In this review, a brief overview of the changes in pregnancy that impact on the pharmacodynamics of drugs is presented, and the main pharmacological groups in psychiatry and their effects during pregnancy are also analyzed.

Three critical periods during pregnancy are identified. The period of the first two weeks is associated with an increased risk of miscarriage. The period from the second to the tenth week is the most risky, as teratogenic alterations affecting fetal development may occur. The period after the tenth week is characterized by alterations in the growth and functional development of the fetus, but they are usually less severe.

Antidepressants, especially selective serotonin reuptake inhibitors (SSRIs) and second-generation antipsychotics are considered the safest, but latter may be associated with metabolic syndrome, congenital heart disease, and neurodevelopmental disorders. Lithium has been associated with teratogenic effects and cardiac malformations, while valproate is associated with major birth defects. Benzodiazepines may have toxic effects and cause withdrawal syndrome in the newborn.

The safety of psychotropic drugs during pregnancy requires an individualized assessment of benefits and risks. Although some groups of psychotropic drugs are considered relatively safe, caution and consideration of

possible complications associated with their use during pregnancy are necessary.

Key Words: psychotropic drugs, Pregnant Women, antidepressants agents, Antipsychotic Agents, Antimanic Agents.

Resumen

La seguridad de los psicofármacos durante el embarazo es un tema crucial en la práctica clínica. En esta revisión, se hace un breve recorrido sobre los cambios en el embarazo que impactan en la farmacodinamia de los medicamentos, además, se analizan los principales grupos farmacológicos en psiquiatría y sus efectos durante el embarazo.

Se identifican tres períodos críticos durante el embarazo. El período de las primeras dos semanas se asocia con un mayor riesgo de aborto espontáneo. El período de la segunda a la décima semana es el más riesgoso, ya que pueden ocurrir alteraciones teratogénicas que afectan el desarrollo fetal. El período posterior a la décima semana se caracteriza por alteraciones en el crecimiento y desarrollo funcional del feto, pero suelen ser menos graves.

Los antidepresivos, especialmente los inhibidores selectivos de la recepción de serotonina (ISRS) y los antipsicóticos de segunda generación se consideran los más seguros, pero estos últimos pueden estar asociados con síndrome metabólico, cardiopatías congénitas y trastornos del neurodesarrollo. El litio se ha asociado con efectos teratogénicos y malformaciones cardíacas, mientras que el valproato está relacionado con defectos congénitos importantes. Las benzodiacepinas pueden tener efectos tóxicos y causar síndrome de abstinencia en el recién nacido.

La seguridad de los psicofármacos durante el embarazo requiere una evaluación individualizada de los beneficios y riesgos. Aunque algunos grupos de psicofármacos se consideran relativamente seguros, es necesario tener precaución y considerar las posibles complicaciones asociadas con su uso durante el embarazo.

Palabras claves: fármacos psicotrópicos, mujeres embarazadas, agentes antidepresivos, agentes antipsicóticos, agentes antimaníacos.

Introduction

Psychotropic drugs are drugs that have their target of action in the central nervous system, can cross the placenta and the blood-brain barrier of the fetus, altering perinatal brain functions, impacting long-term neurological development, causing cardiac malformations and other conditions such as neonatal abstinence (3).

For women, the peak incidence of various psychiatric disorders, such as schizophrenia, occurs during their childbearing years. Among the most common disorders in this period are major depressive disorder and bipolar affective disorder. Prenatal unipolar depression is one of the most frequent conditions, whose symptoms do not differ much from those observed in the nonpregnant population. Its prevalence has been shown to be associated with an increased risk of multiple poor obstetric outcomes, such as miscarriage, obstetric bleeding, cesarean section, and preterm delivery (1).

Inadequately treated maternal psychiatric disorders tend to result in unhealthy behaviors during pregnancy, poor prenatal care, poor infant bonding, and stressful family environments (4). Early detection of these disorders and their appropriate management have an impact on prognosis and prevention of complications (2).

Several maternal, fetal, pharmacological and social factors have been described that influence the outcome of psychotropic drug use, affecting the choice of therapeutic approach with the aim of minimizing the impact on the mother, fetus, newborn and developing child. The potential risk of not treating psychiatric illnesses during pregnancy has increased awareness of the importance of their treatment (4).

Pharmacokinetics during pregnancy

During the gestational stage, several important adaptive physiological changes occur that interfere in the absorption, distribution, metabolism and elimination of the medication, affecting its effectiveness and safety (increase in plasma volume, decrease in pre-pregnancy due to some type of protein binding, increase in glomerular filtration rate, etc.) (5). The most important changes are shown in Table 1:

Table 1. **C**hanges in pharmacodynamics during pregnancy

Absorption	There is a slowing of gastric emptying, decreased gastrointestinal motility and increased intestinal blood flow, a slight delay in absorption is evidenced
Distribution	There is an increase in total body water, as well as a decrease in plasma albumin, which generates a decrease in protein binding favoring an increase in the active form of the drug and its distribution.
Metabolism	There is an increase in the activity of mitochondrial enzymes and a decrease in oxidase system activity, which leads to a modification of the necessary requirements
Elimination	There is an increase in glomerular filtration that increases renal clearance, increasing drug elimination.

The effect of a drug on the fetus and the mother depends on the time of administration. Three periods have been described, the first one of implantation, followed by organogenesis and finally development, each stage presents its particular risks for the fetus (see table 2)

Table 2. Effects of the drug in relation to the time of administration during pregnancy

Implantation period	**Organogenesis period**	**Developmental period**
Initial 2 weeks period	Period from the 2nd to the 10th week.	Period after the 10th week
During this period, there may be a risk of miscarriage, although there is also the possibility that there are no alterations in the embryo	This is the period of greatest risk, since teratogenic alterations may occur. In many cases, the effects are incompatible with life, in others they can drastically affect fetal development.	During this stage, alterations in the growth and functional development of the fetus may occur, but they are usually of lesser severity compared to the previous period

The best-known risk classification is that of the FDA, which originated after the damage caused by the use of thalidomide in pregnant women:

Category:

1. Controlled studies have shown no risk. Low risk of fetal harm.
2. No risks in humans have been described, there are studies in animals where no risks have been reported, its use during pregnancy is accepted.
3, Fetal risk cannot be ruled out. There are animal studies that show adverse effects, but there are no studies in pregnant women. Benefit/ risk should be evaluated.
4. There are indications of fetal risk. There are studies in pregnant women showing risk of adverse effects, so it should only be used in cases where there are no alternatives.
5. Contraindicated in pregnancy, there are studies in pregnant women and in animals which have shown that the potential risks clearly outweigh the possible benefits

Methodology

A search was performed in PubMed using MESH as "psychotropic drugs", "pregnant", "antidepressants agents", "Antipsychotic Agents", "lithium", "valprote", "lamotrigine", several combinations were used with the MESH "pregnant", using "AND" as connector. For this review we mainly used clinical trials published in the last 10 years, written in both Spanish and English.

Psychotropic drugs used in pregnancy

1. Antidepressants

There are several studies that have studied the concentrations of the different antidepressants in the placenta and in the fetus; when analyzing venlafaxine and citalopram, these have shown more penetration in the amniotic fluid, while the lowest were for fluvoxamine and fluoxetine, regarding the umbilical cord plasma, nortriptyline had the highest concentrations followed by bupropion; in breast milk, venlafaxine and escitalopram had higher concentrations (6).

1.1 Tricyclic antidepressants

This group of antidepressants was the first to be developed and their use began in 1950. Although in the beginning they were widely used, they are now reserved only for specific cases (7). These drugs are considered as a last resort due to their low tolerance and the risk of being lethal in case of overdose. However, their use has not been associated with risk of teratogenicity. In a study published in 2017 that included a pregnant population of

18,487 women and compared different types of antidepressants (selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs) and other antidepressants), first-trimester amitriptyline use was found to be associated with an increase in ocular malformations, hearing, facial and neck defects (OR 2. 45, 95% CI 1.05-5.72), as well as digestive defects. However, these associations were not greater than those observed in the population that did not use this drug (7).

Although most TCAs have not been associated with teratogenesis, drugs such as clomipramine have been associated with increased risk of cardiac defects (8). A relationship between tricyclic antidepressants (TCAs) and preterm delivery has not been established. However, an association between TCAs and preeclampsia has been observed in a study conducted in British Columbia, which showed that 10% of the population of more than 100 women who received TCAs developed preeclampsia, compared with 2% who did not (9).

In addition, an association has been found between exposure to TCAs near the time of delivery and postpartum hemorrhage, with a 1.4- to 1.9-fold increase in the risk of postpartum hemorrhage (10). TCA use has also been associated with the occurrence of neonatal withdrawal symptoms, such as hypoglycemia, respiratory disturbances, central nervous system symptoms, and jaundice (8). Adverse effects in pregnant women include constipation, low blood pressure, weight gain, excessive sedation and tachycardia.

1.2 Serotonin Reuptake Inhibitors (SSRIs)

Selective serotonin reuptake inhibitors (SSRIs) are the most widely used drugs in mood disorders. Currently, they are the first line group in the treatment of depressive disorder due to their safety and better tolerance. They are also used in the treatment of panic disorder, obsessive-compulsive disorders, social anxiety and bulimia nervosa (12).

Fluoxetine and citalopram are recognized to have the ability to cross the placenta. The increase in serotonin that occurs with the use of these drugs may affect various tissues, including the placenta, which is suspected to affect vasoconstriction and clotting and cause hematomas. It is suspected that exposure to these drugs during the period of organogenesis may be related to alterations in central nervous system development and craniofacial development (12).

However, studies conducted on this group of drugs have not shown significant association with an increased risk of teratogenicity. A 2016 study in Wales, Norway, and Denmark found no significant additional absolute risk of teratogenicity associated with SSRIs (11). The risk overlaps with the overall population risk (2-4%).

Multiple studies have been found that have reported that SSRIs are associated with increased risk of cardiovascular defects; paroxetine use has been found to increase the risk of heart disease up to twofold, especially right ventricular outflow tract defects 1% of those exposed vs. 0.5% of those not exposed. Other studies have reported up to a 4-fold increased risk of anal atresia with antidepressant use (0.06 % in the general population vs. 0.2 % in those exposed to sertraline) (13).

Newborns exposed to sertraline during the first trimester of pregnancy had a relative risk of anal atresia 4 times higher than newborns exposed to other antidepressants. However, anal atresia is a very rare congenital malformation (5 out of 10,000 neonates, 0.06%), whereas the risk for an infant exposed to sertraline is 0.2% (14).

No association has been found between SSRIs and miscarriage; it has been shown that mood disorders can increase the risk of miscarriage, as well as certain lifestyles such as smoking or drinking; a study conducted in Quebec showed that the incidence of miscarriage was comparable with the control group (13 vs 14%) (15). SSRIs have not been associated with increased risk of withdrawal syndrome, preterm labor, gestational diabetes, postpartum respiratory depression or low birth weight, as well as neonatal mortality (12).

An association has been found between SSRIs and an increased risk of hypertensive disorder in pregnancy. A meta-analysis involving more than one million pregnant women found this association, although confounding factors such as maternal age, diabetes mellitus, and smoking were identified that could influence the results (16). Regarding gestational diabetes mellitus, it has been suggested that the association with SSRIs may have been overestimated, although the available evidence is insufficient to confirm this (19).

The possibility of an association between SSRI use in the third trimester and an increased risk of postpartum hemorrhage has been studied. However, it has been noted that these results may be influenced by the indications for use of SSRIs. It has been shown to be safe to discontinue their use 30 days before delivery to minimize this risk (17).

Regarding possible changes in fetal behavior, SSRI use has been associated with increased activity and exploration behavior. However, no significant differences were found in anxiety, social behavior, learning and memory, ingestive and reward behavior, motor behavior, reflexes, or pain sensitivity (20).

No SSRI is safer than another for use during pregnancy, except paroxetine, which has been associated with congenital cardiovascular malformations. However, this association is controversial, as there are studies that have found no such risk. Currently, although numerous studies have been conducted with SSRIs, there is insufficient evidence to definitively assess the risks. In addition, newer SSRIs such as escitalopram, as well as less commonly used SSRIs such as fluvoxamine, have been less well studied in this context (20, 21).

Guidelines such as the British Association of Psychopharmacology consensus recommend SSRIs as first-line pharmacological treatment for pregestational, prenatal and postnatal depression because of their reproductive safety. Therefore, it is considered a good choice as an antidepressant in patients who have not previously used medication for depression (20, 21).

In patients who are receiving treatment prior to pregnancy, it should not be discontinued abruptly upon discovery of gestation because of the risk of recurrence and withdrawal. The benefit/risk ratio should always be evaluated to make informed decisions. According to a meta-analysis published in 2020, no increased risk of depression relapse during pregnancy was observed in women who discontinued antidepressants compared with those who continued to take them (relative risk [RR] = 1.74; 95 % CI, 0.97 to 3.10; P = 0.06). However, in the sub-analysis, a significantly increased risk of relapse was found in cases of major or recurrent depression (RR = 2.30; 95% CI, 1.58 to 3.35) (21).

There is no consensus on the reduction/discontinuation or maintenance of antidepressants in the period near pregnancy, as it may pose risk of neonatal maladaptation (18).

1.3 Dual antidepressants (SNRIs):

There are few published studies on duloxetine and venlafaxine compared to SSRIs. In studies conducted with duloxetine, no causal association between major malformations has been found.

In a cohort study published in 2020 that included between 2500 and 3000 pregnant women exposed to duloxetine in early pregnancy and bet-

ween 900 and 950 exposed at the end of pregnancy, insufficient evidence was found to consider duloxetine as a teratogen (the percentage of malformations was similar to that of the general population, around 2-3%). However, a small increase in the risk of cardiac malformations was detected. In addition, it has been associated with an increased risk of postpartum hemorrhage, so its use should be individualized, weighing the potential risks against the risk of depression and painful syndrome in pregnant women (22).

Neither duloxetine nor venlafaxine has been associated with spontaneous abortion. A prospective observational comparative cohort study published in 2019, which collected data from the United Kingdom Teratology Information Service (UKTIS) between 1995 and 2018 and included 281 pregnancies, concluded that there was no statistically significant difference in the risk of miscarriage after gestational use of venlafaxine compared with any other antidepressant without exposure (23).

Duloxetine and venlafaxine may be associated with an increased risk of hypertensive disorders of pregnancy, but studies have had a limited sample size to be conclusive (24). Studies on SNRIs have not been able to draw firm conclusions regarding effects on the newborn, such as sedation and impaired sucking (25).

To conclude, the accumulated data are not conclusive, although they have shown safety in the studies performed. It is always important to individualize treatment in pregnant women.

1.4 Atypical antidepressants

Bupropion: its use has been considered safe during pregnancy, making it a good option for the management of smoking, which has been strongly associated with unfavorable outcomes during pregnancy (26). The risk of teratogenicity is considered low, and it does not seem to have been associated with hypertensive disorders of pregnancy, postpartum hemorrhage or complications in the newborn, such as low birth weight. However, a low association with spontaneous abortions has been found (27).

Mirtazapine: Studies are very limited, but there seems to be no association with teratogenic effects. There is no clarity regarding the relationship with spontaneous abortion and preterm delivery. In addition, it has not been associated with hypertensive disorders of pregnancy or postnatal hemorrhage (28).

2. Antipsychotics

2.1 Typical or first-generation antipsychotics

The mechanism of action of this group of drugs consists of blocking dopaminergic D2 receptors. However, due to their multiple adverse effects, several drugs have been synthesized with the aim of achieving more selective actions and better tolerated by patients (29, 30, 31).

For decades, their safety during pregnancy has been questioned, mainly due to neurodevelopmental disorders, although it could also be due to other factors such as genetic or environmental predisposition, and even to the concomitant use of other drugs (32).

In the last three decades, the use of these agents has increased in the pregnant population due to the need to treat a vulnerable population. However, data on their safety and best drugs remain very limited. Current practice suggests considering potential risks and complications when initiating, discontinuing, or adjusting doses of antipsychotics.

According to the consensus made in 2021 by the associations of pediatrics, obstetrics and psychiatry (Federatie Medisch Specialisten), the first-generation antipsychotic with the most evidence is haloperidol. Despite the risk of gestational diabetes and teratogenicity, it has been shown to control psychotic disorders and bipolar affective disorder. In terms of neurodevelopment, there is no evidence to suggest an increase in the incidence of ADHD and autism spectrum disorder (33).

2.2. Atypical or second-generation antipsychotics

During the last few years, second generation antipsychotics have been shown to be a main alternative and have even been presented as the first line of treatment due to their lower risk of adverse effects compared to first generation antipsychotics, as well as their broader spectrum of treatment of affective disorders (31).

These drugs are lipophilic and cross the maternal-placental barrier easily, making them potentially teratogenic or with the capacity to cause serious neurodevelopmental consequences (32), although data in this regard are limited. Autism spectrum disorders and attention deficit hyperactivity disorder (ADHD) are the most commonly associated with their use. However, animal models are often heterogeneous, as receptors in the brain and findings during different gestational stages are often not the same.

Nevertheless, in a cohort study by Wang, it is concluded that there is no direct relationship between the use of second-generation antipsychotics and neurodevelopmental disorders, although the risk may be up to 2-fold higher compared to the general population (32).

An additional disadvantage is related to metabolic syndrome, so it is natural to associate this pharmacological group with a higher incidence of gestational diabetes, a pathology that carries serious consequences for both mother and fetus. A notable change is related to body mass index (BMI), on which quetiapine, clozapine and olanzapine have a significant effect. It is important to keep in mind that psychotic disorders are a risk factor for overweight and obesity (31).

One outcome that could be associated with the use of atypical antipsychotics during pregnancy is congenital heart disease, gastrointestinal tract defects, and cleft palate. Although there could be a higher risk (34), the populations studied usually present important comorbidities such as obesity and the use of licit and illicit substances, in addition to the concomitant use of other psychotropic drugs (35), so it cannot be considered conclusive (36).

Despite the possible risks, the prescription of these drugs has increased mainly in the pregestational period and in the first trimester, but there are still limitations in later trimesters. However, clinical judgment remains critical in balancing the benefits and risks in each individual case. While antipsychotics may be safe during pregnancy, the various studies suggest that they should be administered at the lowest possible dose to reduce the risk of significant sequelae for both mother and fetus.

3. Mood stabilizers

3.1 Lithium: Lithium appears to be fully equilibrated across the placenta as a 1:1 ratio has been found between levels in cord blood and maternal blood. However, lithium levels may decrease as pregnancy progresses, so dose adjustment is necessary (37).

Lithium has been associated with teratogenic effects, especially with cardiac malformations such as Ebstein's anomaly, right ventricular outflow tract obstruction defects, coarctation of the aorta, and mitral atresia. Dose has been found to be related to risk, being higher with doses above 900 mg per day compared to doses below 600 mg (38).

In an international collaborative meta-analysis of six cohort studies involving 22,124 pregnancies, of which 727 were exposed to lithium, no association was found between lithium exposure and predefined pregnancy

complications. However, an increased risk of neonatal readmission after the first 28 days of life was observed in those whose mothers' received lithium during pregnancy (combined prevalence of 27.5% vs. 14.3%). A greater association with major malformations (pooled prevalence of 7.4% vs. 4.3%) was also observed in this study (39).

In another later study, an association was found between lithium and spontaneous preterm delivery, as well as with higher weight for gestational age, neonatal hypoglycemia, and cardiovascular malformations (40). Therefore, the use of lithium should be individualized, weighing the risks of bipolar affective disorder against the risk of lithium use.

3.2 Valproate: Valproic acid can cross the placenta and has been associated with more than 8 major congenital malformations, including neural tube defects, spina bifida, congenital cataracts, craniofacial defects (such as oral clefts and craniosynostosis), cardiovascular malformations, hypospadias, and limb malformations (such as clubfoot and polydactyly) (41).

In addition, among other effects not related to major malformations, decreased IQ and developmental disorders such as autism spectrum disorder and attention deficit/hyperactivity disorder, as well as hearing loss or impairment after in utero exposure have been found (42). The use of this drug is not recommended in pregnant women with epilepsy, for the prevention of migraine headaches and in bipolar affective disorder.

3.4 Lamotrigine: This drug is able to cross the human placenta, and its levels can be measured in the blood of live newborns. It has not been associated with an increased incidence of major congenital malformations, making it an excellent choice in patients with bipolar affective disorder (43).

4. Benzodiazepines

There is still no consensus regarding the existence of congenital malformations, however, it seems to indicate that there is no causal association, studies suggest that there is a relationship with spontaneous abortion and premature delivery (44). Additionally, it has been shown that chronic use of benzodiazepines can cause neonatal toxicity and withdrawal causing low Apgar, apnea, hypothermia, hyperreflexia, hypertonia or hypotonia, lethargy, tremor, vomiting and motor restlessness (45).

Conclusion

The management of mental illness in the pregnant woman presents important challenges for the physician, since the safety of psychotropic drugs during pregnancy requires an individualized assessment of the benefits and risks, and the risks of decompensation of mental pathology must be weighed against the risks of the medication in all cases, offering the safest management. Although some groups of psychotropic drugs are considered relatively safe, caution should be exercised, and possible complications associated with their use during pregnancy should be considered.

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