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REVIEW

Use of antipsychotics during pregnancy and breastfeeding

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Abstract
There is growing acceptance that pregnancy itself is not a protective factor against mental disorders. Indeed, some mental disorders such as psychotic and bipolar disorders may become worse during pregnancy and the immediate postpartum period. In pregnant women with a mental disorder that can be treated with antipsychotics, the known risks—teratogenic, obstetric, neonatal and those affecting the mother—indicate that, in general, the risk of the non-treated disorder is higher than that resulting from the use of antipsychotics and that the reduction in psychoticism improves the overall prognosis of these women. All the antipsychotics marketed in Spain are included in category C of the US Food and Drug Administration, with the exception of clozapine and piperazine, which are included in category B. The use of all of these drugs should be avoided during breast feeding as far as possible. The most reliable current recommendations indicate that optimal control of severe mental disorders should be maintained during pregnancy, the postpartum and subsequent periods. These recommendations also indicate that women with mental disorders must be considered as high risk and that both these women and their pregnancies should be constantly monitored. The currently available scientifi c information does not allow more than relatively secure individually-tailored recommendations to be made. When taking the decision of whether or not to treat with antipsychotics, the use of a risk-benefi t relationship is crucial, with the participation of the woman's partner or legal representative, other physicians and even the clinical pharmacist if necessary.

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Uso de antipsicóticos durante el embarazo y la lactancia

Resumen
Cada vez se acepta más que el embarazo por sí mismo no es un factor protector frente a los trastornos mentales. De hecho, tanto los trastornos psicóticos como los bipolares y otros pueden empeorar durante la gestación y el posparto inmediato. Los riesgos conocidos teratogénicos, obstétricos, neonatales y para la madre si ésta sufre un trastorno mental que pueda tratarse con antipsicóticos permiten afirmar que, en general, el riesgo del trastorno no tratado es mayor que el derivado del uso de antipsicóticos y que la reducción del psicoticismo mejora el pronóstico general de las gestantes. Todos los antipsicóticos comercializados en España están incluidos en la categoría C de la US Food and Drug Administration, menos la clozapina y la piperazina que lo están en la B. Es aconsejable evitar en lo posible el consumo de todos durante la lactancia. Las recomendaciones actuales más solventes indican que ha de mantenerse el control óptimo de los trastornos mentales graves durante el embarazo, el periodo del posparto y el ulterior, que debe considerarse en alto riesgo a las mujeres en esas condiciones y que tanto ellas como sus embarazos hay que monitorizarlos de forma continua. Con toda la información científica disponible en la actualidad no se puede hacer más que recomendaciones de seguridad relativa individualizadas por paciente. En la decisión médica de tratar o no con antipsicóticos es crucial ponderar juiciosamente la relación riesgo/beneficio, con la participación de la pareja o representante legal, de otros médicos y, en su caso, del farmacéutico clínico.

Introduction

The atypical antipsychotics (second generation) marketed in Spain are: amisulpride, aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone, sertindole and ziprasidone, and the typical, classical or neuroleptics are butyrophenones, phenothiazine and thioxanthen. Although antipsychotics are mainly indicated to treat schizophrenia, other psychosis and bipolar disorders, in everyday clinical practice their use is extended for other diverse clinical conditions.

It is well known that any drug received during pregnancy may have lethal, toxic or teratogenic effects on either embryo or foetus, directly by constriction of placental vessels o by acute uterine hypertonia causing anoxic lesion and, indirectly, by changes brought about in maternal biochemical dynamics. Physiological changes inherent in pregnancy and breastfeeding condition absorption, transference, excretion, and metabolism of psychotropic drugs, including antipsychotics. All these drugs go through the so-called placental barrier, usually by simple diffusion; this barrier turns out to be less efficacious than the haematoencephalic barrier to hinder substance distribution. It has been confirmed over a sample of 54 women that antipsychotics go through the placenta in an incomplete manner, and in the same study the proportion that went across was larger for olanzapine, followed by haloperidol, risperidone and quetiapine.[1]

However, the newborn has slow intestinal transit, immature enzymatic systems, and low renal clearance, so that antipsychotics taken by its mother may cause in the newborn baby higher effects than those expected. If, in addition, the baby is premature, feeds only on its mother's milk or presents with any other particular situation, the possibility of adverse reactions increases even more.

But it is a fact that some pregnant or breastfeeding women suffer all sorts of mental disorders, including those that are normally treated with antipsychotics, apart from the large number of them who use antipsychotics as antiemetics.[2] Research into the use of psychotropic drugs during pregnancy and breastfeeding is however almost impossible due to the current legislation in force in Spain. This explains the low quality of scientific information available on antipsychotics, based mainly on cohort retrospective studies, of inadvertent exposure or of diverse records (evidence levels 2b-5)[3] and their results demand extreme caution in order to be able to generalise them.

The objective of the present study is to summarise the information about the risk of treating or not with antipsychotics, the safety of using them for the foetus and the infant, the ethical and legal considerations, and the recommendations for their prescription. Due to the wide-ranging aspects under consideration and the methodological limitations of the studies available, it is not our objective to make a bibliographic revision as is usually the case, including a grouped exposition of the bibliographic findings and their detailed discussion, but to provide a comprehensive updated perspective of an issue that is as complex as interdisciplinary.

Risks of treatment or lack of it

It is gradually being accepted that pregnancy in itself is not a protecting factor against psychiatric disorders in general. In addition to this, psychotic, bipolar disorders and others may become worse during pregnancy. The same is the case with initial postpartum, during which the risk of exacerbation of bipolar disorders[4,5] is high and psychosis prevalence is estimated at 1-2/1,000 cases. A recurrence risk of 70.8% was found in a cohort of pregnant women with bipolar disorders, 27% of whom were undergoing psychotropic treatment with antipsychotics and of this sub-group, 21% discontinued treatment.[6] Over 40% of re-hospitalisations were also found during postpartum of women who had already been hospitalised for psychotic or bipolar episodes during their pregnancy.[7]

Annual incidence of psychosis during pregnancy is of 7.1/100,000 cases.[8,9] However, diverse adverse effects during gestation, such as infections or diabetes, increase the risk of psychosis-like symptoms.[10] For schizophrenia and other psychosis it is considered that, in general, risk due to not treating a given disorder is higher than that derived from using psychotropic drugs, so that reduction of psychotic symptoms improves general prognosis in pregnant women. Schizophrenic patients who remain longer under treatment pose a lower risk of relapse and psychiatric hospitalisations,[11-14] a fact that by analogy is applicable to pregnant women.

Recently, the American College of Obstetricians and Gynecologists[15] has systematised teratogenic, obstetric and neonatal risks due to suffering schizophrenia or bipolar disorder not treated or poorly treated during pregnancy. In cases of bipolar disorder or depressive episode the incidence of underweight in newborn babies, reduced foetal growth, and other postnatal complications increases, as well as the incidence of high plasma concentrations of cortisol and catecholamine in the neonate, infantile crying, and higher rates of admission into neonate intensive care units. In the case of schizophrenic women the results are: higher incidence of congenital malformations in newborn babies (especially in the cardiovascular system), increase of premature births, underweight newborns, foetus with smaller size for their gestational age, placental abnormalities, haemorrhages before delivery, as well as an increase of postnatal deaths.

Indeed, maternal psychotic decompensation during pregnancy may indirectly impact on growth or foetal development because the mother is more likely to experience a deterioration in her habits and conduct, ill alimentary patterns, higher risk of exposure to alcohol or other drugs and a deficient obstetric follow-up, apart from increasing the risk of stillbirth.[6,16-18] In practice, a severe disease associated with pregnancy, as any psychotic episode, bipolar disorder, or drug dependence are, automatically qualified as obstetric risk as high or of level 3.[19] Finally, psychotic decompensation before or after delivery may also cause harmful effects on the baby.

Pregnant women addicted to drugs who require antipsychotic treatment need special attention. They represent a high risk group due to the host of medical and general complications they have. In a recent study, the meconium of newborn babies of 1,209 mothers of low socio-economic level at the Hospital del Mar was analysed, in Barcelona. They tested positive for drug abuse in 10.9% of the total, with specific prevalence of foetal exposure of 4.7% to heroine, 2.6% to cocaine, and 5.3% to cannabinoids.[20] In addition to this, according to the programme of pregnancy control and follow-up of the Public Health General Directorate of the Valencian Community, the psycho-social risk is 9.5% of the total risk of main health hazards recorded during pregnancy in year 2007, and drug addicted pregnant women are part of this group.

It is therefore reasonable that specific assistance services are proposed to provide adequate integral health care for (potential) pregnant women with serious mental disorders. Such provisions would contribute to clinical stability and should specifically include counsel on genetics, pre-natal attention, obstetric complication prevention, reduction on consumption of substances susceptible to abuse, optimisation of antipsychotic treatment, and others.[21,22]

Safe antipsychotic use for foetus and infant

There is partial knowledge about antipsychotics and with significant limitations in relation of some of them to teratogenicity and premature foetal death, perinatal syndrome (some data have been published about perinatal toxicity associated with antipsychotic consumption during the last quarter of pregnancy) and postnatal consequences in development.[23,24] In 2008 Reis et al.[25] published rates of congenital malformation in women who had antipsychotics during their early pregnancy, mainly phenothiazine, compared against the total birth rate in Switzerland, according to the medical registry, the congenital malformation registry, and the hospital discharge registry in that country. Although the authors did not rule out possibly confusing factors in their results, they found a significantly higher association of malformations, mainly cardiovascular or ventricular septal defects.

It has been indicated that atypical antipsychotics could be relatively safe. But in another retrospective study and that therefore does not allow measuring incidence, out of 16 births at Mayo Clinic in the United States from mothers exposed to atypical antipsychotics, one presented with acute malformation.[26] More significant was a follow-up study of 141 pregnant women treated with olanzapine (n = 60), risperidone (n = 49), quetiapine (n = 36) and clozapine (n = 6), whose results supported the argument that atypical antipsychotics appear to have no relation to increased risk of major foetal malformation.[27] These results, however, contradict some former studies of the same group,[28] where it was informed that there could be higher risk of malformations in the neural tube in offspring to schizophrenic mothers treated with atypical antipsychotics due to defective ingestions of folates and obesity frequently present in these patients.

In any case, a few teratogeny tests do not guarantee innocuousness: it seems that most atypical antipsychotics

increase risk of metabolic complications during pregnancy, and also of large newborn infants for their gestational age and with a mean weight significantly higher at birth compared against those born to mothers on classical antipsychotics.[29,30] In addition, almost double risk of gestational diabetes has been informed and up to 40% higher risk of Caesarean sections among pregnant mothers who had antipsychotics, mostly phenothiazine, in their early pregnancy.[25] It is, therefore, reasonable to state that continuing use of antipsychotics during pregnancy and breastfeeding, without consistent proof of concomitant risk of harm for mother and her offspring, sets forth serious clinical questions,[31] apart from ethical issues.

In several countries the regulatory agencies have published pharmaceutical codes that raise conjectures about degree of pregnancy risk of a given drug. It is the case of US Food and Drug Administration (FDA), Australian Drug Evaluation Committee (ADEC), the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) in Germany, and the Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) of the Spanish Ministry of Health and Consumer Affairs, to quote but a few. The European Medicines Agency (EMEA) recommends minimising the risk through an effective contraceptive practice, a recommendation that should always be included in the prospect (the principal official document of pharmaceutical specialty destined to patients) of pertinent drugs.[32] The FDA has not approved the use of any psychotropic drug during pregnancy.[33]

Considerations of ethical and legal nature

Incidence of unplanned or unwanted pregnancies is higher in some risk women groups, such as precisely those suffering serious personality disorders, psychosis or maniac episodes (in particular schizophrenia), or certain drug addictions, which raised ethical and legal questions about their true capacity and autonomy.[34] When prescribing antipsychotics during pregnancy it is critical to provide adequate information to women, respecting their competence to understand, reflect and make rational decisions. However, the highest respect for the patient's values and beliefs does not exempt the medical specialist, and more specially the specialists in psychiatry, from the responsibility of assessing the patient's capacity to decide by herself.

In the particular case of drug dependent pregnant women, these patients are not ignorant of the fact that drug consumption during pregnancy could constitute a crime involving prenatal lesions[35] and it is the duty of the physician to present that patient with therapeutic alternatives to drug abuse that are viable during pregnancy, and that might require the use of antipsychotics when other psychiatric co-morbidity were present.

If the prescription of certain antipsychotic for a pregnant woman suffering a mental disorder adjusts to the indications authorised by the corresponding technical specification (the official document of pharmaceutical specialty destined to health professionals), it will not then be necessary to ask for its "compassionate use". But it is usually recommended to ask for authorisation when prescribing off-label drug use, particularly in this group considered a risk group. The situations when compassionate use for a drug in Spain may be requested are specified in the article 23 of the Spanish Royal Decree 561/1993 of 16 April, and in the European Union, in the document corresponding to the European Medicines Agency.[36] In practice, however, prescribing antipsychotics to pregnant women may be interpreted in a more or less restrictive manner. The technical specifications of many of these drugs include references to pregnancy and breastfeeding amongst the special warnings and cautions of use in the pharmaceutical specialty, with statements such as the following: "only to be used when benefits justify potential risks".

In any case, it is convenient to obtain the informed consent from the pregnant woman or her legal tutor for the use of antipsychotics, and some authors consider this to be necessary for prescribing any psychotropic drug in such a situation.[37] To this respect, the law 41/2002 of 14 November is of forceful compliance in Spain, which regulates the patient's autonomy and his/her rights and obligations in questions of information and clinical documentation, apart from the legislation of each autonomous community such as, for example, the law 1/2003 of 28 January, of the Valencian Government (*Generalitat*), of rights and information to the patient in the Valencian Community.

No clinical trials can be carried out with medication in pregnant women or women in their breastfeeding period, except those trials that have no therapeutic aim and as long as the corresponding ethical committee of clinical research concluded that they do not pose any potential risk for the woman's health, or the foetus or the infant, and that useful and relevant knowledge on pregnancy and breastfeeding would be obtained. Clinical trials with medication for human use are regulated throughout Spain by Title III of the Law 29/2006 of 26 July, on safeguards and rational use of drugs and sanitary products, according to which the rights, safety, and wellbeing of subjects in the trial shall prevail over the interests of science and society.

Prescription recommendations

With all the scientific information available nowadays on antipsychotic treatment in pregnant women the course to follow is to recommend relative safety individualising for each patient, weighing in each case the risk/benefit ratio,[15,23,38-40] including maternal risk and foetal risk in absence of treatment, discontinuation, or suboptimal treatment. Given that efficacy, effectiveness and safety have been shown by the use of antipsychotics, particularly atypical antipsychotics, the point should be centred on pregnant women and their physicians selecting jointly the most appropriate treatment depending on the acute staging of the symptoms, response to prior treatments, and physical condition of the patient. Current recommendations to be taken into account state that optimal control of mental disorders during pregnancy should be kept, as well as during postpartum and afterward. Women suffering acute mental disorders should be considered of high risk and continual surveillance should be carried out on themselves and their pregnancies.[41]

The Spanish consensus over physical health of patients with bipolar disease[42] recommends simplifying treatment to the most and adjusting dosing by maternal haemodilution during the second and the third quarters of pregnancy. The Regional Ministry of Health of the Valencian Community[19] underlines that at the moment of prescribing a drug for a pregnant patient the following must taken into account: none should be administered during the first quarter unless it is absolutely essential; educate women to avoid self-medication, which is the cause of 30% of drug misuse; consider the risk/benefit ratio and prescribe minimal effective dosing; no drug should be considered totally safe for the foetus; avoid drugs recently launched into the market, and use those with which the physician has had more experience in pregnancies. Regarding breastfeeding, and abiding by the list of essential drugs of the WHO,[43] psychotropic and anticonvulsant drugs are permitted as long as side effects are being watched, particularly the infant's sleepiness. More recently, this Regional Ministry, based on the experience gained by the centre of drug information at the pharmacy service of La Fe University Hospital in Valencia, published some reports on teratogeny assessment according to the pharmaceutical risk categories of the FDA (United States FDA Pharmaceutical Pregnancy Categories).[44] In table 1 currently used antipsychotics marketed both in the USA and in Spain are related to the teratogeny risk classification of the FDA and their risk during breastfeeding. Based on the information available at the moment, it is not recommended to prescribe any atypical antipsychotic during breastfeeding.[45]

There are in Spain some guidelines on the clinical use of antipsychotics during pregnancy and breastfeeding. The recommendations from GEOPTE (Spanish Group for the Optimisation and Treatment of Schizophrenia) 2005[46] and the Consensus Committee of Catalonia for the treatment of mental disorders[47] may provide certain orientation to the physician when making decisions, above all with classical antipsychotics. The Consensus Committee of Catalonia is of the opinion that if the pregnancy was not planned in search for better clinical conditions for the mother, it is safer not to discontinue prior antipsychotic treatment but to keep it during all pregnancy. Exceptionally, when psychotic onset occurred during pregnancy it is proposed to choose an antipsychotic according to the other recommendations exposed and the age of the patient.[47] For relatively frequent "puerperal psychosis" the same authors recommend to give those patients the same treatments as for affective psychosis. When the patient is being treated with antipsychotics it is recommended to discontinue breastfeeding.

When under psychoactive treatment during pregnancy, it is preferable to fraction the doses to avoid high plasma values, because it is believed they have a lesser impact on the foetus than a single daily dose.[48] The most extensively evaluated antipsychotics during pregnancy have been high-potency butyrophenones, haloperidol and phenothiazine. Amongst these, dixyrazine and prochlorperazine are used as antiemetics, and the last one as antimigraine.[25] Although as a group classical antipsychotics seem to be not much teratogenic, their potential adverse effects for maternity should also be considered: anticholinergics, antihistaminics, and hypotensors. As a rule, when prescribing antipsychotics during pregnancy it is advised their use as monotherapy, preferably trifluoperazine or haloperidol among the classical ones, and any of the atypical ones, with due caution in lack of adequate information.[23,49-51] Naturally, it is important to know the efficacy of previous treatments that the mother went through.

Table 1 List of antipsychotics marketed in Spain by their teratogeny risk factor in the first quarter of pregnancy (according to FDA) and their risk to breastfeeding.[55]

FDA pregnancy risk categories		Risk categories during breastfeeding
B	C	
	Aripiprazole*	L3
	Chlorpromazine	L3
Clozapine		L3
	Fluphenazine	L3
	Flupenthixol	—
	Haloperidol	L2
	Levomepromazine	L3
	Olanzapine*	L2
	Paliperidone*	—
	Perphenazine	—
	Pimozide	L4
Piperazine		—
Quetiapine*		L4
	Sertindole*	—
	Risperidone*	L3
	Trifluoperazine	–
	Ziprasidone*	L4

L1: the safest; L2: safer; L3: moderately safe; L4: possibly dangerous; L5: contraindicated.
*Atypical antipsychotics.
Category risk is: B < C. There are no antipsychotics in categories A, D and X. The FDA established five pregnancy risk categories. Category A: controlled studies in pregnant women who have not shown risks for the foetus. Drugs considered "safe". Category B: in animals that have not shown malformation risk, but there are no controlled studies in pregnant women. The use of these drugs is generally accepted during pregnancy. Category C: no studies neither in humans nor in animals, or shown to have caused malformation in animals, but no cases have been detected in controlled studies in pregnant women. Category D: evidence of foetal risk, but in certain maternal illnesses the benefits may outdo the risks. Category X: evidence of foetal risk. Risks outdo any benefit. High risk drugs totally contraindicated during pregnancy.

The therapeutic prescription guide of the Spanish agency of medicinal drugs and sanitary products,[52] in its appendix 4 with reference to pregnancy, states the following: "drugs should be prescribed during pregnancy only when expectations of their beneficial effects for the mother outdo those related to foetal risk, and if possible any type of drugs should be avoided during the first quarter. Those drugs that have been used profusely during pregnancy and that, in general, have turned out to be safe will be prescribed with preference over those that are new or for which not much experience is available for such period; likewise, the minimal effective dose will be used". The same guide proposes a relation of drugs that are to be avoided or used with caution during pregnancy and explicit mention is made to atypical antipsychotics amisulpride (that its manufacturing laboratory recommends to avoid) and quetiapine, risperidone and olanzapine, for which their respective laboratories recommend to use only when the benefits outdo their risks. In the case of olanzapine, also, it is established the third as the highest risk quarter and it is specified that lethargy, tremor and neonatal hypertonia have been described.

There is general consent as to minimising foetal exposure to unnecessary medication, whichever this may be. Pregnant women suffering acute mental disorders are usually polymedicated due to frequently combined co-morbidity of psychiatric and non-psychiatric diagnoses.[53] But it is necessary to discriminate for each case which drugs can be left out. To this end the best interrelation as possible is ideal between the patient, her partner, the psychiatrist and also the clinical pharmacist. This last one, in effect, is oriented toward the patient as subject to the need and consumption of medicinal drugs and who suffers or may suffer health problems because of these, according to the modern community concept of pharmaceutical care or pharmaceutical attention. This reciprocal collaboration will contribute to achieving maximum effectiveness when prescribing antipsychotics, reducing the risks involved, and rationalising their use, as well as improving the quality of life of patients. On this direction it had already been proposed to improve the psychiatrist-pharmacist interrelation and specifically training the latter to specialise in the area of psychiatry.[54]

Finally, should there be any doubt about prescribing any antipsychotic in particular to a pregnant woman, the Spanish telephonic information service on teratogens (SITTE) can be contacted. This service provides free informative assistance to consult with the Carlos III Health Institute, at the Spanish Ministry of Science and Innovation, where anyone can consult with any health professional. Its opening hours are Mondays to Fridays in the mornings. However, the Spanish Ministry of Health and Social Policy Web page can be consulted to obtain the technical specifications for almost all the drugs available in Spain (https://sinaem4.agemed.es/consaem/fichasTecnicas.do?metodo=detalleForm).

Conflict of interest

The authors claim not to have any conflict of interests whatsoever in relation to this article.

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