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Risperidone safety in pregnancy. A case report

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The use of risperidone and other antipsychotic drugs during pregnancy is sometimes essential, although it is impossible to design clinical trials to demonstrate the safety of these kinds of drugs. The common method to communicate the absence of drug-related events is through case reports, even though they might be insufficient. This is a case report of a woman with a schizophreniform disorder who continued treatment with risperidone during all her pregnancy, and who gave birth to a healthy baby. The scientific evidence regarding risperidone safety during pregnancy is reviewed and the need to conduct follow-up studies evaluating the consequences of using antipsychotic drugs in pregnant women is stated.

Key words:
Risperidone. Antipsychotic drugs. Pregnancy. Psychosis.

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Seguridad de risperidona en el embarazo. A propósito de un caso

El uso de risperidona y de otros antipsicóticos durante la gestación se hace, en ocasiones, imprescindible, a pesar de la imposibilidad de diseñar ensayos clínicos que refrenden la seguridad de los mismos. El informe de casos clínicos es un modo de constatar la ausencia de hallazgos clínicos al nacimiento, pero puede ser insuficiente. Se presenta el caso de una mujer que padece un trastorno esquizofreniforme y se mantiene en tratamiento con risperidona durante todo el embarazo, que culmina con el nacimiento de un niño sano. Se repasa la evidencia científica respecto a la seguridad de la risperidona en la gestación y se apunta la necesidad de realizar estudios de seguimiento a largo plazo para valorar correctamente el riesgo que se corre a la hora de prescribir antipsicóticos en el embarazo.

Palabras clave:
Risperidona. Antipsicóticos. Embarazo. Psicosis.

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INTRODUCTION

The clinical case of a female patient suffering a schizophreniform disorder with short episodes and *restitutio ad integrum* who, after becoming pregnant, continued with antipsychotic medication with risperidone, is presented. The present article aims to add one case to the medical literature on pregnant women who take antipsychotics, given the ethical problems to conduct controlled clinical trials that provide clear data on the safety in the use of these medications. The evidence in this regards does not provide data on the increase in the appearance of malformations. However, middle and long term neuropsychological injury is doubtful since there are hardly any follow-up studies.

CLINICAL CASE

This is a case of a middle-aged woman with no important medical-surgical background. She does not consume any type of toxic substances and belongs to a family with harmonious dynamics. Her disease goes back seven years when she had her first clinical manifestations. Self-referential and self-injury ideation, with vigilant and perplexed attitude, anxiety, insomnia, depersonalization and derealization phenomena, with the consequent behaviors are described. No psychopathological alterations were found in the examination of the sensory-perceptive sphere or on the awareness level. This first episode appeared suddenly and without apparent precipitating factors. It ended quickly after risperidone was initiated at a dosage of 3-4.5 mg per day. Since then, she has suffered four more episodes, all of them after withdrawal of the medication, either by herself or by the doctor. The description of the symptoms is similar. She has never had affective flattening or emotional blunting or any deficient element. Thus, recovery was complete in all the episodes and the patient has had access to a normal life. After at least one year of being asymptomatic, the patient became interested in becoming pregnant. After careful consideration with the patient, it was decided to progressively discontinue the antipsychotic treatment, however she had to begin it again urgently after a few weeks, due to a relapse in the psychotic manifestations. It was decided to reinit-

iate the antipsychotic treatment (3 mg of risperidone per day) and delay the decision to become pregnant. Within a few weeks, the picture stabilized again, although she expressed guilty feelings and concern about the events beyond her control, which led to the suspicion of an affective disorder. One month later she came to the medical visit, stating she was pregnant. Her affective tone was hyperthymic, she was verbose and hasty, she needed less sleep without this harming her daily activity, which had even increased. It was decided to maintain the treatment with risperidone, reducing it to 2 mg per day and eliminating the associated medication (biperidene). The patient was told about the lack of guaranteed safety of the treatment while stating the importance of maintaining it due to her high risk of relapse and the current symptoms. Her pregnancy occurred without incidences, since the patient was euthymic in the next visit. After six months of symptomatic stability, her dose of risperidone was reduced to 1 mg and a few days before the delivery, it was decided to decrease it to 0.5 mg until the birth. The pediatrician did not contraindicate breastfeeding, although he stressed the adequacy of maintaining the drug treatment. A healthy baby was born, not observing any alteration after the first three months of life.

DISCUSSION

The use of antipsychotics, almost as with any other drug, during pregnancy, is debatable, given the impossibility of conducting controlled clinical studies that support their safety. It is essential to consider both the need for treatment as well as the alteration that such treatment may have on the fetus. Although pregnancy is generally a period of relative stability for patients with schizophrenia, relapses are much more frequent in the immediate post-partum[1]. The risk existing if there is no treatment is derived from the unpredictability that the behaviors governed by psychotic phenomena may have. On the other hand, it is seen that women who suffer a schizophrenic disorder have a higher rate of abortions, fetal deaths, premature births and low-birth weight babies[2]. Thus, in any case, the treatment indication must be carefully weighed, and, in this sense, some orientations[3], summarized in table 1, have been published. These appear to be applicable to all types of drugs during pregnancy.

Utilization of classical antipsychotics during pregnancy is supported by the safety demonstrated over 40 years of its clinical use[4]. The compounds studied most have been chlorpromazine, haloperidol and perfenazine, without having found data in favor of a greater teratogenesis or neurobehavior consequences on the development. On the other hand, phenothiazines have frequently been used in the clinical practice to treat vomits associated with pregnancy and have not been associated to severe congenital malformations[4]. In regards to atypical antipsychotics, some articles published on cases series have tended to conclude that such drugs as olanzapine, risperidone, quetiapine and clozapine are safe[5], as there does not seem to be any major associated teratogeny. Publications with less orientation towards clinical aspects have shown an incomplete passage of haloperidol, risperidone, olanzapine and quetiapine through the placental barrier, although with significant differences between them, with a maximum diffusion of olanzapine and minimum one of quetiapine[6]. A tendency towards hyperglycemia in mothers treated with atypical antipsychotics that associate known specific risks, such as macrosomia, has been seen[7]. A series of cases of women under treatment with risperidone that have had a significant number of patients, most of them captured prospectively, concluded that the drug did not seem to be associated to a greater risk of abortion or malformation than in the general population, although self-limited extrapyramidal symptoms were found in the newborn[8]. Clinical cases have been reported in the same sense, indicating the safety of risperidone during pregnancy, even affirming absolute normality at one year[9] or more than two years after birth[10,11]. However, some studies in rats born to mothers exposed to risperidone refer to alterations in growth, psychomotricity and memory[12] that are related with its D2/5-HT2 antagonism. Both the classical antipsychotics and risperidone, through central dopaminergic blockage, cause hyperprolactinemia with some frequency. This endocrinological alteration is the cause of menstrual and fertility disorders which women who are subjected to these treatments have[13]. It still must be discovered what implications excess prolactin may have on neurofunctional development of the newborn exposed to these treatment during the pregnancy period.

Regarding breastfeeding, this is considered to be contraindicated in the beginning, since it is not considered to be strictly necessary for the correct development of the baby. However, there are already studies that measure the ratio between risperidone and its active metabolite in maternal milk and it has been found to be below that recommended for safe breastfeeding, which in terms of the relative infant dose is 10%[14]. Considering these measurements and a study of only three clinical cases in which no adverse reactions were found in infants breastfed with the milk of mothers under treatment with risperidone[15], the contraindication of breastfeeding while said drug is being administered may be only relative.

Table 1 **Clinical recommendations for the drug management of schizophrenia is pregnancy[3]**

Consider the option of not using the medication
If possible, avoid treatment during the first quarter
Use safer antipsychotics, at minimum dose and with the least possible combinations
Reduce the dose before delivery, and re-establish it immediately after it

In conclusion, the need to treat psychotic episodes is a question that should be carefully weighed. The tendency to relapse in schizohreniform disorders and the unpredictability of the behaviors when there are symptoms of this category speak in favor of the convenience of a minimum, but effective, drug follow-up. In the case in question, the relapses when treatment was suspended and the pregnancy during the last stages of an episode were taken into consideration for the maintenance of the antipsychotic (the same that had already been demonstrated to be effective). However, it is necessary to evaluate the safety of each one of the antipsychotics and to advance in the study of the neurocognitive functions of the children exposed. Although the clinical practice (and the publications directly associated to it) does not provide data that indicate a greater risk of the appearance of malformations, the question is sufficiently important to work on the definition of the consequences derived from the use of antipsychotics during the pregnancy beyond the birth. Risperidone does not seem to present a greater association with malformations in its administration to the pregnant woman. However, it does seem to have a relationship with hyperglycemia and hyperprolactinemia, whose consequences may be unequal. The absence of malformations on birth or of neurocognitive abnormalities after three months of life provides hopeful data, but of relative predictive value. Equally, the indication of maternal breastfeeding must be supported by middle-long term studies, since there are other ways of feeding without needing to expose the child to the drug once the child is born. The evaluation of the risk-benefit relationship, always present when prescribing, and not only in rare situations, seems to require studies that precisely define what the real assumed risk may be.

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