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UPDATE ARTICLE

Pharmacotherapy of obsessive-compulsive disorder during pregnancy: a clinical approach

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Obsessive-compulsive disorder (OCD) is a relatively common psychiatric disorder in the perinatal period. However, specific pharmacological treatment approaches for patients with OCD during pregnancy have not been satisfactorily discussed in the literature. In addition, there are no randomized controlled studies on the treatment of this disorder during pregnancy. The present paper discusses the pharmacological treatment of OCD in the light of data on the safety of antipsychotics and serotonergic antidepressants during pregnancy and their efficacy in the non-perinatal period. Treatment decisions should be individualized because the risk-benefit profile of pharmacotherapy is an important issue in the treatment of pregnant women with any psychiatric diagnosis.

Keywords: Obsessive-compulsive disorder; pregnancy; antidepressants; antipsychotics

Introduction

Obsessive-compulsive disorder (OCD) is a relatively common psychiatric disorder that leads to significant impairment in the quality of life and in the social and occupational functions of the patient.[1-3] The mean age at onset of OCD includes the childbearing years in women.[4] Therefore, OCD may be observed in at least some women during the perinatal period. Although various studies have reported a wide range of prevalence rates, a recent meta-analysis indicated that 2.07% of pregnant women and 2.43% of women in the postpartum period have OCD. Both periods seem to be associated with a higher risk of OCD.[5] The literature also suggests that the severity of symptoms of pre-existing OCD may change during these periods. The rates of worsening and improvement of OCD symptoms have been reported as 8-46% and 10-23% respectively.[6-9]

In the last two decades, there has been growing interest in the use of antidepressants and antipsychotics during pregnancy. While the usage of antidepressants in particular has been extensively discussed in the literature, less attention has been paid to anxiety disorders during pregnancy. This article aims to summarize the major clinical implications relating to the pharmacological treatment of OCD during pregnancy.

OCD and the fetus

The possible effect of psychopathologies on the fetus or child is an important factor that should be taken into account by the psychiatrist when deciding about treatment. However, the available studies have mostly focused on the effects of depression or schizophrenia. Data on the effects of OCD on the fetus or infant are nearly nonexistent. Several studies have shown that general stress or anxiety in the mother are associated with increased resistance to placental blood flow, preterm birth or lower gestational age, increased risk of placental abruptions, poor sleeping and feeding of the baby in the perinatal period, and hyperactivity/attention, cognitive-behavioral, and emotional problems in childhood.[10-17]

Recently, a clinical study has suggested that newborns of women with OCD have significantly lower birth weight and higher levels of tumor necrosis factor-alpha,[18] a proinflammatory cytokine playing a critical role in survival, proliferation, and neuronal differentiation of neural progenitor cells in cord blood.[19] This finding reflects that OCD may potentially affect the neurodevelopment of the fetus.

Psychotropics used in the treatment of OCD and pregnancy

Pharmacological agents that are frequently used for the treatment of OCD in clinical practice are serotonergic antidepressants including selective serotonin reuptake inhibitors (SSRIs) and clomipramine, as well as antipsychotics including haloperidol, risperidone, olanzapine, quetiapine, and aripiprazole. This part of the article focuses on the possible effects of most of these drugs on the fetus.

Antidepressants and pregnancy

SSRIs are the most commonly prescribed psychotropic drugs during pregnancy.[20,21] There are plenty of safety data on this group of antidepressants, although occasionally the data are controversial due to methodological heterogeneities and limitations. More extensive data seem to be available on congenital malformations, poor

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neonatal adaptation syndrome (PNAS), and gestational age as compared to other neonatal outcomes.

Congenital malformations

Despite the existence of concerns, most studies suggest that SSRIs as a group do not appear to be associated with a higher risk of overall birth defects.[22-31] However, paroxetine and most recently fluoxetine are two SSRIs for which increasing evidence shows negative effects on the fetus. A recent meta-analysis by Myles et al.[27] indicated that paroxetine (odds ratio [OR] = 1.29, 95% confidence interval [95%CI] 1.11-1.49) and fluoxetine but not sertraline or citalopram were associated with a higher risk of major malformations. Conversely, Grigoriadis et al.[28] have reported that paroxetine and fluoxetine were not significantly related to major congenital malformations. These authors also reported that when all the studies (regardless of quality threshold, adjustments, or controls) were included in the analysis, a significant connection could be established between fetal congenital malformations and maternal use of fluoxetine. However, according to another meta-analysis, fluoxetine does not appear to increase the overall risk for congenital defects.[32] Three meta-analyses in the literature have reported odds ratios between 1.12 (95%CI 0.98-1.28) and 1.25 (95%CI 1.03-1.51) for congenital defects associated with fetal exposure to fluoxetine.[27,28,32]

Although there are conflicting reports published, a greater number of studies on the use of paroxetine describe deleterious effects such as increased risk of cardiac malformations.[24,26-28,31,33-35] This increased risk is also supported by two recent meta-analyses (reported OR = 1.43, 95%CI 1.08-1.88 and 1.44, 95%CI 1.12-1.86).[27,28] The OR for the same defects in fluoxetine users was reported to be 1.17-1.60 by three meta-analyses.[27,28,32] Based on their meta-analysis, Myles et al.[27] have recommended against elective use of both paroxetine and fluoxetine as first-line antidepressant therapy in the first trimester of pregnancy. To date, similar meta-analysis data are not available for sertraline and citalopram.

Several studies examining escitalopram showed no association with congenital malformations.[30,36,37] Fluvoxamine has the least available data on safety during pregnancy, probably because it is less frequently used by pregnant women compared to other SSRIs.[20,21] Some evidence regarding elevated risk for cardiovascular defects is available for clomipramine, a potent serotonergic tricyclic antidepressant (TCA).[38-40]

Other neonatal outcomes

Table 1 summarizes the relationship between SSRIs and other neonatal outcomes as well as congenital malformations. The most consistent study results refer to PNAS. The reported risk is approximately 5-fold higher in babies exposed to SSRIs than in control babies. Longer usage of SSRIs as well as usage during the late stage of pregnancy may be related to the development of PNAS.[30,41-44]

Meta-analyses and other reports consistently suggest an increase of approximately 1.5-2 fold in the risk for preterm birth (PTB) in women using SSRIs compared to the controls.[26,46,47,58-60] It has been reported that high doses (e.g., more than 40 mg/day for fluoxetine, citalopram, and paroxetine),[61,62] longer exposure,[42,63] and usage during the 2nd and 3rd trimesters[47] seem to be connected with a greater risk of preterm birth. Clinical studies have shown a lack of clear evidence of a negative influence on neurocognitive development with antidepressant usage.[48,49,64] Data are also conflicting regarding the relationship between antenatal antidepressant exposure and other neonatal outcomes such as spontaneous abortion, birth weight, persistent pulmonary hypertension, and autism spectrum disorders.[23,26,35,47,50-57,60,65-69]

Specific information on the risk of other neonatal outcomes in fetuses exposed to clomipramine is lacking. The limited available data suggest that similar to SSRIs, TCAs may be associated with PTB and PNAS.[38] To date, there is no evidence showing adverse effects of antenatal TCA exposure on neurocognitive development in children.[25,38] However, among TCAs, PNAS appears to be most frequently associated with clomipramine.[38]

A few reports have suggested that while the use of venlafaxine is unrelated to congenital malformations, it is similar to SSRIs with regard to other risks for the fetus, such as spontaneous abortion, preterm birth, and PNAS.[25,26,30,31]

Antipsychotics and pregnancy

Congenital malformations

In the last decades, the use of antipsychotic drugs, especially second generation antipsychotics, has increased in pregnant

Table 1 Possible effects of selective serotonin reuptake inhibitors on fetal development[26-28,30,32,34,41,43-57]

Neonatal outcome	Risk vs. controls	Absolute risk level*
Congenital malformation – overall[†]	(0)	Low
Congenital malformation – cardiovascular[‡]	(0)	Low
Spontaneous abortion	(+)	Moderate
Preterm birth	+	Moderate
Low birth weight	(+)	Moderate
Persistent pulmonary hypertension	(+)	Very low
Autism spectrum disorders	(+)	Low
Poor neonatal adaptation syndrome	+	High
Neurocognitive impairment	(0)	Unknown

(0) = no risk but inconsistent data; + = increased risk according to most studies; (+) = increased risk but inconsistent data.
* Risk based on prevalence rate: very low: $\leqslant$ 1.0%; low: 1.1-5.0%; moderate: 5.1-20.0%; high: $>$ 20.0%.
[†] Fluoxetine and paroxetine: (+).
[‡] Fluoxetine: (+); paroxetine: +.

women.[70] However, as a result of relatively fewer prescriptions, information on antipsychotic safety for the fetus is much less than that available for antidepressants. Studies have suggested that antipsychotics are not or only slightly associated with increased risk of congenital malformations.[71-76] At the present time, it is difficult to define a clear connection between the development of malformations and the use of antipsychotics due to the lack of meta-analyses, systematic reviews, and adequate numbers of well-designed studies. Nevertheless, there are growing concerns on this issue. Prospective cohort and medical birth register-based studies have indicated a relatively high prevalence rate of birth defects (5.21-6.2%) in fetuses exposed to antenatal antipsychotic medications. When compared with healthy women, the risk was 1.5-2.5 times higher.[72-74,77]

Overall, first generation antipsychotics (FGAs) and second generation antipsychotics (SGAs) have similar prevalence rates with regard to congenital malformations.[72,73] A prospective cohort study with a large sample size suggested that the increased risk of specific organ malformations was related solely to the cardiovascular system. The incidence rate of these risks in women using SGAs, FGAs, and drugs known to be unharmful to the newborn was 2.8% (OR = 3.21, 95%CI 1.34-7.67), 1.4% (OR = 2.13, 95%CI 1.19-3.83), and 0.6% respectively.[73]

Haloperidol is one of oldest antipsychotic agents. Prior to the emergence of SGAs, for more than 10 years haloperidol was the first choice of medication. In spite of this, very few well-controlled studies are available on its safety during pregnancy.[78,79] In a study of the Swedish Medical Birth Register,[72] the rate of congenital malformation was reported to be 2.6%, vs. 3.6% in a multicenter prospective-cohort study.[80] These rates are within the expected baseline risk for the general population.[81] To date, there is no clear evidence of major teratogenic risk secondary to the use of haloperidol.

Olanzapine appears to be the antipsychotic drug with the largest amount of data regarding use during pregnancy.[82] A recent review of data from global safety surveillance including 610 prospectively identified pregnancies reported a 4.4% prevalence rate of congenital malformations.[81] Risperidone is another frequently reported antipsychotic drug. There is no clear evidence regarding its association with increased risk of birth defects. The reported rates of birth defects in two studies were 3.8 and 3.9%.[72,83] Quetiapine had the lowest placental passage compared with the three medications mentioned above.[84] Despite their limitations, the available studies did not demonstrate an elevated risk.[73] The rate of malformations after fetal exposure to quetiapine is about 3.5%.[73,82] In a prospective study including 44 women using aripiprazole, a high rate of birth defects (6.8%) was reported,[73] which should be confirmed by further studies.

Other neonatal outcomes

The relationship between antipsychotics and spontaneous abortion was not reported to be statistically significant, although some authors have reported higher rates of abortion in the exposed group compared to controls.[81-84] Interestingly, some studies revealed statistically significant differences in the early termination of pregnancy especially due to social reasons in women using these drugs (9.9-12.2%) compared to control pregnant women (1.3-1.8%).[71,73]

Several studies have reported a 1.7-2.5-fold increase in the risk of preterm birth (PTB) with use of antipsychotics.[72,74,77] Conversely, at least two prospective cohort studies suggest that use of SGAs was unrelated to the risk for PTB.[71,73] The literature has very conflicting results about birth weight. A lack of difference between exposed and non-exposed women has been reported for mean birth weight[71,74,77] and proportion of small for gestational age infants.[74] Moreover, the risk of low birth weight[71,72,84] or proportion of small for gestational age infants was not reported to increase for exposed women.[85] Some authors showed that typical antipsychotics but not SGAs were associated with lower mean birth weight of fetus.[73,86] Although two studies with small sample size found a higher risk of large for gestational age babies[74,86] in women taking SGAs, studies based on the Swedish national birth register do not support these results.[72,85]

The risks to the neonate exposed to antenatal antipsychotics are unclear due to the absence of well-designed studies. There are concerns in terms of abnormal muscle movements.[87] Most reports regarding FGAs have concluded that antipsychotics have no adverse effects on newborns.[76] A Swedish Medical Birth Register Study reported no statistically significant increase of neonatal diagnoses such as low Apgar score, respiratory disturbances, hypoglycemia, and neonatal icterus.[72] However, a large prospective cohort study indicated that both FGAs and SGAs were associated with approximately 5-fold increased risk of perinatal disorders, especially the ones related to the nervous system (e.g., jitteriness, somnolence, or seizures).[73] Moreover, a significantly higher risk of being admitted to the neonatal intensive care unit and poor neonatal adaptation symptoms due to usage of SGAs have been reported in another prospective study.[74] Polytherapy, higher doses, and exposure in the last gestational week seem to be more related to these effects.[73,74,77] The prevalence of perinatal events has been reported as 8-30.8% for olanzapine,[73,81,84] 9.5-25.8% for quetiapine,[73,84] and 23.5% for aripiprazole.[73] Newport et al.[84] found that neonatal complications mostly involved the cardiovascular and respiratory systems.

There are relatively consistent study results showing that gestational diabetes mellitus (GDM) is seen more frequently in pregnant women using antipsychotics compared to controls.[72,74,85] The available studies, however, do not provide sufficient data on the risk of GDM for each specific antipsychotic. Boden et al.[85] reported that in contrast to a significant connection between antipsychotics and GDM, there is no significant difference between the users of clozapine/olanzapine and other antipsychotics. However, cases of GDM have been reported most frequently with olanzapine and clozapine.[88]

The long-term behavioral and neurocognitive effects of intrauterine exposure to antipsychotics are currently unknown. Although some studies have reported lower

scores in neuromotor, cognitive, and socio-emotional performances in infants exposed to intrauterine antipsychotics,[89,90] these effects appear not to persist at 12 months of life.[90]

General considerations

The decision regarding treatment regimen for OCD in women during pregnancy is very difficult. The decision must be based on several factors, such as the risks of untreated maternal psychiatric illness and the known or unknown potential effects of psychotropic medications, benefits of pharmacological treatment, and alternative treatments to medication.[30] Decision-making requires detailed psychiatric assessment including individual and family history of psychiatric disorders, side effects or therapeutic effects of medications, severity of disorder, and degree of impairment in occupational, family, and social areas secondary to the disorder.[25] All steps of the treatment should be administered in agreement with the patient and her relatives. If the patient has severe depression and anxiety symptoms, a high suicide risk, considerable feeding and sleep disturbances secondary to OCD, or has mild to moderate OCD that is unresponsive to cognitive-behavioral therapy, pharmacological treatment regimens may be considered.

Drug options

The effectiveness of serotonergic antidepressants such as clomipramine and SSRIs in OCD is well known. It is assumed that these drugs are also effective in the perinatal period despite the lack of placebo-controlled studies. Similarly, augmentation of serotonergic agents with antipsychotics has been well documented. Table 2 shows recommendations and comments on specific antidepressant drug options available for the treatment of OCD during pregnancy.

The choice of drug should be based on several factors including: family and individual history of response or side effects to the medications at any period, safety of the drug for the fetus, and effectiveness of the medications to treat OCD during the non-perinatal or perinatal period in particular. As in the non-perinatal period, SSRIs as a group appear to be first-line drugs during pregnancy.[30,91] However, two SSRIs including fluoxetine and particularly paroxetine are not appropriate for first-line treatment because these drugs are the most frequently associated with congenital malformations and PNAS.[27,28,35,45,95] Nonetheless, these antidepressants may be chosen in women with OCD who do not respond or cannot tolerate other SSRIs due to low elevation of absolute risk of birth defects.[27,28,96,97] Sertraline and citalopram/escitalopram seem to be a more favorable option in the pregnancy period.[27] Despite the lack of evidence on higher risk of malformation, fluvoxamine should be used with caution due to the limited number of studies carried out with this drug. Considering the scientific data currently available, this paper recommends SSRIs for the treatment of OCD during pregnancy in the following order: sertraline, citalopram/escitalopram, fluvoxamine, fluoxetine, and paroxetine.

Clomipramine is another psychotropic drug recommended as first-line agent to treat OCD.[91] Several studies have suggested an approximately 2-fold increased risk of cardiovascular defects associated with clomipramine, although these studies have some methodological limitations.[31-40] Although this is a discouraging factor in the use of this drug, the absolute risk of cardiovascular defects is still low. In addition, clomipramine is related to higher risk of PNAS compared to other TCAs.[38] Its usage may result in additional risk of exposure to a second antidepressant for the fetus, because it is less well tolerated than SSRIs.[91] There are several studies suggesting that venlafaxine may be efficient in OCD.[92,93] It seems to be more favorable with regard to safety compared to clomipramine, however, less evidence is available to support its use in OCD.

The beneficial effects of antipsychotics as an augmentation therapy have been described.[97-99] Most published studies on this topic have included SGAs. Augmentation with haloperidol was found to be effective in at least two

Table 2 Antidepressant options in the treatment of OCD during pregnancy[22,26-32,35-37,40,44,45,91-94]

Drug options	Comments
First-line	
Sertraline Citalopram	Reported to be effective in OCD, but have the least number of studies focusing on the association with birth defects.
Escitalopram	Despite less evidence, safety profile is expected to be similar to that of citalopram.
Second-line	
Fluvoxamine	Inadequate teratogenic data but no report of increased risk of birth defects.
Third-line	
Fluoxetine	Despite an unclear association, there is growing evidence of a role in fetal defects and high risk for PNAS.
Fourth-line	
Paroxetine	In spite of controversial results, this drug is positively associated with fetal malformations. In addition, it has a high risk for PNAS.
Clomipramine	Limited studies suggest increased risk of cardiac malformation and severe perinatal complications. In addition, the risk of maternal intolerance is relatively high, and the risk for PNAS is high.
Venlafaxine	Inadequate teratogenic data despite but no report of increased risk of birth defects. Limited evidence available on efficacy in OCD.

OCD = obsessive-compulsive disorder; PNAS = poor neonatal adaptation syndrome.

meta-analyses including only one placebo-controlled study examining the efficacy of haloperidol.[97,98] Risperidone is the SGA with the most consistent successful results supported by at least three meta-analyses.[98-100] These meta-analyses[98-100] suggest that the effects of olanzapine and quetiapine are no better than those of placebo, despite the existence of some placebo-controlled studies showing beneficial effects of antipsychotic augmentation with these medications.[101,102] However, approximately 35% of the patients respond to augmentation with these two antipsychotics.[98] There are more studies examining quetiapine than olanzapine.[98,100,103] In contrast to the three meta-analyses mentioned above, a meta-analysis by Fineberg et al.[103] based on changes from baseline in total Yale-Brown Obsessive Compulsive Scale indicated efficacy for augmentation with quetiapine. Aripiprazole has been studied in two positive double-blinded clinical trials and a single-blinded randomized study with results that favor the use of aripiprazole.[104-106] A meta-analysis by Dold et al.[100] including a double-blinded study with aripiprazole reported that the results were inconsistent. Conversely, new Canadian clinical practice guidelines recommend the use of aripiprazole in addition to risperidone as first-line adjunctive therapy.[107] Nevertheless, limited safety data during the perinatal period restrains the preference for aripiprazole. Even though acknowledging risperidone as a first-line antipsychotic, based on data regarding the safety for the fetus and effectiveness in OCD, the Canadian guidelines recommend that quetiapine and olanzapine be considered as preferred option especially in women with severe loss in sleep and appetite in the pregnancy period. Haloperidol and quetiapine may be second-line agents, because there are fewer studies suggesting their effectiveness in OCD as compared to risperidone and more studies as compared to olanzapine. At the present time, other drugs may be chosen in preference to aripiprazole because of limited data on safety during pregnancy (Table 3). In further years, aripiprazole may be become a first-line augmenter during the perinatal period, provided adequate data on safety become available.

Dosing

As a general rule, the dose of any drug should be as low as possible during pregnancy. The recommended doses of antidepressant in OCD are higher than the doses used to treat depression.[94,108] Although it is theoretically expected that pregnant women need higher doses of antidepressants as a result of increased activity of the hepatic cytochrome enzymes that metabolize the antidepressants,[109,110] the clinical importance of possible pharmacokinetic changes is unclear. Also, there are not enough studies on the safety of daily doses of antidepressants during pregnancy. There are at least two studies suggesting that a high daily dose of SSRIs is associated with greater risk of PTB.[61,62]

A meta-analysis indicated that low, medium, and high SSRI dose categories produced significantly greater improvement in OCD symptoms when compared to placebo. However, high doses were statistically superior compared to medium and low doses, and there was no significant difference between the low and medium doses. The authors also noted that high and medium doses of SSRIs led to significantly more dropouts due to side effects, and low doses did not significantly differ from the placebo in this measure. In addition, a patient using SSRIs at high doses experienced 9% and 7% greater decline in OCD symptoms compared to low and medium doses respectively.[111] As a result, although high or low doses of SSRIs for OCD appear to be more favorable, the risks of high doses on the fetus should be taken into account during the decision of administration.

Non-response to initial medication

Approximately half of the patients with OCD do not show any significant improvement in symptoms following treatment with a serotonergic antidepressant.[91] There are two main treatment options in unresponsive patients: 1) modification of the serotonergic antidepressant therapy, including a further dose increase, a switch to other

Table 3 Antipsychotic augmentation options in the treatment of OCD during pregnancy[71-74,80-83,87,88,98-100,102,103,106,107]

Drug options	Explanations
First-line	
Risperidone	Consistent study and meta-analyses showing efficacy in OCD and no clear evidence regarding its association with increased risk of birth defects.
Second-line	
Haloperidol	No clear evidence regarding its association with increased risk of birth defects, however, few studies on efficacy in OCD in contrast to the existence of some meta-analyses suggesting positive effects on OCD symptoms.
Quetiapine	No clear evidence regarding association with increased risk of birth defects, however, controversial results in double-blinded studies and meta-analyses about its efficacy in OCD.
Third-line	
Olanzapine	No clear evidence regarding its association with increased risk of birth defects, concerns regarding its connection with gestational diabetes mellitus, and nonsignificant efficacy compared to placebo in meta-analyses including two studies with controversial results in OCD.
Fourth-line	
Aripiprazole	Limited data on the safety in pregnancy and the existence of a prospective study suggesting relatively high malformation rate despite double-blind studies showing efficacy for OCD.

OCD = obsessive-compulsive disorder.

antidepressants, or use a combination of the drugs; 2) augmentation with antipsychotics. Which option is safer in the perinatal period is currently unknown.

Several studies have reported that supratherapeutic doses of SSRIs (e.g., up to 50 mg/day for escitalopram and up to 400 mg/day for sertraline) are connected with significantly higher improvement in OCD symptoms.[112-114] However, this method does not appear to be a desirable first-step treatment in the pregnancy period, because its potential adverse effects on the fetus are unknown and studies regarding its effectiveness in unresponsive patients is inadequate. If administration of such high doses becomes necessary, the pregnant women and exposed fetus must be observed closely.

Of the nonresponders, up to 42% may benefit from a switch between serotonergic antidepressants.[91,115] Actually, this strategy may be more favorable as the first-step in perinatal women compared to other pharmacological strategies. The switching should be firstly between sertraline, citalopram/escitalopram and fluvoxamine during pregnancy.

There are controversial results on the efficacy of the combination of SSRIs with clomipramine.[91,116,117] The combination is associated with risk of clinically significant drug interactions which may lead to potential adverse effects of clomipramine such as seizures.[118] This option does not seem to be feasible as first or second-line pharmacotherapy in the pregnancy period, due to absence of adequate data on both effectiveness for the patient and safety for the fetus. If necessary, clomipramine should be administered at as low doses as possible.

In the non-perinatal period, antipsychotic augmentation is recommended in treatment guidelines.[91,107] Moreover, antipsychotics are the most often prescribed augmentation drugs in international OCD centers.[119] This method may be chosen in the pregnancy period. Nevertheless, there is no adequate data on safety of a combination between antidepressants and antipsychotics during pregnancy. In addition to being only theoretically more effective, it also has potentially higher adverse effects on the fetus. Additionally, only one third of the patients are responsive to the augmentation.[98-100] Consequently, augmentation should be chosen only if other treatment methods including modification of serotonergic antidepressant therapy and cognitive-behavioral therapy are insufficient, namely, if it is necessary and there is a clinical conviction that the augmentation has higher benefits compared to the available status of OCD.

In case the psychiatrist decides to initiate augmentation therapy with an antipsychotic, the decision must be discussed with the patient and her relatives. If antipsychotics are used during pregnancy, the preference order recommended in Table 4 may be considered. The antipsychotics should be used at as low doses as possible. For example, although risperidone is more likely to be effective in doses closer to 2 mg/day,[98] some authors have found that it may be effective even at doses of 0.5 mg/day.[120] A short duration of augmentation therapy may be more appropriate with regards to the safety of the fetus.

Table 4 Steps proposed by the author for pharmacotherapy in OCD patients who do not respond to initial medication during pregnancy

1	Review the current diagnosis and possible medical or psychiatric comorbidities.
2	If there is not any response to the current SSRI at the lowest effective doses, consider switching to another SSRI. If there is a partial response to the initial SSRI at the lowest effective doses, consider increasing dose of current SSRI or switching to another SSRI.
3	Consider switching to clomipramine at therapeutic doses.
4	Discuss supratherapeutic doses of SSRIs, SSRI at therapeutic doses plus clomipramine at low doses, or SSRI at therapeutic doses plus antipsychotics at low doses.
5	Discuss SSRI at therapeutic doses plus antipsychotics at moderate or high doses, or SSRI at therapeutic doses plus clomipramine at moderate or high doses.

OCD = obsessive-compulsive disorder; SSRI = selective serotonine reuptake inhibitors.

Limitations

Most studies investigating the potential risks of antidepressants on the fetus have severe methodological limitations, such as retrospective design, data collected from automated databases that do not declare whether the participants actually used the prescribed medication, and incomplete information with respect to timing of exposure and dosages.[121] The available studies also mostly do not provide detailed information about underlying psychiatric conditions and do not exclude potential confounding effects of psychiatric diagnoses, comorbid conditions, and severity of symptoms. Another important problem is that the evidence on safety of antidepressants or antipsychotics during pregnancy derives primarily from studies using these medications to treat other psychiatric conditions. Although it is reasonable to think that the safety of each specific medication during pregnancy does not vary for patients with different disorders, we cannot affirm this for sure. Thus, we must still learn a good deal about the adverse effects of untreated maternal OCD during pregnancy. However, there are few studies on this topic.

Ideally, the recommendations should be based on controlled pharmacological studies carried out in circumstances that are similar to the non-perinatal period. However, a comparative study examining the effects of treated and untreated maternal OCD on the fetus is not available in the literature. Therefore, it is very difficult to draw definitive conclusions about treatment strategies in this period.

Conclusions

The risk in the decision to treat or not to treat OCD with pharmacological agents in pregnant women is not zero. For this reason, the treatment decision and options should be individualized. For depression or anxiety disorders that are mild-moderate in severity, it is unclear whether treatment with a psychotropic is superior to untreated illness in terms of safety of fetus due to lack of well-designed controlled long-term studies. Considering the

response rate to a single serotonergic antidepressant at therapeutic or supratherapeutic doses, to a combination of them, and to augmentation with antipsychotics, the use of pharmacotherapy in mild to moderate OCD must be carefully weighed. If a decision to use pharmacotherapy is made, sertraline and citalopram/escitalopram as antidepressants, and risperidone as an antipsychotic are recommended for use during pregnancy as first-line drugs. Future studies should investigate the following points: 1) the relationship between congenital malformations and doses of antidepressants; 2) comparisons amongst pregnant women with OCD untreated and treated with an antidepressant in terms of birth outcomes; 3) safety and efficacy of combination options between serotonergic antidepressants and between serotonergic antidepressants and antipsychotics; 4) efficacy and optimum dose of antidepressants during the perinatal period.

Disclosure

The authors report no conflicts of interest.

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