Psychotropic Treatments of Psychotic Disorders during Pregnancy

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Abstract

In Romania there was no concern for the development of a therapeutic protocol or guide for pregnant women under psychiatric treatment and, therefore, initiation of such a discussion is beneficial. Diversification of psychotropic treatments has made an increasing number of pregnant women to be sent to psychiatrists to assess the appropriateness of continuing or changing psychiatric treatment, to prevent possible undesirable consequences for the fetus or even abortion. Most psychiatric medicines used by pregnant women are not subject of study due ethical reasons, the only usable resource in defining an adequate decision being review articles and expert opinion. On the other hand, preexisting or development of serious diseases such as antepartum depression and reactive depression, bipolar disorder, schizophrenia, etc., require an evaluation of maternal capacity. We did a summary of some of the most recent views expressed in the literature to provide the family doctor and obstetrician information designed to induce them to seek interdisciplinary advice whenever appropriate.
Keywords: *pregnant, pregnancy, depression, bipolar disorder, schizophrenia, maternal ability*

Introduction

During the last twenty years we are witnessing an increase in the prevalence and occurrence of mental disorders, as well as a faster diagnosis of such disorders, an increase in the number of marketed psychotropic drugs and a higher number of women who are experiencing pregnancy at an advanced age, including the possible occurrence of late-onset psychiatric diseases and, obviously, the initiation of their treatments[(1)].

We are also motivated by the absence of synthesis materials in the literature of our country which could allow the obstetricians, as well as the psychiatrists and the family doctors to opt for a certain attitude based on evidence.

Food and Drug Administration has set clear categories relating to the possible side effects that any medicines could have on the fetus. This classification can be applied to psychotropic drugs, too.

Category A: no significant risk for fetal abnormalities, proven by means of well controlled clinical studies;

Category B: debatable risk - which cannot be completely documented through experimental studies, neither through well controlled clinical trials;

Category C: only animal studies have shown some effects, but no similar results were obtained in humans or there were no studies performed;

Category D: well controlled or observational studies which show there is a risk for the fetus, but in some instances the therapeutic benefits overbalanced potential risks;

Category X: well controlled or observational studies have shown a strong evidence of fetal risk[(2)].

Even though there is a wide spread belief that pregnancy could have a beneficial effect on various pre-existing conditions, especially the psychiatric ones, this belief cannot stand up when confronted with an analysis based on evidence; moreover, things seem to be quite the opposite both for the mother, and the fetus.

Some family doctors, and even some obstetricians, insist, without any consent from the psychiatrist, that the pregnant woman interrupt any psychotropic medication and in order to support this attitude they bring up specific situations from their individual experience. The studies performed in order to assess psychotropic treatments target both teratogenicity, which usually concerns the first trimester of pregnancy and the organ or muscular-skeletal malformations, and embryotoxicity, which concerns the disorders that can occur in the second and third trimester of pregnancy, including restlessness, spasmodic crying and nervousness.

There is no clear data if, during the antepartum period, pregnancy increases the risk of depression, which, regardless of being pregnant or not, affects 10-16% of women in

Table 1 Estimated prevalence of certain psychiatric disorders during pregnancy[3]

Type of disorder	Disease	Estimated prevalence (%)
Depressive disorder	Major depression (Marcus S.M. et al., 2005; Flynn H.A., Blow F.C., Barry K.L., 2004)	13-20
	Bipolar disorder	unknown
Anxiety disorders	Generalized anxiety disorder (Ross L.E., McLean L.M., 2006; Rogal S.S., Poschman K., Belanger K. et al., 2007)	8.5
	Panic disorder	1-2
	Post-traumatic stress disorder	3.5
	Obsessive-compulsive disorder	0.2-1.2
Eating disorders	Anorexia (Micali N., Simonoff E., Treasure J., 2007)	1.4
	Bulimia	1.6
	Anorexia and bulimia	0.7
Personality disorders		6.4
Psychotic disorders		unknown

the fertile period, and according to other authors reaches a percentage of 25%[4]. As for bipolar affective disorder, there is a greater relapse risk during pregnancy which can be interpreted rather as a consequence of interrupting the maintenance treatment[5]. As for paranoid disorders, the majority of authors agree there is a deterioration of their evolution and this also applies to obsessive-compulsive disorders. There is no convergent data regarding the anxiety disorders, but in our opinion these symptoms increase during pregnancy.

The psychiatric disorders occurred during pregnancy are related to hormonal variations (estrogens, progesterone, cortisol, as well as thyroid hormones), to changes of the social status and usual rhythms and behaviors and modifications of the interpersonal relationships.

There is a high prevalence of depression, affective disorders and other psychiatric disorders, having a high incidence upon the beginning of the fertile period of a woman.

Untreated depression, psychosis and affective disorders can have harmful effects both on the mother, and the child; pharmacotherapy can also cause negative effects on the child.

Because of this, it is very important for the patient treated with psychotropic drugs to discuss with her attending physician about continuing or interrupting the treatment during pregnancy.

Psychotic affective disorders during pregnancy

Antepartum depression and reactive depression

As for **antepartum depression**, it has all the diagnosis difficulties of depression, in general, multiplied by the problems generated by the fact that a normal pregnancy is characterized by sleep disorders, decrease of concentration and physical effort capacity, appetite modifications. Mood changes, decrease of interest or pleasure towards usual activities should be systematically evaluated in order to identify a possible depression as early as possible.

The risk factors of prenatal depression are: personal or family history of affective disorders, dysfunctional marital status and absence of the partner's support, increased number of children, young age of the mother, as well as a low level of education.

Table 2 Risk factors in depression occurred during pregnancy[6]

History of affective disorders
History of postpartum depression
Family history of psychiatric disorders
Limited social support
Marital instability
Recent mourning
Sudden interruption of pharmacotherapy in persons with medical history

Prenatal depression is also the most important risk factor for postpartum depression. As in other situations, depression is characterized by comorbidities, as well as drug or alcohol addiction, it can lead to eating disorders and a reduced attention towards pregnancy, a precarious medical assistance due to non-compliance. All these affect both the mother, and the fetus.

Antepartum depression is probably the least and most inappropriately treated form of depression, partly because of a poor diagnosis, and partly because the mother, as well as the doctor avoids administrating mood stabilizing drugs and any other psychotropic drugs. Only 3% of pregnant depressed women are estimated to take antidepressants[7]. The fact that they do not undergo a therapeutic programme is even more paradoxical especially that an important number of these patients could benefit of psychotherapy or other biological therapies in case of a more severe form.

Reactive depression can occur after a miscarriage, early fetal death, after a traumatic pregnancy or a delivery with complications, when the child has severe malformations or

after the family refused to accept the child. The diagnosis criteria of this depression are similar to the criteria used for any other form of reactive depression: existence of a traumatic event, persistence or deterioration of depressive symptoms after a certain period of time, occurrence of self undervaluation, uselessness and even autolysis.

Bipolar affective disorder

Bipolar affective disorder, the most frequently diagnosed affective disorder, characterized by two phases - manic and depressive, is a pathological circumstance both during the prenatal period, and during postpartum because of the likelihood of transmitting this disorder to the child and because of the problems caused by the maintenance treatment with mood stabilizers administered to most of the patients.

Pregnant women are likely to develop a depression during pregnancy, and the ones who experience a depressive episode during this period are more likely to develop similar episodes during the next pregnancies.

Heredity, as it is transmitted through both parental gene sets, play an important role, but it is not clear how genetic influences will be expressed in the children of manic-depressive persons. In a direct line of such a patient, depression and similar mood disorders will occur with a higher frequency.

A risk of 1% noticed in the general population increased to 15% in children who have one parent diagnosed with manic-depressive disorder. This risk increase cannot be calculated or evaluated individually, and the diagnosis of the child is increased by additional negative influences on character forming in an early age and by stressful life events at later ages. Even though at the present moment there is no valid scientific method which can predict who will and who won't develop a mood disorder, the help of a genetics specialist can be important in giving more accurate advice, based on a family history with bipolar disorders.

Some **treatments with mood stabilizers** can have teratogenic effects (**valproic acid, carbamazepine, lithium salts**). On the other hand, treatment interruption results in an increased rate of depression and manic relapses which can have consequences on the fetus. During the manic episode, alcohol and drug abuse, risky sexual behavior, aggression increase and involvement in incidents and accidents can also represent dangers for the fetus. It is likely that these persons won't either adhere in any way to the medical indications concerning the pregnancy or its complications[8].

A very recent study[9] shows that **valproate** has a negative influence on the development of cognitive capacities of the child (IQ) compared to carbamazepine, lamotrigine or phenytoin and that there is a relation between the administered dosage of valproate and IQ. This relation is absent in other antiepileptic drugs, in which case the IQ of the child is influenced only by the IQ of the mother[10].

Investigators suggested valproate as first-line therapy in women with a pregnancy potential is not recommended, because the administration of this drug is associated with an increased risk of developing a cognitive disorder at the age of three. Administration of valproic acid in the first trimester of pregnancy is associated with an increased risk of malformations. This is why women during the fertile period must not follow a treatment with valproic acid, unless this is essential for their medical status and only if they use an efficient contraceptive method **(FDA.gov). Valproate is included in risk class D.**

Even though many authors think maintaining the treatment with a progressive decrease during the prenatal period would be advisable, there is no consensus as to which medication should be used, neither on the length of the period in which a treatment interruption could be performed. As for the teratogenic effects, valproic acid and carbamazepine are considered to influence the neural tube, especially during the first 5 weeks of pregnancy, and lithium can lead to heart malformations (Ebstein disease). The data concerning the frequency of these malformations is not sufficiently accurate.

Research has suggested that **lithium** can cause a mild increase of the incidence of congenital malformations, when it is administered during the first trimester of pregnancy.

Children exposed to lithium in utero were found to have floppy infant syndrome and thyroid toxicity.

As for **lamotrigine** as a medicine with very few adverse effects, an increase of cases with cheiloschisis or palatoschisis is supposed to occur.

As for the administration of antidepressants during pregnancy, those antidepressants which have the smallest risk of adverse effects for the mother and the child are advised to be taken and only if the risk of events which would occur if not administered is higher than the risk the antidepressant medication has upon the mother and the fetus. There are no specific researches relating to **antidepressants** for very obvious reasons: fear of doctors to administer them, fear of patients to receive medicines.

None of the antidepressant medications is included in category A or B, as these are settled by the FDA classification.

By frequency of prescription, the order is as follows: **SSRI** (citalopram, escitalopram, fluoxetine, paroxetine and setraline), tricyclic antidepressants, SNRI and others[12].

As for **SSRIs** there is an increased risk of teratogenicity when they are administered during the first trimester, especially in the case of paroxetine (increased risk of congenital malformations), and if administered during the last trimester they can cause embryotoxicity and a deficient neonatal adaptation, known as neonatal toxicity or neonatal behavioral syndrome. Its main symptoms are as follows: tremor, eating disorders, irritability, restlessness, rigi-

Table 3 IQ score at the age of 3 (NEAD study, 1999-2004, 309 subjects)

Antiepileptic drugs	Mean IQ value (95% CI)	IQ difference in Valproate group (95% CI)	P
Carbamazepine (n = 73)	98 (95 - 102)	6 (0.6 - 12.0)	.04
Lamotrigine (n = 84)	101 (98 - 104)	9 (3.1 - 14.6)	.009
Phenytoin (n = 48)	99 (94 - 104)	7 (0.2 - 14.0)	.04
Valproate (n = 53)	92 (88 - 97)	-	-

Table 4 Therapeutic management of bipolar affective disorder during perinatal period[11]

Beneficiary Period	Women with a good response to treatment	Women during the condition	Women with a high risk of developing a manic episode
Preconception	■ Discuss about contraceptive methods; ■ Education; ■ Genetic advice; ■ Re-assessment of risks. 1. Progressively reduce medication Or 2. Continue medication: ✓ single therapy; ✓ minimal therapeutic doses; ✓ reduce plasma peak values; ✓ associate Carbamazepine and Valproate with folic acid 4mg ■ Support	In-hospital professional care Education Support Counseling	Psychiatric assessment Education Genetic advice Support
Assessment of a high risk for: ■ recurrent disorder; ■ severe psychiatric disorders; ■ suicidality. Encourage a rigorous planning.			
First trimester of pregnancy	All of the above Monthly measurement of plasma lithium level Control or urea, electrolytes and thyroid function Measurement of Carbamazepine and Valproate plasma levels	Hospital admission Strong antipsychotics + / - Benzodiazepines, if necessary (clonazepam and lorazepam) + / - Mood stabilizers + / - Electrotherapy, if necessary	All of the above
Second trimester of pregnancy	All of the above Measure the plasma lithium level twice every month Control urea, electrolytes and thyroid function Ultrasound display of the fetus Measurement of Carbamazepine and Valproate plasma levels	All of the above	All of the above
Third trimester of pregnancy	All of the above Weekly measurement of the plasma lithium level Control urea, electrolytes and thyroid function Reduce the dose of medicines to half of the usual dosage Ultrasound display of the fetus Carbamazepine: vitamin K 10 mg / day From week 36 to week 40 discuss about the birth methods Inform the anesthesiologist	All of the above	All of the above Take the mood stabilizers into consideration

Table 5 Antidepressant type

Tricyclic	SSRI	IMAO	Other antidepressants
These antidepressants are being used because there is a very wide accumulated experience which shows they do not have teratogenic effects; Tachycardia, irritability and muscular spasms of the new born were described after imipramin; Non-significant increase of spontaneous abortions; Most used: ■ **Nortriptyline** (reduced anticholinergic action); ■ **Amitriptyline**; ■ **Imipramin**. Non-significant teratogenic risk.	A more reduced experience due to novelty; Most information is about fluoxetine, and in the beginning it was thought to have small teratogenic effects (false); **Paroxetine** and **fluvoxamine** did not show major risks; Non-significant increase of spontaneous abortions; Teratogenic risk: 2,9% = not exposed; (**fluoxetine** (3,3%), **citalopram** (3,1%), **paroxetine** (3,4%), **sertraline** (2,0%))	Are not used	Mirtazapine, Reboxetine, Venlafaxine, Nefazodone; There are not sufficient studies in order to demonstrate or invalidate the effects on the pregnant woman

dity and respiratory disorders in addition to which other signs can occur more rarely: seizures, excessive crying, strong reflexes and sleep disorders, which are usually remitted in two weeks. The new born babies who show these symptoms require careful monitoring. This deficient neonatal adaptation is due to the serotonergic toxicity or discontinuation interruption syndrome.

The majority of the **tricyclic antidepressants** have anticholinergic side effects (dry mouth, urine retention, constipation),

and this is why only nortriptiline and desipramine are recommended for administration during pregnancy. **Administration during the first trimester of pregnancy can increase the risk for congenital malformations, but this was not further confirmed.** If they are administered during the third trimester of pregnancy a deficient neonatal adaptation was observed. The new born babies show symptoms such as diarrhea, restlessness and muscular weakness which are due to the rebound cholinergic hyperactivity. Side effects limit to a great extent the use of tricyclic antidepressants during pregnancy.

As for the noradrenaline reuptake inhibitors and the serotonin reuptake inhibitors (venlafaxine and duloxetine), **they have been used very often lately, but information regarding their possible side effects is limited**.

There are no systematic studies about other antidepressants (bupropion, mirtazapine, trazodone and nefazodone).

Most authors consider that one patient who follows a usual treatment with antidepressants and wishes to get pregnant must be evaluated for her status of mental health, medical history and current medication, in order to decide whether to continue or interrupt the treatment.

The antidepressant treatment must not be interrupted unless there is a teratogenic and embryotoxic risk. It is advisable that paroxetine be avoided regardless of the trimester of pregnancy and the pregnant women who take tricyclic SSRIs and SNRIs must be carefully monitored during their third trimester of pregnancy. Duloxetine is to be avoided because there is no sufficient data about its use.

Even though **electroconvulsive therapy (ECT)** is one of the most efficient treatments administered for depression, it still is a final solution even when it should be the first choice. The pregnancy seems to be one of these circumstances because the use of this method exposes the fetus to psychotropic drugs only to a minimal extent and the safety of this method is sufficiently increased[13].

Some authors recommend additional safety measures, such as the existence of a team comprised of a psychiatrist, an obstetrician and an anesthiologist, a gynecology examination before ECT and monitoring the heart beats of the fetus, also taking the administration of oxygen into consideration[14]. If the patient has uterus contractions or any other symptoms which can suggest a premature birth after the administration of the electroconvulsive therapy, this treatment must be stopped.

Schizophrenia

For the patients with **schizophrenia** pregnancy is just another risk factor in addition to the other factors concerning the disease: comorbidities and addictions, especially to tobacco and alcohol, loss of the social status, chaotic social relations, absence of a family support, poverty, malnutrition and deficient health care. These cumulative factors create the ideal premises for the occurrence of a new psychotic episode. The ablactation, necessary after breastfeeding of the child is interrupted, can be difficult because bromocriptine, which is usually used, is a dopamine antagonist and can exacerbate the psychotic symptomatology. Through the indirect effect that some neuroleptic drugs can have on prolactin, they can also cause the increase of milk secretion.

As for the role of estrogens, several authors think they have a psycho-protective role and consider that both postpartum blues and postpartum psychoses occurred during the first weeks after birth would be determined to a sudden decrease of the estrogens immediately after birth. There are studies which showed that administration of estrogens in postpartum psychoses and in postpartum depression had a positive effect[15].

Typical antipsychotic drugs are no longer the first line medication in psychotic disorders.

Butirofenone derivatives (Haloperidol) do not cause any major malformation but, during the late phases of pregnancy, new born babies can show some complications, such as withdrawal symptoms.

There is no teratogenicity evidence for fenotiazine either, and as embryotoxicity it is thought that in case of doses which exceed 500 mg a fetal respiratory distress syndrome can occur.

The administration of typical antipsychotic drugs implies minimal associated risks and these medicines can be used during the entire period of pregnancy. An important negative effect has been shown to occur with medicines that are administered against the extrapyramidal syndrome. This is why it is advisable to avoid their use, reducing the dose that controls the psychic symptomatology to a minimum level.

Atypical antipsychotic drugs. The number of researches on antipsychotic drugs has greatly increased during the last years, especially about atypical neuroleptic drugs; studies show that there are no results that show an increase of risks for major malformations, either in case of olanzapine, risperidone, quetiapine or clozapine[16]. Some signs of neonatal deficient adaptation rarely occurred in relation to aripiprazole. As for clozapine, there are not teratogenic effects, but some overdose cases showed neonatal deficient adaptation with "floppy infant syndrome". The same as for adults, there is a risk for agranulocytosis.

Olanzapine is associated with major metabolic effects in pregnant women, too, being likely to cause massive weight gains and gestational diabetes, as well as a risk increase for exceeding the gestational age of the new born[17].

Quetiapine has not been shown to have teratogenic or embryotoxic effects. Risperidone and ziprasidone seem to be included in the same category, but the latter has been shown to have some teratogenic effects in animals if administered in similar doses as to humans.

There was no significant difference observed concerning the teratogenic effect in a group of children exposed in utero to the effect of typical antipsychotic drugs compared to a group of children exposed to the effect of atypical antipsychotic drugs and a control group exposed to non-teratogenic medicines. Nevertheless, typical neuroleptic drugs cause a significant decrease of the duration of pregnancy compared to the one of the subjects exposed to non-psychiatric drugs. As for atypical neuroleptic drugs, they cause the occurrence of an increased number of macrosomal fetuses (bigger than the gestational age), consequently to causing the metabolic syndrome in the mother. The number of fetuses bigger than the gestational age represents 20% of the total number of children born by women who take atypical neuroleptic medication, compared to 2-3% in the control lots[18].

The use of atypical neuroleptic drugs without restrictions is limited by the absence of studies or by the small number of clinical trials which could prove their exchangeability.

There is a unanimous opinion that changing the class of neuroleptic drugs during pregnancy can lead to important complications for the patient and the fetus.

In general, the preventive treatment of bipolar depression during pregnancy and postpartum should be initiated only when there is a history marked by major depressive episodes, occurred during postpartum, history of cyclothymia, recurrent depression or bipolar disorder type 1 or 2. Any other previous depressions will require only observation and a possible interpersonal psychotherapeutic intervention[19].

Assessment of maternal capacity

The psychiatrist is often required to assess the capacity of a woman to ensure the care and safety of her child if she is to become a mother or if she gave birth and whether she is capable of taking care of the child outside the hospital.

Generally speaking, this concerns a person who has a history of mental disorders or addictions. In other situations, the obstetrician sends the patient to the psychiatrist because he/she observes a total lack of prenatal controls, lack of a stable home, a confused social and family situation or the unusual behavior of the patient towards the child after she gave birth or towards the therapeutic team. The psychiatrist is required to take a decision whether to continue the course of pregnancy during the prenatal period or to initiate certain measures concerning the newborn and the mother (in women who already gave birth).

Considering there are no therapeutic protocols for such patients, the mission of the psychiatrist is a difficult one, without the possibility of giving a clear answer. The psychiatrist is required to assess the possibilities of progress which the situation of the patient may hold, compared to the possible therapeutic strategies. The most important thing is the safety of the new born child and of the mother, the preservation of mother-child couple and the initiation of a realistic therapeutic strategy relating to the mother's problematic situation. All caregivers, if there are any, must be involved in the therapeutic program with a precise purpose of maximizing it. The mother does not always have the capacity to acknowledge her need for assistance and support. Denial and isolation are always regarded as a problem for the binomial relationship mother-child, but they are also extremely dangerous when the mother has mental or addiction disorders.

In some cases, the psychiatrist is required to assess the capacity of the pregnant woman before she must give birth, especially when she refuses the treatment or wants to leave the hospital upon her request.

The classical scenario is one in which the woman goes through a long period in bed and afterwards she insists on leaving the hospital, claiming a crisis situation suddenly occurred at home. Experience shows that most of these patients decide to stay in the hospital after her fears are invalidated and mostly if they receive psychological support from their families and the medical care personnel. If there is an alternative involving an outpatient treatment facility, the pregnant woman will be encouraged to return as soon as possible in the hospital for her obstetric problems.

In all situations, the assessment of the present status and the initiation, continuation or interruption of treatment for psychotic disorders will be made on an individual basis. ■

Therapeutic recommendations for obstetricians dealing with women diagnosed with psychiatric disorders
Make a depression screening of pregnant women, using a standard instrument, such as Edinburgh Postnatal Depression Scale, which can be used in pregnancy, too. The scale was introduced in 1987 by Cox J.L., Holden J.M., Sagovsky R. and can be used with maximum safety.
Coordinate your care with the psychiatric service, especially for women with recurrent or complex psychiatric disorders or psychiatric disorders associated with comorbidities.
Whenever it is possible, add non-pharmacological therapies, such as cognitive-behavioral therapy, interpersonal therapy, support groups or stress management.
Evaluate the risk of psychotropic medications related to the risk of untreated psychiatric disorder, especially when there are significant side effects during pregnancy.
Acknowledge the fact that for some patients with severe or moderate disorders, pharmacotherapy is still the most adequate treatment for preventing relapses.

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