

## PREGNANCY AND PSYCHOPHARMACOTHERAPY

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### ABSTRACT

Pregnancy, a natural and developmental process for women, is a special period of both onset and exacerbation of psychiatric disorders, bringing up with many psychological problems, as well. High incidence of psychiatric disorders in women of childbearing years gives rise to the confrontation of psychiatrists with such situations.

**Key Words:** Pregnancy, psychopharmacology, teratogenicity.

### INTRODUCTION

Pregnancy, a natural and developmental process for women, is a special period of both onset and exacerbation of psychiatric disorders, bringing up with many psychological problems, as well. Though a specifically defined psychiatric disorder is not correlated with pregnancy and differentiation does not exist between pregnant women and non-pregnant women in terms of prognosis, "pregnancy and psychopharmacotherapy" is a special area of interest in psychiatry in relevance to physiological changes associated with pregnancy. The increase of the sensitivity of both the mother and the fetus to psychotropic agents, the neuroendocrine and behavioral effects of many psychotropic agents on the newly developing brain of the fetus and also the negative outcomes of untreated psychiatric disorders on both mother and fetus highlight the essentiality of the management of psychiatric disorders associated with pregnancy, that is highly unique and complex (Miller 1994a). High incidence of psychiatric disorders in women of childbearing years gives rise to the confrontation of psychiatrists with situations (Gelder 1996).

In the management of a pregnant women with a serious psychiatric disorder psychiatrist comes face to face with a dilemma. On one side the difficulty in treating the patient without any medication at all and on the other side the potential risks that the exposed fetus is vulnerable to many unwanted effects such as teratogenicity in the organogenetic sense, behavioral teratogenicity and side effects on the

newborn maintain the basis of this dilemma (Hawkins 1987). The most common situations encountered in psychiatric clinics are: 1) new-onset exacerbation of a pre-existing psychiatric disorder during pregnancy; 2) pre-pregnancy consultation of women with pre-existing psychiatric disorder or currently on psychotropic medication; 3) undesired conception during treatment with psychotropic medication (Cohen 1989).

In spite of the fact that an absolute consensus is not held among the psychiatrists about the psychiatric treatment of a pregnant woman, experience over many years lead the psychiatrist to a conservative approach, i.e. not to recommend psychotropic medication during pregnancy because of the potential risks on the newly-developing fetus. If the symptoms of the patient are of short duration and not severe enough to take the potential risks of any kind of medication, nonmedical treatments are recommended first such as psychotherapy, environmental manipulation and family therapy; especially many psychiatric disorders as mild or moderate depressive disorder, anxiety and sleep disorders can be managed well with psychotherapeutic approaches. Occasionally those nonmedical treatment strategies are beneficial in delaying the necessity of medical treatment till postpartum periods so that the negative outcomes on the fetus is minimized. Although the incidence of the psychiatric disorders during pregnancy is not dramatically high, some women experience their first psychotic or depressive episode during pregnancy. The relapse rate of psychosis is also found to be high during pregnancy (Hauser 1985). In case of severe depression, mania or psychosis hospitalization is a necessity for the safety of both the mother and the fetus. In patients with severe

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psychiatric disturbance, psychotropic medication may be required. In this case, more established drugs of older generation are preferred to newer ones. The drugs are initiated with lowest possible dose and increased in small increments.

In previous reviews, it is well documented that eighty percent of pregnant women were prescribed medications and more than one-third of them might have taken psychotropic medication at some time during their pregnancy (Cohen 1992). This high ratio presents the importance of establishing some basic principles in the management of psychiatric disorders occurring during pregnancy. In the necessity of psychotropic medication the safest approaches must be undertaken, the side effects of the drugs should be considered, the family should be informed about the risk to benefit ratio and psychiatrist should update his knowledge about the issue. In the choice of psychotropic medication within a given class it has been suggested to consider the potential toxic effects of various drugs in somatic and neuro-behavioral basis and the physiological changes during pregnancy for both mother and fetus. Several changes occur during pregnancy that may alter serum concentrations of psychotropic medications. Decreased protein-binding capacity and decreased gastrointestinal motility result in an increase in serum free drug concentration where as increased volume of distribution and increased glomerular filtration rate result in decreased serum concentrations for a given dose. However, with the exception of the tricyclic antidepressants, a clear relationship between therapeutic response and serum concentrations has not been established (Kerns 1986). All of these changes potentially affect the drug concentration which the fetus may be exposed to. Although the fetus and the mother are at equilibrium with respect to circulation, fetus has several different physiological attributes: 1) increased cardiac output, 2) increased blood brain barrier permeability, 3) decreased plasma protein and plasma protein-binding affinity and, 4) decreased hepatic enzyme activity. The net effect of these differences is an increase in the exposure of fetal central nervous system to medications (Stouder 1987).

With regard to the risks of psychotropic medication during pregnancy, gross anatomical damage is formed within the first trimester when organogenesis takes place. Although it was believed that the se-

cond trimester was not a period of risk regarding to psychotropic medication until the recent years, studies showed that second trimester is a period of rapid fetal central nervous system development (Kandel 1995, Harris 1995, Martin 1996, Yudofsky 1997, Zigmond 1999) and higher cortical areas and limbic system are more vulnerable to the toxic effects of the drugs (Robinson 1986). During the third trimester, toxicity occurs as a result of the failure of fetal liver and kidney to metabolize the drugs (Mortola 1989). Although the mortality and morbidity of untreated psychiatric disorder during pregnancy is not clearly documented, the presence of a psychiatric disorder leads to certain risk for both mother and the baby. Anorexia and failure in reality testing may result in malnutrition. A delusional mother may try to stop the pregnancy by abortion in many (and not rarely, dangerous) ways. As a result of auditory hallucinations and commanding voices she may attempt to kill or damage the baby. A drug abusing mother has a risk of damaging both herself and the baby because of nutritional deficiency and impairment of general health. In addition to this, the majority of pregnant women are not aware of their pregnancy for at least 6 weeks; hence, discontinuation of psychotropic drug may occur after the period of greatest risk to the fetus (American Psychiatric Association 1994). Such discontinuations may also carry an increased risk of relapse that may result in an increased risk to the mother. So psychotropic medication is warranted if the functional impairment is sufficient enough to preclude a woman's participation in prenatal care. Another area of concern is the potential negative impact of the neuroendocrine alterations associated with certain psychiatric disorders as depression and anxiety. Altshuler et al (1996) used a MEDLINE search of all articles written in English from 1966 to 1995 to review information on the effects of psychotropic drug use during pregnancy on fetal outcome. Where sufficient data were available and when methodologically appropriate, meta-analyses were performed to assess risk of fetal exposure by psychotropic medication class. Three primary effects were associated with medication use during pregnancy: 1) teratogenicity, 2) perinatal syndromes (neonatal toxicity), and 3) postnatal behavioral sequelae. For many drug classes there are substantial data regarding risk for teratogenicity. Tricyclic antidepressants did not seem to confer increased risk for organ dys-

genesis. The available data indicated that first-trimester exposure to low-potency phenothiazines, lithium, certain anticonvulsants, and benzodiazepines may increase the relative risk for congenital anomalies. However, the absolute risk of congenital malformations following prenatal exposure to most psychotropics was low. They concluded that exposure to certain psychotropic drugs in utero may increase the risk for some specific congenital anomalies, but the rate of occurrence of these anomalies even with the increased risk remains low. Use of psychotropic medications during pregnancy is appropriate in many clinical situations and should include thoughtful weighing of risk of prenatal exposure versus risk of relapse following drug discontinuation. The authors presented disorder-based guidelines for psychotropic drug use during pregnancy and for psychiatrically ill women who wish to conceive.

### **PSYCHOPHARMACOTHERAPY OF DEPRESSION DURING PREGNANCY**

Many recently performed studies suggest an increased rate of depression during pregnancy as high as 10-20% (Schatzberg 1995). Elective abortion, ambivalence about pregnancy and bereavement are accepted as risk factors predisposing and precipitating depression during pregnancy. Although there is a partial increase in women experiencing depression during pregnancy, pharmacotherapy is not always needed. Within the first trimester many women complain about minor depressive symptoms consistent with adjustment disorder. Supportive therapy with reassurance and minimizing environmental stressful stimuli are quite beneficial for these patients. Pharmacotherapy is suitable for severe depressive disorders characterized by neurovegetative dysfunction as insomnia and anorexia.

Tricyclic antidepressants (TCAs) are the most extensively studied group in terms of the effects of psychotropic medication during pregnancy. Early reports in 1970s suggested that administration of TCAs in the first trimester of pregnancy was associated with some abnormalities, especially limb reduction deformities (Wood 1981). Subsequently, various large-scale studies failed to identify any link between TCAs and congenital malformation (Wisner 1993). The effect of TCAs on the developing central nervous system of the humans is not known but in one

study 23 children were followed until the age of 2 years after in utero exposure to TCAs and neurobehavioral abnormalities of any kind could not be identified (Jacobson 1996). But, still it is recommended that this class of medication should be avoided in the first trimester. During the final six months of pregnancy the TCAs are considered to be relatively safe. As TCAs cross the placental barrier easily, the developing fetus is vulnerable to the anticholinergic side effects. Practice and Brown showed that TCAs lead to fetal tachycardia (Prentice 1989). Thus, the less anticholinergic compounds as nortriptyline and desipramine (not available in Turkey yet) are recommended for pregnant women needing somatic treatment for depression (Birsöz 1994). After delivery, the neonate does not have the maternal circulation to metabolize drugs so, a toxicity characterized by cyanosis, irritability, respiratory distress can be observed in neonates. In addition, a tricyclic withdrawal syndrome has been described consisting with above mentioned symptoms (Misri 1991). So it is recommended to withdraw the TCAs several weeks before the delivery in order to minimize the anticholinergic side effects. If necessary, the antidepressants may be reinitiated after the delivery. However, Wisner reported that the TCA dosage requirement for women with depression during pregnancy may increase over the course of pregnancy to maintain adequate therapeutic serum concentrations (Wisner 1988). Overall, current evidence indicates that TCAs and fluoxetine do not present a significant risk of anomalous development (Bernstein 1995).

There are limited human data on the use of monoamine oxidase inhibitors (MAOIs) during pregnancy but MAOIs are known to be teratogenic in animals. One study indicated that in utero exposure to tranylcypromine was associated with fetal malformation. Because of the risk of hypertensive crisis and the availability of safer alternatives, MAOIs are not used during pregnancy (Guze 1989). There are limited data on the use of selective serotonin reuptake inhibitors during pregnancy. One study of first trimester exposure to fluoxetine (mean dose 25.8 mg/day) did not demonstrate an increase in fetal anomalies in 128 women. In this study the rate of spontaneous abortion in the subjects was 14.8% compared to 7.8% in the control subjects. In comparison with TCAs, the results were not significantly different with regard to spontaneous abortion (pas-

tuszak, 1993). Other studies also indicate that fluoxetine is a safe drug during pregnancy-even in the first trimester, if taken accidentally (Bernstein 1995, Goldstein 1997, Nulman 1997). Sertraline and its main metabolite desmethylsertraline were present in the breast milk of nursing women treated with sertraline. Concentrations were affected by aliquot of milk sampled, time after maternal dose, and maternal daily dose. The infants' serum concentrations detected were below the detection limit of most commercial laboratories (Stowe 1997). To our knowledge, no human data have been published on other antidepressants such as bupropion, trazodone, nefazodone and venlafaxine.

As a result, non-pharmacological approaches in addition to hospitalization and supportive therapy are regarded as the first choice in management of depressive pregnant women. If somatic treatment is of inescapable necessity. TCAs as nortriptyline or desipramine are recommended for the second and third trimester. In order to avoid the side effects on the newborn, TCAs should be gradually withdrawn. In case of severe depression with suicidal thoughts and nutritional and physical deterioration, electroconvulsive therapy (ECT) should be considered first since such conditions require more rapid therapeutic response.

### **PSYCHOFARMACOTHERAPY OF BIPOLAR DISORDER DURING PREGNANCY**

Bipolar disorder has a mean age of onset in the early twenties coinciding the childbearing years. Bipolar women need to be informed about both the fetal anomaly risk of the psychotropic medication and manic decompensation risk when the somatic treatment is withdrawn. It is recommended that the psychotropic medications should be withdrawn several weeks before conception (at least six weeks if the drug is fluoxetine). When a woman taking lithium unknowingly gets pregnant, the drug should be gradually discontinued as abrupt withdrawal is associated with manic relapse. With early and mild relapse, hospitalization, reduction of environmental stimuli and elimination of exacerbating stimuli may limit the deterioration of the symptoms. If the symptoms worsen, low dose of antipsychotics are used in order to prevent the deterioration and sedate the patients. A benzodiazepine as diazepam may

reduce the total required dose of either medication used alone. If the patients is not stabilized with these approaches then lithium may be started during the second trimester (Sitland-Marken 1989).

For women using lithium in the first trimester, fetal ultrasonography should be performed at the 18<sup>th</sup> week of pregnancy in order to rule out any cardiac malformation (Cohen 1994). Literature suggests that 50% of infants with Ebstein's anomaly die in the first week of life (Shou 1990). If lithium is a necessity then it must be administered in small and divided doses to decrease the toxicity risk associated with peak serum levels. In the second trimester higher doses of lithium may be necessary as the glomerular rate increases in the mother. Minimal effective serum levels should be maintained. The dosage should be decreased by at least 50% at the delivery time to get rid of toxicity due to abrupt falls in renal filtration rates. In western countries about 0.1% of population receive lithium as a maintenance therapy for bipolar disorder life (Shou 1990). Early studies stated that increased incidence of Ebstein's anomaly and other cardiac malformations were related to in utero exposure to lithium (Suppes 1991). One of the most recent studies suggest a risk of 0.1% for Ebstein's anomaly. The risk for any congenital abnormality in lithium exposed infants was estimated to be between 4-12 which is 2-3 times greater than that in untreated group (Yüksel, 1984). However, first-trimester lithium teratogenic effects had been overestimated in the earlier studies and that the risks of stopping lithium in some patients outweighed the risk of birth defects (Cohen 1994). In the last trimester lithium effects the thyroid gland of the fetus causing goiter. With an insulin-like effect on carbohydrate metabolism, lithium leads to macrosomia. Premature delivery and increased perinatal mortality are known as potential complications. As neonates exhibit decreased renal clearance, the half-life of lithium is generally prolonged, resulting in toxicity characterized by hypothermia, bradycardia, cyanosis and lethargy and may last for up to seven days after delivery. In a Scandinavian study of lithium exposed children born without any physical malformations and reached the age of 5 years, no significant neuro-behavioral differences were found in comparison with unexposed but genetically similar siblings (Shou 1976). This study does not rule out the possibility of behavioral teratogenity in humans but if

present the changes are subtle. As a result, it is not that clear whether in utero exposure to lithium increases the risk for behavioral or affective abnormalities in later life. Despite these risks, lithium is still regarded as the safest mood stabilizer available. In one study the risk for spina bifida associated with fetal exposure to carbamazepine was found to be 1% (Rosa 1991). Correlation with in utero exposure to carbamazepine and craniofacial abnormality was 11% whereas developmental delay 20% and digital hypoplasia 26%. Similarly valproic acid is a known teratogenic drug for humans, with a 1%-2% risk of neural tube defects (Liindhout 1986) and this can be reduced by adding folate to the drug regimen if the continuation of the drug outweighs the discontinuation. In a study carried out by Briggs et al (1994), the most common potential complication of in utero exposure to valproic acid was found to be intrauterine growth retardation.

### **PSYCHOPHARMACOTHERAPY OF SCHIZOPHRENIA DURING PREGNANCY**

Women with schizophrenia are at high risk for exacerbation during pregnancy. For each month medication is withheld, approximately 10% of the schizophrenics relapse (Nurnberg 1984). It has been estimated that approximately 65% of schizophrenics and 26% of those maintained on psychotropics relapse during pregnancy (Spielvogel 1986). Schizophrenia is the most difficult psychiatric disorder to deal with during pregnancy. Somatic changes associated with pregnancy are generally misinterpreted and distorted. Psychotic denial of pregnancy worsens the compliance to the prenatal care. If the pregnancy is confirmed and the patient is stable, it is recommended not to use psychotropics during the first trimester and watch for the first signs of any psychotic symptom. Women experiencing their first psychotic episode during pregnancy should be evaluated to rule out reversible organic causes. Hospitalization may be needed to maintain compliance with prenatal care. High-potency neuroleptics as perphenazine or haloperidol and antiparkinsonian agents should be given in minimal effective dose. Complete amelioration of symptoms is not taken as the target of the treatment since maintaining a self-care is accepted as more realistic achievements during pregnancy.

In contrast to other classes of psychotropic medications, antipsychotic agents have considerably larger database that addresses concerns of neurobehavioral teratogenicity (Elia 1987). Animal studies have not demonstrated teratogenicity with the use of neuroleptics in the period of organogenesis even when used in toxic doses. Early studies studying the children exposed to neuroleptics before 10 weeks of gestation suggested an increase with regard to congenital anomalies when compared to unexposed controls. But, many factors such as maternal age, gravidity, previous miscarriage, pregnancy complications, polypharmacy were not considered. More contemporary studies including prospective studies of tens of thousands of women exposed to neuroleptics in the first trimester do not support an increased rate of malformation (Hill 1979). More important than the teratogenic effects of neuroleptics is the existence of some side effects of neuroleptics as neuroleptic malignant syndrome and extrapyramidal syndromes (EPSs). Like TCAs, neuroleptics cross the placenta easily. Extrapyramidal symptoms as hypertonicity and tremor are seen in the neonates of the mothers taking neuroleptics at the time of delivery. Increased muscle rigidity and tendon reflexes may last about 1 month in the neonates (Calabrese 1985). In addition, newborn of the mothers taking low-potency neuroleptics during the delivery, tachycardia, urinary retention can be observed (Hill 1979). In the pregnant women using neuroleptics, gradual discontinuation of drugs 5-10 days before the delivery can minimize such complications. Although several animal studies have demonstrated that prenatal exposure to antipsychotic medications can cause persistent abnormalities in learning and memory, human studies do not present with similar results with regard in the long term behavioral consequences (Miller 1991). In one study of 14 children exposed to antipsychotics in utero, memory or learning deficits of any kind was not detected by the age of 4. Little is known about the safety of atypical neuroleptics as clozapine and risperidone yet, so it is recommended not to prescribe these drugs during pregnancy (Calabrese 1985) but some recent articles do not show any evidence of increased risk of fetal abnormality in pregnant women taking clozapine (Kaplan 1995).

Prophylaxis EPSs is not recommended. The most widely studied drug in this respect is diphenhydramine. A relation between in utero exposure to dip-

henhydramine during pregnancy and major and minor anomalies was found (Miller 1991). Although not regarded as absolute teratogens, anticholinergic agents should be prescribed only when needed during pregnancy and they should be withdrawn as early as possible to avoid the side effects on the newborn. Finally, although the congenital and neurobehavioral side effects of neuroleptics are regarded as minimal, still they should be avoided during the first trimester as other psychotropics.

### **PSYCHOPHARMACOTHERAPY OF ANXIETY DURING PREGNANCY**

Anxiety disorders that are quite common in women tend to increase during the childbearing years. Before it was thought that in patients with previous anxiety, anxiety is minimized during pregnancy but more recent literature contradicts that assumption. For example several studies have associated the onset of obsessive-compulsive disorder with pregnancy (Brandt 1987). Also it has been stated that symptoms of panic disorder are worsened especially in the last trimester of pregnancy. So anxiety disorders are regarded as exacerbating during pregnancy. Many studies showed that women with mild or moderate anxiety symptoms during pregnancy confront with more complications as preterm labor, preeclampsia, stillbirth and fetal hypoxia. Those complications are related to the increases of catecholamine secretion which in turn result in vasoconstriction of the fetoplacental unit.

The main target of managing anxiety symptoms during pregnancy should be to minimize the risk to the mother and the fetus. Before pharmacological interventions, behavioral techniques as progressive relaxation and biofeedback are recommended. Those techniques in addition to supportive therapy may both prevent the need for medication and if medication is needed, minimize the amount required.

A recent retrospective study of 104339 women found out that at least 2% had received one or more prescriptions for a benzodiazepine. Benzodiazepines cross the placenta easily and the presence of benzodiazepines in the umbilical cord plasma demonstrate that those drugs accumulate in the fetus after prolonged administration (Bergman 1992). Whitelaw (1981) has stated that in contrast to concentrations of other benzodiazepines studied, lora-

zepam concentration were lower in cord blood than in maternal serum. Quite little is known about the effects of lorazepam, alprazolam or clonazepam on the developing fetus. The most studied drug is diazepam. Increased rates of oral clefts in infants exposed to diazepam in utero were reported in 1970s (Shiano 1984). However several other studies failed to demonstrate an increased risk or craniofacial or other malformation even with the first trimester, despite the increased use of benzodiazepines over the last years, a concomitant increase in the incidence of malformation could not be confirmed. Clonazepam was found to have minimal teratogenic risks in one study performed by Sullivan and his friends (1977).

One group has described a "benzodiazepine exposure syndrome" for infant exposed in utero to benzodiazepines that included growth retardation, dysmorphism and both mental and psychomotor retardation (Bergman 1992). Although the data on the teratogenic effects of fetal exposure to benzodiazepines remain controversial, the presence of infant withdrawal syndromes has been described by several groups and symptoms can persist for as long as 3 months. Although the literature suggests that the use of benzodiazepines in the second and third trimester, cord plasma concentrations in the fetus may become greater than in the maternal circulation with the prolonged administration of benzodiazepines, especially with diazepam and oxazepam bypass hepatic metabolism and may therefore have less potential for accumulation in the neonate (Bergman 1992). Pregnant women should be informed that even with early exposure to benzodiazepines, the risk of cleft malformation is approximately 0.4% (Laegreid 1989). As with all drugs, benzodiazepines should be withheld in the first trimester of the pregnancy or at least until after the 10<sup>th</sup> week of gestation when plate closure is completed. It is recommended that benzodiazepines should not be abruptly withdrawn during pregnancy and that if at all possible these drugs be tapered sufficiently prior to delivery to limit neonatal withdrawal. If psychotropic medication is needed in the first trimester, a TCA as nortriptyline is recommended in panic disorder. If it is a necessity to use a benzodiazepine, the smallest effective dose and shortest amount should be given and the drug must be gradually tapered and discontinued a week before the delivery.

**Teratogenic risks of psychotropic medications are as follows (Schatzberg 1997)**

Class	Drug	Risk Category*	Possible Effects
Anxiolytics	Benzodiazepines	D	"Floppy baby", withdrawal, cleft lip
	Hypnotic benzodiazepines	X	Decreased intrauterine growth
Antidepressants	Buspirone	C	Unknown
	TCA's	C/D	Fetal tachycardia, fetal withdrawal, fetal anticholinergic effects, urinary retention, bowel obstruction
MAOIs		C	Rare fetal malformations, fetal withdrawal, rarely used in progeny due to hypertension
SSRIs		B	Increased perinatal complications
Antipsychotics	Classic	C	Rare anomalies, fetal jaundice, fetal anticholinergic effects at birth
	New generation, clozapine, olanzapine, risperidone	B/C	Unknown
Mood stabilizers	Lithium	D	Behavioral effects
	valproate	D	Neural tube defects
	carbamazepine	C	Neural tube defects, minor anomalies

\* U.S. Food and Drug Administration use-in-pregnancy risk categories:

A: Controlled studies show no risk to humans. B: No evidence of risk in humans, but adequate human studies may not have been performed. C: Risk can not be ruled out. D: Positive evidence of risk to humans; risk may be outweighed by potential benefit. X: Contraindicated in pregnancy.

### ECT AND PREGNANCY

ECT is an excellent therapeutic alternative when psychotropic medications have failed or are contraindicated. ECT is considered to be the first-line treatment in pregnant women requiring a rapid therapeutic response. Studies suggest that ECT is quite safe for women in any stage of pregnancy (Wise 1984). Mortality associated with ECT is less than that is observed for inadequately treated depression during pregnancy (especially suicide). The ECT complication rate of 5-6% is less than that for untreated pregnant psychotic women and pregnant women without psychiatric disorder (Miller 1994b). Finally, the rate of miscarriage in the general population is considerably higher than that is observed in pregnant women undergoing ECT, suggesting that ECT does not increase the likelihood of miscarriage. Since the muscles of uterus are not stratified, ECT does not have a direct effect on the womb but after 7-8 months' of gestation, the tonic-clonic contractions may induce labor.

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