DOI: 10.5455/jmood.20110902072926

A Challenging Issue: Should Medications be Prescribed to Pregnant and Depressed Women?

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ÖZET:

Dikkat çekici bir konu: Hamile ve depresyondaki kadınlara ilaç önerilmeli mi?

Erkeklere kıyasla kadınlar daha fazla depresyon yaygınlık oranlarına sahiptir ve özellikle doğurganlık çağında depresyona daha da duyarlıdırlar. Depresyon oranları gebelik dönemindeki kadınlar için %20'lere kadar ulaşabilir. Aslında kadınları tedavi eden bir klinisyenin, kendisini annenin ve bebeğin gelişiminin korunması için en uygun yöntemi seçmeye çalışırken bulması oldukça muhtemeldir. Emniyet konuları ve doğumla ilgili olumsuz sonuçlar gebelikte antidepresan kullanımı ile ilgili başlıca endişe alanlarıdır. Diğer taraftan, tedavi edilmemiş depresyon da anne ve bebek için sağlık komplikasyonlarına yol açma potansiyeline sahiptir. Ancak gebelikte antidepresan kullanımının muhtemel yan etkilerinin daha fazla vurgulandığı ama tedavi edilmemiş depresyonun o kadar önemsenmediği aşikardır. Halihazırdaki çalışmalar gebelik sırasında antidepresan kullanımının emniyetli olup olmadığına dair çelişkili sonuçlar ortaya koymaktadır dolayısıyla da mevcut verilerin yorumlanması çok dikkatli bir şekilde yapılmalıdır. Ebeveynlerle birlikte karar verirken her iki seçeneğin de riskleri ve faydaları göz önüne alınmalıdır.

Anahtar sözcükler: Gebelik, antidepresan emniyeti, teratojenite, tedavi edilmemiş depresyon

Journal of Mood Disorders 2011;1(3):118-25

ABSTRACT:

A challenging issue: Should medications be prescribed to pregnant and depressed women?

Women have higher prevalence rates of depression than men and they are particularly vulnerable to depression in childbearing years. The rates of depression can reach up to 20% of all women during pregnancy. Actually, physicians who treat women are likely to find themselves trying to choose the best option for protection of the mother and for the development of her child. Safety issues and negative birth outcomes are matters of concern with antidepressant use during pregnancy. Otherwise, untreated depression also has potential to cause health complications for both mother and infant. It is obvious that possible adverse effects of antidepressant use during pregnancy are more emphasized but adverse outcomes of untreated depression are underrated. Currently, studies exhibit conflicting results about antidepressant safety in pregnancy period so current data must be cautiously interpreted. The risks and benefits of both options must be taken into account in decision-making process with families.

Key words: Pregnancy, antidepressant safety, teratogenicity, untreated depression

Journal of Mood Disorders 2011;1(3):118-25

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Kabul tarihi / Date of acceptance: 2 Eylül 2011 / September 2, 2011

Bağıntı beyanı: N.A., E.O., M.G.: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

Declaration of interest: N.A., E.O., M.G.: The authors reported no conflict of interest related to this article.

INTRODUCTION

Pregnancy and medical treatment have always been a concern in both medical and public minds. Health professionals engaged in women's healthcare quite often struggle with the decision to find the best option. Pregnancy represents a time of high risk for exacerbation of mental illness in particular. 10% to 15% of women in the reproductive period experience depression during pregnancy and the postpartum period (1). Though treatment of depression during pregnancy often has been debated, antidepressant use during pregnancy was accepted as relatively safe prior to 2005, when FDA released the warning about Paroxetine. In September 2009, Glaxo Smith Kline was punished with a $2.5 million fine to be paid to parents of a boy born with a cardiovascular disease following in utero exposure to Paroxetine. This outcome has skyrocketed the worries about the usage of antidepressant drugs by pregnant women. The discussion focuses especially on safety, birth outcome, health complications, and developmental effects of antidepressant drugs. Those who do not recommend antidepressant treatment emphasize the negative findings of studies on infant development and maternal health. On the other hand, if medication treatment is necessary and not offered, are not there risks? Untreated depression also

has negative consequences on birth outcome, infant and mother health and development. So a depressed pregnant woman and her baby should be kept in mind. Case reports and some research referenced by opponents of antidepressant use not only have conflicting results but also have some methodological problems. Correct interpretation of data and consideration of the possible risks are essential to provide appropriate therapeutic intervention for depressed and pregnant women.

Opponent Arguments About Antidepressant use During Pregnancy

The potential risks attributed to antidepressant use during pregnancy are risk of organ malformation or teratogenesis, risk of fetal loss or miscarriage, risk of neonatal toxicity or withdrawal syndromes during the acute neonatal period, and risk of long-term neurobehavioral sequelae (2).

The first Tricyclic Antidepressants (TCA) was marketed in 1958. Early reports about the antidepressant teratogenicity included a child with limb deformities who had been exposed in utero to TCA (3). This case was caused widespread fear of antidepressant use in pregnancy and drew attention to the teratogenicity of antidepressants for the first time. Recently, Selective Serotonin Reuptake Inhibitors (SSRI), relatively newer and more commonly prescribed antidepressants, also have been investigated. Recent studies have indicated an increased prevalence of congenital malformations, for example anencephaly, omphalocele, craniosynostosis, and more consistently heart defects (4,5). Some research has suggested an increased risk of heart defects, especially with Paroxetine but also Sertraline, Fluoxetine, and Citalopram. Sertraline has been found to be related to right ventricle outflow obstruction (5). Paroxetine has been associated with increased risk for cardiac defects, especially atrial and ventricular septal defects. (6). According to this study, increased risk for major malformation is 1% over the baseline risk and for cardiac defects is 2% over. Based on these findings, Paroxetine has been labeled as risk category D (there is evidence of risk in human but the drug may have benefits that outweigh the risk) from C (animal studies show risk but there are no controlled studies in humans; or studies in animals and humans are not available) by the FDA (Food and Drug Administration). A recent study from Finland provides more evidence that exposure to selective serotonin reuptake inhibitors (SSRIs) in the first trimester of pregnancy increases the risk for major congenital anomalies, particularly cardiac defects (7). In the study, use of Fluoxetine in early pregnancy was associated with about a 2-fold increased risk for isolated ventricular septal defects, whereas Paroxetine was associated with more than a 4-fold increased risk for right ventricular outflow tract defects. In this study, Malm et al. noted that the absolute risk for these specific cardiac anomalies is small: 0.5% and 0.2%, respectively, and they suggested that "clinicians not to consider Fluoxetine or Paroxetine as the first option when prescribing an SSRI to women planning pregnancy."(7).

The second attributed risk of antidepressant use during pregnancy deals with the outcome of the pregnancy. Some studies have reported an increased rate of spontaneous abortions in the antidepressant-exposed groups compared with the nonteratogen-exposed groups. A small but statistically significant risk of low birth weight and premature birth also has been reported. Neonatal symptoms related to antidepressant use during late pregnancy have been observed such as respiratory distress, jitteriness, hypoglycemia, irritability, increased REM sleep, hypotonus, and rarely seizure and cardiac rhythm anomalies (8-10). Recently attention has focused on Persistent Pulmonary Hypertension (PPH) associated with exposure to SSRIs after 20 weeks of pregnancy (11).

The third argument against the use of antidepressants during pregnancy is the potential for long-term neurodevelopmental abnormalities, including cognitive and language impairment and behavioral teratogenesis. Some scientists say, "we always predicted that developmental exposure to these drugs would have some deleterious effects.'' (12). A study on birth outcomes and postnatal neurodevelopment function between ages 6 and 40 months found that lower APGAR scores and lower motor development scores in infants exposed to SSRIs compared with non-exposed children (13). An attenuated response to heel prick pain has also been shown in infants with prenatal SSRI exposure compared with unexposed infants (14). Animal research has shown that early exposure to SSRIs produces selective behavioral changes in adult rats, including increased locomotor activity and decreased sexual behaviour (15). A recent article published in the Archives of General Psychiatry reported an

association between autism and maternal SSRI use during pregnancy. The authors conducted a case controlled study of a Kaiser Permanente database. They reported a greater risk of autism spectrum disorders among children of SSRI users compared to non-users during pregnancy (16).

Rebuttals to Arguments Against Antidepressant use During Pregnancy

Teratogenicity is described as congenital abnormalities or organ malformations that occur over the population baseline rates. The baseline risk of congenital abnormality is 1-3% for general population (17). Since first data about teratogenicity of TCA use, 3 prospective and more than 10 retrospective studies have been conducted on first trimester TCA use (18-21) and none of them reported congenital abnormalities were over baseline.

SSRIs have been reported as causative factor for congenital malformations. The best-studied SSRI, Fluoxetine, has been examined with 5 recent prospective and 4 retrospective studies (18,22-26). Data obtained over 2500 case (531 first trimester) could not find any increased risk above the 1-3%. Recently some SSRIs, especially Paroxetine, have been associated with increased risk with cardiac defects. Data about Paroxetine have been based on a retrospective cohort study conducted by manufacturer of Paroxetine, GSK (6). According to this study, increased risk for major malformation is 1% over the baseline risk and for cardiac defects is 2% over. However, this study has some limitations including retrospective design, use of post-hoc analyses to obtain the adjusted odds ratios for cardiovascular malformations and congenital malformations, lack of matched control group, and limited clinical data such as severity of depression (21). Other studies about Paroxetine did not confirm those findings (27, 28). SSRIs have only been associated with cardiac abnormalities in retrospective studies. Some case reports and epidemiological studies for other SSRIs and another group of antidepressants also did not find any association for increased risk (27,29-31). Two landmark large-scale case-control studies demonstrated that overall SSRI exposure was not associated with congenital cardiac or a majority of other categories of birth defects. Current data on SSRI exposure, including Paroxetine, show no consistent information to support specific morphological teratogenic risks. Most recently, Malm et al. issued a warning about Fluoxetine and Paroxetine saying it, "should not be a first option in women planning to become pregnant." Authors also claimed, "For individual SSRIs, Fluoxetine and Paroxetine were associated with an increased risk for overall major congenital anomalies and cardiovascular anomalies in the crude analysis, but the risk did not remain statistically significant after adjusting for confounding factors." (7). Also, a large number of comparisons might have resulted from the possibility that some of the observed associations might reflect variation by chance. Though there are conflicting results, none of congenital abnormalities attributed to antidepressants have been reported in prospective controlled studies and meta-analysis of these studies. Therefore, reports about teratogenicity of antidepressants during pregnancy must be cautiously evaluated.

The available literature points to an increased risk of negative birth outcomes and neonatal complications. Some studies have reported an increased rate of spontaneous abortions in the antidepressant-exposed groups compared with the nonteratogen-exposed groups. However, these rates of spontaneous abortions have not exceeded the reported 10-20% baseline rate in the general population (18). Although a small but statistically increased risk of low birth weight and premature birth has also been reported, only 1 week early birth has been observed in women who were exposed to antidepressants late in pregnancy. A one-week premature delivery is acceptable even if connected with other pregnancy problems. Neonatal symptoms attributed to antidepressant use during late pregnancy have been described as transient (starting with minutes and limited to several days following delivery), mild and usually not requiring clinical intervention (14). Recently attention has focused on Persistent Pulmonary Hypertension associated with exposure to SSRI after 20 weeks of pregnancy. Though there have been conflicting results, the reported risk is about 1% of this severe but rare complication (11).

There is a limited amount of data regarding the long-term effects temperament, behavior, reactivity, mood, distractibility, and activity level among groups when followed through early childhood. No difference has been detected in behavioral or cognitive development in children exposed to Fluoxetine, TCAs or without medication, in terms of IQ, language, temperament,

behavior, reactivity, mood, distractibility, and activity level among groups when followed through early childhood (27,32,33). Some studies of post-birth development of children exposed in utero to SSRI have been published. All converge on the finding that mental development (on the Bayley Scales of Infant Development) was found to be similar in exposed compared to non-exposed children. A slight delay (within normal limits) of achievement of motor milestones in children exposed during gestation to SSRI has been reported, but no differences have been observed between the exposed and control groups at 19 months (13). Although some animal studies have showed that early exposure to SSRIs might disrupt the normal maturation of the serotonin system and could alter serotonin-dependent neuronal processes, it is not known whether these effects are also seen in humans. A recent article published in the Archives of General Psychiatry reported an association between autism and maternal SSRI use during pregnancy (16). The authors included diagnoses of autism spectrum disorders, maternal lifetime psychiatric history, and SSRI and other antidepressant prescriptions dispensed during pregnancy in the analyses. Maternal depression symptoms and burden of illness during pregnancy have not been evaluated. It is not clear whether the mothers maintained antidepressant treatment or not. Therefore, these data are limited. Further, more definitive investigation into the long-term neurobehavioral effects of prenatal exposure to antidepressants is required.

The Other Side of The Coin

For the sake of protecting the infant and mothers, many physicians and mothers immediately discontinue the antidepressant treatment as soon as the conception has been noticed. Abrupt discontinuation of antidepressants may cause withdrawal syndrome which characterized with nausea and vomiting, diarrhea, diaphoresis, hot or cold flashes, tremors, excess lacrimation, syncope, anxiety, panic attacks, low energy, fatigue, and mood swings (30). Most critically, sudden discontinuation of antidepressants has been associated with relapse of the underlying psychiatric condition (34). Relapse risk is 5 times higher in women with recurrent or resistant depression who have stopped antidepressant treatment during pregnancy (35). Moreover, many people believe that pregnancy has a protective and curative effect on depression. Pregnancy does not have a protective effect (35) therefore; it means that both mother and infant will be exposed to the negative influences of untreated depression. What are the consequences, if a pregnant woman has been untreated? It is well known that especially chronic and repetitive stress results in higher cortisol levels. Depression as an important source of stress may lead to increased cortisol levels, insulin resistance, and gestational diabetes. In addition, depression during pregnancy has been associated with pregnancy induced hypertension and pre-eclampsia (36). In experimental animal studies, the effects of stress on the brain development of rats who were born with depressed mothers have been investigated and following results have been obtained: Lower BDNF and S-100B levels (meaning a decrease in neurogenesis and synaptogenesis), decreased hipocampal volume, increased Caspase-3 activity (meaning an increase in apoptosis), lower 5-HT1A receptor activity in the ventral hippocampus, and tendency to display an anxiety-depression behavior in adulthood when they are confronted with stress (37). Occasionally, depression not only leads to functional impairment but also causes deleterious behaviors as self-medication, use of alcohol, substance abuse, smoking, poor nutrition, and inadequate weight gain, all of which are harmful to both the mother and infant's health. In addition, lack of motivation and self-esteem may result in inadequate prenatal care. (36,38-43). The most notable adverse pregnancy outcomes associated with antenatal depression include increases in spontaneous preterm delivery, low birth weight, and small gestational age (44-51). Recent investigations have shown that infants born to depressed mothers tend to exhibit excessive crying, lower orientation scores, inferior excitability, and few expressions of interest shortly after birth, indicating the possibility of neurodevelopmental consequences of maternal depression in the newborn (48,52). A long-term follow up study (11 and 18 years) showed that children of depressed mothers exhibit lower IQ scores and, more violent behaviors (53,54). The profound impact of maternal depression on the health and well-being of children was recently documented in a multi-site study of children of mothers who were treated with medication as part of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. Children (aged 7-17 years)

were assessed psychiatrically at the study's inception and three months by a team of blinded evaluators. Those children who were free of any psychiatric symptoms at the inception of the study and whose mothers' depression remitted with treatment remained well, while 17% of initially well children whose mothers did not remit acquired a psychiatric disorder (depressive, anxiety, or disruptive behavior disorders). Successful treatment to remission of maternal depression was associated with an 11% decrease in rates of diagnosis for their children; whereas failure to remit resulted in an 8% increase in psychiatric diagnoses in their children. These results suggest that successful treatment of maternal depression has a positive effect on the mental well-being of their school-aged children. As a corollary of this data, a twenty-year follow-up study of adult offspring of depressed parents revealed that they had higher rates of depression, anxiety, substance dependence, work dysfunction, family dysfunction, and physical illness (especially cardiovascular disease) than age-matched offspring of non-depressed parents (55,56).

Perhaps one of the most notable consequences of untreated antenatal depression is the subsequent increase in risk for postpartum depression (57). Postpartum depression is another extremely severe form of perinatal mental illnesses, occurring together with one or more complications such as poor weight gain, suicide, sleep problems, less breastfeeding, poor attachment, infanticide, and increased health care costs (48,52) .

Data Sources and Interpretation

In this section we will discuss the strengths and weakness of the various forms of research based on suggestions about teratogenicity.

Case reports: The first data about teratogens usually originated from case reports. If a case reports exert a specific abnormality that is well described in similar drug exposure, in certain time of fetal or embryonic period, they are useful. Case reports cannot make accurate analysis of abnormality risk. If a defect and exposure occurs more frequently in a pregnant woman, coincidence is unavoidable. Case reports must be cautiously interpreted in order to establish a causal link between exposure to a particular medication (58).

Case series: Several cases can exist, up to hundreds or more. The main limitation of a case series is that there is no control group, so the results cannot be compared to a group representing the population. The sample size of studies assessing the safety of these medications in pregnancy usually is statistically small. Almost 800 cases in each treatment group would be required to detect a two fold increased risk, and thousands of cases would be required to detect rare defects (59).

Epidemiological investigations used in teratology are primarily of two types: cohort studies and case-control studies. In prospective comparative cohort studies, exposures of interest are identified and a prospective follow up of women are enrolled in the study. Following birth of the baby, pregnancy outcomes are obtained and compared with other women who were not exposed to the drug in question. In retrospective case control studies, the outcome is known and the group is compared to another group who were born with the same birth defects. The two groups are then matched on important variables and a search is conducted for evidence of exposure. The point worth emphasizing is that epidemiological studies provide only the means of obtaining quantitative estimates regarding the strength and statistical significance of associations between agent exposures in pregnant women and abnormalities in their children. When doing interpretation for epidemiological studies, one must remember that the maternal disease or situation, which occasioned the exposure rather than the agent itself, may be responsible for an observed association. A statistically significant association in an epidemiological study is never assumed to indicate causality without other evidence to support such a conclusion. Moreover, etiological heterogeneity of human congenital abnormalities or the subtle patterns of anomalies characteristic of many human teratogens limit the usefulness of most published epidemiological studies (58).

Meta-analysis: Since most observational pregnancy outcome studies have small sample sizes, this method is very useful when studying drug use in pregnancy. Combining results across different studies, enlarging the sample size makes a more definitive statement regarding safety/risk of the drug are possible with meta-analysis. Firstly, a literature search is conducted using all available databases including case-control and cohort studies and abstracts presented at scientific meetings which subjects

were similar. The inclusion and exclusion process is carried out. The reviewers then extract the data from the included studies into 2x2 tables and the data are analyzed (58).

Administrative data base studies: Databases are not typically set up for pharmacoepidemiological research as they are primarily developed for various administrative claims payment. For this reason, important data is often missing, especially for studies of drug use and pregnancy outcomes. However, they often contain large numbers of individuals with important information so they have been increasingly used in research, most frequently to conduct post-marketing surveillance. Some registries are driven by pharmaceutical companies (often compelled by national or international drug licensing agencies) and provide data on pregnancy outcome related to the sponsor's own product. Others are organized by independent research groups and they can be more useful as comparative data is used. The major strength of these registries is that often they will contain prospective data, although some do report on retrospective data, they often contain large numbers of exposed women and can be run for several years (58).

Prescription data base studies: Compiled with data from prescriptions that have been filled by the patient. The main strength of this method is the very large sample sizes.

National birth registries: Some countries, mostly in Europe, operate registries where the mother and child pairs are entered after birth and are followed up prospectively.

If we compare these methods according to evidence-based medicine, well-designed cohort or case-control analytical studies are more acceptable than one center or research group researches. Actually, in determination of teratogenecity and toxicity the most valuable source is prospective, randomized, double-blind, placebo controlled studies. Unfortunately they are impossible to conduct during pregnancy. Therefore data must be cautiously interpreted especially when we have conflicting studies.

CONCLUSION

Many clinicians avoid prescribing for fear of possible adverse effects on the pregnancy outcome, neonatal symptoms, and long-term effects. Although some studies report that antidepressant use during pregnancy is related to congenital malformations, negative birth outcome, and neurodevelopmental problems, there are conflicting results. None of them showed so far a clear link between attributed adverse effects and antidepressant use during pregnancy. Also, it is clear that none of psychotropic medications is fully devoid of risks for pregnancy. On the other hand, it is irresponsible to leave severely depressed women who are irresponsive to psychotherapy, or have some difficulties to attend psychotherapy, untreated, even if pregnant. The risks of untreated depression during pregnancy to the mother and the fetus (eg, preterm delivery, poor nutrition, inadequate weight gain, poor prenatal care, inability to care for oneself, substance use, termination of the pregnancy, and postpartum depression) also deserve attention. Antenatal depression is significant not only because of its prevalence but also because of its consequences. Depression can impair the mother's nutritional intake and prenatal care, increase her likelihood of using potentially harmful addictive substances, and lead to suicide attempts. Depression during pregnancy is a strong predictor of postpartum depression, a condition that can have direct consequences for the mother, the baby, and the entire family. Therefore, it could be argued that nothing is more critical than sustaining maternal emotional well-being during pregnancy. On the other hand, current knowledge has been based on several sources of data like case reports, retrospective and prospective studies, and animal experiments. Therefore, determination of any possible adverse outcome requires careful evaluation of data coming from various sources.

In conclusion, clinicians should try to find the safest option and should pay attention to the risks of both medications and untreated depression. In decision-making, clinicians and families must weigh the risks of untreated or undertreated depression. Further, the field needs to better understand the mechanisms by which problematic outcomes occur, with exposure to antidepressants or exposure to depression.

Acknowledgement

The authors thanks to Mr. Cooper Howland for his comments and criticisms.

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