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Therapeutic Approaches for Depression During Pregnancy and Lactation

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Abstract

Objectives: The pregnancy and postpartum period appear to be a time of heightened vulnerability for the development of major depression in some women. The treatment of depressive disorder during pregnancy is an important but complex clinical topic. This article provides a systemic review of treatments for depressive disorder during pregnancy and lactation: Psychotherapy, Pharmacotherapy, Electroconvulsive therapy and other effective treatments.

Methods: PubMed and EMBASE were searched using terms with regard to the treatment of depressive disorders during pregnancy and lactation. Reference lists of related reviews and studies were searched. In addition, relevant practice guidelines were searched using the PubMed. All identified clinical literatures were reviewed and summarized in a narrative manner.

Results: The treatment option for depressive disorders during pregnancy and lactation depends on the severity of depressive illnesses of the individual patient. For mild to moderate depression, the non-pharmacological treatment should be considered first. For moderate to severe depression, pharmacotherapy should be administered in addition to the psychosocial treatment. ECT is recommended for depressive disorder of severe intensity. Treatment strategies are described according to the point of time of pregnancy or lactation. FDA categories for antidepressants during pregnancy and lactation are described. In addition, issues regarding to the electroconvulsive therapy and psychosocial treatment are discussed.

Conclusion: Treatments during pregnancy and lactation requires a comprehensive assessment of the risks and benefits of treatment for both mother and fetus or neonate. Recently, there is growing evidence that the use of tricyclic and selective serotonin reuptake inhibitors during pregnancy and lactation does not result in increased risks of teratogenicity. As the research knowledge is limited, the recommendations should based on the best judgment of clinicians.

Keywords: Depression; Pregnancy; Lactation;Antidepressant; Therapeutic approach

Introduction

About 70% of pregnant women experience depressive symptoms during their gestation period and the prevalence rates of the major depressive disorders during pregnancy range from 10% to 16% [1]. These imply that pregnancy cannot protect women from depression. The factors that increase the depression risk of pregnant women include a history of depression and premenstrual syndrome, motherhood at a young age or single motherhood, lack of social support, multiple births, couple conflict, and ambivalent emotions on pregnancy [2]. When depression during pregnancy is not treated, various problems such as nutritional deficiency and sleep disorder occur. In addition, depressive mothers may not comply with medical instructions, and their risks of smoking/drug addiction and of committing suicide may increase. Moreover, problems such as fetal growth retardation, premature birth, low birth weight, difficult labor, low Apgar scores, increase in the death rate, mental retardation associated with severe neurological or cognitive function disorders, and insufficient attachment formation may develop [2,3]. Thus, mothers have the important task of understanding major depressive disorders during pregnancy, which cover the fields of obstetrics, internal medicine, and psychiatry.

The prevalence rate of major depressive disorder after childbirth is estimated as 10-15% [4]. Major factors of depressive disorders that develop during the perinatal period include a history of postpartum depression and depressive disorders, and a family history of depression, particularly of postpartum depression. Additional factors include low social support, negative life events, an unstable marital relationship, motherhood at a young age, unexpected pregnancy, ambivalent emotions, and newborn health problems, acute or chronic health problems of the mother, insufficient ability to react, and domestic abuse or violation. In minor-age mothers, the prevalence rate of postpartum depression reaches as high as 26% [5].

In principle, medication is avoided during pregnancy. However, in a study [6] that monitored pregnant women with a history of depression, since their pregnancy without depression, 43% of the subjects experienced recurrent depression during their gestation period. The recurrence rate (68%) in the women who stopped taking antidepressant medications was significantly higher than that (26%) in the women who continued taking the medication. Clinicians are often caught in a situation that requires them to choose between discontinuing the prescription of antidepressant medications to pregnant women and prescribing such medications for new depressive pregnant women. Clinicians may be hesitant or reluctant to decide in such a situation. Despite these concerns, many mothers had been reported to have been taking antidepressant medications [7]. According to the report, 42% of the mothers who stopped taking antidepressant medications due to pregnancy resumed their intake of such medications during

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their gestation period due to recurrent depression. About half of them resumed their intake at the first trimester of their pregnancy.

The depression treatment strategy during pregnancy or lactation must take into account the effects of the medications on the mother and the fetus. In this study, the rationale for treating depression during pregnancy and lactation was discussed, and this may produce useful data for such treatment.

Methods

Search strategy

A systemic search strategy was used to identify suitable publications. This involved an online search of the PubMed and EMBASE, using the search terms conducted on 1th August with no time span specified for date of publication :[preg* AND depression (depression(s)/ depressive disorder(s)/ unipolar depression/ dysthymia/ depressive disorder(s)/ depressive episode/ depressive illness/ dysthymic disorder(s)/ minor depression(s)] AND [lactat* (lactat*/ breast feed*/ breastfeed*/ breast-feed*/ human milk) AND depression (depression(s)/ depressive disorder(s)/ unipolar depression/ dysthymia/ depressive disorder(s)/ depressive episode/ depressive illness/ dysthymic disorder(s)/ minor depression(s)]. A total of 84 and 183 hits were returned for the two databases respectively.

Selection criteria

Analysis of the articles followed previously established inclusion and exclusion criteria. We included the following: (i) articles that presented a combination of at least two of the established terms in the abstract, namely [preg* and depression] or [lact* and depression]; (ii) manuscript in English; (iii) original articles; and (iv) "Practice Guidelines" for the "Type of Article" was searched from the "Systemic Review" published by PubMed. Exclusion criteria were as follows: (i) other study designed, such as case reports, case series; (ii) non-original studies including editorials, book reviews, and letters to the editor, and (iii) studies not specifically designed and focused on pregnancy or depression.After applying these selection criteria, each 12(preg*) and 6(lactat*) articles papers were selected as relevant to the present review. In a second step, the reference lists of these 12 and 6 articles were manually checked for any additional studies not identified by computerized literature search. This second step did not reveal any additional studies, resulting in a final sample of 12 and 6 articles to be included in our review. Using these data, the treatment strategy for depression during pregnancy and lactation was discussed in this study.

Results

Depression during pregnancy and lactation must be treated while balancing the risks of non-treatment and the effects of the treatment on the fetus or the newborn baby. Pregnancy or lactation must be considered based on the following three categories of side effects: the risk of fetal abnormality, the toxic effects on the newborn baby during the perinatal period, and the effects on the behavior of the mother after childbirth [8]. Timing is the focal point of the treatment of depression during pregnancy and the lactation period, and the treatment is determined by the severity of the symptoms [6]. For mild or moderate depression patients, psychosocial treatments such as cognitive behavior therapy, interpersonal therapy, group therapy, family therapy, couple therapy, psycho-education, and supportive psychotherapy are recommended [9]. For patients with moderate to severe depression or with a high risk of recurrence of depression, both psychosocial treatments and pharmacotherapy are essential [6]. When the risk of committing suicide is high, or if the patient cannot undergo pharmacotherapy or does not respond to the aforesaid therapies, electroconvulsive therapy (ECT) can be considered [10,11]. The details of a depression treatment strategy are as follows.

Pre-pregnancy depression treatment strategy

The decision to discontinue or continue taking antidepressant medications is based on the severity of the symptoms [12]. When the patient has been free from the symptoms for the past six months after only one depressive episode, it is recommended that she stop taking medications before pregnancy, and to start or maintain psychotherapy [6]. When there is a history of severe repetitivedepressive episodes, a sufficient dose of antidepressant medications is maintained during pregnancy and even after childbirth. When a patient who is sometimes depressive but not receiving treatments wants to be pregnant, psychotherapy may be enough for mild depression; but in the case of severe depression with one or multiple episodes, both psychotherapy and antidepressant medications are required [1,3,7].

Depression treatment strategy during the first gestational period

Fetal abnormality may occur due to the exposure of the fetus to the drugs during the first gestational period. In a female who experiences depressive episodes for the first time during pregnancy, antidepressant medications are prescribed only when the depression is severe or when psychotherapy is not working [3]. In a woman who became unexpectedly pregnant while taking antidepressant medications due to mild depression, the medications are gradually discontinued over several weeks; In a female who experiences depressive episodes for the first time during pregnancy, antidepressant medications are prescribed only when the depression is severe or when psychotherapy are not working [9]. When the severe depression occurred only once, there are no established guidelines for maintaining or discontinuing the medication intake, so frequent and close observations are required to make a decision. In either case, the psychosocial approach shall be the basis of the treatment [3,9].

Depression treatment strategy during the second and third gestational periods

In these periods, miscarriage symptoms and delicate changes in the fetal development must be closely monitored. If pharmacotherapy is required during the first gestational period, they are usually maintained until childbirth. If the symptoms of depression in a woman who is not taking an antidepressant medication deteriorate, the treatment strategy is established according to the severity of the past depression [3]. In the case of a severe history of depression, the medications are used as soon as the first symptom of depression appears; and in the case of a history of mild depression, the medications can be used after the symptoms are fully recognized [12]. In either case, patients with depression accompanied by psychotic symptoms must take a combination of antidepressant and antipsychotic medications, or try electroconvulsive therapy during any gestational period. The history of depression associated with pregnancy is important [12]. If a woman with a history of depression could manage her pregnancy well until its end without treatment, or if a woman has a history of postpartum depression, the medications are used after the last month of pregnancy to prevent postpartum depression (preventive treatment) [12,13].

Depression treatment strategy after childbirth and during lactation

Women with a risk of postpartum depression require close monitoring during their pregnancy and after childbirth. The 7 to 10 days of temporary depressive symptoms after childbirth, the so-called 'postpartum blues,' does not require a pharmacotherapy [4]. The patient is informed that the depression is temporary with a good prognosis. In cases with a history of postpartum depression, preventive treatments such as taking antidepressant medications are necessary, and if discontinued due to pregnancy, must be resumed after childbirth [13]. When mothers want lactation, the benefit of pharmacotherapy and their potential effects on newborn babies are sufficiently explained to the mother before she decides on lactation. The short- or long-term effects of antidepressant medications on breast-feed newborn babies are not yet fully understood, but according to most studies, antidepressant medications pass through the breast milk with limited effects [9]. Nevertheless, there are significant individual differences, and the immature metabolic system of the liver of newborn babies must be considered. It is important for lactating mothers on antidepressant medications to observe their baby's daily sleep, diet, and behavior patterns, and to report them to their doctor when needed [14,15]. In addition, they must inform their pediatricians that their babies are being exposed to antidepressant medications.

Selection and use of the medications

During pregnancy and lactation, the following must be considered in the selection of antidepressant medications: the patient's previous responses to antidepressant medications, the expected effects and side effects of the antidepressant medications, the expected interactions among the simultaneously prescribed medications, and the potential side effects on the mother and the baby [10]. Of course, exposure to drugs must be minimized during pregnancy and the lactation period for minimal drug accumulation in the fetal blood or breast milk. Therefore, the lowest dose of the medications with minimal side effects on fetuses or newborn babies must be selected.

Drug treatment during pregnancy: The US FDA [14] has suggested drug safety grades during the gestation period. Category A drugs have been proven in control group studies to be safe for fetuses when taken during pregnancy. Category B drugs are hazardous in animal experiments, but not in human experiments, or are not hazardous in animal experiments but have not shown evidence of being hazardous to humans because no appropriate studies on humans have been reported. Category C drugs are not supported by animal studies, and have appeared hazardous but inconclusively so in studies on humans, so their hazard on fetuses cannot be discounted and they can be used only when their benefits outweigh their hazards. Category D drugs have been confirmed as hazardous to fetuses, but their benefits to mothers outweigh their potential hazards, so they can be used on a case-by-case basis. Category X drugs are contraindicated for pregnant women or possibly pregnant women because their hazards clearly outweigh their benefits.

In detail, of the tricyclic antidepressants (TCA), amitryptyline, imipramine, and nortriptyline are Category D; and clomipramine, desipramine, doxepine, trimipramine, and protriptyline are Category C. Monoamine oxidase inhibitors(MAOI) have not been sufficiently studied, but they are not recommended for use during pregnancy because there are replaceable medications and may cause hypertensive seizure. Of selective serotonin reuptake inhibitors (SSRIs), fluoxetine, paroxetine, and sertraline are Category B. In meta-analyses, exposure to fluoxetine during pregnancy was confirmed as not associated with the development of abnormalities in major human organs [15]. However, it increased the risk of miscarriage [16]. In a long-term study on mothers who took fluoxetine during pregnancy and on their total of 55 infants, no difference in the overall intelligence and language development of the infants and the control group, nor in their temperaments, moods, arousal states, activity levels, distractibility, and behavioral problems, was observed [17]. According to the Swedish National Registry data [18], the intake of paroxetine during the first gestational period increases the risk of the infant developing congenital heart abnormality, so it is not recommended for use during pregnancy. Sertraline has been reported as not having increased the risk of congenital abnormality, miscarriage, and still birth [18,19]. Fluvoxamine and citalopram are Category C drugs. Fluvoxamine has reportedly not increased the risks of congenital abnormality and miscarriage [19]. In a large-scale study on mothers and their newborn babies exposed to citalopram, the incidence of the development of major abnormalities among them was the same as that in the general population [19]. Among atypical antidepressants, buproprion and maprotiline are classified as Category B. According to the prospectively obtained data from the manufacturer and the prospective study [20], bupropion does not increase the risk of developing abnormalities. Trazodone and venlafaxine are Category C drugs. In a prospective study on 150 mothers exposed to venlafaxine during their pregnancy, no major abnormality was induced when the drug was taken with other SSRIs, as was the case with the control group mothers [21]. There has been no prospective study yet on mirtazapine, but it is a Category C drug. According to the Canadian Guidelines [10] published in 2001, the first-line treatment drug for pregnant women is fluoxetine (level of evidence 1), and the second-line treatment drugs are citalopram, fluvoxamine, partoxetine, and sertraline (level of evidence 2).

During pregnancy, a pharmacodynamics change in the decrease in the blood drug concentration occurs. Many studies on this issue have been reported. In the case of TCA, its dose was suggested to have increased to 1.6 times during pregnancy [22,23]. In the case of SSRIs, about two-thirds of the pregnant women who took fluoxetine, paroxetine, and sertraline eventually increased their dose. In our previous study, we suggested a higher daily dose of SSRI from the end of the second trimester of pregnancy [24].

Drug treatment during the perinatal period: Temporary postpartum depression that develops after childbirth can be cured through patient education and reassurance [10]. When the depressive and physical symptoms persist for more than two weeks, and particularly when there is a history of depression, evaluation and treatment plans for postpartum depression must be prepared. Unless lactation is involved, treatments for postpartum depression are similar to those of general depression [25]. In the Canadian Guidelines [10], fluoxetine and cognitive behavior therapy are suggested as first-line treatments, and interpersonal therapy and patient and family education, as second-line treatments.

When mothers take antidepressant medications until the end of their pregnancy, consequent side effects can develop in their newborn babies immediately after their delivery. In adults, symptoms of side effects usually appear between 24 and 72 hours after the medication intake, and in newborn babies, between 10 and 36 hours after birth. The symptoms include dyspnea, cyanosis, apnea, seizure, newborn baby instability, hypothermia, sucking problem, vomiting, hypoglycemia, muscle strength deterioration or hypertonicity, hyperreflexia, tremor, nervousness, and abnormal crying. These symptoms may be due to the

prenatal drug toxicity or to the withdrawal symptoms. It is difficult to recognize these symptoms because the behavior of newborn babies is not yet well understood, and these symptoms are hardly differentiated from the effects of other internal diseases, obstetric problems, and drug effects. TCA withdrawal syndrome or neonatal withdrawal symptoms are understood to be associated with the noradrenalin and dopamin channels, which are related to cholinergic rebounds [26]. Since SSRI does not affect the choline and adrenalin receptors, no withdrawal symptoms were expected in newborn babies. However, according to recent studies [27], SSRI could cause neonatal abstinence syndrome. The analysis of the frequency of neonatal abstinence syndrome and convulsions of newborn babies showed that the paroxetine frequency, two-thirds, was the highest, followed by the fluoxetine, sertraline, and citalopram frequencies. This may be because paroxetine strongly combines with muscarinic receptors, unlike other SSRIs. Regarding neonatal abstinence syndrome, we advise mothers not to take paroxetine during pregnancy; but if it is unavoidable, we suggest the lowest effective dose. Among new antidepressant medications, venlafaxine reportedly causes neonatal abstinence syndrome. The syndrome disappears within one to 14 days, but clinicians may need to consider gradually reducing the dose of antidepressant medications 10 to 14 days before childbirth to prevent these withdrawal symptoms. After childbirth, the dose is restored to the pre-pregnancy level [2].

Drug treatment during lactation: The US FDA has a separate drug safety grading system during the lactation period [28]. Category L1 includes drugs that have had no reported side effects after many lactating mothers took them, and no side effects in their newborn babies and in controlled studies, did not increase the risk in newborn babies. Category L2 drugs were investigated with a limited number of lactating mothers, and no side effects were reported in their newborn babies. Category L3 drugs are used for newborn babies only when their benefits outweigh their hazards, and there has been no controlled study on them. Category L4 drugs have been reported as hazardous to newborn babies through lactation, but their benefits for mothers outweigh their hazards to babies, so they can be used on a case-by-case basis. Category L5 drugs are clearly understood as hazardous to newborn babies, besides which their hazards outweigh any benefits, so they are contraindicated for lactating mothers.

TCA is usually secreted through the breast milk in a low concentration. Amitryptyline, imipramine, nortriptyline, desipramine, and clomipramine are Category L2 drugs, and trimipramine is Category L3. Since doxepine has metabolites with long half-lives, it is accumulated in newborn babies and is thus classified as Category L5. Fluoxetine is an SSRI and has norfluoxetine, a metabolite with a long half-life, which is accumulated in newborn babies. Its risk to newborn babies is too high, so it is classified as Category L3, and Category L2 for older infants. Fluvoxamine, paroxetine, and setraline are Category L2, and citalopram, L3. Among atypical antidepressants, trazodone is Category L2, and buproprion, maprotiline, nefazodone, and venlafaxine, L3. In the Canadian Guidelines [10], TCA and SSRI are not contraindicated in the preliminary results due to the lack of data on the long-term effects of antidepressant drugs secreted during the lactation period on infant development.

Other treatments: Electroconvulsive therapy can be considered for patients with severe depression, psychotic symptoms, no response to medications, severe side effects that have stopped pharmacotherapy, preference for electroconvulsive therapy after understanding its benefits and risks, and the risk of committing suicide or infanticide. However, the critical point on convulsion can change due to pregnancy, and no prospective controlled study has been conducted yet. In a study on electroconvulsive therapy for 300 women during their gestation period [29], 9.3% of the fetuses showed arrhythmia as a side effect. To reduce this ratio, a modified standard-type electroconvulsive therapy is used three times a week for one to three weeks according to the individual responses.

The transcranial magnetic stimulation (TMS) technique usually has less significant treatment effects than electroconvulsive therapy, but is expected to be used more often in the future because it does not require anesthesia, causes limited deterioration of cognitive functions, and has limited side effects [30]. Light therapy is an alternative pharmacotherapy for women with seasonal depression or postpartum depression or who do not want to take medications. In a recent study [31] on 16 depressed pregnant women, 10,000 lux of light was irradiated for less than 10 minutes each time after the woman got up for 60 minutes daily for at least three weeks. As a result, about half of them experienced improvement of their symptoms without side effects.

In both pharmacotherapy and psychosocial approaches, psychoeducation must be simultaneously performed. The purposes of these combinations are to help mothers and their family to understand the features of depression during pregnancy or the lactation period, and to provide them with the course information and treatments for effective management of depression. In addition to psychoeducation, supportive psychotherapies such as emotional support and reassurance can be used for pregnant women whose functions are not strong enough to allow them to receive cognitive behavior therapy or interpersonal therapy, or who refuse pharmacotherapy. This method can be used together with other psychosocial treatments or independently. Cognitive behavioral treatments are for understanding negative thoughts and beliefs that cause depression and for changing them. Interpersonal therapy is focused on role transition in mothers who need to learn new techniques for themselves. Group therapy is for mothers who have similar experiences with other mothers, and is meant to help them gain social and emotional support. Their spouses can also participate in the group therapy. The couple therapy for marital relationships and family treatments can also be used [2,8-11].

Conclusion

Treatment plans for depression during pregnancy and lactation differ from those for general depression. After our extensive and systematic research, we conclude that the studies on pharmacotherapy for depression patients during their pregnancy and lactation have not been sufficient. Optimal treatment decisions must be made according to the timing and individual situations. The decisions must be based on the evaluation of the risks and benefits, which include the risks of the pharmacotherapy, depression, alternative pharmacotherapy, and delayed effects of psychotherapy, and the risk to the safety of the mothers. It is necessary to inform mothers and their families of the benefits and risks of depression treatments during pregnancy, and to obtain their consent. Early detection of the symptoms is important, and once the treatments begin, efforts to prevent the recurrence of the symptoms must be continuously made even after childbirth.

The treatment methods can be selected according to the severity of the depression from among non-medication methods such as psychosocial treatments and light therapy for mild to moderate depression, and combined psychosocial and pharmacotherapy for moderate to severe depression or high-recurrence-risk depression. Electroconvulsive therapy may be used for depressive patients with a risk of committing suicide, or for patients who cannot tolerate the

medications. The medications must be used based on the available information, and the lowest dose that can produce treatment responses must be selected and changed according to the gestation period. Over the past 10 years, the safety of using SSRI during pregnancy and lactation has been studied and it has been selected as the first-line treatment agent [24], whereas the effects of the recently released antidepressant medications on mothers and fetuses during pregnancy or the perinatal period have been studied less often than has SSRI, so they are still less recommended. In conclusion, clinicians must consider the outcomes of previous studies when they establish a treatment strategy for depression during pregnancy and lactation. Since no clear conclusions have been drawn in this study, clinicians must pay attention to the future study outcomes.

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