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Treating Mood Disorders During Pregnancy

Safety Considerations

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Abstract

Mood disorders in pregnancy may have a negative effect on self care and pregnancy outcome that affects the mother directly and the child indirectly. Thus, some women may require pharmacological treatment. Pharmacotherapy of mood disorders during pregnancy implies specific considerations.

This paper presents an updated review of available studies on the treatment of mood disorders and present knowledge on teratogenicity, neonatal effects and long-term neurobehavioural effects for the different psychotropic drugs, including treatment with selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), other antidepressants, benzodiazepines, lithium, carbamazepine/valproic acid, lamotrigine and novel antipsychotics. However, the existing knowledge on the use of antidepressants and mood stabilising agents during pregnancy is hampered by a lack of results from randomised controlled trials.

SSRIs and TCAs have not been associated with an increased risk of major malformations, but poor neonatal adaptation has been described. Benzodiazepines

used in the first trimester have been associated with orofacial clefts. Mood stabilisers such as lithium, carbamazepine and valproic acid (sodium valproate) are associated with an increased risk of fetal malformations. Both benzodiazepines and lithium may cause adaptation problems in the newborn. *In utero* exposure to novel antipsychotics has not been associated with congenital malformations; however, the data are still limited. The knowledge about long-term neurobehavioural effects in the offspring is still limited for all agents and requires further investigation. Possible adverse effects of fetal exposure must be balanced against the adverse effects of an untreated maternal mood disorder.

The pregnancy period is usually considered to be a time of wellbeing, with biological fulfilment and 'protection' against psychiatric disorders.[1,2] In contrast, the postpartum period is considered to be a high-risk period for depression. However, recent research has shown that the incidence of depression during pregnancy is similar to the incidence of depression in the postpartum period, i.e. 5–10% of women.[3-6] Little is known about the course of bipolar disorder during pregnancy, but the postpartum period is clearly a high-risk period for bipolar episodes.[7,8] The lifetime prevalence of bipolar disorder in the general population is 3–6.5%;[9] however, the prevalence in pregnant women is not known. Childbirth is considered a trigger for severe bipolar episodes and postpartum psychosis sometimes indicates the onset of a bipolar disorder.[10]

For women of childbearing age, mood episodes may pose serious problems since they affect the mother directly and the child indirectly through the mother's behaviours and mood.[11,12] Women with depression often present with decreased appetite and, consequently, lower-than-expected weight gain in pregnancy. A severe depression during pregnancy may contribute to poor self care and poor prenatal care.[13] In addition, pregnant women with depression are also more likely to smoke and to use either alcohol or illicit drugs; behaviours that further increase risk to the fetus.[14,15] A number of studies have reported an association between maternal anxiety and stress during pregnancy and adverse pregnancy outcomes, such as preterm labour and low birth weight.[16-24] Severe depression is also associated with a risk of self-injurious behaviour and suicide.

Pharmacotherapy of mood disorders during pregnancy and lactation implies specific considerations. In addition to the woman, there is a vulnerable little individual. Research-based knowledge on the fetal safety of antidepressants and mood-stabilising agents are limited, since pregnant women have been excluded from drug trials. Literature reviews and treatment recommendations for mood disorders in pregnancy have been published.[25-32] However, the literature on treatment is constantly expanding.

The purpose of this paper is to present an updated review of available studies on the treatment of depression and bipolar disorder in pregnancy. Based on published case reports, prospective and retrospective studies, the present knowledge on teratogenicity, neonatal effects and long-term neurobehavioural effects will be presented for the different psychotropic drugs.

1. The Diagnosis of Depression During Pregnancy

Symptoms such as changes in appetite, sleep, libido and energy levels are normal during pregnancy, but may also be signs of depression. The course of depressive disorders is heterogeneous, from a single depressive episode associated with stressful life events to chronic depression such as dysthymia.

A screening instrument, the Edinburgh Postnatal Depression Scale (EPDS),[33] does not include any somatic symptoms. This scale was developed to detect women with postnatal depression, but has also been validated for use in pregnancy.[34] It must be kept in mind that screening instruments used in low prevalent populations identify a large propor-

tion of false positive cases.[35] Therefore, a positive score on a self-rating questionnaire needs to be followed by an interview clarifying the symptoms of depression and co-existing psychiatric disorders.[10] Since it is assumed that depression during pregnancy does not differ qualitatively from depression during other periods of life,[36] validated general diagnostic instruments for depression can be used.

Some women who present with severe depressive symptoms during pregnancy have an underlying bipolar disorder. The essential feature of bipolar disorder is one or more manic/hypomanic episodes that are usually accompanied by one or more major depressive episodes. Bipolar disorder is, according to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV),[37] subclassified as mixed, manic or depressed depending on the clinical features of the current episode. The severity of the manic or depressive episode is indicated as mild, moderate or severe, with or without psychotic features. A milder form is cyclothymia, where the mood episodes do not meet the criteria for mania or major depression.

2. Pharmacokinetics and Safety Aspects of Treatment

Severe depression normally requires pharmacotherapy. Women who have depression characterised by an impaired ability to take care of themselves, insomnia, risk-taking behaviour, or suicidal ideation are candidates for pharmacotherapy in pregnancy.

Substantial physiological changes may occur during pregnancy that may alter drug pharmacokinetics. These physiological changes can result in lower plasma concentrations of the psychotropic drug.[38] Because of this, it may be necessary to use higher doses of some drugs during the last trimester of pregnancy.[39]

As all commonly used psychoactive medications cross the placental barrier,[40] the woman's health and disease management must be balanced against the risk of the infant's exposure during pregnancy.[26,41,42] Psychotropic drugs have potentially three types of adverse effects on the fetus: (i) teratogenic effects; (ii) neonatal toxicity and withdrawal syndromes; or (iii) long-term neurobehavioural effects that are manifested by adverse behavioural or adverse development in the child. However, neurodevelopmental delay in the child may also be a consequence of having a depressed mother. Congenital malformation is mainly due to first trimester exposures,[43] since the organogenesis takes place in this period.

3. Principles of Treatment During Pregnancy

Depression in pregnant women may be treated according to the same principles as in general. However, non-pharmacological therapies such as psychosocial interventions and psychotherapy may seem more relevant than otherwise. Some women have their first depression in pregnancy. Others have a past history of depression and are taking psychotropic drugs when they become pregnant. When to start, reduce or increase medication are important questions for both groups. Unfortunately, studies on the impact of treatment of depression in pregnancy on adverse outcomes in the mother, her social network or her child are lacking. Risk analyses and estimating the number of women who need treatment to prevent the adverse effects of depression is, therefore, not possible. Hence, the decision to treat depression in pregnancy must still be based on the patient and the doctor's best clinical judgement.

Many women with a bipolar disorder are diagnosed prior to pregnancy since the disease debut is often during childbearing age.

The use of psychotropic drugs during pregnancy depends on illness severity and cycling. Patients with a single past episode of mania or women who are in a current period of long-time affective wellbeing may reduce or discontinue the medication 2–3 months prior to their attempts to conceive. Discontinuation of the medication for women with severe bipolar disorder is not advisable. Anxiolytic drugs may also be used together with antipsychotic drugs to control agitation during manic episodes.

4. Literature Search

In order to obtain the relevant information on current treatment options of depression in pregnancy a systematic literature search was performed in MEDLINE, EMBASE and the Science Citation Index Expanded (ISI) from 1966 to March 2004. The search strategy was (i) 'antidepressive treatment' and 'pregnancy'; and (ii) 'antidepressant drug' and 'pregnancy'. Almost 300 articles were found. The treatment of bipolar disorders in pregnancy was also investigated. The search strategy was (iii) 'bipolar disorder', 'pregnancy' and 'treatment'. In excess of 100 articles were found.

When the search was restricted to reviews and empirical studies (case reports, prospective clinical and retrospective studies) in the English language, 158 articles were included. A total of 83 of these 158 articles were reviews. Randomised controlled trials on psychotropic drugs in pregnant women do not exist.

In addition, the search word 'pregnancy' was combined with the generic name of each relevant psychotropic drug or drug group: fluoxetine (57 articles), paroxetine (17 articles), sertraline (18 articles), citalopram (8 articles), fluvoxamine (7 articles), escitalopram (0 articles), mirtazapine (0 articles), nefazodone (0 articles), trazodone (1 article), reboxetine (0 articles), tricyclic antidepressants (45 articles), monoamine oxidase inhibitors (0 articles), moclobemide (1 article), benzodiazepines (82 articles), buspirone (0 articles), lithium (168 articles), valproic acid (172 articles), carbamazepine (170 articles), lamotrigine (19 articles), risperidone (3 articles), clozapine (13 articles), olanzapine (9 articles), quetiapine (3 articles), ziprasidone (0 articles), aripiprazole (0 articles), amisulpride (0 articles) and sertindole (0 articles). Several articles included information on more than one drug.

The final searches added 548 abstracts to the initial 158 papers that were considered for this review. After restricting the search to empirical studies in the English language, the number of articles was reduced to 313. However, given the constraints of space, only the most relevant articles are included in this review.

5. Treatment Options

5.1 Non-Pharmacological Therapy

Several studies have demonstrated the efficacy of cognitive behavioural therapy and interpersonal psychotherapy in the treatment of moderate depression.[44] Few randomised controlled trials have studied the effect of non-pharmacological therapies during pregnancy. One study suggested that light therapy is beneficial for the treatment of depression during pregnancy if there is a seasonal component to the depression.[45] Another study compared interpersonal psychotherapy to a parenting education programme for antepartum depression.[46] Interpersonal psychotherapy resulted in a significant mood improvement relative to the parenting education programme. Interpersonal therapy has been considered to be particularly useful during pregnancy and postpartum in that it directly addresses issues associated with role transitions and relation to the partner. No controlled trials have been performed on the effect of non-pharmacological interventions on bipolar disorders among pregnant women. Supportive psychotherapy has primarily focused on adherence to medical treatment and daily life function.

The limited knowledge of adverse effects of psychotropic drugs has increased the attractiveness of electroconvulsive therapy (ECT) for pregnant women with severe depression. Pregnancy was earlier considered a specific contraindication for ECT. More recently, ECT during pregnancy has come to be seen as a relatively safe and effective treatment if steps are taken to decrease potential risks. Potential risks include fetal cardiac arrhythmia, vaginal bleeding, uterine contraction, abdominal pain, premature labour, stillbirth, fetal respiratory distress, teratogenicity, aortocaval compression, fetal hypoxia and adverse effects of the anaesthetic medication.[47,48]

In a review including 300 case reports with ECT-treatment for whom no preventive steps were taken, complications were noted in 28 cases (9.3%).[48] The most serious complications were miscarriages (n = 5), stillbirths (n = 3) and congenital anomalies (n = 5). However, neither the number of complications nor the pattern of congenital anomalies suggests a

definite association with the ECT. Caution has been recommended in prescribing ECT to patients in the first trimester of pregnancy.[49]

The preventive steps to minimise potential complications of ECT include discontinuation of non-essential anticholinergic medication, uterine tocodynamometry, intravenous hydration and administration of antacid to raise gastric pH. During ECT, elevating the woman's right hip, external fetal cardiac monitoring and intubation is recommended. Hyperventilation should be avoided. With these extra precautions, ECT may be administered relatively safely and effectively during pregnancy.[48]

5.2 Selective Serotonin Reuptake Inhibitors

Since the selective serotonin reuptake inhibitor (SSRI) fluoxetine was approved in the US for treatment of major depression in 1987, several other SSRIs have been approved and are now used worldwide. The SSRIs are, no doubt, the most widely used group of antidepressant drugs,[50] not only in the general population but probably also in pregnant women in Western countries.

To date, no study suggests an increased risk of congenital malformations for any of the SSRIs (fluoxetine, paroxetine, sertraline, citalopram, escitalopram, fluvoxamine).[51-59] However, one prospective study has reported increased risk for minor anomalies in the offspring of women exposed to fluoxetine in the first trimester.[56] This study has been criticised for lack of control for the severity of depressive illness and maternal age.[60]

Several case reports have described various symptoms in the newborn infant, such as jitteriness, irritability, constant crying, shivering, increased tonus, eating and sleeping difficulties and even convulsions.[61-66] These symptoms may occur in infants who have been exposed *in utero* and abruptly become unexposed after birth.[67] It has been suggested that the mechanism behind these symptoms is CNS serotonergic overstimulation rather than SSRI withdrawal syndrome.[68]

An increased risk of poor neonatal adaption, including respiratory difficulty, cyanosis and jitteriness, among infants exposed to fluoxetine has been described in one prospective study,[56] whereas these symptoms were not seen in other follow-up studies.[51,54,57] Moreover, another prospective study found an increased risk for neonatal respiratory distress after maternal third trimester paroxetine use.[69] A retrospective study found a higher incidence of special nursery care admissions for neonates exposed to fluoxetine in late pregnancy than for infants exposed in early pregnancy.[70] However, in this study, SSRI use in the last part of pregnancy may have been associated with more severe depression and, hence, confounded the results. The neonatal adaption problems after SSRI exposure have seemed to resolve within 2 weeks without specific intervention.[68]

In addition, other perinatal complications such as low Apgar scores,[71-73] low birth weight[56] and prematurity[55,72] have been described among children exposed to SSRIs during pregnancy. In all except one of these studies,[71] possible confounders, such as maternal depression, were not measured during pregnancy and may have confounded the results. A few case reports have described intracerebral haemorrhage in SSRI-exposed neonates,[65,74] but it is not known whether the frequency is higher than in unexposed neonates.

No evidence of neurobehavioural long-term effects have been found in children exposed to a SSRI *in utero*.[54,72,75-77] However, one study suggests that prenatal SSRI exposure may have subtle effects on motor development and motor control[71] and other authors have also expressed concern in this matter.[78]

The possible impact of fluoxetine on human reproduction was recently evaluated by the US Center for Evaluation of Risks to Human Reproduction (CERHR, National Toxicology Program).[79] The CERHR concluded that third trimester exposure to therapeutic doses of fluoxetine is associated with an increased risk of poor neonatal adaptation, as well as increased admissions to special care nurseries. The panel also suspected shortening of gestation and reduced birth weight at term. Finally, they concluded that the long-term implications of these findings

could not be evaluated without further longitudinal data.

5.3 Tricyclic Antidepressants

Tricyclic antidepressants have been used for decades in the treatment of depression. These agents have, to a large extent, been replaced by the SSRIs, since the tricyclic antidepressants have more unfavourable anticholinergic adverse effects. Of the tricyclic antidepressants, desipramine and nortriptyline are preferred in pregnancy since these drugs are the least anticholinergic and the least likely to exacerbate orthostatic hypotension, which often occurs in pregnancies. Studies conducted to date have shown no increased risk of major malformations after *in utero* exposure to tricyclic antidepressants.[52,53,80,81]

Perinatal syndromes in infants exposed to antidepressants *in utero* have been described. Withdrawal syndromes include jitteriness, irritability and, less commonly, seizures.[82-86] In addition, symptoms secondary to rebound cholinergic hyperactivity, such as functional bowel obstruction and urinary retention, have been described.[86] In all reported cases, these symptoms have been transient. In order to avoid these symptoms in offspring, it has been recommended that the dose of tricyclic antidepressants be reduced prior to the time of delivery.[83-85] However, others have argued that tapering the antidepressants may pose a greater risk to the fetus than extrauterine withdrawal and places the woman at risk for relapse.[25] There are still very few studies addressing possible neurodevelopmental delay in the antidepressant-exposed infants.[54,72,76] These studies included 80, 209 and 46 *in utero*-exposed children, respectively.

5.4 Other Antidepressants

Other antidepressants can also be used for the treatment of depressive disorders, such as venlafaxine, mirtazapine, nefazodone, trazodone, reboxetine, moclobemide and monoamine oxidase inhibitors. Some of these drugs are relatively new and have only recently been approved.

Prospective data on 150 women exposed to venlafaxine during the first trimester suggest no increase in major malformation compared with non-exposed controls.[87] However, a larger study is required to ensure there is no increased risk of malformations. To date, prospective data on the use of mirtazapine, nefazodone, trazodone, reboxetine and moclobemide are not available.

Limited information exists on the reproductive safety of monoamine oxidase inhibitors. In a small sample-sized study, including 21 mother-infant pairs, an increase in congenital malformations after *in utero* exposure was reported.[88] Monoamine oxidase inhibitors should also be avoided in pregnant women because of the risk of hypertensive crisis.[89]

5.5 Benzodiazepines

Benzodiazepines have been reported to be effective in the treatment of generalised anxiety and phobic situations. They are discussed here since they are sometimes used in the treatment of depression and in manic episodes to control agitation. They are probably the most widely prescribed psychotropic drugs, with diazepam being the single most prescribed agent in the class.[90]

The potential teratogenicity of benzodiazepines remains controversial, but a large meta-analysis suggested a 2-fold increase in the risk of orofacial clefts.[91] However, the absolute risk of cleft anomalies associated with first-trimester exposure to benzodiazepine is low (<1%).[91]

There is evidence that third trimester exposure to benzodiazepines may cause a specific syndrome in the newborn infant, known as 'the floppy infant syndrome'.[92-94] Hypotonia, lethargy, poor temperature regulation and low Apgar scores characterise this condition. Withdrawal syndromes may also occur.[92-94] There are still very few studies addressing possible long-term effects in the offspring. However, one report suggested a general delay in mental development up to 18 months of age, which was measured by the Griffith's Developmental Scale.[95]

If benzodiazepines are needed during pregnancy, the lowest effective dose should be used. If possible, the use of shorter-acting drugs such as oxazepam

should be considered and use discontinued prior to delivery.

Although benzodiazepines are often used as primary pharmacotherapy in anxiety disorders, cognitive behaviour therapy and SSRIs are considered more effective and safer in pregnancy.[96] There is, to our knowledge, no published data on the effects of *in utero* exposure of the anxiolytic drug, buspirone.

5.6 Lithium

Lithium is widely used as a mood stabiliser in subjects with bipolar disorder. Since approximately half of the patients have their first episode before the age of 30 years, it is inevitable that many women become pregnant while being treated with lithium.

The impact of lithium in pregnancy has been well studied. *In utero* exposure is associated with an increased risk of congenital heart defects. Epstein's anomaly is the most severe cardiac anomaly associated with lithium treatment. However, the absolute risk of Epstein's anomaly is very low (1 of 1000), but the risk is somewhat higher for other, less severe, congenital heart defects.[52,97] Lithium use has also been associated with premature delivery[98] and fetal loss.[99]

The teratogenic risk associated with lithium treatment during pregnancy needs to be balanced against the risk of manic or depressive relapse in the mother following medication discontinuation. Signs of lithium intoxication have been reported in the offspring even at therapeutic maternal blood concentrations of lithium. Such symptoms include hypotonia, cyanosis, lethargy and hypothermia.[100,101] No delayed neurobehavioural development after the neonatal period has been seen. However, to our knowledge, only one study addressing this question has been performed, which was based on the so-called 'Register of Lithium Babies'.[102] The development of *in utero* exposed children was compared with that of their non-exposed siblings. No significant differences were found between the two groups. However, the study sample was small and the information was not based on objective measures, but on the mothers' assessment.

Lithium should preferably be avoided during pregnancy, at least during the first trimester when the organogenesis takes place. If lithium treatment in pregnancy is considered necessary, it is important to use monotherapy, the lowest effective dose and multiple doses to avoid high peak exposures in the infant. The renal lithium clearance increases during pregnancy; hence, the serum lithium concentration falls. Therefore, it is important to repeatedly measure the serum concentration during pregnancy. If the lithium dose has been increased during pregnancy it should be decreased in early labour in order to avoid lithium intoxication in the woman after delivery.[103]

5.7 Antiepileptic Drugs

Carbamazepine and valproic acid have been used as a treatment of epilepsy for decades. These drugs are now also used as an alternative to lithium in the treatment of bipolar disorders.

In utero exposure to carbamazepine and valproic acid has been associated with an increased risk of neural tube defects. Approximately 0.5–1% of the infants exposed to carbamazepine and 1–5% of the infants exposed to valproic acid are reported to have neural tube defects.[52,104] Oral clefts and other congenital malformations have also been described.[105,106] Neural tube defects from any cause are associated with low maternal folate levels. Daily intake of folate (4 mg/day) beginning 4 weeks before conception has been recommended to decrease the risk of neural tube defects.[107] However, a specific protective effect of folate during antiepileptic drug therapy has not been demonstrated in humans.

To our knowledge, there are few reports of neonatal toxicity caused by carbamazepine, whereas the risk of neonatal toxicity seems to be higher for valproic acid.[108] Carbamazepine is metabolised relatively rapidly neonatally, which may explain a relatively low risk of adverse effects in the child. So far, data on prenatal carbamazepine exposure are contradictory regarding neurobehavioural long-term effects[109-111] and scarce regarding valproic acid.[111] It has also been suggested that it is the epilepsy itself

that causes developmental delay in the child. Lower IQ values have been suggested among children of epileptic mothers not using any medication.[112,113] However, others have found no impaired cognitive function.[114]

Many clinicians prefer to prescribe lithium in pregnant women since the risk of Ebstein's anomaly is relatively remote compared with the risk of neural tube defects after exposure to antiepileptics.[25] A substantial proportion of the fetal malformations may be detected by prenatal diagnosis. Therefore, fetal ultrasound examination has been recommended when any of the mood stabilisers are used.[52]

The second-generation antiepileptic lamotrigine has been used as a treatment for epilepsy for more than a decade and is today often the first choice for patients with the condition. Lamotrigine has also recently been approved as a mood stabilising therapy and appears to be less harmful to the fetus than traditional antiepileptic drugs. The International Lamotrigine Registry of GlaxoSmithKline[115] included (until March 2004) 414 pregnant women exposed to lamotrigine monotherapy, of whom 12 women had offspring with major defects. This sample is still of insufficient size to reach definite conclusions about the possible teratogenic risk of this drug. Prospective data on 51 women exposed during pregnancy also suggest that there is no increase in major malformations.[116] However, the sample size was too small to draw any definite conclusions.

5.8 Antipsychotic Agents

Severe depression with psychotic features may require antipsychotic medication. Antipsychotic agents can generally be grouped into three classes: (i) low-potency antipsychotics such as phenothiazines; (ii) high-potency antipsychotics such as haloperidol; and (iii) novel antipsychotics such as risperidone, clozapine, olanzapine, quetiapine, ziprasidone, aripiprazole, amisulpride and sertindole. Some of the novel antipsychotic agents have also been recommended as monotherapy in the treatment of bipolar disorders.

The antipsychotic drugs that have been most thoroughly studied in pregnancy are the phenothiazines (low-potency) and haloperidol (high-potency). A meta-analysis reported a slightly increased risk of congenital malformations after first trimester exposure to low-potency antipsychotic drugs and prenatal exposure may give a small increase of poor outcome.[52] To date, there is no conclusive evidence of an association between the risk of malformation and haloperidol.

There is no conclusive evidence of an increased risk of congenital malformations after exposure to novel antipsychotics. However, few studies have been performed.[117,118] There is, to our knowledge, no data on neonatal effects or neurobehavioural long-term effects associated with the use of novel antipsychotic drugs during pregnancy.

5.9 Summary of Safety Considerations

Table I includes the teratogenicity, neonatal effects and long-term neurobehavioural risks associated with antidepressant and mood-stabilising agents during pregnancy.

6. Conclusions

Diagnosing depression in pregnant women is difficult because many common 'normal' symptoms during pregnancy may be misconstrued as depressive symptomatology. Depressive symptoms may also falsely be interpreted as pregnancy related.

Non-pharmacological interventions may be useful for patients with mild to moderate depressive illness. However, the lack of evidence-based knowledge on non-pharmacological antidepressant therapies in pregnant women is striking.

Pregnant women with severe depression may require pharmacological treatment. SSRIs and tricyclic antidepressants have not been associated with an increased risk of major malformations. However, poor neonatal adaptation has been described. Benzodiazepines used in the first trimester have been associated with orofacial clefts. Mood stabilisers such as lithium, carbamazepine and valproic acid are associated with an increased risk of fetal malformations. Both benzodiazepines and lithium used in high doses in the last trimester of pregnancy may cause adaptation problems in the newborn. *In utero*

Table I. Adverse effects associated with antidepressant and mood-stabilising agents during pregnancy

Drug	Teratogenicity	Neonatal effects	Long-term neurobehavioural effects
Selective serotonin reuptake inhibitors	Appear to be relatively safe	Various perinatal complications	Limited evidence of neurobehavioural effects, requires further investigation
Tricyclic antidepressants	No increased risk of major malformations	Anticholinergic effects and withdrawal syndromes	No conclusive evidence of neurobehavioural effects
Other antidepressants	Limited data	Limited data	Limited data
Benzodiazepines	Possible risk of cleft palate	'Floppy infant syndrome' and withdrawal syndromes	Some evidence of developmental delay
Lithium	Increased risk of cardiac anomalies	Risk of lithium intoxication in the newborn	Limited data
Carbamazepine/valproic acid	Increased risk of neural tube defects, but also other congenital malformations	Limited data	Difficult to determine because of confounding effects of maternal epilepsy
Lamotrigine	Probably no increased risk; however, limited data	Limited data	Limited data
Novel antipsychotics	Probably no increased risk; however, limited data	Limited data	Limited data

exposure to novel antipsychotics has not been associated with congenital malformations; however, the data are still limited. The knowledge about neurobehavioural effects in offspring is still limited for all agents.

The existing knowledge on the consequences of the use of antidepressants during pregnancy suffers from a lack of results from randomised controlled trials. Most of the observational studies can be criticised for inadequate design, such as small sample sizes, short follow-up times and lack of control for confounding factors. Systematic research is needed to gain knowledge on the effects of *in utero* antidepressant exposure on child development. Possible adverse effects of fetal exposure to psychotropic drugs must be balanced against the adverse effects of untreated maternal mood disorders. However, the wellbeing of the mother is crucial for the wellbeing of the fetus.

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References

1. Paffenbarger R. Epidemiological aspects of mental illness associated with childbearing. In: Brockington I, Kumar R, editors. Motherhood and mental illness. London: Academic Press, 1982: 19-36
2. Altshuler L, Hendrick V, Cohen L. Course of mood and anxiety disorders during pregnancy and the postpartum period. J Clin Psychiatry 1998; 59: 29-33
3. Evans J, Heron J, Francomb H, et al. Cohort study of depressed mood during pregnancy and after childbirth. BMJ 2001; 323: 257-60
4. Eberhard-Gran M, Tambs K, Opjordsmoen S, et al. Depression during pregnancy and after delivery: a repeated measurement study. J Psychosom Obstet Gynecol 2004; 25: 15-21
5. Johanson R, Chapman G, Murray L, et al. The North Staffordshire Maternity Hospital prospective study of pregnancy-associated depression. J Psychosom Obstet Gynaecol 2000; 21: 93-7
6. Josefsson A, Berg G, Nordin C, et al. Prevalence of depressive symptoms in late pregnancy and postpartum. Acta Obstet Gynecol Scand 2001; 80: 251-5
7. Brockington I, Cernick K, Schofield E, et al. Puerperal psychosis. Arch Gen Psychiatry 1981; 38: 829-33
8. Kendell RE, Chalmers JC, Platz C. Epidemiology of puerperal psychoses. Br J Psychiatry 1987; 150: 662-73
9. Angst J. The emerging epidemiology of hypomania and bipolar II disorder. J Affect Disord 1998; 50: 143-51
10. Brockington I. Postpartum psychiatric disorders. Lancet 2004; 363: 303-10
11. Watson JP, Elliot SA, Rugg AJ. Psychiatric disorder in pregnancy and the first postnatal year. Br J Psychiatry 1984; 144: 453-62
12. Kumar R, Robson KM. A prospective study of emotional disorders in child-bearing women. Br J Psychiatry 1984; 144: 35-47
13. Zuckerman B, Amaro H, Bauchner H, et al. Depressive symptoms during pregnancy: relationship to poor health behaviors. Am J Obstet Gynecol 1989; 160: 1107-11
14. Peacock JL, Bland JM, Andersen HR. Preterm delivery: effects of socioeconomic factors, psychological stress, smoking, alcohol, and caffeine. BMJ 1995; 311: 531-5
15. Pollack H, Lantz PM, Frohna JG. Maternal smoking and adverse birth outcomes among singletons and twins. Am J Public Health 2000; 90: 395-400

16. Pritchard C, Teo P. Preterm birth, low birth weight, and the stressfulness of the household role for pregnant women. Soc Sci Med 1994; 38: 89-96
17. Rini C, Dunkel-Schetter C, Wadhwa P, et al. Psychological adaptation and birth outcomes: the role of personal resources, stress, and sociocultural context in pregnancy. Health Psychol 1999; 18: 333-45
18. Teixeira J, Fisk N, Glover V. Association between maternal anxiety in pregnancy and increased uterine artery resistance index: cohort based study. BMJ 1999; 318: 153-7
19. Copper R, Goldenberg R, Das A, et al. The preterm prediction study: maternal stress is associated with spontaneous preterm birth at less than thirty-five weeks' gestation. Am J Obstet Gynecol 1996; 175: 1286-92
20. Paarlberg K, Vingerhoets J, Passchier J, et al. Psychosocial predictors of low birthweight: a prospective study. Br J Obstet Gynaecol 1999; 106: 834-41
21. Wadhwa P, Sandman C, Porto M, et al. The association between prenatal stress and infant birth weight and gestational age at birth: a prospective investigation. Am J Obstet Gynecol 1993; 169: 858-65
22. Hedegaard M, Henriksen T, Secher N, et al. Do stressful life events affect duration of gestation and risk of preterm delivery? Epidemiology 1996; 7: 339-45
23. Lobel M, Dunkel-Schetter C, Scrimshaw S. Prenatal maternal stress and prematurity: a prospective study of socioeconomically disadvantaged women. Health Psychol 1992; 11: 32-40
24. Reeb K, Graham A, Zyzanski S, et al. Predicting low birthweight and complicated labor in urban black women: a biopsychosocial perspective. Soc Sci Med 1987; 25: 1321-7
25. Marcus S, Barry K, Flynn H, et al. Treatment guidelines for depression in pregnancy. Int J Gynaecol Obstet 2001; 72: 61-70
26. Ward R, Zamorski M. Benefits and risks of psychiatric medications during pregnancy. Am Fam Physician 2002; 15: 629-36
27. Nonacs R, Cohen L. Depression during pregnancy: diagnosis and treatment options. J Clin Psychiatry 2002; 63: 24-30
28. Altshuler L. The use of SSRIs in depressive disorders specific to women. J Clin Psychiatry 2002; 63: 3-8
29. Newport D, Wilcox M, Stowe Z. Antidepressants during pregnancy and lactation: defining exposure and treatment issues. Semin Perinatol 2001; 25: 177-90
30. Wisner K, Gelenberg A, Leonard H, et al. Pharmacologic treatment of depression during pregnancy. JAMA 1999; 282: 1264-9
31. Grush L, Cohen L. Treatment of depression during pregnancy: balancing the risks. Harv Rev Psychiatry 1998; 6: 105-9
32. Yonkers K, Wisner K, Stowe Z, et al. Management of bipolar disorder during pregnancy and the postpartum period. Am J Psychiatry 2004; 161: 608-20
33. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression: development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry 1987; 150: 782-6
34. Murray L, Cox J. Screening for depression during pregnancy with the Edinburgh postnatal depression scale (EPDS). J Reprod Infant Psychol 1990; 8: 99-107
35. Eberhard-Gran M, Eskild A, Tambs K, et al. Review of validation studies of the Edinburgh Postnatal Depression Scale. Acta Psychiatr Scand 2001; 104: 243-9
36. O'Hara MW, Zekoski E. Postpartum depression: a comprehensive review. In: Kumar R, Brockington I, editors. Motherhood and mental illness. London: Wright, 1988: 17-63
37. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Press, 1994
38. Altshuler L, Hendrick V. Pregnancy and psychotropic medication. J Clin Pharmacol 1996; 16: 78-80
39. Wisner KL, Perel JM, Wheeler SB. Tricyclic dose requirements across pregnancy. Am J Psychiatry 1993; 150: 1541-2
40. Levy G. Pharmacokinetics of fetal and neonatal exposure to drugs. Obstet Gynecol 1981; 58 (5 Suppl.): 9S-16S
41. Cohen L, Rosenbaum J. Psychotropic drug use during pregnancy: weighing the risks. J Clin Psychiatry 2003; 59: 18-28
42. Hendrick V, Altshuler L. Management of major depression during pregnancy. Am J Psychiatry 2002; 159: 1667-73
43. Moore K. The developing human: clinically oriented embryology. 6th ed. Philadelphia (PA): WB Saunders Co, 1998
44. Elkin I, Shea M, Watkins J, et al. National Institute of Mental Health Treatment of Depression Collaborative Research Program: general effectiveness of treatments. Arch Gen Psychiatry 1989; 46: 971-82
45. Oren D, Wisner K, Spinelli M, et al. An open trial of morning light therapy for treatment of antepartum depression. Am J Psychiatry 2002; 159: 666-9
46. Spinelli M, Endicott J. Controlled clinical trial of interpersonal psychotherapy versus parenting education program for depressed pregnant women. Am J Psychiatry 2003; 160: 555-62
47. Rabheru K. The use of electroconvulsive therapy in special patient populations. Can J Psychiatry 2001; 46: 710-9
48. Miller L. Use of electroconvulsive therapy during pregnancy. Hosp Community Psychiatry 1994; 45: 444-50
49. Moreno M, Munoz J, Valderrabanos J, et al. Electroconvulsive therapy in first trimester of pregnancy. J ECT 1998; 4: 251-4
50. Stokes P, Holtz A. Fluoxetine tenth anniversary update: the progress continues. Clin Ther 1997; 19: 1135-250
51. Kulin N, Pastuszak A, Sage S, et al. Pregnancy outcome following maternal use of new selective seretonin reuptake inhibitors: a prospective controlled multicenter study. JAMA 1998; 279: 609-10
52. Altshuler L, Cohen L, Szuba M, et al. Pharmacologic management of psychiatric illness during pregnancy: dilemmas and guidelines. Am J Psychiatry 1996; 153: 592-606
53. McElhatton P, Garbis H, Elefant E, et al. The outcome of pregnancy in 689 women exposed to therapeutic doses of antidepressants: a collaborative study of the European Network of Teratology Information Services (ENTIS). Reprod Toxicol 1996; 10: 285-94
54. Nulman I, Rovert J, Stewart D, et al. Neurodevelopment of children exposed in utero to antidepressant drugs. N Engl J Med 1997; 336: 258-362
55. Ericson A, Kallen B, Wiholm B. Delivery outcome after the use of antidepressants in early pregnancy. Eur J Pharmacol 1999; 55: 503-8
56. Chambers C, Johnson K, Dick L, et al. Birth outcomes in pregnant women taking fluoxetine. N Engl J Med 1996; 335: 1010-5
57. Pastuszak A, Schick-Boschetto B, Zuber C, et al. Pregnancy outcome following first-trimester exposure to fluoxetine (Prozac). JAMA 1993; 269: 2246-8
58. Goldstein D, Corbin L, Sundell K. Effects of first-trimester fluoxetine exposure on the newborn. Obstet Gynecol 1997; 89: 713-8
59. Addis A, Koren G. Safety of fluoxetine during the first trimester of pregnancy: a meta-analytical review of epidemiological studies. Psychol Med 2000; 30: 89-94

60. Robert E. Treatment depression in pregnancy. N Engl J Med 1996; 335: 1056-8
61. Nordeng H, Lindemann R, Perminov K, et al. Neonatal withdrawal syndrome after in utero exposure to selective serotonin reuptake inhibitors. Acta Pædiatr 2001; 90: 288-91
62. Dahl M, Olhager E, Ahlner J. Paroxetine withdrawal syndrome in a neonate. Br J Psychiatry 1997; 171: 391-2
63. Nijhuis I, Kok-Van Rooij G, Bosschaart A. Withdrawal reactions of a premature neonate after maternal use of paroxetine [letter]. Arch Dis Child Fetal Neonatal Ed 2001; 84: F77
64. Spencer M. Fluoxetine hydrochloride (Prozac) toxicity in a neonate. Pediatrics 1993; 92: 721-2
65. Mhanna M, Bennet JI, Izatt S. Potential fluoxetine chloride (Prozac) toxicity in a newborn. Pediatrics 1997; 100: 158-9
66. Kent L, Laidlaw J. Suspected congenital sertraline dependence. Br J Psychiatry 1995; 167: 412-3
67. American Academy of Pediatrics. Committee on drugs: neonatal drug withdrawal. Pediatrics 1998; 101: 1079-88
68. Laine K, Heikkinen T, Ekblad U, et al. Effects of exposure to selective serotonin reuptake inhibitors during pregnancy on serotonergic symptoms in newborns and cord blood monoamine and prolactin concentrations. Arch Gen Psychiatry 2003; 60: 720-6
69. Costei A, Kozer E, Ho T, et al. Perinatal outcome following third trimester exposure to paroxetine. Arch Pediatr Adolesc Med 2002; 156: 1129-32
70. Cohen L, Heller A, Bailey J, et al. Birth outcome following prenatal exposure to fluoxetine. Biol Psychiatry 2000; 48: 996-1000
71. Casper R, Fleisher B, Lee-Ancajas J, et al. Follow-up of children of depressed mothers exposed or not exposed to antidepressant drugs during pregnancy. J Pediatr 2003; 142: 402-8
72. Simon G, Cunningham M, Davis R. Outcomes of prenatal antidepressant exposure. Am J Psychiatry 2002; 159: 2055-61
73. Kallen B. Neonate characteristics after maternal use of antidepressants in late pregnancy. Arch Pediatr Adolesc Med 2004; 158: 312-6
74. Duijvestijn Y, Kalmeijer M, Passier A, et al. Neonatal intraventricular haemorrhage associated with maternal use of paroxetine. Br J Clin Pharmacol 2003; 56: 581-2
75. Heikkinen T, Ekblad U, Palo P, et al. Pharmacokinetics of fluoxetine and norfluoxetine in pregancy and lactation. Clin Pharmacol Ther 2003; 73: 330-7
76. Nulman I, Rovet J, Stewart D, et al. Child development following exposure to tricyclic antidepressants or fluoxetine throughout fetal life: a prospective, controlled study. Am J Psychiatry 2002; 159: 1889-95
77. Heikkinen T, Ekblad U, Kero P, et al. Citalopram in pregnancy and lactation. Clin Pharmacol Ther 2002; 72: 184-91
78. Zeskind P, Stephens L. Maternal selective serotonin reuptake inhibitor use during pregnancy and newborn neurobehavior. Pediatrics 2004; 113: 368-75
79. The National Toxicology Program (NTP). Center for Evaluation of Risks to Human Reproduction (CERHR). Monograph on the potential human reproductive effects of fluoxetine: appendix II: 143, 2004 Nov [online]. Available from URL: http://www.cerhr.niehs.nih.gov [Accessed 2004 Dec 1]
80. Misri S, Sivertz K. Tricyclic drugs in pregnancy and lactation: a preliminary report. Int J Psychiatry Med 1991; 21: 157-71
81. Loebstein R, Koren G. Pregnancy outcome and neurodevelopment of children exposed in utero to psychoactive drugs: the Motherisk experience. J Psychiatry Neurosci 1997; 22: 192-6
82. Bromiker R, Kaplan M. Apparant intrauterine fetal withdrawal from chlomipramine hydrochloride. JAMA 1994; 272: 1722-3
83. Cowe L, Lloyd D, Dawling S. Neonatal convulsions caused by withdrawal from maternal clomipramine. BMJ 1982; 284: 1837-8
84. Eggermont E. Withdrawal symptoms in neonates associated with maternal imipramine therapy [letter]. Lancet 1973; II: 680
85. Schimmell M, Katz E, Shaag Y, et al. Toxic neonatal effects following maternal clomipramine therapy. J Toxicol Clin Toxicol 1991; 29: 479-84
86. Webster P. Withdrawal symptoms in neonates associated with maternal antidepressant therapy. Lancet 1973; II: 318-9
87. Einarson A, Fatoye B, Sarkar M, et al. Pregnancy outcome following gestational exposure to venlafaxin: a multicenter prospective controlled study. Am J Psychiatry 2001; 158: 1728-30
88. Heinonen O, Slone D, Shapiro S. Birth defects and drugs in pregnancy. Littleton (MA): Publishing Services Group, 1977
89. Cooper AJ. Tyramine and irreversible monoamine oxidase inhibitors in clinical practice. Br J Psychiatry Suppl 1989; (6): 38-45
90. Shade RJ, Greenblatt DJ. Use of benzodiazepines in anxiety disorders. N Eng J Med 1993; 328: 1398-405
91. Dolovich L, Addis A, Vaillancourt J, et al. Benzodiazepine use in pregnancy and major malformations or oral cleft: meta-analysis of cohort and case-control studies. BMJ 1998; 317: 839-43
92. Iqbal M, Sobhan T, Ryals T. Effects of commonly used benzodiazepines on the fetus, the neonate, and the nursing infant. Psychiatr Serv 2002; 53: 39-49
93. McElhatton P. The effects of benzodiazepine use during pregnancy and lactation. Reprod Toxicol 1994; 8: 461-75
94. McGrath C, Buist A, Norman T. Treatment of anxiety during pregnancy. Drug Saf 1999; 20: 171-86
95. Viggedal G. Mental development in late infancy after prenatal exposure to benzodiazepines: a prospective study. J Child Psychol Psychiatry 1993; 34: 295-305
96. Nesse R, Zamorski M. Anxiety disorders in primary care. In: Knesper D, Riba M, Schwenk T, editors. Primary care psychiatry. Philadelphia (PA): Saunders, 1997: 132-162
97. Cohen L, Friedman J, Jefferson J, et al. A reevaluation of risk of in utero exposure to lithium. JAMA 1994; 271: 146-50
98. Troyer W, Pereira G, Lannon R, et al. Association of maternal lithium exposure and premature delivery. J Perinatol 1993; 13: 123-7
99. Stewart D, Klompenhouwer J, Kendell R, et al. Prophylactic lithium in puerperal psychosis: the experience of three centres. Br J Psychiatry 1991; 158: 393-7
100. Wisner K, Perel J. Psychopharmacological treatment during pregnancy. In: Jensvold M, Halbreich U, Hamilton J, editors. Psychopharmacology and women: sex, gender and hormones. Washington, DC: American Psychiatric Press, 1996: 191-224
101. Sitland-Marken P, Rickman L, Wells B, et al. Pharmacological management of acute mania in pregnancy. J Clin Psychopharmacol 1989; 9: 78-87
102. Schou M. What happened later to the lithium babies? A follow-up study of children born without malformations. Acta Psychiatr Scand 1976; 54: 193-7
103. Schou M. Treating recurrent affective disorders during and after pregnancy. Drug Saf 1998; 18: 143-52
104. Rosa F. Spina bifida in infants of women treated with carbamazepine during pregnancy. N Engl J Med 1991; 324: 674-7

105. Delgado-Escueta A, Janz D. Consensus guidelines: preconception counseling, management and care of the pregnant woman with epilepsy. Neurology 1992; 45 Suppl. 5: 149-60
106. Shaw G, Wasserman C, O'Malley C, et al. Orofacial clefts and maternal anticonvulsant use. Reprod Toxicol 1995; 9: 97-8
107. MRC Vitamin Study Research Group. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. Lancet 1991; 338: 131-7
108. Kennedy D, Koren G. Valproic acid use in psychiatry: issues in treating women of reproductive age. J Psychiatry Neurosci 1998; 23: 223-8
109. Ornoy A, Cohen E. Outcome of children born to epileptic mothers treated with carbamazepine during pregnancy. Arch Dis Child 1996; 75: 517-20
110. Scolnik D, Nulman I, Rovet J, et al. Neurodevelopment of children exposed in utero to phenytoin and carbamazepine monotherapy. JAMA 1994; 271: 767-70
111. Gaily E, Kantola-Sorsa E, Hiilesmaa V, et al. Normal intelligence in children with prenatal exposure to carbamazepine. Neurology 2004; 62: 28-32
112. Shapiro S, Slone D, Hartz S. Anticonvulsants and parental epilepsy in the development of birth defects. Lancet 1976; I: 272-5
113. Gaily E, Kantola-Sorsa E, Granström M. Intelligence of children of epileptic mothers. J Pediatr 1988; 113: 677-84
114. Holmes L, Rosenberger P, Harvey E. An evaluation of whether maternal epilepsy (no drugs) is associated with an increased rate of cognitive dysfunction [abstract 37]. Teratology 1995; 51: 165
115. GlaxoSmithKline. Lamotrigine Pregnancy Registry. Interim report: 1 September 1992 through 31 March 2004
116. Sabers A, Dam M, A-Rogvi-Hansen B, et al. Epilepsy and pregnancy: lamotrigine as main drug used. Acta Neurol Scand 2004; 109: 9-13
117. Goldstein D. Olanzapine-exposed pregnancies and lactation: early experience. J Clin Psychopharmacol 2000; 20: 399-403
118. Littrell K, Johnson C, Peabody C, et al. Antipsychotics during pregnancy [letter]. Am J Psychiatry 2000; 157: 1342

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