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# Treating Recurrent Affective Disorders During and After Pregnancy

## What Can Be Taken Safely?

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## Contents



## Summary

Since pregnancy and the time thereafter is a precarious period for women with recurrent affective disorders and their offspring, it is important to determine the risk of various treatments for such disorders. This review assesses the risk to the fetus, the perinatal risks for mother and infant, the risks associated with treatment during the puerperium and breastfeeding, and the risks to the later development of the child.

This review considers treatment with lithium, tricyclic antidepressants (TCAs), selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors (SSRIs), monoamine oxidase inhibitors, other antidepressants, and the anticonvulsants carbamazepine and valproic acid (sodium valproate).

According to available evidence, use of lithium, TCAs and SSRIs is justified during and after pregnancy if treatment is required; no prophylactic treatment has a lower risk **:** benefit ratio. The review provides guidelines for the use of these drugs.

Is it safe for women with recurrent affective disorders to receive no treatment during pregnancy? The answer to this question is: no, usually it is not. Such women may require prophylactic treatment during pregnancy, delivery and the puerperium. They may also need treatment for episodes of an affective disorder arising during the pregnancy. Women with depression are at increased risk of killing themselves or their children, while women with manic symptoms tend to smoke and drink without inhibitions and are more accident-prone.

This review discusses the risks and benefits to pregnant women and their offspring of drug treatment for recurrent affective disorders. It is based on the author's own literature database on lithium, and on searches for all the years relevant to this review (the 1960s and thereafter) in Medline and the Danish university libraries. No unpublished data from pharmaceutical companies have been used.

## 1. Lithium

Lithium was the first psychotropic drug that attracted interest in connection with use during pregnancy. It was introduced to psychiatric practice as an antimanic drug,[1,2] and in the 1960s was found to prevent not only manic, but also depressive, recurrences.[3,4] Lithium treatment prevents recurrences of (major) depressive disorder and bipolar disorder with equal efficacy.

### 1.1 Risks to the Fetus

Animal experiments have shown marked teratogenic effects of lithium in, for example, sea urchins, snails, frogs, mice and rats, and although conclusions cannot be extrapolated from effects in one species (e.g. rats) to effects in another species (e.g. humans), lithium treatment could conceivably be teratogenic when given to pregnant women during the first trimester. Lithium had, for about a century, been used in humans for various medicinal purposes, but it had never been given to pregnant women. Therefore, if prophylactic lithium treatment had teratogenic potential, it was vital to discover as quickly as possible whether the risk was such that lithium treatment should be totally avoided in fertile women.

The first observations on children who had been exposed to lithium *in utero* were reassuring, but eventually children with congenital malformations were reported. In 1969, a so-called 'Register of Lithium Babies' was started.[5] It was employed first in Scandinavia, but later joined forces with a US-Canadian register. In notes published at intervals in psychiatric and general medical journals, physicians were urged to submit reports about 'lithium babies', whether healthy or malformed, who came to their attention. A 'lithium baby' was defined as a child born of a woman who had been treated with lithium during at least the first trimester. The first reports were published in 1973.[6,7]

The register was not meant to measure the true teratogenic potential of prophylactic lithium treatment. Since it was based on voluntary reports, over-reporting of abnormalities could be anticipated. A child was more likely to be recognised and reported if it had a malformation than if it was healthy, and gross malformations with a serious prognosis would almost certainly be discovered. From the beginning, this bias was pointed out by the investigators themselves[5-7] and later criticism of them for having used flawed methods is unjustified. The purpose of the register was to give early warning about major teratogenic risks of lithium treatment. When such risks were found not to exist, the register had fulfilled its mission and was closed.

The situation was reviewed in 1990.[8] At the time of its closure in 1979, the register contained information about 225 'lithium babies'. Among these, 11% had visible malformations at birth, compared with a rate of 2 to 4% in the general population. In 18 children (8% of the register), malformations involved the heart and the big vessels (1% in the general population) and there were 6 cases of the cardiac malformation known as Ebstein's anomaly (2.7%, compared with 0.005% in the general population).

When the lithium baby register was started in 1969 psychiatrists were not used to thinking along teratogenic lines and the register's estimate of max-

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imum teratogenic risk of lithium treatment was taken by many as a measure of the treatment's true teratogenic risk. Today, no-one would consider parents' reports about malformed children after the launching of a new psychotropic drug to be a measure of the true teratogenic risk of the drug.

Embryologists from Sweden[9] linked a register of women with manic-depressive disorder with a register of children with congenital malformations. Among 59 children of women who had taken lithium during the pregnancy, 7 children had malformations, 4 of them heart defects (none had Ebstein's anomaly). Among 228 children of women who had not taken lithium, 9 children had malformations, 2 of them heart defects (again, no cases of Ebstein's anomaly). The differences between the 2 groups were statistically significant ($p < 0.05$).

In a prospective study of 50 women in California, US, who used lithium in the first trimester, 2 of the children had malformations, although none had a heart defect.[10] This malformation rate is not higher than that in the general population.

In a US-Canadian prospective study,[11] the researchers recruited and followed 148 women who were taking lithium during the first trimester and who consulted 1 of 4 teratogen information centres. The children were compared with the children of 148 age-matched women who had not taken lithium. In each group, there were 3 children with major congenital malformations. One fetus in the lithium group had Ebstein's anomaly, which was diagnosed at 15 weeks' gestation; this pregnancy was terminated. The difference between the lithium group and the control group was not statistically significant, and the authors concluded that women with major affective disorders who wish to have children may continue lithium treatment, provided that adequate screening tests for cardiac malformations are carried out.

A review[12] pointed out that the first of the 3 cohort studies[9] (n = 59) indicated that the frequency of major malformation with lithium was 1.5 to 3.0 times higher, and the frequency of cardiac malformations 1.2 to 7.7 times higher, than in unexposed women. In the 2 further cohort studies[10,11] (n = 198) the frequency of malformations, including cardiac problems, was not higher than in unexposed women.

A case-control approach has also been used. Canadian embryologists[13] identified 59 children with Ebstein's anomaly. None of the mothers had been treated with lithium. In a control group of children with neuroblastoma, one of the mothers had received lithium. None of 34 US children with Ebstein's anomaly was born to a mother with a history of lithium use during pregnancy.[14] In a Czech study,[15] no child with Ebstein's anomaly was found among 89 exposed to lithium *in utero*; among 168 women in the control group, there was 1 child with this anomaly. A Swedish study with a 'nested case-control' design[16] identified 11 infants with suspected or proven cardiac malformations, 3 (27%) of which had lithium-treated mothers; of the 20 infants without cardiac defects, 4 (20%) had a lithium-treated mother. The mother of 1 child with Ebstein's anomaly had not been given lithium.

### 1.2 Perinatal, Puerperal and Developmental Risks

Lithium is excreted almost exclusively through the kidneys; the renal lithium clearance is usually 20% of the glomerular filtration rate (GFR).[17] The GFR rises gradually during pregnancy and falls abruptly to pre-pregnancy values at the time of delivery; lithium clearance does the same. Four healthy pregnant women were given a small test dose of lithium to determine their lithium clearance; a few months before delivery, the average clearance was 30 ml/min and a few weeks after delivery it was 15 ml/min.[18]

These changes in elimination rate have led to underdosage of lithium to women during pregnancy and overdosage, with signs of intoxication, immediately after delivery.[19-21] Signs of lithium toxicity have also been exhibited by some children shortly after birth, including convulsions, lethargy, flaccid muscle tone, poor sucking, cyanosis, systolic murmurs, cardiac arrhythmia, tricuspid valve regurgitation, respiratory distress, neonatal goitre

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and transient nephrogenic diabetes insipidus.[19,22-32] Diabetes insipidus with the production of a large volume of urine is sometimes an adverse effect of lithium treatment. Diabetes insipidus *in utero* resulting in hydramnios in 2 cases[30,32] was probably caused by the mothers' lithium treatment. Mothers and children recovered within a few days without signs of permanent damage.

In order to avoid underdosage and overdosage of lithium during pregnancy and at delivery, physicians should determine the serum lithium concentration at weekly intervals during the last month of pregnancy, and every second day immediately before and after delivery, so that appropriate dosage adjustments can be made. When it has been necessary to raise the lithium dosage during pregnancy, it should be lowered to the pre-pregnancy level when labour is established.

The risk of manic or depressive recurrences is very high during the puerperium. In a Danish study,[33,34] the frequency of hospitalisations was 8 times higher during the first month after delivery than during periods not related to pregnancy and delivery, and was twice that during the 2nd to 12th month after delivery. It is particularly important that prophylactic treatment is continued or resumed at full dosages immediately after the delivery.[35,36]

During the first week of life, the serum lithium concentration of breastfed infants is about one-half, and during the following weeks about one-third, that of the mother.[37] At one time, it was recommended that bottlefeeding should replace breastfeeding when the mother was receiving lithium treatment.[38] However, not all women followed this advice and this did not usually harm the children, although in connection with a common cold, one child developed confusion and restlessness with a serum lithium concentration of 1.5 mmol/L;[39] a few days after switching to bottlefeeding, all symptoms had disappeared. In recent years, advice has become less categorical about bottle-feeding and breastfeeding. A number of studies have shown that breastfeeding plays an important role for both mother and child, both mentally and physically,[40] and it remains to be answered whether there are more risks or more benefits in abstaining from breastfeeding during lithium treatment.[41]

Most of the children of lithium-treated women are born without malformations, but they might develop functional abnormalities later in life. Information was therefore collected about Scandinavian 'lithium children' who were born without malformations and who had reached the age of 5 years or older – old enough to manifest possible physical or mental deficiencies.[42] The development of these children was compared with that of their non-exposed siblings who shared a number of genetic and environmental conditions with the lithium-exposed children. No significant differences were found between the 2 groups. Quite clearly, with sample sizes of 60 lithium children and 57 siblings, and with information based on the mothers' assessment, such a study could not and was not meant to exclude the possibility of late adverse effects of fetal lithium exposure. It merely showed that, if present, such abnormalities were inconspicuous.

## 2. Antidepressants

In patients with recurrent depressive disorder (major depression), maintenance treatment with antidepressant drugs alleviates or prevents further depressive episodes. In those with recurrent bipolar disorder, the prophylactic action against depression is to some extent offset by the tendency of tricyclic antidepressants (TCAs) to induce rapid cycling and mixed affective states.[43,44]

### 2.1 Risks to the Fetus

The evidence of teratogenicity during use of antidepressant drugs is best characterised in the words of a review from 1996.[45] 'While 3 small studies of first-trimester exposure were prospective, the remainder [of 14 studies listed in the review] consisted of chart reviews or case-control studies including relatively few patients who were exposed to antidepressants in the first trimester of pregnancy. With over 300 000 births described, only 414 cases of first-trimester exposures to TCA

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were noted. When evaluated on an individual basis and when pooled, these studies fail to indicate a significant association between fetal exposure to TCA and high rates of congenital malformations.' However, the review pointed out that the lack of difference between exposed and nonexposed groups may be a result of the small number of patients studied rather than a result of a low teratogenic risk.[45]

In the largest of the prospective studies[46] referred to in the review,[45] 128 pregnant women exposed during the first trimester to the selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitor (SSRI) fluoxetine were compared with 2 matched groups of women exposed to either a TCA or a nonteratogenic agent (acetaminophen, penicillin, dental x-rays). The numbers of malformations in the 3 groups did not significantly differ from each other, and were not higher than those expected in the general population. The study authors[46] emphasised that much larger numbers of exposures would be necessary to rule out teratogenicity of antidepressant drugs.

A later study[47] collected and evaluated data on 689 pregnancies in which there was exposure to TCA and non-TCA antidepressants. 14 live-born babies and 1 fetus had either major or minor malformations; no causal relationship could be established between *in utero* exposure to antidepressants and adverse pregnancy outcome.

A prospective study of 228 pregnant women indicated that the risk of minor anomalies was increased when fluoxetine was given during the first trimester, while the risk of premature delivery and poor neonatal adaptation was increased when fluoxetine was given during the third trimester.[48] This study was criticised on the grounds that it was not randomised, that the depressive illness itself might have played a role, and that there was no properly matched control group.[49-51] In reply, the study authors[52] pointed out that an ideal control group probably did not exist. The drug company marketing fluoxetine reported that 4 of 123 children exposed to fluoxetine *in utero* had malformations, a rate that did not differ from the rate in the general population.[51]

Clinical data concerning paroxetine and sertraline are insufficient or absent, as are data concerning the teratogenic effects of other antidepressants, such as mianserin, trazodone and venlafaxine. The review quoted above[45] referred to a study reported in an inaccessible publication. A small group of women were treated during pregnancy with the monoamine oxidase inhibitors (MAOIs) tranylcypromine and phenelzine; their offspring had a higher than normal rate of malformations. Information is missing about possible teratogenic effects of other MAOIs, including the reversible agents such as moclobemide.

### 2.2 Perinatal, Puerperal and Developmental Risks

When a woman receiving antidepressant prophylaxis gives birth, the newborn is no longer exposed to the drug. Effects resembling abstinence after drug withdrawal have been observed after discontinuation of *in utero* antidepressant exposure, including irritability, jitteriness, eye rolling, breathlessness, acrocyanosis, temperature instability, tachycardia and seizures.[53-58]

In one study involving 23 women with at least 1 previous episode of postpartum depression, 15 chose to take antidepressant treatment during the puerperium and 8 chose not to take such treatment. One woman (8%) in the former group and 5 (62%) in the latter group of patients experienced a depressive relapse.[59]

According to several reports, the sera of children breastfed by women treated with antidepressants have contained low concentrations of the drug,[60-65] and no adverse effects were noted in these children. However, on one occasion the serum of an infant with respiratory depression had a high level of doxepin; it is possible that the child metabolised doxepin at a slow rate. On another occasion, the serum of a nursing child without symptoms had a high concentration of fluoxetine; it is possible that a laboratory error had taken place.[62] The following drugs have been recommended as

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suitable for the treatment of depression during breastfeeding: amitriptyline, nortriptyline, desipramine, clomipramine, dothiepin or sertraline.[62]

135 preschool children who were prenatally exposed to a TCA or fluoxetine had normal language and behavioural development 16 to 30 months after the birth.[66] However, there was no control group, and it is conceivable that subtle changes in the brains of exposed children might become apparent later in life.

## 3. Anticonvulsants

Experiences concerning the teratogenicity of anticonvulsant drugs are based exclusively on use in women with epilepsy. In addition to their anticonvulsant effect, carbamazepine and valproic acid (sodium valproate) are therapeutically effective in patients with mania. Other observations indicate that they also have a prophylactic, mood-stabilising action, but this awaits definitive proof.

### 3.1 Risks to the Fetus

Around 1990, a pattern of minor craniofacial defects, fingernail hypoplasia and developmental delay was observed among children who were prenatally exposed to carbamazepine.[67] In a retrospective study of 99 women who took carbamazepine as the only anticonvulsant during pregnancy, 2 children were born with spina bifida. In a meta-analysis of all cohort studies of carbamazepine exposure during pregnancy, the same author found that 984 women gave birth to 9 children with spina bifida.[68] The author concluded that prenatal exposure to carbamazepine carries a 1% risk of spina bifida, about 14 times the rate in the general population. A recent study from Jerusalem, Israel[69] showed that 6 of 49 children (12%) who were prenatally exposed prenatally to carbamazepine had what was called a 'fetal carbamazepine syndrome' characterised by dysmorphic features and mild mental retardation; 5 of the children had major malformations.

Case-control studies have shown that administration of valproic acid to pregnant women with epilepsy was associated with serious malformations such as spina bifida and other neural tube defects in 1 to 2% of the children.[70-72] A so-called 'fetal valproate syndrome' with craniofacial, abdominal wall, cardiovascular, urogenital and digital malformations, combined with developmental delay, has been found in more than half of the children exposed *in utero* to valproic acid.[73-75] Five of 22 pregnancies (23%) with exposure to valproic acid (some of which ended in spontaneous abortion and some of which went to full term) resulted in major malformations among the offspring.[76] Combination of anticonvulsants involves extra risk.[69]

### 3.2 Breastfeeding and the Child's Later Development

The serum concentration of carbamazepine in a child nursed by a carbamazepine-treated woman was only slightly lower than that in the mother's serum,[77] indicating low risk of lactation.

Mental retardation is a feature of both the 'carbamazepine syndrome' and the 'fetal valproate syndrome'.

## 4. Antipsychotics and Tranquillisers

Antipsychotics and major tranquillisers are not used for prophylaxis of recurrent affective disorders, but they may occasionally be administered in addition to antimanics and antidepressants. Although teratogenic risks have not been demonstrated with certainty, these drugs should be avoided during pregnancy because they may produce tardive dyskinesia in the mother and transient extrapyramidal symptoms in the newborn.[45]

## 5. Discussion

Manufacturers and/or regulatory authorities have warned against the use of every drug discussed in this review during pregnancy. These advisers do not want to take any risks; they warn because then they cannot be held responsible for possible adverse effects. The admonitions are somewhat differently phrased, for example: 'Due to insufficient experience use during pregnancy is

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not recommended'; 'Should not be used during pregnancy'; 'Should not be used during the first trimester'; 'Should be used only on compelling indication'.

The physicians who have clinical responsibility for the patients are in a different position. They must weigh the risk of treating a pregnant woman against the risk of not treating her, and should a negligence claim later be put forward, they must explain in court how they reached their decision and on what evidence they based it. Discussions with the properly informed prospective parents are useful, but they do not lessen the physicians' legal and medical responsibilities.

### 5.1 Risks to the Fetus

Women with recurrent affective disorders are often receiving prophylactic treatment, and discontinuation may lead to recurrences. These recurrences, particularly manic ones, pose a risk to both the pregnancy and the fetus. On the other hand, treatment during pregnancy may harm the fetus. The critical period is between 4 and 12 weeks after the woman's last menstruation, the time when organogenesis takes place.

In the beginning, failure to distinguish between maximum teratogenic risk and true teratogenic risk gave lithium a 'bad press'. Epidemiological studies without the unavoidable bias of the lithium baby register have provided more reassuring results. While one cohort study indicated a somewhat higher frequency of general and cardiac malformations among the lithium-exposed children than among the control group, 2 further cohort studies[10,11] and 4 case-control studies[12-15] did not show an increased number of congenital malformations after prenatal exposure to lithium.

None of the studies concerning the teratogenic effects of TCA and SSRIs have shown a higher frequency of congenital malformations among exposed children than in the general population.[13-16] Although absence of proof of risk is not the same as proof of safety, the findings indicate that the teratogenic risk of these antidepressants is low.

According to the evidence available today, the use of lithium and antidepressant drugs (except perhaps MAOIs) is justified during pregnancy when treatment is needed. There is no prophylactic treatment with a lower risk : benefit ratio.

However, this does not mean that safeguards can be dispensed with.[8,12,57] As a general rule, it is advisable that women of fertile age who receive prophylactic antidepressant treatment:

- use contraceptive measures
- discontinue treatment before a planned pregnancy
- stop treatment when an unplanned pregnancy has been confirmed.

Treatment should be resumed after the first trimester. It is, however, important that each patient's situation is taken into account. If, after previous discontinuations of prophylactic treatment, the women rapidly developed severe recurrences, treatment should not be interrupted. When a pregnant woman has been treated with lithium during the first trimester, she should be examined with prenatal echocardiography and high-resolution ultrasound around 16 to 18 weeks of gestation, in order to detect possible cardiac malformations, some of which may be accessible to surgical correction. Termination should be offered if the defect is severe or inoperable.

Carbamazepine and valproic acid expose the fetus to a substantial risk of congenital malformations and/or developmental delay. Since lithium treatment, with its established prophylactic efficacy and lower teratogenic risk, is available, anticonvulsant drugs should be avoided during pregnancy.

### 5.2 Perinatal Risks to the Mother and Neonate

The changes in renal lithium clearance that occur during pregnancy and delivery, and that might expose mother and child to underdosage or overdosage, respectively, can be managed by appropriate monitoring of serum lithium concentrations and adjustment of lithium dosage.

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Withdrawal symptoms in the newborn have occasionally been observed when, after birth, they were no longer being exposed to antidepressant drugs. Such symptoms could perhaps be avoided by tapering the woman's dosage before delivery, but this hypothesis has not been tested in practice.

### 5.3 Puerperium

The high incidence of manic and depressive recurrences during the puerperium makes it extremely important to continue prophylactic treatment with lithium and antidepressants or to resume therapy very soon after delivery.

### 5.4 Breastfeeding

Official warnings have been issued against breastfeeding when women are receiving any drug treatment. However, concentrations of lithium and antidepressants in the nursing infants' serum are low,[37,60-65] and since numerous studies have demonstrated the importance of breastfeeding for both mother and child,[40] the choice between breastfeeding and bottle-feeding should be discussed with the fully informed parents, and the final decision about this often emotionally charged question left to them.

### 5.5 The Child's Later Development

While children exposed prenatally to carbamazepine or valproic acid are at risk of developmental delay, the development of lithium-exposed children has been shown not to differ from that of their nonexposed siblings.[42] An uncontrolled study of children who were prenatally exposed to TCAs did not reveal functional abnormalities.

### 5.6 Episodes Occurring During Pregnancy

Treatment with a TCA or SSRI may be needed for mild depression, and treatment with lithium may be required for mild mania. For severe depression and mania, electroconvulsive therapy is indicated. The latter has the advantage of being therapeutically effective in both mania and depression, and adverse effects on mother and child have not been observed.[78]

## 6. Conclusion

The time during and after pregnancy is a period of risk for women with recurrent affective disorders and their offspring, and official and manufacturer's warnings against drug treatment are of little use to the clinically responsible physicians. When treatment is needed, it should be given, but precautions and guidelines of the kind outlined here must be adhered to.

A number of studies have shown that the risk of congenital malformations is low when lithium and antidepressants are administered during pregnancy; there is no prophylactic alternative with a lower risk : benefit ratio. Anticonvulsant drugs should be avoided. Perinatal risks for lithium-treated mothers and their children can be managed by appropriate adjustment of dosages. The risks of breastfeeding by women given lithium or antidepressant drugs hardly outweigh the benefits of these drugs. Since the puerperium is associated with a high risk of recurrence, it is particularly important that prophylactic treatment is continued or resumed in full dosage soon after delivery. No developmental anomalies have been observed among children who were exposed prenatally to lithium or antidepressants. Severe episodes of mania and depression that arise during the pregnancy are best treated with electroconvulsive therapy.

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