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Medicines Information Bulletin

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Antidepressants – pregnancy and breast-feeding

Background

It is often necessary to use antidepressants in women who are pregnant or are planning to become so. Rates of depression are at least twice as common in women as in men and peak during women's reproductive years. For every 1000 live births, 100-150 mothers will suffer from a depressive illness[1]. Untreated psychiatric disorders during pregnancy may cause spontaneous abortions, pre-eclampsia, placental abnormalities, decreased foetal growth, preterm labour, preterm delivery, low birth weight, and perinatal and birth complications[2]. Suicide is the second leading cause of maternal death in the UK. Failure to treat postpartum depression may result in prolonged deleterious effects on the relationship between the mother and baby and on the child's psychological, social and educational development.

Antidepressant medication is indicated for the treatment of moderate to severe depression[3]. It has been estimated that a patient with moderate to severe depression who stops an SSRI when she discovers that she is pregnant, will have a 70% chance of depression relapse[4].The main factors to consider when choosing medication in pregnancy are organ malformation (teratogensis), neonatal toxicity and withdrawal symptoms. Antidepressants will pass through to the foetus, therefore it is important to keep drug doses as low as possible and polypharmacy should be avoided whenever possible.

When considering the risk of medicines to the unborn child, the first trimester is the most sensitive time in terms of malformation risks. If medication is started in the third trimester there are no concerns regarding major malformations, however all psychotropic medication given during the third trimester has the potential to cause discontinuation symptoms in the newborn infant following delivery (see below). Depressive symptoms generally tend to peak during the third trimester and fall following delivery[5].

Excerpt from NICE clinical guideline: antenatal and postnatal mental health[18]

Guidance on antidepressants:

Risks to consider:

- ⇒ Lowest known risks during pregnancy: TCAs such as amitriptyline, imipramine, nortriptyline; but most are more likely to cause death if taken in overdose than SSRIs
- ⇒ Lowest known risk with an SSRI during pregnancy: fluoxetine
- ⇒ Foetal heart defects with paroxetine taken in the 1st trimester
- ⇒ Persistent pulmonary hypertension in the neonate with SSRIs taken after 20 weeks gestation
- ⇒ High blood pressure with venlafaxine at high doses, together with higher toxicity index in overdose than SSRIs and some TCAs and increased difficulty in withdrawal
- ⇒ Withdrawal or toxicity in the neonate with all antidepressants (in most cases the effects are mild and self-limiting)
- ⇒ Lower than other antidepressants in breast-milk: imipramine, nortriptyline, and sertraline
- ⇒ Higher levels in breast milk: citalopram and fluoxetine

Actions to take:

- ⇒ Advise a woman taking paroxetine who is planning a pregnancy or has an unplanned pregnancy to stop the drug.

Tricyclic antidepressants (TCAs) in pregnancy:

The current recommendation for which antidepressant to use in pregnancy is based on the accumulated safety data available with them. The older TCAs, such as amitriptyline, desipramine, imipramine and nortriptyline, have been around for the longest period of time and have no evidence of an increased incidence of birth defects above the background incidence of 2-4%. These are considered to be the drugs of choice in pregnancy. There is limited data available for dosulepin, doxepin, lofepramine and trimipramine, so these would not be first line agents.

Tricyclic plasma levels may need to be monitored during pregnancy, especially in the second and third trimester, as altered pharmacokinetics at this time may lead to a sub-therapeutic response. Contact the pharmacy department for further information about how tricyclic plasma levels may be assayed locally. Tricyclics should not be used in mothers at risk of overdose because tricyclic poisoning can lead to foetal harm. A small study of 80 preschool children found that in utero exposure to TCAs did not affect their neurodevelopment (cognitive, language and behavioural development)[2,5].

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Selective Serotonin Reuptake Inhibitors (SSRIs) in pregnancy:

In reality many SSRIs are used in pregnancy because they are so frequently prescribed to women of child bearing age, who become pregnant while taking them. The outcome of several thousands of pregnancies is now known for fluoxetine, citalopram, sertraline and paroxetine and several hundreds with fluvoxamine. There is insufficient data available for escitalopram. The National Terotology Information Service still maintains that fluoxetine is the SSRI of choice because there is most accumulated evidence with this drug, however a recent leading author has suggested that citalopram or sertraline may have a better average safety profile in pregnancy than fluoxetine[2]. Fluvoxamine is probably safe, but data is limited for this drug. Prenatal exposure to SSRIs has been shown not to cause development delay.[1,9]

Paroxetine is not recommended during pregnancy because of recent evidence which suggests an association between first trimester exposure and infant cardiac defects. According to a study run by GlaxoSmithKline, infants exposed to paroxetine in the first trimester had a 4% risk for major malformation and 2% risk for cardiac malformation. Most of the registered cardiac defects were minor[6]. In addition, paroxetine is associated with an increased risk of neonatal withdrawal symptoms compared to other SSRIs (see below). If a woman taking paroxetine becomes pregnant, she should discuss the option of switching to another antidepressant with her doctor. Abrupt cessation of paroxetine can cause significant withdrawal symptoms and is not recommended.

SSRIs have recently been associated with a condition known as persistent pulmonary hypertension of the newborn (PPHN). This condition occurs naturally in an estimated 1 or 2 infants per 1000 and is associated with substantial morbidity and mortality. Use of SSRIs in late pregnancy is thought to increase the risk to 6-12 infants per 1000 babies, therefore the absolute risk of this condition remains low. Maternal risk factors include lower educational level, fever, urinary tract infection, diabetes, caesarean section, antenatal use of NSAIDs and possibly tobacco use[6].

Several authors have suggested that late exposure to SSRIs in pregnancy can cause neonatal complications, including respiratory and central nervous symptoms[8]. Some have argued that it is very difficult to differentiate these findings from withdrawal symptoms of medication. Nevertheless, most authors agree that if these symptoms occur they tend to be transient and self limiting and infants can be managed with supportive care[8].

A meta-analysis reported that SSRI exposure in late pregnancy was related to prematurity and low birth weight, however several authors have pointed out that the increased smoking rate in patients taking antidepressants and the underlying depression must be taken into account when interpreting these results[2,4].

Withdrawal symptoms in the neonate

Short term neonatal withdrawal symptoms have been reported with all antidepressants. Symptoms include jitterness, shivering, tremors, increased muscle tone, feeding and sleep disturbances, irritability, agitation, respiratory distress and excessive crying. Symptoms are usually mild and transient, but may need treatment in a special care unit. Rarely, neonatal convulsions have occurred.

The antidepressants with shorter half-lives, such as paroxetine or venlafaxine are considered to be more likely to cause these problems. There have been case reports of neonatal convulsions after late in utero exposure to paroxetine. It has been suggested that the poor metaboliser genotype of CYP2D6 may be a risk factor for perinatal complications in infants exposed to SSRIs late in pregnancy.

It might be possible to avoid these withdrawal effects by tapering the antidepressants during the third trimester, however consideration should be given to the high risk of relapse on stopping therapy at this vulnerable stage.

Bleeding disorders and hematomas have been associated with the use of SSRIs in adults. Gestational exposure to SSRIs has been shown to reduce platelet serotonin uptake in the foetus. Several cases of hemorrhagic symptoms in newborns have been reported in the literature. Paediatricians should be aware to monitor babies for this post delivery[2].

Monoamine Oxidase Inhibitors (MAOIs) in pregnancy:

MAOIs are generally not recommended for use during pregnancy. They have been associated with a high incidence of toxicity in humans and the possible interaction with tyramine from certain foods may cause an acute hypertensive crisis. In addition, MAOIs can exacerbate pregnancy associated hypertension, which can lead to alterations in placental blood flow and in turn affect foetal growth and development.

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There is conflicting evidence about the association of MAOIs with congenital malformations. A small number of studies and case reports have suggested an increased incidence of congenital malformations with phenelzine and tranylcypromine, however the number of cases is so small that a causal relationship cannot be confirmed. Data on the use of isocarboxazid in pregnancy is very limited and there is no information on the use of moclobemide in pregnancy.

If a mother discovers she is pregnant while taking an MAOI she should discuss the possibility of switching to an alternative agent, taking into account risk of destabilising her mental state with any switch. Exposure to MAOIs is not an indication for termination of a pregnancy and a detailed foetal scan can be recommended to reassure patients. As with other antidepressants, withdrawal symptoms in the neonate may occur.

Other antidepressants in pregnancy:

There is less information available about the newer antidepressants, such as venlafaxine, mirtazapine, duloxetine, reboxetine and trazodone, so these should be avoided in pregnancy if possible. The use of these drugs in the first 3 months of pregnancy is not an indication for termination. Furthermore, a pregnant patient who is stable on these drugs should not be changed to another drug if there is a danger that this will worsen her health.

Venlafaxine: Overall, there is data from almost 300 pregnancies exposed to venlafaxine, none of which indicate a substantial teratogenic risk[2]. It is thought that at least 800 pregnancies would have to be examined to detect a two fold increase in malformations, and many thousands would be needed to pick up on rare defects that the drug might cause[10]. Venlafaxine has a very short half life, so there would be an increased risk of withdrawal symptoms in the neonate.

Duloxetine: There is insufficient experience with this new drug to make any conclusions about its safety in pregnancy. Studies in animals have shown reproductive toxicity at systemic exposure levels of duloxetine lower than the maximum clinical exposure. The potential risk in humans is unknown[11].

Mirtazapine: There is data from about 200 pregnancies with mirtazapine that show no teratogenic effect with exposure to this drug in the first trimester. A prospective study comparing 104 mirtazapine patients to two control groups (one with depressed pregnant women treated with other antidepressants and the other with healthy pregnant women) found that mirtazapine does not increase the risk of major malformations above the baseline rate[12]. In this study both the mirtazapine and the other antidepressant group showed a higher rate of spontaneous abortion and preterm births compared to the healthy pregnant mothers on no medication. This finding has been observed in other studies and may be attributed to the depressive illness rather than the medication. Several authors have described cases where mirtazapine has been used to treat hyperemesis gravidarum in pregnancy with depression[2].

Reboxetine: There is very little data on reboxetine exposure to humans in the literature. The manufacturer states that reboxetine is contra-indicated in pregnancy and that treatment should be discontinued as soon as pregnancy is confirmed to limit foetal exposure to the drug[13].

Trazodone: No indication of teratogenicity was observed in approximately 70 pregnancies where patients were exposed to trazodone in the first trimester of pregnancy[2]. In addition, data from a surveillance study of 112 women exposed to trazodone in the first trimester did not show an increase in congenital malformations[14].

Antidepressants and Breastfeeding:

Drug treatment of depression in a breastfeeding mother can pose a clinical dilemma since the needs of both mother and infant must be balanced. When an antidepressant is indicated, with careful selection of agent and dosage regimen, it is seldom necessary to deny the healthy infant the known benefits of breastfeeding. A decision to treat a breastfeeding mother with antidepressants should involve a case-by-case assessment of the risk benefit ratio. Monotherapy is recommended and the infant should be carefully monitored for sedation, respiratory depression, weight gain and developmental milestones. Premature infants should not be exposed to psychotropic drugs via breast milk as reduced excretory functions may lead to drug accumulation on prolonged exposure and such infants may also be more sensitive to the effects of CNS agents.

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Little is known about the physical or mental development of infants exposed to antidepressants via breast milk. A study in 2005 monitored maternal mood and infant weight at 6, 12 and 18 months in a group of 78 breastfeeding women taking antidepressants, including citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, and venlafaxine plus additional unspecified tricyclic agents in some cases. Infant weights at 6 months did not differ significantly from the normal population. However, infants of mothers who experienced longer, depressive episodes (2 months or more) following delivery weighed significantly less compared with infants whose mothers had only brief depressive episodes or infants whose mothers had no depressive episodes in the post partum period. This finding remained when medication dose and infant birth weight were included as covariates. The study suggests that postnatal depression may influence behaviours that may affect infant weight gain.

Tricyclics and breastfeeding:

The ideal TCA is non-sedating with a shorter half-life, reduced anticholinergic effects, no active metabolites, high protein binding and for which clinical data are available. TCAs most closely meeting these criteria are **imipramine** and **nortriptyline[15]. Lofepramine** has good physicochemical and pharmacokinetic properties but no quantitative studies have been conducted[15]. **Amitriptyline, clomipramine, desipramine** and **dosulepin** are also acceptable[2] however these are more sedating so the infant should be monitored carefully for drowsiness. A handful of case reports have documented adverse effects in infants exposed to **doxepin** through breastfeeding, so this should be avoided.
Risks can further be minimised by using a single daily dose of a TCA and breastfeeding immediately before drug administration. For very young infants feeding frequently, one bottle feed can be substituted to avoid drug peak levels at 1-3 hours post dose. Use of other sedating agents in the mother should be avoided since sedation can be additive. Infants should be monitored for drowsiness or other behavioural changes. The latter have not been noted in clinical practice[15].

SSRIs and breastfeeding:

All SSRIs have been detected in breast milk. In addition adverse effects associated with infant exposure to SSRIs in breast milk have been reported for citalopram, fluoxetine, paroxetine and sertraline[15]. These adverse effects have included symptoms such as excessive crying, poor sleep, colic, watery stools, sedation, hypotonia, raised temperature, hypotension, somnolence and suspected developmental difficulties[15]. Toxic symptoms (mostly moderate) have only been observed in infants exposed to fluoxetine and citalopram[2]. No data are available on escitalopram, although it would be expected to behave in a similar manner to citalopram. Paroxetine has the lowest milk:plasma ratio of the SSRI group[15]. Fluoxetine, citalopram and escitalopram have the longest half-lives of this group.
If an SSRI is considered essential for use in a breastfeeding mother, **fluoxetine** and **citalopram/escitalopram** are best avoided on current evidence particularly in neonates where reduced excretory function may prolong the drug half-life and increase risk of adverse effects. This also applies to mothers treated with these drugs during pregnancy unless there is a clear clinical benefit to their continued use.
There is no clinical indication for women treated with **paroxetine, sertraline** or **fluvoxamine** to stop breastfeeding so long as the infant is healthy and well monitored. If a woman has been successfully treated with one of these agents during pregnancy and requires continued therapy in the post natal period there is no need to change therapy, provided the infant is full term and displays no adverse symptoms following birth. The SSRI should be used for the shortest time and at the lowest effective dose. Long-term exposure to the infant should be avoided where possible due to a lack of evidence and experience relating to their effects on development. Abrupt withdrawal from the mother should also be avoided.

Other antidepressants and breastfeeding:

Newer antidepressants such as **duloxetine** and **reboxetine** are best avoided due to a lack of evidence or safety and clinical experience in breastfeeding women.

There is evidence to suggest that **venlafaxine** and its metabolite O-desmethylvenlafaxine (ODV) transfer into breast milk and it has been calculated that infants receive about 6% of the maternal dose (weight adjusted) of this drug. Compared to other antidepressants this is quite high and clinical experience is still limited in its use in this population. Therefore this should only be used if compelling reasons ensure that the benefit is greater than the risk[2, 16].

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Mirtazapine is probably safe to use[2] although it can be sedating. One case report has suggested that infant exposure to the drug is less than 1% of the maternal dose[2].
One study has suggested that 2% of the maternal dose of **trazodone** is found in the infant following breast feeding. Again this is a sedative drug so should only be used when there are compelling reasons to do so.

The following table describes the relative dose (weight adjusted) of antidepressant that has been observed in infants following exposure to the drug during breastfeeding[2]. Some of these figures have been calculated in single case reports (see *) and others have been calculated in small studies. In general, relative infant doses less than 10% are considered relatively safe depending on the age and stability of the respective infant[5]. The table also shows the half life of each drug[2] and their relative sedative effects as seen in the adult population[17].

Drug	Relative dose	Half life	Sedation[17]
Amitriptyline	Usually not > 2.5%	9-25 hours (active metabolite = nortriptyline)	+++
Clomipramine	1.3-4%	32 hours	++
Dosulepin	Max 7%. Average <1%	9 hours (has active metabolites)	+++
Doxepin	0.3-1%	8-25 hours (active metabolite: 33-81 hrs)	++
Imipramine	Max 7%. Average <2%	6-20 hours	+
Nortriptyline	2-3%	37 hours	+
Citalopram	Max 10%. Average 3-5%	35 hours	~
Fluoxetine	Max 17%. Average 6.5%	4 days (active metabolite: 7 days)	~
Fluvoxamine	0.5% (1.6%*)	16 hours	+
Paroxetine	Max 2%. Average 1%	22 hours	~
Sertraline	2%	26 hours	~
Venlafaxine	Max 9%. Average 6%	26 hours	+
Mirtazapine	1%*	20-40 hours	++
Trazodone	2%	5-13 hours	++

+++ = Marked effect, ++ = Moderate effect, + = Mild effect, ~ = Little/No effect
*Single case reports

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Please ensure that you are using the most up to date information when making decisions about medicine use during pregnancy and /or breast-feeding.

The Trust’s Medicine Information Service is based in the pharmacy department and can be contacted on 01865 455716 or by email: med.info@obmh.nhs.uk