Q&A 252.3

Management of depression in breastfeeding mothers – are selective serotonin reuptake inhibitors (SSRIs) safe?

Prepared by UK Medicines Information (UKMi) pharmacists for NHS healthcare professionals

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Background

In the UK, six selective serotonin reuptake inhibitors (SSRIs) are licensed for the management of depression – citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline. Some of these SSRIs are licensed for the additional indications of panic disorder, generalised anxiety disorder, obsessive compulsive disorder, bulimia nervosa, post-traumatic stress disorder and social anxiety (1).

SSRIs are better tolerated and safer in overdose than other classes of antidepressants and are considered the drugs of first choice for depression (1). A specific withdrawal syndrome has been associated with this class of antidepressants (1).

It may be difficult to distinguish, in the short term, between neonatal withdrawal symptoms following *in utero* exposure and exposure to the drug via breast milk (2).

SSRIs are the antidepressant group for which the most data exist for use in lactation (3).

Answer

Selective serotonin reuptake inhibitors

All six SSRIs have been detected in breast milk (3). Infant intake via milk has been estimated to be between 0.3%- 1.4% (fluvoxamine) and 1.6% - 14.6 %(fluoxetine) of the weight adjusted maternal dose (4).

SSRIs all have relatively long half lives, the shortest being 17 – 22 hours in normal adults for fluvoxamine and the longest being 4 – 6 days for fluoxetine (5, 6). Adult half lives for SSRIs are listed in Table 1 below. The long half lives and reduced drug clearance, especially in neonates and young infants, can lead to drug accumulation and an increased risk of adverse reactions in infants following exposure to the drugs via breast milk (11)

Adverse reactions associated with infant exposure to SSRIs via breast milk have been reported for citalopram, fluoxetine, paroxetine (12), sertraline (2) and escitalopram (13).

The Australian Adverse Drug Reaction Bulletin notes that there may be some overlap of symptoms resulting from drug transfer into breast milk and from *in utero* exposure – agitation, jitteriness, hypotonia and gastrointestinal symptoms. However, sedation has only been reported after drug exposure via breast milk (2).

If an SSRI is considered essential and the prescriber is selecting a drug for use in the postnatal period for a breastfeeding mother, fluoxetine and citalopram are best avoided on current evidence, particularly in neonates where reduced excretory function may prolong the half life leading to drug accumulation and an increased risk of side effects (3, 11).

If a woman has been successfully treated with an SSRI during pregnancy and requires continued therapy in the postnatal period there is no need to change therapy, provided the infant is full term, displays no symptoms and can be adequately monitored (3,14,15).

Although data for other SSRIs in lactation are currently limited, there would appear to be little to differentiate between them and the choice between fluvoxamine, paroxetine or sertraline should be

made on clinical grounds. The SSRI selected should be used for the shortest time and at the lowest effective dose. Long term use should be avoided due to a lack of evidence and experience relating to their effects on infant development (3). Withdrawal symptoms were noted one day after abrupt maternal discontinuation of sertraline 200 mg daily in a 3 week-old breastfed infant (16) and women on SSRIs should avoid this situation.

Table1.

Adult half-lives of some SSRI antidepressants (5-10)

SSRI	Half-life
Citalopram	36 hours
Escitalopram	30 hours
Fluoxetine	4 – 6 days
Fluvoxamine	17 – 22 hours
Paroxetine	24 hours
Sertraline	26 hours

To date, there is no evidence-based support for the hypothesis that SSRIs with a milk/plasma ratio of less than 1 should be preferred in breastfeeding women. Prescribers should consider other parameters when selecting the safest SSRI for the mother. These include the number of well documented published reports of adverse events in breastfed infants and the tendency of each SSRI to produce infant serum levels above 10% of the average maternal serum levels (17).

Even when poor metaboliser status for cytochrome P450 was identified for a mother and infant exposed to paroxetine or for a mother given citalopram, serum levels in the breastfed infants were either undetectable (paroxetine) or low (citalopram) (18).

Neonatal withdrawal symptoms (poor adaptation, jitteriness, irritability and poor gaze control) have been reported in infants exposed to SSRIs in later pregnancy (19). Paroxetine seems to be the SSRI that produces the majority of withdrawal symptoms in exposed infants (20). Withdrawal symptoms are usually self-limiting and generally occur within 24 – 48 hours (longer for fluoxetine) and typically last 1 -2 days (19). In almost all cases minimal or no treatment is needed and breastfeeding should continue (19) unless symptoms persist.

Serotonin has been proposed to have a significant role as a local regulator of lactation (21). A study of 431 primiparous women showed that those taking regular SSRI medication (n=8; 1.9%) were significantly more likely to experience delayed secretory activation (later than 72 hours postpartum). All women in the SSRI group achieved secretory activation by day 7 (22).Further studies are needed to confirm these findings.

A prospective cohort study involving 466 pregnant women compared breastfeeding outcomes of women exposed to SSRIs at the time of delivery, those who discontinued use prior to delivery and non-exposed women (23). Both groups exposed to SSRIs were noted to be significantly less likely to initiate breastfeeding compared to the non-exposed women. The reasons for non-breastfeeding were not evaluated.

Data for individual agents are summarised below.

Citalopram

Data on the use of citalopram in lactation are available for 78 mother-infant pairs. Maternal doses ranged from 20 to 80 mg a day. Citalopram and its metabolites, demethylcitalopram and didemethylcitalopram, pass into breast milk (24-28). In one study, peak levels of citalopram in milk

were seen about 6 hours post dose (24). Estimated infant intake via milk ranged from 0.7 – 7.9% of the weight adjusted maternal dose (25,27,29).

Citalopram has been detected in the serum of breastfed infants whose mothers were taking the drug. Infant serum levels have been estimated to average between 0.9 – 7% of the maternal plasma level (12,18). A plasma level exceeded 10% of the maternal dose in one infant and was described by the authors as being elevated (12). In one study in 9 mother-infant pairs, infant serum levels fell from 64% of maternal concentrations at delivery to 2% at 2 months (28).

Occasional adverse effects in breastfed infants whose mothers were taking citalopram have been reported (29 - 31). A single case each of colic, decreased feeding and irritability/restlessness were reported in 3 of 31 breastfed infants whose mothers were taking citalopram but there was no statistically significant difference in the rate of adverse effects compared to a control group where the mothers did not receive an antidepressant (31). Infant symptoms of irritability/restlessness (31) and uneasy sleep (30) resolved on cessation of breastfeeding. No neuropsychological effects were seen at 18 months in an infant breastfed for 6 months (32).Normal growth and development were noted at 6 months in a breastfed infant whose mother was taking citalopram 60 mg daily (33).

Escitalopram

Escitalopram is the S-isomer of racemic citalopram.

Only limited data are available for the passage of escitalopram into breast milk. In 8 mother-infant pairs studied between 1.5 and 9.5 months postpartum, infant intake of escitalopram was estimated at 7.6 micrograms/kg/day and of the desmethyl metabolite at 3 micrograms/kg/day. Infant intake via milk was 3.9 % of the weight adjusted maternal doses of 10 – 20 mg daily (34). In a separate report in a single mother-infant pair, infant exposure to the drug was calculated as 5.1% of the weight adjusted maternal dose in week 1 post partum and 7.7% in week 7 (35). No adverse effects on infant development were noted in these studies (34,35). Necrotising enterocolitis was diagnosed in a 5 day old breastfed infant whose mother had taken escitalopram 20 mg daily throughout pregnancy and whilst breastfeeding. Symptoms resolved after discontinuation of breastfeeding (13). The authors suggested that the symptoms might be related to the effect of the SSRI on platelet function.

Fluoxetine

Fluoxetine is the SSRI for which the most data are available for use in lactation. Nearly 200 mother-infant pairs have been studied with maternal doses of 10 – 80 mg daily (3). Infant ingestion of fluoxetine/metabolite via milk has been calculated at varying values up to 10% of the weight adjusted maternal dose (4, 12, 36-38). Peak milk levels were seen at approximately 8 hours post dose in one study (39).

Both fluoxetine and norfluoxetine have been detected in the sera of breastfed infants in several studies (12, 37-40). Infant serum levels of fluoxetine ranged from 0 – 59% (mean 7%) of the maternal value in a pooled analysis of 22 mother-infant pairs (12). Infant serum levels of fluoxetine decline with increasing time postpartum but norfluoxetine persists for a longer period (37, 41). Maternal doses of up to 20 mg daily are less likely to produce detectable levels of fluoxetine and norfluoxetine in the infant's serum than higher doses (39).

Adverse reactions to fluoxetine via breast milk are reported more often with fluoxetine than for other SSRIs, although this may reflect wider use of the drug. Colic (36,40,42), decreased sleep, vomiting and watery stools (42), hyperactivity (36), seizure-like activity and cyanosis (43) and hyperglycaemia and glycosuria have been reported in breastfed infants exposed to fluoxetine via breast milk (44). A 3 day –old infant was difficult to arouse, decreased nursing and was moaning and grunting and noted to be hypotonic. Although the infant had been exposed to fluoxetine *in utero* and was somewhat sedated in the first 2 days postpartum, symptoms worsened after milk came in on day 3. The infant slowly returned to normal in the 3 weeks after breastfeeding was stopped on day 11 (45). One study noted decreased weight gain in a group of 26 infants exposed to fluoxetine via breast milk compared to non-exposed controls. However, weights remained within the normal rage (46). No significant effect on mental or motor development of infants exposed to fluoxetine via milk has been noted (37,47,48). A

small study in 30 infants born to mothers who had taken an SSRI in pregnancy noted blunted responses to pain compared to control infants. Six of the 30 infants had been exposed to fluoxetine either prenatally or postnatally via breast milk (40).

A proof-of-principle study, applying population pharmacokinetic modelling, simulated data for 1000 mother-infant pairs to estimate infant drug exposure via breast feeding . The median infant-to-mother ratio of fluoxetine steady state plasma concentrations predicted by the simulation was 8.5% (49). Given the difficulty of undertaking pharmacokinetic studies, this method may offer an alternative approach for infant risk assessment. Further studies are needed to validate this approach.

Fluvoxamine

Published data on the use of fluvoxamine in lactation are limited to 14 mother-infant pairs (3). These show that maternal doses of up to 300 mg daily produce only low levels in milk and would not be expected to cause any adverse effects in breastfed infants, especially if the infant is older than 2 months (50). Estimated infant intake via milk has been estimated as 0.5 – 1.58% of the weight adjusted maternal dose (51-55). In most instances, levels of fluvoxamine in infant sera have been undetectable (12,55-57). In a case report of a single mother who received fluvoxamine 25 mg three times a day, it was calculated that the infant would receive approximately 6 micrograms/kg/day or 0.62% of the weight adjusted maternal dose. The infant serum level of fluvoxamine at 10 hours post dose was 9 nanograms/ml which appears high when considering the estimated dose ingested via milk. The authors suggested that this may be an atypical case or that the infant clearance of the drug was impaired (53).

No adverse effects have been reported in breastfed infants, including limited data of long-term follow-up on growth and development (54,55,58,59).

Paroxetine

Paroxetine is considered by authoritative reviewers as one of the preferred SSRIs for use in lactation (15,60,61). Data on use in lactation are available for about 100 mother-infant pairs (3).

Passage of paroxetine into breast milk is generally low and infant ingestion has been calculated as 0.1 – 4.3% of the weight adjusted maternal dose (62-64). Maternal doses in these studies ranged from 10 – 40 mg daily. In the majority of cases, paroxetine has not been detected in infant sera where this parameter was measured (12,18,56). Even where poor metaboliser status was identified in one mother taking paroxetine 20 mg daily and in her breastfed infant, no paroxetine was detectable in infant serum(18). However, in a group of 20 breastfed infants whose mothers were taking an average of 25 mg paroxetine daily, the average serum paroxetine level at 2 months postpartum was 0.95 micrograms/l which equated to 5% of the maternal serum levels (40).

Occasional mild side effects have been reported in breastfed infants whose mothers were taking paroxetine, especially where paroxetine was used in the third trimester. In these cases, the contribution of the drug in breast milk was unclear (65). Isolated cases of irritability, difficulty in feeding and sedation have been reported (2,3). An 18 month old breastfed infant was hospitalised after a 2 week history of vomiting and found to be hyponatraemic. Similar episodes had occurred 2 and 3 months earlier. The mother had been taking paroxetine 40 mg daily for about a year. Paroxetine was detected in the milk and infant's serum. Breastfeeding was discontinued and 6 weeks later, the infant was thriving. The authors attributed the infant's symptoms to paroxetine-induced syndrome of inappropriate secretion of antidiuretic hormone (66).

Follow up for periods of up to 12 months of infants exposed to paroxetine via breast milk has generally found no adverse effects on weight gain or achievement of developmental milestones (48,59,67,68).

Sertraline

Along with paroxetine, sertraline is considered by authoritative reviewers as one of the preferred SSRIs for use in lactation (15,60,61). Data on use in lactation are available for over 100 mother-infant pairs (3).

The transfer of sertraline and its weakly active metabolite, desmethylsertraline, into breast milk is low. Peak milk levels were seen at 7 – 8 hours post dose in one study (69). Calculated infant ingestion via milk is less than 1% of the weight adjusted maternal dose (12,18,40,70). Mathematical modelling indicated that discarding breast milk 8 – 9 hours post dose decreased infant drug intake by 17.1% (71)

In a pooled analysis of 53 mother-infant pairs, infant serum levels of sertraline were, on average 2%, of the maternal values. Other studies have reported infant serum levels of sertraline to be undetectable (18,40, 72).

Very few adverse reactions have been reported in infants exposed to sertraline via breast milk. Benign neonatal sleep myoclonus was seen in one 4 month-old infant. This resolved spontaneously at 6 months. The relationship to sertraline is unclear (70). Neonatal effects, possibly associated with maternal use of sertraline, have been reported to the Australian Adverse Drug Reaction Advisory Committee for 9 infants (2). Symptoms included jitteriness, poor feeding and sleepiness. Sertraline is a potent inhibitor of the 5HT-transporter function in both CNS and platelets (4). In one study in 14 mother-infant pairs, maternal platelet serotonin was significantly depressed but no effect was seen in the infants (73). Symptoms of serotonergic overstimulation were reported soon after birth in an infant born at 33 weeks (74). The mother had been taking sertraline 150 mg daily in the third trimester, continued after delivery, and breastfed the infant. Hyperthermia, shivering, muscle hypertonia, tremor, irritability were noted in the infant in the first 24 hours after delivery. Over the next 4 days, the infant showed a decreased suckling reflex and reactivity associated with muscular hypotonia, as well as a high stool frequency. Infant serum levels of sertraline on day 5 were 13.2 mcg/L and 52.1 mcg/L for desmethylsertraline. Breast feeding was stopped on day 9 and symptoms resolved. One infant developed symptoms of agitation, poor feeding, restlessness, constant crying, insomnia and exaggerated startle reaction within 24 hours of abrupt cessation of maternal therapy of 200 mg daily (16). Normal weight gain was seen up to 6 months postpartum in 25 breastfed infants whose mothers were taking sertaline (56).

Summary

- SSRIs and their metabolites pass into breast milk in small amounts, generally below 7% of the weight adjusted maternal dose. Infant ingestion via milk is lowest for sertraline and fluvoxamine and highest for fluoxetine.
- SSRIs have relatively long half lives and there is a risk of drug accumulation, especially in the neonatal period when drug clearance values are significantly reduced.
- Premature infants and those with respiratory depression should not be exposed to SSRIs via breast milk.
- There is some overlap in symptoms between drug withdrawal after *in utero* exposure in the third trimester and exposure via breast milk, but sedation has been noted only in the latter circumstance.
- Because of shorter half lives, lower passage into milk and larger pools of data, paroxetine or sertraline are the preferred SSRIs for use in lactation.
- SSRIs should be used at the lowest effective dose and for the shortest possible time.
- Limited data on effects of SSRI exposure via breast milk on weight gain and infant development are encouraging.
- If a woman has been successfully treated with a SSRI in pregnancy and needs to continue therapy after delivery, there is no need to change the drug, provided the infant is full term, healthy and can be adequately monitored.
- Infants exposed to SSRIs via milk should be monitored for sedation, poor feeding and behavioural effects.
- Co-therapy with other sedating agents is best avoided.
- Onset of lactation may be delayed in women exposed to SSRIs at or near term.

Limitations

Data on the use of SSRIs in lactation are still limited, particularly long term follow-up studies. The above outline is provided for general guidance only. Many decisions as to the safety of antidepressant regimens in breastfeeding mothers will need to be taken on a case-by-case basis, particularly if there are unusual circumstances e.g. infant morbidity, requirements for high doses, concurrent medication etc. In these instances, further advice can be sought from the UK Drugs in Lactation Advisory Service provided by the Trent Medicines Information Service or the West Midlands Medicines Information Service.

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- UK Drugs in Lactation Advisory Service – in-house data-base
- Medline and Embase: Standard UKDILAS search pattern found at http://www.ukmi.nhs.uk/activities/specialistServices/default.asp?pageRef=2
  Drug names: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, Serotonin uptake inhibitors (Medline), serotonin uptake inhibitor (Embase)
- Medications and Mothers' Milk Online (Medilact): citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline (monographs)
- Clinical Knowledge Service (antenatal and postnatal depression)
- SIGN website (perinatal mood disorders)
- Electronic Medicines Compendium (Faverin®, Prozac®, Cipramil®, Cipralex®, Seroxat® and Lustral® SPCs)
- US National Library of Medicine Lactmed database: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline (monographs)
- National Institute for Health and Clinical Excellence (NICE) website (antenatal and postnatal mental health)