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Selective Serotonin Reuptake Inhibitor Induced Neonatal Abstinence Syndrome

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Abstract: Depression is common in women of childbearing age and especially during pregnancy and the postpartum period. Selective serotonin reuptake inhibitors (SSRIs) are increasingly being used to treat depression prior to and throughout pregnancy. Up to 30% of the newborn infants exposed to SSRIs may present with clinical signs during the first days after birth. Neonatal abstinence syndrome (NAS) describes this clinical syndrome resulting from prior prolonged exposure to SSRI induced by cessation of the drug. NAS includes a wide spectrum from mild to severe nonspecific symptoms which were categorized into four groups of effects: central nervous system (depression followed by excitation), gastrointestinal, autonomic and respiratory. A protocol for observation of SSRI-exposed newborns is presented including an objective method (Finnegan score) to monitor onset, progression and improvement of NAS symptoms.

Introduction

Depression is common in women of childbearing age (1). During pregnancy increased stress may aggravate depression resulting in a prevalence of up to 12.9% of this disorder (2, 3). The prevalence of depression during the postpartum period continues to be high with 19.2% of women experiencing a major depressive episode within the first three months after delivery (2). Because many women experience depression during the postpartum period, it is often dismissed as part of the "normal" physiological changes that are associated with childbirth (4). However, if untreated, perinatal depression can have severe consequences for the fetus and newborn, as well as for the mother. Although psychotherapy is the first-line treatment for depression during pregnancy or after birth, antidepressant treatment is warranted in some patients. Because selective serotonin reuptake inhibitors (SSRIs) are perceived as safer than alternative medications, they are increasingly being used to treat depression prior to and throughout pregnancy. A recent survey has shown that 2.8% of women use SSRIs for the entire duration of pregnancy (5). This figure translates to 92,000 of approximately 4 million annual live births in the United States. Prolonged fetal exposure to SSRIs may be associated with a neonatal abstinence syndrome (NAS) affecting 30% of newborns (6). The widespread use of SSRIs during pregnancy and the resulting occurrence of NAS warrant a thorough review.

Pharmacokinetics

SSRIs are a group of psychotropic drugs that is chemically unrelated to tricyclics, tetracyclics, monoamine oxidase inhibitors or other antidepressants. They are used to treat depression, but also for obsessive-compulsive and other disorders. The action of SSRIs is thought to be linked to their inhibition of prejunctional reuptake of serotonin, but they do not have receptor-blocking effects. The side-effects of tricyclic and tetracyclic antidepressants may be worrisome in pregnancy and their narrow therapeutic range increases the risk of overdose. SSRIs have a safer therapeutic profile because of their relatively benign side-effects and their safety in overdose (4). The SSRI group is comprised of the following drugs:

1. Fluoxetine (Prozac, Prizma, Flutine, Affectine)
2. Paroxetine (Seroxat, Paxet, Paxol, Paroxetine)
3. Sertraline (Lustral, Zoloft)
4. Fluvoxamine (Favoxil, Luvox)
5. Citalopram (Cipramil, Recital)
6. Escitalopram (Ciprodex, Cipralex)

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Venlafaxine (Efexor, Venla, Viepax) is a selective norepinephrine-serotonin reuptake inhibitor (SNSRI) that is closely related to the SSRIs.

The pharmacokinetic properties of SSRIs (7) are presented in Table 1. This table lists the most commonly recorded adult drug half-life of SSRIs because there is little or no information regarding the newborn. It is of note that during the newborn period, drug half-life is prolonged for most medications, but this is also dependent on drug metabolism. Of the SSRI half-lives, fluoxetine, sertraline and citalopram have a long one with fluoxetine having the longest, paroxetine and fluvoxamine have an intermediate one and venlafaxine has the shortest. A relatively short or intermediate drug half-life has been implicated with an increased risk of NAS after third-trimester exposure.

Transplacental passage determines fetal drug exposure. For drugs with no placental metabolism, transplacental passage is inversely related to molecular weight. SSRIs have a low molecular weight (around 300) with the exception of citalopram (405) and theoretically are able to cross the placental barrier. Placental drug transfer is also determined by duration of drug exposure, liposolubility, protein binding, volume of distribution and other pharmacokinetic factors. Placental transfer of SSRIs has been demonstrated experimentally both in animals and in humans. Pohland et al. (8) demonstrated in the rat that C^{14} labeled fluoxetine and norfluoxetine traversed the placenta during the periods of organogenesis and postorganogenesis and were distributed within the embryonic/fetal tissue, preferentially to the brain and thymus. Stowe et al. (9) studied the passage of SSRIs across the human placenta by measuring their concentrations in maternal serum and umbilical cord blood at delivery. No evidence of accumulation of fluoxetine, paroxetine, or sertraline in the fetal circulation was found. The fetal : maternal drug ratios for fluoxetine, sertraline and paroxetine were 0.94, 0.43 and 0.67, respectively. Hendrick et al. (10) studied transplacental transfer in paired maternal and umbilical serum samples at delivery showing that umbilical cord SSRI concentrations were invariably lower than corresponding maternal concentrations (the mean ratios of umbilical cord to maternal serum concentrations ranged from 0.29 to 0.89). Sertraline and paroxetine had the lowest ratios while citalopram and fluoxetine had the highest. These data suggest fetal drug exposure near delivery may be decreased for sertraline and paroxetine compared to fluoxetine. As fetal drug clearance at term is decreased and approximates only one-third that of adults, it is reassuring to know that third trimester maternal SSRI use does not result in fetal drug accumulation.

Drug protein binding is inversely related to transplacental passage because a protein bound drug cannot cross the placenta. The protein binding of SSRIs is variable (Table 1). This variation in protein binding may explain differences in the ratios for cord-to-maternal-serum concentrations (10). Sertraline is the most highly protein-bound (98%) of the SSRIs, and thus it can traverse the placenta only in minute quantities. Citalopram (80%) and especially Venlafaxine (27%) have the lowest protein binding allowing for increased transplacental drug passage to the fetus.

Table 1. *Pharmacokinetic properties of SSRIs**

Drug	Amine effects	Molecular weight	Protein binding	Half-life	Metabolite half life
Fluoxetine	5-HT	309	94.5%	2–3 days	15 days (norfluoxetine)
Paroxetine	5-HT	329	95%	21 hrs	non-active metabolites
Sertraline	5-HT	306	98%	26–65 hrs	62–104 hrs (desmethyl sertraline)
Fluvoxamine	5-HT	318	80%	15.6 hrs	non-active metabolites
Citalopram	5-HT	405	80%	36 hrs	59 hrs desmethyl citalopram
Escitalopram	5-HT	414	56%	27–32 hrs	59 hrs (s+) desmethyl citalopram
Venlafaxine	5-HT, NE	313	27%	5 hrs	11 hrs o-desmethyl venlafaxine

* Adapted from Hale TW. Medications and mother's milk. 11th ed. 2004, Pharmasoft Publishing, Amarillo, Texas, USA.
5-HT — 5-hydroxytryptamine; NE — norepinephrine

Definition of SSRI-induced Neonatal Abstinence Syndrome

Some controversy exists regarding the definition of the syndrome seen in newborns following prolonged in-utero exposure to SSRIs. The general terms "neonatal complications" (11), "transient neonatal symptoms" (12) or "neonatal effects" (13) have been used by some authors with no attempt at characterization of a specific syndrome. Moses-Kolko et al. (14) and Zeskind and Stephens (15) have used the terms "neonatal behavioral syndrome" or "behavioral symptoms" to describe the transient symptoms seen in the newborn after a minimum of third trimester exposure to SSRIs. "Serotonin syndrome" assumes a direct SSRI drug effect of serotonin or its metabolites. This terminology has been suggested by Isbister et al. (16) and by Laine et al. (17). "Withdrawal syndrome" or "discontinuation syndrome" are used to denote a causal relationship between discontinued exposure to a drug and moderate to severe symptoms (18). These terms have been used in SSRI exposed newborns by Sanz et al. (19), Costei et al. (20) and others (21, 22). Overlap between symptoms caused by drug withdrawal or direct serotonin effects likely exists. Correlation in some infants between symptom severity and cord blood (16) and infant serum levels (23) suggest the possible causative role of serotonin in the clinical syndrome. Conversely, withdrawal syndrome can be proved in symptomatic infants with very low or undetectable levels of drug or active metabolites. This has been shown repeatedly (24–26). Withdrawal can also be demonstrated by showing that timing of peak symptoms does not correspond with peak exposure but appears after a delay of days, which is compatible with drug withdrawal but not with a direct drug effect (6, 27). Also a prolonged duration of symptoms without continued drug exposure is suggestive of drug withdrawal (6, 26).

NAS describes the clinical syndrome resulting from prior prolonged exposure followed by cessation of a causative drug (28). NAS includes a wide spectrum from mild to severe symptoms. Although many of the symptoms are non-specific, the combination of symptoms together with prior exposure to a drug known to cause NAS suggests its possibility. Moderate to severe NAS symptoms are compatible with the definition of a withdrawal syndrome. As NAS includes both mild and severely affected newborns, it is preferable to alternative characterizations of SSRI exposed newborns that do not include all symptomatic newborns.

Clinical Presentation of SSRI-induced Neonatal Abstinence Syndrome

The clinical spectrum of NAS is variable. Factors that increase drug exposure prior to delivery aggravate the clinical syndrome. Specific factors that increase symptom severity include: increased transplacental transfer, decreased drug metabolism and elimination, type of medication (variable effect), increased duration of use during pregnancy (mainly third trimester use), increased dose, decreased time elapsed from last drug use until birth and term delivery (prematurity possibly decreases symptoms).

The onset of symptoms often occurs shortly after birth or within the first few days of life. Infants who do not exhibit symptoms within the first 48 hours of life are unlikely to become symptomatic (6). Shorter drug half-life and a longer elapsed time since last maternal drug dose are associated with earlier onset of symptoms in the newborn infant.

Clinical symptoms are common and seen in 30% of newborns (6, 12). NAS symptoms can be categorized into four groups of effects: central nervous system (CNS), gastrointestinal, autonomic and respiratory effects. The various symptoms are described in Table 2. Symptoms may vary with time. In our experience, initial CNS effects are often those of depression with hypoactivity, hypotonia, lethargy and a weak cry. These symptoms rapidly evolve to those of CNS excitation (23). Commonly seen symptoms are irritability (14, 17, 19), jitteriness (14, 29), abnormal crying (14, 19, 29), altered behavior (14, 15), sleep abnormalities (14, 15), poor feeding (14, 19), vomiting (19), hypotonia (12, 29), hypertonia (14), respiratory distress (12, 14, 20, 29) and increased reflexes (14, 17). Less common symptoms are lethargy, a weak cry or seizures (6, 19). Although most symptoms are non-specific, some symptoms such as transient aphonia (30) have only been reported as a result of SSRI exposure. A previous association of hemorrhage with SSRI exposure (31) has not been recently substantiated (32). Some neonatal

outcomes or symptoms seen in SSRI-exposed newborns are not part of the NAS. One such outcome associated with SSRI exposure is persistent pulmonary hypertension (5, 33). Newborns should be screened for all neonatal outcomes including those that are not part of the NAS (Table 3). Duration of symptoms is variable. For most infants symptoms peak up to 96 hours after birth and then spontaneously subside within a few days (6). Occasionally infants may remain symptomatic for weeks (34).

Table 2. *The frequency of clinical features of SSRI neonatal abstinence syndrome*

Symptom	Common	Occasional	Uncommon
Ia Central nervous system excitation			
Restlessness	x		
Tremor	x		
Hyperactive tendon reflexes		x	
Hypertonicity	x		
Exaggerated Moro reflex		x	
High pitched or continuous cry	x		
Abnormal sleep pattern	x		
Frequent yawning or sneezing			x
Seizures		x	
Ib Central nervous system depression			
Lethargy		x	
Weak cry		x	
Weak sucking	x		
Aphonia			x
Hypotonicity	x		
II Gastrointestinal			
Diarrhea		x	
Dehydration		x	
Vomiting	x		
Poor feeding	x		
Regurgitation	x		
Uncoordinated sucking	x		
III Autonomic			
Temperature instability		x	
Sweating		x	
Nasal stuffiness		x	
Fever (central)		x	
Mottling		x	
IV Respiratory			
Tachypnea	x		
Dyspnea		x	

Protocol for Observation of an SSRI-Exposed Newborn

The various effects of SSRIs should all be considered when following an infant with prolonged in-utero SSRI exposure. Table 3 summarizes a protocol (6) that has been in use since 1998. The Finnegan score (6, 35, 36) may be used to follow signs of NAS. This score is an objective method used to monitor onset, progression, and improvement of NAS symptoms in passively exposed neonates. The score rates 21 symptoms most commonly seen in drug-exposed neonates, and is also used to assess the need for pharmacological intervention and the response to treatment. The total score is determined by adding the score assigned to each symptom group. Higher scores represent more severe abstinence symptoms. A score of 8 or higher in three consecutive measurements is considered an indication for pharmacotherapy. The score should be performed at intervals of 8 hours, unless severe symptoms are noted (Finnegan score ≥ 8), in which case the intervals should be shortened. The newborn should be placed in an incubator and followed closely until signs of NAS normalize (Finnegan score ≤ 3). For many newborns this period of monitoring takes 3–4 days. However, the majority of exposed newborns (70%) have no clinical signs of NAS. For these newborns, if the initial Finnegan scores are normal, the newborn may be put in a regular basinet under medical observation. During the follow-up period the parents are strongly encouraged to be in contact with their newborn and to observe his or her behavior. The newborn may be discharged from the Neonatal Department after a minimum observation period of 48–72 hours if the Finnegan score is normal. Depending on the symptoms exhibited, alternative diagnoses should be considered such as infection, hypoglycemia, hypocalcemia, etc. For newborns with severe symptoms, observation in the Neonatal Intensive Care Unit is recommended.

Unresolved Issues

The long-term effects of in-utero exposure to SSRIs have not been sufficiently studied. Oberlander et al. (37) have shown altered biobehavioral pain reactivity of exposed infants at 2 months suggesting the

Table 3. *Protocol for observation of newborns exposed in-utero to selective serotonin reuptake inhibitors*

Side effects	Clinical signs	Observe
I General	• Increase in prematurity rate • Increase in SGA*** rate • Increase in NICU** admissions	• Routine observation as required by degree of prematurity • Routine observation as required for SGA infants
II Cardiovascular	• Labile blood pressure • Tachycardia • ECG changes (prolonged QT, atrial and ventricular premature beats)	• Monitor blood pressure • Continuous ECG monitor • ECG
III Hematologic	• Anemia, Thrombocytopenia, Neutropenia • Increased hemorrhages	• Complete blood count • Physical examination
IV Metabolic	• Hypoglycemia • Abnormal liver tests • Hyponatremia, Hypokalemia	• Monitor glucose (first hours after birth) • Blood chemistry (2nd day of life)
V NAS*	• CNS signs • Gastrointestinal signs • Autonomic system signs • Respiratory signs	• Finnegan score (6, 36)

* NAS — neonatal abstinence syndrome, ** NICU — neonatal intensive care unit, *** SGA — small for gestational age

possibility of sustained neurobehavioral effect beyond the newborn period. Nulman et al. (38) studied 55 preschool children exposed to fluoxetine and also found no effect on global IQ, language development or behavioral development. Oberlander et al. (12) and Casper et al. (39) assessed exposed infants by the Bayley Scale of Infant Development at the ages of 8 months and 6–40 months, respectively. Both studies found the mental development index to be unaffected but showed a subtle effect on motor development. Although a single study has shown no difference between non-symptomatic and symptomatic infants (12), the long-term effects on the select group of SSRI-exposed infants who develop severe symptoms suggestive of a withdrawal syndrome have not been evaluated.

Treatment of SSRI-induced NAS is controversial. For most infants with NAS, "physiological" reversal of NAS is most readily achieved by reintroduction of the causative drug. For example, when narcotics cause a NAS, giving a similar narcotic allows control of abstinence symptoms. After symptom control, the drug can then be gradually tapered. In SSRI-induced NAS, this approach is not feasible because drug safety has not been established in infants. Therefore, the only currently available therapy is symptomatic treatment. For infants with severe NAS or for infants who develop seizures, phenobarbital is a possible treatment.

Breast-feeding has been shown to decrease the duration and severity of NAS (35). Currently breast feeding is not contraindicated for infants with SSRI-induced NAS, but no randomized controlled trials have been performed in breast-fed infants. Long-term follow-up studies on breast-fed infants are lacking.

Recommendations

- The risk benefit ratio of maternal treatment during pregnancy should be evaluated. If the indication for treatment is unchanged, then treatment should be continued.
- Tapering of SSRIs during the last month of preg-

nancy should theoretically prevent both NAS and direct drug effects. However, it is not known if tapering of medications reduces the risk of NAS.

- Infants born following third trimester exposure to SSRIs should be monitored for NAS symptoms for a minimum period of 48–72 hours with a standardized protocol including the Finnegan score. Infants who develop a NAS should remain under observation until symptom resolution. Neonatal Intensive Care Unit observation is recommended for severely effected infants.
- Breast-feeding is allowed but infants should be observed for any abnormal behavior.
- Treatment of infants with SSRI-induced NAS is symptomatic.
- Therapeutic drug monitoring may be indicated to differentiate between NAS and direct drug affect.

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