even this hematoma might cause hyperbilirubinemia.

*Contributors:* AZ was involved in management of patients, designing of article and critical revision of the manuscript. CT was involved in review of literature, data collection and drafting the manuscript. ND, AYB were involved in management of patient and data collection.

*Competing interests:* None.

*Funding:* None.

**REFERENCES**

1. Maisels MJ. Jaundice. In: Avery's Neonatology. Pathophsiology and Management of the Newborn, 4th edition. Eds. Avery GB, Fletcher MA, MacDonald MG. J.B. Lippincott Company, 1994; p. 603-708.
2. Opalach RM, Karlowicz MG, Katz ME. Neonatal radiology casebook. Splenic hematoma as a cause of hypovolemic shock in a very low birth weight neonate. J Perinatol 1996;16: 313-314.
3. Stoll BJ, Kleigman RM. Jaundice and Hyperbilirubinemia in the Newborn. *In:* Nelson Textbook of Pediatrics. 16th edn. Eds. Behrman RE, Kliegman RM, Jenson HM. WB Saunders Co, 2000; p. 513-519.
4. Halemek LP, Stevenson DK. Neonatal Jaundice and Liver Disease. *In:* Neonatal-Perinatal Medicine. Diseases of the Fetus and Infant. 7th edn. Eds. Fanaroff AA, Martin RJ. Mosby, 2002: vol 1, p. 1309-1351.
5. Simmons MA, Burrington JD, Wayne ER, Hathaway WE. Splenic rupture in neonates with erythroblastosis fetalis. Am J Dis Child 1973; 126 : 679-681.
6. Delta BG, Eisenstein EM, Rothenberg AM. Rupture of a normal spleen in the newborn: report of a survival and review of the literature. Clin Pediatr 1968; 7: 373-376.

# Fluoxetine Withdrawal Syndrome in the Newborn

**Anbarasu Theodore Anbu**
**Annie Theodore**

*A term baby was admitted to our neonatal unit with jitteriness, hypertonia, sneezing and fever. Her mother was on 20 mg of fluoxetine throughout her pregnancy. These symptoms which were possibly due to fluoxetine withdrawal lasted only for a short while. We attempt to look at the reported prevalence of this condition in the literature.*

**Key words:** *Fluoxetine withdrawal, Neonate, SSRI withdrawal.*

Selective Serotonin Re-uptake Inhibitors (SSRI's) such as fluoxetine are increasingly being used to treat depression in pregnant women as they are shown to be relatively harmless to the developing fetus. However, symptoms of SSRI withdrawal have been occasionally reported. Here we describe a neonate who presented with symptoms possibly due to fluoxetine withdrawal.

## Case report

A term infant was born with a birth weight of 3200 g to a 28-year-old mother. The APGAR scores were 9 at 1 and 5 minutes and

*From Pediatric Nephrology Units, Royal Manchester Children's Hospital, Hospital Road, Pendlebury, Manchester M27 4HA. United Kingdom.*
*E-mail: theoanbu@hotmail.com*

*Correspondecne to: Dr. Anbarasu Theodore Anbu, Pediatric Nephrology Unit, Royal Manchester Children's Hospital, Hospital Road, Pendlebury, Manchester M27 4HA. United Kingdom.*

*Manuscript received: February 21, 2005;*
*Initial review completed: March 22, 2005;*
*Revision accepted: August 25, 2005.*

she was nursed in the post natal ward. At 6 hours of age she was noticed to be jittery on handling. As she was otherwise well with normal blood glucose (2.6 mmol/L) she was nursed under close observation in the post natal wards. However she gradually started sneezing and developed a temperature of 37.9 degrees centigrade. Her full blood count, C reactive protein, liver functions and blood culture were within normal limits. Her other blood tests undertaken were blood glucose 4.5 mmol/L, serum calcium 2.36 mmol/L, serum magnesium 0.73 mmol/L, serum sodium 135 mmol/L, potassium 5.4 mmol/L, urea was 4.4 mmol/L and creatinine was 42 μmol/L. By 15 hours of age, she developed increasing jitteriness, vomiting and poor feeding. Her tone was increased in all four limbs. She was admitted to the neonatal unit for further management. At this stage it was found that the mother had been on 20 mg per day of fluoxetine throughout her pregnancy for depression. There was no history of any other drug intake including recreational drugs. She was started on 10% dextrose infusion. Her feeds were stopped transiently and were gradually restarted within few hours, which she tolerated well. By 2 days of age the jitteriness improved and she was transferred to the post natal ward and thereafter discharged home on day 3. Urine drug screen, which included amphetamines, benzodiazepines, cocaine metabolites, methadone and its metabolites, cyclizine, opiates, phenothiazines and tricyclic antidepressants, was negative in the mother and infant and therefore a provisional diagnosis of fluoxetine withdrawal syndrome was made. She was reviewed again at 1 week of age. On examination she was well with only mild jitteriness. Repeat serum electrolytes and blood glucose continued to be within normal limits. The mother was reassured and the baby was sent home. The jitteriness resolved within few days and the infant has been well since.

## Discussion

Fluoxetine is a widely used antidepressant drug in pregnancy. It is also used to treat anxiety, panic disorder and obsessive compulsive disorder. Several studies have shown that it could be safely used in pregnancy. Intrauterine exposure of fluoxetine may lead to neonatal syndrome, which includes withdrawal or toxicity. Most of the data on neonatal problems after maternal SSRI exposure come from case reports, pharmacovigilance updates and systematic follow up studies of SSRI exposed pregnancies.

To date at least 7 isolated case reports on fluoxetine withdrawal or toxicity has been published(1-7). Databases of adverse drug event reports(8-10) and small case series reports(11) provide additional sources of information on the SSRI-related neonatal withdrawal syndrome including fluoxetine. Sanz, *et al*.(8) in their recent analysis of the adverse drug event database of the World Health Organisation (WHO) Collaborating Centre for International Drug Monitoring reported a total of 74 SSRI-related neonatal withdrawal syndrome cases of which 10 were due to fluoxetine (others paroxetine = 51, sertraline = 7, citalopram = 6). The US Food and Drug administration (FDA) Adverse Event Reporting System(9) recorded 57 instances of SSRI-related neonatal withdrawal syndrome by November 2001. Of these 4 were due to fluoxetine (others paroxetine = 35, sertraline = 8, citalopram = 5, fluvoxamine = 2and venlafaxine = 3). By August 2003, out of the 26 SSRI-related neonatal withdrawal syndrome cases, the Australian Adverse Drug Reaction bulletin(10) reported 7 neonates with symptoms due to maternal third trimester ingestion of fluoxetine. In the United Kingdom

(UK) the National Teratology Information Service (NTIS) to date have recorded 8 cases of possible neonatal withdrawal following maternal fluoxetine use in 513 pregnant women (NTIS, Regional Drug & Therapeutics Center, Newcastle, UK, unpublished data 2004).

The clinical presentation of fluoxetine withdrawal depends on the timing and amount of last maternal use, maternal and infant metabolism and excretion. The most commonly reported neonatal symptoms include agitation, irritability, impending seizures, hypertonia or hypotonia, hyperreflexia, drowsiness, jitteriness, feeding problems, persistent crying, tachypnoea, temperature instability, acrocyanosis and tremors. In addition fluoxetine toxicity has been observed as scattered petechiae over the face and trunk along with cephalhaematoma(5), marked motor automatism and skin manifestations(6). It has also been associated with colic(3), lipomeningocele(4), and cardiac arrhythmia(7). Due to its longer half life (2-3 days) the withdrawal symptoms due to fluoxetine are usually mild and self limiting compared to other SSRI's. Moreover it is obvious from the published work that majority of the reported cases of suspected SSRI-induced neonatal withdrawal syndrome are due to Paroxetine and fluoxetine(9).

Management of these infants should include a detailed maternal history and thorough clinical examination in addition to various laboratory tests. A good maternal drug history is vital as the physician who is unaware of a mother's ingestion of the drug may mistake the signs of withdrawal for other neonatal problems like central nervous system infections, hypocalcemia, hypoglycaemia, other electrolyte abnormalities and colic. Also it is equally important that no clinical sign should be attributed solely to drug withdrawal without appropriate assessment and diagnostic tests to rule out other causes. Most of the neonates need only supportive care and could be nursed in the postnatal ward or admitted to neonatal unit for observation, as seen in our patient. More essentially the withdrawal symptoms could be minimised by using the lowest effective maternal dose of fluoxetine.

It is probable that the prevalence of neonatal withdrawal syndrome due to maternal ingestion of fluoxetine might be much more than what's been purported in published medical literature. Although, fluoxetine produces no identifiable major malformations in the developing fetus; obstetricians, mid wives, psychiatrists and paediatricians should be more aware of the existence of this self-limiting illness. This would enable them to better inform and counsel all pregnant women on fluoxetine therapy of the possible adverse effects in the newborn period and assist them in identifying withdrawal symptoms in their newborn.

**Acknowledgments**

We would like to thank the National Teratology Information Service, United Kingdom for helping us with data on the number of newborns with fluoxetine withdrawal syndrome in the United Kingdom.

**REFERENCES**

1. Hale TW, Shum S, Grossberg M. Fluoxetine Toxicity in a Breastfed Infant. Clin Pediatr 2001; 40: 681-684.
2. Spencer MJ. Fluoxetine hydrochloride (Prozac) toxicity in a neonate. Pediatrics 1993; 92: 721-722.
3. Lester BM, Cucca J, Andreozzi L, Flanagan P, Oh W. Possible association between fluoxetine hydrochloride and colic in an infant. J Am Acad Child Adolesc Psychiatry 1993; 32: 1253-1255.
4. Vendittelli F, Alain J, Nouaille Y, Brosset A,

Tabaste JL. A case of lipomeningocele reported with fluoxetine (and alprazolam, vitamin $B_1$ and B6, heptaminol) prescribed during pregnancy. European Journal of Obstetrics & Gynecology and Reproductive Biology 1995; 58: 85-86.

5. Mhanna MJ, Bennet JB, Izatt SD. Potential fluoxetine chloride (Prozac) toxicity in a newborn. Pediatrics 1997; 100: 158-159.
6. Mohan CG, Moore JJ. Fluoxetine toxicity in a preterm infant. Journal of Perinatology 2000; 20: 445-446.
7. Abebe-Campino G, Offer D, Stahl B, Merlob P. Cardiac arrhythmia in a newborn infant associated with fluoxetine use during pregnancy. Ann Pharmacother 2002; 36: 533-534.
8. Sanz EJ, De-Las-Cuevas C, Kiuru A, Bate A, Edwards R. Selective serotonin reuptake inhibitors in pregnant women and neonatal withdrawal syndrome: A database analysis. Lancet 2005; 365: 482-487.
9. CDER 2004 meeting documents. http://www.fda.gov.ohrms/dockets/ac/cder04.html#Anti-Infective. Accessed June 29, 2005.
10. Australian Adverse Drug Reactions Advisory Committee. Maternal SSRI use and neonatal effects. Austral Adverse Drug Reactions Bull Aug 2003; 22: 14.
11. Nordeng H, Lindemann R, Perminov KV, Reikvam A. Neonatal withdrawal syndrome after *in utero* exposure to selective serotonin reuptake inhibitors. Acta Paediatr 2001; 90: 288-291.