Sertraline in Pregnancy: Not that Innocuous. Report of Two Cases and Review of the Literature

Sertralina na Gravidez: Não tão Inócuo. Relatos de Dois Casos e Revisão da Literatura

Flávia Corrêa[1], Fernando Chaves[1], Olga Voutsen[1], Alberto Berenguer[1], Pedro Silva[1]*

***Corresponding Author**/Autor Correspondente:
Flávia Corrêa [flavia.figueiredo.correa@lusiadas.pt]
Rua Abílio Mendes 12, 1500-458 Lisboa, Portugal

Abstract

Sertraline, which is one of the selective serotonin reuptake inhibitors (SSRIs), is commonly used during pregnancy, mainly for the treatment of depressive disorders. Because sertraline use during gestation is perceived as having a favourable risk/benefit ratio, the use of this drug in this context has increased over the past decade. Nevertheless, short-term adverse outcomes occur in up to 30% of infants exposed in utero to SSRIs, and SSRI-related symptoms have been attributed to both direct drug effects and to a withdrawal syndrome. We present two cases of neonatal adverse short outcome after the gestational use of sertraline for treating maternal depression, and discuss the literature and guidelines concerning the use of this drug during pregnancy.

Keywords: Antidepressive Agents/adverse effects; Infant, Newborn; Neonatal Abstinence Syndrome; Pregnancy; Prenatal Exposure Delayed Effects/chemically induced; Sertraline/adverse effects

Resumo

A sertralina, que pertence ao grupo dos inibidores seletivos da recaptação da serotonina, é frequentemente utilizada no tratamento da depressão na grávida. Uma vez que o risco/benefício do seu uso na gravidez é considerado favorável, a sua utilização vem aumentando consideravelmente na última década. No entanto, em 30% dos recém-nascidos cujas mães utilizaram esse grupo de antidepressivos, a evolução a curto prazo não é adequada, sendo os sintomas atribuídos quer a um efeito direto do medicamento, quer a uma síndrome de abstinência neonatal. Neste trabalho apresentamos dois casos onde os recém-nascidos apresentaram, nos primeiros dias de vida, sintomas que podem ser relacionados ao uso materno da sertralina, e também discutimos a revisão da literatura e as *guidelines* em relação ao uso desta droga na gravidez.

Palavras-chave: Antidepressivos/efeitos adversos; Efeitos Tardios da Exposição Pré-Natal; Gravidez; Recém-Nascido; Sertralina/efeitos adversos; Síndrome de Abstinência Neonatal

1. Unidade de Neonatologia, Hospital Lusíadas Lisboa, Lisboa, Portugal.
Received/Recebido: 25/05/2021 - **Accepted/Aceite:** 15/06/2021 - **Published/Publicado:** 30/06/2021

Introduction

Depression occurs in 7%-15% of all pregnancies.[1] Undetected and untreated maternal depression is not only associated with significant adverse risks for the mother, but also exerts a transgenerational effect on the unborn baby.[2] Selective serotonin reuptake inhibitors (SSRI) antidepressants are the commonest prescribed pharmacological treatment for depression and anxiety in pregnancy, being sertraline and paroxetine considered the safest drugs among this group (which is also compound of fluoxetine, citalopram, escitalopram and fluvoxamine).[1] Nevertheless, in recent years several concerns have been raised about SSRI´s reproductive safety, including disturbed fetal development, increased rates of congenital anomalies, increased risks of neonatal complications, neuro-motor delay and even autism.[3] This is concerning once SSRIs are increasingly being used during pregnancy and lactation,[1] with a marked increment in the last year due to COVID-19 pandemic. In this work, we report two cases of neonatal adverse effects caused by maternal use of sertraline and review the available evidence and guidelines for the use of antidepressants in pregnancy.

Case Reports

Case 1

A neonate whose mother used sertraline since the first trimester of the pregnancy until birth. Excepting the depression, the mother had no previous diseases and all the parameters of the gestation were normal. At 37 weeks of gestation, a 2.955 g baby boy was born by a vacuum vaginal delivery after spontaneous labour and epidural anesthesia. Prenatal cardiotocography was always normal and did not explain the serious neonatal cardiorespiratory depression at birth. The newborn had to be resuscitated with endotracheal intubation and naloxone, with a relatively slow respiratory recovery, needing endotracheal ventilation until 12 minutes of life. Apgar index was 4 at first minute, 6 at 5 minutes and 7 at 10 minutes of life. He was transferred to the neonatal intensive care unit (NICU) and needed high-flow nasal oxygen therapy during the first 6 hours of life. The infant presented hypotonia and mild enteric nutrition intolerance at the first 48 hours of life, being discharged from NICU at 6 days of life.

Case 2

A baby boy whose mother used sertraline during the three trimesters of the gestation due to depression and anxiety. It was the second pregnancy of this mother and the infant was delivered by an elective caesarean section at a gestational age of 38 weeks and 5 days. Birth weight was 3500 g and Apgar index was 10/10. At 12 hours of life, the newborn presented high pitched cry, severe hypertonicity, significant tremors, hyperactive tendon reflexes, abdominal distension as well as vomiting and was transferred to NICU. Sepsis was ruled out despite antibiotic therapy was installed. The patient received exclusively parenteral nutrition during the first 72 hours of live and symptoms of central nervous system excitation progressively disappeared until the third day of life. Concerning the gastrointestinal system, the patient presented a meconium plug syndrome that improved with the implementation of enemas and had a radiologic dilated intestinal colon until discharge. He was discharged at 14 days of life with the prescription of enemas at home. Aganglionosis could not be ruled out until the moment. The baby is now 2-month-old and is now presenting mild spontaneous intestinal functioning.

Discussion

Untreated maternal depression during pregnancy has been associated with perinatal adverse outcomes, including premature delivery and low birth weight, apart from potential devasting consequences to the mother[4] As many as one in five pregnant women experience some sort of depressive disorder during pregnancy.[4] Given the risks mentioned above, foregoing antidepressant treatment throughout pregnancy is often not an option for women with depression.[5] Published data show that 2.4% of pregnant women in Sweden during years 2006-2012[6] and 6% in USA during the years 2001-2013 were treated with SSRIs.[7] These numbers are now possibly even higher since pregnant individuals are experiencing substantially elevated anxiety and depression symptoms during the COVID-19 pandemic.[8] In our Department, it was clearly noticed a marked increase in the use of SSRIs by pregnant women in the last year.

All members of these drug classes have been shown to cross the placenta.[9] While most newborns born to women who continue SSRI treatment during pregnancy are healthy and, being the use of SSRIs so widespread disseminated during gestation, there may be a tendency to believe that their use is quite safe in pregnancy. Nevertheless, back in 2011 the Canadian Pediatric Society (CPS) issued a position statement recommending that newborns exposed to SSRIs be observed in hospital for at least 48 hours.[10] The authors focused on three neonatal outcomes that have been highlighted in the literature within the first 48 hours following delivery: neonatal adaptation syndrome, congenital heart defects, and persistent pulmonary hypertension.

Initially, small studies on humans observed no increased risk of major congenital malformations after in utero exposure to SSRIs.[1,11] However, more recent data with larger cohorts suggested an increased risk of atrial/ventricular defects and craniosynostosis with sertraline use in the first trimester of gestation.[12] Nonsertraline SSRIs were associated with an increased risk of craniosynostosis and musculoskeletal defects.[12] Concerning persistent pulmonary hypertension of the neonate (PPHN), a serious and sometimes fatal condition, a recent meta-analysis systematic review concluded that exposure to antidepressants

Table 1. The frequency of clinical features of SSRI neonatal abstinence syndrome.

Symptom	Common	Occasional
IA Central nervous system excitation		
Restlessness	x	
Tremor	x	
Hyperactive tendon reflexes		x
Hypertonicit	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

during pregnancy was associated with a 2-fold increased risk for PPHN.[4] Sertraline was ranked with lowest probability risk for PPHN among all antidepressants.[4]

There is growing evidence that fetal exposure to SSRIs is associated with a neonatal abstinence syndrome.[13] Exposure to an SSRI during pregnancy has been associated with many neonatal symptoms, including respiratory distress, cyanotic events, feeding difficulties, hypoglycemia, and a wide spectrum of neurologic symptoms, ranging from convulsions, neurobehavioral disturbance, sleep disturbances, and increased motor activity to a neonatal withdrawal syndrome.[14] Studies have reported an incidence of neonatal abstinence syndrome in 30% of the newborns whose mother used SSRIs during the second half of the gestation.[13,15] In 13% of these infants, the symptoms are severe enough to meet the definition of a severe neonatal abstinence syndrome.[13] 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.[16] Duration of symptoms is variable. For most infants, symptoms peak up to 96 hours after birth and then spontaneously subside within a few days.[14] Occasionally, infants may remain symptomatic for weeks. Table 1 describes the symptoms of neonatal abstinence syndrome and their frequency.[16]

Neonatal abstinence syndrome should be distinguished from serotonin syndrome (toxicity). Abstinence is more likely with agents with shorter plasma elimination half live (e.g. sertraline),[17] whereas toxicity has been reported with agents with a longer elimination half live of the agent and/or its metabolite (fluoxetine, paroxetine and citalopram).

Currently, affected infants are generally treated conservatively with observation (and respiratory support as required), and tests are done to rule out microbial infection or exposure to other toxic agents (e.g., benzodiazepine, opioids or ethanol). Phenobarbital, which has a long safety record in neonates, may be used to mitigate irritability, rigidity and seizures.[9]

As regards breastfeeding, the authors state that citalopram, escitalopram and sertraline are also compatible with lactation.[18] However, the authors support this conclusion by using parameters whose usefulness in clinical practice is still doubtful.[3] Another study showed that undetectable sertraline levels in infant serum have been reported in 87% of exposed infants with no reported adverse events.[17] It is necessary to weigh the risks to the infant of antidepressant exposure through breast milk against the disadvantage of not receiving mother's milk and being exposed to a relapse of maternal mood symptoms (which may also have tragic consequences for the patient).

Below you will find a summary of Canada, UK and Australia guidelines for the use of SSRIs in pregnancy[10,19,20]:

Recommendations:

1. Parents should be educated prior to delivery about the increased risks for neonatal adaptation syndrome (not very rare), congenital heart defects (very rare), and PPHN (very rare). This includes being informed of the screening their newborn will receive in the first 48 hours.
2. Neonatal Observation during 48 hours: Differential diagnosis and assessment is required for symptoms and signs of neonatal irritability, poor feeding and respiratory difficulties to rule out infectious, metabolic, circulatory and neurological conditions.
3. Focus on supportive care and emphasize that neonatal adaptation syndrome symptoms are usually mild and transient.

In all cases, the use of strategies such as planning for pregnancy, educating the mother and family, regarding the risk/benefit ratio of treatment versus no treatment, and involving in the decision-making process a multidisciplinary team with good expertise in perinatal psychiatry may improve outcomes for the mother-infant dyad. Meanwhile, any conclusion about

what antidepressant should be considered the safest during pregnancy and puerperium must be stated and read with great caution.[3] Although sertraline seems to be the best option among this group, in any way it should be considered a completely safe drug. All neonates whose mothers used sertraline or other SSRI during gestation should be closely monitored in the first 48 hours of life.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.

Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Consentimento: Consentimento do doente para publicação obtido.

Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.

Financing Support: This work has not received any contribution, grant or scholarship.

Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Patient Consent: Consent for publication was obtained.

Provenance and Peer Review: Not commissioned; externally peer reviewed.

ORCID iD: Flávia Corrêa https://orcid.org/0000-0001-6917-5624

References

1. Sie S, Wennink J, van Driel J, te Winkel A, Boer K, Casteelen G, van Weissenbruch M. Maternal use of SSRIs, SNRIs and NaSSAs: practical recommendations during pregnancy and lactation. Arch Dis Child Fetal Neonatal Ed. 2012; 97:F472-F476.
2. du Toit E, Thomas E, Koen L, Vythilingum B, Grobler S, Smith N, Niehaus D. SSRI use in pregnancy: Evaluating the risks and benefits. S Afr J Psychiatr. 2015; 22:48-53.
3. Gentile S. Managing antidepressant treatment in pregnancy and puerperium. Careful with that axe, Eugene. Expert Opin Drug Saf. 2015;14:1011-4. doi: 10.1517/14740338.2015.1037273.
4. Masarwa R, Bar-Oz B, Gorelik E, Reif S, Perlman A, Matok I. Prenatal exposure to selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors and risk for persistent pulmonary hypertension of the newborn: a systematic review, meta-analysis, and network meta-analysis. Am J Obstet Gynecol. 2019; 220:57.e1-57. doi: 10.1016/j.ajog.2018.08.030.
5. Bandoli G, Chambers C, Wells A, Palmste K. Prenatal antidepressant use and risk of adverse neonatal outcomes. Pediatrics 2020; 146:e20192493. doi: 10.1542/peds.2019-2493.
6. Norby U, Forsberg L, Wide K, Sjors G, Winbladh B, Kallen K. Neonatal morbidity after maternal use of antidepressant drugs during pregnancy. Pediatrics. 2016; 138:e20160181. doi: 10.1542/peds.2016-0181.
7. Andrade C. Antidepressant exposure during pregnancy and risk of autism in the offspring, 1: Meta-review of meta-analyses. J Clin Psychiatry. 2017;78:e1047-51. doi: 10.4088/JCP.17f11903.
8. Lebel C, MacKinnon A, Bagshawe, M, Tomfohr-Madsen L, Giesbrecht G. Elevated depression and anxiety symptoms among pregnant individuals during the COVID-19 pandemic. J Affect Disord. 2020;277:5-13. doi: 10.1016/j.jad.2020.07.126.
9. Koren G, Matsui D, Einarson A, Knoppert D, Steine M. Is maternal use of selective serotonin reuptake inhibitors in the third trimester of pregnancy harmful to neonates? CMAJ. 2005;172:1457-9.
10. Cronin C, Donaldson H, Hanley G, Oberlander T, Ryan D, Walker J. Antidepressant use during pregnancy: Considerations for the newborn exposed to SSRIs/SNRIs. Vancouver: Perinatal Services British Columbia Guideline; 2013.
11. Gentile S. The safety of newer antidepressants in pregnancy and breastfeeding. Drug Safety. 2005;28:137-52.
12. Bérard A, Zhao J, Sheehy O. Sertraline use during pregnancy and the risk of major malformations. Am J Obstet Gynecol. 2015;212:795.e1-795.e12. doi: 10.1016/j.ajog.2015.01.034.
13. Levinson-Castiel R, Merlob P, Linder N, Sirota L, Klinger G. Neonatal abstinence syndrome after in utero exposure to selective serotonin reuptake inhibitors in term infants. Arch Pediatr Adolesc Med. 2006;160:173-6.
14. Hayes R, Wu P, Shelton R, Cooper W, Dupont W, Mitchel E, Hartert T. Maternal antidepressant use and adverse outcomes: a cohort study of 228,876 pregnancies. Am J Obstet Gynecol. 2012; 207: 49.e1-49.e9. doi:10.1016.
15. Oberlander TF, Misri S, Fitzgerald CE, Kostaras X, Rurak D, Riggs W. Pharmacologic factors associated with transient neonatal symptoms following prenatal psychotropic medication exposure. J Clin Psychiatry. 2004; 65:230-7.
16. Klinger G, Merlob P. Selective Serotonin Reuptake Inhibitor Induced Neonatal Abstinence Syndrome. Isr J Psychiatry Relat Sci. 2008;45:107-113.
17. Pinheiro E, Bogen DL, Hoxha D, Ciolino JD, Wisner KL. Sertraline and breastfeeding: review and meta-analysis. Arch Womens Ment Health. 2015;18:139-46. doi: 10.1007/s00737-015-0499-y.
18. Weisskopf E, Fischer CJ, Graz MB, Morisod Harari M, Tolsa JF, Claris O, et al. Risk-benefit balance assessment of SSRI antidepressant use during pregnancy and lactation based on best available evidence. Expert Opin Drug Saf. 2015; 14:413-27. doi: 10.1517/14740338.2015.997708.
19. Martin J, Osborn D. Newborn Infants Exposed to SSRI / SNRI Antidepressant Medication during Pregnancy and Lactation. Sydney: Local Health District Guideline; 2020.
20. Munyard P. Maternal Use of SSRIs Neonatal Clinical Guideline V2.0. London: NHS Trust; 2018.