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Neonatal Effects after Selective Serotonin Reuptake Inhibitors and Benzodiazepines Administration during Pregnancy

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Authors' contributions

This work was carried out in collaboration between all authors. Author GE designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author FR managed the supervision and author MD managed the analyses of the study. Authors GA and MG managed the literature searches. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Aims: To evaluate whether the co-administration of benzodiazepines (BDZ) and selective serotonin and serotonin/norepinephrine reuptake inhibitors (SSRI/SNRI) during pregnancy is associated with an increased risk of abstinence symptoms in the newborns.
Methods: Twenty six neonates exposed in utero to SSRI/SNRI were studied. The presence of symptoms possibly due to neonatal abstinence syndrome, BDZ exposure, weight, age at birth and duration of hospitalization were recorded. Blood levels of SSRI/SNRI and BDZ were measured in all neonates.

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Results: Neonatal blood levels of SSRI/SNRI were within or below normal adult therapeutic range in 21 newborns (81%). Thirteen newborns (50%) were symptomatic. Neonates born from mothers receiving co-administration of SSRI/SNRI and BDZ had a higher risk of developing symptoms as compared to those whose mother was not receiving BDZ (9/13, 69% versus 4/13, 31%, $p \leq 0.05$). At birth, symptomatic newborns displayed a significatively lower weight and gestational age than asymptomatic neonates (2609 $\pm$ 301 vs 3112 $\pm$ 310 g, and 36 $\pm$ 1 vs 39 $\pm$ 1 week, respectively, $p < 0.001$). No relationship was found between symptoms and neonatal blood levels of either SSRI/SNRI or BDZ.

Conclusions: Our results suggest that the co-administration of SSRI/SNRI and benzodiazepines during pregnancy may be associated with an increased risk of neonatal symptoms. However, these symptoms are not related to blood levels and may be attributed to prematurity leading to a longer hospital stay.

Keywords: Neonatal abstinence syndrome; serotonin toxicity; selective serotonin reuptake inhibitors; benzodiazepines.

1. INTRODUCTION

Neonatal abstinence syndrome (NAS) is a controversial constellation of signs and neurobehavioral symptoms that occur in infants exposed to drugs known to cause addiction during the third trimester. An historical perspective documented NAS from opioid use during pregnancy as a congenital morphinism [1]. Since the past decade, many authors reported that NAS may also occur after in utero exposure to other psychoactive substances such as antidepressants or benzodiazepines. Poor neonatal adaptation was previously described in infants exposed to fluoxetine in the third trimester of pregnancy as compared with those exposed only in early pregnancy [2]. Since then, many authors reported a prevalence of symptoms attributed to in utero exposure to SSRI/SNRI up to 30% [3-5]. On the other hand, after BDZ exposure a prevalence of 20% of a withdrawal syndrome in symptomatic newborns has been reported [6].

It is well known that women exposed to SSRI/SNRI during pregnancy have a higher risk of preterm delivery, low birth weight and longer hospital stay in neonates [7-8]. Low weight newborns are more susceptible to display symptoms as respiratory distress syndrome and tremors or jitteriness that may be attributed to drug withdrawal [9-10]. Finally, little is known about neonatal blood levels of benzodiazepines and SSRI/SNRI co-administered during the last trimester of pregnancy.

2. METHODS

In our hospital all neonates born from mothers treated with SSRI/SNRI are temporarily admitted to neonatal intensive care. We retrospectively evaluated 26 consecutive neonates admitted to the neonatal intensive care unit from 2013 to 2016 born from mothers administered SSRI/SNRI continuously at least during the third trimester of pregnancy up to delivery. Maternal use of alcohol, tobacco, herbal medicines or drugs of abuse during pregnancy was also investigated. Infant gender, birth weight and gestational age as well as Apgar scores, symptoms and hospital stay were recorded. We adopted the World Health Organization (WHO) definition of preterm birth as less than 37 weeks' gestation and the WHO definition of low birth weight as weight at birth of less than 2500 g. A symptomatic newborn with signs of abstinence was defined if one or more of the following symptoms were present: hypertonia, tremors, respiratory distress, hypoglycemia, hypotonia, seizures or cardiac disturbances. All symptoms were monitored while the babies were being managed. The diagnosis of neonatal abstinence syndrome was defined as an ICD-9 CM code 779.5 using the Finnegan scale, an objective rating used to assess the severity and resolution of neonatal abstinence symptoms. Infant blood serum was collected in the first twenty four hours from delivery to enable measurement of SSRI/SNRI and BDZ concentration. Blood samples were collected only for diagnostic need and we asked the informed consensus from the parents in each case. Statistical analysis was performed using unpaired t test and chi-square were appropriate.

3. LABORATORY

Paroxetine, sertraline, citalopram, escitalopram, duloxetine, lorazepam and lormetazepam in plasma were measured by a certified LC-MS/MS assay (Liquid chromatography-mass spectrometry) and alprazolam in serum was

performed by a validated high-performance liquid chromatography-ultraviolet spectrophotometry (HPLC-UV). The limits of quantitation (LOQ) and detection (LOD) respectively for the assays were: paroxetine (10 and 3 ng/ml), sertraline (6 and 2 ng/ml), citalopram (15 and 5 ng/ml), escitalopram (1.5 and 0.5 ng/ml), duloxetine (1 and 0.31 ng/ml), alprazolam (20 and 10 ng/ml), lorazepam (20 and 10 ng/ml) and lormetazepam (5 and 3 ng/ml). The adult reference therapeutic ranges for paroxetine were 30-160 ng/ml, for sertraline 50-150 ng/ml, citalopram 50-110 ng/ml, for escitalopram 15-80 ng/ml, for duloxetine 30-120 ng/ml, for alprazolam 20-40 ng/ml, for lorazepam 50-240 ng/ml and for lormetazepam 5-25 ng/ml.

4. RESULTS

The study included 26 neonates (11 females and 15 males) born from 25 mothers (one twin pregnancy) under SSRI/SNRI treatment during the last trimester of pregnancy; 12 mothers were also receiving BDZ.

Thirteen neonates (50%) were symptomatic and 13 were asymptomatic. In the symptomatic group, 9 (69%) neonates were born from mothers co-administered BDZ and 4 (31%) had received only SSRI/SNRI ($p \leq 0.05$). In the asymptomatic group only 4 neonates were exposed to SSRI/SNRI and BDZ.

Overall, the mean gestational age of the 26 neonates was 38 ± 1.69 weeks (range 33-40) and their average birth weight was 2861 ± 396 g (range 2050-3500 g). When comparing the symptomatic with the asymptomatic group, symptomatic newborns displayed a significatively lower weight at birth than asymptomatic neonates (2609 ± 301 g versus 3112 ± 310 g, respectively, $p < 0.001$). Accordingly, in the symptomatic group, 8/13 (62%) neonates were preterm births whereas no preterm neonate was observed in the asymptomatic group ($p < 0.001$). The mean gestational age in the symptomatic group was 36 ± 1.5 weeks (range 34-38) and in the asymptomatic group was 39 ± 1.1 weeks ($p < 0.003$). Symptoms are shown in Table 1.

The SSRI/SNRI and BDZ intake is shown in Table 2. All mothers were receiving antidepressants and four of them were administered paroxetine that, for some authors, may be contraindicated during pregnancy but a benefit/risk ratio assessed by their physicians avoided the discontinuation of the drug. SSRI/SNRI and BDZ administration was continued until delivery, no dosage reduction during the last four weeks before delivery was performed. Maternal use of alcohol, tobacco, herbal products and drug abuse were excluded in all but one mother treated with methadone.

At birth, blood concentrations of the benzodiazepines were under the LOQ in all neonates whereas SSRI/SNRI blood levels were found in 21 newborns (81%) and resulted below LOQ in 5 (19%): 3 newborns were asymptomatic and 2 had symptoms. Antidepressant blood concentrations in the neonate, presence of symptoms, maternal SSRI/SNRI/ and co-treatment are also shown in Table 2.

All symptomatic neonates were observed for more 48 hours after remission of symptoms. The asymptomatic neonates were discharged within 72 hours after delivery. In symptomatic newborns a significantly longer hospital stay was found as compared to asymptomatic neonates (14 + 8.1 versus 3.3 + 0.75 days respectively; $p < 0.0001$).

Table 1. Gestational age, weight at birth and symptoms

	All neonates (n° 26)	**Symptomatic newborns (n° 13)**	**Asymptomatic newborns (n° 13)**	**p value**
Gestational age (mean ± SD, wk)	38 ± 1.69	36 ± 1.5	39 ± 1.1	p < 0.003
Weight at birth (mean ± SD, g)	2861 ± 395.7	2609 ± 301	3112 ± 310	p < 0.001
Preterm birth (yes/no)	8/18	8/5	0/13	p < 0.001
BDZ co-administration (yes/no)	13/26	9/4	4/9	p < 0.05
Symptoms, n (%)				
▪ Hypertonia		9 (69%)	---	
▪ Tremors		7 (54%)	---	
▪ Respiratory distress		5 (38%)	---	
▪ Hypoglycemia		2 (15%)	---	
▪ Hypotonia		1 (8%)	---	

Table 2. SSRI/SNRI concentrations in the neonate plasma at birth, symptoms after delivery and associated maternal therapy

Case	Maternal SSRI/SNRI dose, mg/d	BDZ plasma concentrations	Gestational age, wk	Gender	Birth weight, g	APGAR (1 and 5 min)	Symptoms after delivery	SSRI concentrations (ng/ml)
Sertraline								
Case 1	100		40	Female	3500	9/9	No	< LOQ
Case 2	50	Lorazepam < LOQ	33	Male	2057	6/8	Yes	25.6
Case 3	50	Alprazolam < LOQ	37	Male	2735	7/7	Yes	8.4
Case 4	50		38	Female	3440	10/10	No	2.2
Case 5	25	Lorazepam < LOQ	38	Male	3235	9/10	No	6.7
Case 6	50		38	Male	2695	8/8	No	14.8
Case 7	50		39	Female	3475	9/10	No	5.5
Case 8	25		40	Female	2995	9/10	No	4.7
Case 9	100		39	Male	3265	10/10	No	22.9
Case 10	100		36	Male	2640	8/8	Yes	11.8
Citalopram								
Case 11	15	Lormetazepam < LOQ	38	Female	2650	7/9	Yes	55.4
Case 12	20	Lorazepam < LOQ	36	Male	2580	9/10	Yes	37.5
Case 13	15	Alprazolam < LOQ	38	Female	2624	10/10	No	54.8
Case 14	15		38	Male	2850	5/5	Yes	132.9
Case 15	10	Lorazepam < LOQ	40	Male	3320	9/10	Yes	43.30
Case 16	20	Alprazolam < LOQ	39	Female	3480	9/10	No	5.7

Escitalopram								
Case 17	10		36	Male	2610	6/8	Yes	< LOQ
Case 18	10	Alprazolam < LOQ	38	Female	2520	9/10	Yes	< LOQ
Case 19	20	Alprazolam < LOQ	36	Male	2100	9/8	Yes	14.5
Case 20		Alprazolam < LOQ	36	Male	2500	9/8	Yes	16.6
Paroxetine								
Case 21	20		40	Female	3110	9/10	No	< LOQ
Case 22	10		35	Male	2650	5/7	Yes	7
Case 23	20	Lorazepam < LOQ	36	Male	2710	5/9	Yes	10
Case 24	15	Lorazepam < LOQ	38	Female	2860	9/10	No	< LOQ
Duloxetine								
Case 25	30		39	Male	3110	8/9	No	5.9
Case 26	60		38	Female	2670	10/10	No	7.6

5. DISCUSSION

Neonatal abstinence syndrome has been reported both for BDZ and for SSRI/SNRI. Several case reports of pregnant women exposed to benzodiazepines describe neonatal abstinence in the newborns [11-13]. Other studies reported that exposure to benzodiazepines is associated with a withdrawal syndrome in about 20 to 40% of cases [6,14]. In mothers treated with SSRI/SNRI, Levinson-Castiel and his colleagues reported a 30% prevalence of NAS [4] in neonates. It has been also reported that the use of multiple psychotropic agents during pregnancy, particularly BDZ, increases the risk of neonatal behavioral complications [3]. Our data suggest that neonates born from mothers receiving SSRI/SNRI associated with BDZ are more susceptible to develop symptoms. In our series describing 13 symptomatic neonates, 9 were exposed in utero to both antidepressant drugs and BDZ and only 4 of those exposed to only SSRI/SNRI were symptomatic. Excluding the presence of co-administration of BDZ, our findings suggest that NAS due to SSRI/SNRI discontinuation may be lower than previously reported.

The rapid or abrupt withdrawal of the benzodiazepine induces underactivity of inhibitory GABA functions and a surge in excitatory nervous activity, giving rise to many of the benzodiazepine withdrawal symptoms [15].

The symptom described as SSRI/SNRI withdrawal syndrome has contradictory interpretations on whether these signs are better explained by serotonin toxicity attributable to increased serotonin concentration in the intersynaptic cleft due to SSRI/SNRI presence or by a relative hyposerotoninergic state attributable to SSRI/SNRI absence [16-17]. Our results show that blood levels of SSRI/SNRI in neonates are detectable although they are near the lower limit of the therapeutic range. We speculate that, since blood levels of SSRI/SNRI were found in most of our newborns (81%), neonatal symptoms may possible be due to serotonin toxicity and not to discontinuation syndrome in patients exposed to only SSRI/SNRI.

The differential diagnosis of whether NAS is due either to the abrupt interruption of antidepressant exposure or to BDZ discontinuation is more difficult since symptoms of these syndromes are overlapping. On the other hand, we were not able to find effective blood levels of BDZ in our neonates, thus suggesting that in this case, symptoms may be effectively explained by BDZ absence leading to hypoactivity of the inhibitory GABA system.

Another issue, is the gestational age of the symptomatic patients. Preterm infants have a higher risk for respiratory distress syndrome and other respiratory morbidity [9]. Hypoglycemia up to 3 times greater than full-term infants [18], jaundice and feeding difficulties have been also reported. Other authors found that up to two-thirds of healthy newborns may have fine tremor in the first days of life [19] and up to 44% of newborns may be jittery [20]. Since most of symptoms are common between preterm neonates, SSRI/SNRI abstinence and BDZ withdrawal, we recognize that it is cumbersome to attribute all symptoms to a single cause. Therefore we suggest that SSRI/SNRI withdrawal syndrome may be overestimated especially in preterm low weight neonates. Since all premature neonates were symptomatic and hospital stay is longer in these neonates we were not able to distinguish between symptoms attributed to abstinence syndrome or to morbidities arising from prematurity.

A major strength of the present study is that the antidepressant and benzodiazepines blood levels have been measured and they are rarely reported. Although blood levels of these drugs have been measured, we were unable to demonstrate any relationship between blood levels and symptoms. Together with other published findings [3], the results of this study suggest a higher incidence of neonatal symptoms if they are exposed in utero to polytherapy, such as SSRI/SNRI plus BDZ. The limitations of this study include the small sample size of the concomitant BDZ and SSRI/SNRI group, and the lack of a group exposed only to BDZ. Thus it is unclear whether the latter would have also resulted in similar neonatal symptoms such as those after exposure to SSRI/SNRI with BDZ.

6. CONCLUSION

In conclusion, our data do not distinguish between symptoms due to SSRI/SNRI withdrawal or to serotonin toxicity or to GABA underactivity, but clearly suggest that: 1) the co-administration of SSRI/SNRI and benzodiazepines during pregnancy may be associated with an increased risk of neonatal

symptoms 2) low weight and shorter gestational age may enhance the risk of developing symptoms attributed to neonatal abstinence syndrome 3) the majority of neonates born from mothers treated with SSRI/SNRI displayed detectable levels of the drugs but these blood levels were not related with the presence and/or severity of symptoms and 4) newborns with symptoms attributed to SSRI/SNRI and/or BDZ withdrawal have a longer hospital stay.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Pettey G. Congenital morphinism, with report of cases. South Med J. 1912;5(1): 25–27.
2. Chambers CD, Johnson KA, Dick LM, Felix RJ, Jones KL. Birth outcomes in pregnant women taking fluoxetine. N Engl J Med. 1996;335(14):1010-5.
3. 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(2): 230-7.
4. 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(2):173-6.
5. Klinger G, Merlob P. Selective serotonin reuptake inhibitor induced neonatal abstinence syndrome. Isr J Psychiatry Relat Sci. 2008;45(2):107-13.
6. Swortfiguer D, Cissoko H, Giraudeau B, Jonville-Béra AP, Bensouda L, Autret-Leca E. Neonatal consequences of benzodiazepines used during the last month of pregnancy. Arch Pediatr. 2005; 12(9):1327-31.
7. Grzeskowiak LE, Gilbert AL, Morrison JL. Neonatal outcomes after late-gestation exposure to selective serotonin reuptake inhibitors. J Clin Psychopharmacol. 2012; 32(5):615-21.
8. Eke AC, Saccone G, Berghella V. Selective serotonin reuptake inhibitor (SSRI) use during pregnancy and risk of preterm birth: A systematic review and meta-analysis. BJOG. 2016;123(12):1900-1907.
9. Hibbard JU, Wilkins I, Sun L, Gregory K, Haberman S, Hoffman M, Kominiarek MA, Reddy U, Bailit J, Branch DW, Burkman R, Gonzalez Quintero VH, Hatjis CG, Landy H, Ramirez M, VanVeldhuisen P, Troendle J, Zhang J. Consortium on Safe Labor. Respiratory morbidity in late preterm births. JAMA. 2010;304(4):419-25.
10. Huntsman RJ, Lowry NJ, Sankaran K. Nonepileptic motor phenomena in the neonate. Paediatr Child Health. 2008; 13(8):680-4.
11. Barry WS, St Clair SM. Exposure to benzodiazepines in utero. Lancet. 1987; 1(8547):1436-7.
12. McElhatton PR. The effects of benzodiazepine use during pregnancy and lactation. Reprod Toxicol. 1994;8(6):461-75.
13. Weinstock L, Cohen LS, Bailey JW, Blatman R, Rosenbaum JF. Obstetrical and neonatal outcome following clonazepam use during pregnancy: A case series. Psychother Psychosom. 2001; 70(3):158-62.
14. Lind JN, Petersen EE, Lederer PA, Phillips-Bell GS, Perrine CG, Li R, Hudak M, Correia JA, Creanga AA, Sappenfield WM, Curran J, Blackmore C, Watkins SM, Anjohrin S; Centers for Disease Control and Prevention (CDC). Infant and maternal characteristics in neonatal abstinence syndrome–selected hospitals in Florida, 2010–2011. MMWR Morb Mortal Wkly Rep. 2015;64(8):213–6.
15. Authier N, Balayssac D, Sautereau M, Zangarelli A, Courty P, Somogyi AA, Vennat B, Llorca PM, Eschalier A. Benzodiazepine dependence: Focus on

withdrawal syndrome. Ann Pharm Fr. 2009;67(6):408-13.
16. Laine K, Heikkinen T, Ekblad U, Kero P. Effects of exposure to selective serotonin reuptake inhibitors during pregnancy on serotonergic symptoms in newborns and cord blood monoamine and prolactin concentrations. Arch Gen Psychiatry. 2003;60(7):720-6.
17. Haddad PM, Pal BR, Clarke P, Wieck A, Sridhiran S. Neonatal symptoms following maternal paroxetine treatment: Serotonin toxicity or paroxetine discontinuation syndrome? J Psychopharmacol. 2005; 19(5):554-7.
18. Lubchenco LO, Bard H. Incidence of hypoglycemia in newborn infants classified by birth weight and gestational age. Pediatrics. 1971;47(5):831-8.
19. Armentrout DC, Caple J. The jittery newborn. J Pediatr Health Care. 2001; 15(3):147-9.
20. Parker S, Zuckerman B, Bauchner H, Frank D, Vinci R, Cabral H. Jitteriness in full-term neonates: Prevalence and correlates. Pediatrics. 1990;85(1):17-23.

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