Acute Delivery Room Resuscitation of Neonates Exposed to Selective Serotonin Reuptake Inhibitors

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Objective To determine whether full-term neonates with in utero exposure to selective serotonin reuptake inhibitors (SSRI) require respiratory support in the delivery room, as indicated by the standardized Neonatal Resuscitation Program algorithm, significantly more often than nonexposed neonates.

Study design In this retrospective cohort study, we extracted data from medical records of full-term neonates with and without in utero SSRI exposure, defined as documentation of third trimester maternal SSRI treatment. A hospital-based sample was identified at Northwestern Medical Hospital in Chicago, Illinois. Full-term singleton newborns identified in a 6-month period (n = 4933) were selected for study. Neonates with a major congenital anomaly were excluded. The primary outcome was initiation of respiratory support in the delivery room, as indicated by the Neonatal Resuscitation Program algorithm.

Results Of the 4933 full-term singleton neonates, 3.3% were exposed to SSRI in utero. Respiratory support was initiated significantly more often in SSRI exposed (12.9%) than unexposed (4.2%) neonates (covariate-adjusted OR, 4.04; 95% CI, 2.40-6.49). In utero SSRI exposure also was associated with a higher rate of neonatal intensive care unit admission (covariate-adjusted OR, 2.19; 95% CI, 1.30-3.50) and 1-minute Apgar score of ≤5 (covariate-adjusted OR, 3.51; 95% CI, 2.07-5.67).

Conclusions In this cohort, in utero SSRI exposure was associated with a significantly greater odds of resuscitation in the delivery room as well as neonatal intensive care unit admission. Although the mechanism underlying these associations have not been determined and causality cannot be assumed, these findings support a recommendation that third trimester SSRI exposure be considered a risk factor for needing resuscitation. *(J Pediatr 2021;232:103-8)*.

Antidepressants, specifically selective serotonin reuptake inhibitors (SSRIs), are commonly prescribed for pregnant women, with the frequency of exposure increasing from 2.5% in 1998 to 8.1% in 2005.[1] Exposure to SSRIs in the third trimester is estimated to occur in 2.3% of pregnancies.[2]

A neurobehavioral syndrome that consists of a range of signs, including respiratory distress, feeding difficulties, abnormal tone, and neurologic abnormalities, has been described in neonates exposed to SSRIs. Chambers et al prospectively identified women treated with fluoxetine during pregnancy.[3] Infants exposed in the third trimester were more likely to have poor neonatal adaption, including respiratory difficulties, cyanosis with feeding, jitteriness, and higher rates of premature delivery.[3] Moses-Kolko et al described a neonatal behavioral syndrome that consisted of central nervous system, motor, respiratory, and gastrointestinal signs; near term SSRI exposure conferred an overall risk ratio of 3.0 (95% CI, 2.0-4.4) compared with early or no fetal exposure.[4]

A population-based study conducted in Finland (n = 56 775) found that neonates exposed to SSRIs were at higher risk for 5-minute Apgar score of <7, neonatal intensive care unit (NICU) admission, and respiratory distress.[5] A prospective 2-hospital study found that infants exposed to SSRIs throughout pregnancy were more likely to have a 5-minute Apgar score of ≤7.[6] Several investigators have reported an increased risk of NICU admission in infants exposed to SSRIs.[6-8] Norby et al showed that exposed infants were more likely to be treated in a NICU than nonexposed infants (13.7% vs 8.2%, respectively; OR, 1.5; 95% CI, 1.4-1.5).[8]

Effects on the neonatal respiratory system ranging from mild tachypnea to severe respiratory distress requiring assisted ventilation have been reported in neonates exposed to SSRIs.[4] Persistent pulmonary hypertension of the newborn has also been described in exposed neonates.[9] In a registry-based study of the Swedish

PS	Propensity score
SSRI	Selective serotonin reuptake inhibitor
NRP	Neonatal Resuscitation Program
NICU	Neonatal intensive care unit

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population, investigators reported that the use of both noninvasive and invasive mechanical ventilation occurred more frequently in SSRI exposed compared with nonexposed neonates, and third trimester SSRI exposure was associated with a marginally significant increased risk for persistent pulmonary hypertension of the newborn (OR, 1.3; 95% CI, 1.0-1.6).[8]

The objective of this study was to determine whether full-term neonates with in utero SSRI exposure require respiratory support in the delivery room, as indicated by the standardized Neonatal Resuscitation Program (NRP) algorithm, significantly more often than nonexposed neonates.

Methods

This retrospective cohort study used data extracted from maternal and neonatal medical records during a 6-month time period (September 1, 2017, to March 1, 2018) at Prentice Women's Hospital of Northwestern University in Chicago, Illinois. Data were obtained through the electronic Enterprise Data Warehouse, which extracts information directly from the patient electronic health records. This study was performed under approval of the Northwestern University Institutional Review Board with a waiver of consent.

Full-term singleton newborn records were extracted. Newborns with a major congenital anomaly or who were the result of a multi-gestation pregnancy were excluded. Preterm neonates (<37.0 completed weeks of gestation) were excluded owing to the increased need for respiratory support at birth associated with inherent lung immaturity.

Exposure was third trimester maternal SSRI use as determined by documentation in the mother's chart of one of the following drugs on the medical administration record: fluoxetine, sertraline, citalopram, escitalopram, fluvoxamine, or paroxetine. Exposures to opioids and benzodiazepines were also recorded. The primary outcome measure was respiratory support in the delivery room as indicated by the NRP algorithm, defined as assisted ventilation in the form of continuous positive airway pressure or positive pressure ventilation, the delivery of supplemental oxygen, or inserting an advanced airway in the delivery room. Secondary outcome measures included 1- and 5-minute Apgar scores, NICU admission, and birthweight. Demographic data included maternal age, smoking status, mode of delivery, newborn sex, race, and gestational age at delivery.

Statistical Analyses

Mother and infant demographic and birth outcome data were summarized with descriptive statistics. Frequencies and percentages were calculated for categorical variables and mean ± SD or median and range for continuous variables. We present both unadjusted and adjusted analysis results for the outcomes of interest (initiation of respiratory support, NICU admission, and birthweight). Adjusted analysis was based on a list of prespecified clinically meaningful covariates (mother's smoking status, infant race, gestational age, and benzodiazepine exposure). The primary independent variable was SSRI exposure during pregnancy. A simple linear regression was used to define the unadjusted association between SSRI exposure and birthweight. Either a χ^2 test or Fisher exact was used to evaluate associations between SSRI exposure and categorical outcomes.

In addition to covariate adjustment using multiple regression methods and to address potential confounding in the association between SSRI exposure and each outcome, we explored an additional method of controlling for several confounders simultaneously via inverse probability weighting using propensity scores (PS).[10] Weights were defined as $\frac{1}{PS}$, where PS is the probability of SSRI exposure given a list of covariates for all patients exposed to SSRIs and $\frac{1}{1-PS}$ for all patients who were not exposed to SSRIs. Weights were truncated at 20 to prevent single observations from contributing excessive information to analyses that would result in potential biases and unstable model estimates. PS were estimated conditional on mother's smoking status, infant race, gestational age, and benzodiazepine exposure. In each calculation, we used bootstrapping techniques to estimate the weighted SSRI exposure effect on outcome with the corresponding CI. Using PS allows for an additional layer of variability in estimation, and it has the potential to address estimate instability that may be observed with more classical multiple regression techniques involving several confounders at once. All analyses were conducted using R (version 3.5.3, 2019; The R Foundation) and assumed a 2-sided, 5% level of significance. We did not adjust for multiple hypothesis tests.

Results

Between September 1, 2017, and March 1, 2018, 5696 mothers delivered full-term neonates and 4933 maternal-infant dyads were included in the study (**Figure 1**; available at www.jpeds.com). Reasons for exclusion of mothers included inability to match the chart with her neonate (n = 571) because our institutional review board did not allow individual level chart abstraction to relink them and multiple gestation pregnancies (n = 116). Neonates (n = 76) were excluded owing to a major congenital anomaly. Of the remaining 4933 neonates, 163 (3.3%) were exposed to SSRI in utero and 4770 (96.7%) were unexposed (**Figure 1**). The SSRI exposures included the following drugs: fluoxetine (n = 20), sertraline (n = 96), citalopram (n = 14), escitalopram (n = 30), fluvoxamine (n = 1), and paroxetine (n = 2).

Of the 4933 mothers, the mean age was 33 years and the majority were never smokers (n = 4219 [85.5%]). A total of 163 (3.3%) had SSRI exposure in the third trimester (**Table I**). Opioid and benzodiazepine exposure occurred rarely in this sample.

Of the 163 neonates exposed to SSRIs, the majority were non-Hispanic White (n = 133 [81.6%]), the mean gestational age was 38.9 weeks, and the majority were born by vaginal

Table I. Summary of sample by SSRI exposure

Summary of sample	No SSRI use (n = 4770)	SSRI use (n = 163)	Overall (n = 4933)
Mother's age at delivery			
Mean (SD)	33.0 (4.85)	34.5 (4.20)	33.0 (4.84)
Median [Min, Max]	33.0 [16.0, 52.0]	35.0 [23.0, 45.0]	33.0 [16.0, 52.0]
Mother's smoking status			
Never	4085 (85.6)	134 (82.2)	4219 (85.5)
Quit >30 days	253 (5.3)	11 (6.7)	264 (5.4)
Use within 30 days	21 (0.4)	3 (1.8)	24 (0.5)
Unknown	411 (8.6)	15 (9.2)	426 (8.6)
History of opioid use			
No opioid use	4766 (99.9)	162 (99.4)	4928 (99.9)
Opioid use	4 (0.1)	1 (0.6)	5 (0.1)
History of benzodiazepine use			
No benzodiazepine use	4745 (99.5)	159 (97.5)	4904 (99.4)
Benzodiazepine use	25 (0.5)	4 (2.5)	29 (0.6)

Min, minimum; *Max*, maximum.
Values are number (%) unless otherwise indicated.

delivery (n = 116 [71.2%]). Respiratory support was received in 12.9% of exposed neonates compared with 4.2% of those unexposed. Of exposed neonates, 12.3% were admitted to the NICU compared with 5.9% of those unexposed. A higher number of exposed neonates had a 1-minute Apgar score of ≤5 compared with those unexposed, at 12.3% and 4.5%, respectively (**Table II**).

Respiratory support was initiated significantly more often in those exposed to SSRIs compared with unexposed neonates (12.9% vs 4.2%, respectively; unadjusted OR, 3.34; 95% CI, 2.02-5.29). Similar results were seen after adjusting for potential confounding factors including race, smoking, gestational age, and benzodiazepine use by either covariate adjustment or PS weighting (with covariate-adjusted OR, 4.04 [95% CI, 2.4-6.49]and PS-weighted OR, 3.2 [95% CI, 1.85-5.06], respectively) (**Table III** and **Figure 2**).

In utero SSRI exposure was also associated with an increased rate of NICU admission (unadjusted OR, 2.23; 95% CI, 1.33-3.53; covariate-adjusted OR, 2.19; 95% CI, 1.30-3.50; PS-weighted OR, 2.13; 95% CI, 1.18-3.32). The odds of having a 1-minute Apgar of ≤5 were 3.00 times greater in newborns exposed to SSRI (unadjusted 95% CI, 1.79-4.78; covariate-adjusted OR, 3.51; 95% CI, 2.07-5.67; PS-weighted OR, 2.75; 95% CI, 1.5-4.42). Similarly, the

Table II. Summary of delivery outcomes and infant characteristics by SSRI exposure

Infant characteristics and delivery outcomes	No SSRI use (n = 4770)	SSRI use (n = 163)	Overall (n = 4933)
Infant sex			
Female	2305 (48.3)	82 (50.3)	2387 (48.4)
Male	2337 (49.0)	74 (45.4)	2411 (48.9)
Missing	128 (2.7)	7 (4.3)	135 (2.7)
Mother's race			
White or Caucasian	2833 (59.4)	133 (81.6)	2966 (60.1)
Black or African American	407 (8.5)	7 (4.3)	414 (8.4)
Hispanic or Latino	57 (1.2)	1 (0.6)	58 (1.2)
Asian	386 (8.1)	5 (3.1)	391 (7.9)
Other/unknown	1081 (22.7)	17 (10.4)	1098 (22.3)
Missing	6 (0.1)	0 (0)	6 (0.1)
Mode of delivery			
Other	3510 (73.6)	116 (71.2)	3626 (73.5)
Cesearean	1167 (24.5)	43 (26.4)	1210 (24.5)
Missing	93 (1.9)	4 (2.5)	97 (2.0)
Birth outcome			
Live birth admitted to L&D	4522 (94.8)	148 (90.8)	4670 (94.7)
Live birth admitted to SCN	81 (1.7)	9 (5.5)	90 (1.8)
Missing	167 (3.5)	6 (3.7)	173 (3.5)
Gestational age (weeks)			
Mean (SD)	39.4 (1.05)	38.9 (1.07)	39.3 (1.05)
Median [Min, Max]	39.3 [37.0, 42.0]	39.0 [37.0, 42.1]	39.3 [37.0, 42.1]
Infant length of stay			
Mean (SD)	2.41 (1.48)	2.49 (1.21)	2.41 (1.47)
Median [Min, Max]	2.00 [0.00, 41.0]	2.00 [1.00, 10.0]	2.00 [0.00, 41.0]
Missing	70 (1.5)	3 (1.8)	73 (1.5)

L&D, labor and delivery; *SCN*, special care nursery.
Values are number (%) unless otherwise indicated.

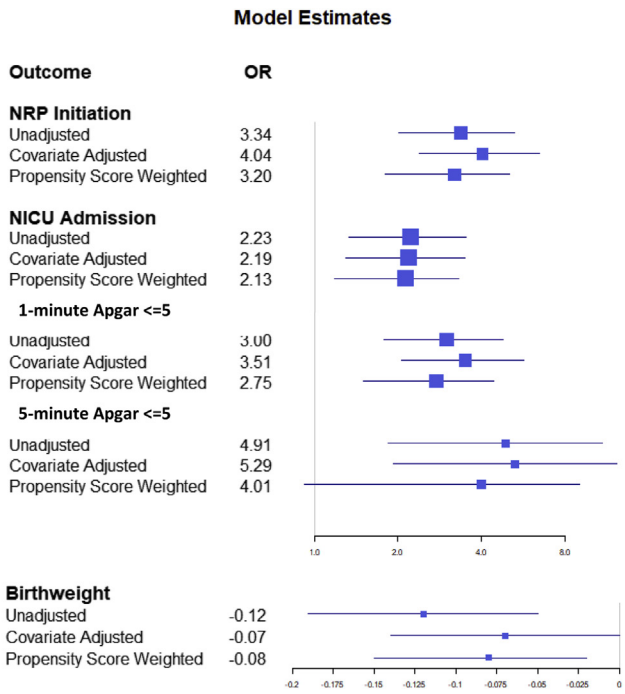
Table III. Summary of the primary analysis

Outcomes	No SSRI use (n = 4770)	SSRI use (n = 163)	Unadjusted estimate (95% CI)	Covariate-adjusted estimate (95% CI)	PS-weighted estimate (95% CI)
Respiratory support initiated					
No respiratory support initiated	4568 (95.8)	142 (87.1)	3.34 (2.02 to 5.29)	4.04 (2.4 to 6.49)	3.2 (1.8 to 5.06)
Respiratory support initiated	202 (4.2)	21 (12.9)			
NICU admission					
Not admitted	4488 (94.1)	143 (87.7)	2.23 (1.33 to 3.53)	2.19 (1.3 to 3.5)	2.13 (1.18 to 3.32)
Admitted	282 (5.9)	20 (12.3)			
Birthweight*					
Mean (SD)	3.41 (0.450)	3.29 (0.434)	−0.12 (−0.19 to −0.05)	−0.07 (−0.14 to 0)	−0.08 (−0.15 to −0.02)
Median [Min, Max]	3.40 [1.00, 5.23]	3.28 [2.20, 4.99]			
Missing	93 (1.9)	4 (2.5)			
1-minute Apgar					
>5	4425 (92.8)	138 (84.7)	3.00 (1.79 to 4.78)	3.51 (2.07 to 5.67)	2.75 (1.5 to 4.42)
≤5	214 (4.5)	20 (12.3)			
Missing	131 (2.7)	5 (3.1)			
5-minute Apgar					
>5	4598 (96.4)	152 (93.3)	4.91 (1.84 to 10.97)	5.29 (1.93 to 12.29)	4.01 (0.92 to 9.03)
≤5	37 (0.8)	6 (3.7)			
Missing	135 (2.8)	5 (3.1)			

Values are number (%) unless otherwise indicated.
*Estimates represent ORs, except for birthweight which represents the average difference in birthweight (kg) between patients exposed to SSRIs and those not exposed.

odds of having a 5-minute Apgar of ≤5 were 4.91 times greater in exposed babies before adjusting for other variables (unadjusted 95% CI, 1.84-10.97; covariate-adjusted OR, 5.29; 95% CI, 1.93-12.29; PS-weighted OR, 4.01; 95% CI, 0.92-9.03); however, the PS weighting resulted in an attenuated effect estimate with wider CIs (Table III and Figure 2).

The specific components of NRP used for neonates receiving resuscitation are shown in Table IV (available at www.jpeds.com). Of the neonates in the cohort who received resuscitation, neonates exposed to SSRIs received supplemental oxygen more often than those unexposed (85.7% vs 74.3%, respectively). However, exposed neonates did not receive mask ventilation (76.2% vs 83.7%,



*Estimates represent odds ratios, except for birthweight which represents the average difference in birthweight (kg) between patients exposed to SSRI and not exposed to SSRI

Figure 2. Summary of the primary analysis.

respectively) or intubation (4.8% vs 5.4%, respectively) more often than unexposed neonates.

Discussion

In our cohort, neonates exposed to SSRIs were more likely to receive respiratory support in the delivery room, have a 1-minute Apgar score of <5, and be admitted to the NICU. Our findings indicate that the reported association between SSRI exposure and respiratory symptoms in exposed neonates is also evident in the immediate postdelivery period.[3,7,8,11-13]

The signs prompting the initiation of respiratory support in the delivery room seem to be transient. The mean length of hospital stay for both the exposed and unexposed groups was 2 days, which implies that for most infants initial respiratory symptoms in the exposed group rapidly resolved despite a higher rate of initial NICU admission. The odds of having a 1- and 5- minute Apgar score of ≤5 were significantly higher in the exposed group. However, there was an attenuated effect with a wider CI when using PS weighting for the 5-minute Apgar score. This may be due to a notably smaller number of infants with a score of ≤5 at 5 minutes (n = 43 total) in comparison with the number at 1 minute (n = 234 total). These findings support transient initial respiratory symptoms that improve with resuscitative efforts.

Neonates exposed to SSRIs received supplemental oxygen more often than nonexposed neonates during a resuscitation. Per NRP guidelines, any resuscitation in a term infant begins with 21% inspired oxygen and increases in procedural intensity until the target oxygen saturation for age is achieved. Because it is less likely for term neonates to require supplemental oxygen after delivery, this finding could indicate a delay in the usual postnatal decrease in pulmonary vascular resistance, as has been observed in fetal rats exposed to fluoxetine.[13] Histologic evaluation in this animal model also revealed pulmonary artery smooth muscle cell proliferation and pulmonary vascular remodeling.[13]

Another proposed mechanism for the early respiratory distress in neonates is premature constriction of the ductus arteriosus. In vivo premature constriction of the ductus arteriosus was observed in SSRI-exposed fetal mice.[5] Serotonin receptors were expressed on ductal tissue isolated from these fetal mice, which constricted in response to both serotonin and SSRI exposure.[11] Isolated ductal cells pretreated with SSRI also demonstrated an attenuated response to a prostaglandin E2-induced vasodilation, which suggested that the ductus arteriosus may default to a constricted state during SSRI exposure, thereby leading to premature constriction with in utero exposure.[11] Further study is needed to determine the mechanism underlying the respiratory findings seen in exposed neonates.

A limitation of our study is the use of retrospective data extraction. It is possible to misclassify maternal SSRI use if it was not reported by the mother or documented in the chart. This would result in neonates exposed to SSRIs being erroneously included in the nonexposed group and would potentially bias our results. Concomitant exposures of important potential confounders such as benzodiazepines, opioids, and other substance use are likely to be underreported in this dataset. These exposures are epidemiologically more probable in women using SSRIs and could represent unmeasured confounders that bias the results away from the null, possibly explaining the observed association. We were unable to examine the association with opioid coexposure owing to a small number (n = 5) of documented neonates exposed to opioids. However, exposure to benzodiazepines was included in the adjusted analyses. We also recognize omitted variable bias because we were not able to adjust for untreated maternal depression or socioeconomic factors in this dataset.

Although we found an association between SSRI exposure and acute delivery room resuscitation, this finding does not imply a causal relationship. Given the omitted variable bias present in all observational studies, many potential unidentified and unmeasured confounders are likely to be present. These include, sociodemographic factors, other drug and environmental exposures (including stress), medical comorbidity, and the underlying maternal depressive disorder and degree of residual symptoms.[14] However, Salisbury et al compared characteristics of poor neonatal adaptation in infants exposed to SSRIs with those exposed to untreated maternal depression.[15] Higher rates of central nervous system stress signs, arousal levels, and poor self-regulation were observed, which suggests an effect of in utero SSRI exposure independent of underlying maternal depression.[15] Potential confounders also include drug coexposures that are common in psychiatric illness. Although we were able to adjust for benzodiazepine exposure in our analyses, we were unable to examine the effect of other medication coexposures.

The American Academy of Pediatrics *Guidelines for Perinatal Care* indicate that the anticipation of the need for neonatal resuscitation at delivery as well as prompt initiation of support are crucial for a successful resuscitation.[16] At our institution, a pediatrician is called to attend deliveries complicated by meconium-stained amniotic fluid or fetal heart rate decelerations; however, we do not currently have a policy that identifies SSRI exposure as a risk factor for resuscitation. Our data suggest that neonates with in utero SSRI exposure are more likely to require resuscitation than those not exposed. Our findings, and other recent publications, suggest that third trimester SSRI exposure should be considered a risk factor for needing resuscitation at delivery.[12] ■

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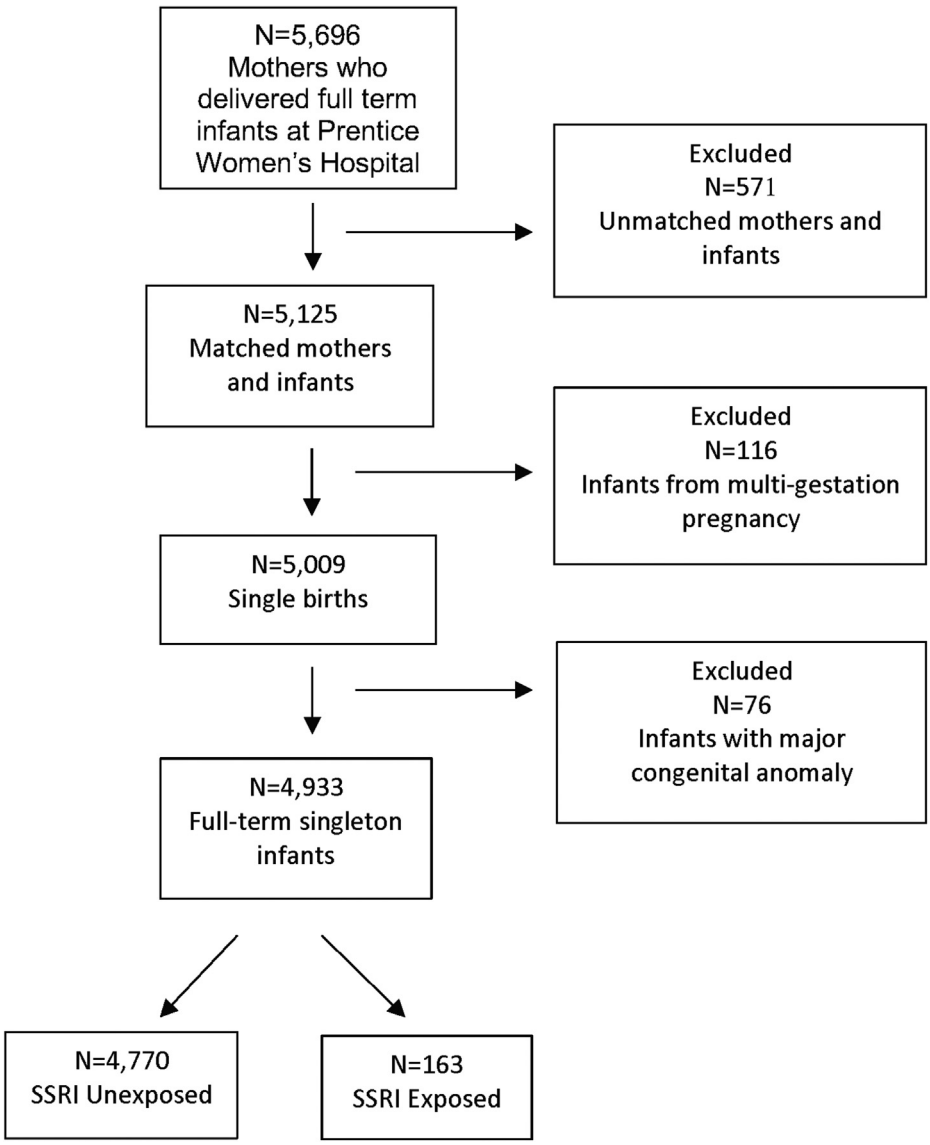

Figure 1. Patients selection.

Table IV. Summary of resuscitation in infants with NRP initiated

Interventions	No SSRI use (n = 202)	SSRI use (n = 21)	Overall (n = 223)
Oxygen			
Yes	150 (74.3)	18 (85.7)	168 (75.3)
No	52 (25.7)	3 (14.3)	55 (24.7)
Mask ventilation			
Yes	169 (83.7)	16 (76.2)	185 (83.0)
No	33 (16.3)	5 (23.8)	38 (17.0)
Intubation for ventilation			
Yes	11 (5.4)	1 (4.8)	12 (5.4)
No	191 (94.6)	20 (95.2)	211 (94.6)

Values are number (%).