SEROTONIN REUPTAKE INHIBITOR USE DURING PREGNANCY:

PERINATAL OUTCOMES

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by

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ABSTRACT

SEROTONIN REUPTAKE INHIBITOR USE DURING PREGANCY: PERINATAL OUTCOMES

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Objective: To assess severity of neonatal behavioral syndrome (NBS) in infants of serotonin reuptake inhibitor (SRI)-treated pregnancies, compared with infants of women with psychiatric illness not treated with medication.

Methods: Retrospective cohort study of pregnancies followed in a prenatal clinic for women with psychiatric illness. Infants of women who received SRI medication through delivery (SRI-treated) were compared with those who did not receive treatment or discontinued medication before the last month of pregnancy (SRI-untreated). NBS was defined as one or more of the following: jitteriness, irritability, lethargy, hypotonia, hypertonia, hyperreflexia, apnea, respiratory distress, vomiting, poor feeding, or hypoglycemia.

Results: Findings of NBS were identified in 28% of 46 SRI-treated pregnancies and 17% of 59 untreated pregnancies. There were no differences in rates of prematurity (4% vs. 7%), fetal growth restriction (6% vs. 2%), transfer to a higher nursery for NBS (11% vs.

10%), respiratory abnormality (7% vs. 5%), or hospitalization duration among infants with NBS findings (2 vs. 6 days).

Conclusions: Findings of NBS were identified in 28% of SRI-exposed neonates. However, these infants were not more likely than unexposed infants to be admitted to a higher nursery, experience respiratory abnormalities, or have prolonged hospitalization.

TABLE OF CONTENTS

PRIOR PRESENTATIONS

Allison E. Jordan, Poster presentation, **28th Annual Society for Maternal-Fetal Medicine: The Pregnancy Meeting**, Dallas, Texas, 2008

Allison E. Jordan, Oral presentation, **6th Annual Doris Duke Clinical Research Fellowship Meeting,** Harvard Medical School, 2007

Allison E. Jordan, Poster presentation, **41st Medical Student Research Forum**, UT Southwestern Medical Center, 2007

LIST OF TABLES

LIST OF FIGURES

CHAPTER I

Introduction

Depression complicates approximately one in 10 pregnancies.[1] Serotonin reuptake inhibitor (SRI) medications are considered the first-line agents for treatment of major depression in women of childbearing age.[2] Based on data from the National Birth Defects Prevention Study (1997-2002), it is estimated that 2 to 3 percent of pregnant women are treated with an SRI.[3] Though initially embraced because of their maternal side-effect profile and low risk of teratogenicity[4-7], SRI medications have recently come under scrutiny.[8]

A major area of concern is that 25 to 30% of infants whose mothers use SRI medications prior to delivery have shown evidence of what has been termed the *neonatal behavioral syndrome* (NBS).[2] NBS has been described as one or more of the following clinical signs, which are listed in the product prescribing information as: "respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying".[9] The product label explains that these features are consistent with either a direct toxic effect or possibly a drug discontinuation syndrome, a position supported by a review from the U.S. Food and Drug Administration.[10] Though many of the above findings are nonspecific, infants exposed to SRI medication late in gestation appear to have a 3-fold increase in risk, compared with either unexposed infants or infants exposed early in gestation.[2]

Based on concerns about NBS and other adverse outcomes, the American College of Obstetricians and Gynecologists recommends that treatment with SRI medications

during pregnancy be individualized, and that the process actively engage the patient's values and perceptions when framing discussion of the risks and benefits of treatment.[8] To provide adequate counseling, providers require knowledge about the severity of NBS, an area in which there has been little research. For example, although the reported features of NBS may include respiratory distress and even seizures, a recent review concluded that NBS "is usually mild, self-limited, and similar to familiar syndromes such as infantile colic".[2] Oberlander and colleagues (2004) reported that all symptoms resolved within 48 hours[11]. Our objective was to assess the severity of NBS and its individual components in infants of SRI-treated pregnancies, compared with infants born to women with psychiatric illness not treated with medication.

CHAPTER II

Study Design

This was a retrospective cohort study of pregnancies followed in a prenatal clinic for women with psychiatric illness at Parkland Hospital between September 1, 2005 and August 31, 2006. Indications for referral to the clinic included need for initiation of psychiatric medication or recent psychiatric hospitalization with need for follow-up care. Fewer than 1% of pregnancies in our county hospital system are followed in this clinic. Multiple gestations were excluded, as were pregnancies complicated by major fetal anomalies, as the anomaly or its treatment might affect NBS detection.

Medical records were reviewed to collect information about history of psychiatric illness, medication(s) used during pregnancy, reported illicit substance use, and obstetrical outcomes. When women were treated with SRI medication, particular attention was paid to when in gestation the medication was taken, at what dosage, and whether the medication was continued through delivery. Women not treated with an SRI, either because the psychiatrist did not feel it was needed or because they refused treatment, were considered untreated controls. For study purposes, women initially treated with an SRI but who discontinued medication prior to the last month of pregnancy were also considered untreated controls. It was not our policy to taper or discontinue SRI medication at the end of pregnancy. One factor that has been associated with increased risk for NBS is concurrent benzodiazepine use, and for this reason, women who received a benzodiazepine in addition to an SRI were analyzed separately.[11] Those who were treated with a non-SRI psychiatric medication alone were excluded from analysis.

In reviewing neonatal records, NBS was considered present if the attending pediatric provider documented one or more of the following prior to hospital discharge: irritability, jitteriness, hypotonia, hypertonia, hyperreflexia, oxygen requirement, apnea, flaring, grunting, retractions, vomiting, poor feeding, or hypoglycemia. Infants requiring transfer to a higher level of nursery care and, in particular, transfer for a respiratory indication, were specifically noted. Since our neonatal records contain a place to document maternal medications, information about the pediatrician's knowledge of SRI exposure was recorded.

Selected pregnancy and infant outcomes were also compared with those of our overall obstetrical population, using a computerized database that contains information from all deliveries at our hospital. Fetal growth restriction was defined as birth weight below the 3rd percentile for gestational age, based on nomograms derived from our hospital population and adjusted for maternal ethnicity and infant sex.[12] Statistical analyses included Student's t-test, chi-square, and Wilcoxon rank sum test. P-values < 0.05 were considered statistically significant. This study was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center.

CHAPTER III

Results

During the study period, 115 women with singleton pregnancies were followed in our prenatal psychiatric clinic and delivered singleton infants at our hospital. There were no stillbirths (> 500 g) or neonatal deaths. Two anomalous infants were excluded, one with congenital diaphragmatic hernia and the other with trisomy 21. An additional 5 pregnancies treated with non-SRI psychiatric medication were excluded. Of the remaining 108 pregnancies, 49 (45%) were SRI-treated at delivery, and 59 (55%) did not receive any psychiatric medication at delivery or in the month prior to delivery (controls). Three SRI-treated pregnancies were also treated with clonazepam; infant outcomes were analyzed separately in these cases.

Demographic characteristics of the SRI-treated and control pregnancies are presented in Table 1. Women treated with SRI medication were approximately 2-3 years older and were less likely to be nulliparous. SRI-treated women were also more likely to have been diagnosed with major depressive disorder and/or anxiety disorder, and they were less likely than untreated women to have been diagnosed with adjustment disorder. There were no significant differences between SRI-treated and untreated groups with respect to gestational age at initiation of prenatal care or reported use of illicit substances, alcohol, or tobacco.

Delivery outcomes are presented in Table 2. There were no significant differences between SRI-treated and control pregnancies with respect to gestational age at delivery, preterm birth, cesarean delivery, birth weight, growth restriction, Apgar score, or umbilical artery pH. No infant in either group had a 5-minute Apgar score < 7 or cord pH

< 7.0; no infant in either group underwent intubation in the delivery room or had culture-proven neonatal sepsis. One infant in each group (2%) required phototherapy for jaundice. During the study period, more than 21,000 women received prenatal care at our hospital and subsequently delivered live born singleton infants. There were no significant differences between the SRI-treated pregnancies and our overall obstetrical population with respect to the incidence of preterm birth (4% vs. 5%, p = 0.7) or growth restriction (6% vs. 3%, p = 0.2).

Components of NBS among infants from SRI-treated and untreated pregnancies are presented in Table 3. There were no differences between groups with respect to the overall number with NBS, need for transfer to a higher level nursery for NBS, or length of hospital stay – either with or without findings of NBS. The length of stay for all infants delivered at our hospital was the same as for the infants with prenatal SRI exposure (median 2 days [Q1,Q3: 2,3 days]). When neonatal findings were evaluated by organ system, neurological abnormalities were the most common, regardless of SRI exposure. No infant had seizure activity, and only one infant in each group was transferred to a higher level of nursery care for a neurological finding. In the SRI-treated group, the infant was transferred after evaluation for jitteriness revealed hypocalcemia and hypomagnesemia. In the untreated group, one infant was diagnosed with neonatal narcotic withdrawal secondary to maternal heroin use, and the infant required methadone treatment and hospitalization for 28 days.

Respiratory abnormalities prompting transfer to a higher level of nursery care were noted in 3 infants with SRI exposure (7%) and 3 infants without SRI exposure (5%). In addition, all 3 of the infants exposed to clonazepam plus an SRI were transferred for

respiratory abnormalities, bringing the total of SRI-exposed infants with respiratory abnormalities to 6 (12%). This was not significantly different from the percentage of unexposed infants with respiratory abnormalities (p =0.33). Given the potential seriousness of such respiratory problems, the hospital course and specific findings prompting transfer for these infants are presented in Table 4. No particular pattern of etiology or symptomology was evident. No infant required intubation, and no infant was diagnosed with persistent pulmonary hypertension. Of the 6 infants with SRI-exposure, 2 were diagnosed with pneumonia based on radiographic findings, one with aspiration; 2 were diagnosed with transient tachypnea of the newborn; and 2 were felt to have respiratory depression or apnea secondary to maternal medication (meperidine in 1 case, multiple medications including clonazepam in the other).

NBS was further evaluated according to the presence or absence of a progress note by pediatric providers that the mother was taking SRI medication (Figure 1). Based on the pediatric provider knowledge of prenatal SRI treatment, there was no significant difference in the proportion of infants with signs of NBS, or in the proportion of infants transferred to a higher level of nursery care for a component of NBS. Specifically, when pediatric providers were aware of prenatal SRI treatment, likelihood of identifying clinical signs of NBS was no greater than when they were not aware of SRI treatment (29% vs. 25% respectively; p = 0.77), and likelihood of transfer to a higher level of nursery care was no greater (9% vs. 17% respectively; p = 0.45).

Among infants from SRI-treated pregnancies, the dosage of medication in those with findings of NBS was compared with the overall cohort. This is presented in Table 5. No woman received either fluoxetine or paroxetine. The most commonly-used SRI

medications were citalopram in 67% and sertraline in 22%, and among infants found to have NBS, 81% were exposed to one of these two medications. For both citalopram and sertraline, the median dosage in the overall group was the same as the dosage taken by those women whose infants had NBS.

CHAPTER IV

Discussion

We found that in 28% of cases, women with psychiatric illness treated with SRI medication through the end of pregnancy had infants with one or more symptoms that collectively have been termed the "neonatal behavioral syndrome (NBS)." Other terms for these symptoms have included "SRI withdrawal," "SRI toxicity," "poor neonatal adaptation," "serotonergic excess," "serotonergic CNS adverse effects," and "serotonin syndrome." The incidence of NBS we identified is quite similar that reported by other investigators.[11,13,14] Our goal was to characterize the clinical import or severity of NBS, to better counsel families concerned about the effects of SRI medications, and if needed, to modify care of exposed infants.

We have two primary conclusions. First, although the individual findings of NBS were fairly common, such infants were not *recognized* as having a particular abnormality. They did not receive special treatment, were not more likely to be admitted to a higher level of nursery care, and were not hospitalized longer than infants of untreated women with psychiatric illness or our overall infant population. Second, in our series, problems of neonatal adaptation were not attributable to prematurity, fetal growth restriction, poor infant condition at delivery, or neonatal jaundice requiring phototherapy. The incidence of reported illicit substance use in both cohorts was similarly low and not likely to contribute to NBS.

There are several limitations to our study. The difference in likelihood of NBS between SRI-treated and untreated pregnancies was not statistically significant; our power was limited by the unexpectedly high prevalence of one or more symptoms of

NBS in control pregnancies (17%). NBS has been only used to describe findings in infants from SRI-treated pregnancies, and the prevalence of these findings in infants of untreated pregnancies (either uncomplicated pregnancies or pregnancies with untreated psychiatric illness) has not been established. We estimated that the percentage might be similar to the overall number of singleton non-anomalous infants who were either admitted or transferred to a higher level of care nursery at our hospital -- 7%. Our sample size was adequate to demonstrate with 80% power that the difference between 28% of SRI-exposed infants developing NBS and 7% of unexposed infants developing NBS was significant. Why did 1 in 6 infants without SRI exposure develop findings consistent with NBS? Two plausible explanations are: (1) because these signs can be nonspecific, variable in severity and timing, and in some instances open to provider interpretation, many newborns may be noted to exhibit them; and (2) maternal major depressive disorder may alter neonatal behavior. For example, uncontrolled maternal psychiatric illness has been associated with neonatal irritability and lower activity levels.[15] It is difficult to assess severity of subjective variables such as jitteriness and irritability, and this is an issue that would be best addressed through prospective study, as it would be important to know the incidence of these behaviors among infants of women without psychiatric illness.

Another limitation may be that, because our study was not blinded, providers may have been more likely to identify problems in infants with SRI exposure. However, there are at least two reasons why we believe this was not the case. One is that SRI-exposed infants in our series had the same incidence of NBS as reported in other series (not higher). The second is that any bias in over-diagnosing SRI-exposed infants with NBS

components would *increase* the difference in NBS incidence between exposed and unexposed infants. Perhaps more importantly, we found no association between the pediatric provider knowledge of SRI exposure and either documentation of findings consistent with NBS or transfer to a higher level of nursery care. Avoidance of such potential biases could only be achieved by prospective study in which pediatric providers were blinded to group assignment.

Several groups of investigators have reported increased rates of preterm birth and fetal growth restriction in the setting of maternal SRI treatment, raising the possibility that the NBS may be related to these adverse obstetrical outcomes. Oberlander and colleagues (2006) compiled population health data from British Columbia and found that infants with SRI exposure had significantly shorter gestations, lower birthweights, and longer hospital stays than infants without SRI exposure.[17] Similarly, Wen and colleagues (2006) reviewed prescription records from the Canadian province of Saskatchewan and reported that women receiving SRI medication during pregnancy had increased odds of preterm birth, low birth weight, and fetal death.[16] Chambers and colleagues (1996), using data from the California Teratogen Information Service, also found that preterm birth is more common in pregnant women treated with fluoxetine in the third trimester than among those with first and second trimester exposure.[13]

One reason why pregnancy outcomes in our series may have been better is that the women in our cohort, who represented fewer than 1% of our prenatal patients, received psychiatric medication as part of a multi-disciplinary team approach. Therefore, even though they remained economically disadvantaged, the resources they received may have obviated other risk factors for adverse outcome that could not be addressed in larger

database reviews. Since the preterm birth rate was only 4% in our series (comparable to our obstetrical population), findings consistent with NBS were not attributable to prematurity.

As there were only 3 infants exposed to both SRI medication and clonazepam in our series, the degree of risk associated with combined exposure is not something we can evaluate. However, it may be noted that Oberlander and colleagues (2004) also identified an increased risk for transient neonatal symptoms when paroxetine was combined with clonazepam, and attributed this to altered paroxetine metabolism, leading to increased drug levels.[11] Evaluation of the pharmacologic relationship between SRI medication and infant effects is complex, as it is based not only on maternal dosage and maternal weight, but on infant weight and complications, and on factors that would impair maternal or infant drug metabolism, including but not limited to genetic polymorphisms.[2,11] Despite considerable effort, the etiology of NBS, whether it is caused by SRI toxicity or withdrawal, or both, depending on individual and medication, remains a topic of debate and likely further study.[2] In our series, the distribution of medications used was similar among those who did and did not have symptoms, and mothers of infants with signs of NBS received virtually the same medication dosage as those without signs of NBS. We suspect that the lack of relationship between NBS and medication dosage is related to the overall low dosage range of medication used and the mild/non-specific nature of the infant findings.

Treatment of depression, particularly at the end of pregnancy, is a topic of ongoing controversy. With numerous case reports and cohort studies detailing potential neonatal risks, the most common being neonatal behavioral abnormalities, clinicians have

been left with difficult decisions in the face of limited evidence.[2] It is not sufficient to simply recommend discontinuation of SRI treatment, as the relapse rate of major depression is as high as 67%,[18] with obvious potential for adverse maternal and infants outcomes. From our perspective, a key unanswered question has been the clinical significance of the NBS findings. A large literature review concluded that although severe symptoms -- including seizures, dehydration, excessive weight loss, hyperpyrexia, or need for intubation can occur, such findings complicate only 1/313 NBS cases.[2] The same review compared the syndrome to colic, with authors explaining that their intention was to place NBS in the context of other mild, non-life threatening syndromes that are familiar to a general audience.[19] Our findings would support that opinion.

Table I. Demographic Characteristics of SRI-treated and Untreated Pregnancies

Characteristic	SRI-treated pregnancies N = 49	Control pregnancies N = 59
Maternal age, years	28.4 ± 5.9*	25.8 ± 5.1
Ethnicity		
Hispanic	41 (84)	43 (73)
Black	4 (8)	11 (19)
White	2 (4)	4 (7)
Other	2 (4)	1 (2)
Nulliparity	6 (12)*	19 (32)
Prenatal care initiated, weeks gestation	22 [17,29]	22 [14.5, 29]
Illicit substance use	2 (4)	3 (5)
Cocaine	0	1 (2)
Heroin	0	1 (2)
Marijuana	2 (4)	2 (3)
Methamphetamine	1 (2)	0
Tobacco use	2 (4)	6 (10)
Alcohol use	1 (2)	2 (3)
Medical Illness		
Hypothyroidism	1 (2)	3 (5)
Asthma	2 (4)	4 (7)
Diabetes (insulin treated)	5 (10)	5 (8)
Seizure disorder	4 (8)*	0
Psychiatric Diagnosis		
Major Depression	32 (65)*	27 (46)
Anxiety disorder	6 (12)*	0
Adjustment disorder	2 (4)*	14 (24)
Bipolar disorder	2 (4)	7 (12)
Other	21 (42)	17 (29)

Data presented as mean ± SD, N (%), and median [Q_1,Q_3].
*P < 0.05 as compared with untreated pregnancies.

Table II. Delivery Outcomes of SRI-treated and Untreated Pregnancies

Outcomes	*SRI-treated pregnancies N = 49*	*Control pregnancies N = 59*
Gestational Age at Delivery, weeks	39 [39,40]	40 [39,40]
Preterm birth < 37 weeks	2 (4)	4 (7)
Cesarean Delivery	15 (31)	19 (32)
Non-reassuring fetal status	1 (2)	3 (5)
Birthweight, g	3274 $\pm$ 559	3335 $\pm$ 505
Birthweight < 3rd percentile	3 (6)	1 (2)
Apgar score at 5 minutes	9 [8,9]	9 [9,9]
Apgar < 7 at 5 minutes	0	0
Umbilical artery pH*	7.27 [7.21,7.30]	7.27 [7.23,7.31]
pH < 7.0	0	0
Infant intubated in delivery room	0	0

Data presented as median [Q_1,Q_3] (range), N (%), mean $\pm$ standard deviation.
*pH data available for 47 SRI-treated pregnancies and 57 untreated pregnancies.

Table III. Neonatal Behavioral Syndrome Components

	SRI-treated pregnancies N = 46*	Control pregnancies N = 59
Neurological finding	9 (20)	7 (12)
Irritability	1 (2)	2 (3)
Jitteriness	4 (8)	4 (7)
Hypotonia	1 (2)	1 (2)
Hypertonia	3 (6)	4 (7)
Hyperreflexia	1 (2)	1 (2)
Respiratory finding	3 (7)	4 (7)
Apnea	0	0
Oxygen requirement	3 (7)	0
Tachypnea	2 (4)	3 (5)
Flaring/Grunting/Retractions	3 (7)	1 (2)
Gastrointestinal finding	2 (4)	5 (8)
Vomiting	1 (2)	1 (2)
Poor feeding	1 (2)	3 (5)
Hypoglycemia	0	3 (5)
NBS		
Any component present	13 (28)	10 (17)
Transferred to higher level nursery	5 (11)	6 (10)
Transferred for respiratory indication	3 (7)	3 (5)
Length of hospital stay, days	2 [2,3]	2 [2,3]
Number hospitalized > 4 days	6 (12)	9 (15)
Infant with NBS, length of stay, days	2 [2,4]	6 [2.3,8.5]
NBS, hospitalized > 4 days	3 (7)	6 (10)

Data expressed at N (%) and median [Q1,Q3].
There were no statistically significant differences between the groups.
*Does not include three infants exposed to clonazepam in addition to an SRI, each of whom was transferred to a higher level nursery for a respiratory indication.

Table IV. Characteristics of infants from SRI-treated pregnancies and control pregnancies transferred to a higher level of nursery care for a respiratory indication

Medication Group		Gestational age, wks	Birth-weight, grams	Hospital stay, days	Findings/Diagnosis
1	SRI-treated pregnancy	39	3500	3	Tachypnea, flaring, grunting, retractions, diagnosed with TTN
2	SRI-treated pregnancy	39	4280	10	Tachypnea, oxygen requirement, diagnosed with pneumonia (aspiration)
3	SRI-treated pregnancy	40	3760	2	Oxygen requirement, due to maternal narcotic in labor, responded to naloxone
4	SRI-treated pregnancy*	35	2445	6	Apnea at 3 hours of life, transient. Medications: haloperidol, levetiracetam, sertraline, clonazepam. Mother also reported marijuana use
5	SRI-treated pregnancy*	37	3058	2	Oxygen requirement, flaring, grunting, diagnosed with TTN
6	SRI-treated pregnancy*	40	3825	6	Tachypnea, diagnosed with pneumonia
7	Control pregnancy	36	2845	9	Tachypnea, hypotonia, poor feeding in setting of hypoglycemia presumed due to maternal insulin-dependent diabetes
8	Control pregnancy	40	3405	6	Flaring and grunting in setting of hypoglycemia. No specific diagnosis
9	Control pregnancy	40	4580	7	Tachypnea, hypotonia, irritability No specific diagnosis

TTN: Transient tachypnea of newborn

Diagnoses of pneumonia were based on chest x-ray findings.

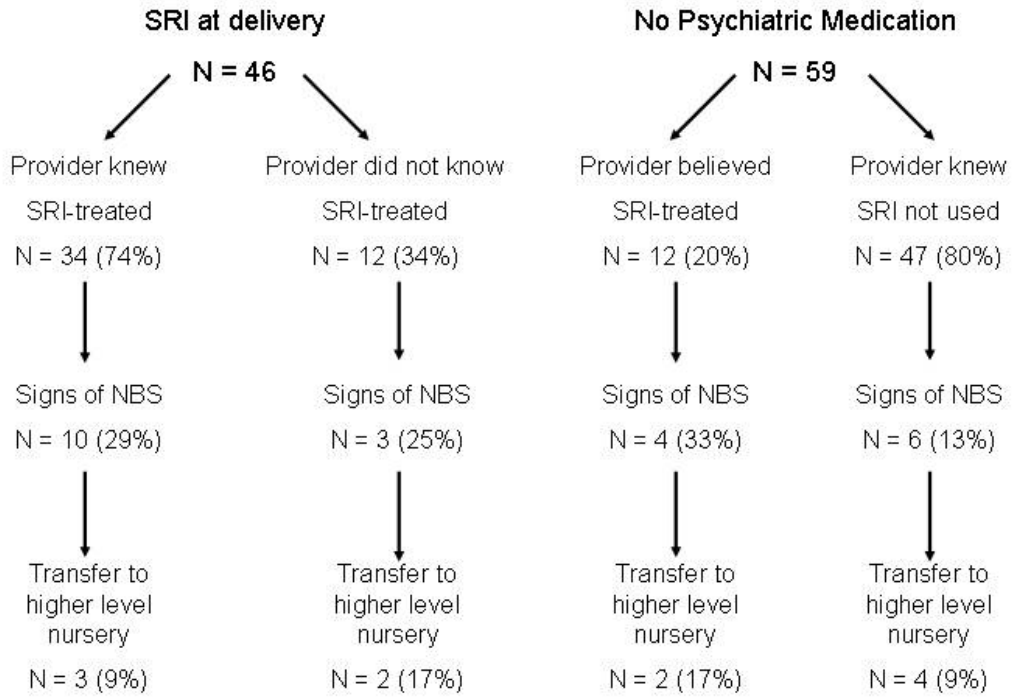
*During pregnancy, treated with clonazepam in addition to SRI medication.

Table V. SRI Medication and Dosage Information

Medication	SRI-treated pregnancies N = 49	Dosage in overall cohort, mg	Number of infants with NBS N = 16*	Dosage in those with NBS, mg
Citalopram (Celexa®)	33 (67)	20 (10-40)	8 (50)	20 (10-40)
Sertraline (Zoloft®)	11 (22)	50 (25-200)	5 (31)	50 (50-200)
Venlafaxine (Effexor®)	3 (6)	75 (75)	2 (13)	75
Escitalopram (Lexapro®)	2 (4)	15 (10-20)	1 (6)	20

Dosage information represents dosage at delivery.
Data expressed as N (%) and median (range).
*Includes 3 infants with NBS exposed to clonazepam in addition to SRI.

Figure 1. Proportion of infants with signs of neonatal behavioral syndrome (NBS), according to pediatric provider knowledge of maternal SRI treatment. Knowledge of maternal SRI treatment did not affect likelihood of identifying a sign of NBS or transfer to a higher level of nursery care. When providers were aware of maternal SRI treatment, likelihood of identifying a clinical sign of NBS was no greater than when they were not aware of SRI treatment (29% vs. 25% respectively; p = 0.77), and the likelihood of transfer to a higher level of nursery care was no greater (9% vs. 17% respectively; p = 0.45.)



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