

Perinatal Services BC

Antidepressant Use During Pregnancy: Considerations for the Newborn Exposed to SSRIs/SNRIs

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Table of Contents

Executive Summary	2
1.0 Introduction	4
2.0 Statement of Women-centred Care	4
3.0 Definitions and Abbreviations	5
4.0 Background & Clinical Significance	5
5.0 SSRI/SNRI Exposure and Neonatal Adaptation Syndrome	6
6.0 Persistent Pulmonary Hypertension	7
7.0 Congenital Heart Defects	8
8.0 Place of birth	8
9.0 Discharge Follow up	9
10.0 Breastfeeding	10
11.0 References	11
Appendix A: Newborns Exposed to SSRIs/SNRIs During Pregnancy Algorithm	13
Appendix B: The ACoRN Process – Primary Survey and Neurological Sequence	14
Development Committee Members and Expert Reviewers	16

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While every attempt has been made to ensure that the information contained herein is clinically accurate and current, Perinatal Services BC acknowledges that many issues remain controversial, and therefore may be subject to practice interpretation.

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Executive Summary and Recommendations

This guideline provides advice for the monitoring, care and follow-up of newborns exposed to selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) in utero. Mood disturbances requiring clinical attention, such as depression and anxiety, are common during pregnancy. While there are risks to pharmaceutical treatment during pregnancy, untreated or incompletely managed depression also carries risks for the exposed newborn. After careful consideration of the risks and benefits of pharmaceutical treatment, many women and their caregivers decide to continue treatment with SSRIs/SNRIs during their pregnancy.

While most newborns born to women who continue SSRI/SNRI treatment during pregnancy are healthy, an increased risk for neonatal behavioral disturbances led the Canadian Pediatric Society (CPS) to issue a position statement in 2011 (titled Selective Serotonin Reuptake Inhibitors in Pregnancy and Infant Outcomes) recommending that newborns exposed to SSRIs in the second half of pregnancy be observed in hospital for at least 48 hours. To further guide clinical practice, a review of the literature and best practice was undertaken by Perinatal Services BC (PSBC) to clarify what constituted surveillance.

In this guideline we focus 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. We recommend that parents be educated prior to the delivery about the increased risks their newborns have for these conditions and be informed about the additional screening their newborn will receive in the first 24 hours.

Approximately one third of newborns exposed to SSRIs/SNRIs in utero will experience neonatal adaptation syndrome (NAS), which generally presents within a few hours following birth and may include a combination of respiratory distress, feeding difficulty, jitteriness, irritability, temperature instability, sleep problems, tremors, shivering, restlessness, jaundice, rigidity, and hypoglycaemia. As with all newborns that present with abnormal signs and symptoms a differential diagnosis should include metabolic, infectious, cardiologic and congenital disorders and appropriate assessments should be pursued. The diagnosis of NAS should only be made after other possible causes of the newborn's symptoms have been ruled out. Typically NAS symptoms are mild and transient, generally resolving within 2 to 3 weeks of delivery. Consider providing supportive care such as a quiet, low-light environment. While it has not been studied in a population of NAS newborns, we recommend using the low-risk, non-invasive interventions shown to improve outcomes in babies suffering neonatal abstinence syndrome, including skin-to-skin contact. This has been shown to improve temperature regulation, breathing regularity, behavioural state, weight gain, and overall newborn health in babies suffering from NAS.

Persistent pulmonary hypertension of the newborn (PPHN) is defined as a failure of the normal relaxation in the fetal pulmonary vascular bed during the circulatory transition that occurs shortly after birth. PPHN is very rare, and occurs with differing severity. There is a slightly increased risk of PPHN in newborns exposed to SSRIs in utero; however the absolute risk is very small. Given that PPHN has a 10% mortality rate; it is recommended that exposed newborns have their vital signs assessed every 4 hours for the first 24 hours following delivery and this should include the use of pulse oximetry to test oxygen saturation (SpO₂) at each assessment. The first SpO₂ should be done at approximately 1-hour post delivery. Newborns with a low SpO₂ should undergo consultation with a pediatrician if available. If a pediatrician is not available, consult BC Women's NICU.

While first trimester use of SSRIs/SNRIs does not significantly increase the risks for birth defects, there appears to be a slightly increased risk of congenital heart defects associated with their use (particularly with exposure to paroxetine). We recommend a thorough clinical exam immediately at delivery and prior to discharge from hospital, and the use of pulse oximetry to screen for congenital heart defects in the first 24 hours and at the time of discharge. If a newborn has a low SpO₂, consult with a pediatric cardiology and consider possible echocardiography. The one-month visit should include a complete newborn clinical exam with particular attention paid to the possibility of septal defects that may not have been detected by initial screening.

Recommendations

- 1 Parents should be educated prior to delivery about the increased risks for neonatal adaptation syndrome, congenital heart defects, and PPHN. This includes being informed of the screening their newborn will receive in the first 24 hours. (A)
- 2 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. Other withdrawals should also be ruled out. (A)
- 3 Focus on supportive care and emphasize that neonatal adaptation syndrome symptoms are usually mild and transient. (A)
- 4 Newborns exposed to SSRIs/SNRIs in utero should have their vitals assessed every 4 hours for the first 24 hours including the use of pulse oximetry at each assessment. The first SpO₂ should be at approximately 1 hour post delivery. Newborns with a low SpO₂ should undergo consultation with a pediatrician if available. If a pediatrician is not available, consult BC Women's NICU. (A)
- 5 All newborns born after in utero exposure to SSRI/SNRI require a complete clinical exam immediately after delivery and prior to discharge from hospital. (A)
- 6 Serious congenital heart defects will likely be discovered through use of clinical examination and pulse oximetry (see recommendation 4). A low SpO₂ should undergo consultation with a pediatrician if available. If a pediatrician is not available, consult BC Women's NICU. If a congenital heart defect is suspected, discuss with Pediatric Cardiology and consider echocardiography. (A)
- 7 The one-month visit should include a complete newborn clinical exam with particular attention paid to the possibility of septal defects that may not have been detected by initial screening. (A)
- 8 Discharge after 24 hours can be considered if the newborn has stable vital signs, a normal SpO₂ at discharge, a normal physical exam, is feeding well, maintaining their temperature, and has no symptoms of NAS. Prior to discharge parents should be advised to see their PCP in 3 to 5 days to ensure the newborn weight is within normal parameters and there are no NAS symptoms. (B)
- 9 Encourage and support breastfeeding. (A)

The recommendations included in these guidelines have been adapted from the Levels of Quality of Evidence for Treatment Recommendations described in the Canadian Task Force on Preventive Health Care (<https://www.canadiantaskforce.ca>).

Recommendation A	There is good evidence to recommend the clinical preventive action
Recommendation B	There is fair evidence to recommend the clinical preventive action
Recommendation C	The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making.
Recommendation D	There is fair evidence to recommend against the clinical preventive action
Recommendation E	There is good evidence to recommend against the clinical preventive action.
Recommendation I	There is insufficient evidence (in quantity or quality) to make a recommendation; however other factors may influence decision making

1.0 Introduction

Mood disturbances, such as depression and anxiety, requiring clinical attention are common during pregnancy. While there are risks to pharmaceutical treatment during pregnancy, untreated or incompletely managed depression also carries risks for the exposed newborn. While increasingly treatment with selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are used, mothers and their clinicians are often left with weighing difficult decisions about the risks and benefits of pharmaceutical treatment during pregnancy. Importantly, the majority of the women who choose to continue SSRI/SNRI treatment will have healthy babies; however, there are some adverse outcomes that occur following delivery that are more common in newborns of mothers who used SSRIs/SNRIs during pregnancy. These outcomes will be the focus of this guideline.

The antidepressant medications most commonly used to treat depression during pregnancy are selective serotonin reuptake inhibitors (SSRIs). These are also the most well studied antidepressants in terms of their potential risk to the newborn. A small number of women use serotonin-norepinephrine reuptake inhibitors (SNRIs) during pregnancy, and while these exposures are not as common and not as well studied, current evidence suggests their inclusion in this guideline is warranted. This guideline will not address other medications that women may be taking.

These guidelines focus on what providers and parents need to be aware of following the birth of a newborn that was exposed to SSRIs/SNRIs in utero to ensure that the baby remains healthy. In 2011, the Canadian Paediatric Society (CPS) released a position statement¹ with recommendations for practitioners who are caring for newborns who were exposed to selective serotonin re-uptake inhibitors (SSRI) during pregnancy. The recommendations called for increased surveillance for the newborn for 48 hrs after delivery. The position statement did not elaborate about the specifics of the surveillance. Even after the publication of this statement, there remained controversy about the evidence. In light of the confusion, PSBC committed to a review of the evidence and to develop a useful guideline for BC health care providers.

The goal of this guideline is to:

- Summarize key reported neonatal outcomes that occur following delivery of newborns with exposure to SSRIs/SNRIs;
- Provide background information for health care professionals (HCPs) to assist in providing anticipatory guidance to parents;
- Recommend specific monitoring criteria for these newborns.

2.0 Statement of Women–Centred Care

Core principles of women–centred care include respect, information sharing, participation and collaboration. Women, their partners and their families should always be treated with kindness, respect, and dignity. The views, beliefs and values of the woman and her family in relation to her care and that of her newborn should be sought and respected at all times. Women should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals².

3.0 Definitions and Abbreviations

HCP Health care professionals

NAS Neonatal Adaptation Syndrome – adverse behavioural symptoms experienced by newborns who have been exposed to SSRI's during pregnancy

O₂ Oxygen

PCP Primary care provider

PPD Postpartum depression – depression that occurs after birth or anytime within the first year postpartum.

PPHN Persistent pulmonary hypertension – a failure of the normal relaxation in the fetal pulmonary vascular bed during the circulatory transition that occurs shortly after birth.

SNRI Serotonin norepinephrine reuptake inhibitors eg; venlafaxine (Effexor), desvenlafaxine (Pristiq), duloxetine (Cymbalta)

SSRI Selective serotonin reuptake inhibitors eg; citalopram (Celexa), fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), Escitalopram (Cipralex, Ciprodex) and Fluvoxamine (Favoxil)

4.0 Background & Clinical Significance

Depression and/or anxiety affect between 15 and 20% of pregnant women^{3, 4}. These disorders during pregnancy can have important implications for the mother, the newborn and family members. While depression and anxiety are often treated with prescription medicines (most commonly SSRIs/SNRIs), there are risks to using SSRIs/SNRIs during the pregnancy period. Research has suggested that there is an association between use of SSRIs/SNRIs during pregnancy and several newborn outcomes. These outcomes include a slight increase in spontaneous abortion, birth defects, small-for-gestational age (SGA), preterm birth, low birth weight, and persistent pulmonary hypertension (PPHN)⁵⁻¹⁰.

However there are also important risks to both mother and newborns of untreated depression. Research has suggested that maternal depression (and/or anxiety) during pregnancy is an independent risk factor for operative delivery¹¹, preterm birth^{12-14,15}, and low birth weight^{13, 14, 16, 17}. Studies comparing the newborns born to mothers with higher depression scores have noted that they appear to suffer from decreased motor tone, more abnormal reflexes, lower activity levels, less robustness and endurance, increased irritability, and inferior orientation compared to babies born to mothers with low depression scores¹⁸⁻²¹.

After careful consideration of the risks and benefits of SSRI/SNRI treatment during pregnancy, many women with moderate or severe depression or anxiety disorders, in consultation with their caregivers, choose to continue pharmaceutical treatment during the pregnancy period. Most recent estimates available for British Columbia suggest that 4.5% of pregnant women who delivered in hospital between April 1, 2001, and June 30, 2006 were treated with an antidepressant during their pregnancy²².

Last year the Canadian Pediatric Society released recommendations with respect to SSRI use in pregnancy and newborn outcomes. One of their recommendations was that newborns with late-trimester SSRI exposure should be observed in hospital for neurobehavioural or respiratory symptoms for a minimum of 48 hours. This PSBC guideline is designed to provide more specific recommendations for caregivers in BC about the duration of monitoring and the monitoring needs of these newborns. We will not make recommendations regarding the ideal treatment of maternal depression during pregnancy in this guideline. Instead, we focus on the neonatal outcomes where caregiver detection and treatment immediately following delivery are crucial for ensuring the long-term health of the newborns. These outcomes include neonatal adaptation syndrome, PPHN and congenital heart defects.

5.0 Neonatal Adaptation Syndrome (NAS)

Recommendations

- 1 Parents should be educated prior to delivery about the increased risks for neonatal adaptation syndrome, congenital heart defects, and PPHN. This includes being informed of the screening their newborn will receive in the first 24 hours.
- 2 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. Other withdrawals should also be ruled out.
- 3 Focus on supportive care and emphasize that neonatal adaptation syndrome symptoms are usually mild and transient.

Newborns who have been exposed to SSRIs/SNRIs in utero occasionally experience neonatal adaptation syndrome (NAS), which generally exhibits as some combination of respiratory distress^{7, 23-26}, feeding difficulty^{23, 27}, jitteriness²³, irritability, temperature instability^{23, 24}, sleep problems²⁸, tremors²⁹, shivering²⁹, restlessness²⁹, convulsions^{24, 30}, jaundice^{27, 28}, rigidity²⁹, and hypoglycaemia^{23, 24, 28, 30}. The neonatal adaptation syndrome following SSRI/SNRI exposure in utero that we describe here has also been referred to as neonatal abstinence syndrome, neonatal withdrawal syndrome, and serotonin discontinuation syndrome. Current evidence suggests that NAS may not be a result of drug withdrawal, as was commonly thought to be the case. A competing hypothesis is that NAS may result from overstimulation of the serotonergic system during development when fetuses are exposed to high levels of serotonin in maternal blood³¹.

While none of these manifestations is specific to SSRI/SNRI exposure, they do seem to occur more often than expected after maternal SSRI/SNRI treatment in late pregnancy. Best estimates suggest that neonatal adaptation syndrome affects about 30% of newborns whose mothers are treated with SSRI/SNRI's late in pregnancy³¹. The average time of onset ranges between birth to 3 days of age and lasts for up to 2 weeks³². The risk of NAS appears to be slightly higher among women who had taken more than one psychotropic agent during pregnancy³⁰. It is important to stress to mothers that, in many cases, neonatal adaptation syndrome is mild, self-limited, and, when presenting with feeding and sleeping difficulties, can be comparable to familiar syndromes such as infantile colic. Furthermore, there have been no reported cases of mortality from NAS. Mothers can be directed to already existing information such as the Period of Purple Crying[®] DVD and booklet for suggestions on soothing the newborn³³.

The following interventions have been shown to be helpful for newborns undergoing drug withdrawal symptoms (although they have not been studied in SSRI/SNRI -exposed newborns specifically): newborns are provided a quiet, low-light environment. Mother-newborn skin-to-skin contact is easily implemented and results in improvement in temperature regulation, breathing regularity, behavioural state, weight gain, and overall newborn health^{34, 35}. While rare, there may be some SSRI/SNRI -exposed newborns exhibiting severe signs of toxicity who will require more aggressive treatments, such as respiratory support, fluid replacement and anticonvulsant therapy^{28, 30, 36}. In these cases, admission to a neonatal intensive care unit (NICU) is required.

6.0 Persistent Pulmonary Hypertension

Recommendations

- 4 Newborns exposed to SSRIs/SNRIs in utero should have their vitals assessed every 4 hours for the first 24 hours including the use of pulse oximetry at each assessment. The first SpO₂ should be at approximately 1-hour post delivery. Newborns with a low SpO₂ should undergo consultation with a pediatrician if available. If a pediatrician is not available, consult BC Women's NICU. (See Appendix A: Monitoring the Newborn Exposed to SSRIs/SNRIs)

Persistent pulmonary hypertension of the newborn (PPHN) is defined as a failure of the normal relaxation in the fetal pulmonary vascular bed during the circulatory transition that occurs shortly after birth. It occurs with various severities. The incidence of PPHN is approximately 2 to 6 cases per 1,000 live births³⁷. PPHN is characterized by pulmonary hypertension that causes right-to-left extra-pulmonary shunting of blood and can lead to severe and potentially unresponsive hypoxemia. The severity can vary from mild and transient respiratory distress to severe hypoxemia and cardiopulmonary instability requiring intensive care support. Mortality is estimated to be around 10% at most tertiary care centres and is related to the etiology of the disorder and the reversibility of changes in pulmonary vasculature³⁸.

While there is some conflicting evidence in the literature, there does appear to be a slightly increased risk of PPHN associated with late pregnancy SSRI/SNRI use. A recent systematic review of the relationship between SSRI/SNRI use and PPHN concluded that there appears to be a small but significantly increased risk of late pregnancy SSRI/SNRI exposure associated with PPHN. While the absolute risk cannot be determined, the authors conclude that it is likely very small³⁹. The largest study to date examining whether SSRI/SNRI use increased the risk of PPHN reported a difference in rates of PPHN between SSRI/SNRI -exposed and unexposed newborns of 1.8 per 1000⁴⁰.

The absolute risk of PPHN is low; however, given the 10% mortality rate and the evidence that does suggest that PPHN occurs more often in newborns exposed to SSRIs/SNRIs in utero, we are recommending oxygen saturation testing every 4 hours for the first 24 hours after birth as a cost effective, accessible method of monitoring which will also help to detect any congenital heart defects in exposed newborns.

7.0 Congenital Heart Defects

Recommendations

- 5 All newborns born after in utero exposure to SSRI/SNRI require a complete clinical exam immediately after delivery and prior to discharge from hospital.
- 6 Serious congenital heart defects will likely be discovered through use of clinical examination and pulse oximetry (see recommendation 4). A low SpO₂ should undergo consultation with a pediatrician if available. If a pediatrician is not available, contact BC Women's NICU. If a congenital heart defect is suspected, discuss with Pediatric Cardiology and consider echocardiography.
- 7 The one-month visit should include a complete newborn clinical exam with particular attention paid to the possibility of septal defects that may not have been detected by initial screening.

It is important to note that the majority of studies indicate that maternal SSRI/SNRI treatment during the first trimester of pregnancy does not significantly increase the overall rate of birth defects. However, there is some evidence suggesting that certain SSRIs/SNRIs (particularly paroxetine) may slightly increase the risk of congenital heart defects^{41,42}.

The best available research, including a meta-analysis suggests that first-trimester maternal paroxetine treatment may increase the risk for certain congenital heart defects about 1.5-fold⁴¹. This suggests that the risk of congenital heart defects in the newborns of women treated with paroxetine during the first trimester of pregnancy may be about 1% (the risk of congenital heart defects in the general population is approximately 0.7%).

While this is a very small increase in risk, congenital heart defects are a leading cause of death in the first year of life⁴³. If defects are not detected early, there is a risk of circulatory collapse with a substantial adverse effect on prognosis⁴⁴. We are recommending that all newborns exposed to SSRIs/SNRIs receive pulse oximetry — a non-invasive, easily administered test that is successful in detecting most serious cardiac heart defects following delivery. This would allow for early treatment of any cardiac defects and prevent readmissions of newborns in cardiac distress. Pulse oximetry has been shown to be highly specific for detection of critical congenital heart defects in asymptomatic newborn babies and has been recommended as universal screening for all newborns⁴⁴⁻⁴⁶. Given the slightly increased risk in this population, we feel this screening is warranted.

8.0 Place of birth

Home births should not be discouraged in women using SSRIs/SNRIs during pregnancy, but midwives should have access to the equipment needed to follow the recommendations in this guideline and be available to continue monitoring an asymptomatic newborn for at least 24 hours. Midwives who do not have access to pulse oximetry equipment or who are not able to provide at least 24 hours of monitoring should encourage mothers requesting a home birth to deliver in hospital or find another midwife with the ability to follow these recommendations. We suggest consultation with a mental health provider prior to deciding for a planned home birth.

9.0 Discharge Considerations

Recommendations

- 8 Discharge after 24 hours can be considered if the newborn has stable vital signs, a normal SpO₂ at discharge, a normal physical exam, is feeding well, maintaining their temperature, and has no symptoms of NAS. Prior to discharge parents should be advised to see their PCP in 3 to 5 days to ensure the newborn weight is within normal parameters and there are no symptoms of NAS.

Given that the majority of babies exposed to SSRIs/SNRIs will be born healthy, we recommend that discharge after 24 hours be considered for newborns who are experiencing no adverse signs and symptoms, who have met the following criteria:

- Normal vital signs for the first 24 hours and at discharge
- Normal oxygen saturation levels for the first 24 hours and at discharge
- Normal physical exam
- Feeding established
- Regulating their temperature well
- No signs or symptoms of NAS

To ensure that the newborn weight is within normal parameters for his/her age, parents should be advised to see their primary care provider (PCP) in 3 to 5 days following discharge from hospital. In BC, a public health nurse contacts new families after discharge from the hospital within 24 to 48 hours. A phone assessment is done and families are identified who require enhanced services. This should include women who were on SSRIs/SNRIs at the time of delivery and therefore this information should be included on the liaison record prior to discharge. The public health nurse should assess that the newborn is feeding well and not displaying signs of neonatal adaptation syndrome. Decisions for early discharge should take into consideration the local Public Health ability to do timely assessments on weekends and stat holidays. Families should be counseled to contact their PCP if they have any concerns.

Families experiencing perinatal mental health issues should receive follow-up and good clinical care in the long-term. Women with depression should be closely monitored throughout pregnancy and the first postpartum year⁴⁷. These women are at increased risk of developing postpartum depression (PPD), which can also have important consequences on a child's development⁴⁸⁻⁵⁰. There is also a possibility that SSRI/SNRI exposure may have long-term effects on a child's neurological development. While current evidence suggests this is a hypothetical, still unproven risk and does not justify avoiding or stopping medication, long-term follow-up is warranted to ensure that the child is developing at the same rate as his/her peers.

10.0 Breastfeeding

Recommendations

- 9 Encourage and support breastfeeding.

Following delivery, the rapid decline of postpartum hormones combined with the stressors of caring for a new child contribute to the increased risks for PPD^{51, 52}. In developed countries, approximately 1/5th of new mothers will experience a depressive episode in the first 3 months following delivery⁵³. Women with a history of depression and anxiety are at even higher risk of experiencing a depressive episode in the postpartum period, so it is important that mothers using SSRIs/SNRIs during pregnancy continue seeing their caregiver regularly^{54, 55}. Women who successfully used SSRIs/SNRIs during pregnancy and their caregivers are likely to decide to continue use of pharmacotherapy during the postpartum period.

While we know that SSRIs/SNRIs enter breast milk, the dose received by the newborn through breastmilk is very small. Research has shown that SSRIs have a good safety profile in breastfeeding mothers⁵⁶⁻⁵⁸. Given that mothers using SSRIs/SNRIs have been shown to be at increased risk of not breastfeeding their newborns⁵⁹, these women need particular counseling and attention regarding the safety of breastfeeding while using these medicines and the benefits of breastfeeding for their newborns. Breastfeeding promotes improved health in newborns and women who breastfeed. Breastfeeding has long-term positive health benefits for individuals who were breastfed and is associated with substantial health care savings. Current evidence suggests that the benefits of breastfeeding outweigh the risks in women using SSRIs/SNRIs. Further information on breastfeeding promotion can be obtained in the Perinatal Services BC guideline “Breastfeeding Healthy Term Infants”⁶⁰.

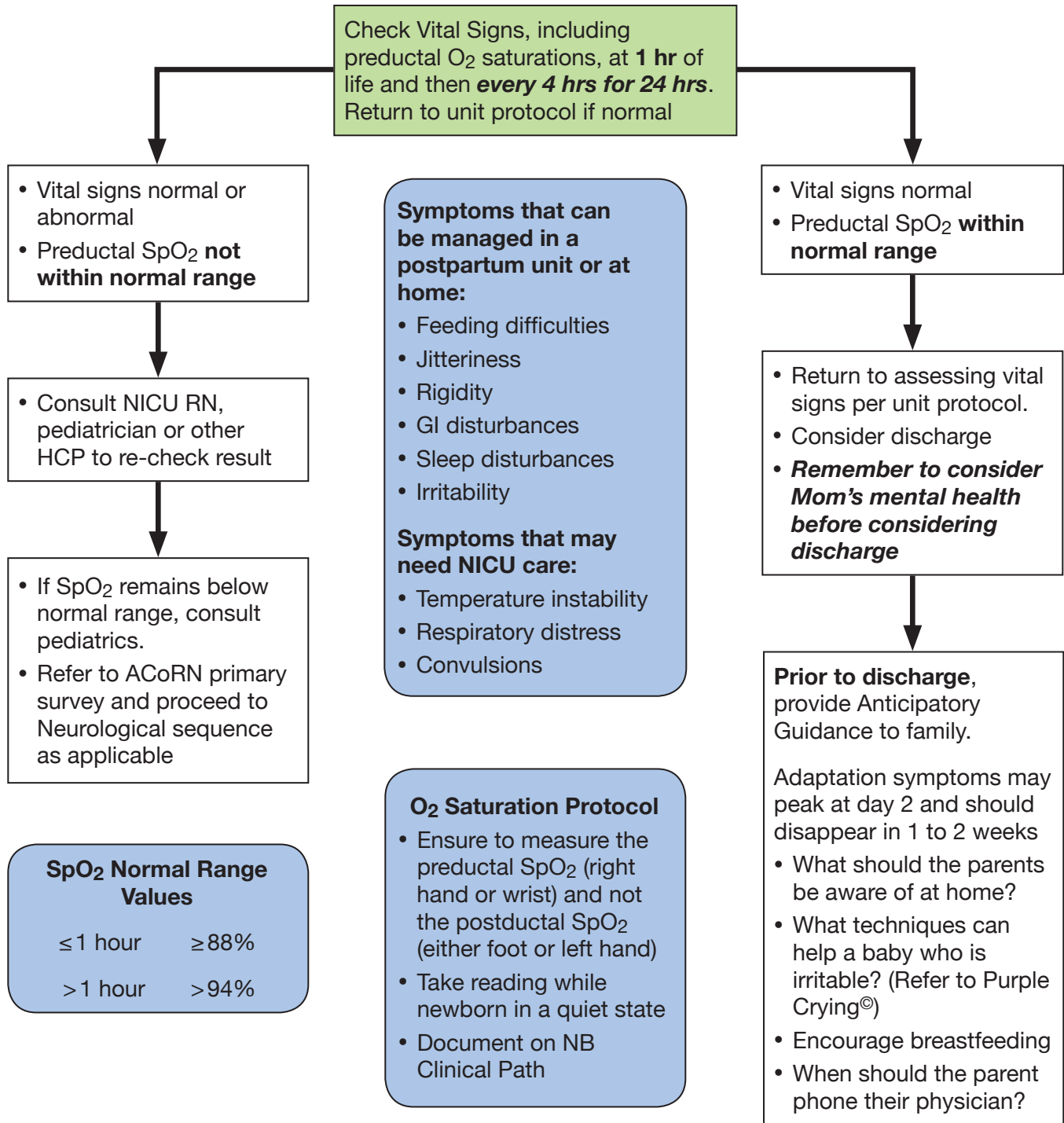
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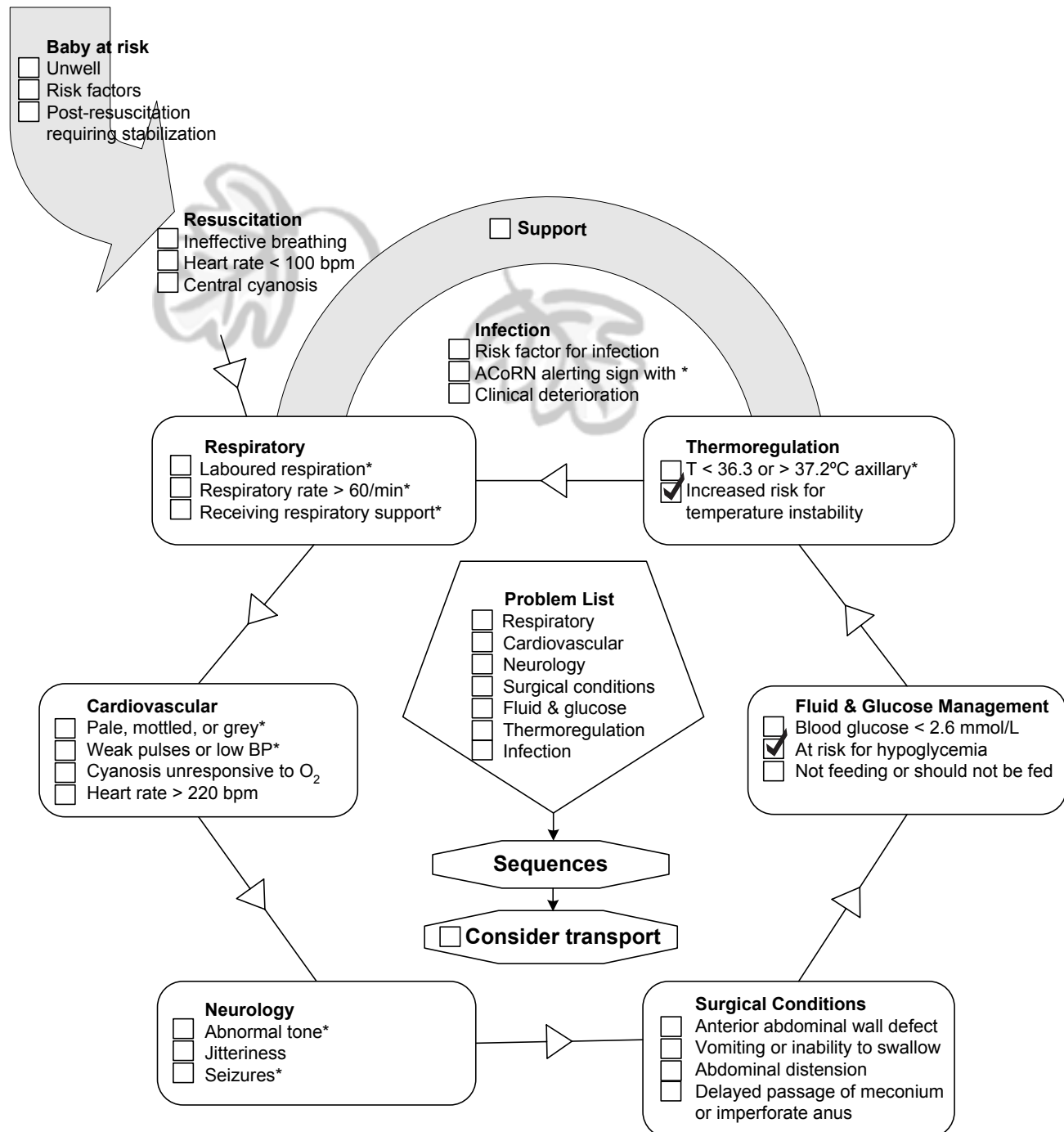
Newborns Exposed to SSRI/SNRIs during Pregnancy Algorithm



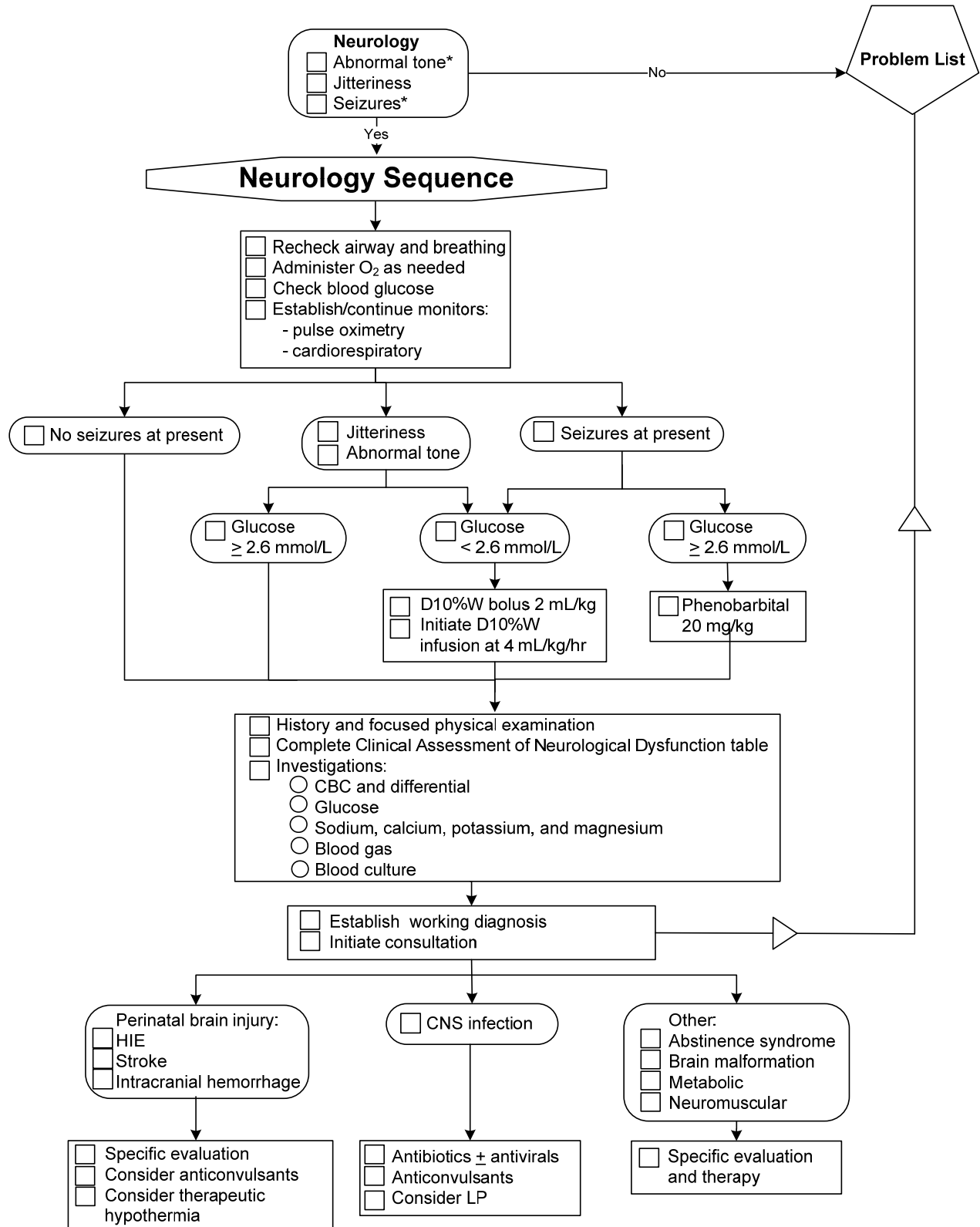
Key			
ACoRN	Acute Care of at-Risk Newborns	NICU	Neonatal Intensive Care Unit
HCP	Health Care Provider	SpO ₂	Oxygen Saturation
NB	Newborn	≤	less than or equal to
		>	greater than



The ACoRN Process



The Neurology Sequence



Blood glucose conversion: 2.6 mmol/L is equivalent to 47 mg/dL

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While every attempt has been made to ensure that the information contained herein is clinically accurate and current, Perinatal Services BC acknowledges that many issues remain controversial, and therefore may be subject to practice interpretation.