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The effect of perinatal exposures on the infant: Antidepressants and depression

Gillian E. Hanley, PhD [a, b], Tim F. Oberlander, MD, FRCPc [a, b, c, *]

[a] Child and Family Research Institute, University of British Columbia, 948 West 28th Ave, Vancouver, BC V5Z 4H4, Canada
[b] School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada
[c] Department of Pediatrics, University of British Columbia, Vancouver, BC, Canada

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Depression, anxiety, or both, during pregnancy are common complications during the perinatal period, with 15–20% of women experiencing depression at some point during their pregnancy. Considerable evidence suggests that untreated or undertreated maternal Axis I mood disorders can increase the risk for preterm birth, low birth weight, and alter neurobehavioral development *in utero*. Serotonin reuptake inhibitor antidepressants are often considered for antenatal therapy, with the goal of improving maternal mental health during pregnancy. Treatment with a serotonin-reuptake inhibitor, however, does not guarantee remission of depression, and in-utero serotonin reuptake inhibitor exposure has also been linked to increased risks for adverse infant outcomes. In this chapter, evidence linking serotonin reuptake inhibitor use with an increased risk for postnatal adaptation syndrome, congenital heart defects, and neonatal persistent pulmonary hypertension is reviewed. Management decisions should include attention to the continuum of depression symptoms, from subclinical to severe major depressive disorder and the long-term developmental risks that might also be associated with pre- and postnatal exposure.

Introduction

Between 15 and 20% of pregnant women suffer from depression or anxiety during the perinatal period [1,2]. Although some women decline pharmacotherapy because of concerns about possible risks

* Corresponding author. Child and Family Research Institute, University of British Columbia, F605A-4480 Oak St Vancouver, BCV6H 3V4, Canada. Tel.: +1 604 875 3200; Fax: +1 604 875 2384.
E-mail addresses: Gillian.Hanley@cw.bc.ca (G.E. Hanley), toberlander@cw.bc.ca (T.F. Oberlander).

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of teratogenicity, about 5–13% of pregnant women choose to treat their mood disorder with a serotonin reuptake inhibitor (SRI) antidepressant [1,3]. Both the disease and its treatment pose risks for mothers and their neonates. Pharmacotherapy poses difficult decisions for the clinician and mother alike, and the evidence supporting a course that promotes both maternal and infant health is often conflicting. Not treating maternal depression is never an option. What are the best options to promoting optimal care for the development and behaviour of infants in mothers who are depressed during pregnancy?

Making sense of studies reporting on the effect of prenatal SRI exposure is challenged by conflicting and contradictory findings, some raising concern [4,5], whereas others offer reassurance [6–8]. This might, in part, reflect the inherent challenge in distinguishing between the effects of the SRI exposure from the effects of the underlying indication for the drug treatment, the maternal mood disturbance, and related confounding influences. Compounding this is that a failure to treat maternal depression, anxiety, or both, effectively can lead to compromised prenatal care, increased risk of obstetrical complications, self-medication, substance abuse, or both, which further affects neonatal health [9–11]. Thus, in examining the evidence, as imperfect as it is, it becomes critical to weigh the risks and benefits of exposing the fetus to maternal mental illness against the risks and benefits of exposure to psychotropic medicines. In this chapter, we aim to present a synthesis of the research evidence on the effects of maternal mood disorders (depression, anxiety, or both) and the use of SRI medicines on neonatal health as a way to guide clinical care of exposed neonates. Three key outcomes (postnatal adaptation syndrome, congenital malformations and persistent pulmonary hypertension) will be used as examples to guide clinical care of the exposed neonate.

Two classes of medications are often combined and referred to as SRIs: selective serotonin reuptake inihibitors that include fluoxetine, paroxetine, sertraline, citalopram, escitalopram, and fluvoxamine; and the selective-norepinephrine reuptake inhibitors, which include venlafaxine, desvenlafaxine, duloxetine, and milnacipran. For the sake of simplicity, no distinction will be made between exposures to either class in this chapter. These medications primarily act by blocking the serotonin transporter (5-HTT), which increases extracellular serotonin levels. Because SRIs readily cross the placenta and the blood–brain barrier [12], maternal prenatal SRI treatment alters central fetal serotonin (5-HT) levels. Serotonin is a widely distributed central neurotransmitter [13], and, given its key role as a developmental signal during early developmental periods [14], it is not surprising that concerns have been raised about the neurobehavioural consequences of altering early 5HT signalling during developmentally sensitive periods [13,15].

Research on the possible adverse outcomes of SRI exposure *in utero*, however, has reported contradictory findings, with many studies reporting no increased risk from exposure to SRIs *in utero* on infant outcomes [16,17]. This confusion can be explained at least partially, by the key challenge of distinguishing between the effects of the SRI exposure and the effects of the underlying indication for the drug treatment, the maternal mood disturbance. Failure to treat maternal depression, anxiety, or both, effectively can lead to compromised prenatal care, increased risk of obstetrical complications, self-medication, substance abuse, or both, not to mention exposure to the detrimental effects of the illness itself. For the most part, the body of evidence that allows us to make clinical sense of these complex and contradictory research findings remains limited. Our challenge remains one of weighing the risks and benefits of exposing the fetus to maternal mental illness against the risks and benefits of exposure to psychotropic medicines. In this chapter, we aim to present a synthesis of the research evidence on the neonatal effects of prenatal maternal mood disorders and SRI exposure. Three key widely reported neonatal outcomes (postnatal adaptation syndrome, congenital malformations and persistent pulmonary hypertension) that are detectable immediately after delivery are used in this chapter to highlight how evidence might be used to guide a clinical approach to care of the newborn of depressed mothers treated with an SRI during pregnancy.

Prenatal maternal mood disturbances and neonatal outcomes

Undertreated maternal depression, anxiety during pregnancy, or both, have been shown to have adverse effects on the mother and the unborn child. Research has suggested that maternal depression, anxiety, or both, during pregnancy is an independent risk factor for operative delivery [18], preterm birth [19–21], and low birth weight [20,22–24]. In a meta-analytic study, depression symptoms during