"PROZAC BABY" – 25 YEARS OF MOTHERISK RESEARCH INTO SSRI's AND ALCOHOL IN PREGNANCY

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Presented at: *Motherisk Update 2014, The Hospital for Sick Children, May 21, 2014, Toronto, Ontario, Canada. The full lecture can be seen at: http://www.youtube.com/watch?v=1ykZ61Y1JCc*

ABSTRACT

A summary of the debate regarding the safety of antidepressants in pregnancy is presented through the story of *Prozac Baby*. This is a diary of a fetus who finds out (to his horror) that his mother intends to abort him due to misinformation she has received. The novel, *Prozac Baby*, was written by Dr. Gideon Koren, based on his experience at Motherisk. An update on the risks of alcohol in pregnancy is also provided.

Key Words: *Depression, pregnancy, SSRIs, fluoxetine, fetal alcohol spectrum disorder, misinformation*

INTRODUCTION

There are many fundamental issues in the discussion of drugs in pregnancy. Some of these relate to a woman's day-to-day life before she plans or knows that she is pregnant. Here are some key challenges that need to be considered:

- Only half of all pregnancies are planned,[1] with the result that many women take medications unknowingly while pregnant.
- Many women need medications for chronic conditions (e.g., epilepsy) and concurrent conditions (e.g., allergies). It is risky for them to discontinue these therapies, as their conditions could worsen.
- Women work with chemicals, are exposed to radiation, and use alcohol or illicit drugs.
- During embryogenesis, drugs and chemicals may adversely affect fetal development.

Other issues can arise during pregnancy.

- The need for medications to treat pregnancy-induced conditions (e.g., morning sickness).
- The anxiety of producing a child with birth defects leads women to not take medications during pregnancy and lactation.
- Pharmaceutical companies avoid developing drugs for pregnant and lactating women due to fear of litigation.

As a result of all of the above, women do not receive appropriate drug therapy even after the first trimester, or for life-threatening conditions.

Perception of Teratogenic Risk

Women's perception of the teratogenic risk of drugs instigates concern about the issues listed above. Even when exposed to non-teratogenic drugs, women were shown to assign themselves a 24% risk.[2] Loebstein and colleagues found that exposure to fluoroquinolones did not result in clinically significant musculoskeletal abnormalities in children exposed in utero, but did result in an increased rate of therapeutic abortion among exposed women (RR = 4.50, 95% CI 0.98-20.57).[3] Similarly, women exposed to rubella vaccine 3 months before conception or during their first trimester had a higher rate of therapeutic abortion, 7.4% vs. 0.0% ($P<0.05$) in the control, unexposed group.[4] Malformation rates, birth weights and developmental milestones were similar for both the exposed and the control groups (n = 94 for each group).

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Exposure to radiation can also cause alarm. For example, in the month after the Chernobyl disaster, it was estimated that 23% of early pregnancies in Athens were terminated because women and their spouses believed they had a high risk of embryonic abnormalities.[5] In addition, pregnant women assign significant teratogenic risk to being exposed to diagnostic radiation.[6,7] In reported cases, neither of these circumstances was shown to present a true risk to the fetus.[4-6] Evidence-based counselling can often prevent unwarranted terminations.[1,8]

A number of factors are necessary to establish teratogenicity of a xenobiotic. According to Shepard and Lemire, the following are among these factors:[9]

- The embryo or fetus must be exposed at a critical time during development.
- Consistent findings have been reported through well-conducted epidemiological studies.
- Teratogenicity has been proven in experimental animal models.
- Specific defects have been consistently associated with a particular agent.

Depression in Pregnancy

Management of depression during pregnancy is important, as up to 20% of pregnant women suffer this disorder. It is therefore good to know that fluoxetine[10,11] and other selective serotonin reuptake inhibitors (SSRIs) appear to be safe overall, from the perspectives of both dysmorphology and neurobehaviour. Unfortunately women and practitioners are not aware of the safety profile of most antidepressants. Furthermore, stopping such drugs can cause abrupt discontinuation syndrome, which can manifest with both physical (e.g., nausea, vomiting, tremors, diarrhea) and psychological (e.g., anxiety, mood swings, depression, suicidal ideation) symptoms.[12]

Many pregnant women discontinue their antidepressants (SSRIs and serotonin-norepinephrine reuptake inhibitors - SNRIs) due to concerns and misinformation, which can lead to discontinuation syndrome. Other women have their dosage reduced to lower ineffective levels. Both situations can result in reversion to depression, increased morbidity, hospitalization, and even drug abuse.

Antidepressants and Malformations

Additional information can be found in a retrospective nationwide study of data from the Danish Medical Birth Registry.[16] The investigators found approximately twice the rate of congenital heart malformations in exposed women and depressed women who ceased drug taking before pregnancy, compared to women with no exposure. There was no decreased risk of malformations at lower SSRI doses, nor for women who discontinued treatment anywhere from 3 to 9 months before pregnancy.

Prozac Baby[i]

- "I was conceived last night at 4am. Sarah and Matt came from New Year's Eve party. Quite drunk. I am not sure she was awake during their fluid exchange. Clearly not awake enough to notice that he did not use a condom…."
- "I am one week old… Mom is quite depressed, but she told her girlfriend that with the Prozac she feels much better."
- "Sarah's mom called…mom was very upset… Her mom told her that Prozac can cause terrible things to unborn babies and that she has just read about it in a women's magazine.… Mom stopped taking her Prozac… gradually she becomes quite depressed."
- "Mom's mom made several phone calls to an old friend of hers, an obstetrician, and booked an abortion for March 16."

[i]Koren G. Prozac baby: Diary of a fetus. Asher J, Illustrator. [Toronto]: Amazon; 2014 Jan 30. 104 p.

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Prozac Baby

- "This is my last day. Sarah is becoming unhappy by the minute. She called the abortion clinic to ask some questions about when and how and all that."
- "Mom had another anxiety attack…her mom told her she read in a newspaper that Prozac babies maybe born very agitated and trembling and have difficulty breathing."
- Dad said, "We'll call Motherisk tomorrow."

Prozac Baby

- "Today is due day…the aquarium began to push my head…Once out, I remembered I need to scream…in prenatal class the lady said that if the baby is silent, they resuscitate him… I don't know what it means but it sounds like torture, so I screamed…"
- "And what about your Prozac," asked granny. "It will poison your milk…" Yes again, this was the voice of my grandma…"

Antidepressants and Adverse Effects on the Newborn

Ten to 30% of newborns that are exposed to antidepressants in utero can have poor neonatal adaptation syndrome.[17] The underlying mechanism is not understood, however, the syndrome seems to be primarily a discontinuation syndrome and mimics maternal withdrawal symptoms: the baby is jittery, inconsolable, has tremors, diarrhea and respiratory distress. The syndrome can resolve spontaneously within 3 to 5 days.[18] It has been proposed that some such cases result from serotonin toxicity caused by the SSRI, rather than withdrawal.[19,20]

Persistent pulmonary hypertension of the newborn (PPHN) has also been shown to occur after in utero exposure to SSRIs. Chambers and colleagues studied a cohort of infants who had PPHN, and although the numbers were small, they calculated an odds ratio of 6.1 (95% CI, 2.2-16.8) for those that had been exposed to an SSRI late in pregnancy compared to controls.[21] Extrapolating their results, they note that the risk of PPHN in infants of mothers on SSRIs late in pregnancy will be "relatively low", i.e., about 1%.

Neurobehavioural aspects of antidepressant exposure have been studied by Nulman and colleagues. They found that intelligence quotient (IQ), language, and behaviour were similar among fluoxetine and tricyclic antidepressant-exposed infants and controls.[22] In a more recent study, Nulman and colleagues found that maternal depressive syndromes, rather than medications, affected child psychopathology,[23] a finding that earlier investigators also reported.[24]

After fetal and neonatal effects of antidepressants we need to consider the effects of maternal antidepressants on the breastfeeding infant. Overall, the per kilogram "normalized" dose of SSRIs and SNRIs delivered in maternal breast milk is less than 5% of the maternal dose. (Refer to the Ito paper in this issue.) The low doses of SSRIs in breast milk may mitigate neonatal withdrawal. It has also been suggested that the lower postnatal growth rate in exposed infants probably correlates with maternal depressive symptoms.

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Postpartum Management of Depressed Women and their Babies

In the neonate, the first task is to rule out PPHN or poor neonatal adaptation syndrome–in some cases both may occur–and treat as needed. Postpartum, women with depression must also be tended to, with continuation of their antidepressant treatment or initiation of SSRIs after 1 to 2 days. Specifically, postpartum depression needs to be ruled out or managed. These women need to be supported to establish breastfeeding. The misperception of risk must be fought with evidence to help both mother and infant.

Meconium Testing for Fetal Alcohol Spectrum Disorder – Promise and Challenges

It is estimated that about 1% of Canadians are afflicted with fetal alcohol spectrum disorder (FASD).[25] These infants, children and adults may have lifelong undiagnosed disabilities.

The major challenge in diagnosing FASD is to establish maternal drinking during pregnancy. An early diagnosis of FASD allows early intervention and improves prognosis. Unfortunately, many cases of maternal drinking are not known or divulged because of shame or fear of losing custody of the infant. The presence of 3 characteristic facial features can indicate FASD: short palpebral fissures, smooth or flattened philtrum, thin vermilion border.

Analysis of meconium may provide information on a mother's drug-taking during pregnancy: it can provide a retrospective account of in utero exposure. Meconium begins to form at about 12 weeks' gestation, approximately when fetal swallowing begins. It is a matrix of water, epithelial cells, lanugo, bile acids and salts, blood group substances, enzymes, lipids, mucopolysaccharides, proteins, trace metals, and other substances. Testing of meconium has advantages over blood and urine testing, as it is discarded material and collection is easy and non-invasive.[26] Many drugs used by the mother can be measured in meconium.[27,28]

In early 1999, Bearer and colleagues published findings of fatty acid ethyl esters of alcohol as potential biomarkers for alcohol in meconium.[29] Later the same year, Klein and colleagues also published small group experiments suggesting a similar approach to determining alcohol exposure in utero.[30] A few years later (in a small study of 27 samples), Bearer and colleagues found that ethyl oleate specifically was strongly related to second and third trimester maternal drinking.[31] The threshold was the equivalent of 1.5 ounces of absolute alcohol per day; sensitivity was 84.2% and specificity was 83.3%.

In 2003 Chan and colleagues tested the meconium of infants born to non-drinking women.[32] They found measurable levels of some FAEEs in a portion of the samples from infants of 207 non-drinking mothers. In order to increase specificity, they used the positive cut-off level of 2 nmol total FAEE/g of meconium, excluding ethyl laurate and ethyl myristate, with resulting 100% sensitivity and 98.4% specificity.

Chan and colleagues also reported on testing to determine whether FAEEs produced by the mother cross into the fetus through the placenta.[33] Their experiments showed degradation of FAEEs by the placenta and proposed that FAEEs found in meconium are a result of in utero transfer of alcohol to the fetus and resulting fetal metabolism.

Advantages of FAEE Meconium Analysis

Positive findings in meconium analysis for FAEE are specific to the heavy drinking population; social drinkers fall below the baseline. Since meconium only starts to form in the second trimester, first trimester fetal exposure to alcohol is undetectable by this test, so accidental exposure when the mother is still unaware of her pregnancy is excluded. A positive result corresponds to sustained alcohol use through the last two-thirds of the pregnancy, associated with an addiction-related use pattern while the mother was aware of being pregnant. It has been shown that maternal drug dependence is associated with a higher risk for child neglect, abuse and psychiatric illness.

Other advantages of meconium testing are that the material is discarded; there are no cultural sensitivities; there is no such thing as "passive"

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exposure; and it is ideal for epidemiological studies on pregnancy and fetal exposure to various elements/compounds.

Ethical / Legal Questions

The question arises as to whether maternal consent is required for testing of meconium. Looking at current legislation, there are inconsistencies in testing of human fluids, e.g., syphilis testing can be done without consent, yet HIV testing cannot. Given that meconium is usually discarded, it can legally be considered abandoned and available for testing without the mother's consent. However, that something is legal does not make it ethical, so one would suggest that the mother should at least be informed that the test will be done.

If used inappropriately, the results of the meconium FAEE analysis could cause shame, stigmatization, and loss of child custody. When used appropriately, the meconium FAEE analysis could allow the diagnosis of FASD in many children who might otherwise not be diagnosed, leading to early intervention. Furthermore, consideration needs to be given to the right of the child to know the cause of their disability.

CONCLUSIONS

Meconium FAEE is a breakthrough method in its ability to identify babies heavily exposed to alcohol in utero. This biomarker can assist in finding an accurate estimate of regional and national incidences of heavy maternal drinking. It can also assist in early identification of babies at risk for FASD. Follow up of these babies can allow early diagnosis of FASD and prevention of secondary disabilities. Similar to other neonatal tests (e.g., for sexually transmitted diseases and HIV), the clinical use of such a test raises ethical sensitivities and debate.

The test is now increasingly used by medical practitioners. Examples of current meconium FAEE screening include disorders whose incidence is much lower than FASD, such as, congenital hypothyroidism (1 in about 4000[34]) and phenylketonuria (1 in about 15,000[35]). The incidence of FASD is about 1 in 100.[25] National discussion and consensus are needed to decide whether meconium FAEE testing should be added to global screening.

Acknowledgments / Funding

Motherisk sponsors include Shoppers Drug Mart (national sponsor), Duchesnay Inc. (Motherisk Morning Sickness (NVP) Helpline), Beer Canada (Motherisk Alcohol and Substance Use Helpline).

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