

THE ANTIOXIDANT EFFECT: CAN WE MITIGATE FETAL ALCOHOL SPECTRUM DISORDER WITH ANTIOXIDANTS?

*Y. Ingrid Goh, HBSc., Joanne Rovet, PhD., Wendy J. Ungar, PhD., Gideon Koren MD.
The Hospital for Sick Children, Toronto, Ontario, Canada*

It is estimated that 46% of women consume alcohol.¹ Given that approximately half of pregnancies are unplanned there is a potential of 23% of babies being unknowingly exposed to alcohol. It is known that alcohol consumption during pregnancy can potentially result in a child having fetal alcohol spectrum disorder (FASD). In the full presentation, fetal alcohol syndrome (FAS) may be the clinical result. FAS alone affects 1-4 of 1000 live births.^{2,3} Children with FASD are less likely to be diagnosed than children with FAS because they rely on confirmation of the mother drinking in pregnancy and these children do not exhibit the pathognomonic facial changes.

The majority of studies on FASD have focused on the mechanism of damage. One such mechanism is oxidative stress which is a result in the production of reactive oxidative species that are generated by the metabolism of ethanol.

It is known that the primary prevention of FASD is avoiding alcohol consumption during pregnancy. This is usually hard for women who have unplanned pregnancy, and a still more challenging goal for women who are addicted to alcohol. To date there is no known treatment for women who have consumed alcohol during pregnancy to increase the chances for having a healthy child.

In vitro studies have shown that antioxidant treatment can attenuate ethanol-damaged neural cells.⁴ In pregnant diabetic women, antioxidants were shown to be beneficial by preventing pre-eclampsia.⁵ The above evidence has led us to design a trial to evaluate the effectiveness of antioxidants in mitigating fetal damage from alcohol exposure in pregnancy. We present this protocol with the hope it will facilitate similar research in other countries. As importantly, other centers may consider joining us in this protocol.

The primary objective of the study is to evaluate whether antioxidants in combination with prenatal multivitamin supplementation will impact the outcome of alcohol exposed pregnancies. The secondary objective is to evaluate the cost-effectiveness of implementing this treatment. It is hypothesized that together these treatments will be beneficial to improving the fetus' health and will result in savings to the health care system and society.

The study is a randomized, three-arm, double-blinded, placebo-controlled trial. One hundred and eighty nine women will be asked to participate in this trial where they will be randomized into one of three possible groups. The first group will receive study medication and prenatal multivitamins. The second group will receive placebo and prenatal multivitamins. The third group will not receive any medications but will be advised to obtain prenatal multivitamins containing at least 0.4mg of folic acid as recommended by Health Canada and the FDA. All groups will receive information and counseling from research staff and if need be, referred to specialists or other social services. All women participating will be advised to discontinue drinking alcohol.

Participants included in the trial must be 0-24 weeks pregnant with a TWEAK score of 3 or greater, a history of binge drinking (5 or more drinks) during pregnancy. Participants will be excluded if they have any co-morbid condition(s) that prevents them from providing meaningful consent. Participants are currently being enrolled into the study through the Motherisk Alcohol and Substance Use Helpline 1-877-327-4636. However, recruitment will be extended to hospitals, treatment programs for addicted women, hostels, shelters, food banks, and community centers.

Pregnant women will be prescreened and informed about the study. If they elect to participate an appointment will be set up either at The Hospital for Sick Children or in their homes. At the first visit, subjects will be asked to provide written informed consent to participate in the study. The medical and obstetrical history as well as social circumstances will be documented. In addition, participants will complete a series of questionnaires and be seen by a study physician for a physical assessment. Blood and urine will be collected to assess for any underlying maternal medical conditions and measure baseline antioxidant levels.

The participant's family physician will be notified of her participation in the study and will be contacted to verify medical history and to access results of tests pertaining to the pregnancy. In addition, results from the blood and urine tests will be sent to participant's doctors. Participants who do not have a family physician will be referred to a family physician by the study staff.

All participants will be asked to take a daily multivitamin and participants in the treatment arms will be asked to take one of each tablet daily. All subjects will receive harm reduction counseling throughout the study. Diaries will be provided to participants to monitor compliance, adverse events, nutrient intake and any problems that may be experienced through the study. The frequency of contact is required to keep the trial participants engaged. Participants randomized into the drug or placebo arm will be contacted at least two times a week. Participants randomized into the counseling arm will be contacted once every two weeks. During this contact, participants will be asked about their general health, pregnancy complications, adverse effects, drinking and drug use pattern and compliance to study.

Due to the vulnerability and high-risk nature of our patient population, measures have been built into the study to encourage retention and compliance with the study and its interventions. These may include the use of outreach workers, food vouchers, transportation assistance, home help and other strategies.

Women will return to the study clinic every two months to have a medical examination, return diaries and remaining study drug, complete questionnaires, give blood and urine samples and monitor compliance and medical status. Subjects

will be issued new diaries and study drug at this time. This pattern will continue until the birth of the child.

Study staff will visit the mother within 24 hours of giving birth. At this time, each mother will be interviewed about the outcome of their pregnancy and any birth complications. The baby will be assessed by study physicians for any dysmorphologies and APGAR scores will be recorded. Meconium and hair will be collected from the baby and analyzed for fatty acid ethyl esters as a biomarker for prenatal ethanol exposure.⁶⁻⁸

The child will be assessed at 1, 3, 6, and 14 months of life. Each visit will consist of a physical examination, a full-scale psychometric test, a health resource use, economic, resource utilization and time loss questionnaire.

Participants who complete the study will have the option of having their child followed yearly at the Motherisk clinic. This is important since the full adverse effects of *in utero* alcohol exposure may take years to unmask. Following children as they develop will enable close monitoring of learning, intelligence, behavioural change, and physical functions. Health care resource utilization will be measured as well as use of community and educational services. From this information, modeling of the impact of long-term cost and consequences will be performed.

To the best of our knowledge, this is the first study to examine the effects of drug treatment to attenuate the onset of FAS and ARND. If successful, it will have tremendous implications for the reduction of the most prevalent and preventable type of mental deficiency. Potential confounders in the study include, age, maternal illness and co-morbidities, other maternal exposures in pregnancy, nutrition, socio-economic status, and education. The randomized design aims to balance these potential confounders among the groups. In addition, although this is a double-blinded, placebo-controlled randomized trial, the third arm receiving only counseling will not be blinded. As such, there may be bias in some outcome measurements. The two treatment arms, however, will be blinded to the participants and to the investigators conducting the assessments. The results will therefore accurately reflect the potential of antioxidants to attenuate

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alcohol-related problems in fetuses exposed *in utero*.

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