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Depression and Its Treatment During Pregnancy: Overview and Highlights

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Clinical depression, also called major depressive disorder, is commonly observed in women of childbearing age. The prevalence rates of depression during pregnancy have been reported as high as 7.4% in the first trimester and 12.0–12.8% in the second and third trimester with even higher rates in the first year after delivery. Maternal depression is associated with an increased risk for preterm delivery, and the risk of preterm delivery increases with increasing severity of depression. Untreated maternal depression can have adverse consequences for both the patient and her offspring, and abrupt discontinuation of psychotropic drugs in pregnancy may be associated with physical and psychological adverse effects including a high frequency of relapse. Most psychotropic drugs affect the serotonergic and catecholaminergic systems in the brain and are known to cross the placental barrier, thus possibly affecting the developing embryo and fetus. Serotonin reuptake inhibitors (SSRIs) seem to be the most commonly used and effective antidepressants with 3–5% of women using SSRIs during pregnancy. Untreated maternal depression can also have adverse consequences for both the patient and her offspring, and abrupt discontinuation of psychotropic drugs in pregnancy may be associated with physical and psychological adverse effects including a high frequency of relapse. Maternal depression is associated with an increased risk for preterm delivery, and the risk of preterm delivery increases with increasing severity of depression. The possible effects of both maternal depression and its treatment in pregnancy are issues of major importance in clinical teratology. Antidepressants might also have long–term neurodevelopmental effects on the prenatally-exposed offspring. This special issue complements the Public Affairs Committee symposium titled “Depression and Its Treatment During Pregnancy”, which was jointly sponsored by the Organization of Teratology Specialists, and the Developmental Neurotoxicology Society at the 2016 Annual Meeting of the Teratology Society in San Antonio, TX.

In this special issue of Birth Defects Research Part C: Embryo Today, the review articles cover the factors to consider when treating depression in the pregnant patient, the effects of untreated maternal depression on the developing fetus and infant as well as the potential

effects of prenatal antidepressant exposure on the incidence of birth defects, other adverse pregnancy outcomes, and neurobehavioral development of the prenatally-exposed offspring. Other topics covered include the role of serotonin in early brain development and its possible alteration by antidepressants (e.g., SSRIs) in animal models, and research into the epigenetics of candidate genes to further understand the etiology of psychosocial alterations in offspring due to maternal depression and/or its medical treatment. Finally, the special issue includes a review of the use of antidepressants during lactation with regard to exposure of the infant via breastmilk and the reported associated effects in the neonate.

In their manuscript "**Treating Depression during Pregnancy**", Angelotta and Wisner provide context for the topic of maternal depression during pregnancy by detailing how the physician should work with the pregnant patient to determine an individualized treatment plan with the goal of optimally controlling the maternal disease while limiting potential risk of the treatment to the developing embryo and fetus. The authors outline what factors should be considered in selecting the appropriate treatment for the patient and emphasize the importance of proper diagnosis of the type of major depressive disorder. When SSRI drug treatment is pursued, Angelotta and Wisner emphasize that the drugs should be administered at optimal dose for the patient based on monitoring of symptoms as well as knowledge of the pharmacokinetic changes, which may affect drug efficacy during pregnancy and after birth.

In their contribution "**Epigenetic alterations and prenatal maternal depression**", Nemoda and Szyf describe the epigenetics of normal development compared to the development of offspring prenatally exposed to maternal depression. They review their research into the monitoring of possible candidate genes that could reflect system-wide epigenetic changes involved in life-long behavior alterations in the offspring prenatally-exposed to maternal depression. In addition, they present some principles in the use of "epigenetic drugs" as possible treatment modalities.

The majority of the papers in the special issue focus on the influence of prenatal exposure to SSRIs and serotonin norepinephrine reuptake inhibitors (SNRIs) on development of the offspring. In their manuscript "**Selective Serotonin Reuptake Inhibitors during Pregnancy: do we have now more definite answers related to prenatal exposure?**", Ornoy and Koren review the non-neurological-related pregnancy outcomes associated with the use of SSRIs and SNRIs during pregnancy from the most recent, larger population-based studies. The authors report a slightly higher rate of cardiac anomalies, but not overall congenital malformations, associated with prenatal SSRI exposure. They also report on higher rates of various pregnancy complications, including poor neonatal adaptation syndrome and persistent pulmonary hypertension of the newborn. However, some of these complications are also elevated in women with untreated depression.

In their contribution "**Variations in neurodevelopmental outcomes in children with prenatal SSRI antidepressant exposure**", Rotem-Kohavi and Oberlander describe their research on the long-term (≥3 years of age) effects on the neurological outcomes of children prenatally exposed to SSRIs, with particular focus on the factors that lead to altered neurobehavioral responses in some, but not all, offspring. Specifically, the authors discuss how maternal disease state, genetics, and environment (e.g., condition of the home) each

affect the neurodevelopment of offspring prenatally exposed to maternal depression, and how these factors may interact to influence the neurobehavioral outcomes of prenatally-SSRI treated offspring later in life.

In their manuscript "**New Insights into how Serotonin Selective Reuptake Inhibitors Shape the Developing Brain",** Gingrich and colleagues describe their research using a mouse model to characterize a serotonin-sensitive period of brain development, which impacts the fronto-limbic system responsible for cognitive, anxiety, and depression-related behaviors. They discuss the effects of developmental exposure to SSRIs on serotonin-sensitive development in the mouse and relate these results to neurodevelopmental effects reported in children prenatally-exposed to SSRIs. Their research suggests that there may be delayed effects on depression in offspring prenatally-exposed to SSRIs, such that physicians may need to consider that timing of exposure, mechanism of action of the antidepressant and the use of well-validated psychotherapies to effectively treat maternal disease, while minimizing risk to the long-term health of the fetus.

The remaining two contributions reviewed the pregnancy outcomes following use of medication for the treatment of depression other than SSRIs and offspring effects related to the use of antidepressants while breastfeeding. In their contribution "**Antidepressants, antipsychotics and mood stabilizers in pregnancy: what do we know and how should we treat pregnant women with depression,**" Ornoy and colleagues review the reported pregnancy outcomes and long-term development of the offspring prenatally-exposed to non-SSRI medications that are used to treat depression. The authors report that the tricyclic and tetracyclic drugs appear to be safe, while some mood stabilizers (e.g., lithium, valproic acid carbamazepine and topiramate) are teratogenic; however, newer antiepileptic drugs and mood stabilizers (e.g., lamotrigine and levetiracetam (kepra)) do not appear to cause higher rates of birth defects or neurodevelopmental alterations.

In their review "**Use of Psychotropic Medications in Breastfeeding Women**", Kronenfeld and colleagues summarize the pharmacokinetic data and offspring development associated with the use of psychotropic drugs during lactation as it is important for many women to continue their treatment regimen for maternal depression after the birth of their child. The authors report that most psychotropic medications are expected to be present in breastmilk at levels with no clinical effects on the offspring; however, a limitation of the literature is that it is primarily case reports, case series and small studies.

Continued research is needed into the most effective treatments for controlling depression in women and the safety of their use during pregnancy and the early postpartum period. It is the purpose of the current issue to further our understanding of the role of endogenous serotonin, maternal disease state, environmental factors (e.g., home environment, smoking, etc.), *in utero* antidepressant exposure, and resulting epigenetics on the long-term outcome of the fetus.