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Review

Trick or treat? Evaluating contributing factors and sex-differences for developmental effects of maternal depression and its treatment

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ABSTRACT

Maternal depression and treatment with selective serotonin reuptake inhibitors (SSRIs), the most common form of pharmaceutical intervention, can both have an impact on infant development. As such, it is difficult for healthcare providers to recommend a course of treatment to expectant mothers suffering from depression, or to women on antidepressant medication prior to pregnancy. This review will discuss the existing research on the developmental impacts of maternal depression and its treatment with SSRIs, with a particular focus on contributing factors that complicate our attempt to disentangle the consequences of maternal depression and its treatment such as the timing or severity of the depression. We will explore avenues for translational animal models to help address the question of "Trick or Treat", i.e.: which is worse for offspring development: exposure to maternal depression, or the SSRI treatment? Further, we will explore sex-dependent outcomes for the offspring in human and animal studies as male and female offspring may react differently to the presence of maternal depression or antidepressant treatment. Without more clinical and preclinical data, it remains difficult for women to make an informed decision regarding their depression treatment before, during, and after their pregnancy.

1. Introduction

Major depression is one of the most common neuropsychiatric disorders worldwide. According to the World Health Organization (2017), major depressive disorder is now the leading cause of poor health and disability in the world. Depression also affects twice as many women as men, often with a time of onset coinciding with childbearing years (for review see: Glover and Clinton, 2016; Gutierrez-Lobos et al., 2002; Kessler, 2003). It is estimated that as many as 30% of pregnant women with depression are being treated with antidepressant medication, with selective serotonin reuptake inhibitors (SSRIs) being the most prevalent form of medication (Glover and Clinton, 2016). SSRIs are currently often recommended for use during pregnancy, as untreated maternal depression has been shown to negatively impact the development of the offspring both during and after pregnancy (Belik, 2008; Brummelte et al., 2017; Field et al., 2006). The potential risk of the drug effects and the risks associated with withdrawal from the drug should be weighed against the known negative effects of exposure to maternal depression (Belik, 2008), however there is a lack of data to really perform this evaluation carefully in each case.

Animal models of depression have become a valuable tool to begin to assess the different long-term risks associated with exposure to maternal depression, and those associated with exposure to treatment with antidepressant medication. Currently, little research exists on the long-term effects of prenatal antidepressant exposure in humans, especially in regards to gender-specific outcomes, but using rodent studies allows us to gain a greater insight into the potential impacts of antidepressant exposure well into adulthood in males and females (also see reviews on this topic by Zucker (2017, 2018)). In this paper, we intend to discuss the current research on both the effects of maternal depression and antidepressant exposure in the perinatal period in both humans and animals, and compare the effects of these conditions with an emphasis on sex-differences. We will discuss the values and the limitations of this research in hopes of encouraging cooperation between healthcare providers and human and animal researchers. We hope that this will lead to advances in translational research, thus eventually helping women to make more informed decisions on treatment avenues for perinatal depression. An overview of clinical and preclinical findings in regards to SSRI treatment during pregnancy can be found in Tables 1 and 2.

2. Etiology and consequences of maternal depression

Depressive disorders in pregnant women are one of the most

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Table 1
Humans/clinical.

	Drug	Dose	Timing of exposure	Effect	Reference(s)
Short-term effects					
Physical	SSRIs (nonspecific)	n/a	1st trimester-birth	Spontaneous abortion	Rahimi et al., 2006
	Fluoxetine	n/a	3rd trimester	Shorter gestational age/preterm birth	Chambers et al., 1996
	SSRIs (nonspecific)	n/a	2nd trimester	Shorter gestational age	Hayes et al., 2012
	SSRIs (nonspecific)	n/a	49+ days after conception	Shorter gestational age	Oberlander et al., 2006
	SSRIs (nonspecific)	n/a	Within 270 days before delivery	Shorter gestational age	Simon et al., 2002
	Fluoxetine	n/a	3rd trimester	Shorter birth length	Chambers et al., 1996
	SSRIs (nonspecific)	n/a	49+ days after conception	Lower birth weight	Oberlander et al., 2006
	SSRIs (nonspecific)	n/a	3rd trimester	Infant convulsions	Hayes et al., 2012
	Sertraline	113.2 ± 72.3 mg	3rd trimester	Respiratory distress	Casper et al., 2003
	Fluoxetine	20 ± 11.9 mg			
	Paroxetine	17.2 ± 10.1 mg			
	Fluoxetine	n/a	3rd trimester	Respiratory difficulty	Chambers et al., 1996
	SSRIs (nonspecific)	n/a	49+ days after conception	Respiratory distress	Oberlander et al., 2006
	SSRIs (nonspecific)	n/a	49+ days after conception	Jaundice	Oberlander et al., 2006
	SSRIs (nonspecific)	n/a	49+ days after conception	Feeding problems	Oberlander et al., 2006
	Fluoxetine	n/a	After 20th week of gestation	Persistent pulmonary hypertension (PPHN)	Chambers et al., 2006
	Sertraline				
	Paroxetine				
	Fluoxetine	n/a	1 month before pregnancy through 1st trimester	Cardiovascular anomalies	Malm et al., 2011
	Paroxetine				
	Sertraline	113.2 ± 72.3 mg	1st trimester (71%) 3rd trimester (74%)	Lower APGAR scores	Casper et al., 2003
	Fluoxetine	20 ± 11.9 mg			
	Paroxetine	17.2 ± 10.1 mg			
	Sertraline	113.2 ± 72.3 mg	1st trimester (71%) 3rd trimester (74%)	Lower psychomotor development scores	Casper et al., 2003
	Fluoxetine	20 ± 11.9 mg			
	Paroxetine	17.2 ± 10.1 mg			
Long-term effects					
Behavioral[a]	SSRIs (nonspecific)	n/a	Preconception (1 year before delivery) & 1st trimester	Autism Spectrum Disorder	Croen et al., 2011
	SSRIs (nonspecific)	n/a	1st trimester	Autism Spectrum Disorder	Harrington et al., 2014
	SSRIs (nonspecific)	n/a	1st trimester 3rd trimester	Autism Spectrum Disorder Developmental delays	Harrington et al., 2014
	SSRIs (nonspecific)	n/a	4 weeks before pregnancy-delivery	No increased risk of Autism Spectrum Disorder	Hviid et al., 2013
	SSRIs (nonspecific)	n/a	Preconception (1 year before delivery) through birth	Autism Spectrum Disorder Developmental delays	Man et al., 2015

[a] Most studies on long-term effects focus on developmental disorders and indicate an increased risk for autism spectrum disorders, however recent meta-analyses indicate that this effect may disappear when controlling for maternal depression (Gentile, 2015; Kobayashi et al., 2016).

common forms of perinatal disease (Hubner-Liebermann et al., 2012) and include symptoms such as weight loss and insomnia that can be unhealthy for both the mother and her developing child.

Though the etiology of depression, and particularly maternal depression, is still not well understood, stress is often cited as a preceding factor in many cases of depression (Parker et al., 2003). Depressed patients often show abnormal hypothalamus-pituitary-adrenal (HPA) axis function and a flattened, but generally high diurnal profile of cortisol release (Parker et al., 2003; Schule, 2007). Further, a recent systematic review revealed that the cortisol awakening response is blunted in cases of major maternal depression (Seth et al., 2016). In this study, hypercortisolemia was linked to transient depressive states while hypocortisolemia was more closely associated with chronic postpartum depression (Seth et al., 2016), underlining the complexity of HPA dysregulation in depressed patients during this period. Moreover, a study by Scheyer and Urizar Jr. (2016) found that lower cortisol awakening response in the first and second trimester of pregnancy, and lower daily average cortisol levels in the second trimester, were associated with higher levels of depression postpartum, suggesting that HPA-axis functioning during pregnancy may play role in the risk for developing postpartum depression.

Any form of dysregulation of the HPA axis during pregnancy or the postpartum may have detrimental consequences for the mother and the child, as stress and HPA axis activation also regulate our immune system. Normally, there is a down-regulation of HPA axis function during pregnancy (Brunton et al., 2008), however, chronic stress and depression may result in the opposite, and this has been associated with an increase in inflammatory markers in a state of stress-induced immunocompromise (Stix, 2007). Increased inflammatory response stimulates lymphocytes to release cytokines, prostaglandins, and interleukins, which are involved in the contractions of uterine muscle in labor and delivery, thus heightening the risk for preterm labor and delivery. In fact, women with symptoms of depression are 1.5 times more likely to give birth to a preterm baby than non-depressed women (Smith et al., 2011).

Interestingly, a new study by Pawluski et al. (2017) showed that the neurobiology of perinatal depression seems to differ from major depression at other times in a woman's life. In particular, they found that depressed postpartum women exhibited an opposite activation pattern of the amygdala and striatum in response to emotional stimuli compared to women with major depressive disorder who did not recently give birth. This further underlines that maternal depression is unique in its underlying etiology and that we need more research to better understand its cause, consequences, and contributing factors. This includes better understanding of the factors relating to the experience of depression in pregnant women in order to determine the best treatment for mitigating the associated risks for both the mother and her child. Some of these factors include: the timing of the onset of depression, its severity and chronicity, and environmental factors contributing to or remediating the depression. As all of these components play a role in

Table 2
Animals/pre-clinical.

	Species	Drug	Dose	Timing of maternal exposure	Effect in females	Effect in males	Reference(s)
Short-term effects							
Physical	Rats (Wistar)	Fluoxetine	12 mg/kg, p.o.	GD11-birth	Reduced litter size (sex not specified)	Reduced litter size (sex not specified)	Olivier et al., 2011
	Rats (Wistar)	Fluoxetine	12 mg/kg, p.o.	GD11-birth	Reduced body weight at PD7 (sex not specified)	Reduced body weight at PD7 (sex not specified)	Olivier et al., 2011
					Increased body weight at PD14, 21, 35, but not PD42 (sex not specified)	Increased body weight at PD14, 21, 35, but not PD42 (sex not specified)	
	Rats (Sprague-Dawley)	Fluoxetine	5 mg/kg, osmotic minipumps	PD1-21	Reduced body weight regardless of stress condition (females gained less than males)	Reduced body weight regardless of stress condition (females gained less than males)	Rayen et al., 2011
		Restraint stress GD 15–20 + 2× GD21					
	Rats (Sprauge-Dawley)	Fluoxetine	10 mg/kg, p.o.	GD11-21	Persistent pulmonary hypertension (PPHN)	No significant differences	Belik, 2008
	Mice (Swiss)	Fluoxetine	7.5 mg/kg, p.o.	GD0-PD21	No significant differences in body weight at birth	No significant differences in body weight at birth	Lisboa et al., 2007
Long-term effects							
Adolescence							
Behavioral Anxiety	Rats (Sprague-Dawley)	Escitalopram +Unpredictable mild stress GD9-20	12.2 mg/kg/day, osmotic minipumps	3 days prior to mating-GD21	Increased anxiety in stress group but not Escitalopram group (EPM)	Not tested	Ehrlich et al., 2015
	Rats (Sprague-Dawley)	Escitalopram +Unpredictable mild stress GD9-20	12.2 mg/kg/day, osmotic minipumps	3 days prior to mating-GD21	Increased anxiety in stress group but not Escitalopram group (OFT)	Not tested	Ehrlich et al., 2015
	Mice (Swiss)	Fluoxetine	7.5 mg/kg, p.o.	GD0-PD21	No significant differences (EPM)	No significant differences (EPM)	Lisboa et al., 2007
	Rats (Sprague-Dawley)	Fluoxetine + restraint stress GD15–20 + 2× GD21	5 mg/kg, osmotic minipumps	PD1-21	No significant effects	Stress males fewer central entries (OFT)	Rayen et al., 2011
Depression	Mice (Swiss)	Fluoxetine	7.5 mg/kg, p.o.	GD0-PD21	Increased immobility (FST)	No significant differences	Lisboa et al., 2007
	Rats (Sprague-Dawley)	Fluoxetine + restraint stress GD15-20 + 2x GD21	5 mg/kg, osmotic minipumps	PD1-21	Stress group less time immobile (FST) Stress + fluoxetine rescued effect	Stress group less time immobile (FST) Stress + fluoxetine rescued effect	Rayen et al., 2011
Impulsivity	Mice (Swiss)	Fluoxetine	7.5 mg/kg, p.o.	GD0-PD21	Not tested	Decreased impulsivity (increased latency to attack in resident intruder)	Lisboa et al., 2007
	Mice (Swiss)	Fluoxetine	7.5 mg/kg, p.o.	GD0-PD21	No significant differences (OFT)	Decreased locomotion (OFT)	Lisboa et al., 2007
Locomotor	Mice (Swiss)	Fluoxetine	7.5 mg/kg, p.o.	GD0-PD21	No significant differences in pain sensitivity (Hot plate)	No significant differences in pain sensitivity (Hot plate)	Lisboa et al., 2007
Physical	Rats (Wistar)	Fluoxetine	12 mg/kg, p.o.	GD11-birth	Not tested	Decreased social play	Olivier et al., 2011
Social	Rats (Sprague-Dawley)	Escitalopram +Unpredictable mild stress GD9–20	12.2 mg/kg/day, osmotic minipumps	3 days prior to mating-GD21	Decreased social behavior in Escitalopram group	Not tested	Ehrlich et al., 2015
Adulthood							
					Not tested	No significant differences (EPM)	

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Table 2 (*continued*)

	Species	Drug	Dose	Timing of maternal exposure	Effect in females	Effect in males	Reference(s)
Behavioral Anxiety	Rats (Sprague-Dawley)	Escitalopram +Unpredictable mild stress GD10-20	12.2 mg/kg/day, osmotic minipumps	3 days prior to mating-GD21			Bourke et al., 2013
	Rats (Sprague-Dawley)	Escitalopram +Unpredictable mild stress GD10-20	12.2 mg/kg/day, osmotic minipumps	3 days prior to mating-GD21	Not tested	No significant differences (OFT)	Bourke et al., 2013
	Rats (Sprague-Dawley)	Escitalopram +Unpredictable mild stress GD9-20	12.2 mg/kg/day, osmotic minipumps	3 days prior to mating-GD21	No significant differences (EPM)	Not tested	Ehrlich et al., 2015
	Rats (Sprague-Dawley)	Escitalopram +Unpredictable mild stress GD9-20	12.2 mg/kg/day, osmotic minipumps	3 days prior to mating-GD21	No significant differences (OFT)	Not tested	Ehrlich et al., 2015
Depression	Rats (Sprauge-Dawley)	Fluoxetine +2× daily injections CORT (40 mg/kg, s.c.)	10 mg/kg, i.p.	PD2-24	No significant differences	Increased anxiety-like behavior (NSF) flx not stress	Gobinath et al., 2016
	Rats (Sprauge-Dawley)	Fluoxetine +2× daily injections CORT (40 mg/kg, s.c.)	10 mg/kg, i.p.	PD2–24	No significant differences	Increased anxiety-like behavior (EPM) flx not stress	Gobinath et al., 2016
	Rats (Long-Evans)	Citalopram	5, 10, 20 mg/kg, s.c.	PD8-PD21	Not tested	No significant differences (EPM)	Harris et al., 2012
	Rats (Wistar)	Fluoxetine	12 mg/kg, p.o.	GD11-birth	Not tested	Increased anxiety-like behavior (NSF)	Olivier et al., 2011
	Rats (Wistar)	Fluoxetine	12 mg/kg, p.o.	GD11-birth	Not tested	No significant differences (EPM)	Olivier et al., 2011
	Rats (Sprague-Dawley)	Escitalopram +Unpredictable mild stress GD10-20	12.2 mg/kg/day, osmotic minipumps	3 days prior to mating-GD21	Not tested	No significant differences (sucrose consumption)	Bourke et al., 2013
	Rats (Sprauge-Dawley)	Fluoxetine +2× daily injections CORT (40 mg/kg, s.c.)	10 mg/kg, i.p.	PD2-24	Increased swimming (FST)	Increased swimming (FST)	Gobinath et al., 2016
	Rats (Wistar)	Fluoxetine	12 mg/kg, p.o.	GD11-birth	Not tested	No significant differences (FST)	Olivier et al., 2011
	Rats (Wistar)	Fluoxetine	12 mg/kg, p.o.	GD11-birth	No significant differences (sucrose preference – sex not specified)	No significant differences (Sucrose Preference - sex not specified)	Olivier et al., 2011
	Mice	Fluoxetine	10 mg/kg, i.p.	PD4-21	Decreased exploratory behavior (sex not specified)	Decreased exploratory behavior (sex not specified)	Ansorge et al., 2004
Exploratory	Rats (Sprauge-Dawley)	Fluoxetine +2× daily injections CORT (40 mg/kg, s.c.)	10 mg/kg, i.p.	PD2-24	No significant differences	Increased locomotor activity in CORT group Decreased CORT + Fluoxetine	Gobinath et al., 2016
	Rats (Wistar)	Fluoxetine	12 mg/kg, p.o.	GD11-birth	Not tested	No significant differences (OFT – distance)	Olivier et al., 2011
Locomotor	Rats (Sprague-Dawley)	Escitalopram +Unpredictable mild stress GD9-20	12.2 mg/kg/day, osmotic minipumps	3 days prior to mating-GD21	No significant differences in social interaction	Not tested	Ehrlich et al., 2015

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Table 2 (*continued*)

	Species	Drug	Dose	Timing of maternal exposure	Effect in females	Effect in males	Reference(s)
	Rats (Long-Evans)	Citalopram	5, 10, 20 mg/kg, s.c.	PD8-PD21	Not tested	Reduced sexual behaviors	Harris et al., 2012
Social	Rats (Wistar)	Fluoxetine	12 mg/kg, p.o.	GD11-birth	Not tested	Decreased social behavior	Olivier et al., 2011
	Rats (Wistar)	Fluoxetine	12 mg/kg, p.o.	GD11-birth	Not tested	No significant differences (sexual behavior)	Olivier et al., 2011
	Rats (Sprauge-Dawley)	Fluoxetine + restraint stress GD15-20 + 2× GD21	5 mg/kg, osmotic minipumps	PD1-21	Increased sexual behaviors	Not tested	Rayen et al., 2014
Physical	Rats (Long-Evans)	Citalopram	5, 10, 20 mg/kg, s.c.	PD8-PD21	Not tested	Reduced body weight at PD21 (10 and 20 mg/kg only) Reduced body weight at PD73–103 (10 mg/kg only)	Harris et al., 2012

CORT – corticosterone, EPM – elevated plus maze, FST – forced swim test, NSF - novelty-suppressed feeding, OFT – open field test.

the experience of depression during pregnancy and the postpartum, it is crucial to investigate their exact contribution in hopes of lessening the negative developmental consequences associated with maternal depression.

2.1. Timing of onset of maternal depression matters for the outcome of the offspring

In many research studies, women are recruited at a variety of points throughout pregnancy, or at times only during the postpartum period, and thus many studies, but not all, distinguish between antenatal and postpartum depression. Women suffering from prenatal depression have shorter gestation lengths, restricted fetal growth, and lower birth weights than women without depression (Apter et al., 2011; Davalos et al., 2012; Hubner-Liebermann et al., 2012). In addition, it has been reported that maternal depressive symptoms, specifically during the second trimester, are negatively correlated with cortical thickness in areas of the right hemisphere that are involved in inhibition and attention control in preschool-aged children (Lebel et al., 2016). Interestingly, this was not the case for depressive symptoms experienced during the first or third trimesters, further demonstrating that the timing of the onset or experiences of depressive symptoms during pregnancy may differentially impact the development of the offspring. Another study correlated depression during the third trimester, but not the first or second trimester, with increased rates of operative deliveries (Chung et al., 2001). These studies indicate that depression during pregnancy alone can have negative developmental consequences, before the infant is exposed to depression postpartum.

Assessing the effects of maternal depression becomes more complicated after parturition. For instance, it has been repeatedly shown that children of mothers suffering from postnatal depression are at an increased risk for mood disorders in adolescence (Halligan et al., 2007; Murray et al., 2011). However, as mentioned below, postpartum depression affects several aspects of parenting and maternal attachment, including more missed pediatric outpatient visits (Flynn et al., 2004), mothers touching the infant less (Ferber, 2004), less positivity overall toward the infant (Field, 1998), and less positive enrichment such as singing and reading with the infant (Paulson et al., 2006). For comprehensive reviews of the impact of maternal depression on mother-infant interaction see: (Beck, 1995; Brummelte and Galea, 2016; Field, 2010; Lovejoy et al., 2000; Martins and Gaffan, 2000). These factors are critical components to the development of the infant, including the resulting attachment style in the mother-infant relationship. In fact, it has been shown that maternal depression during the postpartum period predicts higher rates of insecure attachment (Campbell et al., 2004). Thus, it is difficult to distinguish between the effects of the actual depressive symptoms of the mothers on the child and the effects of her altered parenting behaviors, though one could argue that those go hand-in-hand. However, it is also important to consider the contribution of antenatal depression, as that can lead to a disturbed mother-fetal attachment during pregnancy and this in turn can also impact the relationship between the mother and her child in the postpartum (Dubber et al., 2014), in addition to the fact that many mothers who experience postpartum depression were already suffering from depressive symptoms during pregnancy. Bergman et al. (2010) attempted to address this by measuring prenatal cortisol exposure and assessing attachment styles after birth, and found that higher levels of prenatal cortisol exposure was negatively correlated with cognitive ability in the infant, but this was only true for infants with insecure attachments. Another essential factor in regard to the timing and onset of depression is that women may also enter pregnancy with a concurrent depression. As discussed below, this adds another layer of complexity as this often means that women are already taking antidepressant medication at the time of conception. However, less research has been done to compare the effects of maternal depression that started before or during pregnancy. Taken together, it is clear there is a critical need to collect more detailed information on the occurrence of depressive mood before, during, and after pregnancy due to differences in the consequences for the outcome on child development that may further depend on the child's gender.

2.2. More severe and chronic maternal depression is associated with more drastic outcomes

Depression can manifest in many ways, from mild mood disturbances that may be transient in nature, to a debilitating experience affecting the body, mind, and behavior. The vast array of combinations of severity and duration of depression makes it a complex issue to study in pregnant women and mothers. Existing studies show a variety of results, highlighting the need to take into account the severity of the depression, its chronicity, and the interaction between these two variables.

A study by Brennan et al. (2000) demonstrated that higher maternal depressive scores were associated with greater impairment in vocabulary and more reported behavioral problems in children at age 5. Similarly, the more chronic the depression was, the higher the levels of behavioral problems were and the lower the vocabulary scores. This was further evidenced in a study that found the duration of the maternal depression negatively predicted cognitive scores, while the number of depressive episodes after pregnancy was negatively correlated with language scores in childhood (Nulman et al., 2002), emphasizing why both severity and chronicity should be assessed throughout and after pregnancy, and each may play a separate role in the developmental outcomes of the child. Another study found that infants of mothers with high scores on a depression questionnaire at 26 weeks gestation had lower fractional anisotropy and axial diffusivity in the right amygdala on a magnetic resonance imaging scan at two weeks old compared to infants from mothers with low depression scores (Rifkin-Graboi et al., 2013). In a follow-up study, greater prenatal maternal depressive symptoms were associated with larger right amygdala volume in girls, but not in boys at 4.5 years of age (Wen et al., 2017). These measures indicate a reduced structural connectivity and maturation of an area associated with anxiety and mood. Separating severe depression from moderate or mild depression during pregnancy may enable researchers to more accurately assess the risk of pharmacological intervention during the vulnerable time for the infant's development. However, distinguishing between levels of severity of depression during pregnancy is often difficult, as the DSM-V does not specify exact criteria how to define whether a depressive episode is mild, moderate or more severe. Further research is necessary to clarify the developmental outcomes of depression during pregnancy, while trying to account for the severity of the depression.

2.3. Contributing factors to effects of maternal depression

Environmental factors play an important role in the experience and consequences of maternal depression and should be taken into account whenever possible. For example, low socioeconomic status (SES) has been shown to potentiate the adverse outcomes of maternal depression, possibly related to the limited availability of emotional and mental health resources (Hoffman and Hatch, 2000). One study by Herba et al. (2016) linked the income level of families to a variety of other factors such as food insecurity, perinatal infections, crowded or rural living conditions, and interpersonal violence that may all impact the experience of maternal depression, demonstrating that SES itself may be multifaceted as a modulator to development. On the other hand, studies have suggested that a positive and stimulating environment may reverse some of the negative consequences of maternal depression (Murray et al., 1996). This idea is supported by Black et al. (2007), who demonstrated that parental responsiveness to the infant and opportunities to play at home played key roles in mediating effects of maternal depressive symptoms on the infant. A review by Leung and Kaplan

(2009) indicates factors contributing to the severity of the maternal depression to include: partner or marital difficulties, lack of social support, social isolation, major life events, family violence or history of abuse, and substance abuse.

Depression can also impact maternal health behaviors and maternal bonding in a negative way (Dubber et al., 2014), which in turn may contribute to the negative consequences for the children of mothers with untreated depression. For instance, women with maternal depression are 1.5 times more likely to engage in less healthy feeding and sleep behaviors with their infant (Paulson et al., 2006) and are less likely to seek prepartum care and support (Miller, 1999). Further, they are more likely to smoke cigarettes, drink alcohol, and use cocaine than non-depressed mothers (Zuckerman et al., 1989). These 'unhealthy' maternal behaviors could amplify adverse effects for children exposed to maternal depression, which increases the complexity of studying the consequences of this mental illness and further complicates the decision of whether or not to pharmaceutically treat the maternal depression. It is critical for researchers to investigate as much of the woman's day-to-day life as possible in order to tease apart the relation of environmental factors from the experience of maternal depression and their related developmental effects.

2.4. Gender-specific outcomes after exposure to maternal depression

So far, only a fraction of studies has focused on gender differences in the consequences of maternal depression, and many studies investigating early outcomes relating to mother-infant interactions have not looked at whether maternal depression affects this relationship differently if the infant is male or female, though most studies control for gender in their analysis and aim for an even gender distribution within their study sample (Ali et al., 2013; Evans et al., 2012; Kaplan et al., 2015; Kaplan et al., 2012; Koutra et al., 2013; Nulman et al., 2002; Pargas et al., 2010; Piteo et al., 2012; Sutter-Dallay et al., 2011). Longitudinal human studies are more likely to assess the role of a child's gender in developmental and psychological outcomes after exposure to maternal depression. One recent study by Wen et al. (2017) looking at brain development found an association between prenatal maternal depressive symptoms and amygdala volume in girls but not boys at 4.5 years of age. In line with this, Buss et al. (2012) found an association between higher maternal cortisol levels (albeit in healthy women) in early gestation and an increased amygdala volume and more affective problems in girls, but not boys at 7 years of age. Further, (Lebel et al., 2016) found a stronger negative association between maternal prenatal depressive symptoms and cortical thickness in girls than boys, but more negative correlations between maternal postpartum depression and white matter tract diffusivity in the superior frontal region in boys. This again indicates that boys and girls may have different "sensitive periods" when they are more susceptible to the exposure to maternal depression.

In a measure of cognitive and behavioral development at 18 months postpartum, it was reported that approximately 51% of males and 49% of females suffered developmental delays as a result of antenatal maternal depression, suggesting equal rates of impairment for both sexes (Deave et al., 2008). However, a different study revealed that though both, males and females from 6 to 18 months old had lower cognitive scores if they were exposed to maternal depression, females displayed a greater increase in their scores during this time period than males (Azak, 2012). Similarly, Murray et al. (2010) reported lower cognitive scores in boys at 16 years of age, but not girls exposed to postnatal depression, which suggests that potential gender-differences in resilience or vulnerability to the long-term effects of maternal depression may not be noticeable until later in life. Interestingly, Halligan et al. (2007) demonstrated that more adolescent girls developed depressive disorders after exposure to maternal depression than boys, however, other research failed to find such gender-dependent outcome for depressive-symptoms after exposure to maternal depression (Murray et al., 2011). It is conceivable that the timing of the exposure to depression has an impact on these results, as (Quarini et al., 2016) demonstrated that rates of developing depressive disorders were greater in females if the maternal depression was experienced during pregnancy, but risk was higher in males that experienced maternal depression postpartum. Further, one study had found that adolescent girls who were exposed to maternal depression in early childhood were more likely to suffer from an emotional disorder when compared to boys (Naicker et al., 2012). Looking specifically at anxiety, a study noted that boys had an inverse relationship between intensity of maternal depression and symptoms of anxiety while no association was found in girls (Glasheen et al., 2013). This variation in findings again emphasizes the need to consider the timing as well as severity of maternal depression when investigating its developmental effects in boys and girls. To date, the research does not seem to support a specific phenotype of vulnerability for either boys or girls due to the high heterogeneity of the available data, though some outcomes suggest that females may be more sensitive to depression exposure during gestation, while boys may be more vulnerable to postpartum depression. However, it is clear that we need more research to determine whether there are consistent gender-specific risks for developing emotional or cognitive deficits later in life in response to maternal depression exposure.

3. Consequences of treating maternal depression with antidepressants

As the literature cited above suggests, there is a great need for effective intervention strategies for treating maternal depression due to the adverse associated consequences for the mother and the child. While there are a wide variety of treatment recommendations by healthcare providers for maternal depression, including pharmacological treatment, cognitive behavioral therapy (CBT), or even electroconvulsive therapy (ECT), we will focus mainly on the effects of the pharmacologic approach in this paper. The reason for this is that as many as 30% of depressed women are on antidepressant medication at some point during pregnancy, despite little knowledge on how this impacts fetal development in the long-term (Glover and Clinton, 2016).

Selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) contain a warning by the Food and Drug Administration for the potential for related complications after birth, but they remain commonly used during pregnancy (Koren and Nordeng, 2012) and are widely recognized as a reasonable treatment option (Ray and Stowe, 2014). There are, however, several reports of an increased risk for preterm birth and lower birth weights for infants of women on SSRIs, in addition to cognitive and developmental effects that can last well into childhood (Chambers et al., 1996; Hayes et al., 2012; Oberlander et al., 2006; Simon et al., 2002). In addition, heightened risks for spontaneous abortion (Rahimi et al., 2006), infant convulsions (Hayes et al., 2012), and respiratory distress (Casper et al., 2003; Chambers et al., 1996) have been reported. Recently, SSRI use during pregnancy has also been correlated with higher risks for autism spectrum disorders (Croen et al., 2011), though as reviewed by Gentile (2015), these results remain controversial and the effect can disappear when controlling for the maternal depression (Hviid et al., 2013; Kobayashi et al., 2016; Petersen et al., 2014). Additionally, other reports suggest no associated increased risk for premature birth, lower birth weights, or other major malformations (Casper et al., 2003; Einarson and Einarson, 2005; Emslie and Judge, 2000; Koren and Nordeng, 2012; Rahimi et al., 2006), especially when medications are used as directed within their recommended doses (Kulin et al., 1998). The wide variety in results relating to antidepressant use during pregnancy and lack of a firm consensus amongst research studies may be related to the wide range of variables involved in each study. These variables may include: when the medication was administered, whether the woman takes the medication throughout her pregnancy or discontinues during, what type of antidepressant is being used, and what

dose is being prescribed (Brummelte, 2018). Not to mention all the factors related to the maternal depression itself as discussed above (e.g. onset, chronicity and severity of the depression). Any combination of these factors may differentially impact the results of the research, and more studies are necessary to elucidate the specific impact of each of these variables.

3.1. Timing of antidepressant exposure matters

Studies demonstrate different effects on infant development depending on when the antidepressant treatment was administered. Hayes et al. (2012) correlated filling antidepressant prescriptions in the second trimester of pregnancy with a shortened gestational age, and third trimester SSRI use with infant convulsions (Hayes et al., 2012). Another study found that infants born to mothers who took fluoxetine throughout pregnancy had higher rates of premature delivery, lower birth weights, shorter birth lengths, increased admittance to special-care nurseries, and poorer neonatal adaptation compared to infants born to women who only took fluoxetine in the first and second trimester (Chambers et al., 1996). Interestingly, Harrington et al., 2014 found the highest association with autism spectrum disorder in their sample with first trimester exposure to SSRIs, however more research in this area is necessary, as other studies find no difference in infant outcome between timing or continuing and discontinuing SSRI exposure during pregnancy (Warburton et al., 2010).

In many cases, a woman is already on an antidepressant medication when she becomes pregnant, however it is not uncommon that an antidepressant intervention for depression becomes necessary during pregnancy (Nonacs and Cohen, 2002). The timing of the start of the antidepressant medication is relevant, as the neurotransmitter systems of the fetus begin developing as early as the fifth week of gestation (Sundstrom et al., 1993) and SSRIs can freely cross the placental barrier (Loughhead et al., 2006; Rampono et al., 2009; Wang et al., 2007). The presence of antidepressant medication during pregnancy may result in higher than normal levels of these neurotransmitters in the fetus and considering that they can act as neurotrophic factors this in turn may result in an altered developmental trajectory (Brummelte et al., 2016; Oberlander et al., 2009).

In the fetus, serotonin is originally synthesized in the placenta from a maternal precursor, tryptophan, and accumulates in the forebrain of the fetus early in pregnancy (Bonnin and Levitt, 2011). It then begins modulating developmental processes, including neurogenesis and apoptosis, and guiding axon branching and dendritogenesis (Gaspar et al., 2003). By the tenth week of gestation, serotonergic fibers are present in the cortex (Riccio et al., 2009). Several studies have demonstrated that disrupting 5-HT signaling during fetal development disrupts normal neural development, including the formation of thalamocortical axons (Bonnin et al., 2007). As 5-HT is directly involved in the growth and guidance of these axons (Bonnin et al., 2007), the timing of altered 5-HT in the fetus may differentially impact the development of this pathway and can thus play a crucial role in cortical organization (van Kleef et al., 2012). Another example of this is a study by Janusonis et al. (2004) in which they injected pregnant rats with 5-methoxytryptamine (5-MT), a full agonist at several 5-HT receptors, at embryonic day 12. Offspring of rats treated with 5-MT had lower levels of reelin, a glycoprotein heavily involved in cortical laminar and columnar organization, demonstrating a mechanism by which increased levels of serotonin during development may create abnormalities in the organization of the cortex (Janusonis et al., 2004). Interestingly, human infants exposed to SSRIs during gestation also revealed lower levels of reelin in their umbilical cords at birth (Brummelte et al., 2013). As reelin levels usually decrease throughout gestation, these lower levels may indicate that neurodevelopment may be occurring at an accelerated rate triggered by the SSRI-induced increase of serotonin levels during development (Brummelte et al., 2013). In line with this, levels of S100B, an astroglial-specific Ca2+ - binding protein that is involved in proliferation and survival of glial cells and neurons and thus important for brain maturation, have also been found to be lower in SSRI-exposed neonates at birth (Pawluski et al., 2009). Considering that the role of serotonin during development shifts from neurotrophic factor to neurotransmitter, with different roles during different stages of development, it is conceivable that the timing of exposure to SSRIs - and thus increased levels of serotonin - matters significantly during brain maturation. Thus, the outcome for the fetal brain may be very different if a woman is taking SSRIs only during the first or last trimester or throughout pregnancy. Similarly, reducing SSRI dose or withdrawing from the drug completely and thus removing some or all of the (elevated) serotonin levels from the fetus may also affect brain maturation differently depending on when this change happens. Riccio et al. (2009) demonstrated that increasing 5-HT in mouse cortical slices that were extracted at embryonic day 17, decreased migration of interneurons. After washing out 5-HT, the migratory speed resumed its normal pace and there were no lasting effects on cell fate indicating that the effect of serotonin was reversible. This demonstrates the adaptive plasticity of the fetal brain, and gives plausible support to the idea that discontinuing antidepressant medication during pregnancy may differentially affect the development of the fetus compared to continuing the medication throughout gestation. There is evidence of withdrawal syndromes in up to 30% infants after antidepressant use until parturition (Klinger and Merlob, 2008; Levinson-Castiel et al., 2006; Oberlander et al., 2004). If there are high rates of withdrawal syndromes in newborns after prenatal antidepressant exposure, it is plausible that there may also be a withdrawal syndrome in utero if the medication is discontinued during pregnancy. Depending on the timing of discontinuation, this may also have differential impacts on the infant's development. This is especially important to investigate as studies assessing placental transfer of SSRIs to the fetus estimate exposure to the parent drug at rates ranging from 8 to 78% depending on the type of SSRI (Ewing et al., 2015, for review). Through knowledge of the timing of the development of the serotonergic system, we may be better able to make predictions about which points in embryonic development may be more or less vulnerable to the effects of an antidepressant medication.

3.2. Contributing factors to antidepressant action

Another factor that is often neglected when considering antidepressant use and efficacy during pregnancy and the postpartum, is the fact that pharmacokinetics can drastically change during these time periods. Though only a few studies have been conducted to specifically investigate the changes in SSRI kinetics during the perinatal period, studies on other drugs suggest tremendous changes in metabolism and thus bioavailability of psychoactive drugs during reproductive phases (Tasnif et al., 2016). For instance, drug distribution, protein binding, levels of metabolizing enzymes, renal filtration and secretion can change during pregnancy and postpartum. For sertraline, an SSRI commonly prescribed during pregnancy, one study with 6 participants found no significant mean pharmacokinetic changes across pregnancy, but the range of pharmacokinetic changes between individuals was broad, indicating heterogeneity regarding the impact of pregnancy on sertraline metabolism (Freeman et al., 2008). Further, most women displayed the lowest area under the curve and C-max levels for sertraline in the third trimester suggesting that SSRIs may be less effective in late pregnancy, but this may also result in less exposure to the fetus. Overall, it is conceivable that the large individual differences in pregnancy-induced alterations in pharmacokinetics of antidepressants may play a role in the varying effects on the outcome of exposed children.

Additionally, the extent of the ability of alterations to the 5-HT system to impact neurodevelopment may be linked to genetics. For instance, a polymorphism (short (s) or long (l) alleles) in the promoter region of the serotonin transporter (5-HTT) gene (SLC6A4) has been shown to relate to differences in SSRI efficacy. Collier et al. (1996)

demonstrated this by showing that the short allele is associated with reduced 5-HTT binding and expression, and thus 5-HT reuptake compared to the long allele. Oberlander et al. (2008) investigated whether SLC6A4 genotype will moderate the association between SSRI exposure and adverse consequences for fetal development and found effects that highlight the association between genetic factors and neonatal outcome. First, neonates with the short/short (s/s) allele form in the promotor region of the SLC6A4 gene in combination with SSRI exposure had lower APGAR scores at 5 min after birth, in addition to and higher birth weights after controlling for gestational age. Further, infants with the l/l genotype and SSRI exposure had an increased risk of rapid breathing and jitteriness than infants with other genotypes. Another study by Brummelte et al. (2013) found that infants with at least one short allele of the SLC6A4 gene had higher levels of reelin than infants with both long alleles, and though SRI exposed infants had overall lower reelin levels compared to non-exposed infants, there was no interaction effect of genotype and SRI exposure in this study.

Taken together, it may be beneficial to investigate the maternal and fetal genotype when conducting research on SSRI efficacy and impact during pregnancy (Brummelte et al., 2016). This may help alleviate some discrepancies amongst the literature on the effects of SSRIs during pregnancy, and allow for a more certain consensus amongst researchers.

3.3. Gender-differences in human studies after gestational antidepressant exposure

Unfortunately, not many studies have reported outcomes of gestational antidepressant exposure separately for boys and girls, though most studies control for gender in their analysis. As mentioned above, some recent studies have found an association between antidepressants during gestation and Autism Spectrum Disorder (ASD) or Attention-Deficit Hyperactivity Disorder (ADHD) (Croen et al., 2011; Man et al., 2015). Considering that these neurodevelopmental disorders are usually more prevalent in males, it is not surprising that one study found stronger positive correlation between prenatal antidepressant exposure and susceptibility for developing ASD in boys alone than in a gender-combined analysis (Harrington et al., 2014). Though studies investigating antidepressant exposure separately in males and females are sparse, the few studies out there suggest that there may indeed be sex-dependent outcomes. For instance, our results revealed that girls, but not boys, had lower reelin levels in umbilical cord blood after gestational SRI exposure compared to non-exposed infants (Brummelte et al., 2013). Considering reelin's important role for cell migration during neonatal development it is conceivable that this early sex-dependent effect may contribute to gender-specific differences later in life in SRI-exposed children. Further, it is well-known that serotonin plays a role in sexual differentiation by mediating the hypothalamic pituitary gonadal axis development, which could further explain how SSRI exposure could result in sex-dependent outcomes (Pawluski and Gemmel, 2018).

4. Unique challenges to modeling perinatal depression in animals

Animal research is a valuable tool to help investigate the varying consequences of maternal depression and antidepressant treatment before, during, and after pregnancy. However, due to the subjective and intrinsic nature of the experience of depression, it remains a challenge for researchers to model this disorder in animals. Extensive research has linked high levels of stress or the experience of a stressful event to an increased risk of depression in humans (Fava et al., 1981; Lloyd, 1980; Mitchell et al., 2003) and cortisol, the human stress hormone, is implicated in depression via dysregulation of the HPA axis (Herbert, 2013; Piwowarska et al., 2012) including perinatal depression (Gelman et al., 2015), and depression occurring postpartum (Glynn et al., 2013). This led to the theory that exposure to chronic, unpredictable stress in animals can create a depressive-like phenotype. Briefly, animal models usually involve using an uncontrollable source of chronic stress in order to achieve a detriment in functioning that parallels the experience of depression in humans. Another commonly-used stress-based approach is the direct administration of CORT, the main stress hormone in rodents, instead of subjecting the animal to a particular stressor or set of stressors. Chronic CORT administration at levels similar to those evoked by a stressful event has been shown to increase depressive-like behavior (Gregus et al., 2005; Kott et al., 2016), reduce body weight, and maintain high levels of CORT in serum (Brummelte and Galea, 2010; Kott et al., 2016). Administering exogenous CORT instead of a paradigm of stressful procedures may help to standardize the results of animal models based on stress by limiting factors such as the handling involved in many of the other paradigms and differences in the individual response to chronic stressors amongst animals and sexes.

Another approach to modeling maternal depression is based on ovarian-hormone withdrawal. In these studies, animals undergo a hormone-simulated pregnancy and the following withdrawal from elevated ovarian hormones induced depressive-like behaviors including increased immobility in the forced swim test (FST), sucrose anhedonia, learned helplessness, anxiety-like behavior and increased aggression (Galea et al., 2001; Green et al., 2009; Suda et al., 2008). Further, they found decreased hippocampal neurogenesis (Green and Galea, 2008) and increased mRNA levels of varying hippocampal transporters and receptors (Suda et al., 2008) following a hormone-simulated pregnancy. However, this model focuses on the effects of the depression on the dam, as there are no offspring produced with a simulated pregnancy.

Modeling perinatal depression poses other unique challenges. Procedures such as olfactory bulbectomy or similarly invasive procedures may not be practical approaches during pregnancy. Further, female rats have a different physiology compared to traditionally-used male rats that may impact the effectiveness of common stress-based models. In fact, female and male rats have been shown to vary in responsiveness to different stressors (Dalla et al., 2010) and females have higher basal CORT levels than males, indicating their ability to adapt to stress differently than the opposite sex (Weinstock et al., 1998). Dalla et al. (2008) found that female rats are more sensitive to the forced swim test than males are, but show less helplessness behavior in response to a foot shock than males. Further, pregnancy is associated with a down-regulation of HPA axis sensitivity and thus stress reactivity in females (Brunton et al., 2008; Neumann, 2001). In addition, modeling depression after pregnancy requires some practical considerations. Subjecting a dam to a chronic unpredictable stress paradigm or learned helplessness paradigm would involve periods of separating the dam from her litter, exposing the litter to the stress of separation. Further, the pups would be directly exposed to some stressors such as wet bedding, strobe light etc. This added stressor to the litter may confound the results, as it is different than the litter being exposed to a stressed/depressed dam alone. It is thus a necessary component to models of maternal depression to find a way to model depression in the dam, without impacting the litter with unintentional stress. Therefore, one of the commonly used approaches to model maternal depression during pregnancy or the postpartum is the direct administration of CORT. It avoids the subjective changes in stress sensitivity between animals during these periods and does not expose the litter to any prolonged separation from the dam (Brummelte and Galea, 2010; Brummelte et al., 2012; Brummelte et al., 2006; Gobinath et al., 2016). Despite the challenges in modeling depression in an animal, it is essential to study the effects of antidepressant exposure in animals models of depression, to a) distinguish between effects of the disorder per se compared to the medication and b) because the effects of the medication may differ between healthy and ‘depressed’ animals.

4.1. Modeling timing of onset, severity and other contributing factors of maternal depression in animals

The confounds previously mentioned in the human literature such as the timing of onset of the depression, the severity and chronicity of the depression, and environmental factors associated with the experience of depression and their impact on development can all be studied in animal models with a substantial degree of control over those variables. Further, we have detailed information on neurodevelopmental milestones and sensitive phases in rodent that will help to better understand the underlying mechanisms involved in altered brain maturation after exposure to maternal depression or its treatment. For example, we know that the functional maturation of the fetal HPA axis is completed around gestational day 17 in rats (Boudouresque et al., 1988), a level of specificity that is difficult to obtain in humans and valuable information when studying the effects of maternal depression in a translational manner. Studies have shown that an acute stressor to a dam at gestational day 10 resulted in an increase in adrenocorticotropic hormone (ACTH) and subsequent increase in CORT in the dam, but only an increase in CORT (and not ACTH) in the fetus, indicating a maternal source of CORT only for the fetus at this stage in gestation (Erisman et al., 1990). Other studies have confirmed that administering glucocorticoids or stressing the dam on gestational days 15–19 is the developmental timeframe most vulnerable to cause a long-lasting dysregulation of the HPA axis in the offspring (Fride et al., 1986; see Weinstock (2005) for a complete review). We can use this information from animal studies to develop a timeline of the HPA axis maturation as a means to draw parallels to the developmental processes in humans and gain better insight into the timing at which a fetus may be more vulnerable to the effects of maternal stress and depression. It is necessary, however, to keep in mind that in rodents, the third trimester of pregnancy occurs postnatally (Maier et al., 1997), which poses another challenge to investigating the effects of maternal depression in a translational manner.

Animal models also allow researchers to tease apart the effects of depression occurring before pregnancy, with an onset during pregnancy, during the postpartum period only, or encompassing the entire perinatal period. For example, some studies show that prepartum stress and depression in the dam is related to long-lasting hyperactivation of the HPA response, altered circadian rhythm, high levels of anxiety and depression-like behavior, reduced social interaction, sleep abnormalities, and hedonic deficits in the offspring (Darnaudery and Maccari, 2008; Weinstock, 2001, for review). In a model of postpartum depression, high levels of CORT given via a subcutaneous injection to the dam from postnatal days 1–27 resulted in a depressive-like phenotype in the dams and altered behavioral outcome in the offspring. In particular, offspring of the depressed mothers had high scores in a resistance to capture task, greater locomotor activity, and male offspring showed decreased cell proliferation levels in the dentate gyrus at weaning age (Brummelte et al., 2006). This type of research allows for further investigation on the importance of the timing of maternal depression on the developmental outcomes of the offspring, and can aid in studying the remedial effects of various treatment options to moderate the negative effects of maternal depression in the perinatal period.

Another adaptive feature of animal models of maternal depression is the ability to adjust between mild and severe stress/depression. For instance, offspring of dams given a high dose of CORT (40 mg/kg, ~severe depression) during pregnancy showed more depressive-like behavior in the forced swim test compared to controls, but offspring from dams receiving a low dose (10 mg/kg, ~mild depression) did not show any alterations in forced swim test behaviors (Brummelte et al., 2012). Further, 1 h after a restraint stressor, all high CORT groups had significantly lower CORT levels compared to undisturbed controls, while low CORT offspring showed no significant alteration compared to controls. Interestingly, this study also revealed timing and dosing interaction effects such, i.e. if animals were exposed to low or high CORT in utero they had lower baseline CORT levels compared to controls, but animals exposed to low CORT (but not high CORT) during the postpartum period had higher baseline levels. Taken together, this study demonstrated that maternal glucocorticoid exposure and thus induced depressive-like behaviors in the dam have long-lasting, dose- and timing- dependent effects on offspring's behavioral and neuroendocrine outcome, underlining the importance of taking these factors into account when investigating the consequences of maternal depressive-like behavior.

4.2. Animal models of perinatal antidepressant exposure

Much of our current knowledge on the long-term developmental effects of antidepressant exposure in utero comes from animal research. Animal studies have been invaluable to studying this, as rodents have short gestations, large litter sizes, and the offspring reach adulthood relatively quickly. This is particularly important as the effects of antidepressant exposure early in life may not emerge until well into adulthood and thus we are mainly lacking the human data to investigate these long-term effects (Olivier et al., 2011). A review by Glover and Clinton (2016) highlights some of the present findings on developmental SSRI exposure in rodent models, indicating prominent long-term neurobehavioral and brain adaptations, including disruptions in social behavior, cognition, and behavioral inhibition and despair as well as long lasting changes in serotonergic tone, hippocampal neurogenesis, and epigenetic programming.

Animal studies will help us to gain a better understanding of the underlying mechanisms responsible for the antidepressant-induced changes in behavior and cognitive outcome. Several studies indicate that exposure to SSRIs during the perinatal period disrupts the development of the serotonergic system in rodents by resulting in excess serotonin levels in the immature, fetal brain (Liao and Lee, 2011; Maciag et al., 2006; Weaver et al., 2010). Further, a microarray experiment found that perinatal SSRI exposure induced changes in gene expression for genes involved in neurogenesis, synaptic plasticity, and epigenetic processes in the hippocampus (Glover et al., 2015). Altered gene expression and excess levels of serotonin during early development could result in permanent changes in the functional connectivity and wiring of brain networks that in turn may lead to the behavioral, social, and cognitive changes reported with perinatal SSRI exposure (Brummelte et al., 2013). These findings will eventually help us to understand the complexities of the effects of antidepressant exposure in the peripartum period.

However, there are still many discrepancies amongst animal findings on antidepressant exposure in the perinatal period, and these are likely related to studies using: different SSRI antidepressants, different administration routes, different strains and species of rodents, different timing of drug administration, and different behavioral assays and test conditions in assessing offspring behavior (Glover and Clinton, 2016). Further, animal studies frequently administer antidepressants at the beginning or half-way through pregnancy or early in the postpartum period, an approach that does not resemble the human condition very well. Most frequently, a woman is already on antidepressants before becoming pregnant, and is forced to choose whether or not to continue the medication. Only a few women start the medication during pregnancy and, if so, usually not until symptoms emerge (i.e. not right after conception). This is important as the brain and body will adapt to the presence of the drug in the system, and will try to re-establish its homeostasis with the new continuous presence of the drug. Thus, the body's reaction to the drug will be different in an established versus a new user. However, this is something animal models often do not account for in their approaches, as they begin administration at the first day of pregnancy or on the first day of the postpartum period (Brummelte, 2018).

It is also necessary to investigate the effects of antidepressant exposure during pregnancy using clinically-relevant doses and

administration routes, although this may be difficult to determine sometimes due the different physiology and metabolism between humans and rodents. Doses for fluoxetine administration seem to vary from 5 to 25 mg/kg and oral, subcutaneous and i.p. injections have been used to administer the drug to either the dam or neonatal pups, themselves, with obviously varying effects (for review see Glover and Clinton, 2016). Unfortunately, hardly any study actually measured the drug or metabolite levels in the blood of the dam or pup after administration, which makes it difficult to determine which dose and administration route may be the most appropriate. We recently completed a study investigating the effects of sertraline during pregnancy and measured serum levels on gestational day 16 (treatment started at least 7 days prior to conception). Our findings showed that 20 mg/kg given daily via oral gavage results in clinically-relevant serum concentrations of sertraline (60 ng/ml) that are within the range of human exposure levels (30–150 ng/ml) (Kott et al., 2018). It is important to mention, that serum levels do not necessarily represent levels in the brain, however, brain levels are even more rarely measured.

Another key factor in investigating the effects of antidepressant exposure in the perinatal period in a translational fashion is that it should be done in animal models of depression. Without the combination of exposure to maternal depression and the potential for modulation by antidepressant exposure, the effects of antidepressant exposure alone lose a great deal of translational value, as a healthy pregnant woman would not be on antidepressant medication. As discussed above, there are certain challenges in modeling perinatal depression in animals, but it is important to be able to compare the effects of antidepressant effects in healthy and 'depressed' animals and distinguish them from the effects of the maternal depression alone. One study by Ehrlich et al. (2015) investigated the effects of escitalopram (an SSRI) treatment in a model of maternal stress/depression based on a chronic unpredictable mild stress paradigm and found that regardless of antidepressant treatment, the stress exposure increased anxiety-like behavior in adolescent offspring (Ehrlich et al., 2015). Similarly, a study by Bourke et al. (2013) using the same design found no effect of escitalopram treatment on behavior in adult offspring from either the stressed or the non-stressed dams. Another study used a rodent model of maternal postpartum depression based on high levels of CORT given during the postpartum period and found that pups exposed to CORT and fluoxetine had lower body mass compared to CORT alone or fluoxetine alone (Gobinath et al., 2016).

Last, but not least, another area for improvement in terms of animal research lies in the lack of studies investigating the discontinuation of antidepressant drugs during critical periods of development (Brummelte, 2018; Kott et al., 2018). As discussed earlier, many women are already on antidepressant medication and faced with the decision of whether to continue or discontinue the treatment. In fact, many women do decide to stop their medication shortly after the first trimester (Hayes et al., 2012) and the effect of this has –to our knowledge- not been modeled in animals until recently (Kott et al., 2018). Considering the high prevalence of serotonin withdrawal syndrome in neonatal infants exposed to SSRIs during gestation, it is conceivable that the fetus will undergo a similar withdrawal syndrome in utero if the mother decides to discontinue the drug. Animal models would allow for a detailed study of this phenomenon and whether there are sensitive periods during fetal development that may be more vulnerable to the sudden withdrawal of excess serotonin levels.

4.3. Sex-specific effects of maternal depression exposure and its treatment in animal models

Human studies are often underpowered to fully investigate gender differences in response to gestational antidepressant exposure. Animal research could help fill this gap though many studies still only report data for both sexes combined or only one sex (most commonly males, see Glover and Clinton (2016), review). There is emerging evidence, however, that males and females may have different vulnerabilities for the exposure to maternal depression and its treatment. For instance, male offspring, but not females of dams exposed to high levels of CORT in the postpartum period exhibited more anxiety-like behavior in the elevated plus maze, while both males and females of high CORT at any time (pregnancy, postpartum, or both) had higher resistance to capture scores, which are indicative of more anxious or aggressive-like behavior (Brummelte et al., 2006). Further, several studies have shown sex-specific effects of gestational or postpartum antidepressant exposure. For instance, Gobinath et al. (2016) found that postpartum maternal fluoxetine treatment increased anxiety-like behavior in adult male, but not female offspring, in addition to increasing the density of immature neurons in the hippocampus of males, but decreasing the density in females, regardless of the maternal depression state. Interestingly, Sarkar et al. (2014) found a similar effect of increased anxiety in male offspring after administering 10 mg/kg fluoxetine directly to the pups during postnatal day 2–21. Unfortunately, female offspring were not investigated in this study. Another study investigated the effects of perinatal fluoxetine on anxiety-like and explorative behaviors and found effects of drug-exposure but no differences in the outcome between males and females (Lisboa et al., 2007). Intriguingly, several studies have reported significant decreases in sexual activity in male offspring after perinatal antidepressant exposure (Harris et al., 2012; Rayen et al., 2013; Soga et al., 2010), however, females seem to respond with an increase in sexual activity (Rayen et al., 2014). Further, Pawluski and Gemmel (2018) recently summarized sex-specific findings for SSRI exposure on neurogenesis and hippocampal plasticity and concluded that males may be more sensitive to the effect of maternal stress, while females seemed more vulnerable to the exposure to SSRIs. This underlines that the preference for studying only male offspring creates a gap in our understanding of the full effects of maternal depression and perinatal antidepressant exposure.

Taken together, animal models of maternal depression and antidepressant exposure have significantly advanced our understanding of the consequences of exposure to the offspring, and have helped to illuminate potential underlying mechanisms behind the developmental effects. However, we should strive to improve the translational features of the current model to eventually help human mothers to make more informed decisions about their depression treatment during pregnancy and the postpartum.

5. Conclusion: comparing the effects of maternal depression to those of antidepressants: what should we do?

Researchers have been able to determine that the consequences of developmental exposure to maternal depression are contingent on several components, including the timing of the onset of the depression, the severity and chronicity of the depression, and a variety of environmental factors. This, in combination with a variety of factors relating to the treatment options for depression in pregnant women, creates a complex issue for a woman who is attempting to choose whether or not to continue antidepressant treatment during pregnancy.

Previous strategies have included developing a "risk-benefit" decision-making model for women, where psychiatrists work in tandem with pregnant women and their families and physicians to assess the possible outcomes of the various treatment options in order to ensure that every option is discussed in a clear manner to help depressed women make informed decisions regarding their treatment during pregnancy (Wisner et al., 1999). However, currently there is not a clear enough consensus amongst research finding to make an easy decision. This is highlighted in a recent review by Molenaar et al. (2018), that demonstrated the current discrepancies between clinical practice guidelines for pregnant women on antidepressant medications. For women with existing depression, 4 treatment guidelines suggested continuation of the medication, while 5 guidelines did not advise or discourage the use of the medication during pregnancy (Molenaar et al.,

2018). The severity of the maternal depression may play a role in determining whether or not to treat and/or continue antidepressant treatment: for new mild episodes of depression, the recommendations suggest psychotherapy, while for severe cases, medicating with an SSRI, preferably sertraline and not paroxetine, may be the better option (Molenaar et al., 2018). Additionally, as discussed by Nonacs and Cohen (2002), and Belik (2008) it may be safer for a woman suffering from recurrent depression to continue pharmacological treatment during pregnancy than expose the fetus to the detrimental consequences of maternal depression as described above. Especially considering that research has indicated higher frequencies of relapse of depressive symptoms during pregnancy after discontinuation of antidepressant treatment (Chisolm and Payne, 2016; Cohen et al., 2006). Thus, the decision to continue treatment may need to be based on highly individualized factors incorporating the woman's experience of depression, her home environment, the timing of exposure, and even epigenetic factors (McAllister-Williams et al., 2017).

Due to the potential risks of treating depression during pregnancy by pharmacological means, it is noteworthy to assess valuable treatment avenues that may remediate depression with potentially fewer developmental consequences for the offspring, such as CBT and ECT. Both of these methods have shown some success in treating depression, with ECT being especially beneficial for depression resistant to pharmacological interventions (for review, see Saatcioglu and Tomruk, 2011; Sockol, 2015). Both treatment with antidepressant medication and psychotherapy options may be beneficial for alleviating the symptoms of depression during pregnancy on a situational basis and depending on the preference of the mother after weighing out risks for the offspring. Additionally, in recent years novel treatments for postpartum depression, such as brexanolone, have shown promise in remediating depressive symptoms (Meltzer-Brody and Thorp, 2011), offering additional options for women for symptom relief after parturition.

Though recent studies are indicating that the risk of SSRI medications overall seems relatively low, and that previous studies that had reported higher risks may have failed to control for the underlying depression (Chisolm et al., 2015), the developmental impacts of discontinuing treatment during pregnancy for the fetus are still mostly unknown. In fact, the British Association for Psychopharmacology recommends to avoid sudden antidepressant discontinuation at the beginning of pregnancy due to risks of discontinuation syndrome and relapse (McAllister-Williams et al., 2017). Thus, the goal of present and future research should be to better enable women and healthcare providers to make an educated choice about available treatment options and whether and when to consider discontinuing pharmacological treatment for maternal depression.

Animal studies are valuable in assessing any harmful effects of antidepressant use and understanding the impact of different exposure times, however, animal research also needs to prioritize assessing the therapeutic potential of these medications in animal models of depression to enhance the translational value of this research. Animal models are additionally essential in studying the many effects of discontinuing the antidepressant exposure and withdrawal syndromes, further aiding human research in understanding the consequences of discontinuing antidepressant use and investigating possibilities for remediating the negative effects of withdrawal. From human research, it is apparent that the timing of exposure does play a role in the outcomes of the infant, as such, it stands to reason that the time of discontinuation is equally important.

Taking into consideration the above research and the factors contributing to the variations in results, it is apparent that there is a critical need for a strong collaborative effort between healthcare providers and researchers in both human and animal domains in researching the developmental effects of maternal depression and antidepressant exposure in the perinatal period. Healthcare providers and human researchers can make a concerted effort to gain as much information as possible on each woman's experience of depression, including information on its severity, chronicity, timing of onset, and any environmental factors contributing to her depression. As environmental factors including the lack of a support network at home, low SES, financial insecurity, and a host of other stressors are closely related to the experience of depression and its outcomes, it is necessary to consider all of this information when deciding appropriate treatment options. This increased awareness of the highly individualized and multifaceted experience of depression during and after pregnancy will allow animal researchers to improve existing models of depression to be more reflective of the human experience and gain results with greater translational value. This may include having several animal models of maternal depression, each applicable to a particular manifestation of the depression in humans. Variations in models may include different combinations of the severity, chronicity, and timing of onset of the depression, in order to enable researchers to investigate the effects of antidepressant exposure in different models paralleling the depressive experience in humans and further enhancing the translational value. The intention of this review is to highlight the great progress that has been made thus far, and to inspire collaborative efforts amongst researchers in order to better enable women to make informed decisions on treatment options for depression during the perinatal period.

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Conflicts of interest

None.

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References

Ali, N.S., Mahmud, S., Khan, A., Ali, B.S., 2013. Impact of postpartum anxiety and depression on child's mental development from two peri-urban communities of Karachi, Pakistan: a quasi-experimental study. BMC Psychiatry 13, 274.
Ansorge, M.S., Zhou, M., Lira, Al, Hen, R., Gingrich, J.A., 2004. Early-life blockade of the 5-HT transporter alters emotional behavior in adult mice. Science 306, 879–881.
Apter, G., Devouche, E., Gratier, M., 2011. Perinatal mental health. J. Nerv. Ment. Dis. 199, 575–577.
Azak, S., 2012. Maternal depression and sex differences shape the infants' trajectories of cognitive development. Infant Behav. Dev. 35, 803–814.
Beck, C.T., 1995. The effects of postpartum depression on maternal-infant interaction: a meta-analysis. Nurs. Res. 44, 298–304.
Belik, J., 2008. Fetal and neonatal effects of maternal drug treatment for depression. Semin. Perinatol. 32, 350–354.
Bergman, K., Sarkar, P., Glover, V., O'Connor, T.G., 2010. Maternal prenatal cortisol and infant cognitive development: moderation by infant-mother attachment. Biol. Psychiatry 67, 1026–1032.
Black, M.M., Baqui, A.H., Zaman, K., McNary, S.W., Le, K., Arifeen, S.E., Hamadani, J.D., Parveen, M., Yunus, M., Black, R.E., 2007. Depressive symptoms among rural Bangladeshi mothers: implications for infant development. J. Child Psychol. Psychiatry Allied Discip. 48, 764–772.
Bonnin, A., Levitt, P., 2011. Fetal, maternal, and placental sources of serotonin and new implications for developmental programming of the brain. Neuroscience 197, 1–7.
Bonnin, A., Torii, M., Wang, L., Rakic, P., Levitt, P., 2007. Serotonin modulates the response of embryonic thalamocortical axons to netrin-1. Nat. Neurosci. 10, 588–597.
Boudouresque, F., Guillaume, V., Grino, M., Strbak, V., Chautard, T., Conte-Devolx, B., Oliver, C., 1988. Maturation of the pituitary-adrenal function in rat fetuses. Neuroendocrinology 48, 417–422.
Bourke, C.H., Capello, C.F., Rogers, S.M., Yu, M.L., Boss-Williams, K.A., Weiss, J.M., Stowe, Z.N., Owens, M.J., 2013. Prenatal exposure to escitalopram and/or stress in rats: a prenatal stress model of maternal depression and its treatment. Psychopharmacology 228, 231–241.
Brennan, P.A., Hammen, C., Andersen, M.J., Bor, W., Najman, J.M., Williams, G.M., 2000. Chronicity, severity, and timing of maternal depressive symptoms: relationships with

child outcomes at age 5. Dev. Psychol. 36, 759–766.
Brummelte, S., 2018. Treating maternal depression: considerations for the well-being of the mother and child. Policy Insights Behav. Brain Sci. 5, 110–117.
Brummelte, S., Galea, L.A., 2010. Chronic corticosterone during pregnancy and postpartum affects maternal care, cell proliferation and depressive-like behavior in the dam. Horm. Behav. 58, 769–779.
Brummelte, S., Galea, L.A., 2016. Postpartum depression: etiology, treatment and consequences for maternal care. Horm. Behav. 77, 153–166.
Brummelte, S., Pawluski, J.L., Galea, L.A., 2006. High post-partum levels of corticosterone given to dams influence postnatal hippocampal cell proliferation and behavior of offspring: a model of post-partum stress and possible depression. Horm. Behav. 50, 370–382.
Brummelte, S., Lieblich, S.E., Galea, L.A., 2012. Gestational and postpartum corticosterone exposure to the dam affects behavioral and endocrine outcome of the offspring in a sexually-dimorphic manner. Neuropharmacology 62, 406–418.
Brummelte, S., Galea, L.A., Devlin, A.M., Oberlander, T.F., 2013. Antidepressant use during pregnancy and serotonin transporter genotype (SLC6A4) affect newborn serum reelin levels. Dev. Psychobiol. 55, 518–529.
Brummelte, S., Mc Glanaghy, E., Bonnin, A., Oberlander, T.F., 2016. Developmental changes in serotonin signaling: implications for early brain function, behavior and adaptation. Neuroscience 342 (7), 212–231.
Brummelte, S., Mc Glanaghy, E., Bonnin, A., Oberlander, T.F., 2017. Developmental changes in serotonin signaling: implications for early brain function, behavior and adaptation. Neuroscience 342, 212–231.
Brunton, P.J., Russell, J.A., Douglas, A.J., 2008. Adaptive responses of the maternal hypothalamic-pituitary-adrenal axis during pregnancy and lactation. J. Neuroendocrinol. 20, 764–776.
Buss, C., Davis, E.P., Shahbaba, B., Pruessner, J.C., Head, K., Sandman, C.A., 2012. Maternal cortisol over the course of pregnancy and subsequent child amygdala and hippocampus volumes and affective problems. Proc. Natl. Acad. Sci. U. S. A. 109, E1312–E1319.
Campbell, S.B., Brownell, C.A., Hungerford, A., Spieker, S.I., Mohan, R., Blessing, J.S., 2004. The course of maternal depressive symptoms and maternal sensitivity as predictors of attachment security at 36 months. Dev. Psychopathol. 16, 231–252.
Casper, R.C., Fleisher, B.E., Lee-Ancajas, J.C., Gilles, A., Gaylor, E., DeBattista, A., Hoyme, H.E., 2003. Follow-up of children of depressed mothers exposed or not exposed to antidepressant drugs during pregnancy. J. Pediatr. 142, 402–408.
Chambers, C.D., Johnson, K.A., Dick, L.M., Felix, R.J., Jones, K.L., 1996. Birth outcomes in pregnant women taking fluoxetine. N. Engl. J. Med. 335, 1010–1015.
Chambers, C.D., Hernandez-Diaz, S., Van Marter, L.J., Werler, M.M., Louik, C., Jones, K.L., Mitchell, A.A., 2006. Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. N. Engl. J. Med. 354 (6), 579–587.
Chisolm, M.S., Payne, J.L., 2016. Management of psychotropic drugs during pregnancy. BMJ 532, h5918.
Chisolm, S.S., Schulman, J.M., Fox, L.P., 2015. Adult xanthogranuloma, reticulohistiocytosis, and Rosai-Dorfman disease. Dermatol. Clin. 33, 465–472 (discussion 473).
Chung, T.K., Lau, T.K., Yip, A.S., Chiu, H.F., Lee, D.T., 2001. Antepartum depressive symptomatology is associated with adverse obstetric and neonatal outcomes. Psychosom. Med. 63, 830–834.
Cohen, L.S., Altshuler, L.L., Harlow, B.L., Nonacs, R., Newport, D.J., Viguera, A.C., Suri, R., Burt, V.K., Hendrick, V., Reminick, A.M., Loughead, A., Vitonis, A.F., Stowe, Z.N., 2006. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. JAMA 295, 499–507.
Collier, D.A., Stober, G., Li, T., Heils, A., Catalano, M., Di Bella, D., Arranz, M.J., Murray, R.M., Vallada, H.P., Bengel, D., Muller, C.R., Roberts, G.W., Smeraldi, E., Kirov, G., Sham, P., Lesch, K.P., 1996. A novel functional polymorphism within the promoter of the serotonin transporter gene: possible role in susceptibility to affective disorders. Mol. Psychiatry 1, 453–460.
Croen, L.A., Grether, J.K., Yoshida, C.K., Odouli, R., Hendrick, V., 2011. Antidepressant use during pregnancy and childhood autism spectrum disorders. Arch. Gen. Psychiatry 68, 1104–1112.
Dalla, C., Edgecomb, C., Whetstone, A.S., Shors, T.J., 2008. Females do not express learned helplessness like males do. Neuropsychopharmacology 33, 1559–1569.
Dalla, C., Pitychoutis, P.M., Kokras, N., Papadopoulou-Daifoti, Z., 2010. Sex differences in animal models of depression and antidepressant response. Basic Clin. Pharmacol. Toxicol. 106, 226–233.
Darnaudery, M., Maccari, S., 2008. Epigenetic programming of the stress response in male and female rats by prenatal restraint stress. Brain Res. Rev. 57, 571–585.
Davalos, D.B., Yadon, C.A., Tregellas, H.C., 2012. Untreated prenatal maternal depression and the potential risks to offspring: a review. Arch. Womens Ment. Health 15, 1–14.
Deave, T., Heron, J., Evans, J., Emond, A., 2008. The impact of maternal depression in pregnancy on early child development. BJOG 115, 1043–1051.
Dubber, S., Reck, C., Muller, M., Gawlik, S., 2014. Postpartum bonding: the role of perinatal depression, anxiety and maternal-fetal bonding during pregnancy. Arch. Womens Ment. Health 18 (2), 187–195.
Ehrlich, D.E., Neigh, G.N., Bourke, C.H., Nemeth, C.L., Hazra, R., Ryan, S.J., Rowson, S., Jairam, N., Sholar, C.A., Rainnie, D.G., Stowe, Z.N., Owens, M.J., 2015. Prenatal stress, regardless of concurrent escitalopram treatment, alters behavior and amygdala gene expression of adolescent female rats. Neuropharmacology 97, 251–258.
Einarson, T.R., Einarson, A., 2005. Newer antidepressants in pregnancy and rates of major malformations: a meta-analysis of prospective comparative studies. Pharmacoepidemiol. Drug Saf. 14, 823–827.
Emslie, G., Judge, R., 2000. Tricyclic antidepressants and selective serotonin reuptake inhibitors: use during pregnancy, in children/adolescents and in the elderly. Acta Psychiatr. Scand. Suppl. 403, 26–34.
Erisman, S., Carnes, M., Takahashi, L.K., Lent, S.J., 1990. The effects of stress on plasma ACTH and corticosterone in young and aging pregnant rats and their fetuses. Life Sci. 47, 1527–1533.
Evans, J., Melotti, R., Heron, J., Ramchandani, P., Wiles, N., Murray, L., Stein, A., 2012. The timing of maternal depressive symptoms and child cognitive development: a longitudinal study. J. Child Psychol. Psychiatry Allied Discip. 53, 632–640.
Ewing, G., Tatarchuk, Y., Appleby, D., Schwartz, N., Kim, D., 2015. Placental transfer of antidepressant medications: implications for postnatal adaptation syndrome. Clin. Pharmacokinet. 54, 359–370.
Fava, G.A., Munari, F., Pavan, L., Kellner, R., 1981. Life events and depression. A replication. J. Affect. Disord. 3, 159–165.
Ferber, S.G., 2004. The nature of touch in mothers experiencing maternity blues: the contribution of parity. Early Hum. Dev. 79, 65–75.
Field, T., 1998. Maternal depression effects on infants and early interventions. Prev. Med. 27, 200–203.
Field, T., 2010. Postpartum depression effects on early interactions, parenting, and safety practices: a review. Infant Behav. Dev. 33, 1–6.
Field, T., Diego, M., Hernandez-Reif, M., 2006. Prenatal depression effects on the fetus and newborn: a review. Infant Behav. Dev. 29, 445–455.
Flynn, H.A., Davis, M., Marcus, S.M., Cunningham, R., Blow, F.C., 2004. Rates of maternal depression in pediatric emergency department and relationship to child service utilization. Gen. Hosp. Psychiatry 26, 316–322.
Freeman, M.P., Nolan Jr., P.E., Davis, M.F., Anthony, M., Fried, K., Fankhauser, M., Woosley, R.L., Moreno, F., 2008. Pharmacokinetics of sertraline across pregnancy and postpartum. J. Clin. Psychopharmacol. 28, 646–653.
Fride, E., Dan, Y., Feldon, J., Halevy, G., Weinstock, M., 1986. Effects of prenatal stress on vulnerability to stress in prepubertal and adult rats. Physiol. Behav. 37, 681–687.
Galea, L.A., Wide, J.K., Barr, A.M., 2001. Estradiol alleviates depressive-like symptoms in a novel animal model of post-partum depression. Behav. Brain Res. 122, 1–9.
Gaspar, P., Cases, O., Maroteaux, L., 2003. The developmental role of serotonin: news from mouse molecular genetics. Nat. Rev. Neurosci. 4, 1002–1012.
Gelman, P.L., Flores-Ramos, M., Lopez-Martinez, M., Fuentes, C.C., Grajeda, J.P., 2015. Hypothalamic-pituitary-adrenal axis function during perinatal depression. Neurosci. Bull. 31, 338–350.
Gentile, S., 2015. Prenatal antidepressant exposure and the risk of autism spectrum disorders in children. Are we looking at the fall of Gods? J. Affect. Disord. 182, 132–137.
Glasheen, C., Richardson, G.A., Kim, K.H., Larkby, C.A., Swartz, H.A., Day, N.L., 2013. Exposure to maternal pre- and postnatal depression and anxiety symptoms: risk for major depression, anxiety disorders, and conduct disorder in adolescent offspring. Dev. Psychopathol. 25, 1045–1063.
Glover, M.E., Clinton, S.M., 2016. Of rodents and humans: a comparative review of the neurobehavioral effects of early life SSRI exposure in preclinical and clinical research. Int. J. Dev. Neurosci. 51, 50–72.
Glover, M.E., Pugh, P.C., Jackson, N.L., Cohen, J.L., Fant, A.D., Akil, H., Clinton, S.M., 2015. Early-life exposure to the SSRI paroxetine exacerbates depression-like behavior in anxiety/depression-prone rats. Neuroscience 284, 775–797.
Glynn, L.M., Davis, E.P., Sandman, C.A., 2013. New insights into the role of perinatal HPA-axis dysregulation in postpartum depression. Neuropeptides 47, 363–370.
Gobinath, A.R., Workman, J.L., Chow, C., Lieblich, S.E., Galea, L.A., 2016. Maternal postpartum corticosterone and fluoxetine differentially affect adult male and female offspring on anxiety-like behavior, stress reactivity, and hippocampal neurogenesis. Neuropharmacology 101, 165–178.
Green, A.D., Galea, L.A., 2008. Adult hippocampal cell proliferation is suppressed with estrogen withdrawal after a hormone-simulated pregnancy. Horm. Behav. 54, 203–211.
Green, A.D., Barr, A.M., Galea, L.A., 2009. Role of estradiol withdrawal in 'anhedonic' sucrose consumption: a model of postpartum depression. Physiol. Behav. 97, 259–265.
Gregus, A., Wintink, A.J., Davis, A.C., Kalynchuk, L.E., 2005. Effect of repeated corticosterone injections and restraint stress on anxiety and depression-like behavior in male rats. Behav. Brain Res. 156, 105–114.
Gutierrez-Lobos, K., Scherer, M., Anderer, P., Katschnig, H., 2002. The influence of age on the female/male ratio of treated incidence rates in depression. BMC Psychiatry 2, 3.
Halligan, S.L., Murray, L., Martins, C., Cooper, P.J., 2007. Maternal depression and psychiatric outcomes in adolescent offspring: a 13-year longitudinal study. J. Affect. Disord. 97, 145–154.
Harrington, R.A., Lee, L.C., Crum, R.M., Zimmerman, A.W., Hertz-Picciotto, I., 2014. Prenatal SSRI use and offspring with autism spectrum disorder or developmental delay. Pediatrics 133, e1241–e1248.
Harris, S.S., Maciag, D., Simpson, K.L., Lin, R.C., Paul, I.A., 2012. Dose-dependent effects of neonatal SSRI exposure on adult behavior in the rat. Brain Res. 1429, 52–60.
Hayes, R.M., Wu, P., Shelton, R.C., Cooper, W.O., Dupont, W.D., Mitchel, E., Hartert, T.V., 2012. Maternal antidepressant use and adverse outcomes: a cohort study of 228,876 pregnancies. Am. J. Obstet. Gynecol. 207 (49), e41–e49.
Herba, C.M., Glover, V., Ramchandani, P.G., Rondon, M.B., 2016. Maternal depression and mental health in early childhood: an examination of underlying mechanisms in low-income and middle-income countries. Lancet Psychiatry 3, 983–992.
Herbert, J., 2013. Cortisol and depression: three questions for psychiatry. Psychol. Med. 43, 449–469.
Hoffman, S., Hatch, M.C., 2000. Depressive symptomatology during pregnancy: evidence for an association with decreased fetal growth in pregnancies of lower social class women. Health Psychol. 19, 535–543.
Hubner-Liebermann, B., Hausner, H., Wittmann, M., 2012. Recognizing and treating peripartum depression. Dtsch. Arztebl. Int. 109, 419–424.
Hviid, A., Melbye, M., Pasternak, B., 2013. Use of selective serotonin reuptake inhibitors during pregnancy and risk of autism. N. Engl. J. Med. 369, 2406–2415.

Janusonis, S., Gluncic, V., Rakic, P., 2004. Early serotonergic projections to Cajal-Retzius cells: relevance for cortical development. J. Neurosci. 24, 1652–1659.
Kaplan, P.S., Danko, C.M., Kalinka, C.J., Cejka, A.M., 2012. A developmental decline in the learning-promoting effects of infant-directed speech for infants of mothers with chronically elevated symptoms of depression. Infant Behav. Dev. 35, 369–379.
Kaplan, P.S., Danko, C.M., Cejka, A.M., Everhart, K.D., 2015. Maternal depression and the learning-promoting effects of infant-directed speech: roles of maternal sensitivity, depression diagnosis, and speech acoustic cues. Infant Behav. Dev. 41, 52–63.
Kessler, R.C., 2003. Epidemiology of women and depression. J. Affect. Disord. 74, 5–13.
Klinger, G., Merlob, P., 2008. Selective serotonin reuptake inhibitor induced neonatal abstinence syndrome. Isr. J. Psychiatry Relat. Sci. 45, 107–113.
Kobayashi, T., Matsuyama, T., Takeuchi, M., Ito, S., 2016. Autism spectrum disorder and prenatal exposure to selective serotonin reuptake inhibitors: a systematic review and meta-analysis. Reprod. Toxicol. 65, 170–178.
Koren, G., Nordeng, H., 2012. Antidepressant use during pregnancy: the benefit-risk ratio. Am. J. Obstet. Gynecol. 207, 157–163.
Kott, J.M., Mooney-Leber, S.M., Shoubah, F.A., Brummelte, S., 2016. Effectiveness of different corticosterone administration methods to elevate corticosterone serum levels, induce depressive-like behavior, and affect neurogenesis levels in female rats. Neuroscience 312, 201–214.
Kott, J.M., Mooney-Leber, S.M., Li, J., Brummelte, S., 2018. Elevated stress hormone levels and antidepressant treatment starting before pregnancy affect maternal care and litter characteristics in an animal model of depression. Behav. Brain Res. 348, 101–114.
Koutra, K., Chatzi, L., Bagkeris, M., Vassilaki, M., Bitsios, P., Kogevinas, M., 2013. Antenatal and postnatal maternal mental health as determinants of infant neurodevelopment at 18 months of age in a mother-child cohort (Rhea Study) in Crete, Greece. Soc. Psychiatry Psychiatr. Epidemiol. 48, 1335–1345.
Kulin, N.A., Pastuszak, A., Sage, S.R., Schick-Boschetto, B., Spivey, G., Feldkamp, M., Ormond, K., Matsui, D., Stein-Schechman, A.K., Cook, L., Brochu, J., Rieder, M., Koren, G., 1998. Pregnancy outcome following maternal use of the new selective serotonin reuptake inhibitors: a prospective controlled multicenter study. JAMA 279, 609–610.
Lebel, C., Walton, M., Letourneau, N., Giesbrecht, G.F., Kaplan, B.J., Dewey, D., 2016. Prepartum and postpartum maternal depressive symptoms are related to children's brain structure in preschool. Biol. Psychiatry 80, 859–868.
Leung, B.M., Kaplan, B.J., 2009. Perinatal depression: prevalence, risks, and the nutrition link–a review of the literature. J. Am. Diet. Assoc. 109, 1566–1575.
Levinson-Castiel, R., Merlob, P., Linder, N., Sirota, L., Klinger, G., 2006. Neonatal abstinence syndrome after in utero exposure to selective serotonin reuptake inhibitors in term infants. Arch. Pediatr. Adolesc. Med. 160, 173–176.
Liao, C.C., Lee, L.J., 2011. Neonatal fluoxetine exposure affects the action potential properties and dendritic development in cortical subplate neurons of rats. Toxicol. Lett. 207, 314–321.
Lisboa, S.F., Oliveira, P.E., Costa, L.C., Venancio, E.J., Moreira, E.G., 2007. Behavioral evaluation of male and female mice pups exposed to fluoxetine during pregnancy and lactation. Pharmacology 80, 49–56.
Lloyd, C., 1980. Life events and depressive disorder reviewed. II. Events as precipitating factors. Arch. Gen. Psychiatry 37, 541–548.
Loughhead, A.M., Fisher, A.D., Newport, D.J., Ritchie, J.C., Owens, M.J., DeVane, C.L., Stowe, Z.N., 2006. Antidepressants in amniotic fluid: another route of fetal exposure. Am. J. Psychiatry 163, 145–147.
Lovejoy, M.C., Graczyk, P.A., O'Hare, E., Neuman, G., 2000. Maternal depression and parenting behavior: a meta-analytic review. Clin. Psychol. Rev. 20, 561–592.
Maciag, D., Simpson, K.L., Coppinger, D., Lu, Y., Wang, Y., Lin, R.C., Paul, I.A., 2006. Neonatal antidepressant exposure has lasting effects on behavior and serotonin circuitry. Neuropsychopharmacology 31, 47–57.
Maier, S.E., Chen, W.J., Miller, J.A., West, J.R., 1997. Fetal alcohol exposure and temporal vulnerability regional differences in alcohol-induced microencephaly as a function of the timing of binge-like alcohol exposure during rat brain development. Alcohol. Clin. Exp. Res. 21, 1418–1428.
Malm, H., Artama, M., Gissler, M., Ritvanen, A., 2011. Selective serotonin reuptake inhibitors and risk for major congenital anomalies. Obstet. Gynecol. 118 (1), 111–120.
Man, K.K., Tong, H.H., Wong, L.Y., Chan, E.W., Simonoff, E., Wong, I.C., 2015. Exposure to selective serotonin reuptake inhibitors during pregnancy and risk of autism spectrum disorder in children: a systematic review and meta-analysis of observational studies. Neurosci. Biobehav. Rev. 49, 82–89.
Martins, C., Gaffan, E.A., 2000. Effects of early maternal depression on patterns of infant-mother attachment: a meta-analytic investigation. J. Child Psychol. Psychiatry Allied Discip. 41, 737–746.
McAllister-Williams, R.H., Baldwin, D.S., Cantwell, R., Easter, A., Gilvarry, E., Glover, V., Green, L., Gregoire, A., Howard, L.M., Jones, I., Khalifeh, H., Lingford-Hughes, A., McDonald, E., Micali, N., Pariante, C.M., Peters, L., Roberts, A., Smith, N.C., Taylor, D., Wieck, A., Yates, L.M., Young, A.H., endorsed by the British Association for, P, 2017. British Association for Psychopharmacology consensus guidance on the use of psychotropic medication preconception, in pregnancy and postpartum 2017. J. Psychopharmacol. 31, 519–552.
Meltzer-Brody, S., Thorp, J., 2011. The contribution of psychiatric illness on perinatal outcomes. BJOG 118, 1283–1284.
Miller, L.J.S., A., 1999. Major mental illness during pregnancy. Psychiatry Update 6, 163–168.
Mitchell, A.M., Sakraida, T.J., Kameg, K., 2003. Critical incident stress debriefing: implications for best practice. Disaster Manag. Response 1, 46–51.
Molenaar, N.M., Kamperman, A.M., Boyce, P., Bergink, V., 2018. Guidelines on treatment of perinatal depression with antidepressants: an international review. Aust. N. Z. J. Psychiatry 52, 320–327.
Murray, L., Hipwell, A., Hooper, R., Stein, A., Cooper, P., 1996. The cognitive development of 5-year-old children of postnatally depressed mothers. J. Child Psychol. Psychiatry Allied Discip. 37, 927–935.
Murray, L., Arteche, A., Fearon, P., Halligan, S., Croudace, T., Cooper, P., 2010. The effects of maternal postnatal depression and child sex on academic performance at age 16 years: a developmental approach. J. Child Psychol. Psychiatry Allied Discip. 51, 1150–1159.
Murray, L., Arteche, A., Fearon, P., Halligan, S., Goodyer, I., Cooper, P., 2011. Maternal postnatal depression and the development of depression in offspring up to 16 years of age. J. Am. Acad. Child Adolesc. Psychiatry 50, 460–470.
Naicker, K., Wickham, M., Colman, I., 2012. Timing of first exposure to maternal depression and adolescent emotional disorder in a national Canadian cohort. PLoS One 7, e33422.
Neumann, I.D., 2001. Alterations in behavioral and neuroendocrine stress coping strategies in pregnant, parturient and lactating rats. Prog. Brain Res. 133, 143–152.
Nonacs, R., Cohen, L.S., 2002. Depression during pregnancy: diagnosis and treatment options. J. Clin. Psychiatry 63 (Suppl. 7), 24–30.
Nulman, I., Rovet, J., Stewart, D.E., Wolpin, J., Pace-Asciak, P., Shuhaiber, S., Koren, G., 2002. Child development following exposure to tricyclic antidepressants or fluoxetine throughout fetal life: a prospective, controlled study. Am. J. Psychiatry 159, 1889–1895.
Oberlander, T.F., Misri, S., Fitzgerald, C.E., Kostaras, X., Rurak, D., Riggs, W., 2004. Pharmacologic factors associated with transient neonatal symptoms following prenatal psychotropic medication exposure. J. Clin. Psychiatry 65, 230–237.
Oberlander, T.F., Warburton, W., Misri, S., Aghajanian, J., Hertzman, C., 2006. Neonatal outcomes after prenatal exposure to selective serotonin reuptake inhibitor antidepressants and maternal depression using population-based linked health data. Arch. Gen. Psychiatry 63, 898–906.
Oberlander, T.F., Bonaguro, R.J., Misri, S., Papsdorf, M., Ross, C.J., Simpson, E.M., 2008. Infant serotonin transporter (SLC6A4) promoter genotype is associated with adverse neonatal outcomes after prenatal exposure to serotonin reuptake inhibitor medications. Mol. Psychiatry 13, 65–73.
Oberlander, T.F., Gingrich, J.A., Ansorge, M.S., 2009. Sustained neurobehavioral effects of exposure to SSRI antidepressants during development: molecular to clinical evidence. Clin. Pharmacol. Ther. 86, 672–677.
Olivier, J.D., Blom, T., Arentsen, T., Homberg, J.R., 2011. The age-dependent effects of selective serotonin reuptake inhibitors in humans and rodents: a review. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 35, 1400–1408.
Pargas, R.C.M., Brennan, P.A., Hammen, C., Le Brocque, R., 2010. Resilience to maternal depression in young adulthood. Dev. Psychol. 46, 805–814.
Parker, K.J., Schatzberg, A.F., Lyons, D.M., 2003. Neuroendocrine aspects of hypercortisolism in major depression. Horm. Behav. 43, 60–66.
Paulson, J.F., Dauber, S., Leiferman, J.A., 2006. Individual and combined effects of postpartum depression in mothers and fathers on parenting behavior. Pediatrics 118, 659–668.
Pawluski, J.L., Gemmel, M., 2018. Perinatal SSRI medications and offspring hippocampal plasticity: interaction with maternal stress and sex. Hormones (Athens) 17, 15–24.
Pawluski, J.L., Galea, L.A., Brain, U., Papsdorf, M., Oberlander, T.F., 2009. Neonatal S100B protein levels after prenatal exposure to selective serotonin reuptake inhibitors. Pediatrics 124, e662–e670.
Pawluski, J.L., Lonstein, J.S., Fleming, A.S., 2017. The neurobiology of postpartum anxiety and depression. Trends Neurosci. 40, 106–120.
Petersen, I., Evans, S., Nazareth, I., 2014. Prenatal exposure to selective serotonin reuptake inhibitors and autistic symptoms in young children: another red herring? Br. J. Psychiatry 205, 105–106.
Piteo, A.M., Yelland, L.N., Makrides, M., 2012. Does maternal depression predict developmental outcome in 18 month old infants? Early Hum. Dev. 88, 651–655.
Piwowarska, J., Chimiak, A., Matsumoto, H., Dziklinska, A., Radziwon-Zaleska, M., Szelenberger, W., Pachecka, J., 2012. Serum cortisol concentration in patients with major depression after treatment with fluoxetine. Psychiatry Res. 198, 407–411.
Quarini, C., Pearson, R.M., Stein, A., Ramchandani, P.G., Lewis, G., Evans, J., 2016. Are female children more vulnerable to the long-term effects of maternal depression during pregnancy? J. Affect. Disord. 189, 329–335.
Rahimi, R., Nikfar, S., Abdollahi, M., 2006. Pregnancy outcomes following exposure to serotonin reuptake inhibitors: a meta-analysis of clinical trials. Reprod. Toxicol. 22, 571–575.
Rampono, J., Simmer, K., Ilett, K.F., Hackett, L.P., Doherty, D.A., Elliot, R., Kok, C.H., Coenen, A., Forman, T., 2009. Placental transfer of SSRI and SNRI antidepressants and effects on the neonate. Pharmacopsychiatry 42, 95–100.
Ray, S., Stowe, Z.N., 2014. The use of antidepressant medication in pregnancy. Best Pract. Res. Clin. Obstet. Gynaecol. 28, 71–83.
Rayen, I., van den Hove, D.L., Prickaerts, J., Steinbush, H.W., Pawluski, J.L., 2011. Fluoxetine during development reverses the effects of prenatal stress on depressive-like behavior and hippocampal neurogenesis in adolescence. PLoS ONE 6 (9), 1–9.
Rayen, I., Steinbusch, H.W., Charlier, T.D., Pawluski, J.L., 2013. Developmental fluoxetine exposure and prenatal stress alter sexual differentiation of the brain and reproductive behavior in male rat offspring. Psychoneuroendocrinology 38, 1618–1629.
Rayen, I., Steinbusch, H.W., Charlier, T.D., Pawluski, J.L., 2014. Developmental fluoxetine exposure facilitates sexual behavior in female offspring. Psychopharmacology 231, 123–133.
Riccio, O., Potter, G., Walzer, C., Vallet, P., Szabo, G., Vutskits, L., Kiss, J.Z., Dayer, A.G., 2009. Excess of serotonin affects embryonic interneuron migration through activation of the serotonin receptor 6. Mol. Psychiatry 14, 280–290.
Rifkin-Graboi, A., Bai, J., Chen, H., Hameed, W.B., Sim, L.W., Tint, M.T., Leutscher-Broekman, B., Chong, Y.S., Gluckman, P.D., Fortier, M.V., Meaney, M.J., Qiu, A.,

2013. Prenatal maternal depression associates with microstructure of right amygdala in neonates at birth. Biol. Psychiatry 74, 837–844.
Saatcioglu, O., Tomruk, N.B., 2011. The use of electroconvulsive therapy in pregnancy: a review. Isr. J. Psychiatry Relat. Sci. 48, 6–11.
Sarkar, A., Chachra, P., Vaidya, V.A., 2014. Postnatal fluoxetine-evoked anxiety is prevented by concomitant 5-HT2A/C receptor blockade and mimicked by postnatal 5-HT2A/C receptor stimulation. Biol. Psychiatry 76, 858–868.
Scheyer, K., Urizar Jr., G.G., 2016. Altered stress patterns and increased risk for postpartum depression among low-income pregnant women. Arch. Womens Ment. Health 19, 317–328.
Schule, C., 2007. Neuroendocrinological mechanisms of actions of antidepressant drugs. J. Neuroendocrinol. 19, 213–226.
Seth, S., Lewis, A.J., Galbally, M., 2016. Perinatal maternal depression and cortisol function in pregnancy and the postpartum period: a systematic literature review. BMC Pregnancy Childbirth 16, 124.
Simon, G.E., Cunningham, M.L., Davis, R.L., 2002. Outcomes of prenatal antidepressant exposure. Am. J. Psychiatry 159, 2055–2061.
Smith, M.V., Shao, L., Howell, H., Lin, H., Yonkers, K.A., 2011. Perinatal depression and birth outcomes in a Healthy Start project. Matern. Child Health J. 15, 401–409.
Sockol, L.E., 2015. A systematic review of the efficacy of cognitive behavioral therapy for treating and preventing perinatal depression. J. Affect. Disord. 177, 7–21.
Soga, T., Wong, D.W., Clarke, I.J., Parhar, I.S., 2010. Citalopram (antidepressant) administration causes sexual dysfunction in male mice through RF-amide related peptide in the dorsomedial hypothalamus. Neuropharmacology 59, 77–85.
Stix, G., 2007. A malignant flame. Understanding chronic inflammation, which contributes to heart disease, Alzheimer's and a variety of other ailments, may be a key to unlocking the mysteries of cancer. Sci. Am. 297, 60–67.
Suda, S., Segi-Nishida, E., Newton, S.S., Duman, R.S., 2008. A postpartum model in rat: behavioral and gene expression changes induced by ovarian steroid deprivation. Biol. Psychiatry 64, 311–319.
Sundstrom, E., Kolare, S., Souverbie, F., Samuelsson, E.B., Pschera, H., Lunell, N.O., Seiger, A., 1993. Neurochemical differentiation of human bulbospinal monoaminergic neurons during the first trimester. Brain Res. Dev. Brain Res. 75, 1–12.
Sutter-Dallay, A.L., Murray, L., Dequae-Merchadou, L., Glatigny-Dallay, E., Bourgeois, M.L., Verdoux, H., 2011. A prospective longitudinal study of the impact of early postnatal vs. chronic maternal depressive symptoms on child development. Eur. Psychiatry 26, 484–489.
Tasnif, Y., Morado, J., Hebert, M.F., 2016. Pregnancy-related pharmacokinetic changes. Clin. Pharmacol. Ther. 100, 53–62.
van Kleef, E.S., Gaspar, P., Bonnin, A., 2012. Insights into the complex influence of 5-HT signaling on thalamocortical axonal system development. Eur. J. Neurosci. 35, 1563–1572.
Wang, J.S., Newport, D.J., Stowe, Z.N., Donovan, J.L., Pennell, P.B., DeVane, C.L., 2007. The emerging importance of transporter proteins in the psychopharmacological treatment of the pregnant patient. Drug Metab. Rev. 39, 723–746.
Warburton, W., Hertzman, C., Oberlander, T.F., 2010. A register study of the impact of stopping third trimester selective serotonin reuptake inhibitor exposure on neonatal health. Acta Psychiatr. Scand. 121, 471–479.
Weaver, K.J., Paul, I.A., Lin, R.C., Simpson, K.L., 2010. Neonatal exposure to citalopram selectively alters the expression of the serotonin transporter in the hippocampus: dose-dependent effects. Anat. Rec. (Hoboken) 293, 1920–1932.
Weinstock, M., 2001. Alterations induced by gestational stress in brain morphology and behaviour of the offspring. Prog. Neurobiol. 65, 427–451.
Weinstock, M., 2005. The potential influence of maternal stress hormones on development and mental health of the offspring. Brain Behav. Immun. 19, 296–308.
Weinstock, M., Razin, M., Schorer-Apelbaum, D., Men, D., McCarty, R., 1998. Gender differences in sympathoadrenal activity in rats at rest and in response to footshock stress. Int. J. Dev. Neurosci. 16, 289–295.
Wen, D.J., Poh, J.S., Ni, S.N., Chong, Y.S., Chen, H., Kwek, K., Shek, L.P., Gluckman, P.D., Fortier, M.V., Meaney, M.J., Qiu, A., 2017. Influences of prenatal and postnatal maternal depression on amygdala volume and microstructure in young children. Transl. Psychiatry 7, e1103.
Wisner, K.L., Gelenberg, A.J., Leonard, H., Zarin, D., Frank, E., 1999. Pharmacologic treatment of depression during pregnancy. JAMA 282, 1264–1269.
World_Health_Organization, 2017. Depression: fact sheet. http://www.who.int/mediacentre/factsheets/fs369/en/.
Zucker, I., 2017. Risk mitigation for children exposed to drugs during gestation: a critical role for animal preclinical behavioral testing. Neurosci. Biobehav. Rev. 77, 107–121.
Zucker, I., 2018. Psychoactive drug exposure during breastfeeding: a critical need for preclinical behavioral testing. Psychopharmacology 235, 1335–1346.
Zuckerman, B., Amaro, H., Bauchner, H., Cabral, H., 1989. Depressive symptoms during pregnancy: relationship to poor health behaviors. Am. J. Obstet. Gynecol. 160, 1107–1111.