Perinatal Selective Serotonin Reuptake Inhibitor (SSRI) Effects on Body Weight at Birth and Beyond: A Review of Animal and Human Studies

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Highlights

- Our paper reviews our current understanding of the impact of prenatal SSRI exposure on weight and growth using both human and animal findings.
- Our review extends the previously published review paper by Grzeskowiak and colleagues in Repro Tox in 2012 by including findings beyond infancy, the impact of maternal mood – pre and post natal, and given that the majority our 5HT is in the gastrointestinal (GI) system we speculate that altering 5HT signaling, via SSRI exposure might have an impact on GI function and later weight gain.
- With recent advances in our understanding of the gut-brain axis and the role of 5HT, we raise critical questions about how weight and growth outcomes might be related to SSRI induced changes in the GI microbiome.
- Our paper provides an updated review of the literature (e.g., Leuner et al 2014; Nezvalová-Henriksen et al., 2016), with a particular focus on weight related outcomes beyond birth, developmental aspects of SSRI exposure that might also impact weight and growth, as well as provides detailed suggestions for future research.

Abstract

The long-term impact of selective serotonin reuptake inhibitor (SSRI) antidepressant treatment during pregnancy and postpartum on offspring outcomes is still not clear. Specifically, perinatal SSRI exposure may have long-term consequences for body weight and related health outcomes in the newborn period and beyond. This review focuses on the impact of perinatal SSRI exposure on weight using human and animal findings. The impact of maternal mood is also explored. We propose potential mechanisms for weight changes, including how early alterations in serotonin signaling may have implications for weight via changes in metabolism and motor development. As the majority of serotonin is in the gastrointestinal (GI) system we also speculate that perinatal SSRI exposure might alter the brain-gut relationship, via the microbiome, leading to changes in feeding behavior and weight.

Keywords*:* 5HT, Perinatal Depression, Pregnancy, Body Weight, Stress, Metabolism, Microbiome, Brain-gut axis

1. Introduction

Selective serotonin reuptake inhibitor (SSRI)[1] antidepressants are often used to manage maternal mood disorders during pregnancy and the postpartum period [1]. Approximately 10-20% of women experience depression and/or anxiety during the perinatal period [2] and SSRIs are the most common form of treatment [3, 4]. As SSRIs act to block the serotonin transporter (5HTT), which increases extra cellular serotonin (5HT) levels [5] and they readily cross the brain-blood barrier and the placenta [6], it is conceivable that SSRI-related changes in central 5HT signaling during fetal development [7, 8] could shape early 5HT related growth and development. In humans, prenatal SSRIs have been associated with adverse neonatal outcomes including lower weight at birth, intrauterine growth restriction, preterm delivery, lower APGAR scores, and increased risk for admission to a Special Care Nursery (SCN) or Neonatal Intensive Care Unit (NICU) [9, 10]. Converging evidence with animal studies has demonstrated that perinatal SSRIs are also associated with neurobehavioral abnormalities reflected in altered stress responses, increased anxiety and depression-like behavior, and altered social behaviors in adult offspring [11- 18].

Beyond the possible direct impact on serotonergic signaling associated with developmental exposure to SSRIs, weight and feeding may also be shaped by indirect mechanisms that include altered brain-gut relationship, metabolic consequences, and behavioral disturbances that are increasingly reported following in utero SSRIs exposure such as motor delays [19], attentional disorders [20], cognitive shifts [21], and increased depression during adolescence [22]. Further, given that SSRIs are used in pregnancy to manage maternal mood disorders, which have themselves been associated with changes in weight [23], as well as

[1] This also includes serotonin norepinephrine reuptake inhibitors (SNRIs), in this paper we will refer to SSRI as a grouping that includes both classes of antidepressants

increased risk for a number of developmental disturbances (motor delays, attentional disorders, cognitive delays and increased anxiety/depression), distinguishing the impact of perinatal maternal mood disturbances from the impact of the antidepressant medication exposure remains an urgent challenge. Importantly, given that the majority 5HT is in the gastrointestinal (GI) system, it is conceivable that altering 5HT signaling during development would have an impact on GI function [24, 25]. One prototypic 5HT receptor in particular, 5-HT2C, located in the cerebral cortex, hippocampus, amygdala, and choroid plexus, acts to regulate both food intake and mood [26], raising key questions about the developmental consequences of altering the serotonergic system with perinatal SSRIs and how this might alter the brain-gut relationship leading to changes in feeding behavior and weight.

In this paper, we review relationships between perinatal SSRIs and weight-related outcomes, including evidence from animal studies and human studies[2]. Particular focus will include examining the associations between: (a) perinatal SSRIs, birth weight, and maternal depression, (b) perinatal SSRIs, later weight outcomes, and maternal depression; (c) perinatal SSRIs, altered metabolism, and motor development; and (d) growth, the brain-gut axis development, and the serotonergic system (see Figure 1). It is important to understand how perinatal SSRIs impact offspring weight outcomes as weight itself is an indicator of a number of health outcomes throughout life such as type II diabetes, cardiovascular diseases, asthma, among others [27, 28].

2. Perinatal SSRIs, Birth Weight, and Maternal Depression

There is substantial evidence that prenatal SSRIs shape birth weight in humans and results from recent meta-analyses will be reviewed here, rather than summarizing all empirical

[2] A computerized literature and manual search was conducted to identify relevant English-language studies from first available year to July 2017.

research, allowing us to focus on body weight in offspring later in life (section 3). In brief, meta-analyses have demonstrated that women treated with SSRIs have a higher rate of delivering low birth weight infants than women not exposed to SSRIs [29, 30]. Further, one meta-analysis did find that SSRIs were associated with lower birth weight, with a pooled mean of -74 grams [31] However, when the comparison group was limited to depressed mothers without pharmaceutical treatment, there was no longer an association, suggesting that maternal depression mediated the association between SSRIs and birth weight.

Importantly, a limited number of studies have assessed effects of prenatal SSRIs on birth weight, controlling for gestational age. For example, some studies have identified an increased risk of infants being small for gestational age after SSRI exposure [4, 32]. However, other studies have not found this increased risk [33, 34]. In addition, weight gain during pregnancy has been associated with birth weight [35], yet, to our knowledge, weight gain during pregnancy is not included as a covariate in these studies. In sum, our understanding of the relation between perinatal SSRIs and neonatal birth weight in humans is complicated by a number of issues, including the type of SSRI prescribed, the perinatal timing of exposure, and whether the study accounts for maternal depression, gestational age, and maternal weight gain during pregnancy.

The main limitation of these studies is that any attempt to understand the impact of SSRIs on fetal development must be distinguished between the SSRI treatment itself and the maternal condition that requires the SSRI treatment [36]. A recent systematic review found that prenatal depression was associated with low birth weight [37]. These results are consistent with a meta-analysis that found antenatal depression, which consisted of the applied standards for the categorical measures of depression consistent with the Diagnostic and Statistical manual of Mental Disorders (3rd Edition) or later criteria, was associated with a 49% increased risk of low

birth weight [38]. However, another meta-analysis reported that perinatal depression was associated with a lower gestational age, but not a lower birth weight [39]. One limitation of these two meta-analyses is that they included studies potentially confounded by SSRI medication use, as in these primary studies women taking anti-depressants were not excluded; thus, a more recent meta analysis was conducted to compare neonatal outcomes in pregnant women with depression who did not receive treatment (i.e., pharmacological or nonpharmacological) and women without depression [40]. Results showed that pregnant women with depression who did not receive treatment were at increased risk for lower birth weight compared to women without depression, with a trend toward higher risks with more severe depression. Due to the heterogeneity between the studies included in each of the meta-analyses, it is difficult to know which study should be used to inform both clinical decisions and future research.

To date, a few studies have examined the relation between perinatal SSRIs, depression, and birth weight. Some studies have found an association between prenatal SSRIs and low birth weight, even when controlling for confounding variables including symptoms of maternal depression between groups [41, 4]. As mentioned previously, a recent meta-analysis by Huang et al. demonstrated that women treated with SSRIs during pregnancy have a higher rate of delivering low-birth-weight infants than women not exposed to SSRIs [29]. In addition, moderator analyses revealed studies that used a depressed control group without SSRI exposure yielded larger pooled relative risks (RRs) than studies that used mixed controls, while drug type, study design, and controlling for depression severity were not significant moderators of low birth weight outcomes.

2.1. Animal studies (see Table 1 for details).

Teratogenicity studies with SSRIs were conducted on mice, rats, rabbits, or sheep administered fluoxetine, fluvoxaine, venlafaxine, paroxetine, sertraline, imipramine hydrochloride, and St. John's Wort. Vorhees et al. were one of the first to report that SSRIs reduced birth weight in rats [42]. Similar results have been reported in other studies with rodents [43- 50]. In addition to low birth weight due to prenatal SSRIs, da-Silva et al. also found a sex and treatment effect, females with SSRI exposure had lower birth weight than males and non-exposed females [47].

In contrast to the work of Vorhees and others, Standford and colleagues were one of the first to report that perinatal SSRIs did not affect birth weight in rats [51]. Similar results were found by several other studies with rodents [13, 18, 52- 59), one in sheep [60], and one in rabbits [61]. Importantly, all these studies used a low dose of SSRI that were often more clinically relevant (e.g., fluoxetine < 12 mg/kg/day; for exceptions see 61, 54). In sum, birth weight outcomes are likely influenced by different types of SSRIs, doses, duration of exposure, and animal types.

3. Perinatal SSRIs, Later Weight-related Outcomes, and Maternal Depression (see Table 2 for details)

Beyond the newborn period, there are fewer studies examining the SSRI impact on later weight outcomes. Perinatal SSRIs reduced weight in children ranging in age from 1-to- 71 months [62- 64] and paroxetine exposure through breast milk reduced weight in 3-month-old infants; however, this difference was no longer significant at six and twelve months [65]. Two studies have reported sex differences in weight outcomes during childhood due to prenatal SSRIs. A retrospective cohort study examined the rates of overweight using body mass index (BMI) of 4- and 5-year olds in three groups: mothers who received dispensing for an SSRI (exposed),

mothers with a psychiatric illness but did not have dispensing for an SSRI (untreated), and mothers without psychiatric illness and did not have dispensing for an SSRI (unexposed) [66]. Even after controlling for maternal characteristics (e.g., age, maternal BMI, socioeconomic status, race, fetal growth, etc.), girls of exposed mothers were less likely to be overweight compared to the two other groups, suggesting a possible benefit of prenatal SSRIs. There was no association with overweight in boys. Another study with the same three types of groups and weight outcomes in 7-year-olds also found that girls of untreated mothers were more likely to be overweight than girls of unexposed mothers [67]. Interestingly, boys of exposed mothers were more likely to be overweight compared to the two other groups.

Conversely, other studies investigating perinatal SSRIs failed to find a difference in children ranging in age from 1- to -86 months [68- 77]. It is worth noting that these studies were not specifically designed to assess the impact of SSRIs on postnatal growth and no statistical adjustments were made for relevant maternal and/ or infant characteristics [36; for exception see 77]. Thus, additional research is necessary to determine whether there are long-term effects of perinatal SSRIs on body weight and growth.

With regard to depression and later weight outcomes, there have been no significant relations between the influence of postpartum depressive symptoms and young children's growth two to four years from birth [78 - 81]. However, a study on prenatal stress such as maternal bereavement immediately prior to pregnancy found an observed increased risk of overweight from 10 years of age, suggesting the necessity for long-term follow-up when considering weight outcomes [82]. Taken together, the results from these studies suggest the importance of future research to examine the influence of SSRIs, depression, and weight- both at birth and later developmental periods (e.g., childhood, adolescence, adulthood).

3.1. Animal studies

There is a growing body of research examining perinatal SSRI effects in animals beyond birth and results are mixed (see Table 1). For simplicity, we will categorize the rat lifespan with pre-weaning at postnatal day (P) P0- P21, juvenile at P21- P50, and adult at P50 and beyond [83]. Studies have found that SSRIs during gestation reduced weight at pre-weaning [43, 45, 46, 84], at pre-weaning into the juvenile stage [44, 58], at the juvenile stage [85], or at adulthood [48, 86]. Other studies have found mixed results, with reduced weight: at birth, but not at pre-weaning and during adulthood [42]; at pre-weaning, but not at the juvenile stage [49]; and at pre-weaning, but no difference at the juvenile stage and adulthood [42, 47]. Perinatal SSRIs studies have also revealed sex differences at adulthood with reduced weight in males compared to control males (no difference in females; 44; 45, 85] and another study found reduced weights at different time points for males and female rodents (see Table 1 for details) [87].

Conversely, two studies found that perinatal SSRIs increased weight at the juvenile stage [84] and adulthood [52], while other studies have failed to find a difference in weight in offspring at pre-weaning [86], at adulthood [84], from pre-weaning into the juvenile stage [13, 18, 54, 56], and from pre-weaning into adulthood [16, 52, 59, 88]. In terms of other types of animal studies, gestational SSRIs in sheep reduced weight of lambs at P2 and P3, but with no difference at P5 [60]. In guinea pigs, perinatal SSRIs did not have an effect on weight at P14 and P16 [89].

Other work has administered SSRIs after birth, prior to weaning. This early postnatal exposure to SSRIs reduced weight at the pre-weaning and juvenile stage [90- 92] and at adulthood in offspring [93]. Another study with postnatal SSRIs reduced weight at the pre-

weaning but not at adulthood (5-7 months); however, upon necropsy, both SSRI exposed female (11-12 months) and male mice (6-9 months) had reduced weight than controls [94].

Although limited, the sex-specific differences of perinatal SSRIs and offspring weight reported by some studies [44, 45, 47, 85, 87, 95, 96] expand literature in serotonin knockout rats (5-HTT) which shows that disruption of 5-HTT homeostasis during critical periods of fetal development results in sex-specific alterations in body weight [13, 97- 101]. For example, 5-HTT knockout female rats, who have high levels of serotonin throughout life, appear to be protected against late-onset obesity [100, 101] and reduced weight, but higher abdominal fat [102].

Maternal stress and depression can also affect weight outcomes in offspring and should be considered in animal models investigating perinatal SSRI effects on development. Inducing aspects of maternal depression can be done in rodent models by repeated stressing of the dam prenatally [103, 104] or by administering high levels of corticosterone (the primary glucocorticoid in rats) to dams during the ante- and/or post-partum periods [105, 106]. Repeated stressing of dams reduced birth weight in rat offspring, particularly in male offspring [107] and high levels of corticosterone to the dam during the postpartum period can reduce weight, particularly in male offspring [106]. Interestingly, postnatal SSRIs to offspring, regardless of exposure to prenatal maternal stress, reduced weight at the juvenile stage [92], but there was no difference at adulthood [17, 108]. Gemmel et al. report reduced weight in juvenile female offspring perinatally exposed to SSRIs, regardless of maternal stress [95]. One study showed that postnatal SSRIs in combination with administration of corticosterone postpartum to the dams decreased weight in male, but not female, rat offspring at adulthood [96]. Taken together, animal models are pointing to an effect of perinatal SSRIs on changes in weight. Discrepancies between

these findings may be due to treatment methods, duration of the treatment, stress paradigm, dose of SSRI, and species studied. Thus, future research is needed to examine how both pre- and post-natal SSRIs alters sex-specific weight outcomes in animal models, specifically looking at additional measures such as abdominal fat, diet preference (carbohydrates versus lipids), and metabolism.

4. Perinatal SSRIs, Altered Metabolism, and Motor Development

Convergence of key findings offers compelling reasons for examining associations between perinatal SSRIs and weight-related outcomes in offspring. Serotonin (5-HT) is directly involved in the regulation of eating behavior [109] and reductions in 5-HT function have been associated with negative mood, an increased urge for binge eating [110], and increased consumption of high-fat sweet foods [111, 112]. Conversely, increasing 5-HT through pharmacological intervention has been used for obesity treatment [113], but this SSRI intervention has been associated with increased risk of depression, suicide, and cardiac complication. In addition to 5HT in the brain and peripheral nervous system affecting mood and feeding behavior, the majority of 5HT circulates in the blood, often termed “peripheral 5HT”. Peripheral 5HT may be lower in individuals who are obese and such individuals may have less brown adipose tissue (i.e., brown fat), a critical component to burning calories [114]. In mice, the absence or inhibited tryptophan hydroxylase (Tph1), a critical enzymatic step in the production of 5HT, brown fat becomes more active, possibly suggesting that lower 5HT may play a critical role in reversing or even preventing obesity [115]. However, these findings reflect the role of 5HT in the mature organism and the key question is how this differs from changes in 5HT signaling during critical early periods of development.

4.1. Motor Development.

Perinatal SSRIs has been reported to alter motor development which is perhaps not surprising given serotonin's role in central motor control [116] and may have later consequences for physical activity and weight outcomes. SSRIs have been related to significantly poorer motor quality compared to infants without exposure [30, 117- 121], even when controlling for pre- and postnatal depression, smoking, and alcohol use [19]. However, one study found no evidence of any effect of prenatal depression on infant motor development at 8-9 months [122].

In terms of later child development outcomes, children with SSRI exposure have shown a developmental delay in gross motor function at 6 months of age, especially for boys [123], lower motor quality from 6-40 months of age [68], and elevated odds of failing a psychomotor developmental test from 7-10 months of age [124]. Another study with children between 18-35 months observed that children with antidepressant exposure had lower fine motor scores compared to children without exposure; however, due to lack of power this difference was not significant [125] and similar results were found when the same sample was 4 years olds [126]. However, further research is warranted as the authors were unable to conduct more complex analyses (e.g., sex differences) due to the small sample size. Prolonged prenatal SSRIs were also associated with a decrease in fine and gross motor skills at 3 years of age [127] (for exceptions see 128,) and fine motor control at 4-5 years of age, even compared a second control group that had mothers with a major depressive disorder [129]. In sum, we currently know little about the trajectory of gross motor development in children with SSRI exposure, and these results have important implications for weight because motor proficiency is associated with physical activity [130].

Animal models converge with evidence from human studies as early exposure to SSRIs results in delayed motor abilities in pre-weaning offspring and juvenile offspring [131- 133].

Another study found SSRI exposure caused a transient delay in motor development and decreased activity during the preweaning period, but increased retention time on a rotating rod during the juvenile period [43]. Further, SSRI exposure was associated with decreased activity in juvenile [134] (for review see 135) and increased activity adult offspring [14]. In line with this, 5-HTT knockout rats, which exhibit high levels of 5HT, also show reduced motor activity late in adulthood, but this effect is only evident in male and not female rats [10].

5. Growth, Brain-Gut Axis Development, and the Serotonergic System

The combination of 5-HT and the expression of its receptors in embryonic development has led to the hypothesis that this neurotransmitter may act as a growth regulator in selected developmental events [136]. An example of a 5-HT receptor is 5-HT2C, located in the cerebral cortext, hippocampus, amygdala, and choroid plexus, which regulates food intake, mood, and cerebrospinal fluid [26]. 5-HT regulates the development of many targets throughout the body; for example, a lack of 5-HT in the central nervous system (CNS) in knockout mice lead to a reduction of body growth [137]. This is especially critical as the neonatal brain is more sensitive to toxins than the adult brain [138], suggesting that the introduction of SSRIs during pregnancy may have implications for both growth and the development of the brain-gut axis.

This brain-gut axis consists of bi-directional communication with serotonin (5-HT) as an important signaling molecule in both the CNS and the enteric nervous system (ENS) [26, 139-141]. Given that the gut produces 95% of the body's 5-HT and many serotonin receptors are located in both the brain and the gastrointestinal tract (GI) [26], it is not surprising that changes in 5HT signaling due to SSRIs would lead to altered GI function. A critical component to understanding the possible impact of developmental exposure to SSRIs on growth and metabolism is examining the role of serotonin between the brain and the gut. Recent research has

shown that exposure to SSRIs or tricyclic antidepressants (TCAs) during pregnancy may be associated with atypical development of the ENS [142], and one study found that children exposed to SSRIs in the second and third trimester or to TCAs in the first trimester led to a significant increase in laxative use during the first five years of life compared with non-exposed children, suggesting that both SSRI and TCA exposure influences the development of enteric serotonergic neurons and the brain-gut axis [143].

The term microbiota refers to the consortium of different microorganisms within a microbial community, and the microbiome refers to collective microorganisms and their genomes. Recent evidence indicates that the gut microbiome plays critical roles in shaping early stress and immune responses, neurodevelopment and behavior [26, 144, 145] via the bidirectional communication pathways that comprise the brain-gut axis linking the central nervous system with the GI tract. Gut microbes produce many neurotransmitters [146] also found in the brain whilst also indirectly regulating their production [147] thereby potentially shaping brain development and mental health. These relationships are reflected in associations between the microbiome and stress-related disorders, such as anxiety/depression, risk for neurodevelopmental disorders, and chronic pain.

As mentioned above, it has been hypothesized that 5-HT and the expression of its receptors in the embryo act as a growth regulator in selected developmental events [136]. In support of this, serotonin deficient animal models using serotonin depletion methods show that decreased serotonin levels lead to reduced brain and body growth and recent findings from knock out mouse models which lack of 5-HT in the CNS, show a reduction of body growth [137]. Furthermore, animal models also show that differences in birth weight may alone result in long-lasting differences in central 5-HT, with increased birth weight being associated with increased

levels of 5-HT transporter in the frontal cortex [148]. Taken together, this suggests that disruption of 5-HT production in the gut and brain, with early exposure to SSRIs at a time when the neonate is very sensitive to toxins [138], may produce long term differences in growth, metabolism, and mood via changes in 5-HT production and related physiology of the brain-gut axis. However, to date, we lack evidence that supports links that support the early SSRIs manipulates the development of the brain-gut network.

Recent research has shown that bacteria in our gut play a key role in regulating the brain-gut axis, critical to the regulation of weight, growth, mood, and behavior. The gut bacteria (microbiota) play a role in the regulation of body weight and metabolism as several studies in humans have found a causal link between the composition of microbiota and obesity [149]. Early life stressors, like mother's depressed mood during pregnancy, decrease the richness and diversity of gut bacteria (microbiome) and 5HT signaling bacteria in particular [146]. Moreover, emerging evidence suggests that psychotropic medications such as SSRIs and antipsychotics, such as olanzapine, may have an impact on the microbiome. Recently, SSRIs have been reported to increase production of indole metabolites in the microbiota of depressed SRI-treated adults, possibly reflecting altered tryptophanase-producing bacteria diversity and increased gut 5HT signaling [150]. Similarly, treatment with the antipsychotic olanzapine, which may simultaneously improve depressive symptoms, also appears to shift the microbiota towards a weight gain microbiota profile [151]. Both findings raise intriguing possibilities about the impact of serotonergic medications on the microbiome and possible use of the gut microbiota as treatments for 5HT-related disorders (e.g. depression) that could directly and indirectly have an impact on weight via the microbiome. Whether the gut microbiome acts as a link between early life stress (and SSRI exposure), brain development, and behavior remains a pressing question.

6. Future Directions for Research and Conclusion

Why should we be concerned about offspring body weight? Early life weight is a key indicator of subsequent health outcomes [27, 28] and identifying factors that shape weight patterns across the early life span offer modifiable factors that could lead to early intervention and effective disease prevention. Whether developmental exposure to SSRIs program processes that reflect that disruption of 5-HTT homeostasis during critical periods of fetal development results in alterations in body weight remains to be conclusively demonstrated in humans. In brief, studies with humans found that perinatal SSRIs were associated with lower birth weight, though there is some evidence that this association may be confounded by maternal depression illness severity or attenuated by other factors such as gestation age and weight gain. Research on later weight outcomes in children are inconsistent and inconclusive; however, studies do suggest sex-specific differences in response to perinatal SSRIs or maternal depressive symptoms. Studies with animals show that perinatal SSRI exposure result in lower birth weight and generally lower weight during the juvenile period; however, longer weight-related outcomes are mixed, particularly in adulthood and also show sex-specific effects.

There are many reasons why there is limited research on the effects of perinatal SSRIs and offspring weight related outcomes, especially in humans. For example, identifying a sufficiently large enough sample with adequate data on perinatal SSRI exposure, pregnancy/ delivery outcomes, and long term follow up is quite challenging. However, improvements in study design are possible at minimal added cost. For example, as mentioned above, controlling for maternal depression is important to separate the observed effect of the SSRI from the disease. This can be undertaken by administering a depression symptom scale, such as the Hamilton Depression Scale (HAM-D) [152] or the Edinburgh Postnatal Depression Scale [153] for cohort

studies or using psychiatric diagnosis codes for studies using population health data. In addition, there is evidence that smoking during pregnancy is associated with birth weight [154] and women with depression may be more likely to smoke during pregnancy [155- 157]. Thus, maternal smoking data, which can also be collected at minimal cost, should be considered in analyses examining the relationship between SSRIs, depression, and birth weight.

Another challenge to doing research in this area is the issue of clarifying clinically significant differences from statistically significant differences [10]. Larger sample sizes will have no difficulty establishing statistically significant differences, and outcomes that are of minimal consequences (e.g., reduction in mean birth weight of 40 grams), could hardly be considered clinically significant. Thus, in future, researchers need to interpret their results from both a statistical and clinical context to better inform women using SSRI treatment during pregnancy and/ or during postpartum.

In sum, differentiating the contribution of perinatal SSRIs and maternal depression on weight-related outcomes in children is challenging because: (a) researchers tend to study the effects of one exposure without controlling for the other, (b) SSRI exposure occurs at different times and dosages, and (c) depression is associated with multiple confounders (e.g., smoking, substance abuse, overweight/ obesity). As perinatal SSRIs and perinatal depression have been linked to lower birth weight in both animal and human studies, and the long-term weight-related outcomes of children beyond two to four years of age is not well known, an important implication of these findings is that pregnant women should be universally screened for depression and be given treatment options before childbirth. Untreated antenatal depression has serious consequences for both infant and child development, thus, women, and their obstetrical

team, will need to weigh the benefits and cost of treating their depression with SSRIs, especially in situations when psychotherapy is not desired or available.

Conflict of interest statement.

The authors declare that they have no financial relationships with any persons or organizations that could bias the work described in the manuscript. They have no conflicts of interest.

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Figure 1. Schema for Selective Serotonin Reuptake Inhibitor Exposure and Later Weight Outcomes
Model

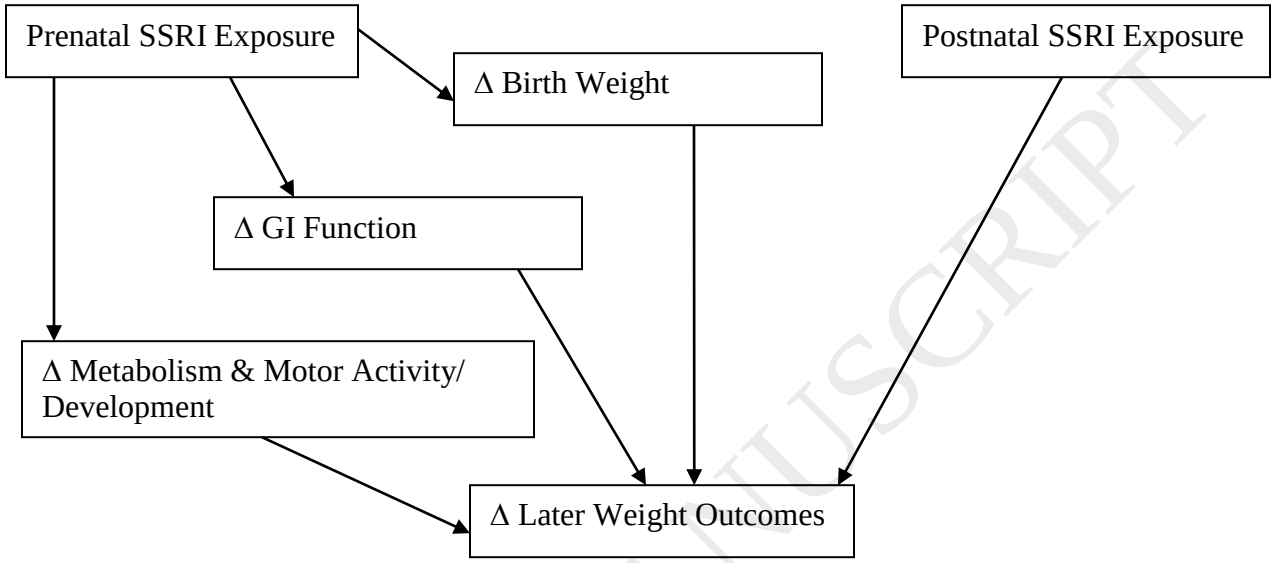

Figure 1. SSRI = selective serotonin reuptake inhibitor; GI = gastrointestinal.

Table 1

Summary of laboratory animal research investigating how perinatal SSRI affects offspring weight.

Age weight Investigated	Sex	Species	SSRI dose/day	SSRI Admin	Results	SSRI Admin Type & Notes	Reference
P0-95	F	Wistar rats	FLX 5mg/kg	G0-P21	FLX did not affect weight at P0, P7, P14, P21, & P90-95	Oral gavage to dams	53
P0-79	F/M	Sprague-Dawley rats	FLX 1mg/kg FLX 5mg/kg FLX 12mg/kg	G7-20	FLX reduced weight at P0; 12mg group had lowest weight; FLX did not affect weight at P7 and P79	Drinking water to dams	42
P0-56	F/M	Wistar rats	FLX 8mg/kg FLX 12mg/kg	G6-20	FLX reduced weight at P0; 12mg groups had lowest weight; FLX reduced weight gain between P0-21 (preweaning) in 12mg groups; FLX did not affect weight gain between P21-56 (post weaning)	Drinking water to dams	43
P0-110	F/M	Wistar rats	FLX 8mg/kg FLX 16mg/kg VEN 40mg/kg VEN 80mg/kg	G15-20	FLX and VEN reduced weight at P0; FLX 8mg and FLX16mg groups had lowest weight at P0; F offspring had lower weight than M and control animals at P0; FLX and VEN did not affect weight at P25 and P110	Oral gavage to dams	47
P0-70	F/M	Sprague-Dawley rats	FLX 10mg/kg	G13-20	FLX reduced weight at P0-28; FLX reduced weight in M rats compared to control M rats at P70	s.c. injections to dams	44
P0-182	F/M	Wistar rats	FLX 10mg/kg	14PB-P21	FLX did not affect weight gain at P0-182; FLX increased weight for F rats at P182	Food cubes to dams	52
P0-21	F/M	Wistar rats	FLX 0.4mg/kg FLX 1.7mg/kg FLX 17mg/kg	G7-P21	FLX reduced weight at P0; FLX 17mg/kg had lowest weight at P0; FLX did not affect weight at P21	Oral gavage to dams	49
P7-63	F/M	Wistar rats	FLX 12mg/kg	G11-P1	FLX reduced weight at P7; FLX increased weight at P14, P21,	Oral injection to dams	84

					and P35; FLX did not affect weight at P42-63		
P0-30	F/M	Wistar rats	FLX 10mg/kg	G0-P21	FLX did not affect weight at P0; FLX reduced weight at P3-30	Saline solution to dams	58
G20	F/M	Fischer rats	FLX 2mg/kg FLX 5mg/kg FLX 12.5mg/kg	G6-15	FLX did not affect weight at G20 in fetuses	Oral gavage to dams	61
G28	F/M	Dutch Belted rabbits	FLX 2.5mg/kg FLX 7.5mg/kg FLX 15mg/kg	G6-16	FLX did not affect weight at G28 in fetuses	Oral gavage to dams	61
P0	F/M	Sprague-Dawley rats	FLX 5.62mg/kg	G7-P0	FLX did not affect weight at P0	Oral gavage to dams	51
P0-100	M	Wistar rats	FLX 7.5mg/kg SJW 100mg/kg	G0-P21	FLX did not affect weight at P0, P21, and P100; SJW did not affect weight at P0, P21, and P100	Oral gavage to dams	59
P14-63	F/M	Hartley guinea pigs	FLX 7mg/kg	G1-P0	FLX did not affect weight at P14 and P63	Osmotic pump to pregnant sows	89
P1-120	F/M	Wistar rats	FLX 5mg/kg FLX 10mg/kg	G13-20	FLX reduced weight at P1; 10mg group had the lowest weight; FLX reduced weight in M rats at P60, P80, and P120	s.c. injections to dams	45
~G118- 132-P9	F/M	Dorset/ Suffolk sheep	FLX 98.5µg/kg	8 days[a]	FLX did not affect weight on P0; FLX reduced weight gain on P2 and P3; FLX did not affect weight gain on P5	i.v. infusion to pregnant ewe	60
P0-70	F/M	Swiss mice	FLX 7.5mg/kg	G0-P22	FLX did not affect weight on P0; FLX did not affect weight gain on P8, P15, and P22	Oral gavage to dams	13
P140	F/M	C57Bl/6 mice	FLX 25mg/kg	G14-P12	FLX reduced weight on P140	Drinking water to dams	48
P3-20	F/M	C57Bl/6-JIco mice	FLX 0.3mg/kg FLX 0.6mg/kg FLX 0.8mg/kg FLM	G8-G18	FLX and FLM did not effect weight at P3, P20, and P90; Body weight for F and M mice were not significantly different at P3, P18,	Intraperitoneal injection to dams	16

			4.2mg/kg		and P20		
G21	F/M	Sprague-Dawley rats	FLX 10mg/kg	G11-G21	FLX did not affect weight at G21	Oral gavage to dams	55
P2-120	F/M	Wistar rats	FLX 10mg/kg	G14-G28	FLX did not affect weight at P2; FLX reduced weight at P60	Osmotic pump to dams	86
P0-75	F/M	Wistar rats	5mg/kg	G0-P21	FLX did not affect weight at P0, P7, P14, P21	Oral gavage to dams	56
P1-120	F/M	Swiss mice	FLX 7.5mg/kg	G0-P21	FLX did not affect weight at P1 and P120	Oral gavage to dams	88
P28-132	F/M	Wild mice	PAR 22.5mg/kg	8PB-P28	PAR reduced weight at P28 (when mice were weaned); PAR reduced weight in M mice at ~P100, no difference in F mice at ~P132	Rodent chow to dams	85
P0-5	F/M	CD-1 mice	PAR 30mg/kg	14PB-G17	PAR reduced weight at P0-5, body weights not reported for P6-90	Food bars to dams	46
P3-120	F/M	CD-1 mice	PAR 30mg/kg	14PB-P1	PAR reduced weight for F mice at P3, P45, P75 and P95; PAR reduced weight for M mice at P1, P3, and P5; PAR reduced weight for second generation M mice at P1 and P3	Food bars to dams	87
P0-21	F/M	Wistar rats	VEN 7.5mg/kg VEN 37.5mg/kg VEN 70mg/kg	G15-20	VEN did not affect weight at P0-21	Drinking water to dams	54
P0	F/M	Fischer rats	PAR 10mg/kg	G14-21	PAR reduced weight at P0	Oral administration to dams	50
P21	F/M	bHR/bLR Sprague-Dawley rats	PAR 10mg/kg	7PB-P21	PAR did not affect weight at P0	Drinking water to dams	57
P0-21	F/M	Sprague-Dawley rats	FLX 5mg/kg	P1-21	FLX did not affect weight at P0-21	Minipump to dams	18
P79	M	Sprague-Dawley rats	FLX 10mg/kg FLX 10mg/kg +CORT CORT	P2-23	FLX + CORT reduced weight compared to other groups in adult M rats	s.c. injection to dams	96
P0-90	F/M	Sprague-Dawley rats	Prenatal Stress +	P1-21	FLX reduced weight in adolescent	Osmotic minipump to	17, 92, 108

			FLX 5mg/kg Non-stress + FLX 5mg/kg Prenatal stress control Non-stress Control		offspring regardless of prenatal stress; FLX did not affect weight at adulthood	dams	
Admin to offspring instead of dams							
P21-110	F/M M	C57Bl/6 mice	FLX 10mg/kg; FLX 10mg/kg	P4-P21; P90-110	FLX reduced weight on P21 and P90; FLX restores weight during adulthood for M rats	Intraperitoneally to offspring; Some males administered FLX during adulthood	93
P6-14	F/M	C57BL/6 mice	SER 5mg/kg	P1-14	SER reduced weight gain at P6-14; SER did not affect weight ~P140-196 (5-7 months); SER reduced weight at necropsy for F mice (11-12 months); SER reduced weight at necropsy for M mice (6-9 months)	Intraperitoneal injection to offspring	94
P4-21	M	Wistar rats	SER 5mg/kg SER 10mg/kg SER 15mg/kg	P1-21	SER 10mg group reduced weight at P6-21; SER 15mg group reduced weight at P4-21	Administered to offspring	91
P1-21	M	Wistar rats	CIT 5mg/kg CIT 10mg/kg	P1-21	CIT 5mg group reduced weight at P14-21; CIT 10mg group reduced weight at P7-21	Administered to offspring	90

Note. [a]Timing not specified. P = postnatal day; G = gestational day; M = male; F = female; FLX = Fluoxetin; FXM = Fluvoxamine; VEN = Venlafaxine; PAR = Paroxetine; SER = Sertraline; IH= Imipramine hydrochloride; SJW = St. John's Wort; CIT = Citalopram; s.c. = subcutaneous; PB = prior to breeding; bHR = Bred high responders to novelty; bLR = Bred low responders to novelty; CORT = corticosterone, model of stress/ depression.

Table 2

Summary of human research investigating how perinatal SSRI affects offspring weight beyond birth.

# of Pt.	Group	Design	Age Investigated	Results	Notes	GA	Reference
80 55 84	TA FLX Control	Prospective	16- 86 months	No Diff in weight (percentile); TA = 58, FLX = 54, Control = 51, p = .32	*ND	No Diff	76
46 40 36	TA FLX D	Prospective	15- 71 months	FLX reduced weight (percentile) compared to TA; TA = 63.5, FLX = 46.9, D = 55.4, p = not reported	*ND	No Diff	62
62 62 54 62	VEN SSRI D Control	Prospective	3-6 years	No difference in weight (percentile); VEN = 61.3, SSRI = 63.9, D = 61.3, Control = 59.0, p = not reported	*ND	No Diff	74
45 45	SSRI Control (Siblings)	Prospective	3- 6 years	No difference in weight (percentile); SSRI = 57.20, Control = 60.27, p = .54	*ND	No Diff	75
51 63	FLX Control	Cohort	1- 12 months	No difference in weight gain, p = .51, exact weights not reported, abstract results	*ND	Not Reported	73
26 38	FLX during pregnancy + BF FLX during pregnancy only	Retrospective	1- 6 months	FLX during pregnancy and BF reduced weight, exact weights not reported, analysis controlled for maternal and infant characteristics		No Diff	63
10 10	CIT Control	Cohort	12 months	No difference in weight (grams), CIT = 10560, Control = 9810, p = .14	*ND	No Diff	70
11 10	FLX Control	Cohort	12 months	No difference in weight (grams), FLX = 9760, Control = 9830, p = .89	*ND	No Diff	71
78	AD + BF	Cohort	6 months	No difference in weight (kg) compared to normative population sample (7.3), AD = 7.26, for girls p = .79, for boys p = .24	*ND	Not reported	72
31 13	SSRI D	Cohort	6- 40 months	No difference in weight (percentile); SSRI = 48.4, D = 46.7, p = .86	*ND	No Diff	68
14 18 23	SSRI 1st Trimester SSRI 2nd / 3rd Trimester SSRI 1st/ 2nd/ 3rd Trimester	Cohort	14 months	No difference in weight (percentile), 1st = 45.9, 2nd/ 3rd = 45.1, 1st/ 2nd/ 3rd = 49.2, p = .89	*ND	No Diff	69

27 27 19	PAR for 2 weeks while BF Control + BF Control + No BF	Prospective	3, 6, 12 months	PAR reduced weight (grams) at 3 months (PAR = 5498, Control + BF = 6030, Control + No BF = 5396, p = .01), no difference in weight at 6 months (PAR = 7334, Control + BF = 7608, Control + No BF = 7209, p = .19) and 12 months (PAR = 9351, Control + BF = 9543, Control + No BF = 9230, p = .57), analysis controlled for maternal and infant characteristics		No Diff	65
27 27	AD Control	Prospective	1 month	AD reduced weight (grams) at 1 month, AD = 4032.05, Control = 4582.95, p < .01, Cohen's d = .88	*ND	Reduced gestational age	64
71 204 6285	SSRI UPI Control	Retrospective	4- 5 years	SSRI group was less likely to be overweight (percentile) compared to UPI group control group in girls, SSRI = 15.2, UPI = 26.4, Control = 28.4; No differences in overweight risk in boys, SSRI = 26.3, UPI = 27.6, Control = 28.2; analysis controlled for maternal and infant characteristics, p values not reported		No Diff	66
127 490 35568	SSRI UPI Control	Retrospective	7 years	SSRI exposure increased risk for overweight (percentile) compared to UPI group and control group in males only when analysis controlled for maternal and infant characteristics; UPI group at increased risk to be overweight (percentile) and have an elevated BMI z-score than control group in females only when analysis controlled for maternal and infant characteristics, exact percentiles and z scores reported in study		No Diff	67
46 31 97	SSRI D Control	Prospective	2, 12, 26, and 52 weeks	No Diff, p = .20, exact weights reported in figure so not easily reported, when analysis controlled for maternal and infant characteristics, p = .87		SSRI reduced gestation	77

Note. # of Pt. = number of participants; GA = gestational age; TA = Tricyclic antidepressants; FLX = Fluoxetine; Diff = difference; D = Depression without treatment of SSRI; SSRI = selective serotonin reuptake inhibitor; VEN = Venlafaxine; *ND = Study not designed to assess impact of SSRIs on growth, no adjustments made for maternal or infant characteristics, weight only reported as descriptive statistics; BF = breastfeeding; CIT = Citalopram; AD = Antidepressant (SSRI, serotonin and noradrenaline reuptake inhibitors or noradrenergic and specific serotonergic antidepressants); PAR = Paroxetine; UPI- Untreated psychiatric illness.