Citizen Petition

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Commissioner, Food and Drug Administration
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WO 2200
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Food and Drug Administration
Department of Health and Human Services
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RE: FDA Petition to Add a Boxed Warning to SSRI Antidepressants Regarding Risks of Pregnancy Complications and Alteration of Fetal Brain Development.

Dear Commissioner Makary,

We are submitting this petition under the Federal Food, Drug, and Cosmetic Act (FDCA) and under Food and Drug Administration (FDA) regulations at 21 C.F.R. 10.30 to request that the Commissioner of Food and Drugs immediately add a boxed warning to Selective Serotonin Reuptake Inhibitor antidepressants (SSRIs) regarding their increased risks of pregnancy complications and alteration of embryofetal brain development (for simplicity, the term "fetal" will be used in the remainder of the petition rather than "embryofetal.")

1) There is widespread scientific agreement that serotonin plays a crucial role in pregnancy, in overall fetal development, and specifically in fetal brain development (Berard, 2019; Bonnin, 2011; Cote, 2007; Daubert, 2010.)

2) The SSRIs are known to disrupt the serotonin system (Berard, 2019; Wong, 2005).

Therefore, given the two points above, (and the fact that SSRIs freely cross the placenta [Rampono, 2009]), it must then follow that SSRIs almost certainly impact the pregnancy and alter fetal brain development. Common sense leads to that conclusion. That conclusion is now also supported by basic science research, numerous animal studies, and human data.

There is now more than sufficient scientific evidence to support labeling changes warning of the effects that the SSRIs have on pregnancy and the fetus – especially the developing fetal brain. Adding a boxed warning will be in the best interest of the public because it will properly inform women of childbearing age, pregnant women, providers, and the public. It will allow patients to weigh this effect when considering the risks, benefits, and alternatives to these medications.

The Purpose of this Citizen Petition

This petition is meant to encourage the FDA to more effectively warn patients and the public about the risks of SSRI use in pregnancy so that patients can make informed choices. Much media attention and social media commentary (particularly since the July 21, 2025 FDA SSRI and Pregnancy panel) has focused on the issues of pill-shaming pregnant women or restricting a pregnant woman's right to choose how she approaches her mental health, or pulling SSRIs off the market. This petition is not calling for any of that.

Women of childbearing age and pregnant women with depression deserve compassionate care. They should not be made to feel guilty, and their healthcare choices should be supported. Part of compassionate care is providing accurate information regarding risks of medication. In many cases, this is not currently occurring. With proper information, women can make an informed choice regarding their treatment options. They should then be supported in those choices.

A. ACTIONS REQUESTED

We are requesting that the FDA add a boxed warning to SSRIs to inform patients, providers, and the public that use of these medications during pregnancy has been shown to be associated with increased rates of pregnancy complications and alteration of fetal brain development.

We would propose the following boxed warning:

PREGNANCY COMPLICATIONS AND FETAL BRAIN DEVELOPMENT WARNING
The use of Selective Serotonin Reuptake Inhibitors (SSRIs) during pregnancy has been linked to increased rates of pregnancy complications (miscarriage, birth defects, preterm birth, low birthweight, preeclampsia, postpartum hemorrhage), neonatal complications, and alteration of the developing fetal brain.

The remainder of the label should be changed corresponding to this warning, including (for example, in the "Contraindications and Warnings," "Precautions," and "Limitations of Use" sections.)

B. STATEMENT OF GROUNDS

The FDA has the authority to require that drug manufacturers appropriately describe drug risks on the label. The current SSRI labels have limited warnings regarding pregnancy complications, and they do not include any warning regarding the impact of the drugs on the developing fetal brain. Serotonin is known to play a critical role in pregnancy, overall fetal development, and particularly fetal brain development. SSRIs are known to disrupt the serotonin system. Therefore, these drugs would be expected to impact the pregnancy and alter fetal brain development. Numerous animal studies and human studies demonstrate the effects of these drugs on pregnancy and on the developing fetal brain. It is critical that a boxed warning be added to SSRI drug labels to warn of these effects.

B1. Boxed Warning

In the FDA's Guidance for Industry document, in the description of when to use a boxed warning, the following is stated:

"A boxed warning is ordinarily used to highlight for prescribers one of the following situations:

There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using the drug

OR

There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation)

OR

FDA approved the drug with restrictions to ensure safe use because FDA concluded that the drug can be safely used only if distribution or use is restricted (e.g., under 21 CFR 314.520 and 601.42 "Approval with restrictions to assure safe use" or under 505-1(f)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) "Risk Evaluation and Mitigation Strategies" " Elements to assure safe use).

Infrequently, a boxed warning can also be used in other situations to highlight warning information that is especially important to the prescriber (e.g., reduced effectiveness in certain patient populations). Information included in the WARNINGS AND PRECAUTIONS and CONTRAINDICATIONS sections should therefore be evaluated to determine whether it warrants inclusion in a boxed warning.

Boxed warnings are most likely to be based on observed serious adverse reactions, but there are instances when a boxed warning based on an anticipated adverse reaction would be appropriate.

For example, a contraindication to use during pregnancy based on evidence in humans or animals that drugs in a pharmacologic class pose a serious risk of developmental toxicity during pregnancy would usually be in a boxed warning for all drugs in that class, even those in which the adverse reaction has not been observed."

In our estimation, the adverse reactions of SSRIs in pregnancy are serious enough to merit a boxed warning. Birth defects, miscarriage, and neurobehavioral issues are examples of serious developmental toxicity. But the complications don't just involve the baby. Postpartum hemorrhage and preeclampsia are also associated with SSRI use in pregnancy. These are serious complications and are two of the leading causes of maternal morbidity and mortality.

So there is evidence of a serious risk of developmental toxicity during pregnancy as well as evidence of a serious risk of conditions (i.e. preeclampsia and postpartum hemorrhage) that can lead to severe maternal morbidity and mortality.

B2. Current Label

In general, in terms of pregnancy complications, the current labels on SSRIs warn about three main issues:

-1. Persistent Pulmonary Hypertension in the Neonate.
-2. Withdrawal in the Neonate.
-3. Postpartum Hemorrhage.

Also mentioned, though not definitively warned about, are some of the following:
-Reported increases in major birth defects ("results are inconclusive")
-Delayed fetal ossification (rats and rabbits)
-Increase in the number of stillborn pups and pup deaths (rats)
-An increased risk of congenital cardiac defects (sertraline)

There is no clear warning regarding the risks of miscarriage, preterm birth, low birthweight, and preeclampsia or the impact on the developing fetal brain and the accumulating evidence of disruption of fetal brain development.

The medication guides for the SSRIs are similarly lacking; newborn issues are mentioned but not much more than that.

It is not an exaggeration to state that a woman reading a current SSRI label could come away with the perception that the drugs really haven't been shown to be associated with many complications (other than newborn issues and "less than twofold risk" of postpartum hemorrhage.) But this is not what the actual research evidence shows. Improved warnings are sorely needed.

B3. Conceptual Framework / Basic Science

Serotonin plays a crucial role in pregnancy and fetal development (Berard, 2019). For example, it plays a critical role in placental development and function (Velasquez, 2013) and in the development of the fetal brain during the embryonic and fetal periods (Gingrich, 2017; Hanswijk, 2020, Bonnin, 2011, Cote, 2007, Daubert, 2010.) There is widespread scientific agreement regarding this. Since serotonin was discovered in the 1930s-1940s, much research and numerous scientific papers have detailed the essential role serotonin plays in the correct form, function, and "wiring" of the fetal brain (Tate et al, 2021).

SSRIs alter the serotonin system. There is also widespread scientific agreement about this (Wang, et al., 2020; Wong, et al., 2005). SSRIs have been shown to cause neuronal apoptosis (Schaz, et al., 2011). And SSRIs have profound effects in the whole human body, not just the brain. For example, one study showed that patients on SSRIs have a 14-fold reduction in their platelet serotonin levels (Peters, 2019). SSRIs have also been linked to adverse lipid profiles (Richards-Belle, 2023). And they have been associated with mitochondrial dysfunction (Then, 2017.)

SSRIs and their metabolites substantially cross the placenta. Several studies have now demonstrated this (Hendrick, et al., 2003; Rampono, 2009; Ewing, 2015). The fetal to maternal ratio is greater than 50% for most drugs and their metabolites (Ewing, 2015.)

If serotonin plays a key role in fetal development (which it does) and if SSRIs cross the placenta and disrupt the serotonin system (which they do), then SSRIs would be expected to alter fetal development. And this is what the studies show.

Basic science research has looked at the impact of SSRI antidepressants on the placenta and embryo, as well as on neurons and brain development and the research has found effects. For example, Warkus et al., (2018) showed that various key developmental regulators were affected by fluoxetine, particularly those involved in mesodermal differentiation and fluoxetine inhibited canonical Wnt signaling. These results suggest that the SSRI-independent actions of fluoxetine, namely inhibition of canonical Wnt signaling and reduction of cellular proliferation, are largely responsible for the observed adverse morphogenetic impacts.

Domingues, et al., (2023) reviewed animal studies on SSRI use in utero and concluded "the increase in maternal circulating serotonin due to SSRI use is likely associated with decreased blood flow to the uterus, placenta, and fetus. The decreased vascular perfusion limits placental and fetal growth causing placental pathology."

In 2012, Kaihola, et al., found that higher doses of Fluoxetine showed effects on the timing of developmental stages in embryos. Additionally, Fraher et al., (2016) demonstrated in an animal model that SSRIs inhibit bone development by affecting osteoblast maturation during embryonic development and MSC differentiation.

There are a large number of studies showing that SSRIs impact fetal development, many of which are reviewed in the remainder of this petition.

B4. Impact on the developing fetal brain.

Basic science research

A number of basic science studies have investigated the impact of SSRIs on brain development. A sample of these are listed below.

-Zhong, et al (2020) used an organotypic human induced pluripotent stem cell (iPSC)-derived brain model to show that "At therapeutic blood concentrations, which lie between 20 and 60 ng/ml, Paroxetine led to an 80% decrease in the expression of synaptic markers, a 60% decrease in neurite outgrowth and a 40-75% decrease in the overall oligodendrocyte cell population, compared to controls. These results were consistently shown in two different iPSC lines and indicate that relevant therapeutic concentrations of Paroxetine induce brain cell development abnormalities which could lead to adverse effects."

-Tate, et al (2021) studied the effects of fluoxetine on a human fetal cortex model. They found impacts on neurite formation, synapse formation, and neuronal activity.

-Vichier-Guerre, et al (2017) studied the impact of paroxetine and sertraline on neural crest stem cells and they concluded that "This evidence suggests paroxetine and sertraline alter normal NCSC behavior and may thereby disrupt cardiac and craniofacial development."

Animal Studies

Numerous animal studies have been conducted in this area. The methods and results are somewhat mixed but there are a large number of studies that show significant impacts of the SSRI antidepressants on the developing brain. The following is from a recent paper (Bobula, 2024)

"Experiments on rodents have confirmed that [fluoxetine] FLX can transfer from the organism of the dam to the offspring (Kiryanova et al., 2013; Maloney et al., 2018). A number of animal studies investigated the effects of maternal FLX exposure on offspring behavior in later life (Glover and Clinton, 2016), however only a handful of them examined the consequences for the offspring when dams were exposed to FLX during the whole pregnancy and lactation period. FLX exposure is often related to decreased exploratory locomotion in the offspring as well as deficits in social and sexual behaviors, and occurrence of anxiety- and depression-like phenotypes (Kiryanova et al., 2013). Other studies reported decreased anxiety-like and depression-like behavior and social communication (Maloney et al., 2018). There are sex differences in the effects of perinatal FLX exposure on the behavior of the offspring in adolescence (Ramsteijn et al., 2020). These behavioral alterations have been linked to

disturbances in glutamatergic transmission in the prefrontal cortex and hippocampus, including decreased expression of NMDA receptor, metabotropic glutamate receptor 1 (mGluR1) and postsynaptic density protein 95 (PSD-95) that coincide with the anxiety-like and depression-like phenotype (mPFC) of the offspring mice (mPFC of female young adult offspring)."

Other studies demonstrating the effects of SSRIs on the developing animal brain include:

-Bond, A., et al (2020). "Perinatal fluoxetine exposure results in social deficits and reduced monoamine oxidase gene expression in mice."

-Van der Knaap, at al (2021) "Perinatal SSRI exposure affects brain functional activity associated with whisker stimulation in adolescent and adult rats."

-Chen, et al. (2021). "The effects of maternal SSRI exposure on the serotonin system, prefrontal protein expression and behavioral development in male and female offspring rats."

-Pawluski, et al (2023). "Gestational stress and perinatal SSRIs differentially impact the maternal and neonatal microbiome-gut-brain axis."

-Bhat, et al (2023). "Prenatal SSRI exposure increases the risk of autism in rodents via aggravated oxidative stress and neurochemical changes in the brain."

Human Studies

There are numerous human studies that have investigated whether prenatal SSRI exposure alters brain development. Studies show evidence of brain impacts in utero (e.g. fetal ultrasound studies), during the neonatal period, and longer-term, with changes in such things as behavior, learning, and mood.

In Utero Ultrasound Studies: Fetal sleep / fetal movement

Fetal ultrasound studies have demonstrated that SSRIs can affect both fetal movement and sleep (Mulder, et al., 2011; Salisbury, et al., 2024). These two findings provide support to the notion that SSRI exposure in utero is disrupting neurodevelopmental processes.

-Mulder et al (2011) did prenatal ultrasound in the first, second, and third trimester. They found that: "Fetuses exposed to standard or high SSRI dosages compared with control, unmedicated, or low-medicated fetuses showed significantly increased motor activity at the beginning (T1) and end of the second trimester (T2). They particularly exhibited disrupted emergence of non-rapid eye movement (non-REM; quiet) sleep during the third trimester, characterized by continual

bodily activity and, thus, poor inhibitory motor control during this sleep state near term (T3). The SSRI effects on the fetus were dose related, but independent of SSRI type. The results demonstrate changes in fetal neurobehavioral development associated with standard and high SSRI dosages that are observable throughout gestation."

-Salisbury, et al (2024) did prenatal ultrasound at 26-30 weeks and 32-36 weeks. They reported that the SSRI exposed fetuses had increased rates of third trimester fetal movement and shorter periods of quiescence. These findings were associated with greater SRI bioeffect (lower platelet serotonin levels) with a higher rate of spontaneous movements and shorter quiescent boutlengths. The phenotype of increased rates of third trimester fetal movement and shorter periods of quiescence associated with greater SRI bioeffect is similar to the restless or fidgety infant behavior associated with the Neonatal Adaptation Syndrome. However, the SRI-associated phenotype might also reflect neurodevelopmental alterations in sleep-related systems which are known to be affected by 5-HT.

Increased umbilical cord length

The two studies above demonstrate that prenatal SSRI exposure is associated with increased rates of fetal movement (Mulder, 2011; Salisbury, 2024.) Increased fetal movement may also lead to increased length of the umbilical cord. At least two studies have found that SSRI exposure is associated with longer umbilical cords (Kivisto, 2016 and Bernhardsen, 2025.)

-Kivisto, et al (2016) wrote: "SSRI exposure appeared to be associated with increased umbilical cord length. The observation related to increased umbilical cord length may be explained by an SSRI-induced increase in the movements of the developing foetus."

-Bernhardsen, et al (2025) stated: "We ... observed a possible linear dose–response effect of SSRI exposure during pregnancy on increased placental weight, PBWR (placental birthweight ratio), and umbilical cord length. ... A suggested explanation [from the above study] was increased hyperactivity in SSRI-exposed foetuses, which in turn could lead to lengthening of the umbilical cord."

In utero fetal heart rate assessment

The fetal heart rate can be used as an indicator of fetal status and function of the neurocardiac axis. At least two studies have looked at the effects of maternal SSRI use on fetal heart rate parameters. These studies found significant differences between the SSRI group and controls.

-Rurak, et al (2011) studied fetuses at 36 weeks in 29 SSRI-treated women with mood disorders versus 45 controls. They found that the SSRI-exposed fetuses had less fetal heart rate variability,

fewer accelerations, and shorter duration of high-variability episodes and that these did not change across the day in SSRI-exposed fetuses, whereas all increased significantly in the nonexposed. The SSRI-exposed fetuses also had middle cerebral arteries (MCA) with a smaller cross-sectional area and lower MCA pulsatility index. The SSRI-exposed newborns had hemoglobin and hematocrit levels that were significantly increased, which the authors felt might be due to hypoxia. They concluded: "Prenatal SSRI exposure reduced fetal MCA flow resistance and fHR variability, before and after an SSRI dose, controlling for maternal mood. These changes and the SSRI-related increased red cell indices suggest possible fetal hypoxia."

-Campbell, et al (2021) studied 148 pregnant women before and 5-hours after their typical SSRI dose. Following maternal SSRI dose, short-term HRV (heart rate variability) decreased in the SSRI-exposed fetal groups (there were two.) Further, episodes of high heart rate variability decreased post-dose relative to baseline, but only among SSRI-Non-Depressed group fetuses. Higher maternal SSRI doses also predicted a greater number of fetal HR decelerations. Fetuses exposed to unmedicated maternal depressed mood did not differ from Controls. The authors of the paper concluded: "Fetal HR increased while fetal HR variability decreased in SSRI-exposed fetuses relative to the AM/pre-dose assessment, reflecting an acute effect of SSRI exposure."

EEG Studies

There are at least 3 electroencephalogram (EEG) studies that have investigated the impacts of prenatal SSRI exposure on the developing fetal brain:

-Videman et al. (2017) did EEGs on newborns at 1 and 2 weeks post-delivery and showed that "[t]he computational EEG analyses disclosed a reduced interhemispheric connectivity, lower cross-frequency integration, as well as reduced frontal activity at low-frequency oscillations" in the SSRI exposed newborns.

-Grieve et al. (2019) did EEGs on newborns around 6 weeks after delivery and showed that "Exposure to serotonin selective reuptake inhibitors (SSRIs) during pregnancy also alters characteristics of EEG bursting activity during infancy, but differently than maternal depression."

-Tokariev et al (2022) used previously collected EEG data (Videman, 2017) and found that "prenatal SRI exposure in human offspring may cause selective effects on cortical network activity that further links to neurodevelopmental outcomes. Our results are fully in line with the overall notion from the recently accumulated literature (Videman et al., 2017: Brown-Lum et al., 2020; Wisner et al., 2020; Kautzky et al., 2021) that *in utero* drug exposures may cause subtle, yet measurable changes in the brain structure and function."

MRI Studies

Twelve MRI studies have investigated whether maternal prenatal SSRI use alters fetal brain development. All of them found that SSRIs did impact the developing brain. We review them briefly (in reverse chronological order) here.

-1. Zanni, et al (2025) did MRI studies on 11-13 year olds and showed that "adolescents exposed to SSRIs *in utero* exhibited higher anxiety and depression symptoms than unexposed adolescents and also had greater activation of the amygdala and other limbic structures when processing fearful faces."

-2. Koc, et al (2023) did MRI studies on children from ages 7-15 and showed that "prenatal SSRI exposure was associated with reduced global gray and white matter volume in children from 7 to 15 years of age."

-3. Moreau, et al (2022) performed MRI studies on children at age 9 and they found that "prenatal SSRI exposure was associated with larger surface area in the left superior parietal region and thicker left lateral occipital cortex."

-4. Campbell, et al (2021) did MRI studies on postnatal day 7 and found that SSRIs altered corpus callosum (CC) microstructure. They concluded: "Our findings suggest that CC microstructure may have a sex-specific, localized, developmental sensitivity to prenatal SSRI exposure."

-5. Salzwedel, et al (2020) did MRI studies on newborns at 2-6 weeks of age to investigate the impact on the brain of SSRIs as well as nicotine, alcohol, opioids, marijuana, and cocaine. They found that the SSRIs had the largest effects: "In descending order, the three legal drugs (SSRIs, nicotine, and alcohol) were most impactful, followed by opioids, marijuana, and cocaine."

-6. Rotem-Kohavi et al (2019a) did MRI studies on postnatal Day 6 and found that "the SSRI group showed higher provincial hub values in Heschl's gyrus relative to the depressed-only group."

-7. Rotem-Kohavi et al (2019b) did MRI studies on 6-day-old neonates and wrote: "We found an association between prenatal SSRI exposure and increased functional connectivity synchronization or hyperconnectivity of RSNs in the newborn infant, relative to control infants and infants of nonpharmacologically treated depressed mothers."

-8. Lugo-Candelas et al (2018) did MRI studies on term newborns at 3-4 weeks and showed "significant gray matter volume expansion in the right amygdala and right insula in SSRI-

exposed infants compared with both healthy controls and infants exposed to untreated maternal depression … The SSRI group showed a significant increase in connectivity between the right amygdala and the right insula with a large effect size compared with healthy controls and untreated depression. They concluded **"Our findings suggest that prenatal SSRI exposure has an association with fetal brain development, particularly in brain regions critical to emotional processing."**

-9. Podrebarac, et al (2017) did MRI studies on preterm newborns shortly after birth and 8 weeks later. They showed that "SSRI-exposed neonates exhibited increased FA [fractional anisotropy] and decreased MD, AD and RD [mean, axial, radial diffusivity] values in the superior white matter ($p<0.05$). FA values in the basal ganglia and thalamus were significantly lower in neonates antenatally exposed to SSRIs, compared to non-exposed ($p=0.004$). Lower NAA/Cho [N-acetylaspartate to choline ratios] values ($p=0.04$) and higher Lactate/Cho values ($p=0.004$) in posterior gray matter were evident in neonates exposed to SSRIs." They noted: "Preterm newborns exposed to antidepressants *in utero* had impaired brain maturation."

-10. Jha, et al (2016) did MRI studies on newborns at roughly 4 weeks after birth and they showed that "SSRI-exposed neonates exhibited widespread changes in white matter microstructure compared to matched controls."

-11. Salzwedel, et al (2016) did MRI studies on neonates at 2-6 weeks in order to study the effects of prenatal cocaine exposure. They noted that "cocaine by selective-serotonin-reuptake-inhibitor (SSRI) interactions were detected, suggesting the combined use of these drugs during pregnancy could have additional consequences on fetal development."

-12. Knickmeyer, et al (2014) performed MRI studies on children at 1-2 years of age to assess for Chiari I Malformation. They concluded: "This study found a striking increase of CIM in children with prenatal SSRI exposure."

In summary, MRI studies consistently show that prenatal SSRI exposure alters fetal brain development.

Neonatal Withdrawal Syndrome / Poor Neonatal Adaptation

Neonatal complications (ie the Neonatal Withdrawal Syndrome or Poor Neonatal Adaptation syndrome) have been reported in 20-80% of exposed pregnancies (Mamillapalli, 2025).

The current drug label does warn about this. For example, the Zoloft warning reads:

"Neonates exposed to ZOLOFT and other SSRIs or SNRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. These findings are based on post-marketing reports. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. In some cases, the clinical picture was consistent with serotonin syndrome."

Many of these complications are related to impact on the fetal brain during pregnancy and the neonatal period. The label correctly notes that "these features are consistent with … a direct toxic effect of SSRIs and SNRIs." But this reasoning raises an important issue: If we are seeing evidence for a direct toxic effect in the newborn period, then it is highly likely (basically, certain) that there are ongoing direct toxic effects to the fetus during the pregnancy itself.

Longer-term issues

The study of whether in utero SSRI exposure affects longer term outcomes (eg language and motor development, school performance, mood disorders) poses numerous research challenges. The scientific literature in this area is mixed. However, there are many studies that do show an association between SSRI exposure in utero and future complications.

Language

-Singal, et al (2020) studied kindergarteners and found that "Exposure to SSRIs or SNRIs during pregnancy was associated with an increased risk of developmental vulnerability and an increased risk of deficits in language and/or cognition."

-Smearman, et al (2020) studied elementary school children who were exposed to SSRIs in utero, and they found "an association between SRI exposure and reduced pragmatic language scores."

-Johnson, et al (2016) studied preschool children and found a "significant association between prenatal SRI exposure and preschool outcomes, including expressive language and behavior problems."

-Handal, et al (2016) studied children and "detected a significant association between long-term use of SSRIs during pregnancy and delayed language competence in the offspring only when folic acid supplementation was used concomitantly."

-Brown, et al (2016) studied children in Finland and found that “Offspring of mothers who purchased SSRIs at least twice during pregnancy had a significant 37% increased risk of speech/language disorders compared with offspring in the unmedicated group.”

-Skurtveit, et al (2014) assessed children in Norway and concluded: “Prolonged use of SSRI during pregnancy was associated with lower language competence in children by age three independently of depression.”

-Weikum, et al (2012) studied language development at 36 weeks gestation and also at 6 and 10 months postnatal. They found that “Whereas the control infants responded as expected (success at 6 mo and failure at 10 mo) the SRI-exposed infants failed to discriminate the language differences at either age.” And in utero (at 36 weeks), the SSRI exposed fetuses also performed differently than the controls.

Other Educational achievement

-Christensen, et al (2021) studied Danish school-aged children (around 8-15 years old) and found that those exposed to SSRIs in-utero had lower mathematics scores.

-Kragholm, et al (2018) found that “in utero SSRI exposure in all three trimesters was associated with delayed elementary school start” in schoolchildren in Denmark.

Depression, anxiety, and other mood issues

-Hanley, et al. (2015) studied 3- and 6-year-old children and found “Higher levels of internalizing and anxious behaviors were reported in SRI exposed children at both 3 and 6 [years] of age compared with children who were not exposed.”

-Brandlistuen, et al. (2015) studied Norwegian children at 18 and 36 months and “showed that prenatal antidepressant use was specifically associated with increased anxiety symptoms.”

-Hermansen, et al (2016) studied Norwegian children 5-6 years of age and found that those exposed to SSRIs in utero had increased internalizing problems.

Constipation

The majority of the body’s serotonin is synthesized not in the brain, but in the gastrointestinal tract. Gestational exposure to selective serotonin reuptake inhibitors appears to alter gut innervation and delays colonic motility. At least three studies have demonstrated an association with constipation.

-Nijienhuis, et al. (2012) published a cohort study on pharmacy prescription databases and found a correlation between Children exposed *in utero* to SSRIs, more often received laxatives prescriptions, suggesting a clinical diagnosis of constipation.

-Salisbury, et al. (2020) reported data from two prospective, naturalistic, longitudinal cohort samples. They studied pregnant women and their children's gastrointestinal health at pre-school and elementary school year follow ups. This research presents prospective data demonstrating significant associations between prenatal SSRI exposure and children's gastrointestinal (GI) problems such as constipation.

-Kildegaard, et al. (2025) demonstrated prenatal SSRI exposure to be associated with an increased risk of developing functional constipation in a group of Danish children over a 15-year period.

Autism

Autism is a neurodevelopmental disorder characterized by deficits in social interaction, repetitive behaviors, and communication difficulties. It can be a challenging area to study because of the wide spectrum of findings with varying degrees of severity. Rates have been rising significantly during the time period where SSRI use in pregnancy has been increasing. Several animal and human studies over the years have investigated whether there is an association between prenatal SSRI exposure and the development of autism.

Animal Studies (Autism)

-In 2004, Ansorge, et al. published a landmark paper in the journal Science (Ansorge, 2004.) This paper showed that mice that were exposed to Prozac during development had altered emotional behaviors. In the conclusion of that paper (21 years ago) Ansorge warned: "The use of SSRI medications in pregnant mothers and young children may pose unsuspected risks of emotional disorders later in life."

-In 2011, Simpson, et al studied the effects of Celexa on rats and they also found concerning changes in the brains and behaviors of the exposed offspring (Simpson, 2011.) They warned: "our findings are consistent with the possibility that dysregulation/dysfunction of the 5-HT [serotonin] system during early brain development may be the critical contributing factor in the etiology of ASD [autism spectrum disorder]."

-Bond, et al (2020) administered fluoxetine non-invasively to female mice throughout gestation and early lactation, and then examined social interaction behaviors in offspring. They also measured whole brain gene expression levels of monoamine oxidase A (MAOA), the primary metabolizing enzyme for serotonin. They "found deficits in sociability and social novelty-seeking behavior in the juvenile offspring of SSRI-treated mice, and these behaviors persisted into young adulthood." They also "found decreased MAOA expression in the brains of offspring of SSRI-treated mice." They concluded: "Our findings suggest that exposure to antidepressants during the prenatal and early postnatal period may negatively affect social development. Moreover, reduced MAOA expression may play a role in the mechanistic pathway linking SSRI exposure and behavioral deficits symptomatic of autism."

-Bhat, et al (2023) performed a study on neonatal male western albino rats. They showed that the "SSRI (fluoxetine) induced significant neurochemical abnormalities in the rat brain by increasing lipid peroxide (MDA), Interferon-gamma (IFN-γ), and caspase-3 levels and by depleting Glutathione (GSH), Glutathione S-transferases (GST), Catalase, potassium (K+), and Creatine kinase (CK) levels, similarly to what has been discovered in the PPA model of autism when compared with control." They concluded: "Prenatal fluoxetine exposure plays a

significant role in asset brain damage in newborns; further investigation of fluoxetine as an autism risk factor is thus warranted."

-Arzuaga, et al (2023) showed that fluoxetine exposure in mice led to an increase in stereotyped behaviors. They wrote: "This set of findings could suggest that effective treatments for maternal stress during pregnancy may also have some negative consequences for certain offspring."

Several other animal studies were thoroughly reviewed by Sato, et al (2022) in their section on SSRIs, Serotonin Metabolism, and ASD in Animal Models:

"Investigations of pregnant rodents have improved our understanding of 5-HT [serotonin] dynamics and its alterations by SSRIs during pregnancy. Analyses of *Pet1* knockout mice, in which most dorsal raphe neurons lacked 5-HT, revealed that 5-HT in the fetal forebrain was of placental and not maternal or fetal origin (Bonnin, 2011). The blockade of SERTs using the serotonin-norepinephrine transporter inhibitor venlafaxine by gavage from E8 to E20 decreased placental weight and SERT expression in the placenta in rats (Laurent, 2016). The inhibition of 5-HT signaling with the 5-HT_2 receptor antagonist ketanserin by gavage from E15 to E20 reduced placental weight and placental blood flow in rats (Furuhashi, 1991). SSRI use during pregnancy could result in lifelong consequences on the brain in offspring (Rosenfeld, 2020), but the underlying mechanism is complex, including fetal exposure to SSRIs and alterations of 5-HT supply from the placenta. Decreases in placental weight and blood flow that are associated with maternal treatment with SSRIs could also lower the supply of oxygen and nutrients to the fetus and result in lower offspring weight, which might affect fetal brain development.

In contrast to VPA [valproic acid], few studies have investigated how prenatal exposure to SSRIs affects social behavior in offspring (Table 2). At the behavioral level, fluoxetine administration in mice that began before pregnancy or from early gestation to late-gestation or delivery produced ASD-like behavioral deficits in offspring, decreased USVs in pups, disrupted social interaction, enhanced social dominance, and increased tactile hypersensitivity (Maloney, 2018; Yu, 2019; Bond, 2020). Citalopram, an SSRI with particularly high specificity for blocking SERT compared with dopamine and norepinephrine transporters, also altered behavior in mouse offspring, decreased sociability, decreased social preference, decreased locomotor activity, and increased anxiety-related behavior when given during late gestation (Zahra, 2018). In fetal brains that were exposed to fluoxetine, neurons in the prefrontal cortex exhibited a reduction of the frequency of inhibitory synaptic currents, and interneurons exhibited an increase in intrinsic and serotonin-induced excitability (Yu, 2019). Prefrontal cortex tissue from the fluoxetine-exposed brain exhibited high mRNA levels of 5-HT_{2A} receptor (Yu, 2019). Striatal extracts from mice that were prenatally exposed to citalopram expressed higher levels of NMDAR1 and CaMKIIα, which were associated with morphological changes in the striatal neurons and decreases in

dendritic length, number, and branch patterns (Zahra, 2018). Prenatal exposure to SSRIs is suggested to result in excessive 5-HT signaling and altered E/I balance.

The effects of therapeutic interventions in these models also appear to be consistent with these findings. High 5-HT level in the brain that are caused by reexposure to fluoxetine in adulthood recovered tactile hypersensitivity (Maloney, 2018). The 5-HT_{2A} receptor antagonist MDL100907 suppressed abnormal excitability in neurons in the prefrontal cortex and reversed social preference in a model of fluoxetine-induced ASD (Yu, 2019). In a citalopram model, high levels of NMDAR1 and CaMKIIα were normalized by postnatal treatment with memantine, which was associated with the recovery of sociability and social preference (Zahra, 2018). More research is required to determine whether and how exposure to SSRIs *in utero* affects fetal brain development and causes social deficits.

The aforementioned interventions can be partially replicated by manipulating genes that are involved in 5-HT neurotransmission because 5-HT levels are consistently changed in these models (i.e., either elevated or depleted). The most extensively investigated models are *SERT* knockout mice and rats (Kalueff, 2010). In these animals, extracellular 5-HT levels are several times higher, and consequently the density of 5-HT_{1A} and 5-HT_{1B} receptors is decreased (Fabre, 2000; Mathews, 2004; Shen, 2004; Homberg, 2007a; Olivier, 2008). Diverse behavioral phenotypes are observed in *SERT* knockout rodents, such as an increase in anxiety and fear (Kalueff, 2010), that may affect social behavior in *SERT* knockout animals. Intact sociability was observed in *Sert* $^{-/-}$ and *Sert* $^{+/-}$ mice, reflected by the time spent sniffing a novel mouse or a novel object (Moy, 2009). The heterozygous loss of *Sert* aggravated deficient sociability in *Pten*$^{+/-}$ mice, a genetic model of ASD that is associated with the activation of mTORC1 activity (Page, 2009). Reciprocal social interaction in the resident-intruder paradigm was unaffected in *Sert* $^{-/-}$ and *Sert*$^{+/-}$ rats (Homber, 2007b). A recent study reported deficits in social interaction, sociability, and social novelty in *Sert* $^{-/-}$ and *Sert* $^{+/-}$ mice (Tanaka, 2018). This was associated with high levels of 5-HT in the brain in *Sert* $^{-/-}$ mice but not in *Sert* $^{+/-}$ mice. Impairments in social interaction were ameliorated by restricting the dietary intake of tryptophan (i.e., the precursor of 5-HT), which lowers 5-HT levels in the brain (Tanaka, 2018). Constitutively elevated 5-HT levels are thus considered to disrupt social behavior.

Reducing 5-HT concentrations in the brain, opposite to *SERT* deletion, may also give rise to ASD. One method to reduce 5-HT levels is to introduce a gain-of-function mutation of the *SERT* gene. *SERT* Ala56 mice that expressed an ASD-associated variant in humans exhibited elevations of 5-HT clearance in the brain and ASD-related social impairments and repetitive behavior, but forebrain 5-HT levels did not change in the mutants (Veenstra-VanderWeele, 2012). This increase in 5-HT clearance was reversed by MW150, a p38α mitogen-activated protein kinase inhibitor, which also normalized social dominance in the tube test (Robson, 2018). Brain 5-HT levels can also be depleted by deleting the tryptophan hydroxylase 2 (*TPH2*) gene,

which is essential for synthesizing 5-HT in the brain. *TPH2* knockout mice exhibited diverse ASD-related behaviors, including impairments in social interaction, an increase in marble burying, and deficient early developmental milestones (Kane, 2012). Female *TPH2* knockout mice exhibited high levels of aggression against co-housed mice and an increase in defensive behavior when paired with a knockout mouse (Kästner, 2019). These studies suggest that prenatal increases and decreases in fetal 5-HT levels may result in the subsequent development of ASD."

While the animal studies show varied results on the precise effects of SSRI antidepressants, the overall scientific research evidence clearly shows that these drugs have an impact on the developing brain.

Human studies (Autism)

A number of human studies have been done over the years to research the link between SSRIs and autism. Several of these studies and meta-analyses have demonstrated an association.

-Croen, et al (2011) performed a population-based case-control study at the Kaiser Permanente Medical Care Program in Northern California. They found that in adjusted logistic regression models there was a 2-fold increased risk of ASD [autism spectrum disorder] associated with treatment with selective serotonin reuptake inhibitors by the mother during the year before delivery (adjusted odds ratio, 2.2 [95% confidence interval, 1.2-4.3]), with the strongest effect associated with treatment during the first trimester (adjusted odds ratio, 3.8 [95% confidence interval, 1.8-7.8]). No increase in risk was found for mothers with a history of mental health treatment in the absence of prenatal exposure to selective serotonin reuptake inhibitors.

-Rai, et al (2013) performed a population based nested case-control study in Sweden and found the following: "In the subsample with available data on drugs, this association [with autism] was confined to women reporting antidepressant use during pregnancy (3.34, 1.50 to 7.47, P=0.003).

-Harrington, et al (2014) found that among boys, prenatal SSRI exposure was nearly 3 times as likely in children with ASD relative to TD [typical development] (adjusted odds ratio [OR]: 2.91; 95% confidence interval [CI]: 1.07-7.93); the strongest association occurred with first-trimester exposure (OR: 3.22; 95% CI: 1.17-8.84). Exposure was also elevated among boys with DD [developmental delays] (OR: 3.39; 95% CI: 0.98-11.75) and was strongest in the third trimester (OR: 4.98; 95% CI: 1.20-20.62). Findings were similar among mothers with an anxiety or mood disorder history. They concluded that "In boys, prenatal exposure to SSRIs may increase susceptibility to ASD or DD."

-Gidaya, et al (2014) used Denmark's health and population registers to study this issue. There were 1.5 % of cases and 0.7 % of controls exposed to SSRIs during the pregnancy period, and higher effect estimates observed with longer use. They concluded: "We found evidence that in utero exposure to SSRIs increases a child's risk associated with ASD."

-El Marroun, et al (2014) found that "compared with unexposed children, those prenatally exposed to SSRIs also were at higher risk for developing pervasive developmental problems (OR = 1.91, 95% CI 1.13–3.47), but not for affective problems. Children prenatally exposed to SSRIs also had more autistic traits (*B* = 0.15, 95% CI 0.08–0.22) compared with those exposed to depressive symptoms only." They concluded: "Our results suggest an association between prenatal SSRI exposure and autistic traits in children. Prenatal depressive symptoms without SSRI use were also associated with autistic traits, albeit this was weaker and less specific. Long-term drug safety trials are needed before evidence-based recommendations are possible."

-Man, et al (2015) performed a systematic review of the literature and concluded: "The findings of this meta-analysis and narrative review support an increased risk of ASD in children of mothers exposed to SSRIs during pregnancy."

-Andalib, et al (2017) performed a meta-analysis and systematic review and concluded: "The evidence from the present study suggests that prenatal exposure to SSRIs is associated with a higher risk of ASD."

B5. Miscarriage

The use of antidepressants is widespread among women of childbearing age. Estimates are that around half of all pregnancies are unplanned. Many young women are taking SSRIs before they discover they are pregnant. Therefore, it is important to provide proper warnings on the risks of pregnancy complications that result from early exposure to SSRIs for women of childbearing age.

Many human studies have shown an association between SSRI use in pregnancy and an increased risk of miscarriage or spontaneous abortion. The cause of the increased risk of miscarriage with SSRI use is not fully understood. Animal studies suggest that SSRIs influence placental formation and development. The increase in maternal serotonin likely promotes vasoconstriction of the uterus and placenta, with potential impact on placental development and function. (Domingues, et al, 2023) These changes in the placenta during early gestation could be one variable related to the increase in miscarriages of pregnancies exposed to SSRIs.

The unexpected ending of a pregnancy can take a significant emotional toll on a woman. Miscarriage can predispose a woman to depression, due to grief from the loss as well as post-loss biological and hormonal changes.

Given the evidence from the human and animal studies, the miscarriage risk necessitates stronger warning labels for childbearing age women and the public.

Animal Studies

A large number of animal studies have been conducted over the years. Many of them have shown increased rates of pregnancy complications with SSRI exposure, including increased embryonic resorption and decreased litter size. (Vorhees, 1994; Bauer, 2010; Cabrera, 2020)

-Bauer, et al (2010) exposed mice to drinking water either with or without fluoxetine. They noted: “Significant findings within this study include the decrease in live birth rate and in the mean litter size in dams receiving [fluoxetine] compared to dams receiving H2O. These findings potentially suggest a physiological alteration at the placenta level during implantation.”

-Domingues, et al (2022a) investigated the effects of two SSRIs, fluoxetine and sertraline, on pregnancy and neonatal outcomes in mice and reported the low dose of sertraline and the high dose of both fluoxetine and sertraline caused a reduction in the number of pups born, or pregnancy maintained.

Human Studies

-Broy, et al (2010) provided a meta-analysis on the association between adverse pregnancy outcomes and gestational exposure to antidepressants with data on spontaneous abortions. Out of 15 prospective cohort studies, in the adjusted analyses of the SSRI group, paroxetine (OR = 1.7; 95% CI = 1.3 - 2.3) was significantly associated with the risk of spontaneous abortion.

-Nakhai-Pour, et al (2010) used a nested case–control study design, to obtain data from the Quebec Pregnancy Registry for 5124 women who had a clinically detected spontaneous abortion. After adjustment for potential confounders, they found "that the use of antidepressants during pregnancy was associated with an increased risk of spontaneous abortion (OR 1.68, 95%CI 1.38–2.06). Stratified analyses showed that use of selective serotonin reuptake inhibitors alone (OR 1.61, 95% CI 1.28–2.04), serotonin–norepinephrine reuptake inhibitors alone (OR 2.11, 95% CI 1.34–3.30) and combined use of antidepressants from different classes (OR 3.51, 95% CI 2.20–5.61) were associated with an increased risk of spontaneous abortion. When we looked at antidepressant use by type versus no use, paroxetine use alone (OR 1.75, 95% CI 1.31–2.34) and venlafaxine use alone (OR 2.11, 95% CI 1.34–3.30) were associated with an increased risk of spontaneous abortion."

-Klieger-Grossmann, et al (2012) analyzed 213 women taking escitalopram and compared them to 212 women on other SSRIs and 212 on nonteratogens. They reported spontaneous abortion rates were higher in both antidepressant groups compared with controls (8.5%; P = .066). Spontaneous abortion rates were nearly double in both antidepressant groups (15% and 16%) compared with controls.

-Nikfar, et al (2012) reported on a meta-analysis of pregnancy outcomes following exposure to SSRIs in a series of 25 case studies, the odds ratio (OR) values are 1.87 (95% CI: 1.5 to 2.33, P< 0.0001) for spontaneous abortion. They demonstrate an increase in risk of spontaneous abortion following the use of SSRIs during pregnancy.

-Kjaersgaard, et al (2013) reviewed prescription databases and identified out of 114,721 women taking an SSRI during pregnancy, 11.4% ended in a spontaneous abortion. Antidepressant exposure was associated with a relative risk of 1.14 for spontaneous abortion.

-Almeida, et al (2016) retrospectively studied 41,964 cases and compared women on SSRIs. The miscarriage relative risk for antidepressant users compared with unexposed depressed women was thus 1.2 (1.0-1.4). They concluded "Antidepressant use in the first trimester is associated with an increased risk of miscarriage when compared with either nondepressed or depressed unexposed women, even after accounting for induced abortions".

B6. Birth defects

Serotonin plays a crucial role in embryonic development (Berard, 2019.) There is widespread scientific agreement on this. Serotonin plays a role not solely as a neurotransmitter, but also as a crucial cell-signaling molecule and cell communication molecule during embryogenesis. The serotonin that the embryo uses comes from maternal sources as well as from the developing embryo itself. "Thus, appropriate signaling requires a delicate balance and correct concentrations of serotonin in specific locations (Berard, 2019)." In the embryo "serotonergic signaling controls cell proliferation, regulation of cell shape and cell movement patterns, neurogenesis and brain patterning, heart morphogenesis, eye development, and craniofacial morphogenesis."

"The fact that SSRIs readily cross the placenta (Rampono, 2009) and the fact that these drugs are designed to alter extracellular concentrations of 5-HT create a recipe for disrupting these delicate balances of the neurotransmitter and, hence, its ability to act as a signaling molecule (Berard, 2019.)"

From a commonsense standpoint, if serotonin plays a crucial role in embryonic development (which it does) and if SSRIs disrupt the serotonin system (which they do), then they must alter embryonic development. And this is what the animal and human studies show:

Animal studies

Numerous animal studies have been conducted using rodents and rabbits, as well frogs, chicks, and zebrafish. These studies have shown that SSRIs impact embryonic development and can lead to birth defects.

-Fraher, et al (2016) showed in zebrafish that citalopram and sertraline exposure compromises embryonic bone development. The authors wrote: "Our data indicated that both citalopram and sertraline decreased bone mineralization during zebrafish embryogenesis and osteoblast activity during differentiation. It is reasonable to speculate that these effects could hold true in human fetuses, which could present future health risks. A negative effect on bone maturation in the fetus could have lifelong implications as it has been shown that skeletal growth in adulthood is influenced by intrauterine development."

-Saluan, et al (2024) showed in mice that that *in utero* exposure to Citalopram can cause significant deviations in craniofacial form. They concluded: "Altogether these data indicate that prenatal SSRI exposure affects craniofacial form in multiple tissues and specifically at growth sites and centers of the skull."

-Olivier et al (2013) reviewed many other studies in this area:

"A higher mortality rate has been found in neonatal rodents after prenatal SSRI exposure (Noorlander et al., 2008; van den Hove et al., 2008) and it has been postulated that heart malformations may be one reason for this increase in mortality. Noorlander (2008) also found that the majority of fluoxetine-exposed offspring died postnatally because of severe dilated cardiomyopathy. Moreover, the ratio of thickness of the left ventricle to the radius of the left ventricle cavity was significantly decreased in prenatal fluoxetine-exposed mouse offspring both at PND20 and during adulthood. These data clearly show that prenatal fluoxetine exposure (0.8 mg/kg/day; i.p.) severely affects heart development, resulting in an increased death rate in offspring. In vitro, (Sari and Zhou, 2003) found that paroxetine significantly decreased the rate of proliferation of fetal heart cells (E13) from rats, particularly cardiac myocytes and, to a lesser degree, non-muscle cells. Fluoxetine and sertraline also have similar influences on the proliferation of cardiac cells in the mouse embryo (Yavarone et al., 1993). These data indicate that changes in prenatal 5-HT levels influence the proliferation of the embryonic heart cells, at least *in vitro*. Fluoxetine has furthermore been shown to affect cell viability and differentiation from undifferentiated ES cells to cardiomyocytes in a dose-dependent manner. Analysis of tissue-specific markers showed also that fluoxetine inhibits mesodermal development, but it promotes ectodermal differentiation (Kusakawa et al., 2008). In another study, late two-cell stage embryos incubated with fluoxetine for 6 h were more likely to develop into blastocysts compared to the controls. Exposure to fluoxetine for 24 h showed a reduction in blastocyst formation, suggesting a time dependent effect of fluoxetine on blastocyst formation. It also appears that these effects are, in part, due to altered TREK signaling (Kim et al., 2012). In humans, the cardiomyocyte proliferation is essentially complete at birth, whereas in rodent's cardiomyocyte growth and proliferation is robust for the first 14 days after birth (Clubb and Bishop, 1984; Walsh et al., 2010). Haskell et al. (2012) injected mouse offspring with sertraline from PND1 to PND14, reflecting the third trimester in humans, and found that sertraline-exposed offspring showed increased heart rate and activity levels, as well as smaller left ventricular internal diameters in diastole and decreased stroke volumes, indicating changes in the cardiac morphology. Taken together, both *in vitro* and *in vivo* early-exposure to SSRIs have adverse consequences for the developmental outcomes of the heart."

Human studies

A large number of human studies have investigated links between SSRI exposure and birth defects. Many of these have found an association – particularly with cardiac defects and craniosynostosis.

-Wogelius, et al (2006) performed a population-based cohort study in Denmark and found that women with prescriptions during the second or third month of pregnancy gave birth to 31 (6.8%) children with congenital malformations. The corresponding aRR was 1.84 (1.25-2.71).

-Berard, et al (2015) performed a population-based cohort study in Quebec, Canada and found that Sertraline use during the first trimester of pregnancy was associated with an increased risk of atrial/ventricular defects and craniosynostosis above and beyond the effect of maternal depression. Non-sertraline SSRIs were associated with an increased risk of craniosynostosis and musculoskeletal defects.

-Reefhuis, et al (2015) and scientists from the Centers for Disease Control and Prevention used an expanded dataset from the National Birth Defects Prevention Study and found that that some birth defects occur 2-3.5 times more frequently among the infants of women treated with paroxetine or fluoxetine early in pregnancy.

-Anderson, et al (2020) and scientists from the Centers for Disease Control and Prevention also used the National Birth Defects Prevention Study and found associations between several antidepressants and various birth defects.

-Huang, et al (2023) studied maternal exposure to SSRIs and SNRIs and the risk of congenital abnormalities in the offspring. Their meta-analysis included twenty-one cohort studies and seven case-control studies. They found both classes of drugs to be associated with birth defects. Specifically, they found maternal exposure to SSRIs was associated with a higher risk of congenital cardiovascular abnormalities (pooled OR: 1.25 with 95%CI: 1.20, 1.30), anomalies of the kidney and urinary tract (pooled OR: 1.14 with 95%CI: 1.02, 1.27), anomalies of digestive system (pooled OR: 1.11 with 95%CI: 1.01, 1.21), abdominal birth defects (pooled OR: 1.33 with 95%CI: 1.16, 1.53) and musculoskeletal malformations (pooled OR: 1.44 with 95%CI: 1.32, 1.56).

B7. Pre Term Birth

Multiple animal and human studies indicate an association between SSRI use during pregnancy and earlier birth. Preterm birth is a major clinical problem throughout the world. It is the leading cause of infant mortality: approximately 75% of perinatal deaths occur among preterm infants.

The precise mechanisms leading to the association between SSRIs and preterm birth is not known with certainty. SSRIs impact placental development, as mentioned previously. Also,the use of SSRIs during pregnancy may increase maternal serotonin. The increase in the mother's circulating serotonin could influence vasoconstriction of the uterus and placenta. From the animal literature, it appears that altering the serotonin system of the mother during pregnancy has unintended side effects to the placenta, leading to premature labor.

Animal Studies

-Domingues, et al., (2022b) investigated the effects of fluoxetine on gestation and pregnancy complications in a sheep model. They reported that the fluoxetine treated group demonstrated a statistically significant decrease in mean gestation length.

-Domingues, et al., (2023) provided a review of the current animal literature and concluded "the increase in maternal circulating serotonin due to SSRI use is likely associated with decreased blood flow to the uterus, placenta, and fetus. The decreased vascular perfusion limits placental and fetal growth causing placental pathology and increasing the risk for low birth weight/small for gestational age and preterm birth, which are associated with neonatal morbidity."

Human Studies

The following human studies demonstrate the relationship between SSRI use during pregnancy and preterm birth.

-Chambers, et al (1996) prospectively studied 228 pregnant women taking fluoxetine and compared the outcomes with 254 women not taking the drug. "the rate of premature birth was significantly higher in the exposed-late group (14.3 percent) than in the exposed-early group (4.1 percent) or the control group" (5.9 percent) ($P = 0.03$).

-Suri, et al (2007) studied 49 women with major depressive disorder who were treated with antidepressants during pregnancy (group 1), 22 women with major depressive disorder who were either not treated with antidepressants or had limited exposure to them during pregnancy (group 2), and 19 healthy comparison subjects (group 3). They found rates of preterm birth of 14.3%, 0%, and 5.3% respectively.

-Wisner, et al (2009) provided a prospective observational study of 238 pregnant women with 71 women exposed to SSRI during pregnancy. In the continuous SSRI exposure group, more than 20% of the infants were delivered preterm and the proportions of late- and early-preterm births were similar.

-Colvin, et al (2011) ran a population based study based on a national pharmaceutical claims dataset. Out of the 3703 women prescribed and taking an SSRI during pregnancy, the women who were dispensed an SSRI were statistically more likely to give birth prematurely (adjusted odds ratio [aOR], 1.4; 95% confidence interval [CI], 1.2–1.7).

-Ross, et al. (2013) surveyed delivery outcomes after exposure to antidepressant medication in a systematic review and found preterm delivery was significantly associated with antidepressant exposure during pregnancy.

-Yonkers, et al (2012) conducted a prospective cohort study of 2793 pregnant moms and extracted data on birth outcomes from hospital charts and found that the use of a serotonin reuptake inhibitor, both with and without a major depressive episode was associated with preterm birth.

-Huang, et al (2014) performed a meta-analysis of the relationship between antidepressant use and pregnancy and the risk of preterm birth. The researchers found that antidepressant exposure during pregnancy was associated with significant increased risks of pre-term birth.

-Huybrechts, et al (2014) reported on a meta-analysis of 41 studies, finding from the reviews of the literature is consistent with an association between antidepressant use during pregnancy and preterm birth.

-Eke et al (2016) retrospectively studied 93,982 women on antidepressants during pregnancy in and 1,143,687 in the control group. After adjusting for confounders, the incidence of pre term birth was significantly higher in the group of women treated with SSRIs compared with controls (adjusted OR (aOR) 1.24, 95% CI 1.09–1.41). This higher risk remained significant even when comparing depressed women on SSRI with women not on SSRI.

-Yang, et al (2017) studied 214 pregnant women: 41 (19.2%) belonged to the SRI group, 94 (43.9%) belonged to the Mood Disorder group, and 79 (36.9%) belonged to the Comparison group. Rates of preterm birth were 24.4%, 7.4%, and 8.9% respectively.

B8. Low birth weight

SSRIs have widespread effects on the mother, placenta, and fetus and there are several mechanisms by which SSRIs may affect fetal growth. Women on SSRIs can have changes in appetite (Anekwe, 2024) and weight loss as well as changes in thyroid function (Caye, 2020). SSRIs affect the formation of the placenta, vascular remodeling, serotonin signaling in the placenta, placental hormone production, and nutrient transport. SSRIs can lead to vasoconstriction reducing oxygen and nutrient delivery to the fetus (Domingues, 2023). In the fetus itself, serotonin plays a key role in cell proliferation and differentiation and synaptogenesis (Bonnin, 2011) – impacting development of the brain, bones (Fricke, 2023), and gut, as well as other organs.

Numerous animal and human studies have been performed on this topic with much evidence showing an association between maternal prenatal SSRI use and low birthweight.

Animal Studies

Several animal studies have shown an association between SSRI exposure and decreased birth weight (da Silva, 1999; Cagiano, 2008; Van den Hove, 2008; Muller, 2013; Domingues, 2022b.)

Human Studies

Several human studies have shown an association between SSRI use in pregnancy and low birth weight.

-Chambers, et al (1996) prospectively studied 228 pregnant women taking fluoxetine and compared the outcomes with 254 women not taking the medication. “For full-term infants, mean birth weight was significantly lower and birth length significantly shorter in the exposed-late group than in either the exposed-early or the control group. Similarly, the proportion of full-term infants at or below the 10th percentile for birth weight according to the growth curves of the National Center for Health Statistics was higher in the exposed-late group.” The relative risk for SGA was 4.8 (1.1 – 20.8).

-Simon, et al (2002) retrospectively studied 185 women taking SSRIs and compared them to 185 unexposed. They found an increased rate of low birthweight with a RR of LBW of 2.73 and RR of SGA of 4.38.

-Oberlander, et al (2006) studied 119,547 pregnancies in British Columbia, Canada. They found that SSRI use was associated with an increased risk of low birth weight and respiratory distress, even when maternal illness severity was accounted for.

-Klieger-Grossmann et al (2012) studied 213 women taking Escitalopram and compared them to 212 women on other antidepressants and 212 on non teratogens. They found a relative risk for low birthweight of 4.51 (from Zhao, 2018).

-Grzeskowiak, et al (2012) retrospectively studied 221 women who received a dispensing for an SSRI during pregnancy, 1566 had a psychiatric illness but did not receive a dispensing for an SSRI, and 32,004 did not have a psychiatric illness and did not receive a dispensing for an SSRI. They found an increased relative risk of low birthweight of 2.26.

-Zhao, et al (2018) performed a meta-analysis of SSRI use and risk of low birth weight and small for gestational age. They concluded: “Our results are similar to those reported in previous meta-analyses where antidepressant exposure during pregnancy was associated either with LBW or SGA.”

B9. Preeclampsia

Preeclampsia is a major issue in obstetrics. It affects approximately 5-10% of pregnancies in the US. Most cases are associated with good maternal, fetal, and neonatal outcomes, but serious morbidity and mortality can occur with this condition. The precise pathophysiology is not known with certainty, but it most likely involves abnormal/altered placental development.

Serotonin plays a crucial role in placental development and function (Bonnin, 2011, Rosenfeld, 2020; Peric, 2022.) Given that the SSRIs disrupt the serotonin system, one could anticipate that they would alter placental development and could increase preeclampsia rates.

Animal studies

There is no exact model for preeclampsia after SSRI exposures in animals. However, various animal and cellular studies have been done showing vascular, placental, and hemodynamic changes that are consistent with some of the elements of the pathophysiology of preeclampsia. This is discussed in Domingues, et al (2023). Ellenberger, et al (2025) recently reviewed this.

Human studies

-Toh, et al (2009) studied 5,731 women with non-malformed infants and no underlying hypertension who participated in the Slone Epidemiology Center Birth Defects Study in 1998-2007. They found increased rates of gestational hypertension and preeclampsia in SSRI users. Moreover, they found that those who continued beyond the first trimester had the highest rates (RR for PEC 4.9 [2.7-8.8].)

-Reis and Kallen (2010) did a retrospective study and reported an association between antidepressant treatment chronic hypertension, along with many other birth complications. Additionally, an increased risk of persistent pulmonary hypertension of the newborn (PPHN) was also verified through the study.

-Palmsten, et al (2012) conducted a study of 69,448 pregnancies in women with depression using population-based health-care utilization databases from British Columbia (1997–2006). They found that SSRI use was associated with increased rates of preeclampsia. They found that SNRIs and tricyclic antidepressants showed an even stronger association. Having a diagnosis of depression was not associated with preeclampsia.

-Avalos, et al (2018) conducted a retrospective, population-based cohort study linking automated clinical and pharmacy databases including comprehensive electronic medical records of 21,589 pregnant Kaiser Permanente Northern California members between 2010 and 2012. They found

that SSRIs were associated with increased rates of preeclampsia. Depression itself was not associated with preeclampsia.

-Bernard, et al (2019) performed a large prospective cohort of 7866 pregnant women. They found increased rates of PEC with exposure in the first and early second trimester (< 16 weeks.) The RR for SSRIs was 3.09 (1.22-7.85). (The RR for SNRIs was 6.46 (2.49-16.78.)

-Palmsten, et al (2020) found that moderate and high sustained SSRI exposure appeared to be associated with at least a borderline increased risk of preeclampsia. This study, however, did not compare SSRI continuers to nonusers, but rather to discontinuers (many of whom were on medication through a significant portion of the first trimester.)

B10. Postpartum Hemorrhage

Postpartum hemorrhage (PPH) is a leading cause of maternal morbidity and mortality. Numerous studies have demonstrated an association between SSRI use and PPH and a recent Lancet review identified SSRI use as a risk factor for PPH (Yunas, 2025.)

The exact mechanisms by which SSRIs lead to increased rates of PPH are not known but SSRIs have been shown to profoundly lower platelet serotonin levels (Peters, 2019.) The increased risk of bleeding is not seen solely in PPH. Numerous other studies have shown a link between SSRI use and upper gastrointestinal bleeding, intracranial hemorrhage, surgical bleeding, and other areas.

The current label *does have a warning* regarding PPH with use of SSRIs. However, the wording of the label may not be accurate and **currently appears to downplay the risk**.

The current label states: "Based on data from published observational studies, exposure to SSRIs, particularly in the month before delivery, has been associated with a less than 2-fold increase in the risk of postpartum hemorrhage." Elsewhere it states: "Use of ZOLOFT in the month before delivery may be associated with an increased risk of postpartum hemorrhage."

Using the term "less than 2-fold" is problematic. First, some well-done studies have found more than a 2-fold increase in risk (Lindqvist, 2014; Öndemark, 2024; and Viguera, 2024). Second, "less than 2-fold" is inexact. How much less? Finally, "less than 2-fold" has a suggestion of reassurance (as in: "these drugs do increase your risk of PPH, but it's less than 2-fold.") Postpartum hemorrhage can be deadly. The warning on postpartum hemorrhage should reflect the seriousness of this condition. Better wording would be "has been associated with up to or greater than a 2-fold increase in the risk of postpartum hemorrhage as well as increased risk of needing a blood transfusion." Alternatively, the wording can be "has been associated with increased risk of postpartum hemorrhage and blood transfusion."

(Jackson, et al (2024) found increased risk of postpartum hemorrhage as well as need for blood transfusion. This finding of an association between SSRIs and blood transfusion has also been noted in other settings: for example, after orthopedic surgery (Belay, 2019), and after cardiac and other surgeries (Sajan, 2016.)

B11. Confounding by Indication

Virtually all of the human studies, using the crude data, show some degree of increased complications in the SSRI-treated group (and the crude risk ratios are often quite high.) Some SSRI advocates argue the associations can be dismissed because there is confounding by indication (ie depression). However, ascribing the complications to depression (and not the antidepressants) has several limitations.

First, many of the research studies that associate depression itself with pregnancy complications are considered to be of low quality.

Second, the observed effects of depression itself on pregnancy outcomes tend to be small.

Third, it's not entirely clear how to adjust for depression. Many of the studies do compare the SSRI group to a depressed-nonmedicated group and many of these studies still find increased risk in the SSRI group. Some SSRI advocates state that this is due to lack of sufficient adjustment for depression. However, many of these same SSRI advocates argue that the SSRIs are highly effective at reducing depression. If the SSRIs are highly effective at treating depression, why does the SSRI group consistently have poorer OB outcomes than the depressed-nonmedicated group, and why would we have to keep "adjusting" for the depression that the SSRIs are supposed to be highly effective at treating?

Finally, the "confounding by indication" argument entirely misses the chemical-exposure aspect of this issue. In this regard, it's interesting to note how many papers there are on SSRIs and pregnancy that do not discuss the chemical aspect of this topic. With science, it's important to look at the entire body of evidence. It's not fair to just find fault with the human studies because there is no randomized-controlled trial in pregnancy. One must look at the basic science evidence and the animal studies - as well as use common sense. What all of these streams of evidence show is that the SSRIs are indeed chemicals that do have chemical impacts on mom and baby. And, in this regard, it makes sense scientifically that we would find increased complication rates in the chemically-exposed SSRI group.

B12. Exposure misclassification

Trying to ascertain whether SSRIs are associated with various complications and altered fetal development can be a complex research undertaking.

Correctly identifying exposure and timing of exposure is crucial. For example, when miscarriage or birth defects are studied, SSRI use in early pregnancy is the key time to look at. When preterm birth or low birthweight, or postpartum hemorrhage are studied, exposure through the pregnancy including (and especially) third trimester is important. Exposure throughout pregnancy is also likely important for brain alterations.

However, many of the studies on SSRIs and pregnancy do not strictly establish that patients are using throughout pregnancy. Those that do often show higher risks in that group.

Given this issue of exposure misclassification, some of the best studies in this area may be the ones with smaller sample sizes where ongoing SSRI use during the pregnancy is known/more likely to be occurring. For example, with preterm birth if one looks at the study by Suri (2007) and also by Yang (2017) we see smaller studies, but the effect on preterm birth is clear.

-Suri, et al (2007) studied 49 women with major depressive disorder who were treated with antidepressants during pregnancy (group 1), 22 women with major depressive disorder who were either not treated with antidepressants or had limited exposure to them during pregnancy (group 2), and 19 healthy comparison subjects (group 3). They found rates of preterm birth of 14.3%, 0%, and 5.3% respectively.

-Yang, et al (2017) studied 214 pregnant women: 41 (19.2%) belonged to the SRI group, 94 (43.9%) belonged to the Mood Disorder group, and 79 (36.9%) belonged to the Comparison group. Rates of preterm birth were 24.4%, 7.4%, and 8.9% respectively. This is very similar to the findings of Suri (2007) with the SSRI group having a significantly higher preterm birth rate than the depressed/not medicated group and the controls.

In both of these studies, the researchers suggest that they were fairly certain there was ongoing SSRI exposure through the pregnancy, whereas in many of the very large epidemiologic studies, it is not clear that we know that the women are actually taking the SSRIs throughout the pregnancy.

B13. All studies were not described in this document

The scientific literature on SSRIs and pregnancy is vast. For each subject covered in this Citizen Petition there are often a number of studies – sometimes a very large number of studies. A thesis could be written individually on a number of the specific subjects covered in this petition.

In some cases, we have tried to describe each study. For example, we believe we have summarized all postnatal MRI studies (12), all postnatal EEG studies (3), and all exposed-offspring constipation studies (3). In other cases (e.g. preterm birth) we presented a select few. This was done for space and time considerations and to demonstrate that there is scientific research evidence showing harm and that better warnings are needed. The presence of these positive studies should provide an impetus to warn patients and the public that there is scientific evidence showing risk.

Our intention is not to "hide" the negative studies. In most research literature on medication or chemical harm, there are negative studies. And that is the case with SSRIs and pregnancy. There are certainly negative studies in the literature that we have not presented here. We feel that many of these negative studies have significant limitations. For example, many likely suffer from misclassification and, perhaps, overadjustment – inappropriately reducing the evidence of harm initially found in the crude data.

In our opinion, the presence of negative studies in this area does not obviate the need for proper warning to pregnant women and the public given the overall preponderance of the scientific evidence.

B14. SNRIs and other antidepressants

This petition has focused on the SSRI antidepressants. However, other antidepressants are used by pregnant women as well, including the SNRIs, bupropion, MAOI, and tricyclics.
Many studies look at the issue of "antidepressants" in general. In most of those, the SSRIs are, by far, the predominant group used. Some of the studies try to account for the different classes of antidepressants. There is certainly evidence that the SNRIs in particular (like the SSRIs) are associated with pregnancy complications and that they alter fetal development. A general warning for the SNRIs could also be considered, though the amount of study has been less than on the SSRIs.

B15. Relapse of Depression vs. Withdrawal: Current Label

In the Clinical Considerations subheading of the Pregnancy section of the Label, current SSRI labels contain a section on relapse of depression with stopping the drug, which reads as follows:

"Disease-associated Maternal and/or Embryo/Fetal Risk
A prospective longitudinal study followed 201 pregnant women with a history of major depression who were euthymic taking antidepressants at the beginning of pregnancy. The women who discontinued antidepressants during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressants. Consider the risks of untreated depression when discontinuing or changing treatment with antidepressant medication during pregnancy and postpartum."

Many patients do experience significant symptoms when stopping SSRIs. And it's important that this fact be included in the counseling. It should be part of any risks, benefits, and alternatives discussion. However, it is not clear that the constellation of symptoms represents "relapse" or "withdrawal." (discontinuation.) Over the years, it has become increasingly clear that many patients do experience withdrawal symptoms when stopping these drugs.

The paper which to which the label is currently referring regarding the 201 pregnant women (Cohen, 2006a) never once mentions the word "withdrawal" in its text. In the study it appears that all symptoms were assumed to represent relapse. (That paper (Cohen, 2006a) also needed to add a correction to acknowledge that most of the authors had financial ties to antidepressant makers – which were not disclosed in the original publication (Cohen, 2006b.)

We would recommend changing the SSRI labels on this issue of withdrawal vs. relapse.

B16. A note about SSRI effectiveness

Some SSRI advocates make the argument that depression itself is associated with pregnancy complications such as miscarriage, preterm birth, and other issues. Furthermore, they state that SSRIs are effective treatments for depression. Therefore, they argue that use of SSRIs in pregnancy, by treating depression actually helps to prevent obstetrical complications and leads to better pregnancy outcomes.

Overall, in the randomized-controlled trials in nonpregnant patients, the research appears to show minimal benefit (improvement in symptoms) with use of SSRI antidepressants.

When it comes to SSRI use in pregnancy, the research evidence shows that SSRI-treated pregnancies have *increased* rates of obstetrical complications. In study after study, moms on SSRIs are having worse pregnancy outcomes (i.e. more miscarriage, more preterm birth, more postpartum hemorrhage.) The raw data virtually always shows more complications in the SSRI group.

In most of these studies, the researchers "adjust" or "correct" the data. In some of these studies the associations with complications sometimes loses statistical significance – so the authors report no association with the complication. But essentially none of the available studies in approximately four decades of research shows improved pregnancy outcomes in the SSRI group.

To emphasize the point, of the hundreds of studies that have been done on this topic over the past four decades, close to 100% of them do not show improved pregnancy (obstetrical) outcomes in the SSRI-treated group. The SSRI-treated pregnancies virtually always do worse.

B17. Conclusion

Depression is an important issue and patients suffering with depression deserve compassionate care. Part of compassionate care is providing accurate information regarding risks of medications (as well as benefits and alternatives) so that patients can make informed choices.

Common sense would dictate that medications that impact the human body and brain would also impact the developing fetus. SSRIs are known to have such impacts.

Serotonin plays a crucial role in fetal formation and development. The SSRIs disrupt the serotonin system. Therefore, the conclusion is inescapable that these drugs would be expected to disrupt fetal development.

Numerous basic science studies, and animal and human data support the assertion that SSRI antidepressants impact the pregnancy and alter fetal brain development.

The current label on the SSRI antidepressants is completely inadequate as far as warning patients and the public regarding the impact of these medications in pregnancy. We are clinicians who regularly see patients in the office. Many women report that the only counseling they received on the use of the SSRIs in pregnancy is that "the SSRIs are safe and don't affect the baby." This is not adequate counseling. But this is essentially what the current label on these medications is saying.

It's essential that FDA add more and stronger warnings to the SSRI labels in order to properly inform patients and the public.

C. ENVIRONMENTAL IMPACT

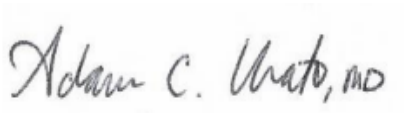
We claim categorical exclusion under 21 C.F.R 25.31(a) from the environmental assessment requirement. An active assessment is not required because the requested action would not increase the use of the medications that are the subject of this petition.

D. ECONOMIC IMPACT

Will be submitted upon request.

E. CERTIFICATIONS

We certify that, to the best of our knowledge and belief, this petition includes all information and views on which this petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.



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