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Selective Serotonin Reuptake Inhibitor Use During Pregnancy and Major Malformations: The Importance of Serotonin for Embryonic Development and the Effect of Serotonin Inhibition on the Occurrence of Malformations

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Abstract

Bioelectric signaling is transduced by neurotransmitter pathways in many cell types. One of the key mediators of bioelectric control mechanisms is serotonin, and its transporter SERT, which is targeted by a broad class of blocker drugs (selective serotonin reuptake inhibitors [SSRIs]). Studies showing an increased risk of multiple malformations associated with gestational use of SSRI have been accumulating but debate remains on whether SSRI as a class has the potential to generate these malformations. This review highlights the importance of serotonin for embryonic development; the effect of serotonin inhibition during early pregnancy on the occurrence of multiple diverse malformations that have been shown to occur in human pregnancies; that the risks outweigh the benefits of SSRI use during gestation in populations of mild to moderately depressed pregnant women, which encompass the majority of pregnant depressed women; and that the malformations seen in human pregnancies constitute a pattern of malformations consistent with the known mechanisms of action of SSRIs. We present at least three mechanisms by which SSRI can affect development. These studies highlight the relevance of basic bioelectric and neurotransmitter mechanism for biomedicine.

Keywords: maternal depression, congenital malformations, SERT, ion channel, asymmetry, laterality

Introduction

Teratogens are factors that alter or interfere with embryonic development resulting in malformations, death, growth retardation, or functional deficits in the embryo or fetus.[1] That drugs can act as human teratogens has been accepted by the medical and scientific communities for >50 years. Agents such as thalidomide, retinoic acid, and antiepileptics, to name a few, are compounds that are teratogens as demonstrated by epidemiological methods, principles, and criteria. Recent epidemiological research has shown that selective serotonin reuptake inhibitors (SSRIs), the most commonly used class of antidepressants, by their common mechanism that inhibits reuptake of serotonin or 5-hydroxytryptamine (5-HT) by the serotonin transporter (SERT or 5-HTT), increase the risk of spontaneous abortions, major congenital malformations, intrauterine growth retardation, prematurity, and cognitive delay.[2–20]

In addition to the fact that data are accumulating that demonstrate a risk of major congenital malformations associated with SSRI use during gestation, the efficacy of these drugs for the treatment of depression has been questioned. For example, due to increased maternal metabolism during pregnancy,[21] SSRI drug dosage should be increased to maintain the same prepregnancy effectiveness.[22] However, evidence shows that the majority of women maintain or decrease their SSRI dosage once their pregnancy is diagnosed.[21] Therefore, if there were benefits to SSRI use before pregnancy, this is no longer the case during pregnancy. Furthermore, the majority of depressed women are moderately depressed,[23] and the risk to the unborn child of using SSRIs outweights the benefits in this population, given that exercise or psychotherapy is now known to be effective alternatives to taking the drugs.[23]

According to the United States Food and Drug Administration (FDA)'s Established Pharmacologic Class,[24] SSRIs are an established pharmacological class because they all

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have the same mechanism of action, which is to inhibit 5-HT reuptake by SERT, thereby increasing extracellular concentrations of the neurotransmitter. By these criteria, the drugs sertraline, paroxetine, citalopram, escitalopram, and fluoxetine belong to this established pharmacological class.[24] In fact, all drugs with potent serotonin reuptake inhibiting effects constitute a class—this includes SSRIs but also venlafaxine, desvenlafaxine, duloxetine, and clomipramine.

This review presents the available evidence concerning the effects of SSRIs on the fetus during pregnancy as well as the role of 5-HT in normal embryonic development. We posit at least three types of mechanisms by which SSRIs can affect development (Fig. 1): by altering endogenous serotonin levels in embryonic tissues, alteration of developmental signaling through modulation of electrogenic ion channels, and perturbation of calcium signaling pathways. Also, the impact of maternal depression and the effectiveness and risk of SSRIs in preventing or treating depression in pregnant women are discussed. The safety of prescribing SSRIs to treat depression and related conditions in women of childbearing age is of paramount public health importance, given the potentially serious outcomes for the unborn child.

The Importance of Serotonin for Normal Embryonic Development

Serotonin is not only a neurotransmitter but also a profoundly important medium for cell to cell communication among many cell types during embryogenesis.[25–27] It has been implicated in several developmental events in addition to its roles in regulation of the nervous system.[28–43] Most of the data on serotonin's role during embryogenesis are derived from model systems, in which definitive functional experiments can be performed that are impossible in human embryos for ethical reasons. It should be kept in mind that the fundamental mechanisms of cell biology and developmental pathways are highly conserved among vertebrate species; this is why organisms from yeast, to fruit fly, and to frog are responsible for many breakthroughs in human biomedicine (including birth defects, stem cell biology, and cancer). A range of animal models, including mammals such as rodent and rabbit, together with nonmammalian animals, such as *Xenopus* (frog), chicks, and zebrafish, provide vital information regarding the common and evolutionarily ancient mechanisms that orchestrate individual cell behaviors essential for normal development.

The embryo's serotonin pool derives from two sources: zygotic and maternal. Mammalian embryos generate their own serotonin very early, long before the nervous system appears. For example, mouse embryonic stem cells synthesize 5-HT,[44] and both 5-HT and SERT are found in oocytes and cleavage-stage embryos of many species.[45,46] Moreover, serotonin generated by the mother is passed on to the developing embryo through placental uptake and transport.[43] Recent work has shown that serotonin is a key signaling molecule and is a medium for communication among cells during embryogenesis.[28,29,35,36,42,47] Thus, appropriate signaling requires a delicate balance and correct concentrations

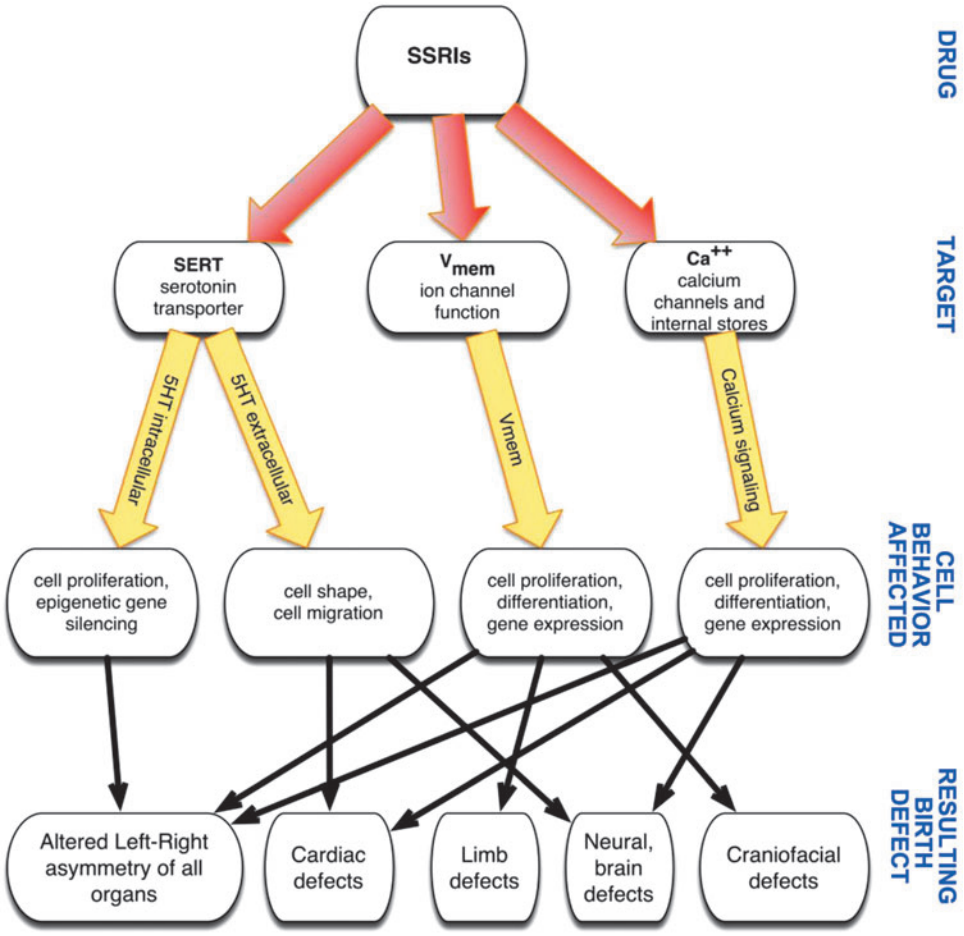

FIG. 1. Three types of mechanisms by which SSRIs can affect development. SSRIs, selective serotonin reuptake inhibitors.

of serotonin in specific locations. Total 5-HT levels measured in blood are not sufficient to detect imbalances in this type of signaling because the relevant levels are within and adjacent to key cell types within the embryo and not in the maternal or fetal circulations. The fact that SSRIs readily cross the placenta[48] 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.

Serotonin signals in two basic modes. In the extracellular mode (Fig. 2A), 5-HT arrives at the surface of target cells by diffusion from external locations and activates any of a family of seven extracellular serotonin receptors.[49] The serotonin source can be remote cell types,[29] or may indeed be

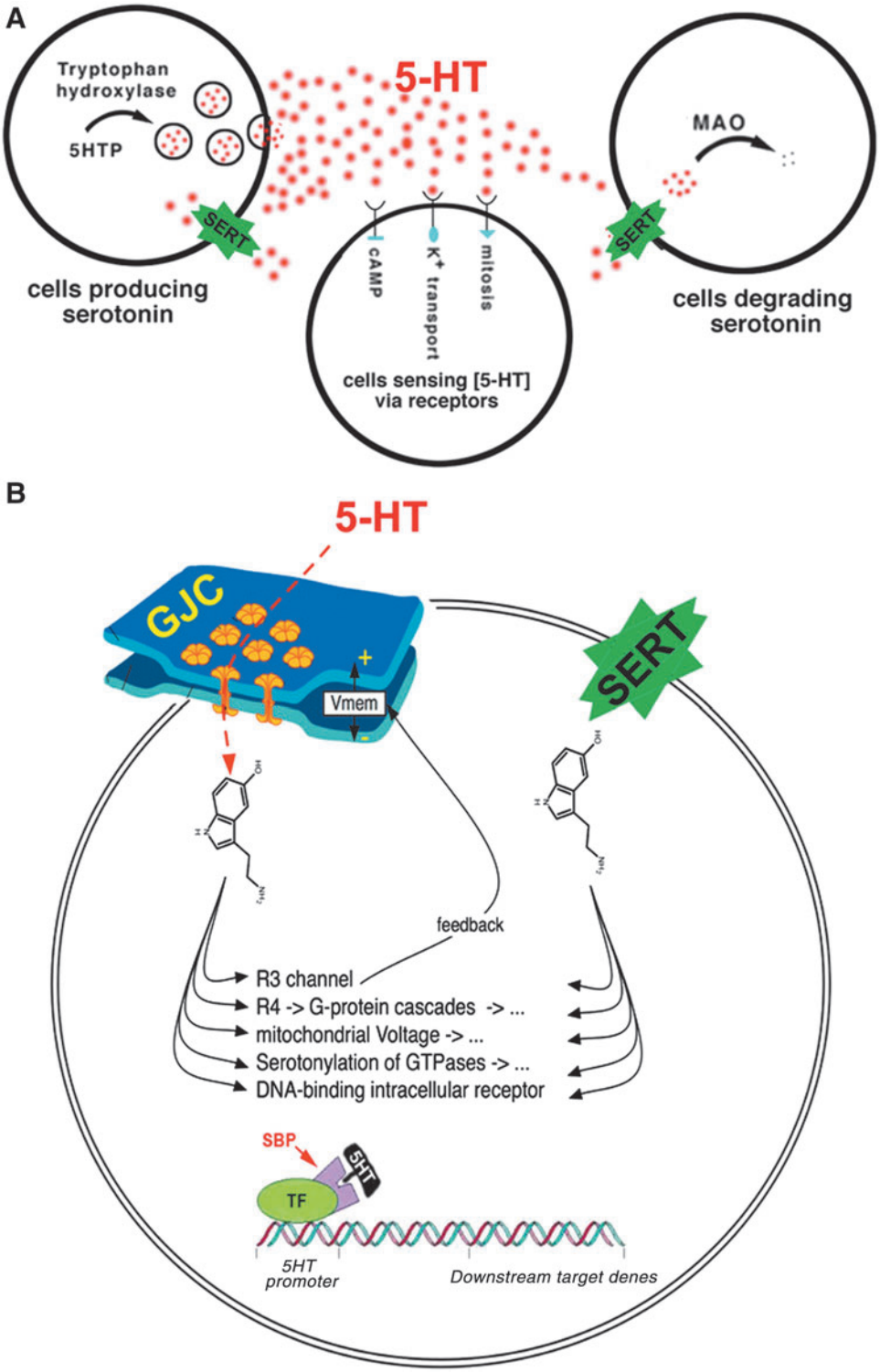

FIG. 2. Two basic modes for serotonin signals. **(A)** Extracellular mode. **(B)** Intracellular mode.

secreted and received by the same cell (autocrine signaling). In the intracellular mode (Fig. 2B), serotonin arrives intracellularly through SERT-mediated import or through gap junction channels with neighboring cells.[36,50–56] Levels of intracellular serotonin control cell division,[57] cytoskeletal dynamics,[58–60] second messengers (adenylate cyclase and histone deacetylase),[61–63] and developmental gene expression. This occurs through binding to intracellular serotonin binding proteins,[64] including Mad3 and 5-HT-R2,[65,66] and by serotonylation of a variety of key molecules.[67–70]

Developmental serotonin signaling participates in a number of patterning events. One is establishment of body organ laterality—the invariant positioning of the visceral organs and heart. Consistent left–right (LR) asymmetry is a highly conserved feature in amphibians, reptiles, birds, fish, and mammals, all of which orient their hearts and visceral organs with the same biases in placement and morphology. In fact, the most basic cell signals for establishing laterality are conserved among many diverse species, including plants, nematodes, frogs, and humans.[47,71] This conservation is important because it means that the basic mechanisms of LR asymmetry can be readily studied in model organisms.[72] Errors in establishing laterality result in heterotaxy and include an important class of human birth defects with serious medical implications for the patient.[73–76] It has been shown in chick and frog models that serotonergic signaling is required for the left and right sides of the body to acquire their identity and properly orient asymmetric organs such as the heart, stomach, liver, and others.[28,35,36,42,65,77–79] In addition, serotonergic signaling controls cell proliferation,[80–85] regulation of cell shape and cell movement patterns,[29,47,86–89] neurogenesis and brain patterning,[90,91] heart morphogenesis,[92] eye development,[93] and craniofacial morphogenesis.[39,94–96]

SSRIs can block 5-HT uptake by the ectoplacental cone (early placenta in rodents) and placenta.[43] Importantly, the SERT, a membrane protein that transports serotonin across cell membranes, acts as a key regulator of serotonin availability both inside and outside of cells. Although the name ''reuptake inhibitor'' for compounds that block SERT focuses on transport of serotonin into cells, SERT can also run in reverse to provide a source of serotonin to surrounding cells.[97,98] This process is key to the regulation of certain kinds of stem cell derivatives.[29] Thus, SSRIs affect mechanisms dependent on extracellular serotonin (mediated by plasma membrane receptor types 1–7) and mechanisms dependent on intracellular serotonin (epigenetic marking through HDAC1 and serotonylation of other signaling molecules).

Not only the mature nervous system but also many early embryonic cells utilize serotonin as a signaling messenger.[59,60,99–102] Thus, by design and purpose, any of the class of SSRI drugs will profoundly affect the concentrations of this key molecule and thus the 5-HT-dependent signaling that is necessary for completing normal embryogenesis.

Bioelectricity: A Teratogenic Mechanism for SSRIs in Addition to Serotonergic Pathways

There is another mode of action by which SSRIs can perturb embryogenesis, distinct from the primary effects on SERT and serotonin levels. A number of studies have shown that SSRIs can bind to and modulate the activity of numerous ion channels in mammalian cells, including sodium, chloride, and potassium channels.[103–115] Binding to these channels is relevant to the origin of birth defects because ion channel activity, such as serotonergic signaling, is not only a function of the nervous system but also a major mechanism for coordinating cell processes during embryonic morphogenesis of many organ systems.[116,117]

Data on developmental bioelectricity reveal that ion channels set up precisely patterned endogenous electric fields and voltage gradients regulating the formation of the heart, limb, brain, eye, and face.[118–127] Human channelopathies (mutations disrupting bioelectric signaling) have revealed how disruption of ion channels can play a role in the causation of birth defects, including Andersen–Tawil syndrome,[128,129] urogenital malformations,[130,131] Angelman syndrome,[132,133] Beckwith–Wiedemann syndrome,[134–136] and defects of the face,[137] heart, central nervous system, and neck.[138] Recently, Gelb and coworkers[139] discovered numerous ion channel mutations, including some involving channels directly modified by SSRIs, which result in birth defects of the heart (including laterality defects predicted by earlier work in frogs[28,35,36,42,140–142]) and of the limb in mouse embryos. These data clearly confirm that the results obtained from frog models are directly relevant to mammalian development.

Transmembrane resting potentials (determined by specific ion channels) regulate proliferation and differentiation in a range of somatic and stem cell populations *in vivo*.[126,143] The known interactions of SSRIs with sodium, potassium, and chloride ion channels[103,104,106,107,109–111,113–115] suggest the likelihood that SSRI exposure of the fetus will perturb the fine-tuned bioelectrical signaling that enables individual cells to differentiate and arrange themselves in correct anatomical structures.[144]

Based on these effects of 5-HT as a signal molecule potentially regulating development of a variety of organ systems through effects on general cell processes, such as proliferation and migration, it is easy to understand how SSRIs can cause multiple types of birth defects. In fact, this outcome appears to be exactly what occurs as shown by epidemiological studies.[5–9,11,13–15,145–147] In turn, this multiplicity of birth defects then ''dilutes'' the data because incidences of any single defect may be low, making it difficult to identify statistically significant associations between *in utero* drug exposure and teratogenicity. However, the ''array'' of defects observed after exposure to SSRIs may represent a single classification of abnormalities with a common origin, hence a pattern of malformations.

For example, as stated previously, 5-HT is an important signaling molecule for establishing laterality by specifying the left–right (LR) axis on approximately the 14–16th days of gestation in humans (postconception).[28,35,36,42,65,77–79] The establishment of this axis is essential for normal development and disruptions in this process, as can be caused by SSRIs, resulting in heterotaxy. Individuals with this condition have abnormalities of positioning of organ systems, including the spleen, heart, liver, and gut, and a wide variety of birth defects.[75,148–152] The most sensitive organ to disruptions in laterality signaling is the heart[73,151] and virtually every type of heart defect can occur when this signaling is altered, including atrial septal defect, ventricular septal defect, double outlet right ventricule, hypoplastic left ventricles, hypoplastic right

ventricles, tetralogy of Fallot, single ventricle, atrial inversions and isomerisms, ventricular inversions, and transposition of the great arteries among others.[73,149,153–155] A variety of other defects may also occur, particularly vascular defects, such as total anomalous pulmonary venous return.[14,156] There is also a link between laterality abnormalities and midline defects that has been documented in the clinical literature since at least the mid 1990s. All types of midline defects have been observed in patients with laterality abnormalities, including neural tube defects, cleft lip and palate, gastroschisis, omphalocele, anal atresia and stenosis, and caudal dysgenesis.[75,148–152,156] In fact, midline defects so commonly occur when laterality signaling is disrupted that if a patient has a midline defect, it has been estimated that they are 3 times more likely to have a laterality issue as compared with patients without a midline defect, and 100 more times than the general population.[148,151] Furthermore, because many patients are never specifically assessed for laterality issues, these rates are likely under-reported. More importantly, individuals with midline defects do not require laterality abnormalities to be classified as having disrupted laterality signaling as the primary etiology of their midline malformation. This point has been proven in studies of family members with known mutations to laterality genes. In such families, a high incidence of family members exhibit only a single midline malformation, such as cleft palate or a neural tube defect, with no other abnormality.[151,152,156] The reason that midline defects are common is probably due to the fact that as development proceeds, the different axes, including the anterior–posterior (cranio–caudal), dorso–ventral, and LR, must be coordinated in specifying the origin and position of the different organ systems.[152,157–159] Therefore, if one axis, such as the LR, is abnormal, it disrupts the coordinated effort and results in a variety of defects, some of which might not appear to be related directly to effects on the targeted axis. Hence, a midline defect might occur due to a disruption in laterality signaling. Thus, the SSRIs may produce a variety of birth defects through a common mechanism of altering 5-HT concentrations and through a common pathway of disrupting 5-HT signaling responsible for establishing the LR axis at 14–16 days of gestation. This explanation readily explains the variety of seemingly unrelated defects seen at birth after SSRI exposure *in utero*.

SSRIs and Major Congenital Malformations in Humans

Depressive symptoms are common during pregnancy, and SSRIs are the most frequently used antidepressants to treat pregnant women.[21,160,161] Studies concerning the adverse effects of SSRI exposure during gestation on the developing fetus have indicated an increased risk of various congenital malformations,[2,5–10,18] but inconsistencies between study results remain.[11–13,162,163] These could potentially be explained by indication bias wherein the effect of the drug and the indication are correlated and not fully accounted for,[6,145,164] or misclassification bias wherein exposure and/or outcome assessment have not been validated.[165]

Gestational use of SSRI has been associated with an increased risk of various major congenital malformations.[2,5–14,18] This has been repeatedly shown in large well-designed population-based studies with sufficient statistical power. Indeed, over the past 20 years, data on the risk of malformations associated with intrauterine exposure to SSRI have been accumulating, even more so after 2005, when the warning on the risk of heart defects associated with paroxetine exposure during pregnancy was issued.[166] Although the magnitude of the risk varies from one study to another, and between organ systems, it remains that as early as the mid-'90s, sufficient signals on the risk of major congenital malformations on human pregnancy exposures to SSRIs have been available.

Overall, SSRIs as a class and SSRI-specific drugs increase the risk of major congenital malformation by at least 30% during pregnancy (30–130% increase in risk);[2,7,9,10,13,15,18] the risk also increases with increasing dosage, which is supportive of a dose–response relationship,[6,15] and longer duration of use during pregnancy, which is consistent with a cumulative effect.[10] Although some studies lack statistical power, the majority of risk ratio estimates are >1, indicating an increase in risk. Even after considering the potential for bias, confounding and chance finding, the evidence-based literature demonstrates that prenatal exposure to SSRIs as a class causes an increased risk of congenital malformations in infants exposed *in utero* during the critical developmental time period. Given that major malformations are rare, more weight should be put on repetitions of findings or defects with known mechanisms of action than statistical significance, which solely depends on the number of exposed cases.[164]

SSRIs as a class increase the risk of major cardiac malformation by at least 60% as compared with nonuse during pregnancy.[2,7,9,11,14,15,18,146] The published peer-reviewed evidence on sertraline, fluoxetine, citalopram, escitalopram, and paroxetine consistently demonstrates an increase in the risk of cardiac malformation from a 9% increased risk to more than four times the risk seen in nonusers. Although some cardiac defects are rarer and would require a very large sample size, which would be very difficult to acquire, there is evidence on some of the specific types of cardiac defects. Hence, SSRI as a class and SSRI-specific drug use during gestation have been associated with an increased risk of atrial and ventricular septal defects,[2,5–9,11,14,15,18,145,164] right and left ventricular outflow track obstruction,[5,8,18] conotruncal defects,[5,8] transposition of the great arteries,[5] tetralogy of Fallot,[5] pulmonary valve stenosis,[5] and patent ductus arteriosis.[14]

SSRIs have also been shown to increase the risk of craniosynostosis (odds ratios range from 1.94 to 2.5).[2,5,8,15,145] Of note, the critical period of development for craniosynostosis may extend beyond the first trimester as shown by Alwan et al.[5] who estimated a 90% increase in risk associated with second and third trimester exposure to SSRIs. However, Berard et al.[145] showed that exposure at any time during pregnancy did not change findings. SSRI as a class also increases the risk of gastrointestinal defects (omphalocele, gastroschisis, esophageal atresia, anal atresia, hypertrophic pyloric stenosis, and vesicoureteric reflux)[5,8,14,15]; neural tube defects (anencephaly and spina bifida)[5,8,11]; cleft lip with or without palate[8,11,14]; limb defects[5,8,14,167]; and other defects such as diaphragmatic hernia,[5,8] hypospadias,[8] undescended testis,[8] and cystic kidney disease.[14] All of these phenotypes are potential outcomes of perturbed serotonergic, bioelectrical, and calcium signaling. Furthermore, there is consistent evidence showing that SSRI as a class at least doubles the risk of persistent pulmonary hypertension of the newborn.[168–171]

Finally, SSRI as a class, and all SSRIs-specific drugs have been found to increase the risk of spontaneous abortions.[3,4,172]

Given that embryos with severe malformations are predominantly miscarried,[164] this suggests that the true impact of antidepressants on the occurrence of defects is much higher than would be apparent from examination of embryos that survived to birth.

In summary, SSRIs considered separately or as a class have consistently been shown to increase the risk of major congenital malformations in general, and major organ system malformations specifically, even after considering the different magnitude of effects reported in studies. Defects observed at birth have similar embryonic origins and can be considered a pattern of malformations as already explained.

The Role of Depression

Recent reviews of prenatal mental health issues note that 35% of pregnant women have depressive symptoms and there are claims that 10% of them are depressed.[173] One problem with this formulation is that having symptoms, even meeting every single one of the operational criteria for depression, does not necessarily mean a person is depressed. The point prevalence of major depression is 3.8% at the end of the first trimester, 4.9% at the end of the second trimester, and 3.1% at the end of the third trimester of pregnancy rather than the 10–15% routinely reported.[174] When arguments for treating prenatal depression are put forward, they state that untreated depression leads to smoking, alcohol and drug intake, poor self-care, suicide, and postnatal depression.[175] They furthermore infer that there may be a direct toxic effect of untreated depression on the fetus.[176] Finally, they point to effects on the development of the child in later life, arguing that these are substantial and deleterious.[177] There are no known direct toxic effects of prenatal depression on the fetus. There is no known endocrine change linked to the majority of common nervous disorders that affect pregnant women that could affect the fetus. Maternal depression during pregnancy is not associated with the risk of congenital malformation, hence is not a risk factor for malformations. However, lifestyles associated with maternal depression, such as smoking,[178] alcohol use,[179] and lack of folic acid use,[180] have been implicated in the occurrence of major congenital malformations. Therefore, maternal depression is often used as a proxy for associated lifestyles.

Mothers who are depressed during pregnancy are, however, at increased risk of postpartum depression,[181] and have lower mother-to-child attachment after delivery.[182] If prenatal depression leads to a postnatal depression, there is always the opportunity to treat the depressive disorder vigorously at that time without risk to the fetus. Nevertheless, depression should be monitored during gestation and appropriate treatment (exercise and psychotherapy)[183,184] should be considered. Furthermore, SSRIs are transferred to breast milk when used during the postnatal period, and thus have the potential to impact newborns during this time window.

Effectiveness of SSRIs During Pregnancy

Until the advent of SSRIs, the term depression in general referred to a more serious condition than major depressive disorder (MDD) now refers to. This more serious condition was originally called melancholia, later becoming endogenous depression. We know little about the risks of leaving classic or severe depressive disorders of this type untreated. Melancholia is extremely rare in women who are pregnant, or in women of childbearing age. SSRIs are not given for classic or severe depressive disorders since the drugs are not effective in treating these conditions. These drugs are less effective than older antidepressants such as clomipramine for more severe depressive disorders. SSRIs are marketed for and given to women with anxiety and depressive symptoms. The lack of evidence concerning the efficacy or effectiveness of SSRI therapy, together with the fact that numerous studies have documented their detrimental effects on embryonic and fetal development mandates that alternative nonpharmacological interventions should be recommended for pregnant women with a resort to medication being a secondary option. At present, little consideration is given to nonpharmacological treatments with proven efficacy, such as exercise[183] or psychotherapy.[184]

In 2006, the FDA held hearings on the issue of warnings regarding suicidality based on data from adult trials of antidepressants including all SSRIs. These trials in total contained close to 100,000 patients, >50,000 of whom were depressed patients. Aside from the question of suicidal acts, data from all short-term placebo-controlled adult trials for MDD for the past 15–20 years show that antidepressants in general have minimal effectiveness. When data from all randomized trials are combined, 5 out of every 10 patients respond to the drugs, but in the same trials 4 out of every 10 patients respond to placebo.[185] Therefore, only 1 in 10 patients put on treatment responds specifically to the drug they have been put on, whereas 5 out of 10 either fail to respond or respond adversely.[185] The high placebo response means that in many cases, the natural history of depressive disorders is to resolve spontaneously; in other instances, diet and hygiene will provide effective treatments, or assistance from the patient's physician to help work out problems at home or at work will solve the issue. Therefore, evidence-based findings demonstrate that in all instances, not just in the case of pregnant patients, SSRIs are not an effective treatment protocol for depression and should only be used for patients who do not respond to a conservative approach. Furthermore, issues regarding efficacy and the potential for harming babies should be made clear to pregnant women so they can opt an alternative treatment.

In the event that a particular prenatal depression or anxiety state is judged to require active treatment rather than simply employing monitoring measures, treatments such as interpersonal therapy (IPT) and cognitive behavioral therapy, which for this level of severity are as efficacious as drug treatment, can be considered. Indeed, given the role of social factors associated with the nervous states found during pregnancy, IPT that originated as a treatment for postnatal depression would appear to be particularly suitable for prenatal disorders.[186]

For moderate to severe or melancholic depressive disorders, guidelines such as those issued by the National Institute for Health and Clinical Excellence (NICE) recommend tricyclic antidepressants rather than SSRIs.[187]

Conclusion

The Bradford Hill criteria[188] are useful in evaluating causality between an exposure and an outcome. Although these criteria are used to assess causation, not all of them

need to be fulfilled to establish general causation. Evidence indicates that SSRI use during pregnancy is interrupting and/or disturbing essential events during the embryonic stage and organogenesis, which initiates a cascade of events that are causing spontaneous abortions and major congenital malformations. Epidemiological evidence in humans is consistent, and findings have been replicated in different patient populations; a dose–response has also been established. Malformations identified that all have similar embryonic origins and thus demonstrate a pattern of malformation. Mechanistic data unequivocally demonstrate that three major pathways known to be crucial for patterning of many embryonic organ systems, serotonergic signaling, bioelectric signaling, and calcium signaling all can be perturbed by SSRIs. The importance of these pathways in regulating cell behavior and multiple patterning systems during embryogenesis clearly suggests that SSRIs have the potential to cause birth defects. Given that all SSRIs have a similar mechanism of action, they should be considered as a class of compounds producing the same adverse effects on development.

Maternal depression has not been shown to increase the risk of major congenital malformation. The majority of depressed pregnant women have mild to moderate depression for which SSRIs are ineffective. At present, the risk–benefit ratio does not support the use of SSRIs during pregnancy. It is important that depression be monitored, but nonpharmacological therapies, such as exercise or psychotherapy, should be considered as a first line treatment during the gestational period. More broadly, because of the tight relationship between ion channel-mediated signaling and downstream neurotransmitter transduction steps operating during development, the mechanistic and epidemiological data on SSRIs serve as a primary example of the interplay between basic work in developmental bioelectricity and biomedicine.

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Authors' Contributions

The concept and design of this study were done by A.B., M.L., T.S., and D.H.; the article was drafted by A.B., M.L., T.S., and D.H.; and critical revision of the article and important intellectual content were carried out by A.B., M.L., T.S., and D.H. All coauthors have reviewed and approved of the article before submission.

Disclaimer

The article has been submitted solely to this journal and is not published, in press, or submitted elsewhere.

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