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REVIEW ARTICLE

Antidepressant use in pregnancy: are we closer to consensus?

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Abstract
We specify and summarize significant data from recent large studies in a tool with which to aim at consensus on the question of whether and how serotonin-reuptake antidepressants should be used in pregnancy, on the basis that concern for the mental health of the mother should not vie for primacy with concern for the short-, medium-, and long-term health of the child, but must be best served together. Side effects are small but significant over the majority of 11 categories, perinatal and into adolescence. In clinical practice, alternatives for serotonin-reuptake medication in pregnancy should be more actively pursued.

Keywords Antidepressants · Anxiety · Depression · Pregnancy · Psychological treatment · Side effects

Introduction Over the past decade, a debate is gaining substance as to what treatment should be recommended to the significant number of women who suffer depression or anxiety and find that they are pregnant (15–20% women lifetime depression incidence; 8% of pregnant women) or develop such mental health symptoms during pregnancy. Health professionals want to mitigate the suffering caused to pregnant women by mental conditions. However, the present principal means to that goal is antidepressant and anxiolytic medication, which has risks—although not yet fully defined—for the unborn. Said debate needs, more than opinions, hard data to reach valid conclusions. Prescribing antidepressants in pregnancy as well as taking such drugs supposes accepting an increased risk of pregnancy loss, congenital malformations, neonatal adaptation syndrome, persistent pulmonary hypertension of the newborn, autism spectrum disorder, and long-term neurocognitive deficits. Rather laconically, some authors propose that, when these risks have a limited prevalence, for example not exceeding the 1–3% of congenital problems considered "normal" in the general population, there should be no special cause for concern (Robinson 2015).

The argument that pregnancy mishaps also may—and do—occur because of other causes or that negative effects associated with antidepressants will be small does not liberate the physician from the duty to avoid doing harm. The woman should be offered valid options. Neither does it liberate the pregnant woman from concern over nocive effects on her child. Depression in pregnancy harms both, and that should not be ignored.

Study design on this subject has lacked rigor in some cases. Scientifically, research comparing treating a pregnant woman with antidepressants or not treating her at all should include control groups on alternatives such as early screening methods, non-medication, and psychological treatments (O'Connor et al. 2016). If it does not, the comparison is incomplete, and its results must be valued accordingly. Also, consequences as to maternal effects and fetal effects are phenomena in different universes and, as such, incomparable and without any "benefit–risk ratio" (Koren and Nordeng 2012). Avoidable negative effects on offspring can hardly be "compensated" by beneficial effects on maternal depression. Significant identified negative effects should not be valued as "normal" based upon statistics on their class of problems of the past.

Over these decennia, many authors have critically interpreted study results, being aware of these apparent errors in logic or medical morality. Genetic and cell-level causal mechanisms of malformations after the use of antidepressants and other psychoactive substances are being studied. Animal-model studies with common antidepressants such as citalopram identified some of these mechanisms (Durham et al. 2015), while human research had already been able to observe other such mechanisms or identify alterations produced by antidepressants in placental cells (Seth et al. 2015) or in fetal brain matter (Jha et al. 2016).

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Our work centers on large studies that may reflect small but significant and long or very long-term effects.

> "… not entertaining any proposition with greater assurance than the proofs it is built upon will warrant." John Locke[1]
> "The wise person proportions his beliefs to the evidence." David Hume[2]

Method The search was made for studies preferably $N>$ 50,000 for higher discriminative value and meta-analyses since 2010, with the keywords, in databases including PubMed, Cochrane Library, PsycINFO, Scopus; no language limits, pursuing upcoming links. Initial results obtained 93 publications, of which 44 were relevant for this analysis.

Results

Meta-analysis and health register-type studies intend to determine effect sizes that are sensitive to specific populations (Dwyer et al. 2017), and, as a result, new recommendations may be forthcoming for women, government health agencies, and professional organizations, even though laboratory evidence is not yet complete. These prospective studies of medical data and not of patient perception reduce biases (Bérard et al. 2017a, b), including those against the null hypothesis in retrospective registries of gestational drug exposure (Etwel and Koren 2016). Not all register studies supply results that go in the same direction, however, and their design differences need to be weighed with care.

Yet, the cumulative data may be close to construing a conclusion that only a decade ago was considered speculative (Campagne 2007). From specific genes to placental cells, from pre-pregnancy to third-quarter use, over the past decade, a considerable number of adequate studies on pre-pregnancy and ante-natal antidepressant use have measured significant effects. The more generally prescribed selective serotonin reuptake inhibitors (SSRIs) and selective serotonin-norepinephrine reuptake inhibitors (SNRIs) are most represented in negative effects. This does not mean that all study results conclude against SSRIs or SNRIs in pregnancy. However, any conclusion of results depends on study design, economic factors, and data in which alternative treatments have not usually been represented. With noticeable exceptions, research has been limited to just comparing treating depression in pregnancy with antidepressants, and not treating it at all. Alternative treatments of proven efficacy, though generally available at comparable cost and endorsed by leading authorities, have a still limited use in pregnancy and are restricted to minor or moderate depression, thus perpetuating the "drugs-yes, drugs-no dilemma" for cases of severe or major depression. Professional guidelines reflect the efficacy of alternative treatments, mainly cognitive–behavioral therapy and psychosocial (lifestyle) changes. Clinical trials are underway to specifically compare women tapering SSRIs in pregnancy with the use of cognitive psychotherapy, as against continuing SSRIs (Molenaar et al. 2016). Although studies do not often control for pre-pregnancy antidepressant use (which is relevant, as we shall see), budding research including non-drug alternatives for SSRIs is, by itself, a paradigm shift. Voices (Chisolm and Payne 2016; Akioyamen et al. 2016) defending antidepressant use in pregnancy as being "relatively safe" are still no exception. Nearly 50 years ago, Ayd (1968) recommended the following that should be consensus by now: "Hence, one of the commandments of governing rational psychopharmacotherapy should be 'Thou shall not prescribe psychoactive drugs during the first trimester except when absolutely necessary.'" The fact that animal studies or small studies on humans have not demonstrated a strong teratogenic potential of most antidepressants does not diminish the essential value of Ayd's recommendation. We need to look at large human studies to get a clear picture. The reality that non-pharmaceutical alternative treatments of depression are available but hardly used confirms that study objectives and treatment recommendations are influenced by other interests. Moreover, depression is often present before pregnancy but undiagnosed or untreated or may originate during pregnancy. More than half of women with depression may not be diagnosed as such. Ko et al. (2012) identified 375 pregnant and 8657 non-pregnant women aged 18–44 with a past-year major depressive episode (MDE), from 2005 to 2009 nationally representative data. An MDE in pregnant women (65.9%) went undiagnosed more often than in non-pregnant women (58.6%). Only half of depressed pregnant (49.6%) and non-pregnant (53.7%) women received treatment with prescription medication, being the most common form of treatment for both pregnant (39.6%) and non-pregnant (47.4%) women, followed by psychological counseling (36.3% of pregnant and 35.5% of non-pregnant women).

Although in most research the size of negative effects was found to be limited, these were in many cases significant and, thus, must be considered by the clinician. The accumulated evidence is inducing professionals and national health authorities to revise present standard practice and recommendations and to adopt changes that include steering away from generalized antidepressant use in pregnancy.

Doubts have been expressed as to the efficacy of antidepressants and attributed positive effects to placebo effects. A Cochrane review by Moncrieff et al. (2004) summarizes the following facts of the dilemma: (a) recent meta-analyses show that SSRIs have no clinically meaningful advantage over placebo; (b) claims that antidepressants are more effective in more severe conditions have little evidence to support them;

[1] An essay concerning human understanding. London, 1689
[2] An enquiry concerning human understanding. Clarendon Press, Oxford, UK, 2000, edited by Tom L. Beauchamp (EHU).

and (c) methodological artifacts may account for the small degree of superiority shown over placebo.

Authoritative recommendations have been forthcoming. In 2009, "The Management of Depression During Pregnancy: A Report from the American Psychiatric Association (APA) and The American College of Obstetricians and Gynecologists (ACOG)"(Yonkers et al. 2009) included the recommendation that mild to moderate depression "may" be treated with psychotherapy. This does not mean that, today in the US, psychotherapy is the first option, probably because of insufficient availability of therapists.

In the United Kingdom, the National Institute for Health and Clinical Excellence (NICE) has gone a step further. The "Antenatal and postnatal mental health" guideline recommends stopping antidepressants in all women with mild or moderate depression who become pregnant and recommends psychological treatment and psychosocial intervention. The Improved Access to Psychological Therapies (IAPT 2007) (Clark 2011) confirmed the British government's commitment to psychological treatments for depression as the first option. In Australia, the similar National Perinatal Depression Plan (2008) is proving wide-reaching and influential. Up to now, data on the clinical impact of these recommendations are scarce and many countries have no similar initiatives. Existing reports and guidelines should contribute to both medical and psychotherapeutic solutions being considered on their merits, unhampered by prejudice or unfamiliarity.

These guidelines do not imply that antidepressants are never needed in pregnancy. As said, they have their place and merits. In utero exposure to either maternal depression or antidepressants carries risks to the developing fetus, and decisions about the use of antidepressants during pregnancy must be taken on a risk–benefit analysis based on the best evidence of the risks of treating or not treating maternal depression. However, validated alternative treatment options must be included.

In general, depression is not an immediate life-threatening event for the pregnant woman, nor does it constitute an immediate danger for the fetus. The UK National Perinatal Epidemiology Unit puts it at sixth place of maternal mortality rates, for all perinatal—and thus predominantly postpartum—incidents. The woman becomes aware of her changed mood and may ask for help, or the treating physician may have the good sense to screen for depression. This gives some time to decide upon treatment. Out of common sense, professional responsibility, and ethics, preference should be given to the least noxious solutions. In view of their consistently positive results, psychological, psychosocial, or alternative solutions such as acupuncture to mild, moderate, or major depression are valid treatment options to be implemented accordingly (Manber et al. 2010). In 2012, Khan et al. reviewed data from the Food and Drug Administration (FDA 2017) Summary Basis of Approval reports of 62 pivotal antidepressant trials consisting of data from 13,802 depressed patients. This was followed by a systematic review of data from 115 published trials, $n = 10.310$, evaluating the efficacy of psychotherapies and alternative therapies for depression. When calculating symptom reduction, they found similar efficacy of antidepressants and psychotherapies, although a combination of psychotherapy and antidepressants for major depression provided a slight advantage compared to antidepressants alone or psychotherapy alone, which in turn were not significantly different from alternative therapies or active intervention controls. In a similar venue, a 2011 meta-analysis by Sockol et al. found no significant difference in effect sizes of medication and non-medication treatment in perinatal depression. A 2013 meta-analysis of direct comparisons in depressive and anxiety disorders by Cuijpers et al. also confirmed both treatment categories to have similar effect sizes. Thus, there are alternatives to antidepressants, with a similar efficacy and without any toxicity.

We aim to try and reflect the broader picture of the issue, and although this presents statistical challenges, research results as to different symptoms and probabilities measured in different clinical situations can be combined into an informative tool, with the main known side effects associated with antidepressant use in pregnancy divided into the following categories. Additionally, the specific moment when antidepressants were used proved to be relevant is as follows: (a) up to 12 months before pregnancy, (b) the first trimester, (c) the second trimester, and (d) the third trimester. Register studies usually do not specify symptoms of depression nor consistency in their use.

1. *Poor neonatal adaptation (PNA) or neonatal abstinence syndrome (NAS) or postnatal adaptation syndrome (PNAS)*. This is a common occurrence, considered evidence of a withdrawal or toxicity-like mechanism and caused by diverse psychoactive substances and drug abuse. It is quantified with Finnegan's neonatal abstinence score (NAS), of which an 8-item abbreviated version exists (Kieviet et al. 2015). A clear review (Kieviet et al. 2013) states the following: "In most infants, symptoms are mild, such as sleep disturbances. Severe symptoms, such as convulsions, are rare. However, of all infants exposed to an SSRI in utero, 20%–77% develop symptoms of PNA." In other studies, mild NAS (> 4) was found in up to 30% of infants (Forsberg et al. 2014; Levinson-Castiel et al. 2006). Over the past decade, NAS has seen an explosive growth worldwide. From 2000 to 2012, its incidence quintuplicated (McQueen and Murphy-Oikonen 2016). However, because of the common combined use of antidepressants with substances such as opioids and habits such as smoking or alcohol consumption (Patrick et al. 2015), clinical cause–effects may become unclear. As to NAS on account of opioid use,

legal responsibilities for doctors and patients are becoming an issue. The increase in NAS has produced an unprecedented focus on the syndrome from both the political–judicial sphere and the medical community. In an attempt at more fetal protection, judges and prosecutors have taken a hard line against women who use prescribed and non-prescribed opioids during pregnancy, including arrest, civil commitment, detention, prosecution, and loss of custody, or termination of parental rights (Kaltenbach and Jones 2016). With a view to the accumulating evidence as to antidepressants, their use may become similarly considered and prescribing physicians be confronted with this added responsibility.

Although PNA effects are mostly short term, long-term negative results exist but not always in the same direction. In a Finnish national birth cohort, treatment of maternal psychiatric disorders with SSRIs during pregnancy was linked to a higher risk of neonatal maladaptation (Malm et al. 2015). Pregnancies were classified as exposed to SSRIs ($N = 15{,}729$), unexposed to SSRIs but with psychiatric diagnoses ($N = 9652$), and unexposed to medications and psychiatric diagnoses ($N = 31{,}394$). Not only has a tendency towards smaller head circumference been established in several studies, but also—in a small study—changes in behavior at 2–6 years, when infants who developed NAS had normal cognitive ability but were at an increased risk for social–behavioral abnormalities (Klinger et al. 2011, $N = 30$). The consequences of NAS are likely to be independent of its cause; thus, the information as to any significant NAS population is to be considered relevant whatever the cause, for instance opioid use. Children with NAS related to opioid use were found more likely to be rehospitalized during childhood for maltreatment, trauma, and mental and behavioral disorders even after accounting for prematurity. This consequence continues into adolescence as found in a study that compared 3842 infants with NAS with 1,018,421 live-born infants without this diagnosis (Uebel et al. 2015). However, mild NAS/PNA symptoms are not always considered clinically relevant, and, thus, long-term results of maternal SSRI/SNRI use are statistically independent of manifest PNA. Other neonate conditions such as persistent pulmonary hypertension of the newborn (PPHN) must not be confounded with PNA. The FDA Advice on Drug Safety on PPHN states that present evidence is conflictive and current depressive treatment should be considered on its clinical merits, thus giving an independent reason for considering PNA to be a recognized common negative side effect of SSRI use in pregnancy. Other long-term effects of SSRIs are referred to in the following texts.

2. *Congenital anomalies*. These comprise several defects and malformations, some detectable through an altered epigenetic expression at placental level or in cord blood. Epigenetic mechanisms are important for the regulation of gene expression and differentiation in the fetus and the newborn child, with life-long impact on child health. Recent register and dose–response studies (Jordan et al. 2016; $N = 519{,}117$) encountered that SSRI use at A and/or B produces significantly higher risks at A and B as to heart defects. This risk is identifiable at a very early moment in pregnancy. Although the study found that the increase in prevalence of all major anomalies combined did not reach statistical significance (3.09% [400/12,962] vs. 2.67% [13,536/506,155]; OR 1.09, 0.99–1.21), it is being said that increase in the total number of anomalies was—an already clinically relevant—16%. The recently updated Canadian cohort study, $N = 18{,}487$, did find a statistically significant risk of increase for several malformations, including cardiac, musculoskeletal, craniofacial, digestive, and respiratory defects as well as craniosynostosis, on account of SSRI and other serotonin-related antidepressants in utero exposure (Bérard et al. 2017a, b). The authors reflect in their conclusion that the marginal effectiveness of these drugs for most cases of depression and the significant increase in anomalies demand caution with antidepressant use during pregnancy and to consider alternative non-drug options. This uncountered argument has been present in the discussion for decades.

Another early detectable genetic factor is an altered HSD11B2 gene expression in the placenta (Seth et al. 2015). The study question was as follows: which effects on placental gene expression can be measured in depressed groups as compared to antidepressant-exposed groups and controls? Depressed and antidepressant-exposed groups both displayed markedly lower placental HSD11B2 expression levels than controls. This makes any justification of antidepressant use unsustainable with the argument that untreated maternal depression would have worse effects than SSRIs. The same goes for anxiety, as a 2012 study confirmed (O'Donnell et al.). Therefore, antidepressant medication is considered unlikely to provide overall protection against a placental and thus fetal effect. The fact that antenatal depression and antidepressant exposure during pregnancy are associated with altered gene expression in the placenta was confirmed for several genes. Alterations of the genes picked for validation were more robust among antidepressant-treated women than depressed women (Olivier et al. 2015; Gentile and Fusco 2016). Further research confirmed that exposure to either antidepressants or untreated maternal depression was found to induce epigenetic changes and to interfere with physiological fetal behavior. There are indications but no conclusive evidence of epigenetic changes in cord blood in association with use of antidepressants (Viuff et al. 2016).

3. *Changes in brain white matter*. Most studies we cite give statistical probabilities or correlations. Direct observation of negative effects of antidepressants is exceptional and of great clinical importance. Changes in the white brain matter, composed of myelinated tracts and forming the structure of the central nervous system, have long-term effects on learning and other functions. If SSRIs have detrimental effects on the fetus, do these affect the brain? Jha et al. (2016), in an exhaustive and clarifying study ($N = 204$), established direct causal significant changes in brain white matter due to SSRI use during B and C, but no such changes due to maternal depression (sic). Moreover, in this study, the fetus of women who elected to stay on medication often constituted a more severely affected subgroup than women stopping medication.
4. *Stillbirths/miscarriage*. Jordan et al. (2016) in their $N =$ 519,117 study encountered a significantly higher risk of stillbirth because of SSRI use during A and B. Referring to the relative harm for the fetus, also in 2016, a $N =$ 41,964 study (Almeida et al. 2016) found antidepressant use in the first trimester (B) to be associated with an increased risk of miscarriage when compared with either non-depressed or depressed but unexposed women, even after accounting for induced abortions.
5. *Developmental incidences* include low birth weight (LBW), small for gestational age (SGA), and pre-term birth (PTB) < 37 weeks. Previously considered of a transient nature, it is now recognized that these infants have increased rates of perinatal morbidity and mortality. Previously established cut-offs for LBW in a recent cohort study ($N = 979{,}912$) were found to be too restricted, making birthweight an even more decisive factor for future infant health (Iliodromiti et al. 2017). LBW is confirmed to have many possible negative consequences, some until now unsuspected such as affecting the degree of airway dysanapsis and mechanical ventilatory constraints (Duke et al. 2017). In a recent population study, early-term birth was found to be related to posterior diabetes and obesity-related disorders (Paz-Levy et al. 2017). Consequential links to (mental) health problems in the child, adolescent, or adult are reported, supported by twin studies indicating less brain volume for lower birth weight (Casey et al. 2016). In 2012, a Dutch study, $N = 7696$, found untreated maternal depression to be associated with slower rates of fetal body and head growth. The study illustrates the dilemma we referred to earlier as to benefits for the mother that combine with damage for the child. Here, pregnant mothers treated with SSRIs had fewer depressive symptoms and their fetuses had normal body growth but did have more delayed head growth and were at increased risk of preterm birth (El Marroun et al. 2012). A meta-analysis (Huang et al. 2014) found antidepressant use in pregnancy to be significantly associated with LBW (RR 1.44, 95% confidence interval (CI) 1.21–1.70) and PTB (RR 1.69, 95% CI 1.52–1.88). A 2016 meta-analysis, $N = 1{,}237{,}669$ of which 93,982 are in the exposure group, also indicated a significant risk for PTB attributed to SSRI use during pregnancy (Eke et al. 2016).

   A Norwegian sibling-controlled cohort study (Nezvalová-Henriksen et al. 2016), $N = 27{,}756$ of which 194 are exposed, concluded that SSRI use during 2 (not 1) trimesters related to significant LBW and SGA that were not explained by maternal depression, genetics, or family environment. The established average loss of 205 g means a 5.62% loss according to Norwegian growth charts (Júlíusson et al. 2009). However, in the same year, a much smaller single-clinic $N = 7267$ study (Venkatesh et al. 2016) found apparently different results. Of women screened for depression antepartum, those with depressive symptoms had an increased likelihood of preterm and very preterm delivery as well as having an SGA neonate. However, in this study, such risk was not apparent among women who were treated with an antidepressant medication. In view of the other studies cited previously, and the 2014 meta-analysis confirming the relationship between antidepressants and PTB (Huybrechts et al.), these results are difficult to explain, other than with study size and design. In a subsequent observational study, the same authors added “Antidepressant exposure during pregnancy does not confer an increased risk of preterm birth nor growth restriction in women recently treated for depression, but also does not appear to markedly improve these outcomes” (Venkatesh et al. 2017). In the earlier-referenced Finnish national birth register study, treatment of maternal psychiatric disorders with SSRIs during pregnancy was linked to a lower risk of preterm birth and cesarean section but a higher risk of neonatal maladaptation (Malm et al. 2015). These contrasting findings in a minority of studies provide indications of a possible selectively protective role of SSRIs on some deleterious reproductive outcomes, possibly in those cases where maternal depressive symptoms were severe.
6. *Persistent pulmonary hypertension of the newborn (PPHN)*. Its relationship with maternal antidepressant use was confirmed in several large studies. A register study of the five Nordic countries with $N = > 1.6$ million (infants born after gestational week 33) (Kieler et al. 2012) led authors to conclude the following: “The risk of persistent pulmonary hypertension of the newborn is low, but use of SSRIs in late pregnancy increases that risk more than twofold” (study part of the US Medicaid Analytic eXtract, 2000–2010. (Huybrechts et al. 2015) $N = 128{,}950$). The adjusted odds ratio (aOR) was found

to be 4.59% for SSRI use after the 20th week, against an overall aOR of 0.59 (Bérard et al. 2017a, b) $N = 143{,}281$.

7. *Epilepsy/seizure disorder.* A Danish longitudinal statistical study from 1997 to 2008 (Mao et al. (2016)), $N =$ 734,237, revealed up to a 27% higher risk of epilepsy on account of pre-pregnancy (2–6 months before), first and second trimester antidepressant use, and noticeably higher if mothers had a registered diagnosis of depression in the 6 months before or during pregnancy. Children of mothers who used antidepressants from 2 to 6 months before pregnancy but not during pregnancy also had an increased risk of epilepsy (aHR 1.36; 95% CI 1.07–1.73), confirming possible SSRI nocive after-effects.
8. *Neurodevelopmental disorders* are comprised of autistic traits (attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD)). In 2014, a Dutch study (El Marroun et al., $N = 5796$) found 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. In view of similar study results, Pedersen (2015) suggested that studies should specify if the risk of ASD in newborns on account of antidepressants during pregnancy could have been due to maternal depression. Shortly after, it was found that maternal depression did not alter the significant increase in ASD risk after SSRI exposure (Boukhris et al. 2016). In a longitudinal 11-year study, $N = 145{,}456$, SSRI use in the second and/or third trimester was significantly associated with an increased risk of ASD (22 exposed infants; adjusted hazard ratio, 2.17; 95% CI, 1.20–3.93). The earlier-cited Finnish register study did not, however, find an association between SSRI use and ASD or ADHD (Malm et al. 2016). At the same time, a critical review on the subject (Gentile 2015) warned against potential biases in the research. However, its author found that six out of eight studies revised confirmed that antenatal exposure to SSRIs may increase the risk of ASDs. In view of the magnitude of this severe risk, he suspects a "fall of Gods", since for many years SSRIs have been considered first-choice treatment for antenatal depression. Later study results caution against the use of SSRIs and SNRIs, such as Castro et al. (2016), $N = 10{,}148$, confirming that pre-pregnancy antidepressant exposure significantly increased the risk for ASD and ADHD. However, no such association was found with prenatal SSRI use, suggesting that medication prior to pregnancy is especially relevant for ASD/ADHD risk, another example of delayed nocive effects of psychoactive medication in the short and medium terms, or of epigenetic changes produced in very early stages of pregnancy.

Long-term changes in offspring These are consequences of antidepressant use that are especially preoccupying and difficult to control. Norwegian register study data do not support the notion that perinatal maternal depression is particularly detrimental to children's long-term psychological development, as the most robust effects were found for maternal depression occurring during preschool years (Gjerde et al. 2017).

9. *Depression in offspring at adolescence* (Malm et al. 2016). $N = 74{,}754$ in four groups: SSRI exposed ($N =$

Table 1 Negative effects of SSRI antidepressant use in pregnancy

Pre- and peri-natal effects	Estimated incidence	Effects at short/long term	Significant or just increase	Study size *N*
PNA/NAS	Low Apgar 1.68%	Short	Significant	845,345
Anomalies	0.26% vs 0.17% (heart)	Short + Long	Significant	519,117
Brain	Widespread	Long	Significant	204
Still-birth	3.65% vs 3.13%	Short	Significant	519,117
LBW/SGA/PTB	6.8% vs 5.8%	Short + Long	Significant	1,237,669
PPHN	0.2% (aOR 4.59% increase from 0.59)	Short	Significant	143,231
Epilepsy	aHR 1.27%, > 27% increase	Long	Significant	734,237
Autism ADHD/ASD	2.17% vs 1%	Long	Significant	145,456
Long-term effects				
Depression offspring	8.2% vs 1.9%	Long	Significant	74,754
Speech/school/motor disorders	0.0087, 37% increase	Long	Significant	56,340
SGA offspring	− 2.3 days	Long	Significant	392,029

Study size *N:* largest published study to date

aHR, adjusted hazard ratio; aOR, adjusted odds ratio (here considered equivalent); PNA, poor neonatal adaptation; NAS, neonatal abstinence syndrome, including postnatal adaptation syndrome; LBW, low birth weight; SGA, small for gestational age; PTB, pre-term birth

15,729); exposed to psychiatric disorder, no antidepressants ($N = 9651$); exposed to SSRIs only before pregnancy ($N = 7980$); and unexposed to antidepressants and psychiatric disorders ($N = 31{,}394$). In this Finnish national register study, prenatal SSRI exposure was associated with increased rates of depression diagnoses in early adolescence but not with ASD or ADHD.

10. *Speech, scholastic, and motor disorders in offspring from birth to 14 years*. A significantly increased risk of these disorders was found in offspring in the SSRI-exposed and unmedicated groups during pregnancy ($N = 56{,}340$), compared with offspring in the unexposed group (Brown et al. 2016), another example of higher negative results for SSRI-treated versus untreated depression.
11. *Birth size and gestational age (SGA) in offspring*. Crude analyses of register data revealed associations between prenatal SSRI exposure and offspring birth size and gestational age (Viktorin et al. 2016; $N = 392{,}029$). However, in the within-family analyses of that study, only the association between SSRI exposure and reduced gestational age (−2.3 days; 95% confidence interval −3.8 to −0.8) was confirmed.

Statistical significance of the evidence from the cited research on effects on offspring of pre-pregnancy and antenatal antidepressant use The clinician as well as health authorities or providers should, to an extent, consider the woman's personal situation for the decision on how to treat depressive symptoms and depressive disorders in pregnancy. Any healthcare in pregnancy should, where possible, be adapted to the patient and the possibilities available. However, the necessary guidelines for such adaptation depend on what we referred to as hard data but these—to a measure—depend on the interpretation of the evidence available. In turn, interpretation depends on hypotheses and study design, these being possible confounders (Table 1).

Conclusion

We commenced our introduction referring to the ongoing debate on perinatal antidepressant use. Guidelines presently only ask for careful evaluation of each particular case, which is no more than the bare obligation of the medical professional. The continuous worldwide increase in antidepressant use—also during pregnancy—indicates that a more robust awareness of the risks involved in their use is necessary. The availability of psychological, psychosocial, and alternative solutions of proven efficacy gives the clinician an important flexibility in options.

We argue that the available evidence warrants, nay, obliges a change in overall policy, in the sense of the following:

1. In depression, in all its grades, in and before pregnancy, SSRI or related antidepressants should only be prescribed after finding that other established treatments do not work well for the patient.
2. Reaching consensus as to that mentioned previously should be a professional priority.
3. Comparative longitudinal studies of the efficacy and nocive effects of all available treatments are needed.

Compliance with ethical standards

Ethical approval This article does not contain any studies with human participants performed by the author.

Conflict of interest The author declares that he has no conflicts of interest.

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