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Links between serotonin reuptake inhibition during pregnancy and neurodevelopmental delay/spectrum disorders: A systematic review of epidemiological and physiological evidence

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Abstract.
OBJECTIVE: To investigate possible linkages between neurodevelopmental delay and neurodevelopmental spectrum disorders and exposure to medication with effects on serotonin reuptake inhibition during pregnancy.
METHODS: We systematically reviewed the epidemiological literature for studies bearing on this relationship in children born with neurodevelopmental spectrum disorder and related conditions, as well as animal studies giving serotonin reuptake inhibitors to pregnant animals and in addition reviewed the literature for proposals as to possible mechanisms that might link effects on serotonin reuptake with cognitive changes post-partum.
RESULTS: The odds ratio of Autistic Spectrum or related Disorders in children born to women taking serotonin reuptake inhibiting antidepressants during pregnancy in case control studies was 1.95 (95% C.I. 1.63, 2.34) and in prospective cohort studies was 1.96 (95% C.I. 1.33, 2.90).
CONCLUSIONS: There appears to be a link between serotonin reuptake inhibition in pregnancy and developmental delay and spectrum disorders in infancy leading to cognitive difficulties in childhood. More work needs to be done to establish more precisely the nature of the difficulties and possible mechanisms through which this link might be mediated.

Keywords: Autism spectrum disorder, neurodevelopmental delay, neurodevelopmental spectrum disorders, antidepressants, serotonin reuptake inhibitors, pregnancy

1. Background

The clinical syndrome later called autism was first reported in 1943 [1]. The first studies of the prevalence of autism or autistic disorder (AD) in the 1960s pointed to a rate of 4 per 10,000 [2, 3]. Later studies indicated the existence of a spectrum of disorders, and brought the term autistic spectrum disorder (ASD) into being in the mid-1990s [4]. The diagnosis of ASD has probably widened since then,
and ASD also now includes other syndromes such as Pervasive Developmental Disorder and Aspergers Disorder so that it is difficult to know how closely current clinical usage of an ASD diagnosis maps onto AD and ASD as first conceived. Current estimates are that ASD in research studies occurs at a rate of more than 1 in 70 children [5, 6].

Kanner autism was recognized before the emergence of modern psychotropic drugs, and given its submergence in ASD, it may not now be possible to establish whether it is linked to commonly used psychotropic medications. A number of clinical pictures linked to psychotropic drug use, fetal anticonvulsant syndrome (FACS), fetal valproate syndrome (FVS), and fetal alcohol syndrome (FAS) and fetal alcohol spectrum disorder (FASD) have been described since 1970. Aside from the link to treatment, the clinical features of these disorders are consistent with a diagnosis of ASD but not Kanner autism. A growing number of epidemiological studies point to an increase in rates of ASD. This translates popularly into concerns about a change in the prevalence of “autism”. The increase seems almost certain to be driven in part by changes in diagnostic labelling and the emergence of research instruments on which patients with cognitive impairments who show signs of social impairment, but who would previously have had other diagnosis, come up as meeting the criteria for ASD [7].

It is unclear whether the incidence of Kanner autism has changed. It is also unclear whether the net of new instruments hauls in cases of FASD, FACS or FVS not recognized as such, and where in these cohorts children affected by maternal gestational SSRI intake might sit.

ASD is not a traditional disease entity. Against this background it seems prudent to broaden the scope any investigation to look not just at ASD but also at neurodevelopmental delay and perhaps neurodevelopmental spectrum disorders.

It also seems appropriate to broaden the investigation to all domains that might shed light on any assessment of the likelihood of a true association: human epidemiological studies, animal studies and evidence supporting the biological plausibility of a link. A combination of these domains is of importance where the association has serious implications.

1.1. Biological plausibility

As regards a linkage between antidepressant use and neurodevelopmental issues, serotonin is notably the most primitive of neurotransmitters; it has a role in early reproduction, and as a result it has long been recognized that acting on serotonin during the gestational period has the potential to cause significant problems [8, 9].

In 1960, linked to studies of the effects of antidepressants on serotonin, Ashcroft suggested that there might be a lowering of serotonin in depression [10]. By 1970, Ashcroft and others had discounted this link [11].

In contrast in 1961, a first report was published of elevated serotonin levels in autism [12]. This finding has been consistently replicated since [13–15].

In the early 1960s, a first linkage was made between serotonin and birth defects in animal studies [16–18]. In the early 1970s the first reports linking serotonin reuptake inhibiting antidepressants to birth defects appeared [19]. In 1990, the first independent study linking SSRI intake to teratogenic potential in animal studies was published [20].

As of the 1980s, following descriptions of Fetal Anticonvulsant Syndrome (FACS) and Fetal Valproate Syndrome (FVS), characterized by prominent deficits in social communication and other ASD features [21, 22], a consensus emerged that psychotropic drugs could produce behavioral teratological effects even if they did not show clear anatomical abnormalities such as cardiac or neural tube abnormalities after use during pregnancy [23].

These developments led companies producing novel centrally acting drugs in the 1980s, including SSRIs, to undertake animal studies. In the case of the SSRIs, the animal studies looked at embryo-
lethality and gross malformations, but an associated objective was to investigate the behavior of neonatal pups. Many of these company studies show a dose related fetal death and other features consistent with a teratogenic capability. The existence of these studies designed to look for evidence of behavioral consequences of SSRI intake during pregnancy for the most part remains unknown with the studies unpublished and the data inaccessible.

There is however a growing set of independent animal studies demonstrating birth defects linked to SSRI use with a range of mechanisms that may underpin these effects [24]. Consistent with these studies and mechanisms, a series of epidemiological studies from 1998 onwards have demonstrated that SSRIs come with a teratogenic potential [25–52]. These findings are summarized in Healy et al. [53] and Berard et al. [24].

Finally published animal studies consistently show that pups born to animals administered antidepressants during pregnancy show a range of behavioral changes indicative of reduced social confidence and communication deficits consistent with a diagnosis of neurodevelopmental spectrum disorders in humans [54–61].

1.2. Objectives

Question: Is there evidence to suggest a link between maternal ingestion of SSRI antidepressants during pregnancy and later effects on measures of cognitive function that may lead to diagnoses of behavioral deficits in children exposed in utero, primarily a diagnosis of ASD?

Question: If a link exists, is there evidence from animal intervention studies of a biological mechanisms that might underpin the effect?

2. Methods

2.1. Design

We carried out a systematic search for all epidemiological studies linking the use of serotonin reuptake inhibiting antidepressants during pregnancy to ASD, and related constructs such as developmental delay or pervasive developmental disorder in offspring. In addition we searched for publications relevant to the range of possible mechanisms through which antidepressant usage might give rise to a diagnosis of ASD in offspring. We followed the MOOSE Guidelines for meta-analyses and systematic reviews of observational studies [62].

2.2. Search strategy

We searched Embase, OVID and the Cochrane Library to identify English-language abstracts published up to December 2015. Search terms and strategy were determined by the investigators with advice from a librarian. We applied the following search terms in various combinations which was adapted for each database: Search terms: antidepressants, selective serotonin reuptake inhibitors, SSRIs, pregnancy, autistic spectrum disorder, developmental delay, autism, ADHD, birth defects.

We also hand-searched reference lists of included and excluded articles for articles of potential relevance.

2.3. Data management

Abstracts were retrieved and screened and articles determined to be of potential relevance were retained. These articles were screened in detail and articles meeting inclusion criteria were included.
Each abstract screened and each potentially relevant article retrieved was reviewed independently by two authors (JLN and DM). Discordances were resolved by discussion among the three authors. Review articles were excluded, though references were hand searched for other relevant original data-containing studies.

Abstracts were included for analysis (human) if they satisfied the following inclusion criteria:

- Provided exposure data on gestational SSRI use
- Provided quantitative measures of cognitive behavioral or developmental function in the children exposed in utero
- Controlled for exposure to other potentially teratogenic medications

Abstract were included for analysis (animal) if they

- Provided data on gestational antidepressant use
- Provided quantitative measures relevant to cognitive behavioral or developmental outcomes

We did not restrict by study design but quantitative results had to be available. We excluded articles where we could not obtain an English translation, review articles, and studies where we had abstracts. Data from included articles were extracted using a standardized form describing the following study characteristics: year, target population, location, sample size, study design, outcome measure, knowledge gaps, key conclusions and study setting. We assessed for duplicate citations and tools.

Where the data on outcomes was available within the published study, we abstracted it from each of these studies. Where the data was not available, we wrote to the authors to request it.

2.4. Statistical analyses

All analyses were conducted using Review Manager 5.2 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012).

We performed two main analyses, one assessing the association between maternal SSRI use in pregnancy and ASD and the other assessing the association between maternal SSRI use in pregnancy and other neurodevelopmental abnormalities related to autism.

There are methodological issues in plotting these data. In studies looking at children, some less than a year old, it is only possible to look at developmental delay rather than at outcomes that by consensus point to specific failures of social communication rather than cognitive impairment in general. Some studies present outcomes across a range of soft neurological indicators (up to 10 in one study). In order to plot the data, it is necessary therefore to take a representative measure from each study to include in the forest plot. This has been outlined in the appended tables. All data are available from the authors which will permit others to enter different data sets into the plot, as indicated.

3. Results

The flow chart (Fig. 1) shows the study search results. Our search retrieved 112 citations of which 67 were potentially relevant abstracts. Of these 67 abstracts screened, 38 articles fit the inclusion criteria. Of these 27 were human studies and 11 were animal studies. Suitable data was available for abstraction in the papers from 21 studies and included in the human dataset. We did not receive responses for requests for data from the three Motherisk studies [64–66] and Suri et al. [67]. Casper et al. [68] and Galbally et al. [69] indicated an inability to access the data at the time it was requested.

Eleven animal studies were identified with adequate data for abstraction from the published papers.
Human study participant size ranged from 36 to 654,000. 16 of the 21 studies included in the analysis used a cohort design and 5 were case controlled.

Most of the included studies point to a linkage between SSRIs and ASD, with almost all published studies pointing to increases in risk even if in individual studies the increase is not significant [68–83]. Some studies reported they found no increase in risk [64–66], however data was not available from the publications of these studies and a request for data to the authors received no response.

A study by Malm and colleagues has found that women taking SSRIs show a 10 fold greater incidence of Fetal Alcohol Spectrum Disorders (FASD) compared with women not on SSRIs [43]. These findings are supported by adverse event reports of FASD and behavioral effects consistent with FASD to FDA for all SSRIs and reports of SSRIs causing compulsive alcohol intake [84]. The Malm findings suggest other studies should look for this clinical syndrome which overlaps with ASD and in particular should not discount the effects of alcohol intake as a confounder.

The results of the individual case-control epidemiological studies as well as the combined effect and statistics are presented in Fig. 2 (see Table 1 also).

Fig. 2. Analysis of Case Controlled Studies.
Table 1
Notes for Fig. 2 forest plot

<table>
<thead>
<tr>
<th>Authors</th>
<th>Type of antidepressants</th>
<th>Study Outcome</th>
<th>Additional analyses available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Croen et al. 2011</td>
<td>SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline,)</td>
<td>Prenatal exposure to SSRI</td>
<td>Additionally looked at ‘exposure to ANY antidepressant’ (OR = 2.10, CI 1.23–3.58).</td>
</tr>
<tr>
<td>Rai et al. 2013</td>
<td>SSRIs (fluoxetine, citalopram, paroxetine, sertraline).</td>
<td>ASD diagnosis.</td>
<td>Figures also available for 'all antidepressants' and risk of ASD: (OR = 2.27, CI: 1.4–3.71).</td>
</tr>
<tr>
<td>Harrington et al. 2014</td>
<td>SSRIs (Fluoxetine, sertraline, paroxetine, citalopram, escitalopram).</td>
<td>Prenatal exposure to SSRI</td>
<td>Additionally looked at children with developmental delay vs controls.</td>
</tr>
<tr>
<td>Clements et al. 2014</td>
<td>All Antidepressants (High affinity – paroxetine, duloxetine, sertraline, escitalopram, fluoxetine; Moderate affinity – citalopram, fluvoxamine, venlafaxine; Low affinity – nefazodone, bupropion, mirtazapine)</td>
<td>Prenatal exposure to antidepressants</td>
<td>Additionally looked at children with ADHD vs controls (OR = 1.67, CI 1.67–3.34) – see Fig. 3a and 3b.</td>
</tr>
<tr>
<td>Gidaya et al. 2014</td>
<td>SSRIs (fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, escitalopram).</td>
<td>Prenatal exposure to SSRI</td>
<td></td>
</tr>
</tbody>
</table>

Figure 3a and 3b outline the effects on other neurodevelopmental outcomes (see Table 2 also). Figure 3a includes the Malm FASD figures. Figure 3b offers the same data with Malm excluded.

3.1. Potential mechanisms

In terms of the effects of antidepressants on neurodevelopment, we have abstracted a range of mechanisms through which gestational SSRIs might impact on cognitive function that recent literature supports.

First, as noted above serotonin has a role in embryogenesis and there is convincing evidence that disturbing this function leads to defects in many systems from cardiac through to neurological [24]. In addition to evidence for gross birth defects, there has been evidence from animal studies for over a decade that SSRIs can lead to abnormalities in cerebral architecture [85–87]. We have not found any studies demonstrating normal brain architecture. These changes appear linked to reduced exploratory behavior and reduced reactivity [88].

Second, SSRIs have profound effects on sexual behavior and this can be expected to have longer term consequences in the social domain [55, 56, 89].

Third, SSRIs can induce compulsive alcohol intake [84] and this might be expected to make some contribution to the epidemiological picture. The study by Malm et al. [43] suggests it does.
Fourth, a noted feature of SSRIs is that they produce the experience of blunted emotion [90]. Linked to this it would appear, they lead to decrements in our abilities to read emotion [91]. These behavioral effects are consonant with changes that will register on instruments currently used to detect communication difficulties and are likely to lead to an ASD diagnosis.

This point has become of greater interest in the light of evidence linking acetaminophen (paracetamol) to ASD [92]. While the link here might arise indirectly, if acetaminophen is used to treat a fever, this medicine also appears to have comparable effects to SSRIs on sociability in animals [93] and on the ability of people to read emotions [94]. Acetaminophen also has effects on S-1 receptors so there is a considerable overlap in its mechanism of actions with SSRIs.

Both acetaminophen and SSRIs may therefore mediate their effects through end-stage behavioral changes. These behavioral changes can endure for months after treatment stops in adults. If administered in utero, one possibility is that such changes may be even more likely to endure and produce an ASD clinical picture.

Fifth, given that current diagnoses of ASD may include children with general cognitive problems rather than specific disturbances of a discrete communication function, a range of treatment related fac-

Fig. 3. (a) Analysis of Prospective Cohort Studies (including Malm et al. 2011, FAS data). (b) Analysis of Prenatal Prospective Cohort Studies (excluding Malm et al. 2011, FAS).
<table>
<thead>
<tr>
<th>Authors</th>
<th>Type of antidepressants</th>
<th>Study Outcome</th>
<th>Additional analyses available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortensen et al. 2003</td>
<td>All antidepressants (breakdown not specified) authors emailed 29.04.15 to verify.</td>
<td>Abnormal psychomotor development (Boel test) at 7–10 months</td>
<td>Exposure also to anti-epileptics, neuroleptics and benzos.</td>
</tr>
<tr>
<td>Misri et al. 2006</td>
<td>SSRIs (fluoxetine, paroxetine, sertraline)</td>
<td>Internalising behaviour (depression, anxiety, withdrawal) at 4 years (Child Behaviour Checklist composite scores)</td>
<td>–</td>
</tr>
<tr>
<td>Oberlander et al. 2007</td>
<td>SSRI (breakdown not specified)</td>
<td>Clinically elevated externalising scores (attention, aggression, ADHD, ODD) at age 4 years.</td>
<td>–</td>
</tr>
<tr>
<td>Figueroa 2010</td>
<td>SSRI (breakdown not specified).</td>
<td>ADHD diagnosis at age 5 years.</td>
<td>–</td>
</tr>
<tr>
<td>Pedersen et al. 2010</td>
<td>All antidepressants (SSRI -fluoxetine, citalopram, paroxetine, sertraline; TCAs; Other e.g. venlafaxine).</td>
<td>All developmental milestones at 6 months combined (i.e. motor, attention, cognition, language)</td>
<td>–</td>
</tr>
<tr>
<td>Malm et al. 2011</td>
<td>SSRIs (Fluoxetine, sertraline, paroxetine, citalopram, escitalopram).</td>
<td>Foetal alcohol spectrum disorders (FAS)</td>
<td>–</td>
</tr>
<tr>
<td>Hviid et al. 2013</td>
<td>SSRI (breakdown not specified)</td>
<td>ASD diagnosis</td>
<td>–</td>
</tr>
<tr>
<td>de Vries et al. 2013</td>
<td>SSRIs Fluoxetine, sertraline, paroxetine, citalopram) plus venlafaxine (low dose).</td>
<td>Monotonous movements at 3–4 months</td>
<td>Figures also available for General movements during first week after birth (OR = 3.04, CI:1.33, 6.91).</td>
</tr>
<tr>
<td>Austin et al. 2013</td>
<td>SSRIs (Fluoxetine, sertraline, paroxetine, citalopram, escitalopram, venlafaxine, fluvoxamine, dothiepin).</td>
<td>Motor development (Bayley composite scores) at 18 months:</td>
<td>Figures also available for cognitive development (OR = 5.06, CI: 0.25–102.72) &amp; language development (OR = 2.84, CI: 0.30–27.16) 18 months.</td>
</tr>
<tr>
<td>Hanley et al. 2013</td>
<td>SRIs</td>
<td>Neurodevelopment at 10 months (Bayley scale)–Gross motor.</td>
<td>Figures also available for fine motor, cognitive, communication, social-emotional and adaptive behaviours.</td>
</tr>
<tr>
<td>Laugesen et al. 2013</td>
<td>All antidepressants (breakdown not specified)</td>
<td>ADHD diagnosis at age 8 years.</td>
<td>–</td>
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</table>

*(Continued)*
Table 2
(Continued)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Type of antidepressants</th>
<th>Study Outcome</th>
<th>Additional analyses available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorensen et al. 2013</td>
<td>SSRI (breakdown not specified)</td>
<td>ASD diagnosis.</td>
<td>Figures also available for ‘all antidepressants’ and risk of ASD (OR = 1.43, CI: 1.18–1.74). In addition authors looked at SSRIs exposure and exposure to all antidepressants and risk of autism.</td>
</tr>
<tr>
<td>Clements et al. 2014</td>
<td>All Antidepressants (High affinity – paroxetine, duloxetine, sertraline, escitalopram, fluoxetine; Moderate affinity – citalopram, fluvoxamine, venlafaxine; Low affinity – nefazodone, bupropion, mirtazapine)</td>
<td>Prenatal exposure to antidepressants and risk of ADHD.</td>
<td>–</td>
</tr>
<tr>
<td>Knickmeyer et al. 2014</td>
<td>SSRIs (Sertraline, fluoxetine, citalopram, paroxetine).</td>
<td>Chiari I malformations 1-2 years</td>
<td>–</td>
</tr>
<tr>
<td>El Marroun et al. 2014</td>
<td>SSRIs (Fluoxetine, sertraline, paroxetine, citalopram, fluvoxamine).</td>
<td>Pervasive developmental problems at 1.5 years</td>
<td>Figures also available at 6 yrs.</td>
</tr>
<tr>
<td>Skurtveit et al. 2014</td>
<td>SSRI (breakdown not specified)</td>
<td>Not achieving best language competence category (long complicated sentences) at age 3 years</td>
<td>–</td>
</tr>
<tr>
<td>Boukhris et al. 2015</td>
<td>SSRI used in Forest plots (Figs. 2 and 3).</td>
<td>ASD diagnosis (following exposure during 2nd/3rd trimester).</td>
<td>All antidepressants (also breakdown given for type – SSRI, SNRI, MAOI, tricyclic and others).</td>
</tr>
</tbody>
</table>

 tors from SSRI withdrawal to postnatal operative interventions to correct birth defects may contribute to the potential of these drugs to give rise to ASD clinical pictures.

Finally when considering these mechanisms it would be a mistake to focus solely on a supposed ASD. It is important to establish the full range of effects these drugs have and there is emerging but as yet unpublished literature that rates of ADHD for instance may be increased in children born to mothers on SSRIs. Any mechanisms proposed need to be able to account for such changes also.

4. Discussion

The Forest plots show the consistency of the findings to date. Whether looking at a strict diagnosis of ASD, including just case-control or all observational studies or assessing other neurodevelopmental outcomes, SSRIs have a consistent pattern of association with poorer outcomes. The increase in rates of developmental delay linked to SSRI use in pregnancy may also be consistent with increased rates
of diagnoses of ASD in the offspring of women exposed to these treatments. It is unclear what this linkage means. Some of the data may reflect dyspraxia or related soft neurological signs that need not necessarily be accompanied by cognitive or social impairments, and may disappear in later life.

These findings are supported by consistent findings in the animal studies reviewed, and by the existence of a number of biologically plausible mechanisms in humans.

This review builds on previous reviews by Gentiles [95] and Mann et al. [96]. Gentiles provided a narrative review of the evidence, though did not perform a meta-analysis. In contrast to Mann et al. we have included two important studies in the review [70, 73] and included meta-analysis or and review of studies of other neurodevelopmental outcomes as well as systematically reviewing quantitative evidence from animal studies.

There is moreover a range of mechanisms through which the effects of SSRIs might lead to outcomes attracting an ASD diagnosis. To move our understanding forward will require a consideration of both epidemiological findings and physiological studies. The reason to review these physiological mechanisms is that the epidemiological evidence is at a point where it is now clear that greater specificity in clinical phenotypes is needed in order to make sense of possible links between treatment and outcomes.

The state of the developing science maps onto the respective roles of epidemiology and biology in elucidating the risk of birth defects on doxylamine (Bendectin). Doxylamine is used for nausea in pregnancy. In the 1970s it was linked to cardiac and limb defects [97]. However several early epidemiological studies cast doubt on the link between doxylamine and birth defects [98–101].

Reviewing all epidemiology studies on doxylamine, it is clear that while many studies show no increase in risk, a majority show some increase in risk compared with non-treatment [102–114].

There is now a greater understanding of the critical time periods when drugs can lead to cardiac and other defects, making it clear that the epidemiological findings must be interpreted against a background that recognizes that women rarely start taking doxylamine before week 6–8 and by this time the risk of cardiac defects has all but been eliminated [115]. This fact makes any increase in risk notable.

There is a further background. Doxylamine is an anti-histamine. There appears to be an increased risk of birth defects on serotonin reuptake inhibiting antihistamines, such as doxylamine, compared to non-serotonin reuptake inhibiting antihistamines [116] and similarly an increase in risk on serotonin reuptake inhibiting antidepressants, not found in antidepressants that are inactive on the serotonin system [53, 117].

Because doxylamine intake starts relatively late in the first trimester, epidemiological studies while indicating it is unlikely to cause birth defects may on their own be unable to settle the question as to whether it has a potential to cause birth defects. In making a judgment as to whether this drug poses risks, biological evidence is informative, although it also has its limitations.

As the case of acetaminophen indicates, we do not at this point know whether the physiological effects of serotonin reuptake inhibiting drugs on developmental delay are mediated at a molar level altering our social perceptions or at an ionic level. Gross cardiac defects might be linked to changes in sodium ion flow for instance with behavioral effects stemming from cognitive effects of the drugs.

There is a need for the epidemiology to remain biologically informed and for biologists to be aware that diagnoses of ASD and the instruments used in epidemiological studies might mislead them as to what physiological factors should be explored further. Nothing better illustrates this than the evidence from Malm et al. study [43], which is consistent with known effects of SSRIs in triggering alcohol intake in a sub-population of subjects and a recent RCT showing poorer drinking outcomes with citalopram treatment for alcohol dependence disorder [118].

This Malm study also indicates that while it has been routine to adjust for confounders such as alcohol intake that such adjustments may be mistaken in the case of serotonin reuptake inhibiting
antidepressants with SSRIs having effects on both alcohol and nicotine intake as well as glucose levels.

4.1. SSRIs in pregnancy

For SSRI usage to have played a part in increasing rates of ASD, we would expect there to be evidence that there has likely been an increase in the use of these drugs in women of child-bearing years and a more relaxed medical and public attitude about the use of these drugs during pregnancy.

Unlike earlier antidepressants where the market was largely in older age groups, it was clear that a large part of the market for SSRIs would be to women of child-bearing years.

In the early 1990s when the SSRIs were marketed first, the prevailing wisdom was that giving psychotropic drugs in pregnancy was to be avoided; regulators supported avoidance [119], professional bodies supported avoidance [120], and leading psychiatrists warned of the teratogenic potential of psychotropic drugs [121–123].

There was not thought to be any increase in the incidence of mood disorder during pregnancy [124]. There was not thought to be any risk from mood disorders to the fetus; the risk from mood disorders lay in the risk posed to the mother such as suicide [125].

In contrast today it is common to hear claims that depression directly or indirectly causes birth defects; to see a conflation of depressive symptoms with depressive illnesses, so that rates of 15–20% for depressive disorders are cited when this should only apply to depressive symptoms [53]; and it is not widely noted that the majority of states treated with these drugs left untreated clear up spontaneously within weeks.

In 2015, in the absence of any intervening data that depression causes birth defects or that SSRIs are effective in antenatal depression, it is possible to find the same authors who advocated caution about the use of antidepressants in the early 1990s, supporting claims that:

- Depression can cause birth defects [126]
- Antidepressants do not cause birth defects or cognitive problems [127]
- That coming off antidepressants is inadvisable [128]
- Professional bodies endorse the use of antidepressants [129]

If SSRIs work, as claimed by marketing, namely by correcting a serotonergic abnormality it might be thought they would reduce the risk of things going wrong. But there is no such abnormality and treatment with an SSRI on balance will leave serotonin systems more abnormal that they were to begin with [130].

If working means that SSRIs reduce risky behaviors including alcohol and drug intake, the evidence is somewhat to the contrary; SSRIs may increase alcohol and drug use [84, 131].

4.2. Alternative explanations

Concerns about a link between SSRIs and birth defects have met the following counter arguments that are as readily applicable here.

First, rates of ASD from these studies, as is the case with rates of birth defects on SSRIs, fall within the background rate of the population at large and on this basis it is claimed that even where the rates in the treated group exceed those in the control group, these rates can be discounted [see 128, 132]. This argument is not valid for birth defect studies where the background rate is determined by the study design. The argument is misplaced for a condition like ASD or neurodevelopmental spectrum disorders where the background rate appears to be changing by the year.
Second, studies of SSRI use during pregnancy show a consistent rate of problems and that when all studies are meta-analyzed the risks disappear. We have not been able to analyze all studies as some groups, such as the Motherisk group, refuse to share their data.

Third, it is claimed that depression causes both birth defects and ASD and is endemic in pregnant women at rates of 15–20%. We believe there is no good evidence for these propositions.

Fourth, it is proposed that there are no adequate and well-conducted studies in this area. This statement means that there are no RCTs and assumes the reader will accept the proposition that only RCTs can demonstrate if an antidepressant causes birth defects or ASD or not. In our opinion this position is incorrect. RCTs can get the answer as badly wrong as any other epidemiological study [see 133]. To establish what is happening will need judgements that take both the epidemiological and biological data into account. It is only when there is a good understanding of what is happening that an appropriate RCT can be designed.

Finally, it is claimed that the results cited from a majority of studies show no statistically significant difference between women treated and those not treated. For some if an increase in risk is not significant, they take a view that there is in fact no increase in risk. This is not the most widely accepted view in the field [134]. The visual plots of the meta-analyses demonstrate this point clearly.

5. Conclusion

ASD is at present an amorphous entity and has some roots in classic autism but now appears to encompass areas formerly termed learning disabilities or developmental delay. Across this spectrum there is evidence that the intake of serotonin reuptake inhibiting drugs may lead to poorer outcomes, although little clarity at present as to the most likely mechanisms involved.

Further progress in this area will require greater precision in terms of clinical phenotypes and efforts to control for intervening variables such as operative interventions for birth defects or alcohol intake in pregnancy.

The area calls out for the establishment of comprehensive pregnancy registries.

Conflict of interest

DH and DM are potential expert witnesses in a case involving SSRIs and ASD but this case arose toward the date of completion of this article. JLN has no competing interests as regards the subject matter of this study.

Author contributions

Prof David Healy: principal investigator and primary author;
Dr Joanna Le Noury: data collection, analysis, study write up and review;
Prof Dee Mangin: data collection, analysis, study write up and review.

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