

The ethics of randomized placebo controlled trials of antidepressants with pregnant women

David Healy^{a,*}, Derelie Mangin^b and Barbara Mintzes^c

^a*Department of Psychiatry, Cardiff University, Cardiff, UK*

^b*Department of Public Health and General Practice, Christchurch School of Medicine, University of Otago, New Zealand*

^c*Department of Anesthesiology, Pharmacology and Therapeutics, University of British Columbia, Vancouver, Canada*

Abstract. In recent years, a number of authors have advocated the merits of conducting randomised controlled trials (RCTs) of antidepressants in women with nervous disorders during the prenatal period. However, a critical review of the literature indicates RCTs are not justifiable. At a time when it has become clear that a significant proportion of the existing literature on the use of pharmaceutical agents is ghostwritten, ethicists and others making assertions that RCTs are needed risk becoming part of an apparatus that plays down the hazards of treatment and promotes the use of treatments that may be harmful.

Keywords: Antidepressants, birth defects, pregnancy, miscarriage, ghost-writing

1. Introduction

There have been recent calls for aggressive pharmacological treatment of “depression” in pregnant women, and arguments for randomised controlled trials of antidepressants with pregnant women. It is our contention that these reflect a misunderstanding of the epidemiological literature and faulty science around the risks and benefits of these drugs in pregnancy, and that this misunderstanding is fuelled by the commercial imperatives and strategies of the companies manufacturing these drugs.

In an article, for instance, Coverdale et al. [11], arguing the case for randomized controlled trials of antidepressants with pregnant women point out that there were no controlled trials of antidepressants in pregnant women, even though 35% have depressive symptoms, 10% are depressed and up to 8% are on treatment. They suggested 4 questions needed to be asked in order to determine whether it was reasonable to proceed with a trial or not: First, is there evidence of efficacy of antidepressant use during pregnancy? Second, is there documented causality of serious far reaching and irreversible clinical harm to the fetal or neonatal patient? Third, is there documented causality of serious, far-reaching and irreversible clinical harm to pregnant women in a placebo arm? Fourth are there no or only rare documented occurrences of less serious injury to the fetal or neonatal patient?

*Corresponding author: E-mail: HealyD@cardiff.ac.uk

In discussing these questions, they noted that antidepressants may be associated with teratogenicity, and with spontaneous abortion, and have been associated with primary pulmonary hypertension, a withdrawal syndrome in the neonate, and both low birth weight and preterm delivery. However they temper this with comments that while lower birth weight may happen on antidepressants, neonatal withdrawal is transient and occasional, and point to evidence suggesting there is no adverse effect of treatment on child development. They note increased rates of spontaneous abortions in patients taking antidepressants but suggest that this issue may be confounded by the presence of depression and that therefore the apparent increase has not been shown to be caused by antidepressants.

On the issue of possible teratogenicity, citing several reviews [20, 40], they state “there is limited evidence of teratogenic effects from antidepressants during pregnancy. Demonstrated statistical association in a cohort study does not support a judgement of causality”.

There are other very similar articles and editorials making a case that the consequences of not treating pregnant women with nervous problems with antidepressants may outweigh any adverse effects of treatment [37, 51], and stating that until a controlled trial is undertaken we will not know whether antidepressants have adverse effects on unborn children [50]. These articles need to be set against a background of marketing of antidepressants to physicians and consumers that focus on women of child bearing years to drive demand for these medicines.

While holding to an ethical principle that pregnant women and their unborn children deserve at least as good evidence, or perhaps better, for both the benefits and the harms of any treatments they might take as any other group of patients, there are a number of grounds on which to take issue with the position of papers that suggest the current epidemiological evidence is insufficient as regards the hazards of treatment to forestall the conduct of an RCT.

First, there is the question of whether there is any reason to believe antidepressants “work” in the manner many of the above authors appear to think they do, and based on current data whether there is any reason to believe a trial of these drugs is warranted in pregnancy. Second, there is the issue of what risks untreated antenatal depression poses to the unborn child. Third, what is the status of our knowledge regarding the hazards to the fetus of treatment with antidepressant drugs. Linked to this are questions about how to demonstrate any causal relationship between a treatment like prescribing an antidepressant and an effect such as a birth defect. Fourth, there are some broader questions about the forces that have led us to even consider this question of performing RCTs of antidepressants in pregnancy given the current state of the evidence.

2. Is a trial of antidepressants warranted in pregnancy?

The evidence for the effectiveness of antidepressants in the general population is not convincing. When assessing the risks of suicidality posed by antidepressants in 2006, the Food and Drug Administration asked companies for all placebo controlled trials undertaken in depression. They summarised the data received from trials that had enrolled over 100,000 patients [46]. In brief these trials demonstrated that 5 out of every 10 patients recruited “responded” on the outcome measure used, a physician rated disease specific rating scale, while 4 out of 10 responded to the placebo on the same measures – only 1 in 10 patients therefore show a specific response to the active drug. The results are even less impressive if the data from other rating scales, representing the patient’s point of view, such as quality of life scales, were used. This data, while available in the FDA analysis, has remained largely unpublished. Strikingly, on measures of efficacy such as the mortality rate in the active treatment arm compared with placebo, there

was a 1.69 fold higher rate of suicide in the active treatment arm of these trials than there was in the placebo arm [46]. So only half of patients treated, 'respond' and up to 80% of the apparent response is linked to placebo factors. If clinicians are to follow the evidence then, they would resort to non-pharmacological interventions in the first instance, and only turn to antidepressants in refractory cases. Following the evidence in this fashion would in a number of instances result in patients remaining drug free in the first trimester of pregnancy.

While it is important to ensure that women who are pregnant have as good data in support of anything they might take as any other group within society, against a background of potential teratogenicity, much stronger evidence of efficacy in the general population would seem needed before such a trial in pregnant women is warranted. In the FDA analysis of the antidepressants 50% of trials have thrown up negative results [46]. Selective publication of trials, and selective publication of data from trials, conceals this. Given the risks of teratogenicity, the prospect of a series of repeated negative trials is hard to justify. This is an issue we pick up below.

3. What are the risks of leaving antenatal depression unmedicated?

The risks of leaving antenatal depression unmedicated can be thought of from two angles – the risk to the pregnant women, and the risk to the child. First it is helpful to consider the magnitude of the problem. It is common to find suggestions that 35% of pregnant women have depressive symptoms and that 10% of them are depressed [11]. One problem with this formulation is that it is based on symptom counts. Having symptoms, even meeting every single one of the operational criteria for depression, does not necessarily mean a person is depressed and requiring medication. Conflating epidemiological studies of depressive *symptoms* with rates of moderate to severe major depressive *disorder* where drug treatment might be considered in non pregnant adults is a profound clinical mistake. The point prevalence of major depression is 3.8% at the end of the first trimester, 4.9% at the end of the second and 3.1% at the end of the third trimester of pregnancy [18].

3.1. Risks for the child

There is an inference that there may be a direct toxic effect of untreated depression on the fetus. Some authors point to effects of untreated depression on the development of the child in later life, arguing that these are substantial and deleterious. There are no known direct toxic effects of antenatal depressive symptoms on the fetus. There is for instance no known endocrine change linked to the majority of common nervous disorders that affect pregnant women. The only psychiatric disorder for which there is any proven endocrine abnormality is melancholia, and even in this case the endocrine disturbances are of a lesser degree to those found in severe physical stress or frank endocrine disorders. Melancholia is furthermore rare. The traditional wisdom is that this disorder can arise in pregnancy, but that it commonly clears with birth, and is not extended into the postnatal period [6]. For moderate to severe or melancholic depressive disorders, guidelines such as those issued by Britain's National Institute for Health and Clinical Excellence (NICE) recommend tricyclic antidepressants and electroconvulsive therapy (ECT) is a further option.

Postnatal depression does have effects on the bonding between mother and child and does affect the physical and mental development of the child, leaving them prone to affective instability in later life and with impaired cognitive performance relative to their peers in childhood [5]. There is however no evidence that antenatal depression does this. Furthermore while first trimester depression is a risk factor

for post natal depression, most (71%) first trimester depression does not go on to postnatal depression and most (64%) postnatal depression is not associated with first trimester depression [32]. If antenatal 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.

3.2. Risks for the mother

An increasing number of articles now argue that the consequences of leaving antenatal depression untreated are serious. The suggestions are that lack of treatment can lead to smoking, alcohol and drug intake, poor self-care, suicide and postnatal depression [1, 51]. We can find no evidence to support these assertions nor any advantage from antidepressant use for these outcomes. While suicide is one of the leading causes of maternal death in pregnancy, the overall rate of maternal death is very low and most maternal suicides occur after delivery [28]. In placebo controlled trials of antidepressants there are more suicides in the active treatment arms of these trials than in the placebo arms suggesting these drugs might increase rather than decrease this risk [46].

A further point commonly made is that: “Women who stop taking antidepressant medications seem to put themselves at risk for relapse”. However the study from Cohen et al. on which this claim is made is a study in a highly selected population, likely to have a high relapse rate and not representative of a primary care population [9]. The participants had depression for a mean of 15.4 years, with 44% having had 5 or more episodes of depression. It is not clear that these subjects had a tapered withdrawal, or that any effort was made to distinguish between withdrawal and relapse, which often overlap.

This study in our opinion raises a key ethical issue, not noted elsewhere at present. There is an acceptance that SSRIs cause dependence. If they also cause birth defects, then any women of child bearing years, pregnant or not being offered this treatment option needs to be informed before she starts of the risk of both birth defects and dependence.

4. Antidepressants and teratogenesis

Despite the availability of many review articles on antidepressants in pregnancy at present it is difficult to find any reviews linking antidepressants with teratogenesis – other than the original epidemiological studies that point to the existence of a risk. The epidemiological data is indeed so strong when viewed in aggregate that the difficulty in finding review articles that note this hazard is remarkable. While randomised controlled trials are regarded as the strongest design, the combined epidemiological data is strong enough here that randomised controlled trials are unnecessary to inform clinical decision making, and cannot be justified on ethical grounds as equipoise does not exist.

It is helpful to consider the data on paroxetine as an illustration as it has been the focus of some attention. In 2005, GlaxoSmithKline were required by FDA to change the warning label on paroxetine to a pregnancy category D. This change was consequent on a study undertaken by the company published 2 years later [10].

As of 2008, when the Coverdale article [11] had been written, this and 14 other studies had been reported from 1998 onwards [2, 4, 7, 13, 15, 25, 26, 29, 30, 34, 42, 44, 47–49] that contained paroxetine specific data and were adjudged by GlaxoSmithKline to be sufficiently methodologically sound to include in a meta-analysis [53]. These included case cohort and medical records studies.

Overall they gave a clear risk of major defects for paroxetine taken in the first trimester with an odds ratio of 1.3 (95% CI 1.1, 1.6) and an odds ratio for specifically cardiac defects of 1.5 (95% CI 1.2, 1.9). In

terms of figures on the risks of overall defects 10 studies gave an increase in the odds ratio of a defect, 3 gave a decrease and 2 returned a relative risk of 1.0. In terms of the 13 studies that provided information on cardiac defects, 9 studies gave an increase in the odds ratio of a defect.

Diav Citrin 2005 [15]	OR 3.5	(95% CI 1.1–11.2)
Bakker 2006 [3]	OR 1.5	(95% CI 0.5–4.3)
Vial 2006 [48]	OR 1.2	(95% CI 0.3–4.7)
Alwan 2007 [2]	OR 1.7	(95% CI 0.9–3.1)
Berard 2007 [4]	OR 1.4	(95% CI 0.5–3.9)
Cole 2007 [10]	OR 1.5	(95% CI 0.7–2.9)
Kallen 2007 [25]	OR 1.6	(95% CI 1.0–2.5)
Louik 2007 [29]	OR 1.4	(95% CI 0.8–2.5)
Chambers (unpubl.)	OR 10.8	(95% CI 0.5–225.8)

One study suggested no effect.

Davis 2007 [13]	OR 1.0	(95% CI 0.5–2.3)
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There were three studies that suggested an effect in the opposite direction.

Nash (unpubl.)	OR 0.4	(95% CI 0.1–1.7)
Kulin 1998 [26]	OR 0.8	(95% CI 0.1–7.0)
Malm 2005 [30]	OR 0.7	(95% CI 0.1–5.0)

Of the studies that did not support a risk of paroxetine, some indicated a clear risk on other SSRIs [34], while many of the studies pointing to risks with paroxetine also point to risks with other SSRIs.

Two of the studies that had then been done were not included. In one, there was a marked increase of risk for both cardiac defects and major birth defects on antidepressants compared to non-treatment but also an interaction between antidepressants and benzodiazepines [36]. In the second, there was no data for specific antidepressants but again an increase in risk with antidepressants compared to non-treatment [52].

Since this data was posted a further small study has appeared, in which there was no demonstrable increase in risk on SSRI antidepressants, odds ratio 0.4 (95% CI 0.14, 1.4) however this was not separated out by trimester, and there were no data on heart defects by individual drugs [50]. Another study of SSRI use pointed to an increased prevalence of septal heart defects with an odds ratio of 1.99 (95% CI 1.13, 3.53) with a fourfold increase in risk if more than one SSRI was used. It found no increase in risk for paroxetine, although the numbers were small [38]. Finally a study in 2009 using echocardiographic confirmation of cardiac defects gave an increased risk with paroxetine with an relative risk of 2.79 (95% CI 1.02, 7.62), with an overall increased risk of heart defects on any SSRI, relative risk 2.17 (95% CI 1.07, 4.39) [31].

4.1. Cause and effect and RCTs

Many articles argue that randomized controlled trials offer evidence on cause and effect in a manner that for instance cohort studies do not. There is little basis for this claim, and in fact no birth defect has ever been established on the basis of a controlled trial. Indeed, significant adverse effects of a drug, birth defect or otherwise, are not ordinarily demonstrated by means of randomized trials, except perhaps in the case of Vioxx. Randomized trials are a subset of epidemiological studies that control for confounding influences by a method that often allows much smaller samples of subjects to be recruited than cohort studies. However they are not essential to demonstrate causality. Many important causal

links have been demonstrated through cohort designs such as the link between breastfeeding and better educational outcomes [22] or the link between lead exposure in children and poorer long term educational and behavioral outcomes [17]. No-one would suggest an RCT of lead paint exposure in the face of this evidence.

The issue stemming from the data currently available is whether there is a clear signal of risk and if this signal emerged, after which undertaking an RCT of antidepressants in pregnancy might have been deemed as unethical as undertaking one for lead paint exposure. The answer hinges around what meaning to attribute to a point estimate and its related confidence interval.

The position taken in many articles typically is that if the 95% confidence interval around the odds ratio for a hazard includes the figure 1.0, there is no risk as there is no statistical significance. This argument is simply wrong [19]. The only meaning of statistical significance is that there is less than 5% chance that the real odds ratio, not the estimate, is smaller than 1. With a *p*-value greater than 0.05, e.g. 0.06, there is still a 94% chance of risk and that is unquestionably of clinical significance. There is unlikely to be a risk if the point estimate for the odds ratio is itself 1.0 or shifted to the left. But if the point estimate lies to the right of 1.0, there is likely to be a risk. The confidence interval simply indicates the precision of the estimate. The fact that the 95% confidence interval still includes the figure 1.0 does not mean that there is no increase in risk. It is more likely to mean the study is underpowered with too small a sample size. If a large majority of studies using different methods find an equivalent shift to the right, as GlaxoSmithKline have found, then it is highly likely there is an increase in risk and the aggregate data from a number of small studies is enough in this case to demonstrate a clear signal of risk.

This can be brought out by a thought experiment. Assume a doctor is forced to put a patient, likely to become pregnant, on one of two drugs for a particular clinical condition, both of which come with a risk of birth defects. If drug A has an odds ratio of 1.8 with a 95% confidence interval stretching from 1.1 to 2.5, and drug B comes with an odds ratio of 8.1 with a 95% confidence interval stretching from 0.92 to 25.2, the safer of the two drugs is drug A rather than drug B. Drug B is likely to be 4 times riskier than drug A.

The question of when the epidemiological data pointing strongly to the existence of a risk of birth defects can be considered within this context. As of 2002, there were 4 studies available. The Kulin study from 1998 [26], which pointed to an odds ratio of a birth defect on paroxetine compared to non-treatment of 1.8 (95% CI 0.6, 5.4).

A further study appeared in 2001 from Unfred et al. [47] showing a rate of major malformations of 4.2% with paroxetine vs. 0.05% for controls. This is a greater than 8-fold increase in risk on paroxetine. This study still awaits full publication. Another study that appeared in abstract form in 2002 from Diav-Citrin et al. [14] in 2002 had a rate of 3.9% for major malformations on paroxetine vs. 2.1% in controls. As of 2002, there had been only one smaller study failing to show an increase in risk on paroxetine but it did show an increased risk on other SSRIs [44].

The Kulin et al. [26] paper also reports an excess of therapeutic and spontaneous abortions on treatment. Combining the data offered for spontaneous and therapeutic abortions gives 20.2% on SSRI vs. 12.7% for controls; an odds ratio of 1.7 (95% CI 1.1, 2.9). In the case of spontaneous abortions alone, the figures are 13.5% compared to 8.9% for controls; an odds ratio of 1.6 (95% CI 0.9, 2.9). When data on spontaneous abortions are reported in the cohort studies cited above, they consistently point to an excess in women taking antidepressants. If spontaneous abortions are linked to a greater frequency of birth defects than term births, then the true rate of birth defects linked to antidepressant intake seems likely to be substantially greater than estimates based on term births only.

These studies and the consistency of their data make a strong case for an increase in risk. They also establish a date, after which we would argue that in terms of equipoise, an RCT of antidepressants in pregnancy became increasingly difficult to justify.

Finally, in terms of assessing causality it is traditional to marry epidemiological with mechanistic or laboratory studies, often in animal populations when the issue is a pregnancy linked adverse event. It has been known for 40 years that serotonin has a trophic function in embryogenesis, regulating cell migration in tissues such as the embryonic gut, heart and nervous system [27, 33, 35, 43, 54] despite this, as of 2009 there had been no rigorous published studies looking at the possible teratogenic effects of antidepressants.

Laboratory analysis has now demonstrated clear teratogenic effects on a number of antidepressants, in particular serotonin reuptake inhibitors, and especially with paroxetine [45]. The signal was stronger for paroxetine than for other serotonin reuptake inhibitors such as cocaine. The findings from this laboratory study are consistent with what is known of the mitogenic functions of serotonin and with the pattern of defects that have emerged in recent epidemiological studies. At present the data is best explained in terms of potency of action on the serotonin reuptake site. This suggests the problems may be dose dependent, for which both laboratory and epidemiological studies provide some evidence [4, 45]. The evidence of a dose-response gradient further supports an argument for a causal link between treatment and effect. If an action through serotonin systems is the mechanism through which these drugs pose a risk, then other drugs that inhibit serotonin reuptake such as tricyclic antidepressants and antihistamines pose some risk, perhaps dependent on dose.

4.2. Other hazards

Aside from teratogenic effects, the evidence now indicates antidepressants are associated with prematurity, as well as low birth weight [21, 30], and pulmonary hypertension [8] when given in the course of pregnancy. Finally, there is little dispute that antidepressants can trigger a neonatal withdrawal syndrome after birth. This was first noted in 1972 [16]. The risk seems most clear in the case of paroxetine, for which there has been a greater number of reports to regulators of dependence and withdrawal effects than for any other psychotropic drug, both in those taking the treatment and in neonates [12, 41].

There are at present no agreed procedures to manage difficult withdrawal syndromes. As a consequence, an indeterminate number of women of child-bearing age put on antidepressants will find it difficult or impossible to stop treatment should they wish to have a drug-free pregnancy.

5. Why this debate?

In our view calls for RCTs of antidepressants in pregnancy are not ethically justified on the basis of the evidence as outlined above. But the reality of current clinical practice and opinion is at odds with our view. How did this situation come about?

Until very recently, the standard clinical view was that all medications including antidepressants should not be used in pregnancy, unless there was a clear clinical need, and there was an absence of signals of harm. While some older textbooks offer this view, there are few if any recent reviews in mental health and related journals that point to the existence of hazards of treatment or argue against treating antenatal nervous conditions with antidepressants. Given the clear evidence outlined of risks stemming back almost a decade, and the available evidence as regards the relatively modest benefits of treatment, this switch in treatment philosophy calls for an explanation in its own right.

While there are many influences on the changing culture of medical practice, commercial influences appear to be a key issue in this instance. There is convincing evidence that a number of the reviews and academic presentations in this domain advocating treatment or denying hazards have been ghostwritten [39] or commissioned by companies [23] or have been written without the competing interests of their authors being revealed [24].

A good case can be made that a key influence surrounding the use of antidepressants in pregnancy lies in the similar efforts by companies, using academics, to engineer a comparable switch in culture as happened in the case of prescribing antidepressants to children. At the time that controversy blew up, the entire literature appears to have been written by either company personnel or medical writers, even though in a number of instances it was published under the names of distinguished academics.

This has implications for any calls for or consideration of the ethics of undertaking RCTs in antenatal care. Given company involvement in the construction of the evidence that increasingly underpins clinical practice, and the bias involved, it is highly unlikely that calls for RCTs of antidepressants in pregnancy will lead to the design and publication of trials that illuminate the real evidence base for the risks and benefits of the clinical practice with pharmaceuticals. What is more likely is that there will be a further amassing of data where the evidence for efficacy is overblown and that for hazards is minimised – data to manipulate decision making rather than inform it. It is this process that has already led to large numbers of women taking antidepressants in pregnancy in good faith despite increasing evidence of harm in the data.

The sources of information relied upon by physicians for information on the efficacy and hazards of pharmaceuticals have become adulterated by the influence of the companies at all levels, including the published literature. This has undermined the ability of physicians to access independent and reliable information about these products in order to make the best decisions for their patients. Given this current situation it would seem prudent to strengthen the original imperative of avoiding medication use in pregnancy rather than to suggest a controlled trial is ethical because there is equipoise on the issue.

Given what we know thus far, how likely is an individual pregnant woman who might consider enrolling in a clinical trial of antidepressants to be adequately protected against harm? Is she to be informed that the jury is not in on the potential for spontaneous abortion, teratogenicity, neonatal withdrawal syndromes, and persistent pulmonary hypertension? Does she need to be told there is a strong likelihood that both she and her doctor have been extensively exposed to misrepresentation of the meaning of a depression diagnosis and the known benefits and harms of antidepressants? What if anything will the informed consent procedures in a clinical trial say about these issues if the trial is run by a company or is using proprietary products?

Conflict of interest

David Healy and Derelie Mangin have been expert witnesses in paroxetine induced birth defect cases. Barbara Mintzes has no conflicting interests to declare.

References

- [1] L.L. Altschuler, L. Cohen, M.P. Szuba, V.K. Burt, M. Gitlin and J. Mintz, Pharmacologic management of psychiatric illness during pregnancy: Dilemmas and guidelines, *American J Psychiatry* **153** (1996), 592–606.
- [2] S. Alwan, J. Reefhuis, O. Rasmussen, R. Olney and J. Friedman, Use of selective serotonin reuptake inhibitors in pregnancy and the risk of birth defects, *New England J Med* **356** (2007), 2684–2692.
- [3] M. Bakker, S. Kerstjens-Frederikse, M. Van den Berg, L. De Jong-Van den Berg and H. De Walle, Use of selective serotonin reuptake inhibitors in early pregnancy and risk of cardiac malformations, *Pharmacoepidemiol Drug Saf* **15** (2006), S81.

- [4] A. Berard, E. Ramos, E. Rey, L. Blais, M. St-Andre and D. Oraichi, First trimester exposure to paroxetine and risk of cardiac malformations in infants: the importance of dosage, *Birth Defects Research* **80** (2006), 18–27.
- [5] L. Bonari, N. Pinto, E. Ahn, A. Einarson, M. Steiner and G. Koren, Perinatal risks of untreated depression during pregnancy, *Can J Psychiatry* **49** (2004), 726–735.
- [6] I.F. Brockington, *Motherhood and Mental Illness*, Oxford University Press, Oxford, 1996.
- [7] R.C. Casper, B.E. Fleisher, J.C. Lee-Ancayas, A. Gilles, E. Gaylor, A. DeBattist and E. Hoyme, Follow-up of children of depressed mothers exposed or not exposed to antidepressant drugs during pregnancy, *J Pediatr* **142** (2003), 402–408.
- [8] C.D. Chambers, S. Hernandez-Diaz, L.J. Van Marter, M.M. Werler, C. Louik, K.L. Jones and A.A. Mitchell, Selective serotonin reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn, *N Engl J Med* **354** (2006), 579–587.
- [9] L.S. Cohen, L.L. Altshuler, B.L. Harlow, R. Nonacs, D.J. Newport, A.C. Viguera, et al., Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment, *JAMA* **295**(5) (2006), 499–507.
- [10] J.A. Cole, S.A. Ephross, I.S. Cosmatos and A.M. Walker, Paroxetine in the first trimester and the prevalence of congenital malformations, *Pharmacoepidemiology and Drug Safety* **16** (2007), 1075–1085.
- [11] J.H. Coverdale, L.B. McCullagh and F.A. Chervenak, The ethics of randomized placebo controlled trials of antidepressants with pregnancy women: a systematic review, *Obstetrics and Gynecology* **112** (2008), 1361–1368.
- [12] M.L. Dahl, E. Olhager and J. Ahlner, Paroxetine withdrawal in a neonate, *British J Psychiatry* **171** (1997), 391–394.
- [13] R. Davis, D. Rubanowice, H. McPhillips, M. Raebel, S. Andrade, D. Smith, M. Ulcickas Yood and R. Platt, Risks of congenital malformations and perinatal events among infants exposed to antidepressant medications during pregnancy, *Pharmacoepidemiol Drug Saf* **16** (2007), 1086–1096.
- [14] O. Diav-Citrin, S. Shechtman, D. Weinbaum, J. Arnon, R. Weinberg and A. Ornoy, Pregnancy outcome following gestational exposure to paroxetine: a prospective controlled cohort study, *Teratology Society Abstracts* (2002), DOI 101002/tera.10073, p. 298, abstract 13.
- [15] O. Diav-Citrin, S. Shechtman, D. Weinbaum, R. Wajnberg, M. Avgil, E. De Gianantonio, M. Clementi, C. Weber-Schoendorfer, C. Schaefer and A. Ornoy, Paroxetine and fluoxetine in pregnancy: a prospective multicentre, controlled observational study, *Br J Clin Pharmacology* **66** (2008), 695–705.
- [16] E. Eggermont, J. Reveschot, V. Deneve and M. Casteels-Van Daele, The adverse influence of imipramine on the adaptation of the newborn infant to extrauterine life, *Acta Paediatrica Belgica* **26** (1972), 197–204.
- [17] D.M. Fergusson, L.J. Horwood and M.T. Lynskey, Early dentine lead levels and educational outcomes at 18 years, *J Child Psychology & Psychiatry & Allied Disciplines* **38** (1997), 471–478.
- [18] N.I. Gavin, B.N. Gaynes, K.N. Lohr, S. Meltzer-Brody and G.Y.S. Gartlehner, Perinatal depression: a systematic review of prevalence and incidence, *Obstet Gynecol* **106**(5 Pt 1) (2005), 1071–1083.
- [19] D. Healy, The antidepressant tale: figures signifying nothing? *Advances in Psychiatric Treatment* **12** (2006), 320–328.
- [20] M.E. Hemels, A. Einarson, G. Koren, K.L. Lanctot and T.R. Einarson, Antidepressant use during pregnancy and the rates of spontaneous abortions: a meta-analysis, *Am J Pharmacother* **39** (2005), 803–809.
- [21] V. Hendrick, L.M. Smith, R. Suri, S. Hwang, D. Haynes and L. Altshuler, Birth outcomes after prenatal exposure to antidepressant medication, *Am J Obstet Gynecol* **188** (2003), 812–815.
- [22] L.J. Horwood and D.M. Fergusson, Breastfeeding and later cognitive and academic outcomes, *Pediatrics* **101**(1) (1998), E9.
- [23] Grassley C.E., Letter to James Wagner, President, Emory University, June 2nd 2009, from Senator CE Grassley, US Senate, http://s.wsj.net/public/resources/documents/WSJ_LtrEmoryUni_090609.pdf, 2009.
- [24] Incomplete financial disclosure, *JAMA* **296** (2006), 170. doi:10.1001/jama.296.2.170
- [25] B. Kallen and P.O. Olausson, Maternal use of selective serotonin re-uptake inhibitors in early pregnancy and infant congenital malformations, *Birth Defects Res A Clin Mol Teratol* **79** (2007), 301–309.
- [26] N.A. Kulin, A. Pastuszak, S.R. Sage, B. Schick-Boschetto, G. Spivey, M. Feldkamp, K. Ormond, D. Matsui, A.K. Stein-Schechman, L. Cook, J. Brochu, M. Rieder and G. Koren, Pregnancy outcome following maternal use of the new selective serotonin reuptake inhibitors: a prospective controlled multicenter study, *JAMA* **279** (1998), 609–610.
- [27] J.M. Lauder, Neurotransmitters as growth regulatory signals: Role of receptors and second messengers, *TINS* **16** (1993), 233–240.
- [28] G. Lewis (ed.), *The confidential enquiry into maternal and child health (CEMACH). Saving mothers' lives: reviewing maternal deaths to make motherhood safer – 2003–2005. The Seventh Report on Confidential Enquiries into Maternal Deaths in the United Kingdom*. CEMACH, London, 2007.
- [29] C. Louik, A. Lin, M. Werler, S. Hernandez-Diaz and A. Mitchell, First trimester use of selective serotonin-reuptake inhibitors and the risk of birth defects, *New England Journal of Medicine* **356** (2007), 2675–2683.

- [30] H. Malm, T. Klaukka and P.J. Neuvonen, Risks associated with selective serotonin reuptake inhibitors in pregnancy, *Obstetrics and Gynecology* **106** (2005), 1289–1296.
- [31] P. Merlob, E. Birk, L. Sirota, N. Linder, M. Bevant, B. Stahl and G. Klinger, Are selective serotonin reuptake inhibitors cardiac teratogens? Echocardiographic screening of newborns with persistent heard murmur, *Birth Defects Research Part A, Clinical and Molecular Teratology* **85** (2009), 837–841.
- [32] J. Milgrom, A.W. Gemmill, J.L. Bilszta, B. Hayes, B. Barnett, J. Brooks, et al., Antenatal risk factors for postnatal depression: a large prospective study, *J Affect Dis* **108**(1–2) (2008), 147–157.
- [33] J.R.D. Moisewitsch and J.M. Lauder, Serotonin regulates mouse cranial neural crest migration, *Proc Natl Acad Sci USA* **92** (1995), 7182–7186.
- [34] C.M. Nash, C.M. O’Connell and A.A. Howlett, Neonatal outcomes associated with maternal antidepressant use in a population cohort of Nova Scotian pregnancies between 1993 and 2004, *Paediatrics and Child Health* **12** (SA) (2007), 42.
- [35] C.G. Nebigil, D.S. Choi, A. Dierich, P. Hickel, M. Le Meur, N. Messadeq, J.M. Launay and L. Maroteaux, Serotonin 2B receptor is required for heart development, *Proc Nat Acad Sci* **97** (2000), 9508–9513.
- [36] T.E. Oberlander, W. Warburton, S. Misri, W. Riggs, J. Aghajanian and C. Hertzman, Major congenital malformations following prenatal exposure to serotonin reuptake inhibitors and benzodiazepines using population based health data, *Birth Defects Research Part B: Developmental and Reproductive Toxicology* **83** (2008), 68–76.
- [37] B.L. Parry, Assessing risk and benefit: to treat or not to treat major depression during pregnancy with antidepressant medication, *Am J Psychiatry* **166** (2009), 512–514.
- [38] L.H. Pedersen, T.B. Henriksen, M. Vestergaard, J. Olsen and B.H. Bech, Selective serotonin reuptake inhibitors in pregnancy and congenital malformations: population based cohort study, *BMJ* **339** (2009), b3569.
- [39] Paroxetine across the lifespan, *Psychopharmacology Bulletin* **37**(Suppl. 1) (2003).
- [40] R. Rahimi, S. Nikfar and M. Abdollahi, Pregnancy outcomes following exposure to serotonin reuptake inhibitors: a meta-analysis of clinical trials, *Reprod Toxicol* **22** (2006), 571–575.
- [41] E.J. Sanz, C. De-las-Cuevas, A. Kiuru, A. Bate and R. Edwards, Selective serotonin reuptake inhibitors in pregnant women and neonatal withdrawal syndrome: a database analysis, *Lancet* **365** (2005), 482–487.
- [42] S. Schloemp, W.E. Paulus, K. Sterzik and F. Stoz, Congenital malformations after antidepressant medication with paroxetine in early pregnancy? *Human Reproduction* **21**(Suppl. 1) (2006), i12.
- [43] D.L. Shuey, T.W. Sadler and J.M. Lauder, Serotonin as regulator of craniofacial morphogenesis: site specific malformations following exposure to serotonin uptake inhibitors, *Teratology* **46** (1992), 367–378.
- [44] G.E. Simon, M.L. Cunningham and R.L. Davis, Outcomes of prenatal antidepressant exposure, *Am J Psychiatry* **159** (2002), 2055–2061.
- [45] W.N. Sliot, H.C. Bowden and T.D. Yih, *In vitro* and *in vivo* reproduction toxicology of 12 monoaminergic reuptake inhibitors: Possible mechanisms of infrequent cardiovascular anomalies, *Reproductive Toxicology* (2008), doi:10.1016/j.reprotox.2009.04.005
- [46] M. Stone and L. Jones, Clinical review: relationship between antidepressant drugs and adult suicidality, Tables 16 and 18. <http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4272b1-index.htm>, 2006.
- [47] C.L. Unfred, C.D. Chambers, R. Felix, K. Kao, L. Dick, S. Alvarado and K. Lyons-Jones, Birth outcomes among pregnant women taking paroxetine (Paxil). OTIS annual meeting, *Teratology* **63** (2001), 321–324.
- [48] T. Vial, M.P. Cournot, N. Bernard, P. Carlier, P. Jonville-Bera, M.J. Jean-Pastor, C. Bajhoux, E. Robert, E. Elefant and J. Descotes, Paroxetine and congenital malformations: A prospective comparative study, *Drug Saf* **29**(10) (2006), 911–1010.
- [49] S.W. Wen and M. Walker, The use of selective serotonin reuptake inhibitors in pregnancy, *J Obstet Gynaecol Can* **26** (2006), 819–822.
- [50] C.L. Wichman, K.M. Moore, T.R. Lang, J.L. St Sauver, R.H. Heise and W.J. Watson, Congenital heart disease associated with selective serotonin reuptake inhibitor use during pregnancy, *Mayo Clinic Proceedings* **84** (2009), 23–27.
- [51] K.L. Wisner, D.K. Sit and B.H. Hanusa, Major depression and antidepressant treatment: impact on pregnancy and neonatal outcomes, *Am J Psychiatry* **166** (2009), 557–566.
- [52] P. Wogelius, M. Norgaard, M. Gislum, L. Pedersen, E. Munk, P.B. Mortensen, L. Lipworth and H.T. Sorensen, Maternal use of selective serotonin reuptake inhibitors and risk of congenital malformations, *Epidemiology* **17** (2006), 701–704.
- [53] GlaxoSmithKline Clinical Studies Register. Epidemiology Study: First Trimester Exposure to Selective Serotonin Reuptake Inhibitors (SSRIs) and the risk of birth defects, www.gsk-clinicalstudyregister.com/files/pdf/24089.pdf
- [54] M.S. Yavarone, D.L. Shuey, H. Tamir, T.W. Sadler and J.M. Lauder, Serotonin and cardiac morphogenesis in the mouse embryo, *Teratology* **47** (1993), 573–584.