REVIEW ARTICLE

Drug Saf 2011; 34 (11): 1027-1048
0114-5916/11/0011-1027/$49.95/0

Investigating Outcomes Following the Use of Selective Serotonin Reuptake Inhibitors for Treating Depression in Pregnancy

A Focus on Methodological Issues

Luke E. Grzeskowiak,[1] *Andrew L. Gilbert*[1] and *Janna L. Morrison*[2]

1 Quality Use of Medicines and Pharmacy Research Centre, Sansom Institute for Health Research, School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, SA, Australia
2 Early Origins of Adult Health Research Group, Sansom Institute for Health Research, School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, SA, Australia

Contents

Abstract

The aim of this review was to critically appraise the existing literature with a particular focus on identifying methodological issues associated with studying outcomes following the use of selective serotonin reuptake inhibitors (SSRIs) during pregnancy.

Existing studies evaluating outcomes following prenatal SSRI exposure suffer from a number of important methodological limitations that should be taken into account when interpreting their results. The contradictory results obtained from prospective and retrospective cohort studies and case-control studies could be accounted for by dissimilarity between study populations, selection bias, detection bias, confounding, or differences in underlying maternal illness, data sources used, exposure classification, follow-up and statistical power/analysis. Only a small number of studies actually account for underlying maternal illness and how this may lead to adverse pregnancy outcomes. Even when such information is available, studies that include data on maternal illness have small sample sizes, limiting the statistical power to identify statistically and clinically relevant associations. Pregnancy outcomes may be confounded by the higher incidence of smoking, alcohol consumption and substance abuse frequently encountered amongst those suffering from depression, factors that are often insufficiently controlled for.

While evidence of associations between prenatal SSRI exposure and adverse pregnancy outcomes are conflicting, there is an urgent need to evaluate how the particular SSRI used, the dose, timing and duration of use, genetics (maternal, paternal and/or fetal), concomitant medication use, maternal characteristics and underlying maternal illness all interact to alter pregnancy outcomes.

As depression affects 10–25% of women aged between 25 and 44 years,[1] many women enter pregnancy with either a history of, or existing, depressive symptoms. In addition, a number of women develop depressive symptoms during pregnancy, with up to 13% of women estimated to suffer from depressive symptoms at some stage during pregnancy.[2] Therefore, women and healthcare professionals are often faced with difficult decisions regarding the initiation or continuation of antidepressant use during pregnancy, with any decisions to interrupt or withhold treatment requiring a complex assessment of the risks and benefits associated with treatment.[3]

Over recent years, there has been a growing awareness of the importance of identifying and effectively managing depression during pregnancy, given the strong associations between prenatal and subsequent postnatal depression,[4-6] and the negative impact depression has on pregnancy outcomes and subsequent child health and development.[7-18] In the US, use of antidepressant medications has increased from 2% of pregnancies in 1996 to 7.6% of pregnancies in 2005.[19] Of particular interest is the use of selective serotonin reuptake inhibitors (SSRIs), which increased from 1.5% of all pregnancies in 1996 to 6.4% in 2005, making them the most used antidepressant during pregnancy.[19]

SSRIs exert their pharmacological effects by selectively inhibiting the reuptake of serotonin (5-HT) at the presynaptic junction, resulting in an increased concentration of serotonin in the synaptic cleft and thus enhanced serotonergic neurotransmission.[20] Since their introduction into clinical practice in the 1980s, SSRIs quickly replaced

tricyclic antidepressants as the treatment of choice for many psychiatric disorders, due largely to their more favourable safety profile and reduced toxicity in overdose.[3,21,22] Consequently, there has been an increase in the number of women of childbearing age taking SSRIs, many of whom continue to take SSRIs throughout pregnancy, despite limited evidence of their safety in pregnancy.

While numerous studies have been undertaken to assess outcomes following SSRI use during pregnancy, evidence generated is inconclusive. In light of this, we have attempted to critically appraise the existing literature with a particular focus on identifying methodological issues associated with studying outcomes following the use of SSRIs during pregnancy. Outcomes covered include congenital malformations, spontaneous abortions, neonatal outcomes and child neurodevelopment.

To address these issues, MEDLINE and EMBASE were searched from their inception to 31 November 2010 using the search terms 'SSRI', 'fluoxetine', 'citalopram', 'paroxetine', 'sertraline', 'fluvoxamine' and 'escitalopram' in association with 'pregnancy', 'prenatal exposure', 'depression', 'malformation', 'birth defect', 'miscarriage', 'spontaneous abortion', 'neonatal complications', 'child/infant development/neurodevelopment'. Papers were limited to the English language and studies in humans. The reference lists of identified articles were examined for additional relevant publications.

1. Depression During Pregnancy

A challenge in investigating outcomes following SSRI use during pregnancy is that of differentiating the effects of exposure to the drug itself from that of the underlying maternal illness. For the purposes of this review, the focus will be on SSRI use for depression.

Depression during pregnancy has been associated with numerous adverse pregnancy outcomes, including miscarriage,[7,23] preterm delivery,[10,14-17] low birthweight,[9-13] intrauterine growth restriction[17,24,25] and increased admissions to neonatal care units.[25] In addition, depression has been associated with an increased risk of gestational hypertension[9] and subsequent pre-eclampsia.[26] Depressed mothers may also be less likely to obtain prenatal care and attend prenatal clinics, further augmenting the potential for adverse pregnancy outcomes.[5] These adverse pregnancy outcomes, however, may be confounded by the higher incidence of smoking, alcohol consumption and substance abuse frequently reported amongst those suffering from depression.[5] The lack of control for confounding, and issues related to small sample sizes, infrequent adjustment or consideration of medication use (including antidepressant use), as well as other methodological limitations, preclude definitive conclusions regarding the association between depressive symptoms and adverse pregnancy outcomes.

One concern of poorly managed prenatal depression is the risk of worsening depression, which may lead to suicidal ideation or attempts.[5] Women with major depression who discontinue antidepressant therapy prior to pregnancy have a significantly increased risk of depression relapse (68%) compared with women who maintain their antidepressant therapy (26%), with that risk related to length of illness and the number of past depressive episodes.[27] Studies have shown that prenatal depression is associated with postpartum depression,[4-6] worsening of depressive symptoms[27] and increased suicide attempts.[28] Postpartum depression is of significant concern because of its well demonstrated negative impact on mother-infant attachment and cognitive, emotional and behavioural development in the offspring.[18,29]

2. A Critique of Study Designs

Ethical, medical and medico-legal concerns limit our ability to study the risks and benefits associated with SSRI use during pregnancy through randomized controlled trials. This limits our investigations to the use of observational study designs such as prospective and retrospective cohort studies and case-control studies, each with their own strengths and limitations.

2.1 Cohort Studies

Cohort studies can be retrospective or prospective in nature, or a combination of both. The

main characteristic of a cohort study is that it begins with a group of women who are exposed to a medication of interest and follows these individuals over time to enable the assessment of a range of outcomes. A challenge associated with cohort studies involves the correct identification of women who are exposed to the medication of interest and the appropriate identification of a suitable control group of women who are not exposed to the medication of interest.

To date, the majority of prospective cohort studies have been carried out by teratogen information services[30-35] where women are identified while requesting information about the safety of a medication during pregnancy and then followed to determine the outcome of their pregnancy. Information is often gathered prospectively through maternal interviews, questionnaires and clinical assessments, and in some cases this information is confirmed by reviewing medical records.[33,35] Selection bias is a concern with studies undertaken using teratogen information services, as women who utilize these services may not be reflective of the general population.[36] The identification of a suitable control group of women who are not exposed to the medication of interest is also a challenge, with researchers often having to rely on a control group comprising of women who contacted the centre regarding other exposures during pregnancy that are considered not likely to be associated with the outcome under investigation.

Pregnancy exposure registries are also utilized to prospectively identify cohorts of women with an exposure of interest.[37] Most pregnancy exposure registries, however, rely on voluntary reporting of medication exposures, which may introduce bias if pregnancies that are more likely to be associated with adverse pregnancy outcomes are more likely to be those that are reported. In particular, it is important to note situations where data are reported to pregnancy registries after the outcome has occurred as this may be introduce reporting bias, with negative outcomes more likely to be reported than normal outcomes.

The strength of the prospective cohort design is the prospective, systematic collection of data, including exposures, confounders and outcome information. In addition, as ascertainment of exposure takes place before the outcome is known, recall bias can be avoided.[38] Medical birth registers that contain prospectively collected data on medication exposure during pregnancy (e.g. Swedish Medical Birth Register) have also been used to identify cohorts of women for prospective cohort studies.[39] While a major strength of these registers is that they are population-based, there is potential for incomplete data on medication exposures during pregnancy due to non-reporting of medication use.[40] Finally, purpose-built prospective birth cohort studies (e.g. Danish National Birth Cohort Study) are increasingly being used to investigate a wide range of outcomes following medication exposures during pregnancy.[41] These come at considerable expense but have the major advantage of collecting detailed data on many exposures, confounders and outcomes of interest across large cohorts of women and their children over long periods of time. A limitation affecting these and other prospective studies, however, is the extent of loss to follow-up, where information on outcome variables for some subjects may not be obtained.[38] This issue is particularly important in situations where loss to follow-up may differ between study groups. In addition, any study that relies on patient consent to participate can be subject to response bias if there are differences in characteristics between those who choose to participate in a study and those who do not.[42]

In contrast to prospective cohort studies, retrospective cohort studies are often less resource intensive and less time consuming, making them an increasingly popular alternative, with the major difference to the prospective cohort design being that exposure and outcome ascertainment occurs at the time that the retrospective cohort study begins. Traditional retrospective cohort studies have relied on data obtained from interviews or questionnaires and therefore can be affected by recall bias where, compared with mothers of healthy children, mothers of affected children may be more likely to recall medication exposures during pregnancy.[43] More recently, researchers are beginning to construct large retrospective cohort studies utilizing linked healthcare and administrative datasets.[44-53] The major advantage of these studies is that data are collected

prospectively in a routine fashion (e.g. as prescription records or hospital discharge summaries), stored electronically and the data can be linked at the individual patient level. The prospective collection of data eliminates the potential for recall bias. Use of linked datasets enables the identification of very large cohorts of women and their offspring, which is particularly useful in assessing rare outcomes such as congenital malformations. In addition, as data have already been collected, it enables studies to be undertaken in a more timely and cost-efficient manner than is possible with other research methods. This, however, is also the greatest limitation associated with studies relying on healthcare administrative data, as these data were not collected with the intention of being used for research purposes. Thus, the data may lack the necessary detail for investigating associations between medication exposures and pregnancy outcomes, especially in relation to potential confounders. Furthermore, studies utilizing linked prescription records rely on the assumption that the date of dispensing and amount of medication supplied coincides with the time and duration the medication was actually taken, which may not be completely accurate.

2.2 Case-Control Studies

Case-control studies are usually retrospective and consist of a group of patients, the 'cases', with the outcome being investigated (e.g. those with a congenital malformation) who are compared with another group, the 'controls', who do not have the outcome of interest (e.g. those without a congenital malformation). Case-control studies are particularly useful for generating sufficient statistical power to investigate rare outcomes associated with prenatal SSRI exposure.[38] As information is often collected in a retrospective fashion, case-control studies can be subject to recall bias. While recall bias can be addressed through the use of hospital, pregnancy or pharmacy records to validate exposures or outcomes, this relies on the assumption that these data sources contain complete and accurate information, which is not always the case. For example, does the absence of data on whether someone used a medication during pregnancy mean that they did not use that medication, or could it just be incomplete? Furthermore, the period of recall can also differ substantially between studies, with some concluding within 6 months of delivery[32,54] and others including women up to 2 years following delivery.[34,55] In addition, there is also the potential for response bias, with up to 30–40% of women declining to participate in some case-control studies and consent rates differing between those exposed and not exposed to SSRIs.[54,55]

3. Congenital Malformations

Prospective cohort studies,[30-35,56] retrospective cohort studies[44-53,57,58] and case-control studies[54,55,59-61] have been undertaken to investigate the relationship between congenital malformations and prenatal exposure to SSRIs.

Studies either report on major[30-34,45-47,50-55,59,60] or minor[31,45,47,51] malformations, or a combination of both,[44,48,49] while a number focus purely on cardiovascular malformations.[35,56,58,61] Major malformations are classified as structural or functional abnormalities that have significant medical or social consequences,[32] while minor malformations are classified as structural defects that have no cosmetic or functional importance.[31]

3.1 Focus on Paroxetine

In late 2005, GlaxoSmithKline® (GSK), the manufacturer of paroxetine, together with regulatory bodies from around the world, including Australia, the US, Canada and the UK, issued media releases concerning the safety of paroxetine during pregnancy. This decision was made primarily on the basis of results from two studies, one sponsored by GSK[62] and another independently undertaken by Kallen and Olausson.[50] Preliminary unpublished results from the GSK study suggested that, compared with other antidepressants (including SSRIs and other classes of antidepressants), paroxetine use during the first trimester was associated with an increased risk of congenital malformations (odds ratio [OR] 2.2; 95% CI 1.34, 3.63) and cardiovascular malformations (OR 2.08; 95% CI 1.03, 4.23).[62] The most

commonly reported cardiovascular malformations were ventricular septal defects.[62] These preliminary results were based on retrospective analysis of data from two large US insurance healthcare databases, which included births from 1995 through 2002, of which 591 infants were exposed to paroxetine alone.[62]

Following the inclusion of births from January 2003 through September 2004 (an extra 224 infants), an updated analysis of the GSK study demonstrated an association between paroxetine and congenital malformations (OR 2.03; 95% CI 1.26, 3.25), but not cardiovascular malformations (OR 1.47; 95% CI 0.74, 2.89).[44]

In contrast, Kallen and Olausson[50] utilized data from three Swedish health registers to identify 6555 infants with first trimester exposure to an SSRI. When compared with the remainder of the population who were not exposed to an SSRI (n = 873 876), SSRI exposure was not associated with an increased risk of congenital malformations (OR 0.89; 95% CI 0.79, 1.07).[50] Further subgroup analysis, however, showed a significantly increased risk for cardiovascular malformations following exposure to paroxetine (OR 1.63; 95% CI 1.05, 2.53), but not other SSRIs.[50] Following exclusion of women with a high body mass index (BMI), women born outside of Sweden, women who previously had difficulties getting pregnant and women who were exposed to certain other medications (antipsychotics, sedatives, hypnosedatives, folic acid, non-steroidal anti-inflammatories and antiepileptic drugs), there was nearly a 3-fold increase in the risk of cardiovascular malformations following exposure to paroxetine (OR 2.93; 95% CI 1.52, 5.13) and an even greater increase in the risk of septal defects (ventricular and atrial) (OR 3.23; 95% CI 1.30, 6.65).[50]

Three subsequent studies have found an increased risk of congenital malformations following prenatal exposure to paroxetine,[34,44,59] while no other studies have found an association with cardiovascular malformations overall. Individually though, studies have demonstrated an association between paroxetine exposure and specific cardiovascular malformations, including right ventricular outflow obstruction defects (OR 3.3; 95% CI 1.3, 8.8;[54] OR 2.5; 95% CI 1.0, 6.0[55]) and atrial septal defects (OR 5.7; 95% CI 1.4, 23.7).[61]

A total of 20 studies investigating first trimester paroxetine exposure and congenital malformations were analysed together in a recent meta-analysis.[63] This meta-analysis found an increased risk of congenital malformations overall (OR 1.2; 95% CI 1.1, 1.4), likely due to an observed increase in cardiovascular malformations (OR 1.5; 95% CI 1.2, 1.8). Absent from this meta-analysis, however, are a number of recently published studies that have shown no association between prenatal paroxetine exposure and congenital malformations or cardiovascular malformations.[35,51,57] Consequently, the association between paroxetine and cardiovascular malformations is still the subject of much debate, as evidenced from two recent, but conflicting, commentaries from experts in the field.[64,65] Even if paroxetine were to be considered teratogenic, the question becomes whether this suspected teratogenicity is specific to paroxetine, or applies to other SSRIs as well.

3.2 Risks Associated with Other Selective Serotonin Reuptake Inhibitors (SSRIs)

A number of studies have demonstrated an association between prenatal SSRI use and an increased risk of congenital malformations (OR 1.3; 95% CI 1.1, 16;[57] relative risk [RR] 1.34; 95% CI 1.00, 1.79[48]). The risk was greatest for cardiovascular malformations (OR 1.7; 95% CI 1.1, 2.5;[57] RR 2.17; 95% CI 1.07, 4.39[56]), particularly septal heart defects (OR 1.99; 95% CI 1.13, 3.53).[51] Other studies have found no association between SSRI exposure and congenital malformations.[32,45-47,49-53,60] Individually, first trimester exposure to sertraline (OR 3.0; 95% CI 1.4, 6.4),[57] citalopram (adjusted risk difference 2.28; 95% CI 0.19, 4.36)[52] and fluoxetine (OR 4.47; 95% CI 1.31, 15.27)[34] have all been associated with an increased risk of cardiovascular malformations. In particular, both sertraline (OR 3.25; 95% CI 1.21, 8.75;[51] OR 3.3; 95% CI 1.5, 7.5;[57] OR 2.0; 95% CI 1.2, 4.0[54]) and citalopram (OR 2.52; 95% CI 1.04, 6.10)[51] have been associated with an increased risk of septal heart defects.

One case-control study found that first trimester exposure to any SSRI was associated with an increased risk of omphalocele (OR 2.8; 95% CI 1.3, 5.7), craniosynostosis (OR 2.5; 95% CI 1.5, 4.0) and anencephaly (OR 2.4; 95% CI 1.1, 5.1).[55] Individually, paroxetine was associated with omphalocele (OR 8.1; 95% CI 3.1, 20.8), sertraline with anencephaly (OR 3.2; 95% CI 1.1, 9.3) and fluoxetine with craniosynostosis (OR 2.8; 95% CI 1.3, 6.1).[55] An additional case-control study found an association between sertraline and omphalocele (OR 5.7; 95% CI 1.6, 20.7).[54]

3.3 Ascertainment of Outcome

Because of differences in the definitions of congenital malformations, the observed prevalence of malformations reported in different studies is not always directly comparable. The majority of studies only include congenital malformations reported in liveborn infants,[30,31,34,44,45,48-54,56-59,61] while at least three studies include congenital malformations reported in infants who were stillborn.[46,55,60] Some authors have reported poor validity in using information on congenital malformations gathered from stillborn infants or elective abortions as justification for their exclusion.[51] However, there is evidence that women taking antidepressants have a higher rate of ultrasound examinations than women not taking antidepressants, potentially introducing detection bias and increasing the observed rate of malformations amongst fetuses exposed to SSRIs.[66] If these women go on to have elective terminations, relying purely on congenital malformations reported in liveborn infants could potentially underestimate the risk associated with SSRI exposure. In addition, the increased risk of neonatal hospital admission that has been reported following prenatal exposure to SSRIs could also introduce detection bias. This could result in the detection of malformations that would otherwise go unnoticed if the infant was not admitted to hospital following delivery.

Furthermore, there are differences between studies in relation to the age of infants assessed for congenital malformations. There is no standardized approach, with timing varying from 1 month to 3 years of age.[35] This has significant consequences, particularly for the detection of cardiovascular malformations such as septal defects that commonly resolve spontaneously in the first few months or years of life without treatment.[64] Some malformations may remain undetected in infants with short-term follow-up, while others may have resolved spontaneously by the time of later follow-up. Notably, some studies report cardiovascular malformations even if they resolved spontaneously,[50] while others exclude them from analysis.[35,57]

Numerous studies rely on discharge summaries following hospital admission to detect congenital malformations, meaning only congenital malformations that required admission to hospital would be identified.[48,49,52,57,59] This may result in a bias towards the detection of more severe (and therefore possibly more clinically relevant) congenital malformations, but could also introduce detection bias if children of mothers taking SSRIs are more likely to take their child to hospital for various health-related complaints, increasing the detection rate of congenital abnormalities that would otherwise go unnoticed. Other studies utilize population-based birth defects registries that rely on voluntary reporting of congenital malformations,[46,61] some of which require informed consent to be given by parents before their child can be included on the register.[61] In one birth defects registry, a reported 20% of parents do not consent to including their child on the register.[61] This is a particularly important source of potential bias if consent rates differ between women exposed and not exposed to SSRIs during pregnancy.

In a unique study, Merlob et al.[56] actively screened all infants born in their hospital for cardiac murmurs on the first day of life and found an increased risk of cardiovascular malformations following prenatal exposure to SSRIs (RR 2.17; 95% CI 1.07, 4.39). Those performing the screening were not always blinded to the exposure status of the infants. Notably, they detected a larger number of cardiovascular malformations than the reported background rate of cardiovascular malformations, owing to the increased detection of mild asymptomatic malformations that would otherwise have gone unnoticed.[56] Importantly, all cardiovascular malformations

identified in the exposed group were mild and asymptomatic, often resolving spontaneously.

3.4 Timing and Duration of Exposure

Many studies focus on identifying exposures during the first trimester.[30-35,44,46,48-52,54-57,60,61] However, in one study, 45% of those in the exposed group were exposed only during the third trimester;[45] in two others, women were classified as exposed as long as they took an SSRI at some stage during their pregnancy, irrespective of timing.[47,58] Despite evidence from embryological studies highlighting critical periods in which exposures can alter fetal development (e.g. the greatest period of sensitivity towards structural cardiovascular malformations encompasses the second and third months of pregnancy),[67] few studies have investigated differences between use during these periods and the first trimester as a whole. In one study, a higher risk of congenital malformations was found among those women who were dispensed an SSRI in the second or third month of pregnancy (RR 1.84; 95% CI 1.25, 2.71) compared with those who were dispensed an SSRI at any other stage during the first trimester (RR 1.34; 95% CI 1.00, 1.79), although these risks were not compared with each other to determine if the difference was statistically significant.[48]

3.5 Maternal Dose

Most studies did not collect data on SSRI dose used during pregnancy[45-51,53-58,60,61] and, even from those that did, the majority did not use dose in the analysis of any outcomes.[30-35,52,58,59] Two studies have found no dose-response relationship between SSRI exposure and congenital malformations,[34,52] while another found an increased risk of congenital malformations and cardiovascular malformations following exposure to paroxetine at an average daily dosage >25 mg/day.[59] In this study, 25% of women had an average daily dose >25 mg/day.[59]

3.6 Confounding

No studies have compared the rate of congenital malformations amongst only depressed women who were exposed or not exposed to SSRIs during the first trimester of pregnancy, although four studies did include women taking other antidepressants in their control group.[30,33,44,59] Ramos et al.[60] restricted their analysis to women with a diagnosed psychiatric illness, excluding those with psychotic illness or mental retardation. Even by limiting inclusion to women with psychiatric illness, some may still have been taking antidepressants for illnesses other than depression. The remainder of studies included in their control groups: women not exposed to an SSRI (but it is unclear if they excluded women exposed to other antidepressants),[47,48,56,58] women not taking an SSRI or other antidepressant,[31-35,46,49-54,57] or historic population controls.[37]

In an attempt to obtain similar maternal characteristics between control and treatment groups, some studies have matched each woman in the exposed group to a woman in the control group. This was accomplished by either matching according to maternal age (±2 years),[30,33] or advanced matching based on multiple variables such as year of delivery, maternal age, parity, social status and geographic area,[46,47] or even previous psychiatric diagnosis.[45,46] However, the majority of studies did not perform any matching when identifying a control group.[34,35,48-56,58-61]

Other studies have attempted to address potential confounding according to underlying maternal illness by comparing outcomes among women exposed to different antidepressants.[50] This may not be completely effective if there are underlying differences related to the disease state which influence the choice of a particular SSRI over another. For example, sertraline and escitalopram have been reported to be more efficacious than fluoxetine in relation to therapeutic response based on a meta-analysis of 117 randomized controlled trials conducted from 1991 to 2007.[68] Therefore, sertraline and escitalopram may be more likely to be prescribed to patients with more severe depression.

Furthermore, it is clear that women take SSRIs for many conditions; therefore, it is possible that differences in underlying maternal illness (not just in disease severity) could introduce bias. Based on calls made to a Teratogen Information

Counselling Service based in Canada, Bar-Oz et al.[66] demonstrated that significantly more women reported using paroxetine for anxiety or panic disorders (49.3%) than women taking other SSRIs (19.9%) [OR 4.11; 95% CI 2.39, 7.08]. This difference has important clinical implications as the observed difference in risk currently observed with paroxetine over other SSRIs may be confounded by differences in maternal illness.

More recent studies that compare outcomes only in women with depression, or use propensity score matching to adjust for key differences between exposed and non-exposed women, have failed to detect any increased risk in congenital malformations following the use of paroxetine during pregnancy. While previous results obtained regarding paroxetine may highlight potential differences in underlying behaviours or risk profiles of women with depression versus those with anxiety or panic disorders, no studies have compared outcomes among women exposed to SSRIs according to underlying maternal illness.

Given the well noted associations between maternal age, smoking, socioeconomic status, coexisting medical conditions and maternal BMI and poor maternal and neonatal outcomes, it is not surprising to see these amongst the most common statistical adjustments (table I). Factors associated with the severity of depression (i.e. depression diagnosis, number of psychiatric visits or hospitalizations prior to or during pregnancy) together with other significant factors often associated with depression, including antenatal care and substance use, have rarely been considered. Notably, a large number of studies made no statistical adjustment for potential confounders.[30-33,45,49,56,58]

Similarly, the exclusion criteria of studies differ substantially, with some excluding women

Table I. Statistical adjustments in studies investigating congenital malformations and neonatal outcomes (e.g. birthweight, gestational age) following prenatal selective serotonin reuptake inhibitor exposure

Statistical adjustments	No. of studies	
	congenital malformations	neonatal outcomes
Maternal age	13[46-48,50-55,57,59-61]	9[31,46,47,53,69-73]
Smoking status	9[34,46,48,50,51,53-55,57]	9[31,45,46,53,69-71,73,74]
Birth year	8[48,50,53,54,57,59-61]	3[53,69,73]
Socioeconomic status	6[46,47,51,55,59,60]	3[31,46,47]
Parity	6[46,47,50,53-55]	8[31,45-47,53,69,71,73]
Diabetes mellitus	5[48,54,59-61]	NA
Hypertension	4[54,55,59,60]	2[31,70]
Geographic area	3[48,59,60]	NA
Alcohol use	3[54,55,61]	3[31,71,73]
Epilepsy	3[48,54,61]	NA
Maternal body mass index	3[53,54,61]	3[53,71,73]
Living alone	2[59,60]	NA
Depression diagnosis prior to pregnancy	2[52,59]	NA
Physician visits prior to pregnancy	2[52,59]	NA
Prenatal visits	2[52,59]	NA
Race	2[54,55]	4[31,45,72,73]
Visits to psychiatrist before or during pregnancy	2[52,59]	NA
Substance use	1[47,52]	3[45,47,70]
Emergency department visits or hospitalizations in the year before or during pregnancy	1[59]	NA
History of birth defects in family	1[54]	NA
Caffeine consumption	NA	1[71]
Use of other psychotropic drugs prior to delivery	NA	1[31]

NA = not assessed.

with hypertension,[51] diabetes mellitus,[51,55,57,59] epilepsy,[52,57] women taking other psychotropic medications,[51] women exposed to known or suspected teratogens,[32-35,50,59] women with a chronic medical illness for which they take regular medication[46] and infants with chromosomal or genetic defects.[32,34,48,54-57]

Differences between studies in relation to inclusion and exclusion criteria and adjustments for confounders are essential to understand. In one study, more than 30% of women in the SSRI exposed group were also exposed to a benzodiazepine,[60] while in another, 3.5% were exposed to more than one antidepressant during the first trimester.[50] No statistical adjustments were made for potential confounding due to concomitant exposure to a benzodiazepine or additional antidepressant. This potential for confounding was recently demonstrated by Oberlander et al.,[52] who observed an increased risk of congenital malformations only following exposure to both an SSRI and benzodiazepine during the first trimester, but not with either medication alone. This increased risk could be the result of important medication interactions or underlying physiological differences between women who took only one medication compared with both medications together.

Some studies included women with a multifetal pregnancy, including each liveborn infant in the analysis,[34,50,60] or just one of the infants in the analysis,[55] while the remainder of studies only analysed outcomes for singleton births. Other studies have only included each woman's first pregnancy in the final analysis.[59,60]

3.7 Clinical Summary

While much focus has been on paroxetine use during pregnancy, there is no clear evidence that paroxetine confers a greater risk of congenital malformations, particularly cardiovascular malformations, over any other SSRI. The collective evidence suggests that there is a low risk of malformations following prenatal exposure to SSRIs. Any risk of cardiovascular malformations following exposure to SSRIs appear to be small, especially in absolute terms, with many reported to be mild, asymptomatic and commonly resolved spontaneously before 12 months of age. These malformations appear to be related to exposures occurring during the second and third months of pregnancy, in line with the critical periods of cardiac embryology. One study observed an increased risk of congenital malformations only following paroxetine doses of >25 mg/day and, while this finding has yet to be corroborated in other studies, it may emphasize the importance of using the minimum effective dose for treating depression during pregnancy.

4. Spontaneous Abortions

A number of prospective cohort[30-32,75] and case-control[23] studies have investigated the relationship between antidepressant use during pregnancy and the incidence of spontaneous abortions.

One prospective cohort study demonstrated a statistically significant increased risk of spontaneous abortions amongst 128 women taking fluoxetine during the first trimester of pregnancy compared with an age-matched control group of 128 women exposed to other medications considered to be non-teratogens (15% vs 8%; $p = 0.03$).[30] Further analysis, however, of 74 women taking fluoxetine during pregnancy compared with a matched control group of 74 women taking tricyclic antidepressants, showed no significant difference in the risk of spontaneous abortions (14% vs 12%; $p = 0.31$), suggesting that depression itself may be the cause of an increased rate of spontaneous abortions, or that both SSRIs and tricyclic antidepressants increase the risk of spontaneous abortions through a common mechanism.[30]

Other prospective cohort studies have failed to demonstrate any statistically significant difference in spontaneous abortions among women taking SSRIs during the first trimester.[31,32,75] Importantly, none of these studies identified were adequately designed to be able to investigate any association between prenatal SSRI exposure and spontaneous abortions. Three of the studies presented no data on when women were enrolled in the study,[30,32,75] while in one study, there was a marked difference between the number of women exposed and not exposed to an SSRI during pregnancy who were enrolled in the first trimester

(82% vs 61%, respectively).[31] As the risk of spontaneous abortion decreases as the pregnancy progresses, enrolling women at different stages of pregnancy introduces significant bias.

The most recent evidence for a potential association between prenatal exposure to SSRIs and spontaneous abortions comes from a case-control study involving 5124 women with clinically detected spontaneous abortions who were each matched to ten controls (51 240 controls in total).[23] Utilizing linked Canadian administration databases, they demonstrated a statistically significant association between SSRI use during pregnancy and spontaneous abortion (OR 1.68; 95% CI 1.38, 2.06), with the association strongest for paroxetine (OR 1.75; 95% CI 1.31, 2.34).[23] Exposure was defined as dispensing an SSRI from the first day of gestation to the date of spontaneous abortion for cases, or equivalent gestational age for controls. Exposure to more than one antidepressant was associated with an even greater risk of spontaneous abortion (OR 3.51; 95% CI 2.20, 5.61).[23] This association was independent of the effect of physician-diagnosed depression itself, which was also associated with an increased risk of spontaneous abortion (OR 1.19; 95% CI 1.03, 1.38).[23]

4.1 Timing and Duration of Exposure

While most studies focused on SSRI exposure in the first trimester, in one study only 169 of 228 women in the exposed group had first trimester exposure to an SSRI.[31] Including all women in the initial analysis would have introduced significant bias, as those enrolled in the study later on in pregnancy would be expected to have a significantly reduced risk of having a spontaneous abortion compared with those enrolled at the start of their pregnancy. Notably, the rate of spontaneous abortion amongst those actually exposed during the first trimester was 13.6%, higher than originally described (10%).[31] No statistical tests were undertaken to compare outcomes in only those women exposed during the first trimester to the control group.

Nakhai-Pour et al.[23] recently demonstrated a relationship between the risk of spontaneous abortion during pregnancy and the duration of antidepressant exposure prior to pregnancy, with a longer duration of antidepressant exposure prior to pregnancy appearing to be protective against the risk of a spontaneous abortion. Those who took antidepressants for more than 6 months prior to pregnancy had a decreased risk of spontaneous abortion (OR 0.72; 95% CI 0.54, 0.95) compared with those who had only taken them for <1 month prior to pregnancy (OR 1.18; 95% CI 0.95, 1.45).[23] This could possibly be explained by a down-regulation of serotonin receptors in the uterus following prolonged exposure to antidepressants, which leads to a reduced risk of triggering contractile activity and a spontaneous abortion.

4.2 Maternal Dose

While all studies collected information on dose used during pregnancy, only one study that included prenatal exposure to paroxetine conducted a sub-analysis according to dose.[23] This study demonstrated a statistically significant dose-response relationship between the dose of paroxetine during pregnancy and the risk of spontaneous abortions.[23]

4.3 Confounding

It is important to consider elective abortions when assessing the impact of prenatal SSRI exposure on spontaneous abortions. An early elective termination of pregnancy would preclude a later spontaneous abortion. Similarly, an early spontaneous abortion would preclude a later elective termination of pregnancy. Therefore, it is important to include an accurate denominator when calculating the prevalence of spontaneous abortions. It may be more accurate to assess outcomes on a week-by-week basis or, as two studies have, to exclude women with elective abortions during pregnancy from analysis.[23,30] Notably, the two studies that excluded women with elective abortions from analysis are the only two studies to demonstrate an increased risk of spontaneous abortions following SSRI exposure.[23,30]

Only the recent case-control study by Nakhai-Pour et al.[23] made adjustment for multiple potential confounders. They adjusted for

maternal age, socioeconomic status, gestational age at time of abortion, maternal co-morbidities (diabetes, cardiovascular disease, asthma, untreated thyroid disease, depression, anxiety and bipolar disorder), history of spontaneous abortion and elective abortion, visits to psychiatrists, number of prescribers, number of visits to physicians, duration of exposure to antidepressants and other medications in the year before pregnancy, and number of prenatal visits, visits to obstetricians and other medication use during pregnancy.[23]

4.4 Clinical Summary

Because of a paucity of methodologically sound studies, there is currently insufficient evidence to draw definitive conclusions about any relationship between prenatal SSRI use and spontaneous abortions.

5. Neonatal Outcomes

A mix of retrospective[17,45-47,53,69,70,76,77] and prospective[30-34,71,72,78-82] cohort studies and case-control studies[73,74,83] have been used to investigate neonatal outcomes following prenatal exposure to SSRIs.

There are conflicting data on the incidence of adverse outcomes for babies of women treated with SSRIs during pregnancy. Some studies have found an association between prenatal SSRI exposure and low birthweight (<2500 g),[17,31,34,47,69,84] while other studies have not.[32,45,46,53,71,72,78,85-87] There is additional evidence that prenatal exposure to SSRIs is associated with decreased mean birthweight,[31,34,45,46,84] but this has not been demonstrated in all studies.[17,30,32,33,71,78-82,87] Few studies have assessed birthweight after accounting for gestational age, with some identifying an increased risk of infants being born small for gestational age (SGA),[17,31] while others have not.[53,69] There are also conflicting data around SSRI exposure and the length of gestation (term 40 weeks), with some studies showing an increased incidence of premature birth (<37 weeks' gestation)[31,45,47,49,53,69,71,72,88,89] and decreased mean gestational age at birth,[34,45,46,71,84,87,90] while others have found no difference in the incidence of prematurity[17,30,33,34,70,78,83] or mean gestational age at birth.[32,33,46,78-82,85,86] Results from a 2005 meta-analysis of 20 studies found an increased risk of low birthweight (OR 3.64; 95% CI 1.01, 13.08), but not prematurity (OR 1.85; 95% CI 0.79, 4.29), associated with prenatal exposure to SSRIs.[91]

Furthermore, exposure to SSRIs *in utero* has also been associated with decreased Apgar scores at birth[31,45,46,53,69,71,72,78,80] and increased Neonatal Intensive Care Unit (NICU) or Special Care Nursery (SCN) admissions.[17,31,33,46,71,76,78,88,92] This observed increased risk of hospitalizations could be explained by the greater incidence of neonatal withdrawal syndrome and/or poor neonatal adaptation observed in infants exposed to SSRIs during gestation.[31,53,70,93] Neonatal withdrawal syndrome is characterized by irritability, abnormal crying, tremor and convulsions, while poor neonatal adaptation is characterized by respiratory distress, tachypnoea, jitteriness, lethargy, and poor tone or colour.[17,31,34,47,49,69,79,84,88,94-96] A recent meta-analysis demonstrated that prenatal exposure to SSRIs was associated with an increased risk of SCN/NICU admissions (OR 3.3; 95% CI 1.45, 7.54) and neonatal withdrawal syndrome (OR 4.08; 95% CI 1.20, 19.93).[91] Notably, symptoms associated with neonatal withdrawal syndrome following exposure to SSRIs are usually mild and self-limiting, commonly disappearing over 2–14 days.[70,95]

Lastly, Chambers et al.[31] were the first to provide evidence that maternal use of SSRIs in late pregnancy could be a risk factor for the rare, but serious and sometimes fatal, respiratory condition, persistent pulmonary hypertension of the newborn (PPHN).[31] Since then, only three further studies have been specifically undertaken to investigate this outcome.[53,73,74] Two large case-control studies[73,74] and one retrospective cohort study[53] have found an association between prenatal SSRI exposure and PPHN (adjusted OR [AOR] 6.1; 95% CI 2.2, 16.8;[73] AOR 3.6; 95% CI 1.2, 8.3;[74] AOR 3.44; 95% CI 1.49, 6.79[53]).

Notably, the absolute risk is noted to be only relatively small given the low prevalence of PPHN in the general population (increased from 0.1% to 0.5%).[97] The greatest risk of developing

PPHN has been associated with late gestation exposure to SSRIs (i.e. after 20 weeks' gestation), with no increased risk observed when SSRI use was restricted to the first half of pregnancy.[31,73]

5.1 Timing and Duration of Exposure

Studies classified women as exposed to an SSRI if they were dispensed at least one SSRI during pregnancy,[17,34,45-47,69] or reported taking an SSRI at some stage during pregnancy,[30,32,53,71] while others required exposure to an SSRI in the 2 weeks prior to delivery for inclusion.[70]

Chambers et al.[31] found an increased risk of prematurity, admission to SCN and poor neonatal adaptation following 'late' exposure (exposed during the last trimester) to fluoxetine compared with 'early' exposure (exposed during the first trimester only). However, of those with 'late' exposure to fluoxetine, the majority (82.2%) were actually exposed to fluoxetine during all three trimesters. Therefore, it is unclear whether the results reflect risks associated with 'late' exposure to fluoxetine, or to fluoxetine throughout pregnancy, compared with exposure during the first trimester alone.

In contrast, Malm et al.[46] analysed pregnancy outcomes amongst 360 women with exposure to an SSRI during at least the second and third trimester (with some exposed during all three trimesters) compared with 1010 women with exposure only during the first trimester. Interestingly, they found no difference in mean gestational age at birth, or birthweight between the two groups, but found a statistically significant increase in the number of infants born at <32 weeks' gestation in the group of women with only first trimester exposure.[46] No statistical adjustments were made for potential confounders. An increased risk of low Apgar score at birth (OR 1.6; 95% CI 1.0, 2.4) and admittance to SCN/NICU (OR 1.6; 95% CI 1.1, 2.2) was also observed in 597 women with third-trimester exposure compared with 1000 women with only first-trimester exposure.[46]

In comparison, Simon et al.[45] compared outcomes of 84 infants exposed in only the third trimester to SSRIs with 84 matched controls, finding a statistically significant reduction in mean gestational age and Apgar score at birth, but no difference in mean birthweight. In contrast, when they compared outcomes amongst 101 infants exposed in only the first or second trimester, with 101 matched controls, they found a statistically significant reduction in mean gestational age and mean birthweight, but not Apgar scores.[45] The increased risk observed with late gestation or exposure throughout pregnancy to SSRIs may reflect differences in the underlying severity of maternal illness, where those with more severe illness required medication for a longer period of time during pregnancy. In addition, Simon et al.[45] observed greater reductions in mean birthweight, mean gestational age and Apgar scores amongst infants whose mothers received two or more prescriptions for an SSRI during pregnancy, suggesting that duration of exposure is important.

There have been some suggestions that pregnant women should stop or taper their dose of antidepressant in the 2 weeks prior to delivery to minimize the risk of neonatal symptoms.[95] More recent evidence, however, suggests that reducing exposure to SSRIs towards the end of pregnancy has no significant clinical effect on improving neonatal health.[98] Warburton et al.[98] used linked healthcare and administrative databases to compare outcomes amongst 1605 infants exposed to an SSRI during the last 14 days of pregnancy with 2122 infants exposed to an SSRI, but not in the last 14 days of pregnancy. They found no difference in a range of neonatal outcomes, including length of stay in hospital, convulsions, feeding problems, jaundice or respiratory problems between the two groups.[98] Tapering or stopping an SSRI during late pregnancy may be viewed as a way of improving neonatal health, but this would require consideration of the importance of continuing maternal therapy to manage depressive symptoms.

5.2 Maternal Dose

Only Levinson-Castiel et al.[93] have observed a dose-response relationship between paroxetine use during pregnancy and poor neonatal adaptation. Other studies either did not have data on maternal SSRI dose[17,45-47,53,69,71,74,77] or did not perform any subgroup analysis.[30-34,70,73,76,78-82]

Furthermore, there is no evidence of a correlation between cord blood or newborn plasma concentrations and neonatal symptoms.[90]

5.3 Confounding

Few studies have directly compared neonatal outcomes amongst women taking SSRIs during pregnancy to women with depression who were not taking any antidepressants during pregnancy.[17,71,82] Control groups in other studies comprised of women not taking an SSRI during pregnancy (but it is unclear if they were taking other antidepressants),[47] women not taking any other antidepressants,[30,31,33,34,45,53,69,70,79-81] or a specific group of women not taking antidepressants who did not suffer from a psychiatric illness[71] or depression.[72]

A number of studies matched exposed and non-exposed groups according to maternal age,[30,33,45] year of birth,[45-47,73] place of birth (i.e. hospital),[46,47,73] mother's postcode,[46,47,73] lifetime use of antidepressants[45] and/or lifetime history of psychiatric treatment.[45]

Two studies utilized more advanced propensity score matching (based on a large number of socio-demographic and illness variables) to identify, within the total cohort, individuals who were very similar to each other apart from the exposure of interest.[17,98]

Oberlander et al.[17] demonstrated an increase in prematurity, respiratory distress, jaundice and length of hospital stay, together with a reduction in mean birthweight, among infants prenatally exposed to SSRIs. Notably, following propensity score matching (including matching according to severity of depression), prenatal SSRI exposure was only associated with an increased risk of low birthweight and respiratory distress.[17]

While propensity score matching does not equate to true randomization, as it is based on proxies of comparability and not true comparability, it can be considered the best technique available in the absence of true randomized controlled trials. These results provide strong evidence that prenatal SSRI exposure may be associated with some adverse pregnancy outcomes, but also that underlying maternal depression is a significant confounder.

Potential confounders most often identified and adjusted for in studies investigating neonatal outcomes include maternal age, smoking status, parity and race (table I). Less commonly adjusted for were socioeconomic status, alcohol use, substance use and other aspects related to maternal depression that are known to have negative impacts on pregnancy outcomes (table I).

A number of studies did not perform any statistical adjustments for potential confounders.[30,32-34,77,78,82,84] At least one study included multi-fetal pregnancies in their analysis,[34] despite well known differences in growth rates and pregnancy outcomes compared with singleton births. Additionally, only two studies specifically excluded women taking other antidepressants, benzodiazepines or antipsychotics.[17,70]

5.4 Effect of Prematurity

An important issue in the analysis of neonatal outcomes is consideration of potential confounding due to prematurity. One could argue that prematurity acts as an intermediary, rather than a confounder, between prenatal SSRI exposure and adverse neonatal outcomes. Therefore, adjusting for prematurity could adjust away any associations between exposure and outcome. In saying this, there appears to be little doubt that adverse neonatal outcomes seen following prenatal SSRI exposure are not solely due to an increased risk of premature delivery, as evidenced from studies that restricted analysis to term infants and still demonstrated an increased risk of adverse neonatal outcomes.[69]

There is evidence, however, of a greater incidence of adverse neonatal outcomes, such as poor neonatal adaptation among premature infants prenatally exposed to SSRIs, which may be related to pharmacokinetic differences, particularly as a result of reduced clearance due to immature drug metabolism pathways. Among infants exposed to SSRIs during the last 2 weeks of gestation, Ferreira et al.[70] demonstrated that 100% of those born prematurely had symptoms associated with poor neonatal adaptation, compared with only 69.1% of infants who were born at term ($p = 0.002$). In addition, 41% of infants in the premature control group also displayed symptoms

associated with poor neonatal adaptation. While premature neonates suffer from immature lung and CNS development, predisposing them to a range of complications, including respiratory distress syndrome, irritability and convulsions, prenatal SSRI exposure appears to increase the risk of these complications further.[70]

5.5 Clinical Summary

Evidence regarding maternal use of SSRIs and an increased risk of low birthweight and/or prematurity in infants is conflicting. It is likely that any elevated risk of low birthweight could be attributable to early births of babies that had appropriate weight for their gestational age, but further research is required.

There is more convincing evidence that exposure to SSRIs during late gestation is associated with an increased risk of admission to SCN/NICU, and neonatal withdrawal symptoms and/or poor neonatal adaptation that are usually mild and self-limiting. These outcomes are likely to be associated with dose, duration and timing of exposure during pregnancy. Therefore, it is important that healthcare providers are advised of a woman's use of SSRIs during pregnancy, especially during late pregnancy, so that neonates can be observed in the immediate postnatal period and appropriate care and support can be provided if necessary. There is currently no clear evidence that women should be told to stop or taper their SSRI dosage during late pregnancy.[99]

Other perinatal complications include the reported increased risk of PPHN following prenatal exposure to SSRIs, with the greatest risk attributed to those exposed later in pregnancy.[99] The absolute risk is relatively small given the low prevalence of the disease in the general population (increase from 0.5–2 per 1000 to 3–12 per 1000),[99] but it further signifies the need for neonates exposed to SSRIs during late pregnancy to be observed in the postnatal period for potential complications.

6. Child Neurodevelopment

Long-term outcomes have been assessed using prospective[78,85,86,100,101] and retrospective[42,45] cohort studies. The majority of these have focused on outcomes in children <4 years of age,[42,45,78,85,86] with only two studies including data from children aged 4–5 years.[100,101] Collectively, these studies have analysed neurodevelopment in childhood amongst approximately 900 infants exposed to an SSRI during pregnancy, with almost 50% of those coming from one study.[42]

Oberlander et al.[102] demonstrated that infants exposed to SSRIs *in utero* have an attenuated response to acute pain during heelsticks compared with infants who were not exposed to SSRIs.[102] Follow-up evaluation of those same infants at 4 years of age revealed no difference in internalizing,[101] externalizing or attentional behaviours[100] between those who were exposed and not exposed to SSRIs. Internalizing behaviours examined include depression, anxiety and withdrawal; externalizing behaviours included aggression, defiance and tantrums.[101]

No studies have demonstrated any statistically significant differences in cognition, language development or behaviour between children exposed and not exposed prenatally to SSRIs.[78,85,86] While Simon et al.[45] found no difference in motor or speech delay between infants exposed and not exposed prenatally to SSRIs, two more recent studies have demonstrated an association between SSRI exposure and delayed psychomotor development.[42,78]

Casper et al.[78] compared neurodevelopment outcomes in children of depressed mothers exposed and not exposed to a range of SSRIs *in utero*.[78] Following a single-blinded assessment between the ages of 6 and 40 months, no significant differences were observed between the groups in relation to mental development and attention, orientation and emotional regulation. Children exposed to SSRIs, however, demonstrated statistically significant differences in motor development, with notable differences in fine motor movements and tremulousness.[78]

In the largest and most recent study undertaken to date, Pedersen et al.[42] investigated the effects of prenatal antidepressant exposure on normal milestone development at 6 and 19 months of age in children taking part in the Danish National Birth Cohort Study. From a total cohort of 81 946

children eligible for the study, 415 were exposed to an antidepressant (336 to an SSRI) at some stage during gestation, while 489 were born to mothers with depression who did not take an antidepressant during pregnancy.[42] At 19 months of age, there was an association between antidepressant exposure during the second or third trimesters and an inability for children to occupy themselves for >15 minutes (OR 2.1; 95% CI 1.09, 4.02). In addition, there were notable delays in the time taken for children exposed to antidepressants during the second or third trimester to reach developmental milestones such as sitting without support (15.9 days later; 95% CI 6.8, 25.0) and walking (28.9 days later; 95% CI 15.0, 42.7) compared with children of mothers with untreated depression. This association was also strongest for males.[42] Despite these delays, achievement of developmental milestones was still within the expected normal range of child development. Therefore, while statistically significant, the clinical relevance of such findings is unknown.

Table II. Neurobehavioural tests used in studies to assess developmental outcomes in children parentally exposed to selective serotonin reuptake inhibitors

Neurobehavioural test and developmental outcome assessed	Age at test in study
Cognition	
Wechsler Preschool and Primary Scale of Intelligence – Revised[100]	1.5–5 y
Cognition, motor and language development	
Bayley Scales of Infant Development – II[78,85,86,100]	15–30 mo
McCarthy Scales of Children's Abilities[85,86]	30–71 mo
Temperament and behaviour[a]	
Achenbach Behaviour Checklist[85,86]	24–86 mo
Carey Temperament Scales[85,86]	<24 mo
Child Behaviour Checklist[100,101]	1.5–5 y
Child Teacher Report Form[100,101]	1.5–5 y
Language development	
Reynell Developmental Language Scales[85,86]	15–71 mo

a Including internalizing and externalizing behaviours.

6.1 Ascertainment of Outcome

A large number of diverse tests have been used to assess a broad range of developmental outcomes in children with prenatal SSRI exposure (table II). While a detailed description of the way in which these tests are performed and the exact differences between these tests is beyond the scope of this review, the key message is that because of the variety of outcome measures used and the small sample sizes in each study, it is very difficult to compare results.

6.2 Timing and Duration of Exposure

Nulman et al.[85] observed no difference in global IQ values, language development and behavioural development in children exposed to fluoxetine during the first trimester only and those exposed to fluoxetine throughout the entire pregnancy. However, Pedersen et al.[42] demonstrated a statistically significant difference in motor function between infants exposed to an SSRI during the second or third trimester compared with those exposed only during the first trimester.[42] These findings could reflect differences in the critical periods of CNS development in which SSRI exposure can influence neurodevelopment in later life.

6.3 Maternal Dose

No studies have investigated any associations between maternal dose during pregnancy and child neurodevelopment outcomes despite the fact that many studies have collected data on maternal dose.[78,85,86,101] Oberlander et al.[100] found no association between cord blood concentrations at birth and externalizing behaviours in infants exposed to SSRIs.

6.4 Confounding

Only two studies have compared outcomes of infants or children of depressed mothers who were exposed and not exposed prenatally to SSRIs,[42,78] or who were taking other antidepressants.[85] The remainder of studies have compared outcomes with a control group that was not exposed prenatally to SSRIs and whose mothers were not depressed during pregnancy.[45,85,86,100,101]

Given the potential adverse effects of prenatal exposure to more than one psychotropic medication,

Pedersen et al.[42] excluded infants of women exposed to psychotropic medications other than antidepressants. This is in contrast to other studies that have identified statistically significant differences between exposed and non-exposed groups in relation to prenatal use of anxiolytics, but did not exclude or statistically adjust for these differences in the analysis.[86]

Studies have adjusted for a range of confounders including maternal age,[42] infant sex,[42] age at follow-up,[42,85] breastfeeding,[42] maternal IQ,[85,86] problems during pregnancy,[42] socioeconomic status,[85,86] depression severity during pregnancy,[42,85] mother-child connection,[42] postnatal symptoms of depression,[42,100,101] postnatal difficulties,[42] smoking during pregnancy,[42,86] alcohol exposure during pregnancy[42,86] and history of poor neonatal adaptation.[100]

6.5 Loss to Follow-Up

Loss to follow-up is a particularly important source of bias for studies investigating outcomes that may not become apparent until many years later. This is particularly important for the two studies by Misri et al.[101] and Oberlander et al.,[100] for example, which utilized the same cohort of children prenatally exposed to SSRIs. They originally identified 82 women to participate in the study, of which 52 agreed to participate. One woman had a spontaneous abortion and another five left the study prior to delivery. Over 4–5 years a further 24 women and their children were lost to follow-up, leaving a total of only 22 children exposed prenatally to SSRIs in the study.[100,101]

Pedersen et al.[42] also suffered from a large loss to follow-up in their study, although the rate of loss to follow-up between the study groups was similar (58% vs 54%).

6.6 Clinical Summary

The collective evidence of prenatal exposure to SSRIs suggests that SSRI exposure is not associated with impaired neurodevelopment; however, there have been major differences in study design, patterns of SSRI use, age at follow-up, outcome measures used and adjustment for confounding.[36,103] Therefore, it is difficult to draw any conclusions about the long-term effects of prenatal exposure to SSRIs on fetal brain development given the general heterogeneity of studies undertaken. In addition, as no study has followed children beyond early childhood, neurobehavioural abnormalities that may become evident later in life have not been determined.[104]

Given the importance of serotonin as a neurotransmitter within the CNS, and its role in neurogenesis, migration and differentiation of the human brain, the potential long-term effects of *in utero* exposure to SSRIs remain an important area of concern.[91,105] Studies demonstrating the potential role that the serotonergic system plays in the etiology of disorders such as schizophrenia, autism and depression raise further questions regarding potential long-term effects of prenatal SSRI exposure.[106,107] Further large, population-based studies are required to investigate the potential adverse effects of *in utero* exposure to SSRIs on fetal brain development, with longer-term follow-up of children into adulthood needed.

7. Challenges in Assessing Outcomes with SSRIs in Pregnancy

No one particular research approach is able to completely delineate the effects of SSRI use during pregnancy, highlighting the importance of recognizing the limitations associated with different study designs when comparing results. The contradictory results obtained from prospective and retrospective cohort studies and case-control studies may be accounted for by heterogeneity between study populations, selection bias, detection bias, confounding and differences in underlying maternal illness (i.e. women taking an SSRI for depression vs women taking it for anxiety or panic disorders), data sources used, exposure classification (i.e. dose, duration and timing), follow-up and statistical power/analysis.

While a detailed description of statistical limitations is beyond the scope of this review, there are a number of issues that are pertinent to studies on SSRI use during pregnancy. The first is that we must be cautious in the interpretation of statistically significant results, given the large

number of comparisons and statistical tests that are often undertaken. Multiple testing, as occurs with subgroup analyses, increases the potential for 'chance' findings. At the frequently utilized 5% significance level (95% CI) there is a 5% chance of obtaining a statistically significant result that is false (i.e. due to chance alone). With studies performing 20–40 individual tests, there is a possibility that 1–2 will be statistically significant by chance alone.

The second issue is sample size, which will determine statistical power. While studies may report differences as not statistically significant, they may not have had sufficient power to detect a statistically significant finding in the first place. Some studies only have statistical power to detect large increases in risk. For example, Andrade et al.[77] was powered to detect a 6-fold difference in the prevalence of PPHN among infants exposed prenatally to SSRIs, while other studies were powered to detect a 4-fold increase in risk of major malformations.[30] Studies with low power are still useful in ruling out large increases in risk, but studies with much larger sample sizes are required to more accurately define smaller, but still clinically relevant, differences.

Finally, there is the issue of differentiating clinically significant differences from statistically significant differences. This is particularly important for studies with large sample sizes, which often have no difficulty establishing statistically significant differences. For example, outcomes that are of little or no consequence, such as a statistically significant reduction in mean birthweight of 50 g, could hardly be considered clinically significant, whereas a small increase in the risk of a rare but serious adverse outcome, such as PPHN, can have significant clinical and public health importance given the prevalence of SSRI use.

8. Future Directions for Research on SSRI use during Pregnancy

Despite numerous studies suggesting that depression itself is associated with poor pregnancy outcomes, and the potential confounding of pregnancy outcomes due to differences in characteristics of women with and without depression, there is actually a dearth of quality studies comparing outcomes between those receiving pharmacotherapy or psychological interventions and those receiving no therapy for depression,[108] especially studies with sufficiently large sample sizes to generate statistically and clinically significant results.

Furthermore, while much emphasis is placed on considering the risks and benefits of medication use during pregnancy, there is a bias towards investigating the risks associated with SSRI use during pregnancy, with little focus on the potential benefits that treatment may provide. What is the optimum SSRI dose during pregnancy, given the significant physiological changes that occur over the three trimesters? Does treating depression during pregnancy with an SSRI reduce the prevalence of adverse pregnancy outcomes that would otherwise be expected if these women were not given an SSRI? Does treating depression during pregnancy with an SSRI reduce the incidence or severity of postpartum depression, and therefore reduce the negative impact postpartum depression has on mother-infant bonding and subsequent child health and development?

Further complexities are introduced when we question which SSRI is the safest, or riskiest, to use during pregnancy. While all SSRIs inhibit serotonin reuptake, across the class there are differences in regard to molecular structure, selectivity, receptor binding and pharmacokinetics.[109] Differences in drug metabolism, for example, could play an important role in explaining how outcomes may differ depending on the SSRI used. SSRIs including paroxetine, fluoxetine and fluvoxamine are metabolized by the cytochrome P450 (CYP) isoenzyme 2D6, while citalopram, escitalopram and sertraline are metabolized by CYP2C19, among others.[110-112] During pregnancy, CYP2D6 is induced, increasing metabolism of its substrates and therefore decreasing their plasma concentrations, possibly necessitating the need to increase the dose during pregnancy.[113] In contrast, CYP2C19 activity is decreased during pregnancy.[113]

In addition to changes in metabolism that occur during pregnancy, the presence of genetic polymorphisms in CYP enzymes can dramatically alter

SSRI plasma concentrations. For example, paroxetine is primarily metabolized by CYP2D6.[114] For example, if 5–10% of Caucasians have an inactive CYP2D6 allele, as evidenced in some studies,[114] and are therefore poor metabolizers, one would expect 5–10% of women to have higher blood concentrations of paroxetine, fluoxetine and fluvoxamine than those with normal CYP2D6 function, and therefore a potentially higher incidence of adverse events. The importance of genetic polymorphisms is highlighted in a case report of a neonate who demonstrated severe neonatal withdrawal symptoms following exposure to paroxetine during late gestation and was found, through genotyping, to have reduced CYP2D6 function.[115]

Despite differences between SSRIs in relation to pharmacology, pharmacokinetics and pharmacodynamics, their relationship with pregnancy outcomes has not been well investigated. These differences may hold the key to understanding conflicting results obtained from studies to date and could help to further elucidate which women, if any, are at an increased risk of an adverse pregnancy outcome if they were to take an SSRI during pregnancy.

9. Conclusions

Numerous observational studies have been undertaken to investigate a wide range of outcomes associated with the use of SSRIs during pregnancy. Many of these studies, however, suffer from a number of important methodological limitations that must be taken into account when interpreting their results both individually and collectively (when compared with other studies).

There is an urgent need for further research evaluating how the particular SSRI used, the dose, timing and duration of use, genetics, concomitant medication use, maternal characteristics and underlying maternal illness all interact to confer an increased or decreased risk of adverse pregnancy outcomes following exposure during pregnancy.

Acknowledgements

Janna L. Morrison was supported by a Career Development Award from the National Heart Foundation of Australia and the National Health and Medical Research Council, and a South Australian Cardiovascular Research Network Fellowship (CR10A4988). Luke E. Grzeskowiak and Andrew L. Gilbert have no conflicts of interest to declare that are directly relevant to the content of this review.

References

1. Wisner KL, Zarin DA, Holmboe ES, et al. Risk-benefit decision making for treatment of depression during pregnancy. Am J Psychiatry 2000; 157 (12): 1933-40
2. Bennett HA, Einarson A, Taddio A, et al. Prevalence of depression during pregnancy: systematic review. Obstet Gynecol 2004; 103 (4): 698-709
3. Emslie G, Judge R. Tricyclic antidepressants and selective serotonin reuptake inhibitors: use during pregnancy, in children/adolescents and in the elderly. Acta Psychiatr Scand 2000; 101 (403 Suppl.): 26-34S
4. O'Hara MW, Swain AM. Rates and risk of postpartum depression-a meta-analysis. Int Rev Psychiatry 1996; 8 (1): 37-54
5. Bonari L, Pinto N, Ahn E, et al. Perinatal risks of untreated depression during pregnancy. Can J Psychiatry 2004; 49 (11): 726-35
6. Ryan D, Milis L, Misri N. Depression during pregnancy. Can Fam Physician 2005; 51 (8): 1087-93
7. Sugiura-Ogasawara M, Furukawa TA, Nakano Y, et al. Depression as a potential causal factor in subsequent miscarriage in recurrent spontaneous aborters. Hum Reprod 2002; 17 (10): 2580-4
8. Nelson DB, McMahon K, Joffe M, et al. The effect of depressive symptoms and optimism on the risk of spontaneous abortion among innercity women. J Womens Health (Larchmt) 2003; 12 (6): 569-76
9. Paarlberg KM, Vingerhoets AD, Passchier J, et al. Psychosocial factors and pregnancy outcome: a review with emphasis on methodological issues. J Psychosom Res 1995; 39 (5): 563-95
10. Steer RA, Scholl TO, Hediger ML, et al. Self-reported depression and negative pregnancy outcomes. J Clin Epidemiol 1992; 45 (10): 1093-9
11. Preti A, Cardascia L, Zen T, et al. Obstetric complications in patients with depression: a population-based case-control study. J Affect Disord 2000; 61 (1-2): 101-6
12. McAnarney ER, Stevens-Simon C. Maternal psychological stress/depression and low birth weight: is there a relationship? Arch Pediatr Adolesc Med 1990; 144 (7): 789-92
13. Field T, Diego M, Dieter J, et al. Prenatal depression effects on the fetus and the newborn. Infant Behav Dev 2004; 27 (2): 216-29
14. Dayan J, Creveuil C, Herlicoviez M, et al. Role of anxiety and depression in the onset of spontaneous preterm labor. Am J Epidemiol 2002; 155 (4): 293-301
15. Dayan J, Creveuil C, Marks MN, et al. Prenatal depression, prenatal anxiety, and spontaneous preterm birth: a prospective cohort study among women with early and regular care. Psychosom Med 2006; 68 (6): 938-46
16. Orr ST, James SA, Blackmore Prince C. Maternal prenatal depressive symptoms and spontaneous preterm births

among African-American women in Baltimore, Maryland. Am J Epidemiol 2002; 156 (9): 797-802

17. Oberlander TF, Warburton W, Misri S, et al. Neonatal outcomes after prenatal exposure to selective serotonin reuptake inhibitor antidepressants and maternal depression using population-based linked health data. Arch Gen Psychiatry 2006; 63 (8): 898-906
18. Austin MP, Lumley J. Antenatal screening for postnatal depression: a systematic review. Acta Psychiatr Scand 2003; 107 (1): 10-7
19. Andrade SE, Raebel MA, Brown J, et al. Use of antidepressant medications during pregnancy: a multisite study. Am J Ostet Gynecol 2008; 198 (2): 194.e1-5
20. Van Harten J. Clinical pharmacokinetics of selective serotonin reuptake inhibitors. Clin Pharmcokinet 1993; 24 (3): 203-20
21. Mant A, Rendle VA, Hall WD, et al. Making new choices about antidepressants in Australia: the long view 1975-2002. Med J Aust 2004; 181 (7 Suppl.): 21-4S
22. Goldstein BJ, Goodnick PJ. Selective serotonin reuptake inhibitors in the treatment of affective disorders: III. Tolerability, safety and pharmacoeconomics. J Psychopharmacol 1998; 12 (4 Suppl.): 55-87S
23. Nakhai-Pour HR, Broy P, Berard A. Use of antidepressants during pregnancy and the risk of spontaneous abortion. CMAJ 2010; 182 (10): 1031-7
24. Hoffman S, Hatch MC. Depressive symptomatology during pregnancy: evidence for an association with decreased fetal growth in pregnancies of lower social class women. Health Psychol 2000; 19 (6): 535-43
25. Chung TKH, Lau TK, Yip ASK, et al. Antepartum depressive symptomatology is associated with adverse obstetric and neonatal outcomes. Psychosom Med 2001; 63 (5): 830-4
26. Kurki T, Hiilesmaa V, Raitasalo R, et al. Depression and anxiety in early pregnancy and risk for preeclampsia. Obstet Gynecol 2000; 95 (4): 487-90
27. Cohen LS, Altshuler LL, Harlow BL, et al. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. JAMA 2006; 295 (5): 499-507
28. Appleby L. Suicide during pregnancy and in the first postnatal year. BMJ 1991; 302 (6769): 137-40
29. Pearlstein T, Howard M, Salisbury A, et al. Postpartum depression. Am J Ostet Gynecol 2009; 200 (4): 357-64
30. Pastuszak A, Schick-Boschetto B, Zuber C, et al. Pregnancy outcome following first-trimester exposure to fluoxetine (Prozac). JAMA 1993; 269 (17): 2246-8
31. Chambers CD, Johnson KA, Dick LM, et al. Birth outcomes in pregnant women taking fluoxetine. N Engl J Med 1996; 335 (14): 1010-5
32. Kulin NA, Pastuszak A, Sage SR, et al. Pregnancy outcome following maternal use of the new selective serotonin reuptake inhibitors: a prospective controlled multicenter study. JAMA 1998; 279 (8): 609-10
33. Sivojelezova A, Shuhaiber S, Sarkissian L, et al. Citalopram use in pregnancy: prospective comparative evaluation of pregnancy and fetal outcome. Am J Ostet Gynecol 2005; 193 (6): 2004-9
34. Diav-Citrin O, Shechtman S, Weinbaum D, et al. Paroxetine and fluoxetine in pregnancy: a prospective, multicentre, controlled, observational study. Br J Clin Pharmacol 2008; 66 (5): 695-705
35. Einarson A, Pistelli A, DeSantis M, et al. Evaluation of the risk of congenital cardiovascular defects associated with use of paroxetine during pregnancy. Am J Psychiatry 2008; 165 (6): 749-52
36. Alwan S, Friedman JM. Safety of selective serotonin reuptake inhibitors in pregnancy. CNS Drugs 2009; 23 (6): 493-509
37. Goldstein DJ, Corbin LA, Sundell KL. Effects of first-trimester fluoxetine exposure on the newborn. Obstet Gynecol 1997; 89 (5): 713-8
38. Irl C, Hasford J. Assessing the safety of drugs in pregnancy: the role of prospective cohort studies. Drug Saf 2000; 22 (3): 169-77
39. Källén BAJ. Methodological issues in the epidemiological study of the teratogenicity of drugs. Congenit Anom (Kyoto) 2005; 45 (2): 44-51
40. Stephansson O, Granath F, Svensson T. Drug use during pregnancy in Sweden: assessed by the Prescribed Drug Register and the Medical Birth Register. Clin Epidemiol 2011; 3: 43-50
41. Olsen J, Melbye M, Olsen SF, et al. The Danish National Birth Cohort: its background, structure and aim. Scand J Public Health 2001; 29 (4): 300-7
42. Pedersen LH, Henriksen TB, Olsen J. Fetal exposure to antidepressants and normal milestone development at 6 and 19 months of age. Pediatrics 2010; 125: e600-8
43. Werler MM, Pober BR, Nelson K, et al. Reporting accuracy among mothers of malformed and nonmalformed infants. Am J Epidemiol 1989; 129 (2): 415-21
44. Cole JA, Ephross SA, Cosmatos IS, et al. Paroxetine in the first trimester and the prevalence of congenital malformations. Pharmacoepidemiol Drug Saf 2007; 16 (10): 1075-85
45. Simon GE, Cunningham ML, Davis RL. Outcomes of prenatal antidepressant exposure. Am J Psychiatry 2002; 159 (12): 2055-61
46. Malm H, Klaukka T, Neuvonen PJ. Risks associated with selective serotonin reuptake inhibitors in pregnancy. Obstet Gynecol 2005; 106 (6): 1289-96
47. Wen SW, Yang Q, Garner P, et al. Selective serotonin reuptake inhibitors and adverse pregnancy outcomes. Am J Ostet Gynecol 2006; 194 (4): 961-6
48. Wogelius P, Nørgaard M, Gislum M, et al. Maternal use of selective serotonin reuptake inhibitors and risk of congenital malformations. Epidemiology 2006; 17 (6): 701-4
49. Davis RL, Rubanowice D, McPhillips H, et al. Risks of congenital malformations and perinatal events among infants exposed to antidepressant medications during pregnancy. Pharmacoepidemiol Drug Saf 2007; 16 (10): 1086-94
50. Kallen B, Olausson PO. Maternal use of selective serotonin re-uptake inhibitors in early pregnancy and infant congenital malformations. Birth Defects Res A Clin Mol Teratol 2007; 79 (4): 301-8
51. Pedersen LH, Henriksen TB, Vestergaard M, et al. Selective serotonin reuptake inhibitors in pregnancy and congenital malformations: population based cohort study. BMJ 2009; 339 (231): b3569
52. Oberlander TF, Warburton W, Misri S, et al. Major congenital malformations following prenatal exposure to serotonin reuptake inhibitors and benzodiazepines using

population-based health data. Birth Defects Res B Dev Reprod Toxicol 2008; 83 (1): 68-76

53. Reis M, Källén B. Delivery outcome after maternal use of antidepressant drugs in pregnancy: an update using Swedish data. Psychol Med 2010; 40: 1723-33
54. Louik C, Lin AE, Werler MM, et al. First-trimester use of selective serotonin-reuptake inhibitors and the risk of birth defects. N Engl J Med 2007; 356 (26): 2675-83
55. Alwan S, Reefhuis J, Rasmussen SA, et al. Use of selective serotonin-reuptake inhibitors in pregnancy and the risk of birth defects. N Engl J Med 2007; 356 (26): 2684-92
56. Merlob P, Birk E, Sirota L, et al. Are selective serotonin reuptake inhibitors cardiac teratogens? Echocardiographic screening of newborns with persistent heart murmur. Birth Defects Res A Clin Mol Teratol 2009; 85 (10): 837-41
57. Kornum JB, Nielsen RB, Pedersen L, et al. Use of selective serotonin-reuptake inhibitors during early pregnancy and risk of congenital malformations: updated analysis. Clin Epidemiol 2010; 2: 29-36
58. Wichman CL, Moore KM, Lang TR, et al. Congenital heart disease associated with selective serotonin reuptake inhibitor use during pregnancy. Mayo Clin Proc 2009; 84 (1): 23-7
59. Berard A, Ramos E, Rey E, et al. First trimester exposure to paroxetine and risk of cardiac malformations in infants: the importance of dosage. Birth Defects Res B Dev Reprod Toxicol 2007; 80 (1): 18-27
60. Ramos E, St-Andre M, Rey E, et al. Duration of antidepressant use during pregnancy and risk of major congenital malformations. Br J Psychiatry 2008; 192 (5): 344-50
61. Bakker MK, Kerstjens-Frederikse WS, Buys C, et al. First-trimester use of paroxetine and congenital heart defects: a population-based case-control study. Birth Defects Res A Clin Mol Teratol 2010; 88 (2): 94-100
62. GlaxoSmithKline. EPIP083 (preliminary report) epidemiology study: preliminary report on bupropion in pregnancy and the occurrence of cardiovascular and major congenital malformations [online]. Available from URL: http://ctr.gsk.co.uk/summary/bupropion/studylist.asp [Accessed 2010 Jul 15]
63. Wurst KE, Poole C, Ephross SA, et al. First trimester paroxetine use and the prevalence of congenital, specifically cardiac, defects: a meta-analysis of epidemiological studies. Birth Defects Res A Clin Mol Teratol 2010; 88 (3): 159-70
64. Scialli AR. Paroxetine exposure during pregnancy and cardiac malformations. Birth Defects Res A Clin Mol Teratol 2010; 88 (3): 175-7
65. Berard A. Paroxetine exposure during pregnancy and the risk of cardiac malformations: what is the evidence? Birth Defects Res A Clin Mol Teratol 2010; 88 (3): 171-4
66. Bar-Oz B, Einarson T, Einarson A, et al. Paroxetine and congenital malformations: meta-analysis and consideration of potential confounding factors. Clin Ther 2007; 29 (5): 918-26
67. Sadler TW. Susceptible periods during embryogenesis of the heart and endocrine glands. Environ Health Perspect 2000; 108 (3 Suppl.): 555-61S
68. Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. Lancet 2009; 373 (9665): 746-58
69. Kallen B. Neonate characteristics after maternal use of antidepressants in late pregnancy. Arch Pediatr Adolesc Med 2004; 158 (4): 312-6
70. Ferreira E, Carceller AM, Agogue C, et al. Effects of selective serotonin reuptake inhibitors and venlafaxine during pregnancy in term and preterm neonates. Pediatrics 2007; 119 (1): 52-9
71. Lund N, Pedersen LH, Henriksen TB. Selective serotonin reuptake inhibitor exposure in utero and pregnancy outcomes. Arch Pediatr Adolesc Med 2009; 163 (10): 949-54
72. Wisner KL, Sit DKY, Hanusa BH, et al. Major depression and antidepressant treatment: impact on pregnancy and neonatal outcomes. Am J Psychiatry 2009; 166 (5): 557-66
73. Chambers CD, Hernandez-Diaz S, Van Marter LJ, et al. Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. N Engl J Med 2006; 354 (6): 579-87
74. Kallen B, Olausson PO. Maternal use of selective serotonin re-uptake inhibitors and persistent pulmonary hypertension of the newborn. Pharmacoepidemiol Drug Saf 2008; 17 (8): 801-6
75. Einarson A, Fatoye B, Sarkar M, et al. Pregnancy outcome following gestational exposure to venlafaxine: a multicenter prospective controlled study. Am J Psychiatry 2001; 158 (10): 1728-30
76. Cohen LS, Heller VL, Bailey JW, et al. Birth outcomes following prenatal exposure to fluoxetine. Biol Psychiatry 2000 Nov 15; 48 (10): 996-1000
77. Andrade SE, McPhillips H, Loren D, et al. Antidepressant medication use and risk of persistent pulmonary hypertension of the newborn. Pharmacoepidemiol Drug Saf 2009; 18 (3): 246-52
78. Casper RC, Fleisher BE, Lee-Ancajas JC, et al. Follow-up of children of depressed mothers exposed or not exposed to antidepressant drugs during pregnancy. J Pediatr 2003; 142 (4): 402-8
79. Laine K, Heikkinen T, Ekblad U, et al. Effects of exposure to selective serotonin reuptake inhibitors during pregnancy on serotonergic symptoms in newborns and cord blood monoamine and prolactin concentrations. Arch Gen Psychiatry 2003; 60 (7): 720-6
80. Heikkinen T, Ekblad U, Palo P, et al. Pharmacokinetics of fluoxetine and norfluoxetine in pregnancy and lactation. Clin Pharmacol Ther 2003; 73 (4): 330-7
81. Heikkinen T, Ekblad U, Kero P, et al. Citalopram in pregnancy and lactation. Clin Pharmacol Ther 2002; 72 (2): 184-91
82. Suri R, Altshuler L, Hendrick V, et al. The impact of depression and fluoxetine treatment on obstetrical outcome. Arch Womens Ment Health 2004; 7 (3): 193-200
83. Toh S, Mitchell AA, Louik C, et al. Antidepressant use during pregnancy and the risk of preterm delivery and fetal growth restriction. J Clin Psychopharmacol 2009; 29 (6): 555-60
84. Lewis AJ, Galbally M, Opie G, et al. Neonatal growth outcomes at birth and one month postpartum following in utero exposure to antidepressant medication. Aust N Z J Psychiatry 2010; 44 (5): 482-7

85. Nulman I, Rovet J, Stewart DE, et al. Neurodevelopment of children exposed in utero to antidepressant drugs. N Engl J Med 1997; 336 (4): 258-62
86. Nulman I, Rovet J, Stewart DE, et al. Child development following exposure to tricyclic antidepressants or fluoxetine throughout fetal life: a prospective, controlled study. Am J Psychiatry 2002; 159 (11): 1889-95
87. Zeskind PS, Stephens LE. Maternal selective serotonin reuptake inhibitor use during pregnancy and newborn neurobehavior. Pediatrics 2004; 113 (2): 368-75
88. Costei AM, Kozer E, Ho T, et al. Perinatal outcome following third trimester exposure to paroxetine. Arch Pediatr Adolesc Med 2002; 156 (11): 1129-32
89. Maschi S, Clavenna A, Campi R, et al. Neonatal outcome following pregnancy exposure to antidepressants: a prospective controlled cohort study. BJOG 2008; 115 (2): 283-9
90. Oberlander TF, Misri S, Fitzgerald C, et al. Pharmacologic factors associated with transient neonatal symptoms following prenatal psychotropic medication exposure. J Clin Psychiatry 2004; 65 (2): 230-7
91. Lattimore KA, Donn SM, Kaciroti N, et al. Selective serotonin reuptake inhibitor (SSRI) use during pregnancy and effects on the fetus and newborn: a meta-analysis. J Perinatol 2005; 25 (9): 595-604
92. Hendrick V, Smith LM, Suri R, et al. Birth outcomes after prenatal exposure to antidepressant medication. Am J Obstet Gynecol 2003; 188 (3): 812-5
93. Levinson-Castiel R, Merlob P, Linder N, et al. Neonatal abstinence syndrome after in utero exposure to selective serotonin reuptake inhibitors in term infants. Arch Pediatr Adolesc Med 2006; 160 (2): 173-6
94. Galbally M, Lewis AJ, Lum J, et al. Serotonin discontinuation syndrome following in utero exposure to antidepressant medication: prospective controlled study. Aust N Z J Psychiatry 2009; 43 (9): 846-54
95. Moses-Kolko EL, Bogen D, Perel J, et al. Neonatal signs after late in utero exposure to serotonin reuptake inhibitors: literature review and implications for clinical applications. JAMA 2005; 293 (19): 2372-83
96. Sanz EJ, De-las-Cuevas C, Kiuru A, et al. Selective serotonin reuptake inhibitors in pregnant women and neonatal withdrawal syndrome: a database analysis. Lancet 2005; 365 (9458): 482-7
97. Wooltorton E. Persistent pulmonary hypertension of the newborn and maternal use of SSRIs. CMAJ 2006; 174 (11): 1555-6
98. Warburton W, Hertzman C, Oberlander TF. A register study of the impact of stopping third trimester selective serotonin reuptake inhibitor exposure on neonatal health. Acta Psychiatr Scand 2010; 121 (6): 471-9
99. Yonkers KA, Wisner KL, Stewart DE, et al. The management of depression during pregnancy: a report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists. Gen Hosp Psychiatry 2009; 31: 403-13
100. Oberlander TF, Reebye P, Misri S, et al. Externalizing and attentional behaviors in children of depressed mothers treated with a selective serotonin reuptake inhibitor antidepressant during pregnancy. Arch Pediatr Adolesc Med 2007; 161 (1): 22-9
101. Misri S, Reebye P, Kendrick K, et al. Internalizing behaviors in 4-year-old children exposed in utero to psychotropic medications. Am J Psychiatry 2006; 163 (6): 1026-32
102. Oberlander TF, Eckstein Grunau R, Fitzgerald C, et al. Prolonged prenatal psychotropic medication exposure alters neonatal acute pain response. Pediatr Res 2002 Apr; 51 (4): 443-53
103. Gentile S. SSRIs in pregnancy and lactation: emphasis on neurodevelopmental outcome. CNS Drugs 2005; 19 (7): 623-33
104. Maciag D, Simpson KL, Coppinger D, et al. Neonatal antidepressant exposure has lasting effects on behavior and serotonin circuitry. Neuropsychopharmacology 2005; 31 (1): 47-57
105. Whitaker-Azmitia PM. Serotonin and brain development: role in human developmental diseases. Brain Res Bull 2001; 56 (5): 479-85
106. Winter C, Reutiman TJ, Folsom TD, et al. Dopamine and serotonin levels following prenatal viral infection in mouse: implications for psychiatric disorders such as schizophrenia and autism. Eur Neuropsychopharmacol 2008; 18 (10): 712-6
107. Whitaker-Azmitia PM. Behavioral and cellular consequences of increasing serotonergic activity during brain development: a role in autism? Int J Dev Neurosci 2005; 23 (1): 75-83
108. Rubinow DR. Antidepressant treatment during pregnancy: between Scylla and Charybdis. Am J Psychiatry 2006; 163 (6): 954-6
109. Nutt DJ, Forshall S, Bell C, et al. Mechanisms of action of selective serotonin reuptake inhibitors in the treatment of psychiatric disorders. Eur Neuropsychopharmacol 1999; 9 (3 Suppl.): 81-6S
110. Rudberg I, Hermann M, Refsum H, et al. Serum concentrations of sertraline and N-desmethyl sertraline in relation to CYP2C19 genotype in psychiatric patients. Eur J Clin Pharmacol 2008; 64 (12): 1181-8
111. Hemeryck A, Belpaire FM. Selective serotonin reuptake inhibitors and cytochrome P-450 mediated drug-drug interactions: an update. Curr Drug Metab 2002; 3 (1): 13-37
112. Yu BN, Chen GL, He N, et al. Pharmacokinetics of citalopram in relation to genetic polymorphism of CYP2C19. Drug Metab Dispos 2003; 31 (10): 1255-9
113. Pavek P, Ceckova M, Staud F. Variation of drug kinetics in pregnancy. Curr Drug Metab 2009; 10 (5): 520-9
114. Goodnick PJ, Goldstein BJ. Selective serotonin reuptake inhibitors in affective disorders: I. Basic pharmacology. J Psychopharmacol 1998; 12 (3 Suppl.): 5-20S
115. Laine K, Kytölä J, Bertilsson L. Severe adverse effects in a newborn with two defective CYP2D6 alleles after exposure to paroxetine during late pregnancy. Ther Drug Monit 2004; 26 (6): 685-7

Correspondence: Mr *Luke Grzeskowiak*, Quality Use of Medicines and Pharmacy Research Centre, Sansom Institute for Health Research, School of Pharmacy and Medical Sciences, University of South Australia, GPO Box 2471, Adelaide, SA 5001, Australia.
E-mail: grzly001@mymail.unisa.edu.au