Outcomes Associated With the Use of Selective Serotonin Reuptake Inhibitors for Depression in Pregnant Women

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Methods: A systematic review of the past five years of English-language published literature was conducted using MEDLINE, CINAHL, and ISI Web of Science using keywords depression, pregnancy, SSRI, and subordinate headings. Articles of original research examining outcomes of SSRI exposure during pregnancy were selected. Meta-analyses and case reports or series were excluded. Fifteen studies, three of which compared SSRI exposure to untreated depression, were retrieved and analyzed for quality and significant results.

Results: Multiple significant relationships between SSRIs and birth defects and between SSRIs and adverse neonatal outcomes were reported, but few results were in agreement across studies, and fewer results were of statistical or clinical significance after adjustments for known confounders were completed. Limited results showed that SSRI exposure and untreated depression carry similar risks to mother and child.

Discussion: Current guidelines suggest individualized treatment for women with perinatal depression. Additional prospective research efforts, perhaps even randomized placebo-controlled trials, are needed to quantify and qualify possible risks of SSRI exposure in pregnant women. Such work should be on large populations and should control for depression as an independent risk factor.

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A Clinical Graduate Project Submitted to the Faculty of the
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Biography

Erin Cramer was born in Sandpoint, Idaho and grew up around the United States and Germany as a military dependent. He graduated from high school in Troy, Montana and embarked upon a career in athletic training after graduating from Montana State University and the graduate program at the University of Oregon. In an effort to achieve a more stable personal life and broaden his knowledge and abilities in medicine, he returned to school following twelve years of service to patients and athletes primarily in Oregon. Following graduation, he and his wife look forward to joining a community and contributing to the well-being of its residents, while raising their sons to appreciate the lives they lead and seize the opportunities they encounter.
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**Keywords:** depression, pregnancy, SSRI
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List of Abbreviations

CI  Confidence Interval
HPA  Hypothalamic-Pituitary-Adrenal Axis
NICU  Neonatal Intensive Care Unit
OR  Odds Ratio
PPHN  Persistent Pulmonary Hypertension of the Neonate
SCN  Special Care Nursery
SSRI  Selective Serotonin Reuptake Inhibitor
INTRODUCTION

Overview

Depression is a very common condition in women, with an estimated lifetime incidence of 20%.\(^1\) Incidence is greatest between the ages of 20 and 40, coinciding with the typical childbearing years.\(^2\) While there is a belief that pregnancy may be a maternally protective time of emotional well-being,\(^3\) the incidence of depression in pregnancy has been variously reported to be between 10 and 25%,\(^4-7\) and may be vastly underreported due to the common feelings of stigma and guilt that may lead pregnant women to avoid treatment.\(^8\) The medical literature contains many reviews that address depression and pregnancy.\(^3,\, 9-12\)

The risk factors for depression in pregnancy are many. The most significant is a prior history of depression.\(^6,\, 13,\, 14\) Others include younger age, living alone, limited social support, a history of abuse, relationship conflict, and ambivalence about the pregnancy.\(^6,\, 13,\, 15\) About 50% of all pregnancies are unplanned,\(^16\) and many women find themselves unprepared for the major changes ahead of them when they learn of their pregnancy.

Depression in pregnancy is associated with a number of adverse outcomes. It is postulated that depression, stress, and anxiety can activate the hypothalamic-pituitary-adrenal (HPA) axis and other hormone systems, leading to hormonal imbalances during pregnancy and which can influence the timing and onset of delivery.\(^3,\, 17\) Depression is also linked to fetal abnormality, spontaneous abortion, gestational hypertension and pre-eclampsia, neonatal intensive care unit (NICU) admissions, low birth weight, and
premature birth. Most seriously, depression in pregnancy is associated with suicide, with as many as 15% of untreated women attempting suicide during pregnancy. As few as 13% of depressed pregnant women obtain treatment for their depression. Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed medications for depression, but only 2-3% of pregnant women are estimated to take them. In fact, 50% of women who use SSRIs for depression reduce or cease using, either unilaterally or at the suggestion of their doctors, when discovering their pregnancies. This is likely due to a combination of the mixed evidence indicating the possibility of adverse effects and of the tendency to use extreme caution with pregnancy. This concern and associated reduction in treatment leads to a depression relapse rate of approximately 70% during pregnancy.

The historical literature is replete with research on SSRIs. Fluoxetine has been the subject of the most extensive investigation, followed by paroxetine. The newer SSRIs, sertraline, citalopram, and escitalopram have been less extensively examined, but not ignored. Birth defects generally occur in the first trimester of gestation, and fluoxetine appears to be relatively safe when used in early pregnancy. Paroxetine was linked to cardiac malformations in early study, leading to voluntary warning label revision by its maker in 2005. The newer SSRIs also appear to be safe in the first trimester.

A tremendous amount of research has been conducted into the use of SSRIs during the third trimester, with substantially varied outcomes. The majority of information available indicates that SSRI use late in pregnancy may be associated with adverse neonatal manifestations, including behavioral changes, motor symptoms, respiratory distress,
somatic symptoms, and gastrointestinal symptoms, but that these manifestations are mild, transient, self-limiting, and ultimately not associated with any instances of neonatal death.

So, in its crudest form, the debate between treating perinatal depression with SSRI and foregoing treatment can be reduced to death, or lack thereof. Some depressed women, left untreated, die by their own hand, while no women being treated with SSRIs were reported to have committed suicide in any of the literature reviewed for this work. There is a scarcity of literature comparing treated and untreated perinatal depression, and every study to date has been subject to methodological limitations relating to the ethics of experimentation on mothers-to-be.

Of additional concern is the likelihood that factors other than depression are responsible for the results of prior and future investigation. Depressed women are more likely to make unhealthy choices, whether antenatally, perinatally, or postnatally. They are more likely to smoke, to drink alcohol, and to abuse other substances. They may receive less prenatal care, or avoid it altogether. Maternal age, race, and socioeconomic status are additional factors independent of depression that can adversely impact pregnancy.

**Purpose of Study**

The best research would attempt to control for all potential confounders while recruiting enough participants to permit statistically and clinically significant results. There is a dearth of historical research that accomplishes this optimum outcome. The purpose of this work is to systematically review the most recent clinical research regarding SSRI use in pregnancy, with a particular interest in studies that compare both treated and untreated
perinatal depression. Pregnant women must make decisions that impact both maternal and fetal health, and they are subject to both internal and external influences when doing so. Few scenarios carry the emotional weight of pregnancy.

**Clinical Question**

The question of whether a pregnant woman with depression would be better off using SSRIs than avoiding them is an important one, commonly encountered in primary care. Health care providers who consult available guidelines and literature find that no easy-to-apply standard exists, and that risks must be weighed on an individual basis. Because of the individual nature of treatment, because of the equivocal nature of the evidence in the historical record, and because of the frequency with which the situation is encountered, it is imperative to remain abreast of new information relevant to this question.

**METHODS**

**Search Strategy**

This systematic review examines original research that contributes to the understanding of the risks and benefits of SSRI use in pregnancy, particularly with regard to perinatal and neonatal outcomes. Only studies published in the last five years comparing SSRI exposure to non-exposure in pregnancy are included. Randomized controlled trials, cohort studies, and case-controlled studies, both prospective and retrospective, are included, even though retrospective studies using maternal interviews to glean data about
past events may be subject to recall bias. Meta-analyses and case reports are not addressed.

A search of the literature published in the previous five years was conducted on the MEDLINE, CINAHL, and ISI World of Science databases using the following search terms: depression, pregnancy, SSRI. Subsidiary MeSH terms were selected where appropriate and permitted by the search engine (IE- “serotonin uptake inhibitors” secondary to “SSRI”). Subsequent examination of bibliographic entries in retrieved works yielded additional studies for consideration.

Inclusions/Exclusions

The search was then limited to English language publications and adult subjects. Studies with a focus on antidepressants other than SSRIs, on postpartum depression, or on outcomes beyond the neonatal period were excluded. After these exclusions, fifteen articles, of which only three purported to compare both SSRI exposure and untreated depression, were appraised. (see table 1).

Using an original method (see table 2), a relative score representing quality and validity was assigned to each article. Higher scores were awarded for population/cohort studies, for prospective and controlled investigations, and for large sample populations. Lower scores were earned by retrospective studies, those with minimal effort to minimize confounding factors, and those with smaller experimental groups. No studies were eliminated from the review by score. Scores guide the review but do not preclude the consideration of good premise with poor execution.
RESULTS

Birth Defects

Some studies looked specifically at the relationship that SSRIs may have to congenital malformations, generally confining investigation to SSRI use in the first trimester of pregnancy, when most birth defects occur. Others examined SSRI use over the entire pregnancy and reported malformation outcomes as part of a larger picture. Nine of the fifteen reviewed articles contributed new knowledge about these risks.

In a retrospective study with over 13,000 participants published in the New England Journal of Medicine, Alwan et al reported in 2007 that first trimester use of SSRIs, as a class, was not associated with any of several major birth defects, including those cardiac in nature. Class associations were reported for three rare defects, anencephaly (Odds Ratio (OR) 2.4, Confidence Interval (CI) 1.1-5.1), craniosynostosis (OR 2.5, CI 1.5-4.0), and omphalocele (OR 2.8, CI 1.3-5.7). A few single drug associations were reported, but it is noteworthy that paroxetine was associated with only one cardiac defect, right ventricular outflow tract obstruction defects (OR 2.5, CI 1.0-6.0).37

In the same issue of the New England Journal of Medicine, Louik et al found similar risks of first trimester paroxetine exposure for right ventricular outflow tract obstruction defects (OR 3.3, CI 1.3-8.8), but did not find evidence of association to anencephaly, craniosynostosis, or omphalocele.38 Both studies used data from the Slone Epidemiology Center Birth Defects Study, and had seemingly large populations (Louik et al had more than 15,000), but lamented that their sample sizes relatively limited the statistical power of their research, particularly when focusing on very rare outcomes.37, 38
In another study with large numbers, Swedish academics Källén and Olausson used national health registries to gather data on SSRI exposures and were able to establish only one malformation association for the class of medicines despite SSRI use in 6,481 subjects and an overall control population greater than 860,000. Cystic kidney malformations were statistically significant (OR 3.50, CI 1.60-6.65), but the researchers noted that the number of malformations, only nine, was small and that distinctly different morphology present among the nine suggested five separate etiologies. Like the above mentioned works, the Swedish study looked specifically at paroxetine and cardiac malformations, and did note an association, but only when all cardiac malformations were considered together (OR 1.63, CI 1.05-2.53).39

Only one other article published a positive association between SSRI and birth defects, and it was a study of much smaller scale that addressed birth defects only in broad terms. Somewhat counter to the other findings, Diav-Citrin et al showed only an association between fluoxetine and major malformations (OR 4.47, CI 1.31-15.27). Prior to considering maternal age, smoking status, and other factors, a crude association existed for paroxetine, but it ceased to be significant following adjustment.40

Five articles reported no statistically significant link between SSRI and congenital malformation.41-45 Malm et al explored SSRIs both as a group and individually, and noted no differences in their matched 1782 pairs of subjects.41 In another, smaller study of citalopram only, Sivojelezova et al found no significant differences across groups when analyzing spontaneous abortion, stillbirth, and major malformation. They also noted no incidence of cardiac malformation in their population of 132 women exposed to SSRIs.43 Three other works, primarily focused on prenatal outcomes but including first
trimester SSRI exposure, reported with minimal detail, incidental lack of relationship between SSRI exposure and birth defects in their respective populations.\textsuperscript{42, 44, 45}

**Late Gestation**

Some research has focused on the possible maternal effects of SSRI use in late gestation. If SSRI use is implicated in factors such as maternal weight gain or gestational hypertension, it may be a significant reason for poor pregnancy outcomes through indirect means.

Wisner et al reported no significant differences in maternal weight gain among their multiple experimental populations when looking at both treated and untreated perinatal depression.\textsuperscript{45} However, in an examination of gestational hypertension and pre-eclampsia, Toh et al found a significant association between continuous SSRI use and the development of pre-eclampsia (OR 4.86, CI 2.70-8.76).\textsuperscript{46}

**Gestational Age**

Gestational age and preterm delivery have been widely evaluated. While slightly different, the two are closely related, and an examination of average gestational age can yield subtle differences that would be ignored if preterm delivery were the only focus. To that end, both Oberlander et al (38.8 weeks vs. 39.2 weeks, p<0.001)\textsuperscript{47} and Malm et al (39.1 weeks vs. 39.4 weeks, p<0.001)\textsuperscript{41} report slight but statistically significant differences in gestational age among their study populations.

Perhaps of more clinical significance, several authors have described preterm delivery differences in their studies. Preterm infants are most commonly defined as those born
before thirty-seven weeks gestational age, but one article defined the threshold as thirty-six weeks.\textsuperscript{42} Maschi et al reported significant differences at thirty-six weeks over control populations both for any SSRI use in pregnancy (OR 2.31, CI 1.14-4.63), and for continuous SSRI use (OR 4.35, CI 1.31-14.07).\textsuperscript{42}

Oberlander et al based their findings on over 100,000 subjects in a governmental register. They report significant differences in rates of preterm delivery when comparing SSRI use to untreated depression (9\% vs. 6.5\%, \(p<0.001\)) and when comparing untreated depression to women without depression (6.5\% vs. 5.9\%, \(p<0.007\)).\textsuperscript{47}

Wisner also compared SSRI use to untreated depression and controls, and recorded unadjusted significance between all groups. However, when adjusted for maternal age, race, and other factors, only SSRI use continued to be associated with preterm delivery (OR 5.43, CI 1.98-14.84). Untreated depression lost significance following adjustment (OR 3.71, CI 0.98-14.13).\textsuperscript{45}

One more article published findings linking SSRI use to preterm delivery and lower gestational age. For gestational age, Suri et al found significance in comparisons of SSRI use and untreated depression (38.5 weeks vs. 39.4 weeks, \(p<0.05\)), and of SSRI use and controls (38.5 weeks vs. 39.7 weeks, \(p<0.05\)), but not between untreated depression and controls. Differences in preterm delivery rates were also significant between SSRI use and controls (14.3\% vs. 5.3\%, \(p=0.05\)).\textsuperscript{48}

Conversely, two studies published contrary results about SSRIs and preterm delivery or gestational age. In their study of three groups of 132 subjects comparing citalopram to other antidepressants and controls, Sivojelezova et al identified no association in any of
their cohorts. Ferreira et al reported greater incidence of prematurity in their SSRI-exposed group, but no statistically significant association was evident after adjustment for confounding variables.

**Birth Weight**

Seven studies reported comparison results for absolute birth weight or low birth weight defined as below the tenth percentile, but only three studies showed any significant statistical relationship between SSRI use and absolute birth weight. Malm et al recorded a difference of ninety-nine grams between groups (p<0.001), Dubnov-Raz et al reported finding a mean difference of 230 grams (p=0.04), and Oberlander et al found thirty-two grams difference between SSRI use and untreated depression (p=0.05) and twenty-four grams difference between untreated depression and unexposed controls (p<0.001). No study reported significant differences among groups when examining birth weight below the tenth percentile.

**Other Outcomes**

Other neonatal outcomes of interest include Apgar scores, admission to special care units or neonatal intensive care units, persistent pulmonary hypertension of the neonate (PPHN), length of hospitalization, jaundice, and respiratory distress.

**PPHN** Wichman et al found no relationship between SSRI use and PPHN in a study of 808 exposed neonates, but Chambers et al, in their study of 377 neonates with PPHN found a significant link between late pregnancy use of SSRI and PPHN (OR 6.1, CI 2.2-16.8).
**QT Prolongation** In a relatively small study of 52 infants with neonatal QT prolongation, matched to controls, Dubnov-Raz et al recorded a nineteen millisecond mean difference (p<0.001) between the group exposed to SSRIs and the comparison group. The abnormalities resolved without intervention over the course of several days, and were reportedly of no long-term concern.

**Apgar Score** Apgar scores were examined in four studies, and neither Wisner et al, Suri et al, nor Dubnov-Raz et al reported any statistically significant relationship between SSRI exposure and Apgar scores at one minute or five minutes, with or without adjustment for maternal age and race. Malm et al found a difference between third trimester exposure and earlier exposure (OR 1.6, CI 1.0-2.4) for one-minute Apgar score.

**SCN/NICU Admission** Several studies evaluated the possibility of a relationship between SSRI use and admission to a special care nursery (SCN) or a NICU. Sivojelezova et al found a link between third trimester exposure to citalopram and SCN/NICU admission (OR 4.2, CI 1.7-10.3). Malm et al reported similar findings, with third trimester SSRI exposure carrying more risk (OR 1.6, CI 1.1-2.2) than earlier prenatal exposure. Differing conclusions were made by Suri et al, Maschi et al, and Ferreira et al, none of whom published evidence of a link to the need for specialized care.

**Other Neonatal Signs** Jaundice, convulsions, feeding issues, central nervous system abnormalities, and respiratory distress were examined in several studies with mixed results. Wisner et al and Maschi et al found no significant relationships between
any of their study groups and various neonatal behavioral and adaptation signs.\textsuperscript{42,45} Ferreira et al found a relationship between SSRI exposure and neonatal signs as a group, but not individually. Nearly 78\% of the exposed neonates versus 41\% of the controls (p<0.001) presented with one or more signs (OR 3.1, CI 1.3-7.1).\textsuperscript{49} Sivojelezova et al, looking only at citalopram, reported a relationship between third trimester exposure and neonatal complications (OR 1.5, CI 1.0-2.4).\textsuperscript{43}

The study by Oberlander et al is noteworthy because of its sheer size. This permitted them to observe statistical, if not necessarily clinical, significance in many measures. They noted differences in length of hospitalization, incidence of respiratory distress, feeding problems, jaundice, and convulsions when comparing SSRI exposure to untreated depression. However, when they matched the participants by propensity score, in an attempt to compare women of relatively equal levels of depression, the differences in neonatal outcomes disappeared with the exception of the incidence of respiratory distress (4.4\%, p=0.006).\textsuperscript{47}

**DISCUSSION**

**Study Limitations**

The articles included in this review reflect a variety of research methods, and their results are of variable quality. Attempting to study the effects of a class of medications on pregnant women and unborn children is limiting, and ethical considerations prevent randomized controlled trials in most cases. As such, prospective and retrospective population, cohort, or case-matched studies comprise the bulk of the available research.
Retrospective study can be effective, and many of the studies in this review are retrospective in nature. Four of them, Alwan et al, Chambers et al, Louik et al, and Toh et al rely on interviews with participants at as long as one year after the behaviors and exposures being investigated.\textsuperscript{37, 38, 46, 51} This presents a possible recollection bias mentioned by the authors of the articles in question. Other retrospective studies\textsuperscript{39, 47} used institutional databases and registries that are perhaps more reliable than personal recollections of subjects, but the researchers must still place reliance on data of the past that was recorded by complete strangers. Thus, the results of retrospective study must always be evaluated with some degree of skepticism.

This topic also highlights the limitations of small studies. Events such as birth defects are often so rare that even studies like Alwan et al and Louik et al can reach opposing conclusions even though their respective studies each looked at more than ten thousand subjects. Smaller studies like Wisner et al, with only 238 women, hardly seem to stand a chance of achieving meaningful statistical significance for events as rare as birth defects are in absolute terms.

**Confounders**

Confounding variables are another crucial part of every one of these papers. Some populations simply aren’t equal. As discussed earlier, depressed women are more likely to smoke, to drink, and to make poor health care decisions. Nearly every research team attempted to control for a variety of variables, and their adjusted data commonly lost statistical significance in the process. This isn’t cause for lament, but merely evidence that this complex puzzle makes meaningful results much more difficult to achieve.
Bias can be introduced due to the presence of depression alone. Bar-Oz et al noted\textsuperscript{52} that women using antidepressants in pregnancy had a 30\% higher rate of ultrasound usage than other women, and that this difference could be responsible for a detection bias great enough to result in the increases in cardiac malformation that have been noted in infants exposed to paroxetine in utero.\textsuperscript{52}

The impact of depression, as an independent risk factor for adverse outcome, has not been well investigated to date. Only three articles in this review, Wisner et al, Oberlander et al, and Suri et al, have made an attempt to investigate depression separately from depression and SSRI use\textsuperscript{,45,47,48} and only one other\textsuperscript{53} from an excluded time period, was located during the literature search. The sheer size of the study likely helped Oberlander et al observe significant associations where Wisner et al and Suri et al could not, as did their unique attempt to match levels of depression with their propensity score system.\textsuperscript{47}

**Future Avenues**

Based on the varied results of the most current research presented here, additional study is clearly warranted. Future researchers should follow the lead of Wisner et al and Suri et al, with prospective study of women with varying SSRI status, and should improve on their foundation by recruiting larger numbers of participants. They should do a better job of following the participants, of quantifying their exposures, of eliminating confounding variables, and of clearly documenting and presenting the results of their work.

Future research should attempt to replicate past study as well. When a respected journal publishes two works with oppositional conclusions in the same issue, as the New England
Journal of Medicine did with Alwan et al and Louik et al, it can be assumed that the true conclusion is still available for discovery or confirmation.

Considering postpartum depression in the discussion is another avenue for future research. Adding levels of complexity doesn’t make the work any easier, but the clinical scenarios faced by patients and providers are inherently complex and often more than a little messy. In the meantime, the prudent clinician will continue to follow available guidelines and treat each patient with individual consideration.

Is it time for randomized clinical trials? At least one team believes that placebo-controlled randomized clinical trials of SSRI in pregnant women can and should be performed within today’s standards of ethical research. Even using this systematic review, one could cite several examples where SSRIs were not associated with birth defects or with anything other than transient neonatal outcomes.

**CONCLUSION**

The question of whether or not to use SSRIs in managing perinatal depression is an important and practical one for the practicing health care provider. The current standard of care entails treating each patient as her individual circumstances warrant. Some evidence suggests that SSRIs increase the likelihood of birth defects and prematurity, both of which are significant occurrences, complicating efforts to care for mother and child. The picture is clouded by other evidence suggesting there is no link between SSRI use and adverse outcomes. The wise clinician will strive to understand, not only the relative risks, but also the absolute risks associated with treatment options, and by doing so help his or her patient navigate and manage her own health.
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<th>Study/Design</th>
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<td>Wichman et al (2009)</td>
<td>25214 infants</td>
<td>SSRI vs. no SSRI</td>
<td>CHD, VSD, PPHN</td>
<td>2/5. No evidence of homogeneity or confounding factors in maternal population.</td>
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<tr>
<td>Wisner et al (2009)</td>
<td>107 women and 131 controls</td>
<td>SSRI and depression vs. no SSRI, no depression</td>
<td>Birth defects, maternal weight gain, birth weight, preterm birth, neonatal outcomes</td>
<td>4/5. Stratifies depression independently. Larger sample sizes needed for significance following adjustments for confounders.</td>
</tr>
<tr>
<td>Diav-Citrin et al (2008)</td>
<td>724 women and 1467 controls</td>
<td>Fluoxetine or paroxetine in 1st trimester vs. no SSRI</td>
<td>Birth Defects, birth weight, gestational age, neonatal complications</td>
<td>3/5. Good design, but small sample and lack of independent consideration of depression. Participants were self-referred.</td>
</tr>
<tr>
<td>Ferreira et al (2008)</td>
<td>76 mothers and 90 controls</td>
<td>SSRI in 3rd trimester vs. no SSRI</td>
<td>Premature birth, admission to SCN, neonatal outcomes</td>
<td>2/5. Small study with limited evidence of population homogeneity. Twins not excluded.</td>
</tr>
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<td>Alwan et al (2007)</td>
<td>9622 infants with birth defects and 4092 controls</td>
<td>SSRI in early pregnancy vs. no SSRI</td>
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<td>3/5. Rare malformations make associations difficult despite large numbers.</td>
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<td>Suri et al (2007) Prospective case-control</td>
<td>49 women, 41 controls (2 groups: 22 &amp; 19)</td>
<td>Antidepressants and depression vs. no medications, no depression</td>
<td>Gestational age, birth weight, Apgar score, admission to SCN</td>
<td>2/5</td>
</tr>
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<td>Oberlander et al (2006) Retrospective Cohort</td>
<td>119547 mothers and infants</td>
<td>SSRI and depression vs. no SSRI, no depression</td>
<td>Birth weight, preterm birth, length of hospitalization, neonatal symptoms</td>
<td>4/5</td>
</tr>
<tr>
<td>Malm et al (2005) Retrospective case-control</td>
<td>1782 women, 1782 controls</td>
<td>SSRI vs. no SSRI</td>
<td>Birth defects, gestational age, birth weight, Apgar score, admission to SCN</td>
<td>3/5</td>
</tr>
<tr>
<td>Sivojelezova et al (2005) Prospective case-control</td>
<td>132 women, 264 controls (2 groups of 132)</td>
<td>Citalopram vs. non-SSRI antidepressants, no antidepressants</td>
<td>Birth defects and perinatal complications</td>
<td>2/5</td>
</tr>
<tr>
<td>Criterion</td>
<td>Score +1</td>
<td>Score 0</td>
<td></td>
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<tr>
<td>Study Type</td>
<td>Randomized controlled trials, Prospective cohort, Prospective case-controlled</td>
<td>Retrospective, Case series, Case study</td>
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<tr>
<td>Sample Size</td>
<td>Total participants &gt;1000</td>
<td>Total participants &lt;1000</td>
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<tr>
<td>Confounding Factors</td>
<td>Acknowledgement and explanation of confounders, Comparison of group attributes, Adjustment for confounders, Explanation for non-adjustment</td>
<td>No acknowledgement of confounders, No comparison of group attributes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clearly Evident and Accurate</td>
<td>Clear and accurate data sets or tables, Concise explanation of results in appropriate groupings</td>
<td>Errors in reporting, Hidden information, Logic disconnects</td>
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<tr>
<td>Results</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Independence of Depression</td>
<td>Untreated depression presented as an independent variable, Depression state is considered in data adjustment for confounders</td>
<td>Depression ignored as variable</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TABLE 2: Appraisal Criteria
REFERENCES


