Antidepressant Use in Pregnancy: An Evaluation of Adverse Outcomes Excluding Malformations

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ABSTRACT

Background: To date, many studies have been published regarding the safety of antidepressant use in pregnancy. However, most have been regarding a possible association with major malformations and there have been relatively few studies that have examined other infant outcomes specifically.

Objective: To evaluate possible adverse effects of antidepressant use in pregnancy.

Methods: We searched the literature, using Medline, PUBMED, Embase, and Reprotox, and retrieved key articles and reviews of the topic. We examined all outcomes with the exception of major/minor malformations.

Results: We did not find an overall increased risk associated with lower mean birthweight, small for gestational age or long-term neurodevelopmental adverse outcomes. However, there does appear to be a significantly increased risk for spontaneous abortion, preterm birth and low birthweight less than 2,500gm. In addition, a possible increased risk for Persistent Pulmonary Hypertension of the Newborn (PPHN) and evidence of Poor Neonatal Adaptation Syndrome (PNAS) following use in late pregnancy. All of the observed risks were of a very low magnitude and the clinical significance of these results is unknown.

Conclusions: This information should not preclude a pregnant women from being treated for depression if required, as untreated depression is also associated with adverse effects on the infant. However, further research needs to be conducted where it is possible to control for maternal depression, in order to evaluate whether these adverse events are due to the underlying maternal illness, the antidepressant, or possibly a combination of both.

Adrienne Einarson/The Motherisk Program is a recipient of an unrestricted educational grant from Eli Lilly Inc. Canada, to examine the safety of duloxetine (Cymbalta®) during pregnancy.
Laura Lorenzo has no possible conflicts of interest.

BACKGROUND

Women are twice as likely than men during their lifetime to experience both anxiety and depression, most of which occur during their years of reproductivity (1). During pregnancy, the period prevalence rate for a major depressive episode is 18.4% (2). A study from the National Birth Defects Prevention from ten U.S. states (3), documented that among 6,582 mothers included in the study, 298 (4.5%) reported use of an antidepressant during pregnancy. The authors reported that antidepressant use at any time during pregnancy had increased from 2.5% in 1998 to 8.1% in 2005 and is probably higher since this data was compiled, as overall use of antidepressants in the general population has increased exponentially (4). Although these numbers are from the U.S., it likely reflects prevalence throughout the world, as the World Health Organisation ranks depression as the leading cause of disability worldwide and estimates an effect on approximately 120 million individuals (5).

Due to fears of teratogenicity, it is not an unusual occurrence for women to discontinue their medication, especially psychotropic drugs, upon diagnosis of pregnancy. Data from a large U.K. database of primary care information

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reported that although antidepressants prescribing in pregnancy increased almost 4-fold between 1992 and 2006, pregnancy was a major determinant for antidepressants discontinuation (6). It should be noted that pregnant women who discontinue their medication are exposed to possible relapse of illness. In one study (7), of 36 women who were contacted following this decision, 26 (70.3%) of the women reported physical and psychological adverse effects, with 11 reporting psychological effects only, 11 reported suicidal ideation and four were admitted to hospital. Prior to discontinuing their antidepressant, all of the women were euthymic. Another group (8) reported that among 82/201 depressed women who continued to take their antidepressant throughout pregnancy, 21 (26%) relapsed, compared with 44 (68%) of the 65 women who discontinued medication.

UNTREATED MATERNAL DEPRESSION

Few studies have been conducted specifically to examine the risk of untreated maternal depression and the rates of preterm birth. A recent metanalysis (9) reported that depression during pregnancy was associated with modest significant risks of preterm birth (RR=1.13; 95% CI, 1.06-1.21) and low birth weight (RR=1.18; 95% CI, 1.07-1.30), although possible effects of antidepressants could not be excluded. Another review (10) did focus exclusively on non-medicated antenatal depression and offspring outcomes. Despite the heterogeneity of outcome measures, findings from this review suggested that prenatal depression negatively impacted a developing fetus, with implications extending into childhood (i.e., shorter length of gestation, fetal growth restriction and/or lower birth weight). In addition, newborns of depressed mothers showed a biochemical/ physiological profile that mimics their mothers' prenatal biochemical/physiological profile including elevated cortisol, lower levels of dopamine and serotonin, greater relative right frontal EEG activation and lower vagal tone (11). These findings were thought to reflect more general developmental issues that may impact the individual throughout adulthood.

Untreated depression during pregnancy may also cause women to use other substances, that can adversely affect pregnancy outcomes which was confirmed in a recent study, where researchers followed 195 women throughout pregnancy to evaluate the use of medicinal agents and habit-forming substances, and prenatal depression was associated with decreased prenatal vitamin compliance and increased use of hypnotics and tobacco (12). Regarding obstetric outcomes, another study reported that depression in late pregnancy was associated with increased risk of epidural analgesia (33% vs. 19%, p =.01, adjusted RR = 2.56, 95% CI 1.24-5.30), caesarean sections and instrumental vaginal deliveries (39% vs. 27%, p =.02, adjusted RR = 2.28, 95% CI 1.15-4.53), as well as more admission to neonatal intensive care units (24% vs. 19%, p =.03, adjusted RR = 2.18, 95% CI 1.02-4.66) (13).

The impact of antidepressant treatment on pregnancy outcomes has been explored mainly focused on major malformations. Other outcomes, like fetal growth, spontaneous abortion, perinatal events or infant neurodevelopment, have received relatively less attention. However, these outcomes could be affected by untreated depression. Hence, the following is a summary of outcomes following depression in pregnancy, treated pharmacologically with antidepressants.

FETAL GROWTH

The growth of the fetus provides information about the course of pregnancy and may anticipate the health aspects of postnatal development. Methods to estimate fetal growth, birth weight, and timing of delivery are outcomes frequently used in epidemiological studies (14). A child born weighing less than 2,500 grams is considered low birthweight, and if the birth occurred prior to 37 weeks gestation, both outcomes involve an increased risk of morbidity and mortality of the newborn but do not represent different endpoints. A low-birthweight baby can be born full term, and a premature baby may not be low birth weight. A measure used to combine these aspects is intrauterine growth retardation, known as "small for gestational age" (SGA) and is a baby whose birth weight is below the 10th percentile, based on birth weight reference curves and stratified by infant gender and gestational age (15).

The impact of antidepressants on fetal growth has been evaluated (16-37) with a diversity of outcome measures. Using different data sources, and with different results, most of the studies lacked an adequate control group of women with untreated depression. Also lacking in many of the studies is antidepressant dose, duration of exposure and the severity of depression. In summary, despite heterogeneity of outcomes, we did not find an overall increased risk associated with lower birth weight or small for gestational age. However, there does appear to be a significantly increased risk for preterm birth and infants born less than 2,500gm (Table 1).

Table 1. *Fetal Growth*

First author and year	Drugs studied	Study design	Exposed n	Comparison group n	Source of data	Primary outcome
Chambers 1996[16]	Fluoxetine	Prospective cohort	228	254	TIS California	Birth size, gestational age
Results: Higher rates of premature delivery (RR 4.8; 95% CI 1.1-20.8) and lower birth weight (188 gr. ;p .02) with late pregnancy exposure						
Simon 2002[17]	TCAs SSRIs	Prospective cohort	TCAs = 209 SSRIs = 185	Matched controls for each exposure (209; 185)	Prepaid health plan (USA)	gestational age, birth weight, head circumference at birth
Results: No difference in any outcome for TCAs exposed vs. non-exposed. For SSRIs exposed, decreased gestational age (≤ 36 weeks, OR 4.38 [1.57-12.22])						
Oberlander 2006[18]	SSRIs	Prospective cohort	SSRIs prescriptions = 1451	Depressed without SSRIs prescriptions = 14234 Non-depressed controls = 92192	Administrative database	birth weight <10th percentile for gestational age, gestational age <37 weeks
Results: infants of mothers with SSRIs prescriptions had more incidence of birth weight <10th percentile for gestational age (p .02) than those of mothers with untreated depression (propensity score matched). No differences in other outcomes						
Davis 2007[19]	SSRIs, TCAs and other AD	Retros-pective cohort	SSRIs = 1047 TCAs = 221 Other AD = 173	Control = 49667	Administrative database	Perinatal adverse events
Results: Increased risk of preterm delivery for SSRIs exposed (RR 1.45; 95%CI 1.25, 1.68) and TCAs exposed (RR 1.67; 95%CI 1.25, 2.22).						
Suri 2007[20]	SSRIs, TCAs and other AD	Prospective cohort	Depressed mothers using AD = 49 (group 1)	Depressed mothers not using AD = 22 (group 2) Healthy controls = 19 (group 3)	Outpatients of UCLA Women's Life Center clinic	gestational age at birth, birth weight
Results: Groups 1, 2 and 3 differed in gestational age at birth (38.5 weeks, 39.4 weeks, 39.7 weeks, respectively; p .004) and rates of preterm birth (14.3%, 0%, 5.3%, respectively; p .05). No differences found in birth weight. Outcomes not affected by pregnancy depression.						
Oberlander 2008[21]	SRIs	Prospective case-control	Early exposure = 1575	Late exposure = 1925	Administrative database	birth weight <10th percentile for gestational age, gestational age <37 weeks
Results: No significant differences between early and late exposure after propensity-score matching. Only low birth weight in the limit of significance (p .05). (30gm difference between groups)						
Toh 2009[22]	SSRIs Non-SSRIs	Retros-pective cohort	SSRIs = 192 (first trimester = 106; beyond first trimester = 86) non-SSRIs = 59	5710 unexposed to AD	Slone Birth Defects Center Epidemiological Study	Preterm delivery SGA
Results: No greater risk of preterm delivery (OR 1.12 [0.64-1.95]) in SSRIs exposed. Compared to non exposed, there were more premature births in non-SSRI exposed (OR, 2.23; 95% CI 1.02-4.88) and more SGA offsprings among women who maintained SSRIs beyond the first trimester (OR, 3.0; 95% CI, 1.7-5.5).						
Maschi 2008[23]	SSRIs TCAs	Prospective cohort	Paroxetine = 58 Fluoxetine = 32 Amitriptyline = 26	Non exposed = 1200	Drug and Health Information Centre, Italy	Neonatal adverse events and Special Care Unit admission rate
Results: Exposed women had more premature births than unexposed (OR 2.31 95% CI 1.14-4.63). Adjusting for time of exposure, the association remained significant only in the group who had received antidepressants throughout pregnancy						
Lund 2009[24]	SSRIs alone or in combination	Prospective cohort	SSRIs = 329	Positive psychiatric history/ No SSRI Use = 4902 No Psychiatric History = 51 770	Aarhus Birth Cohort (Denmark)	Gestational age Preterm birth Birth weight Head circumference
Results: Mean gestational age was 4.5 days (95% CI, −6.2 −2.8) shorter in children born to SSRI exposed mothers vs. non exposed, and 3.8 days (95% CI, −5.6 −2.0) shorter vs. women with history of psychiatric illness. Risk of preterm birth was twice that of women of the other two groups (vs. women without history of psychiatric illness: adjusted OR, 2.02; [95%CI, 1.29-3.16]; vs. women with a history of psychiatric illness: OR, 2.05 [95% CI, 1. 28-3.31]). No differences in head circumference.						
Einarson 2009[25]	SSRIs Other AD	Prospective cohort	928	928	TIS Motherisk Program	Fetal growth
Results: 82 (8.8%) preterm deliveries in the antidepressant group and 50 (5.4%) in the comparison group. OR: 1.7 (95% CI: 1.18–2.45). and 89 (9.6%) SGA in the exposed group and 76 (8.2%) in the comparison group; OR: 1.19 (95% CI:0.86–1.64). Mean birth weight in the antidepressant group was 3,449±7591 g and 3,455±7515 g in the comparison group (P=.8)						

First author and year	Drugs studied	Study design	Exposed n	Comparison group n	Source of data	Primary outcome
Wisner 2009[26]	SRIs	Prospective cohort	Continuous SSRI exposure = 48 Partial SSRI exposure = 23	No SSRI, no depression = 131 Continuous depression, no SSRI = 14 Partial depression, no SSRI =22	Outpatients	infant birth weight and preterm birth
Results: Continuous SSRI and continuous depression groups had a 20% increase in premature births compared with the others three groups (partially exposed and control). Continuos depression RR 3.71 [0.98–14.13]). Continuous SSRIs RR 5.43 [1.98–14.13]. Association between continued use of SSRIs and preterm delivery was strengthened when adjusting for age and race						
Lewis 2010[27]	SSRIs SNRIs	Prospective cohort	27	27	Obstetrical clinic in Melbourne	gestational age at birth, neonatal growth outcomes at birth and then at 1 month postpartum
Results: Children of mothers exposed to antidepressants were more likely to be born prematurely (mean gestational age 38.86 vs 39.86; p .005) and were of shorter length (49.30 vs. 51.44 cm; p .001) and lower birth weight (3273 vs. 3671 gr.; p .010) than children of non-exposed mothers.						
Reis 2010[28]	TCAs SSRIs SNRIs	Prospective	14821 women and 15017 neonates (3 groups: early, late and both)	1 062 190 women with 1 236 053 infants in the population	Swedish Birth Registry	maternal delivery diagnoses, infant neonatal diagnoses
Results: Increased preterm birth for all exposures (TCAs OR 2.36 [1.89–2.94]; SSRIs OR 1.46 [1.31–1.63]; SNRIs OR 1.98 [1.49–2.63]). SNRI exposure showed a higher risk for low birthweight than SSRI and a significant SGA effect, not present in the other two groups.						
Ramos 2010[29]	SSRIs TCAs other ADs	Case-control	Cases = 404 pregnancy sub analysis cases = 128.	Controls = 2302 Sub analysis controls = 810	3 administrative databases (Canada) Sub analysis with questionnaire about potential confounders	SGA
Results: prescriptions of ADs other than SSRI and co-administration of two or more classes of ADs were associated to SGA only during 2nd trimester (aRR 2.25 [1.30–3.92]; aRR 3.48 [1.56–7.75] respectively). In sub analysis of questionnaire respondents associations remained significant (aRR 2.41 [1.07-5.43]; aRR 3.28 [1.28-8.45] respectively).						
Roca 2011[30]	SSRIs	Case-control	Women with depressive or anxiety disorder = 84	Matched controls = 168	General teaching hospital	Obstetrical and neonatal outcomes
Results: Rates for preterm birth were higher in the exposed group (OR=3.44, 95% CI=1.30-9.11). Following stratification, exposure to a high-dose was associated with lower gestational age (p=.009) and higher rates of prematurity (OR=5.07, 95% CI=1.34-19.23).						
Klieger-Grossmann 2012[31]	Escitalopram SSRIs Other ADs	Prospective cohort	Escitalopram = 213	Other AD = 212 Nonteratogens = 212	TIS Motherisk Program Swiss TIS Florence TIS	pregnancy outcomes
Results: Higher rate of low birth weight (<2500 g) in the escitalopram group (9.9%) compared with those exposed to other ADs (3.6%, P = .038) and nonteratogens (2.1%, P = .003). No differences in other outcomes						
Nordeng 2012[32]	TCAs SSRIs	Prospective cohort	Pregnancy exposed = 699	Non-exposed = 61648 Prior pregnancy exposed = 1048	Norwegian Mother and Child Cohort Study. Medical Birth Registry of Norway	Birth weight Preterm birth
Results: Adjusting for maternal level of depression and a wide range of other potentially confounding factors, exposure to antidepressants during pregnancy was not associated with increased risk of preterm birth (adjusted OR, 1.21; 95% CI, 0.87-1.69) or low birth weight (adjusted OR, 0.62; 95% CI, 0.33-1.16).						
Grzeskowiak 2012[33]	SSRIs	Retros-pective cohort	With SSRIs prescriptions and psychiatric illness = 221	No prescriptions, no psychiatric illness = 32004 No prescriptions, psychiatric illness = 1566	Administrative databases (Women's and Children's Health Network, South Australia)	preterm delivery, low birth weight, small-for-gestational age
Results: Infants of women with pregnancy prescription of SSRIs had a twice increased risk of preterm delivery (aOR, 2.68; 95% CI, 1.83-3.93), low birth weight (aOR, 2.26; 95% CI, 1.31-3.91), but not small-for-gestational age (aOR, 1.13; 95% CI, 0.65-1.94) compared with infants of mothers with psychiatric illness but no SSRI use during pregnancy. Data collection of women with psychiatric illness couldn't account for severity. So, confounding by maternal illness cannot be ruled out						

First author and year	Drugs studied	Study design	Exposed n	Comparison group n	Source of data	Primary outcome
Hayes 2012[34]	SSRIs TCAs Other ADs	Retrospective cohort	Depressed with 1-2 prescriptions = 10,700 Depressed >3 prescriptions = 6196	Not classified as depressed = 195,079 Depressed, no prescriptions = 16,901	Administrative database (Tennesse-Medicaid)	Pregnancy outcomes
Results: Most women (75%) discontinued prescriptions before or during first trimester. Filling 1, 2, and 3 antidepressant prescriptions during the second trimester was associated with shortened gestational age by 1.7 (95% CI 1.2–2.3), 3.7 (95% CI,2.8–4.6), and 4.9 (95% CI, 3.9 –5.8) days, when controlled for potential confounders including diagnosis of previous depression, comorbid psychiatric diagnosis and multiple psychiatric medications.						
Yonkers 2012[35]	SRIs	Prospective cohort	Depressive episode and use of SRIs = 55 No depressive episode but use of SSRI = 238	No depressive episode no SRI use (control) = 2194 Depressive episode and not use of SRI = 167	Obstetrical practice and hospital-based clinics	Preterm birth Early preterm birth (< 34 completed weeks' gestation) Late preterm birth (34-36 completed weeks' gestation)
Results: Using SSRIs with or without depression in pregnancy was not associated with elevated risk of preterm birth in general. The risk for early preterm birth) was similar for all the groups. After adjustment, significant risk for late preterm birth emerge in both groups exposed to SSRIs, with (OR 3.14; 95%CI 1.5–6.8) or without (OR 1.93; 95% CI 1.2–3.2) depression in pregnancy but not for depression only exposure (OR 1.34, 95% CI 0.71–2.5).						
El Marroun 2012[36]	SSRIs	Population-based Prospective cohort	Women using SSRIs = 99	No SSRIs, no depression (control) = 7027 No SSRIs and clinically relevant depressive symptoms = 570	Generation R Study (Netherlands)	Birth outcomes Fetal body and head growth
Results: SSRI-exposed children had higher risk for preterm birth (OR 2.14 [1.08-4.25]). Children of mothers with depressive symptoms not using SSRIs showed a slower rate of fetal weight gain (−4.4 g/week; p .001) and head growth (−0.08 mm/wk; p .003), while children in the SSRI-using group did not. Both groups showed a reduction in fetal head circumference, more pronounced in SSRIs exposed children (−0.18 mm/week; p .003).						
Dubnov-Raz 2012[37]	SRIs	Prospective cohort	40	40	Sheba Medical Center	growth parameters
Results: No differences regarding bone density, but infants exposed to SSRIs had a smaller head circumference (33.8±1.2 vs 34.4±1.1 cm, p=0.005).						

ADs: antidepressants; SSRIs: selective serotonine reuptake inhibitors; SRIs: serotonine reuptake inhibitors (includes SSRIs and venlafaxine); Other ADs: other antidepressants except SSRIs and tricyclics; TCAs; tricyclics antidepressants

SPONTANEOUS ABORTION

Spontaneous abortion is a common adverse pregnancy outcome, estimated to occur in up to 15% of all viable pregnancies, but is difficult to estimate the precise incidence, as it is usually unknown when conception occurred. For example, early pregnancy losses are more frequent but could be misidentified as a delayed menstrual period if a woman is unaware of being pregnant (14).

Recently, two studies designed specifically to evaluate this outcome (38, 39) found an increased risk of spontaneous abortion in those women who received antidepressants. Despite differing methodology, results were similar in both studies. However, the major limitation is that neither group was able to effectively control for maternal depression. Former studies included miscarriage as secondary outcome (40-45) and found no increased risk except for bupropion (43) (Table 2). In summarizing the data on spontaneous abortion, there does appear to be a small but significantly increased risk for spontaneous abortion associated with antidepressant use in early pregnancy.

POOR NEONATAL ADAPTATION SYNDROME (PNAS)

Exposure to an SSRI during pregnancy has been associated with neonatal symptoms including: jitteriness, difficulty feeding, respiratory problems, low blood sugar, and neurological symptoms (sleep disturbances and increased motor activity) (46) and it was unclear if this was the consequence of withdrawal or toxicity. In 2005, a report (47) documented an association between third trimester SSRIs exposure and neonatal signs described as "withdrawal syndrome" (convulsions, irritability, abnormal crying and tremor). Furthermore, gastrointestinal and neurological signs could also represent withdrawal, as they are similar to those described in adults following discontinuation of SSRIs treatment, while respiratory difficulties appear to be related with toxicity as observed in animal models (48). Subsequently, further studies have since been published reporting on varying degrees of these symptoms (49-57) (Table 3). In summarizing the data regarding this outcome, the occurrence of these symptoms has been reported to be from 10-30%, with no apparent dose response. Most importantly, the symptoms resolve within a week with no apparent long term adverse effects.

Table 2. *Spontaneous Abortion (SA)*

First author and year	Drugs studied	study design	Exposed n	Comparison group n	Source of data	Primary outcome
Pastuzsak 1993[40]	Fluoxetine TCAs	Prospective cohort	Fluoxetine = 128 TCAs = 74	Controls = 128	TIS Motherisk Program	Malformations, miscarriage
Results: Fluoxetine exposed had a nonsignificant risk for miscarriage when compared with women exposed to nonteratogens (RR 1.9 [0.92 -3.92]). The rate of miscarriages in the fluoxetine group was comparable with the TCAs group (13.5% and 12.2% vs 6.8% in the nonteratogens).						
Kulin 1998[41]	SSRIs	Prospective cohort	267	267	TIS Canada and USA	Malformations miscarriage
Results: No differences in miscarriage						
Einarson 2001[42]	Venlafaxine SSRIs	Prospective case-control	Venlafaxine = 150	SSRIs = 150 Nonteratogens controls = 150	TIS Motherisk	Malformations, miscarriage
Results: No differences in miscarriage (12% exposed versus 7% non-exposed, p .24)						
Chun-Fan-Chan 2005[43]	Bupropion Other ADs	Prospective cohort	Bupropion = 91	Other ADs = 89 Nonteratogens controls = 89	TIS Motherisk	Pregnancy outcomes
Results: Bupropion exposure had more miscarriages compared to non teratogenic exposures (14.7% vs. 4.5%, p 0.009), but similar to other AD						
Sivojelezova 2005[44]	Citalopram	Prospective cohort	132	Other ADs = 132 Nonteratogen controls = 132	TIS Motherisk Program	Birth outcomes
Results: No differences in miscarriage: 11% vs 10% for other SSRIs and 10% for non teratogenic exposure						
Djulus 2006[45]	Mirtazapine	Prospective case-control	Mirtazapine exposed = 104	Other AD = 104 Nonteratogens controls = 104	TIS from Canada, Israel, Italy, UK and Australia	Abortions, pregnancy outcomes
Results: No significant differences in miscarriages (19% vs 17% other AD and 11% for controls)						
Einarson 2009[38]	SSRIs SNRIs Other ADs	Prospective cohort	937	937	TIS Motherisk Program	Spontaneous abortion
Results: Increased risk of SA in those women who received antidepressants (RR 1.63 95% CI 1.24-2.14), representing a rate of 13% in exposed vs. 8% in the unexposed						
Nakhai-Pour 2010[39]	SSRIs SNRIs TCAs Other ADs	Nested case-control	Cases = 5124	Controls = 51240	Administrative database (Canada)	Spontaneous abortion
Results: Out of 5124 cases of SA, 5.5% of the women had at least one prescription of antidepressants during pregnancy, compared with 1401 (2.7%) of controls (OR 1.68 95% CI 1.38-2.06).						

SSRIs: selective serotonine reuptake inhibitors; SNRIs: serotonine and noradrenaline reuptake inhibitors; Other ADs: other antidepressants except SSRIs and tricyclics; TCAs; tricyclics antidepressants

PERSISTENT PULMONARY HYPERTENSION (PPHN)

Persistent pulmonary hypertension of the newborn is defined as a failure of the normal relaxation in the fetal pulmonary vascular bed during the circulatory transition. This occurs shortly after birth, with varying degrees of severity, in approximately 2-6 cases per 1,000 live births (58). It is a syndrome characterized by marked pulmonary hypertension that causes right-to-left extra-pulmonary shunting of blood (59).

There have been six published studies reporting on the possible association with an increased risk for PPHN associated with antidepressant use in late pregnancy (28, 60-64) (Table 4). However, because of small sample sizes and quality issues in studies, the absolute risk cannot be determined, although it is probably less than 1%. It also appears that other factors such as performing a caesarean section, may play a larger role than SSRI use (60).

QTc PROLONGATION IN THE NEWBORN

Prolongation of the QT interval is a risk factor for malignant arrhythmias and sudden death with some researchers examining the possibility that unknown, symptom free and untreated QTc prolongation in the newborn may result in the sudden death of a seemingly healthy adolescent (65). There is only one study reporting on this outcome, where researchers performed electrocardiograms on 52 newborn infants exposed to SSRIs in utero as well as 52 healthy control newborns and the two groups were matched for gestational age (66). The mean QTc was significantly longer in the group of newborns exposed to antidepressants as compared with control subjects (409 +/- 42 vs 392 +/- 29 milliseconds). Five (10%) newborns exposed to SSRIs had a markedly prolonged QTc interval (>460 milliseconds) compared with none of the unexposed newborns. However, all of the

Table 3. *Poor Neonatal Adaptation Syndrome (PNAS)*

First author and year	Drugs studied	Study design	Exposed n	Comparison group n	Source of data	Primary outcome
Chambers 1996[16]	Fluoxetine	Prospecti-ve cohort	228	254	TIS California	Neonatal adaptation
Results: Third trimester had higher rates admission to special-care nurseries (RR 2.6; 95% CI 1.1-6.9), and poor neonatal adaptation, including respiratory difficulty, cyanosis on feeding, and jitteriness (RR 8.7; 95% CI 2.9-26.6)						
Costei 2002[49]	Paroxetine	Prospecti-ve cohort	3rd trimester exposure = 55	1st/2nd trimester exposure = 27 Nonteratogens controls = 27	TIS Motherisk Program	Discontinuation syndrome in neonates
Results: Neonatal complications (respiratory distress, hypoglycemia, jaundice) more frequent in third trimester exposed (p .03). Only third trimester exposure associated with neonatal distress (OR 9.53 [1.14-79.1])						
Casper 2003[50]	SSRIs	Prospecti-ve cohort	Children of depressed mothers using SSRIs = 31	Children of depressed mothers not using SSRIs = 13	Women's Wellness Clinic	Bayley Scales of Infant Development Birth outcomes
Results: No significant differences on most birth outcomes and follow-up measures. SSRIs exposed infants had low 5 min APGAR score (p<.00)						
Laine 2003[51]	Citalopram Fluoxetine	Prospecti-ve cohort	20	Non-exposed = 20	Outpatients	Neonatal symptoms and cord blood monoamine concentration
Results: SSRIs exposed neonates had lower APGAR score at 15 min (p .02), lower cord blood 5HIAA concentrations (p .02) and more serotonergic symptom score during first 4 days after born (p .008). No differences at 2 weeks and 2 months.						
Zeskind 2004[52]	SSRIs	Prospecti-ve cohort	17	Non-exposed = 17	Carolinas Medical Center (USA)	Neonatal behavior, motor activity
Results: Exposed neonates were more tremorous (p .038), had less changes in behavioral states (p .05), fewer different behavioral states (p .009) and more periods of active (REM) sleep (p .001), compared with non-exposed newborns.						
Sivojelezova 2005[44]	Citalopram	Prospecti-ve cohort	132	Other ADs = 132 Nonteratogen controls = 132	TIS Motherisk Program	Birth outcomes
Results: Increased risk for NICU admission (RR 4.2 [1.71-10.26]). No further differences in other outcomes						
Malm 2005[53]	SSRIs	Prospecti-ve cohort	SSRIs purchases = 1782 (1, 2 and 3 trimester)	Matched Controls = 1782	Administrative database (Finland)	Treatment in SCU or NICU
Results: compared with infants exposed only during the 1st trimester, exposed in the 3rd trimester were more often treated in SCU or NICU (P .009, adjusted OR 1.6, [1.1-2.2])						
Levinson-Castiel 2006[46]	SRIs	Prospecti-ve cohort	SRIs exposed = 60	Non exposed = 60	Tertiary care center	Neonatal abstinence symptoms (Finnegan Score)
Results: Abstinence symptoms in 18 exposed neonates vs. no controls						
Maschi 2008[23]	SSRIs TCAs	Prospecti-ve cohort	Paroxetine = 58 Fluoxetine = 32 Amitriptyline = 26	Non exposed = 1200	Drug and Health Information Centre, Italy	Neonatal adverse events and SCU admission rate
Results: No differences in PNAS or admission to SCU.						
Boucher 2008[54]	SSRIs SNRIs TCAs Other ADs	Case - control	AD exposed = 73	Non exposed controls = 73	secondary and tertiary care facilities	adverse effects on the neonates
Results: Exposed neonates had increased risk of alertness alteration (OR 37 [8–174]), altered muscular tone (OR 20 [5–71]), feeding and GI problems (OR 3.8 [1.7–8.1]), tachypnea (OR 2.5 [1.1–5.3]), and neurological problems (8/73 vs 0/73; P .006).						
Lund 2009[24]	SSRIs alone or in combination	Prospecti-ve cohort	SSRIs = 329	Positive psychiatric history/No SSRI Use = 4902 No Psychiatric History = 51 770	Aarhus Birth Cohort (Denmark)	5-minute Apgar score, and admission to NICU.
Results: SSRIs exposed neonates had increased risk for NICU admissions (adjusted OR 2.39; 95% CI, 1.69-3.39 vs. control group, and OR 2.04; 95% CI, 1.42-2.94 vs. infants of mothers with psychiatric history) and for low 5 min APGAR scores (adjusted OR, 4.44; 95% CI, 2.58-7.63 and adjusted OR, 6.58; 95% CI, 3.39-12.74, respectively).						

First author and year	Drugs studied	Study design	Exposed n	Comparison group n	Source of data	Primary outcome
Reis 2010[28]	Tricyclics SSRIs SNRIs	Prospecti-ve	14821 women and 15017 neonates (3 exposure groups: early, late and both)	1 062 190 women with 1 236 053 infants in the population	Swedish Birth Registry	Infant neonatal diagnoses
Results: Increased neonatal complications in late vs. early exposure and higher with both exposures: hypoglycaemia (OR 1.56 [1.36–1.79]), respiratory diagnoses (OR 1.65 [1.46–1.85]) and low Apgar score (OR 2.34 [1.96–2.79]). The OR is significantly increased for these outcomes primarily after the use of TCAs but also of SNRIs and SSRIs. Increased risk for jaundice after the use of TCAs and SNRIs.						
Casper 2011[55]	SSRIs	Prospecti-ve cohort	Whole pregnancy exposure = 23	1st trimester exposure = 14 2nd/3rd trimester exposure = 18	Women's Clinic at Stanford University	Pregnancy outcomes
Results: Increased length of prenatal exposure to SSRIs was associated with low APGAR scores at 1 and 5 min (OR 3.0 [CI 1.2, 7.8] and 5.2 [CI 1.0,26.8] respectively) and specifically on activity subscale (OR for a low score (<2) on this scale were 3.8 and 6.0 at 1 and 5 min, respectively). Also, longer exposure associated with more admission to NICU (p<.03)						
Kallen 2012[56]	Central nervous system (CNS) active drugs	Prospecti-ve	15045 live born infants of mothers who redeemed prescription of CNS-active drugs during 2nd/3rd trimester	Rest of the population	Swedish Birth Register and the Prescribed Drug Register (between 2006-2008)	Neonatal symptoms
Results: Increased risk of neonatal symptoms in newborns of mothers receiving various types of CNS-active drugs, used alone: respiratory diagnoses (OR, 1.51; 95% CI, 1.41-1.63), hypoglycemia (OR, 1.49; 95% CI, 1.36-1.63) and low Apgar score (OR, 1.33; 95% CI, 1.17-1.53), more marked with benzodiazepines. The OR for any neonatal symptom after maternal use of only an SSRI was 1.82 (95% CI, 1.62-2.05), and after use of SSRI combined with 1 or more other drug was higher (OR, 2.46; 95% CI, 2.06-2.93).						
Hayes 2012[34]	SSRIs SNRIs TCAs Other ADs	Retrospec-tive cohort	Depressed with 1-2 prescriptions = 10,700 Depressed >3 prescriptions = 6196	Not classified as depressed = 195,079 Depressed, no prescriptions = 16,901	Administra-tive database (Tennesse-Medicaid)	Respiratory distress and convulsions
Results: Respiratory distress was 1.1 (95% CI, 0.9 –1.3), 1.4 (95% CI, 1.1–1.8), and 1.6 (95% CI, 1.2–2.0) times more common among infants born to women who filled 1, 2, and 3 prescriptions during the second trimester						
Grzeskowiak 2012[33]	SSRIs	Retrospec-tive cohort	With SSRIs prescriptions and psychiatric illness = 221	No prescriptions, no psychiatric illness = 32004 No prescriptions, psychiatric illness = 1566	Administrative databases (Australia)	Neonatal hospitalization and length of hospital admission
Results: Infants of women with pregnancy prescription of SSRIs had a twice increased risk of admission to hospital (adjusted OR, 1.92; 95% CI, 1.39-2.65), and length of hospital stay longer than 3 days (adjusted OR, 1.93; 95% CI, 1.11-3.36) compared with infants of mothers with psychiatric illness but no SSRI use during pregnancy, who had only an slight increased risk of neonatal hospital admission (adjusted OR, 1.21; 95% CI, 1.07-1.38).						
Smith 2012[57]	SSRIs	Prospecti-ve cohort	No pregnancy depression, SSRIs use 3rd trimester = 6	No pregnancy depression, no SSRIs use = 61	Yale Pink and Blue cohort	Neonatal outcomes and behavior, sleep, motor activity
Results: Exposed newborns had shorter gestational age (1 week, p .02), lower 5 min APGAR score (p .01) and less motor activity, with marginal difference (p .05). No differences were found in sleep patterns.						

SSRIs: selective serotonine reuptake inhibitors; SNRIs: serotonine and noradrenaline reuptake inhibitors; Other ADs: other antidepressants except SSRIs, SNRIs and tricyclics; TCAs; tricyclics antidepressants. SCU: special care unit. NICU: neonatal intensive care unit

drug-associated abnormalities normalized in subsequent electrocardiographic tracings. The authors concluded that "although these infants were free of serious adverse effects, additional research is necessary to determine whether antenatal use of SSRIs is associated with malignant arrhythmias in the first days of life."

LONG-TERM NEURODEVELOPMENT

The use of antidepressants medications throughout pregnancy exposes the fetal brain at a time of maximum central nervous system (CNS) development, therefore may potentially influence neurotransmitter binding in an immature brain. Long-term outcomes could be influenced not only by serotonergic but also by dopaminergic and noradrenergic neurotransmitter systems, such as attention, impulse control, aggression, affect regulation, cognition and motor performance (67).

There remains a paucity of studies examining neurodevelopmental outcomes of children exposed to prenatal use of antidepressants, probably due to the numerous methodological issues associated with conducting these types of studies (68-76) (Table 5). In summarizing the data, despite these limitations, the majority of studies found no

Table 4. *Persistent Pulmonary Hypertension of Neonate (PPHN)*

First author and year	Drugs studied	study design	Exposed n	Comparison group n	Source of data	Primary outcome
Chambers 2006[61]	Fluoxetine	Nested case-control	infants with PPHN = 377	Matched controls = 839	Slone Epidemiology Center Birth Defects Study	PPHN
Results: Maternal use of SSRI after week 20 associated with PPHN (OR 6.1 [2.2–16.8]) Absolute risk with SSRI use in late pregnancy: 6 – 12 per 1000.						
Andrade 2009[62]	SSRIs	Retrospective cohort	Exposed = 1104	Matched controls = 1104	Medical records	Prevalence of PPHN
Results: Similar prevalence exposed vs. non exposed (2.14 per 1000 vs. 2.72 per 1000)						
Wichman 2009[63]	SSRIs	Retrospective cohort	Exposed = 808 (53 in 3rd trimester, 119 in 2nd and 3rd trimester)	Non exposed = 24406		PPHN
Results: No increased risk for PPHN in SSRIexposed infants						
Reis 2010[28]	TCAs SSRIs SNRIs	Prospective	14821 women and 15017 neonates, early and late exposure	1 062 190 women with 1 236 053 infants in the population	Swedish Birth Registry	Neonatal diagnoses
Results: PPHN in late pregnancy exposure RR 2.56; [1.17– 4.85]. Early exposure RR 2.30 [1.29– 3.80].						
Wilson 2011[60]	SSRIs	Case-control	20 cases	Case/Controls ratio 1:6	Madigan Army Medical Center	PPHN
Results: cesarean delivery (CD) prior to the onset of labor increased the risk for PPHN: OR 4.9 [1.7-14.0]						
Kieler 2012[64]	SSRIs	Retrospective population-based cohort	SSRIs exposed = 30115	All birth in population	National Health registries from Denmark, Finland, Iceland, Norway, and Sweden	PPHN
Results: PPHN OR 2.1 [1.5-3.0], similar for each type of SSRIs.						

SSRIs: selective serotonine reuptake inhibitors; SNRIs: serotonine and noradrenaline reuptake inhibitors; TCAs; tricyclics antidepressants

Table 5. *Neurodevelopment*

First author and year	Drugs studied	study design	Exposed n	Comparison group n	Source of data	Primary outcome and measurement
Nulman 1997[68]	TCAs Fluoxetine	Prospective cohort	TCAs = 80 Fluoxetine = 55	Non-exposed controls = 84	TIS Motherisk Program	Bayley Scales of Infant Development, McCarthy Scales of Children's Abilities, Reynell Developmental Language Scales.
Results: No differences were seen in terms of IQ and language in infants between 16 and 86 months of age exposed during at least the first trimester						
Nulman 2002[69]	TCAs Fluoxetine	Prospective cohort	TCAs = 46 Fluoxetine = 40	Non-exposed controls = 36	TIS Motherisk Program	Bayley Scales of Infant Development, McCarthy Scales of Children's Abilities and Reynell Developmental Language Scales.
Results: No significant differences in IQ, language, behavior and temperament in infants between 15 and 71 months of age after controlling for maternal illness. Negative association between maternal depression and IQ, and number of postnatal depressive episodes and language.						
Casper 2003[50]	SSRIs	Prospective cohort	Children of depressed mothers using AD = 31	Children of depressed mothers not using AD = 13	Women's Wellness Clinic	Bayley Scales of Infant Development Birth outcomes
Results: No significant differences on most birth outcomes and follow-up measures. SSRIs exposed infants had low scores on psychomotor development index (p. 02) and motor quality (p. 05).						
Oberlander 2004[70]	SSRIs	Prospective cohort	46	Non-exposed controls = 23	British Columbia Women's Hospital	Bayley Scales of Infant Development at 2 and 8 months
Results: No developmental differences in infants exposed to SSRIs during the 2nd and 3rd trimester compared to unexposed, and also between those with or without transient neurobehavioral symptoms at birth						
Misri 2006[71]	SSRIs	Prospective cohort	Children of anxious/ depressed mothers medicated = 22	Non-exposed controls = 14	British Columbia Women's Hospital	Child Behavior Checklist and Child-Teacher Report Form
Results: No differences in childhood internalizing behavior at age 4 between exposed or unexposed children. Increased parental reports of child internalizing behaviors associated with maternal symptoms of depression ($F=5.43$, $df=1,36$, $p<0.05$) and anxiety ($F=6.88$, $df=1,36$, $p<0.05$).						

First author and year	Drugs studied	study design	Exposed n	Comparison group n	Source of data	Primary outcome and measurement
Oberlander 2007[72]	SSRIs	Prospective cohort	Children of anxious/ depressed mothers medicated = 22	Non-exposed controls = 14	British Columbia Women's Hospital	Child Behavior Checklist and direct observations
Results: No differences in externalizing behavior in exposed vs non-exposed. More report of internalizing behaviors in mothers with higher levels of stress, anxiety, and depressed mood.						
Pedersen 2010[73]	ADs	Prospective cohort	407 infants exposed to SSRIs 479 infants of untreated depressed mothers	79189 infants of non-depressed untreated mothers	Danish National Birth Cohort	Developmental milestones at 6 and 19 months reported by the mother
Results: Children with second- or third-trimester exposure to antidepressants were able to sit 15.9 days (95% CI 6.8 –25.0) and to walk 28.9 days (95% CI: 15.0–42.7) later than children of women not exposed to ADs but still within the normal range of development.						
Klinger 2011[74]	SSRIs	Prospective cohort	Children with PNAS (30) vs. children without (52)		Schneider Children's Medical Center of Israel	Neurodevelopmental evaluation at the age of 2 to 6 years
Results: No difference in mean cognitive ability (106.9±14.0 vs 100.5±14.6, P 0.12) and developmental scores (98.9±11.4 vs 95.7±9.9, P 0.21). PNAS associated with increased social-behavior abnormalities (OR 3.03, P 0.04) and advanced maternal age (OR 1.12, P 0.04).						
Galbally 2011[75]	ADs	prospective case-controlled	22	Non exposed controls = 19	Mercy Hospital for Women and private psychiatrists	Bayley Scales of Infant Development at 23.09 (SD 3.82) months (control) and 28.53 (SD 6.22) months (exposed)
Results: Children exposed to ADs in pregnancy scored lower on motor subscales in particular on fine motor scores than non-exposed children without statistical significance. No association found between maternal depression and neurodevelopment.						
Casper 2011[55]	SSRIs	Prospective cohort	Whole pregnancy exposure = 23	1st trimester exposure = 14 2nd/3rd trimester exposure = 18	Women's Clinic at Stanford University	Bayley Scales of Infant Development at 14 months
Results: Longer SSRIs exposure associated with increased risk for lower Psychomotor Developmental Index and Behavioral Rating Scale scores in infancy (p=0.012 and p=0.007, respectively)						
Croen 2011[76]	ADs	Population-based case-control study	298 case children with ASD	1507 randomly selected control children	Medical records	Autism spectrum disorders (ASD)
Results: increased risk of ASD associated with treatment with SSRIs by the mother during the year before delivery about 3%. No increase risk for mothers with history of mental health treatment in the absence of prenatal exposure to SSRIs.						

ADs: antidepressants; SSRIs: selective serotonine reuptake inhibitors; TCAs; tricyclics antidepressants. PNAS: poor neonatal adaptation symdrom

differences between those exposed and the controls on any of the neurodevelopmental outcomes that were measured.

CONCLUSION

Following an extensive review of the literature, in order to evaluate whether antidepressants are associated with adverse pregnancy and infant outcomes, excluding major malformations, we did not find appreciable increases in any of the outcomes we examined. We did not find an overall increased risk associated with low birthweight, small for gestational age or long-term neurodevelopemental adverse outcomes. However, there does appear to be a significantly increased risk for spontaneous abortion, preterm birth and infants born less than 2,500 gm. In addition, a possible increased risk for Persistent Pulmonary Hypertension of the Newborn (PPHN) and evidence of Poor Neonatal Adaptation Syndrome (PNAS) following use in late pregnancy. The observed risks were of a very low magnitude and the clinical significance of these results is unknown. When a woman suffers from depression during pregnancy, this information will assist her and her health care provider when weighing the benefits and/or risks of treatment with an antidepressant. It should be kept in mind when making this important decision, that untreated depression is also associated with adverse effects on the infant. Many of those effects have been associated too with antidepressants expo-

sure. Further research needs to be conducted where it is possible to control for maternal depression, in order to evaluate whether these adverse events are due to the underlying maternal illness, the antidepressant, or possibly a combination of both.

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