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Antidepressant Use in Pregnant and Postpartum Women

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Abstract

Women in their reproductive years are at increased risk of experiencing depressive and anxiety disorders. As such, it is likely that pregnant women will undergo treatment with antidepressants. We review the risk of adverse pregnancy outcomes and perinatal and neonatal complications of the offspring related to in utero exposure to antidepressants. The literature shows that antidepressant exposure is associated with fetal growth changes and shorter gestations, although effects are small. There are a number of reports of transitory neonatal signs after exposure to antidepressants. No specific pattern of malformations has been consistently associated with antidepressants, with the possible exception of paroxetine and cardiac malformations. There is inconclusive evidence of a link between antidepressants in late pregnancy and persistent pulmonary hypertension in the newborn. While antidepressant use in pregnancy is well studied, confounding factors that can adversely affect pregnancy and birth outcomes may contribute to some of the findings.

Keywords

Pregnancy; Antidepressants; Serotonin Reuptake Inhibitors; Tricyclic Antidepressants; Adverse Effects

INTRODUCTION

Approximately 20% of women are at risk of developing a depressive disorder and 30% may experience the onset of an anxiety disorder at some point in their lives (Kessler et al 1994). The period of greatest risk for development of a mood or anxiety disorder is between adolescence and menopause. Thus, it is likely that pregnant women will be diagnosed and

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undergo treatment with a psychotropic medication to ameliorate symptoms of one of these conditions (Vesga-Lopez et al 2008). Epidemiological data show that over 50% of women will take a prescription medication in pregnancy, and the most frequently used class of agents is the selective serotonin reuptake inhibitors (SSRIs) (Mitchell et al 2011). In general, data with regard to the risk of prescription medication use in pregnancy tends to be limited. However, this is not true for SSRIs and some serotonin-norepinephrine reuptake inhibitors (SNRIs), which now enjoy a substantial database. This review provides an overview on the use of antidepressants in pregnancy and the potential risks and benefits to mothers associated with use of these pharmacological treatments.

It should be noted at the outset that for unipolar mood disorders, and anxiety disorders, pharmacotherapy is not the only efficacious option. Indeed, many individuals, including pregnant women, will find relief from treatment with an empirically-based psychotherapy (Yonkers et al 2009). Additionally, some women may spontaneously improve from an episode of illness. On the other hand, there are women for whom psychotherapy is not sufficiently efficacious or acceptable, who may require pharmacotherapy to stay well. For this group of individuals, treatment is neither cosmetic nor optional and thus needs to be evaluated carefully.

A number of different outcomes to both mother and her children are relevant for pregnant women. Accordingly, this review focuses on exposure to an SRI in pregnancy and risk of: spontaneous abortion, fetal malformation, fetal demise, preterm birth, small for gestational age (and related metrics of low birth weight and intrauterine growth retardation), as well as perinatal and neonatal complications to the offspring.

METHODS

We searched the following databases for relevant studies: MEDLINE (OvidSP 1946–January Week 4 2013), Embase (OvidSP 1974–2013 February 11), PsycINFO (OvidSP 1967 to January Week 5 2013), Cochrane Library (Wiley Online). All searches were conducted on February 5, 2013 except for Embase, which was conducted on February 12, 2013 and was updated in July of 2013. The search strategies used controlled vocabulary terms and synonymous free text words to capture the concepts of antidepressants and pregnancy/postpartum depression. The search strategy was not limited by study design or language of publication. The full strategy is available from the authors. We examined the reference lists of all included articles to identify further articles.

In our review and when available, we focused on large epidemiologic studies that were published in English. The nature of the database meant that the studies reviewed are largely observational studies rather than clinical trials. Smaller studies and mechanistic studies were cited when necessary to provide background or additional information. Rather than limit the review to stronger studies only (e.g. those that attempted to control for confounding), we point out limitations of selective studies alongside the results of those reports.

EPIDEMIOLOGY OF ANTIDEPRESSANT USE, UNIPOLAR MOOD DISORDERS AND ANXIETY DISORDERS IN PREGNANCY

The overall use of prescription medication by pregnant women has increased steadily over the past three decades. In the United States, antidepressant treatment in pregnancy has shown a particularly dramatic increase from 2% in 1996 to over 7% by 2008 (Andrade et al 2008, Mitchell et al 2011). The antidepressants taken most frequently were the SSRIs; sertraline and fluoxetine were among the top 20 prescription medications taken in in the first trimester of pregnancy during the years 1997–2003 (Mitchell et al 2011). The pattern of antidepressant use across pregnancy is variable. The peak prevalence for antidepressant use occurs in the first trimester, probably because a number of women who are undergoing treatment unexpectedly become pregnant. Treatment decreases in the second trimester and increases again around the time of delivery (Andrade et al 2008, Hayes et al 2012).

It is not likely that the risk of a unipolar mood disorder differs across pregnancy although studies are not consistent on this issue. The largest systematic quantitative review found overlapping confidence intervals for point prevalence rates of minor and major depressive disorder (MDD) during the three trimesters of pregnancy (Gavin et al 2005). This same systematic review showed similar rates of minor depressive disorder and MDD among pregnant and postpartum women. A large, retrospective epidemiological study did not find substantial differences between pregnant and non-pregnant women with regard to risk for mood and anxiety disorders although the risk of unipolar MDD was slightly higher in postpartum women (Vesga-Lopez et al 2008). Of note, some population-based linked health data (Munk-Olsen et al 2006) document a lower risk of seeking treatment for a mood or anxiety disorder in pregnancy as compared to the year after pregnancy. Whether pregnant women have lower rates of illness or are less comfortable seeking care, cannot be discerned from such data. Certainly, a reluctance to take psychotropic medication during pregnancy is likely to reduce psychiatric treatment seeking in pregnancy.

There is a small and discrepant literature with regard to the risk of depressive relapse in pregnancy. A five-fold higher rate of relapse was found in one multicenter study that investigated the risk of relapse for women with recurrent MDD after discontinuation of antidepressant treatment (Cohen et al 2006), while another study found no increased risk of relapse (Yonkers et al 2011). In all likelihood, differences in the severity of illness at least partially explain the differences in risks: women with severe, recurrent MDD, particularly if they have been euthymic for less than 6 months, were at risk of relapse (Yonkers et al 2011) and antidepressant discontinuation with this high risk group may worsen the prognosis (Cohen et al 2006). Women with mild illness may be able to stop medication during pregnancy without experiencing a new episode of illness (Yonkers et al 2011). There is insufficient information with regard to the risk of and course for anxiety disorders if medication is discontinued in pregnancy.

Associations between maternal use of antidepressants in pregnancy and adverse birth, or other perinatal complications, need to be placed into context in order to appreciate the limitations that on what can be inferred. Confounding may be related to maternal psychiatric illness, which is not frequently available in large data sets. When information is available, it

is typically in the form of medical billing diagnosis codes or dimensional symptom measures. As well, maternal health habits such as smoking, illicit drug and alcohol use, poor prenatal care and obesity can confound birth outcomes (Yonkers et al 2009). Use of drugs and alcohol are not always accurately reported in registries or by self-report. This is particularly important because women who take antidepressants are also more likely to have poor health habits (eg smoking and alcohol use), to be older, to be consumers of other prescription medication and to have elevated body mass index (Hayes et al 2012, Reis & Kallen 2010). They are also more likely to have complications such as diabetes and hypertension (Reis & Kallen 2010). Thus, analyses that do not consider these confounders need to be interpreted with caution.

SPONTANEOUS ABORTION

An accepted epidemiological definition of spontaneous abortion, or miscarriage, is the spontaneous termination of pregnancy prior to 20 weeks gestation(22 weeks from the last menstrual period), or before the fetus has achieved 500 grams (Lawn et al). Legal definitions of abortion may vary by state. The vast majority (~80%) of spontaneous abortion occurs by 12 weeks gestation with rate estimates of about 30%(Cunningham et al 2010a). Early spontaneous abortion is difficult to determine because perhaps as many as two-thirds are “clinically silent.” The risk of spontaneous abortion increases with age, parity and prior miscarriage as well as certain chronic medical conditions and environmental exposures. However, most early spontaneous abortion is the result of chromosomal abnormalities (Cunningham et al 2010a). A cautionary note with regard to the source of the data relates to self-report information. Participants who provide outcome data may state that they experienced a spontaneous rather than a voluntary termination of pregnancy because of the stigma associated with the latter. Voluntary terminations occur to a higher degree among women who take antidepressant agents (Chambers et al 1996, Einarson et al 2009).

Studies that evaluated risk of spontaneous abortion as it relates to antidepressant exposure largely focus on late events, which are much less frequent than early spontaneous abortion. Recruitment procedures heavily influence the ability of a study to show differences in spontaneous abortion rates since events decrease as pregnancy progresses. In an earlier meta-analysis of six small studies (Hemels et al 2005), rates of spontaneous abortion ranged from 11% to 15% among women who took antidepressants (SSRIs, SNRIs and tricyclic antidepressants (TCAs)) as compared to 7% to 11% among women who did not take antidepressant agents. Given the nature of the data, psychiatric illness status was unknown. The adjusted odds ratio (OR) was 1.36 (95% confidence interval (CI) of 1.15–1.61) and did not differ substantially among the classes of antidepressant agents. This netted a number needed to treat to harm of 26. All of the studies that contributed to this meta-analysis were derived from teratogen information services, including two-thirds from the Toronto Motherisk service. Similar rates and risks of spontaneous abortion were found by Einarson and colleagues (Einarson et al 2009) in a subsequent report from the Motherisk program.

Further replicating the risk level associated with antidepressant use in pregnant women was the rate of clinically recognized spontaneous abortion found in a nested case cohort study that was derived from population-based linked health data in Quebec (Nakhai-Pour et al

2010). This data-base included 69,742 women, of whom 5124 (7.3%) experienced a clinically recognized spontaneous abortion. Information was available on diagnostic codes and medication that was dispensed. On average, miscarriage events occurred at about 10 weeks of gestation. Women who took antidepressant agents were 68% more likely to experience spontaneous abortion (95% CI=1.38–2.06). They were also more likely to have a spontaneous abortion if they had a depressive disorder diagnosis (OR=1.19; 95% CI= 1.03–1.38). Multiple different antidepressants (OR= 3.51; 95% CI= 2.20–5.61) as well as higher dosages of paroxetine or venlafaxine were associated with spontaneous abortion. Although these data were controlled, the use of administrative databases precluded detection of earlier pregnancies and did not provide data on smoking, recreational drug use or obesity, all of which are risk factors for spontaneous abortion.

Summary

The results of these studies suggest that use of antidepressant in early pregnancy is associated with a modestly elevated risk of clinically recognized spontaneous abortion. They are consistent with results of several recent meta-analyses (OR=1.87; 95% CI=1.5–2.33) (Nikfar et al 2012b) and (OR=1.45; 95% CI=1.22–1.72) (Ross et al 2013) that found a modest elevation in risk of spontaneous miscarriage with antidepressant treatment. However, confounding as a result of unmeasured or incompletely measured health factors such as prior pregnancy loss, obesity, substance abuse, etc, may confound the findings.

FETAL DEATH

Fetal death or “stillbirth” is listed in the International Classification of Disease as “death prior to the complete expulsion or extraction from its mother of a product of conception…” The fetus does not show signs of life and is greater than 22 weeks gestation and more than 500 gm (Lawn et al). Fetal death may occur in the early or late fetal stage (>1000 gm, greater than 28 weeks gestation and/or > 35 cm in length; i.e. third trimester fetal death); it may also occur before the onset of labor or during labor and delivery. Differences in operationalizing fetal death and collection of accurate information across and within countries, including the United States, make estimates of fetal death difficult. This is especially true for early fetal death. Rates of fetal death are higher in low income (eg. sub-Saharan Africa) as compared to high income countries. In high income countries, the rate of third trimester fetal death is approximately 5 per thousand (Lawn et al). About 6 out of every thousand women will experience either early or late stillbirth in the United States (Spong et al). Rates are twice as high (11.1/1000) for blacks as they are for non-Hispanic whites (4.8/1000) (Spong et al). General medical conditions such as diabetes, hypertension, obesity and autoimmune disorders occur at higher rates among women who have a stillbirth. These factors are also more common in women with depressive disorders.

We were unable to find data evaluating the possible association between fetal death and antidepressant use in the United States. However, large registries from other countries failed to find associations between antidepressant use and fetal death (Colvin et al 2012, Jimenez-Solem et al 2012, Stephansson et al 2013).

Summary

Data from the United States are limited and thus information is not available on associations between maternal antidepressant use and fetal death for ethnic and racial minority women in the United States. However, based upon other data, there is no association between fetal death and maternal antidepressant use in pregnancy.

CONGENITAL MALFORMATIONS

Congenital malformations are structural or functional abnormalities present at birth. Congenital malformations represent a spectrum from major malformations, resulting in death, impaired function, or serious cosmetic defect, to minor, which are common and do not result in impairment. The incidence of major congenital malformations is 2 to 3 percent, with heart defects the most common type (Cunningham et al 2010b). They can be due to genetic syndromes or due to factors in the intrauterine environment, although the precise etiology is known in only about 35% of cases. While exposure to specific medications during the first trimester of pregnancy is known to cause birth defects, it is thought that less than 1% of congenital malformations are due to the effects of medications (Cunningham et al 2010b). None the less, medications are an important cause of malformations as they are potentially modifiable risk factors. This section will review the data on the association of antidepressants and congenital malformations.

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) have been available since the 1950's, but are now second-line agents and used less commonly than the better tolerated SSRIs SNRIs and other newer generation antidepressants. None the less, they continue to be prescribed for treatment of mood and anxiety disorders as well as in the treatment of chronic pain. As would be expected of medications that are lipophilic and depend upon good central nervous system penetration, the placental passage of TCAs is substantial with one study finding that over 60% of maternal serum levels are transferred to the placental system (Loughhead et al 2006). Two large epidemiologic studies report the risk of congenital malformations after TCA exposure. Using a large United States-based health maintenance organization (HMO) database of 221 infants exposed to TCAs and 49,663 infants without antidepressant exposure, there was no increase in relative risk (RR) of congenital malformations (RR 0.86, 95% CI 0.57–1.30) after stratification for maternal age, season of birth, and HMO (Davis et al 2007). Results from a Swedish population-based linked health registry differ. The strengths of this database is that it includes detailed information on concurrent medication use, comorbid general medical conditions, as well as a wealth of information on delivery complications. Data on health habits (eg. cigarette smoking) are obtained from nurse interview at the beginning of pregnancy. The single time point for such information renders it somewhat limited, although prescription medication use can be ascertained longitudinally from medical records. Information on psychiatric illness or the indications for treatment have not been included in the database used by this group. Through analyses with this database, Reis et. al. (Reis & Kallen 2010) found a statistically significant increase in relatively severe malformations (adjusted OR=1.36; 95% CI 1.07–1.72) and any cardiovascular malformation (adjusted OR=1.63; 95% CI 1.12–2.36) after adjusting for

maternal age, parity, smoking, body mass index (BMI), and year of birth. Several smaller studies (Nulman et al 1997, Pastuszak et al 1993, Simon et al 2002) and a large case control study (Ramos et al 2008) did not demonstrate an association of major malformations with TCA exposure.

Selective Serotonin Reuptake Inhibitors

As with TCAs, SSRIs have good placental passage. (Hendrick et al 2003) There are numerous reports estimating the risk of congenital malformations after in utero exposure to SSRIs. Most large studies using national databases have not observed an elevation in the cumulative major malformation rate in association with SSRI exposure in pregnancy after adjusting for potential confounders (Colvin et al 2011, Davis et al 2007, Malm et al 2011, Pedersen et al 2009, Reis & Kallen 2010, Wen et al 2006). A dissenting report was from an analysis of a large Danish registry that found a small increase in the rate for malformations; this analysis included adjustment for maternal smoking status, age, parity, and year (OR 1.3; 95% CI 1.1–1.6) (Kornum et al 2010). Smaller studies that primarily used cohorts drawn from teratogen information services, are similar to the large national databases and do not show an effect of SSRI treatment on the overall major malformation rate (Einarson et al 2001, Kulin et al 1998, Simon et al 2002, Sivojelezova et al 2005, Wisner et al 2009).

Several studies analyzed the specific risk of cardiovascular malformations after exposure to SSRIs. Two large, well designed case-control studies failed to identify an association of SSRI exposure and congenital heart defects, including total (Louik et al 2007) or specific classes of heart defects (Alwan et al 2007). Studies of large population databases are more mixed, with the finding of a small increase in cardiovascular malformations in two studies (Colvin et al 2011, Kornum et al 2010), and three studies failing to observe an association of heart defects with SRI exposure (Malm et al 2011, Pedersen et al 2009, Reis & Kallen 2010). In a large single site study, there was no increase in overall heart defects after exposure to either SRI or venlafaxine (Wichman et al 2009). This study was drawn from the same Swedish registry used by Reis & Kallen.

A 2013 meta-analysis attempted to estimate the risk of congenital malformations and cardiovascular defects after exposure to antidepressants, which included all classes but were primarily composed of SRIs [Grigoriadis, 2013 #24186]. Due to concerns about variations in study quality, the authors created a tool to evaluate quality based on characteristics of the sample, control group, exposure and outcome measurements, follow-up and controlling for potential confounders. There was no statistically significant effect of antidepressant exposure on the relative risk (RR) of major congenital malformations (1.07; 95% CI, 0.99–1.17) when the analysis was restricted to studies that met the quality threshold. However, there was a small statistically significant risk of cardiovascular malformations (RR = 1.36; 95% CI, 1.08–1.71). This result persisted after limiting the analysis to studies reporting data adjusted for confounding. This finding was echoed by a second meta-analysis that included a larger number of studies with substantial heterogeneity (Nikfar et al 2012a).

Several other groups attempted to address the risk of congenital malformations after exposure to specific agents, rather than class of medications. Attention was drawn to paroxetine after the United States Food and Drug Administration responded to two studies

and increased the pregnancy risk category of paroxetine. Using a United States insurance database, Cole et. al. [Cole, 2007 #24044] reported that relative to other antidepressants, exposure to paroxetine was associated with an increase in all congenital malformations (OR 1.89; 95% CI 1.20–2.98), but not cardiovascular malformations (OR 1.46 95%CI 0.74–2.88), after adjustment for maternal age and comorbity, infant sex, specific medication exposures, and health care. This study is strengthened by the fact that the reference group was exposed to other antidepressants, rather than a comparator group not exposed to antidepressants. Thus, it is less likely to be plagued by selective confounding due to health habits or underlying illness as are studies with healthy comparator groups. The other study, using the Swedish registry, did not find an association with total malformations, but identified an increase in cardiovascular malformations (OR 1.63; 95% CI 1.05–2.53) (Kallen & Otterblad Olausson 2007) an update of this study continues to demonstrate a small, but significant increase in risk for paroxetine (OR 1.66; 95% CI 1.09–2.53) (Reis & Kallen 2010). The risk is mainly for ventricular and atrial septal defects.

Other large epidemiological studies have failed to observe an association of paroxetine with either total or cardiovascular malformations (Colvin et al 2011, Davis et al 2007, Kornum et al 2010, Malm et al 2011, Pedersen et al 2009). One case control study found an association of paroxetine with total malformations only at doses of paroxetine >25mg daily (OR 2.23; 95%CI 1.19–4.17) (Berard et al 2007); however other case-control studies did not find an association of paroxetine with total malformations(Ramos et al 2008) or cardiovascular malformations (Louik et al 2007). Meta-analytic reviews have attempted to address these conflicting results. A meta-analysis conducted by GlaxoSmithKline reported an increase in total malformations (OR 1.24; 95% CI 1.08–1.43) and cardiovascular malformations (OR 1.46; 95% CI 1.17–1.82) (Wurst et al 2010). The 2013 meta-analysis by Grigoriadis et. al., did not find an association of paroxetine with major malformations (RR 1.63; 95% CI 1.05–2.53), but did identify an increase in total cardiovascular malformations after paroxetine exposure (RR 1.63; 95% CI 1.05–2.53) [Grigoriadis, 2013 #24186].

As noted above, fluoxetine is one of the most commonly used antidepressants in pregnant women (Mitchell et al 2011). In large cohort studies, there was no effect of fluoxetine on total malformations (Colvin et al 2011, Malm et al 2011, Oberlander et al 2008, Pedersen et al 2009). Of these studies, only investigators who used a Finish administrative database found a significant effect of fluoxetine on cardiovascular malformations (OR= 1.40; 95% CI 1.01–1.95) (Malm et al 2011). Similarly, small studies from teratogen information services did not observe differences in total malformations(Chambers et al 1996, Nulman et al 1997, Pastuszak et al 1993), although one study did find a statistically significant increase in cardiovascular malformations (OR=4.47; 95% CI 1.31–15.27) (Diav-Citrin et al 2008). The meta-analysis by Grigoriadis also analyzed data for an effect of fluoxetine on malformations, finding an association with total malformations (RR=1.25; 95% CI 1.03–1.51), but not cardiovascular malformations (RR=1.33; 95% CI 0.92–1.90) (Grigoriadis et al, Grigoriadis et al 2013).

Other antidepressants

For venlafaxine, studies using the Swedish database, an administrative database from British Columbia, Canada, and a small teratogen information service-based study did not find an association with exposure on total and cardiovascular malformations (Einarson 2001, Oberlander et al 2008, Reis & Kallen 2010). However, a recent case-cohort analysis that specifically focused on venlafaxine reported associations between first trimester use and a number of malformations including anencephaly, cleft palate, gastroschisis and some cardiac malformations, which raises concerns (Polen et al 2013). It should be acknowledged that this report is based upon only a few cases in the population and the retrospective nature increases the possibility of recall bias.

Several important studies have assessed possible associations between bupropion and fetal malformations. Buproprion is FDA-approved for use in smoking cessation as well as for treatment of depression. Nicotine is a teratogen and clinicians actively counsel women to avoid smoking in pregnancy. Accordingly, bupropion may be administered to pregnant women to promote smoking cessation. Results from a teratogen information service did not demonstrate an effect of exposure of bupropion in utero on risk of malformations (Chun-Fai-Chan et al 2005). However, a case-cohort study from the National Birth Defects Prevention Study found an elevated risk (OR=2.6; 95% CI=1.2–5.7) of left outflow tract cardiac (Alwan et al 2010) defects. This particular study included adjustments for age, race, cigarette smoking, parity and muliti-gestation delivery. However, it excluded women with a depressive disorder who were not undergoing antidepressant treatment so it may have been limited in its ability to control confounding. In a report that compared other antidepressant agents to bupropion with reference to teratogenic risk, there was no elevation in malformations for offspring whose mothers took bupropion in pregnancy (Cole et al 2007b).

There is a paucity of studies evaluating the risk of malformations in association with in utero exposure to other antidepressants. Smaller studies did not find associations between malformations and mirtazapine (Djulus et al 2006), or trazodone and nefazodone (Einarson et al 2003).

Summary

The available data with regard to the risk of congenital malformations following exposure to antidepressants is dominated by information on SSRIs and to a lesser extent, venlafaxine. Many of the published reports conflict with regard to a possible association of SSRIs, and specifically paroxetine, with congenital malformations. The conflicting results are likely are result of differences in the cohorts under study and the power to detect differences in rare events; other studies reported multiple comparisons or had a limited ability to adjust for potential confounding. Registry studies are helpful in that they provide information on large numbers of participants but they often rely on data about prescriptions being filled and cannot confirm that antidepressants were actually taken. Despite these drawbacks, it is fair to say that SSRIs are not major teratogens (Greene 2007). The possible exception is paroxetine in that multiple reports link it with cardiovascular malformations and as reflected by the results of a 2013 meta-analysis (RR=1.63) (Grigoriadis et al, Grigoriadis et al 2013).

The severity of congenital malformations is subjective, and some cardiovascular defects resolve spontaneously with minimal functional impairment.

GESTATIONAL AGE AND PRETERM BIRTH

The most common parameter to assess gestational age is preterm birth although some research groups also report gestational age as a continuous outcome. Preterm birth is a useful outcome measure since it is linked to nearly two-thirds of neonatal deaths. In epidemiological terms, it is operationalized as a live birth occurring prior to 37 completed weeks of pregnancy. Studies use a variety of methods to date pregnancy including ultrasound, last menstrual period and estimation according to neonatal size and development at birth. The most accurate estimate is garnered from late first trimester or early second trimester ultrasound. Estimation by dates, later ultrasound and post-delivery examination follow in terms of accurate assessment of gestational dates.

Tricyclic Antidepressants

A large health maintenance organization study (n=76,833 unexposed and 339 exposed to TCAs) found increased risk for preterm birth among women who were exposed to TCAs in pregnancy (11% for TCA vs 6.6% for unexposed; RR=1.67; 95% CI=1.25–2.22) although researchers were only able to control for maternal age and season in their analysis (Davis et al 2007). A population-based linked health registry from Sweden (Kallen 2004, Reis & Kallen 2010) drew upon the outcomes of 1,236,000 pregnancies, including over 2400 women who were undergoing treatment with a TCA (Reis & Kallen 2010). Approximately 5% of women delivered an infant preterm; women who were undergoing treatment with a TCA were more likely to deliver preterm, as compared to women who were not taking a TCA in pregnancy (OR=2.36; 95% CI=1.89–2.94). (Reis & Kallen 2010) These and the findings from Davis (Davis et al 2007) are similar to those from two smaller studies that used different data sources. Those investigations found the odds of preterm birth nearly doubled when mothers took a TCA (Simon et al 2002, Toh et al 2009) as compared to no antidepressant treatment, although confidence intervals for both studies crossed one. Results from a Tennessee Medicaid database showed that women who used a TCA in the second trimester of pregnancy were significantly ($p<.0001$) more likely to have a shorter gestation (<32 weeks or <37 weeks) as compared to women who were not taking a TCA (Hayes et al 2012).

Selective Serotonin Reuptake Inhibitors

Associations between SRI use and preterm birth have been studied extensively. Many reports included both SSRIs and SNRIs. Early studies with small sample sizes did not support an association between SSRI use and preterm birth (Casper 2010, Chambers et al 1996, Colvin et al 2011, El Marroun et al 2012, Pastuszak et al 1993) although larger studies that were subsequently published, with some notable exceptions, (Calderon-Margalit et al 2009, Nordeng et al 2012) strongly support such an association (Colvin et al 2011, Lund et al 2009, Maschi et al 2008, Oberlander et al 2006, Reis & Kallen 2010, Wen et al 2006, Yonkers et al 2012). Not surprisingly, these results are consistent with a 2013 meta-analysis

that pooled a subset of currently available studies (Ross et al 2013), which found an OR of 1.55 (95% CI=1.38–1.55).

The large Swedish health registry database that was referenced earlier compared rates of preterm birth in mothers who were undergoing treatment with a TCA, SSRI and SNRI (Reis & Kallen 2010). The highest OR was for mothers undergoing treatment with a TCA (OR=2.36; 95% CI-1.89–2.94, *see above*), followed by a SNRI (OR=1.98; 95% CI=1.49–2.63) and then a SRI (OR=1.46; 95% CI=1.31–1.63). The overlapping confidence interval between SRIs and SNRIs does not support a difference between these classes but neither of these confidence intervals overlap with TCAs suggesting that there is something different about the risk associated with TCAs as compared to SRIs and SNRIs. However, in current practice, clinicians typically attempt to achieve depressive symptom stability first with an SSRI and will turn next to an SNRI and lastly to a TCA. The TCAs may also be used to treat comorbid illnesses or complicated illnesses. Thus, illness severity and other health behaviors may confound the relationship between antidepressant use and preterm birth (Nordeng et al 2012).

A population based linked health registry study from Western Australia (n=25,180) compared some of the commonly used SSRIs (citalopram, fluoxetine, paroxetine and sertraline) and their associations with preterm birth (Colvin et al 2011). The adjusted ORs were in the 1.4–1.7 range with overlapping confidence intervals suggesting no difference in outcomes between agents. This could be a result of comparable effects on preterm birth within the class of SSRIs or results that are due to other similarly shared factors such as health habits.

Few studies have evaluated whether medication dose has on impact on preterm birth risk but at least one report found that higher dosages were associated with greater risk (Roca et al 2011). The timing of exposure may influence risk of preterm birth but results vary. Some work indicates that women who continue SSRI treatment into the third trimester have higher rates of preterm birth (Toh et al 2009) while another study found that antidepressant use in the second trimester had a greater effect on preterm birth risk as compared to other trimesters (Hayes et al 2012). Importantly, many reports show that even first trimester use of an SSRI is associated with preterm birth although more sustained exposure to SSRI in pregnancy seems to correlate with shortened gestations (Oberlander et al 2008).

A minority of studies attempted to control for level of depressive symptoms or psychiatric disorders in their analyses (Calderon-Margalit et al 2009, El Marroun et al 2012, Grzeskowiak et al 2012, Nordeng et al 2012, Oberlander et al 2006, Suri et al 2007, Wisner 2011, Yonkers et al 2012). Two of these reports failed to find an association between SSRIs and preterm birth after controlling for psychiatric symptoms although the measures of psychiatric illness were indicative of general emotional distress rather than an illness diagnosis (Calderon-Margalit et al 2009, Nordeng et al 2012). Nonetheless, the possibility that the underlying illness, which prompted treatment, may play a role in risk of preterm birth speaks to the difficulty of establishing a direct feto-toxic effect in available cohort studies. In response, one study found that SSRI use is associated more highly with spontaneous rather than indicated delivery; the association held even after analytic control

for adverse health habits, previous preterm birth, a depressive disorder and illness severity (Yonkers et al 2012). This would favor a direct role for the SRIs in biologically determined preterm birth although it was an associative study with a modest sample size of 2654, including only 293 women who took an SRI, which limits inferences of causation.

Other Antidepressants

As noted, some information about SNRIs is included with data exploring risks of SSRIs. The Swedish registry found that women who used SNRIs and norepinephrine reuptake inhibitors (NRI; eg mianserin and others) had a higher BMI, age and rates of smoking as compared to mothers who used SRIs in pregnancy. This could contribute to a higher risk estimate for preterm birth associated with these agents as compared to SSRIs (Lennestal & Kallen 2007). Smaller studies from teratogen information services find that women who underwent treatment with mirtazapine (Djulus et al 2006), nefazadone/trazodone (Einarson et al 2003) and bupropion (Chun-Fai-Chan et al 2005) have somewhat shorter pregnancy duration as compared to controls but the numbers of participants in these studies were small.

Summary

Preterm birth occurs at a higher rate among mothers who take antidepressants. A meta-analysis that included reports published prior to June of 2010 found a pooled OR=1.55 (1.38–1.75) (Ross et al 2013). There are no randomized trials that allow a non-confounded assessment of the risks of antidepressant use as it relates to preterm birth. Many of the factors that appear to increase the risk of antidepressants on preterm birth (higher dose, longer treatment periods, choice of agent) are confounded by illness severity factors. Larger exposure databases lack detailed information on indications for treatment and many also lack data on health habits (eg. cigarette and other substance use). Still, a direct biological effect of antidepressant exposure on preterm birth is suggested by the consistency of findings and meta-analyses. The fact that spontaneous preterm birth is higher in SRI users as compared to non-users even when health habits, depressive disorders and psychiatric illness severity is considered suggests a biological role for antidepressants. (Yonkers et al 2012). However, if the association is causal, the overall risk is modest and the duration of pregnancy is typically shortened by only 3–5 days (Yonkers et al 2012).

FETAL GROWTH

Several parameters are used to assess differences among exposures that are associated with fetal growth. Low birth weight is commonly used as an outcome measure because it simply depends on the weight of the neonate at birth. It is also available on many birth certificates that often do not have the length of gestation. However, many babies that are born small are also born early and thus weight at birth may be appropriate for their early birth and gestational age. The parameter small for gestational age (SGA) considers the length of gestation and the size of the offspring while controlling for gestational duration. Small for gestational age is a categorical outcome that is typically operationalized as the bottom decile of age-corrected weight of a baby as compared to others in the cohort (e.g. national sample), stratified for sex and race. A third metric is intrauterine growth restriction. Technically this is a prospective, intrauterine measure that is also a medical diagnosis; it relies upon

measures of fetal growth in pregnancy. This is often not available in large epidemiological studies that are designed to evaluate the possible impact of environmental exposures among thousands or tens of thousands of individuals. In this section, we provide information on whichever of these parameters are available. If SGA is available in addition to LBW, we comment on SGA since it is specific for growth and not age of offspring.

Tricyclic Antidepressants

Early, small studies, found no association between fetal growth and use of antidepressants in pregnancy (Simon et al 2002), a finding echoed by the Swedish registry. Specifically, while the Swedish registry did find a higher rate of low birthweight delivery among TCA-using mothers as compared to those who did not take a TCA (Kallen 2004) the effect was due to early delivery since there were no differences in the rate of SGA. Similarly, a large Canadian registry that included pregnant women who took TCAs in pregnancy, did not find an increased risk of delivering and infant who was SGA (Ramos et al 2010).

Selective Serotonin Reuptake Inhibitors

Reports on the possible effects of SSRIs on fetal growth are mixed with many research groups finding significantly different rates among exposure groups (Chambers et al 1996, Colvin et al 2011, El Marroun et al 2012, Klieger-Grossmann et al 2010, Toh et al 2009, Wen et al 2006), while others do not (Calderon-Margalit et al 2009, Grzeskowiak et al 2012, Hayes et al 2012, Kulin et al 1998, Maschi et al 2008, Nordeng et al 2012, Oberlander et al 2008, Pearson et al 2007, Ramos et al 2010, Reis & Kallen 2010, Simon et al 2002, Wisner et al 2009).

A large Dutch study evaluated depressive symptoms as well as SSRI use prospectively in a cohort of 7696 pregnant women (El Marroun et al 2012) and conducted serial ultrasound examinations to determine any effect of these exposures on fetal growth. The offspring of mothers who underwent SSRI treatment had slower head growth, although body growth was not reduced if depressive symptoms were minimized. Toh and colleagues (Toh et al 2009), in a retrospective cohort study, found a higher rate of SGA delivery to mothers who took an SSRI in pregnancy as compared to untreated mothers but only if treatment continued beyond the first trimester; they did not control for maternal illness. A Canadian health registry study (Wen et al 2006) found that low birth weight deliveries occurred at a higher rate in mothers who underwent SSRI treatment in pregnancy compared to those who did not but they did not consider gestational age or critical factors such as smoking.

A large study that controlled for confounding psychiatric diagnosis found that women who took SSRIs had a higher rate of low birth weight deliveries but not small for gestational age babies, again suggests that preterm delivery was the reason women delivered smaller babies (Grzeskowiak et al 2012). Similarly, results from an analysis of a Tennessee database on SSRIs and birth outcomes failed to show differences in birth size for offspring who were exposed compared to those who were not exposed (Hayes et al 2012). Of note, this analysis controlled for maternal psychiatric illness (codes recorded in the database), cigarette and other hazardous substance use. Additional studies that controlled for psychiatric diagnosis via recorded registry codes or depressive symptoms obtained from the participant also failed

to find that infants born to mothers who took SSRIs in pregnancy were more likely to be born small for gestational age (Nordeng & Spigset 2005, Oberlander et al 2008, Ramos et al 2010).

Other antidepressants

There was no difference between the birth weight among mothers who took bupropion as compared to either use of other antidepressants or no antidepressant treatment in one small teratogen information service study (Chun-Fai-Chan et al 2005).

Summary

Although the data evaluating an association between antidepressant use in pregnancy and fetal growth are mixed, although an association between this exposure and outcome is not strongly supported. Tricyclic antidepressant use in pregnancy does not appear to be associated with SGA. Most of the larger and stronger studies that controlled for confounding due to substance misuse and psychiatric disorder, did not find an association between SRI use in pregnancy and fetal growth abnormalities. The few studies that show an association, find a very small effect on fetal growth. In their meta-analysis that included studies published before 2010, Ross and colleagues only find a 74 gm difference between babies exposed to maternal antidepressant use in pregnancy and those who were not. When their model included a covariate for psychiatric illness, there was no statistical difference between antidepressant exposure groups (Ross et al 2013). Given these findings, fetal growth effects should not be a major concern mothers who take antidepressants in pregnancy.

POSTNATAL COMPLICATIONS AND BEHAVIORAL EFFECTS

Neonatal and Post-neonatal Demise

A population based linked health registry study found that the rate of neonatal deaths was higher among children exposed to an SSRI in utero as compared to those not exposed (0.9% vs 0.5%; OR=1.8; 95% CI=1.26–2.60) (Colvin et al 2012). However, mothers who took SSRIs, as compared to non-treated mothers, were older and more likely to smoke and this analysis did not adjust for those factors or for mental illness. Both mental illness and cigarette use have been associated with neonatal death, in particular sudden infant death syndrome, so these are important factors to consider in associative analyses. This is illustrated in a Nordic registry study of over 1.6 million births (Stephansson et al 2013). Potential associations between SRI use and neonatal as well as post neonatal deaths were attenuated and non-significant after models added potential confounding factors.

Persistent Pulmonary Hypertension

Persistent pulmonary hypertension of the newborn (PPHN) is a potentially life-threatening condition in which pulmonary vascular resistance fails to decrease following delivery. This results in ineffective oxygenation and can lead to respiratory failure. PPHN is rare and occurs in approximately 1 to 2 per 1000 births (Graves et al 1988, Walsh-Sukys et al 2000). Meconium aspiration, neonatal asphyxia, cardiac malformations and sepsis are some of the leading causes of PPHN. Known risk factors include prematurity, maternal smoking, obesity and cesarean section delivery (Hernández-Díaz et al 2007).

Serotonin Reuptake Inhibitors

Chambers et al first linked SSRI use in late pregnancy to PPHN in 2006 in a case-control study (Chambers et al 2006). They found that SSRI use after 20 weeks' gestation was associated with PPHN (adjusted OR=6.1 (95% CI 2.2–16.8)). Maternal use of other antidepressants were not associated with PPHN. Since then there have been six additional studies evaluating the association between PPHN and SSRI exposure. Three of these studies showed no association between SSRI exposure and PPHN (Andrade et al 2009, Wichman et al 2009, Wilson et al 2011) while the remainder showed an increased risk of PPHN in SSRI-exposed infants (Kallen & Olausson 2008, Kieler et al 2012, Reis & Kallen 2010). For these latter studies, the estimated odds ratio (ranging from 2.1 to 3.57) was much lower than what was found by Chambers. Of note two of these studies used the same cohort (Kallen & Olausson 2008, Reis & Kallen 2010). The existing seven studies on SSRI exposure and PPHN have identified a total of 83 cases of PPHN in an estimated 36,014 exposures to SSRIs. A recent detailed review by Occhiogrosso et al. evaluated the first six studies, and concluded that the evidence linking SRIs and PPHN is not strong (Occhiogrosso et al 2012).

The most recent study, not included in Occhiogrosso's review, is a large population-based cohort study utilizing data from health registries of five Nordic countries that examined over 30,000 women who used SRIs in pregnancy (Kieler et al 2012). They found that exposure to any SRI in late pregnancy (>20 weeks' gestation) was associated with an increased risk of PPHN, adjusted OR=2.1 (95% CI 1.5–3.0). The risk was similar across all SSRIs, indicating a class effect. This study controlled potential confounders including maternal smoking, obesity, age, cesarean delivery, growth restriction and psychiatric illness. However, there was still confounding by indication as women who did not use antidepressants but had a psychiatric hospitalization were more likely to have infants with PPHN. In addition, like most other studies, the cases of PPHN were identified only with medical record ICD-9 codes without validating the diagnosis (e.g. no echocardiograms, or preductal and postductal oxygen saturation).

It should be noted that the two prospective studies that did not find an association between SRI exposure and PPHN, were small and underpowered to detect an association between exposure and a relatively uncommon event such as PPHN (Andrade et al 2009, Wichman et al 2009). Conversely, two of the positive studies were case-control studies, which tend to overestimate the magnitude of the risk (Chambers et al 2006, Kallen & Olausson 2008). They are also vulnerable to recall bias if drug use is self-reported. Risk may also be overestimated if mothers of infants with poor outcomes are more likely to recall or report drug exposures than women with healthy infants. Antidepressant exposure may be associated with other factors, such as smoking or obesity, which also modulate risk.

There are many factors associated with depression that may account for the association between SSRIs and PPHN, rather than exposure to antidepressant itself. Obesity, cesarean section and smoking, known risk factors for PPHN, are more common in depressed women. The risk of PPHN increases fourfold in infants born at 34–36 weeks' gestation, and as discussed earlier, untreated depression and treatment with SSRIs during pregnancy have been linked to reduced length of gestation. The role that these factors may play in the association between SSRIs and PPHN has not been thoroughly examined. Further research

to clarify the effects of SSRIs and depression on the pulmonary vascular of the fetus is needed.

Other Antidepressants

Only a few studies have examined exposure to SNRIs, TCAs and other antidepressants and report conflicting results (Kieler et al 2012, Reis & Kallen 2010). One found that exp osure to SNRIs, TCAs, and other antidepressants at any time in pregnancy increased the risk of PPHN, RR=3.44 (95% CI 1.49–6.79) (Reis & Kallen 2010), while the others found no increase in the risk of PPHN with exposure to antidepressants other than SSRIs (Kieler et al 2012)[Chambers, 2006 #1921]

Summary—The current literature shows either a small association or no association between PPHN and maternal SRI use in late pregnancy but this rare outcome may be difficult to detect. It is important to note that “association” does not mean “causation.” Furthermore, the absolute risk is extremely small and may not justify avoiding or discontinuing antidepressants in late pregnancy. In fact, this is the stance the FDA took in 2012, stating that based on the evidence it is premature to reach any conclusion about a possible link between SSRI use in pregnancy and PPHN.

Neonatal Behavioral Syndrome

Maternal antidepressant use, including maternal treatment with SSRIs in the third trimester has been associated with neonatal adverse events that include irritability, jitteriness, trouble feeding, tremor, agitation, hypertonia, hyperreflexia, respiratory distress, seizures, vomiting, and excessive crying (Boucher et al 2008, Dahl et al 1997, Moses-Kolko et al 2005, Spencer 1993). Symptoms usually develop at delivery and are time limited, resolving within two weeks with supportive care. The more severe symptoms, including apnea, seizures and temperature instability, may require special care nursery admission. Whether these signs are due to SSRI discontinuation, direct toxic effects of the antidepressant medication, or maternal use of other substances, is not clear although the consensus of opinion is that it is due to the former (Haddad et al 2005, Kallen 2004, Laine et al 2003, Rampono et al 2009, Sanz et al 2005, Zeskind & Stephens 2004).

A 2005 review (Moses-Kolko et al 2005) examined thirteen case reports and nine cohort studies that identified maternal SSRI exposure and included neonatal outcomes. Based on their analysis of five of the cohort studies that defined a neonatal behavioral syndrome (Chambers et al 1996, Cohen et al 2000, Costei et al 2002, Laine et al 2003, Oberlander et al 2004), SSRI exposure was associated with an overall risk ratio of 3.0 (95% CI 2.0–4.4) (Moses-Kolko et al 2005). These findings have been corroborated by more recent studies, which have found neonatal behavioral syndrome in up to 30% of infants exposed to SSRIs in pregnancy (Rampono et al 2009, Sanz et al 2005). While most studies found that SSRI exposure in utero can result in self-limited neonatal behavioral syndrome, three studies have failed to find a difference in neonatal complications among women exposed to SSRIs compared to those with no exposure (Maschi et al 2008, Suri et al 2011, Warburton et al 2010).

To complicate the picture even more, some hypothesize that maternal illness contributes to a neonatal behavioral syndrome (Laine et al 2003, Oberlander et al 2006, Smith et al 2013, Zeskind & Stephens 2004). Studies that attempted to address this issue compared women with depression treated with an SSRI to women with untreated depression but results are mixed. Studies reported that women who were depressed and treated with SSRIs compared to women with depression not treated with antidepressants had greater rates of special care nursery admissions (Suri et al 2007) and respiratory distress and feeding problems (Oberlander et al 2006). A study that compared unexposed neonates to neonates whose mothers took an SRI but were euthymic during the assessment period, found that the exposed neonates, compared to controls, had lower APGAR scores, poorer motor development, greater tremulousness but no differences in sleep parameters (Smith et al 2013). In contrast, a more recent study found no difference in Apgar scores, special nursery admissions or Brazelton Neonatal Behavioral Assessment Scale (BNBAS) scores in women with depression treated with or without SRIs and healthy controls (Suri et al 2011). It is worth noting that the latter two studies had blinded infant raters and utilized a standardized assessment (BNBAS). Further research that can differentiate neonatal complications from SSRI exposure and psychiatric illness is needed.

Summary—Studies that evaluated a possible neonatal behavioral syndrome in association with in utero exposure to SRIs have several limitations. Most notably, the definition and diagnosis of the syndrome is difficult because of the constellation of non-specific symptoms and lack of standard assessment across studies. Another limitation is surveillance bias (e.g. infant assessments are not blinded) and recall bias. Despite these limitations, the current evidence suggests neonatal behavioral syndrome is associated with SSRI exposure, and is most often reported with fluoxetine, paroxetine, and venlafaxine (Chambers et al 1996, Cohen et al 2000, Costei et al 2002, Ferreira et al 2007, Kallen 2004, Laine et al 2003, Oberlander et al 2006, Sanz et al 2005).

Neurodevelopmental Effects

Neurodevelopment occurs throughout gestation and serotonin (5-HT) plays a vital role in the development of the fetal central nervous system (CNS). The serotonergic system affects neuronal development from cell migration and axon growth to synaptic communication (Lauder 1993). It is conceivable that prenatal exposure to medications that have the potential to modify synaptic serotonin concentrations may alter fetal and infant neurodevelopment. Only a few studies investigating the neurodevelopment of infants exposed in-utero to maternal antidepressants are available and have shown inconsistent results.

Two studies by Nulman and colleagues have concluded that in-utero exposure to either TCAs or the SSRI fluoxetine do not affect global IQ, language, or behavioral development in children from ages 1–7 years (Nulman et al 2002, Nulman et al 1997). In a more recent study this group evaluated children exposed to SSRIs, venlafaxine or untreated depression (Nulman et al 2012), and found that antidepressant exposure did not predict IQ or behavioral problems but like earlier studies, maternal mood predicted child behaviors (Misri et al 2006, Oberlander et al 2007).

Conversely, data by Casper et al. suggests that in-utero exposure to SSRIs is associated with slower psychomotor development compared to a healthy comparison group (Casper et al 2003), but found no association between length of gestational SSRI exposure and mental development or clinically discernible psychomotor effects (Casper et al 2011). The did not control for nicotine or other substance use In a recent study, Pederson et al., found a small developmental delay in gross motor function milestones related to antidepressant exposure late in pregnancy (Pedersen et al 2010). However, the association did not persist beyond 19 months, evaluations were based upon parental report only and it had no clinical significance as all children were within the normal range of development.

Two recent studies suggest an association between autism spectrum disorders (ASDs) and prenatal exposure to antidepressants (Croen et al 2011, Rai et al 2013). The first is a population-based case-control study from 2011 (Croen et al 2011), which evaluated medical records of 298 children with ASD and 1507 control children and their mothers from the Childhood Autism Perinatal Study. The study found a greater risk of ASDs in children exposed to SSRIs during pregnancy compared to unexposed children, 6.7% (n = 20) versus 3.3% (n = 50), respectively, with an adjusted odds ratio of 2.2, with first trimester exposure raising the risk to 3.8. The second study was a case-control study from Sweden (Rai et al 2013), with 4429 cases of ASDs (1828 with and 2601 without intellectual disability) and 43,277 matched controls without ASD identified from the Stockholm Youth Cohort. This study found that a history of maternal depression was associated with an increased risk of ASD in the offspring (adjusted OR=1.49, 95% CI 1.08–2.08), and that antidepressant exposure (SSRIs or non-selective monoamine reuptake inhibitors) was associated with an increased risk of ASD without intellectual impairment only (OR = 2.54, 95% CI 1.37–4.68). Both studies controlled for history of psychiatric disorders, maternal age, parity, and maternal education.

While we cannot rule out that exposure to antidepressants may affect the risk of having a child with ASD, it is important to note that case-control studies often over-estimate risk, and can only show an association and not prove causation. Antidepressant treatment might be indicative of other exposures that may lead to increase in risk for autism. Women that remain on antidepressants during pregnancy are likely to have a more severe illness, and therefore greater genetic vulnerability for psychiatric illness, which has been associated with an increased risk for ASD. The impact of mood symptoms and the burden of illness during pregnancy on the risk for autism were not assessed in these two studies. Furthermore, depressed women are more likely to use tobacco, alcohol and illicit drugs. Neither study controlled for this in their analysis nor did they control for the risk factor of obesity. Further studies are needed, which address other contributing factors, before any determination on the risk of antidepressant exposure and the risk of ASD can be made.

Summary—The current evidence is limited and not unanimous in excluding possible long-term detrimental neurodevelopmental repercussions of infants' exposure to antidepressants in pregnancy. Fetal neurodevelopment might be susceptible to antidepressant exposure, but the effects, if any, are limited and may be compensated for over time. The studies that assess autism risk are confounded by other critical exposures. An important thing to consider is the

influence of maternal mood and depression severity on behavioral and neurocognitive outcomes.

SUMMARY AND CONCLUSIONS

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SUMMARY POINTS

1. For most outcomes, results are mixed and no investigation is able to adequately control for confounding factors. This is critical because a number of factors that are often not measured such as smoking, other drug use, obesity, concurrent medication use and poor prenatal care, all of which occur at a higher rate among women who use antidepressants, may explain the small effects seen in many of the observational studies.
2. Areas of relative consistency include: a possible effect of antidepressants on spontaneous abortion, a lack of effect on fetal death, a possible association between paroxetine and cardiac malformations, a likely effect of antidepressants on preterm birth and the probable effects of antidepressant exposure on a neonatal behavioral syndrome.
3. In general, none of the effects mentioned above are large; serious consequences are particularly rare.
4. Clinicians should inform patients of possible risks of treatment, but an informed and nuanced approach is best so that patients who require treatment are not unnecessarily alarmed at the prospect of treatment.
5. Non-pharmacological approaches, such as psychotherapy, are critical contributors to our therapeutic armamentarium and may be considered first line by many clinicians for a variety of patients, including those with mild to moderate illness. Women with severe depressive disorders may also prefer a trial of non-pharmacologic treatment but should be supported in their decision if there is a need for medication in pregnancy.