Physician Assistant Scholarly Project Papers   Department of Physician Studies

2018

Treating Peri and Postnatal Depression and Anxiety

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By

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Bachelor of Science in Respiratory Therapy, University of Mary, 2014

Scholarly Project

Submitted to the Graduate Faculty of the

University of North Dakota

In partial fulfillment of the requirements for the degree of

Maser of Physician Assistant Studies

Grand Forks, North Dakota

March, 2018

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Abstract

While diagnoses of depression and anxiety are not uncommon for women during pregnancy and after delivery, one of the greatest challenges in the plan of treatment is to ensure that the offspring are kept safe while the psychological well-being of the mother is appropriately cared for. The objective of this literature review is to evaluate the commonly prescribed treatment methods for prenatal and postnatal depression, focusing on the efficacy of antidepressant medications and nonpharmacologic treatments while evaluating the effects these medications have on the fetus/breastfeeding infant. The method of research included 15 studies completed with within the past ten years on women who were pregnant or who had delivered a baby within the past 12 months. One study did evaluate long-term effects on offspring, which included a participant number of 3,342 children who were exposed to antidepressants during pregnancy. Two Cochrane Review evaluations were also included in this research. The total number of participants in the studies were 8,069 women. Limitations of the results were due to small sample sizes in several of the studies and few studies available that directly evaluate this population of women and children. The compiled data results suggest that while cognitive group therapy does provide depression symptom improvement in prenatal and postnatal depression and anxiety, antidepressant medications tend to have a positive effect earlier in treatment. Unfortunately, many of these antidepressant medications have also been proven to have both short and long tern effects on the offspring exposed to pharmacologic treatment.

Introduction

Within the primary care practice, providers have many opportunities to care for patients with anxiety and depression diagnoses. Not only are solid relationships built between the provider and patient, but there are also the important aspects of trust and rapport that aide in the effective management of mental health disorders. According to the National Guideline Clearinghouse guideline summary, first line treatment for severe or chronic major depression disorder as diagnosed by the Patient Health Questionnaire-9 (PHQ9) screening, is a referral to behavioral health in combination with antidepressant therapy (2012). Guideline recommendations for the general adult population suggest that any class of antidepressants are first-line treatment options such as: selective serotonin reuptake inhibitor (SSRI), tricyclic antidepressants (TCA), serotonin-norepinephrine reuptake inhibitor (SNRI), norepinephrine reuptake inhibitor (NRI), and dopamine agonists (DA) (National Guideline Clearinghouse, 2012).

One difficult area in the treatment of both depression and anxiety is in the prenatal and breastfeeding patient population. Unfortunately, research has shown that the prevalence of depression during pregnancy and the postpartum time are quite high. During pregnancy, the prevalence of depression appears to be in the spectrum of 6-13% (Charlton et al., 2014) and possibly up to 15% (Van Lieshout et al., 2017). When considering the prevalence of depression and anxiety throughout pregnancy, research has shown an increase in stress levels at 16 weeks of gestation and again towards the end of pregnancy, which correlated with elevated depression scores at this time (Rallis et al., 2014). After delivery, the incidence increases to almost 20% (Van Lieshout et al., 2017).

Providers and patients must work together to determine the best path of action for this unique situation of caring for both the pregnant patient's mental health and her unborn child. This scholarly project primarily focuses on the mental health aspect of prenatal care and the cost-to-benefit considerations included when choosing a treatment option. Two main options are considered, including pharmacologic treatment and behavioral therapy which will be evaluated on both effective management of the mother's psychological state as well as provision of a safe environment for the unborn child.

Statement of the Problem

One difficult area in the treatment of both depression and anxiety is in the prenatal and breastfeeding patient population. Providers and patients must work together to determine the best path of action for this unique situation of caring for both the pregnant patient's mental health and her unborn child.

Research Questions

In the pregnant and breastfeeding population, what is the efficacy of antidepressant medication treatment for patients diagnosed with depression and/or anxiety?

In pregnant patients diagnoses with depression and/or anxiety, what are the fetal effects resulting from use of antidepressants during pregnancy?

In breastfeeding patients diagnosed with depression and/or anxiety, are there effects caused from the transfer of antidepressant medications from mother to infant during lactation?

In patients diagnosed with depression and/or anxiety during pregnancy and postpartum, what is the effectiveness of treatment options such as cognitive behavioral health therapy?

The Introductory section stated above brings awareness to the increased rate of depression during pregnant and postpartum women, which is a challenging factor for providers and patients to manage effectively and safely. In stating the research questions above, the upcoming literature review will delve deeper into the current research available on pharmacological and nonpharmacological treatment for the diagnosis of depression in pregnancy and postpartum. Within the Discussion section, a review and comparison of the research findings will provide a platform for the current data on treatment of depression in women of childbearing age who are either pregnant or breastfeeding.

Methods

The collection of research and data for this scholarly project included a specific study population of women within childbearing ages eighteen to forty years old who were either pregnant or breastfeeding during the time of the study. The research was selected first by randomized clinical trials within the past ten years in order to ensure recent data collection throughout the literature found from PubMed, PsychINFO, Cochrane, and PsychiatryOnline. The selection criteria for subjects as stated above was quite specific to women who were currently pregnant or breastfeeding, but did include research completed outside of the United States to gain more of an international, unbiased perspective.

The research methods used consisted of data collection from PubMed, PsycINFO, Cochrane Review, and PsychiatryOnline. First, a search was completed on PubMed to include the keywords of "Pregnancy AND depression." 874 results were found and were then filtered by clinical study within the past ten years. Finally, irrelevant studies were excluded that did not include depression or pregnancy after which two results were found to use in this research. My next search was of the subject heading "prenatal depression" with a keyword of "treatment". When filtered again by date and study, there were twenty-four results. The links were evaluated and two studies directly relating to depression during pregnancy were used for this research. The next search focused on anxiety treatment in pregnancy using the keywords of "pregnancy," "anxiety," and "treatment". Again, results were filtered by a date of recent ten years and included comparative and multicenter studies with human subjects. This resulted in 121 links, which were reviewed and five results directly relating to pregnancies without comorbidities were found. The studies excluded did not pertain to depression treatment options and those studies that included patients with multiple comorbidities. The final search included keywords, "Antidepressants,

pregnancy AND postpartum, AND effectiveness." Filters were applied to include randomized control trials in the past ten years. Three search results were present, with one link evaluating the effectiveness of pharmacotherapy in comparison to psychosocial intervention which was added to the list of sources for this project.

PsycINFO was the next database searched. The initial filter set was a past date of 10 years. The first search completed was with the keywords "depression treatment in pregnancy." The result was 204 links with only one final study directly correlating to depression treatment with serotonin reuptake inhibitors (SSRIs) in pregnancy. The keywords "pregnancy, depression, pharmacology, behavioral therapy" were used in the next search with a filter of human subjects. Ten results appeared, and were filtered by continuing studies or unrelated research, and one link was added to relevant research. The next search included the keywords "pregnancy, depression, anxiety." There were fifty-two links and the topics not relating to perinatal treatment were excluded, with one result added to the research. The final search was with keywords "pregnancy, depression AND SSRI benefits" for studies within the past 10 years in qualitative study form. There were seven results, with one result evaluating the effectiveness of SSRI use during pregnancy.

Within Cochrane Review, the first search included "Antidepressant use in pregnancy" and came up with five results. Within these five results, one review focused on SSRI use in postnatal depression. When the search was widened to "Antidepressants, pregnancy," six results were present, with the one other result focusing on antidepressant use in pregnancy as a proposed protocol which was not applicable to this research project.

A search on PsychiatryOnline was next completed using keywords, "antidepressants, pregnancy, effectiveness." Once filtered to contain the past ten years in the category of

"Antidepressants," thirty-one results were present. Of these results, one study related specifically

to comparison of untreated depression and antidepressant use in pregnancy which was added to

the list of sources for this project.

Literature Review

As explained above in the Methods section, the study population for this research focused on women ages 18-42 who were either pregnant, recently delivered, or breastfeeding during the time of the study. Once collected, the data was then categorized according to the research topic. The focus of this research project evaluates four key themes. The first two specifically evaluate antidepressant medication effectiveness during pregnancy and postpartum an assess the effects the medications have on fetal development and growth long-term. The next theme was to evaluate antidepressant medication transfer to the infant during lactation. Finally, the next category of data collection evaluates the effectiveness of cognitive behavioral therapy for management of anxiety and depression, during both the prenatal and postpartum timeframes.

Depression and Pathophysiology of Antidepressant Medications

As stated above in the Introduction, depression and anxiety during pregnancy and postpartum is not an uncommon occurrence for women. Depression symptoms are hypothesized to be caused by a deficiency of synaptic neurotransmitters such as serotonin, norepinephrine, and dopamine (Bardal et al, 2011, p. 369). Specific criteria within the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM V) states specific symptom criteria in a 2-week period that signifies a change from previous functioning ability. At least one of the symptoms must be a depressed mood or loss of interest/pleasure (American Psychiatric Association (2013). As shown below in the literature review studies, there are multiple certified screening tools available to clinicians to evaluate for the presence of depression.

When discussing postnatal depression, the diagnostic criteria is the same as non-pregnancy related depression. According to *CURRENT Diagnosis and Treatment: Obstetrics & Gynecology* by Decherney, Nathan, Laufer, and Roman (2013), postpartum depression

specifically is characterized by, "Depression that begins in the 12 months after delivery… symptoms must be present nearly every day for at least two weeks" (p. 367).

The methods of action for antidepressants vary on the type of medication used but all work to improve the mood in diagnosed depression. Specifically, in this collection of research, SSRIs are the primary class of antidepressants prescribed, followed by SNRIs and then bupropion. SSRI medications (examples include fluoxetine, paroxetine, fluvoxamine, sertraline, citalopram, and escitalopram) act by binding to the serotonin reuptake transporter, thereby inhibiting the reuptake of serotonin in the synaptic cleft and increasing the amount of serotonin available to bind to the postsynaptic receptors (Bardal et al, 2011, p. 369). SNRI medications (venlafaxine, desvenlafaxine, duloxetine, milnacipran, etc.) work by a slightly different mechanism of action and increase the available concentration of both serotonin and noradrenaline within the synaptic cleft (Bardal et al., 2011, p. 373). Bupropion is in the class of atypical antidepressants, noradrenaline and dopamine reuptake inhibitors (NDRIs). The mechanism of action for bupropion is to inhibit the presynaptic reuptake of dopamine and noradrenaline which leads to an increased availability of both neurotransmitters in the synaptic cleft (Bardal et al., 2011, p. 378). The treatment effectiveness of antidepressant medications typically take several weeks for results to be present. These different classes of medications are primarily noted in the following studies.

Introduction to Themes

Within the scope of this literature review, an assessment of current practices using antidepressants and nonpharmacologic means of treating depression will be completed. The efficacy of antidepressant medications will be evaluated during both pregnancy and postpartum. Next, the effects of antidepressant medications on the fetus will be reviewed, along with effects

on the infant during lactation. Finally, the effectiveness of nonpharmacologic treatment methods such as therapy sessions will be evaluated for the management of depression during pregnancy and postpartum.

Theme A: antidepressant pharmacotherapy efficacy during pregnancy and postpartum

The study completed by Charlton et al. (2014) in Europe intended to closely observe the correlation between SSRI's prescribed before, during, and after pregnancy. This was a large, population-based study that included 721,632 participants and 86,943 deliveries with information collected through data collection through databases. Six electronic healthcare databases throughout Europe were used to include pregnancy and prescription information from January 1, 2004 to December 31, 2010. The Denmark database collection ended on December 31, 2009. Women were included in the study who had been present in the database with the necessary data: prescription records one year prior to the pregnancy through one year after pregnancy. The SSRIs in the study specifically included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, and escitalopram (Charlton et al., 2014).

Results from the study found that prescriptions for SSRIs in the second and third trimesters were markedly lower compared to pre-pregnancy and first trimester, but then increased again in the postpartum period after delivery. Of all the deliveries, 5.4% [95% confidence interval (CI_{95}), 5.3-5.4%] of the women were found to have received a prescription for an SSRI in the year leading up to pregnancy. During pregnancy, however, the use of SSRIs fell to 2.3% (CI_{95}, 2.2-2.3%). The percent of individuals with an SSRI prescription prior to pregnancy decreased upon determination of pregnancy, with at least 40% discontinuing their prescription during pregnancy. In the year after pregnancy, SSRI prescriptions were noticeably

higher in the United Kingdom databases compared with the other four, however, by six months postpartum, prescription SSRIs returned to the pre-pregnancy levels stated above (Charlton et al., 2014).

A prospective observational study by Wisner et al. (2009) evaluated the effects of major depression and antidepressant treatments in pregnancy and neonatal outcomes. The study completed maternal evaluations at gestation weeks 20, 30, and 36. There were 381 pregnant women, ages 15-44 years old, categorized into separate groups: no SSRI use and no depression, continuous SSRI exposure, partial SSRI exposure, continuous MDD with no SSRI use, and a fifth group of women with partial MDD with no SSRI exposure (MDD for at least part of the pregnancy). Women who reported alcohol abuse or dependence were excluded from the study. Severity of the participant's depression was evaluated using the Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement (SIGH-ADS). Outcomes of the research focused on SSRI treatment effectiveness and neonatal effects which will be explained below in Theme B (Wisner et al., 2009).

Results from the research found that of the 381 participants, 238 were eligible and provided the necessary neonatal outcome data. In the evaluation of subjects, data showed that women who were in the group with continuous MDD and no SSRI treatment during pregnancy reported more alcohol use (more than one drink per week or binge drinking) than either of the groups receiving SSRI treatment and the group categorized by no SSRIs and no depression. The most commonly prescribed SSRIs were sertraline (34%), fluoxetine (25%), and citalopram or escitalopram (23%). Several other treatment regimens included combination therapy which included an SSRI with bupropion or an SSRI with a tricyclic antidepressant (18%). It was found that the women not exposed to SSRIs and with no depression had lower depressive symptoms

and a higher functional status. The women with no SSRI exposure but diagnosed with MDD had a higher mean depressive symptom level when compared to all other groups. In relation to weight, SSRI use and depression were not related to maternal weight gain. Women with depression did have non-significantly higher mean pre-pregnancy body mass index (BMI) scores when compared to other subjects and tended to have a lower mean weight gain (Wisner et al., 2009).

A pragmatic two-arm individually randomized controlled trial by Sharp et al. (2010) evaluated the effectiveness of antidepressant therapy compared to psychosocial therapy in women diagnosed with postnatal depression (PND) using the International Classification of Diseases version 10 (ICD-10) criteria. Participants were from Bristol in south-west England, south London, and Manchester in north-west England. Women were recruited between January 2005 through August 2007 if they had recently delivered a live birth, were living with their baby, and were over age eighteen. Exclusions were applied if the mother had a stillbirth/neonatal death, infant was over 26 weeks old, foster/adopted infants, women with psychosis, alcohol/drug abuse, or those who were already receiving depression treatment. There were 254 women participating in the study who were randomly assigned the treatment methods of antidepressant (usually a SSRI) or non-directive counseling (listening) sessions. At four weeks of treatment, women were allowed to receive the alternate treatment intervention if they wished. Evaluation of the treatment's effectiveness was measured by the women's satisfaction, perspective from the general practitioner prescribing the antidepressant, and the trained health visitor administering the listening sessions (Sharp et al., 2010).

Evaluation of depression was scored according to the baseline Edinburgh Postnatal Depression Scale (EPDS) score, with a score of ≥13 suggesting depression. Therefore, to ensure

false positives were not missed, a baseline score of ≥ 11 was used to diagnose depression. The results of the study found that at four weeks of treatment, of the 106 women who were assigned to the antidepressant group with a baseline EPDS score of ≥ 13, 45% had improved to an EPDS score of ≤ 13. At eighteen weeks, the improvements appeared in 60 of the 90 responders (62%). In the comparison group receiving active listening, 20% showed improvement in their EPDS scores to ≤ 13 at four weeks. At eighteen weeks, 51% of the participants had improved. When this information was analyzed using Complier- Average Causal Effect (CACE), the difference in EPDS scored when comparing those taking an antidepressant versus those not was -4.2 (CI$_{95}$ -6.8 to -1.6). Eleven of the sixteen women interviewed at the conclusion of the study reported beneficial effects from taking the antidepressant medications. Four reported no effects from the medication, and one woman reported feeling angry and manic on the medication (Sharp et al., 2010).

A Cochrane Review by Molyneaux, Howard, McGeown, Karia, and Trevillion (2014) sought to evaluate the effectiveness of antidepressant therapy in postnatal depression in comparison to other forms of treatment such as social support and psychological intervention. Their method of data collection was to use the Cochrane Depression, Anxiety and Neurosis Group's Specialized Register (CCDANCTR) which included relevant randomized controlled trials from *The Cochrane Library,* MEDLINE, EMBASE, and PsycINFO up through the date of July, 2014. Within the six trials, 596 participants were included. All of the studies had a controlled parallel group in their research (Molyneaux et al., 2014).

Results of this review were grouped by study design. Four of the studies compared SSRIs with a placebo. The SSRIs used were sertraline, paroxetine, and fluoxetine. Of these four studies, two of them also incorporated psychological therapy into the treatment groups. Three of the four

studies (total of 146 participants) found that the random assignment of women to the SSRI treatment group had an increased response and remission rate from depression when compared to the placebo group [response ratio (RR): 1.43%]. The other study did not evaluate response or remission rates. Another group within this Cochrane review included one study that compared antidepressant therapy with treatment as usual for the first four weeks which were then followed by listening visits. The data did show increased improvement rates in the antidepressant treatment group when compared the treatment-as-usual group. However, there did not appear to be a difference in the later follow-up when comparing antidepressant therapy and listening visits. In a specific study comparing sertraline with nortriptyline (a tricyclic antidepressant), there did not appear to be any difference in effectiveness. Through the data collection process, it was found that women using the SSRIs did tend to experience side effects from the medications (Molyneaux et al., 2014).

Theme B: antidepressant pharmacotherapy and fetal effects

A population-based cohort study was completed by Handal et al. (2016) in Norway which evaluated the effects of SSRI treatment during pregnancy and the relationship to motor development in children. The method of study included pregnant women from 1999-2008 which included 51,404 children and 45,003 mothers. Using an Ages and Stages Questionnaire (ASQ), fine and gross motor skill questionnaires were completed by mothers three years after delivery and were then averaged to find the score. Interestingly, only 3.5% of the children had an ASQ score that was greater than three which suggested clinical significant fine motor impairment, however the children exposed to SSRI's in pregnancy had a slightly higher percentage compared to children who were not exposed with a 95% CI of -0.2 to 4.4%. There was also a shift towards delayed motor development found with exposure to SSRI with a stronger shift correlating to

increased exposure to SSRI use (Handal et al., 2016). Within the discussion section, Handal et al. (2016) found, "In this large prospective cohort study we found that treatment with SSRIs during longer periods of pregnancy was weakly associated with a delay in both fine and gross motor development in children aged 3 years" (p. 1914).

A study by Hannerfors et al. (2015) compared the levels of corticotropin-releasing hormone (CRH) in depressed pregnant women receiving SSRI medications and those not. Specifically, the study assessed second trimester CRH serum concentration levels on women who were pregnant compared to depressed women not on SSRIs and healthy controls. Results suggested that women who were on SSRI treatment tended to be smokers, more obese, often developed preeclampsia, and had a shorter gestational length which tended to result in a preterm delivery. The CRH serum concentration was also increased at 16-20 weeks gestation but did not differ significantly in levels depending on SSRI. In comparison to the untreated, undepressed women, there were less pregnancy complications with noticeably lower CRH serum concentrations. The women with untreated depression did not have differing CRH serum concentrations compared to controls (Hannerfors et al., 2015).

An observational prospective comparative cohort study completed in 2012 by Klieger-Grossmann et al. (2012) sought to evaluate the effects of escitalopram during pregnancy. Study participants included 6,582 mothers, of which 298 who reported use of an antidepressant during pregnancy (Klieger-Grossman et al., 2012). This study also evaluated which antidepressants were used, which included SSRIs as number one (3.8%) with bupropion second most commonly used (0.7%). Data was collected from 1998-2005 from women with a mean age of 33.1 +/- 2.3 years and at the beginning of the cohort study were all taking escitalopram before becoming pregnant.

Of the two hundred and thirteen infants born to mothers taking escitalopram, 81% were live births, 15% were spontaneous abortions, 1.7% (3) stillbirths, 11% (19) premature births, and 1.7% (3) had a major malformation upon delivery. It was also found that the rate of low birth weight, less than 2500 grams, was higher in escitalopram-exposed infants (9.9%) when compared to infants exposed to other antidepressants (3.6%) which resulted in P=.038 and non-teratogen exposure (2.1%) with P=.003 (Klieger-Grossman et al., 2012). The study found no differences in incidence of infant malformation, premature birth rates, stillbirths, or Neonatal Intensive Care (NICU) admissions. The last noticeable research results found that spontaneous abortions were almost twice as frequent in both the escitalopram and other antidepressant groups when compared to the control group. The escitalopram resulted in 15% spontaneous abortions and other antidepressants were 16%, whereas the control group only experienced 8.5% spontaneous abortions (Klieger-Grossman et al., 2012).

In a population based cohort study completed by Rai et al. (2017), research was focused on finding if a correlation exists between antidepressant use and autism in offspring in Sweden. Specifically, the study was designed to evaluate the use of antidepressants in pregnancy by the mother. Data was collected from 2001-2011 from the Stockholm youth cohort for ages 0-17 who lived in Stockholm County at the time (longer than four years). Children under four years of age were excluded due to less reliability for a true autism diagnosis as well as those children who were not linked to the medical birth register or who were not linked to their biological mothers (Rai et al., 2017).

The results of the study found that of the 3,342 children who were exposed to antidepressant medications during pregnancy, 136 (4.1%) were diagnosed with autism. In the comparison group, there were 12,325 children whose mother had a psychiatric disorder as

diagnosed by ICD-9 and ICD-10 codes but did not take antidepressants during pregnancy. Within this control group, 353 (2.9%) of children were diagnosed with autism. Finally, the control group contained 238,943 children whose mothers had no record of psychiatric disorder or use of antidepressants during pregnancy, with a correlation of 4,889 (2.1%) of children diagnosed with autism. With this statistical evidence, it was found that exposure to antidepressants during pregnancy increased the risk of a diagnosis of autism in children compared to children not exposed, specifically for the diagnosis of autism without an intellectual disability with an odds ratio of 1.57 and confidence interval of 1.21 to 2.04 (Rai et al., 2017). Although there is no numerical data attached, the study also found that when these results were categorized into SSRI versus non-SSRI antidepressants, the risk of autism in offspring seemed to be similar for both groups (Rai et al., 2017).

A study published in 2009 evaluated the placental transfer of SSRI and SNRI antidepressants along with neonatal effects by authors Rampono et al. This prospective observation study included 75 pregnant women recruited at 18-32 weeks gestation. Exclusions applied were any known substance abuser and those who used any medication known to cause altered infant behavior. Of the 75 participants, 30 did not use antidepressants and were placed within the control group. Forty-five women were placed in the treatment group and were using SSRI (27 women) or SNRI (venlafaxine only) antidepressants.

The results of the study found that when tested at delivery, distribution of metabolites and drug in the cord/maternal serum were high in the SSRI's escitalopram, fluoxetine, and fluvoxamine (0.7-0.86 as the medial values) but lower in the SSRI sertraline, N-desmethylsertraline, and paroxetine (medial values of 0.36, 0.4, and 0.15, respectively). In 3-day-old infants, SSRI concentrations were lower than cord serum (range 12-65%). SNRI

(venlafaxine) median concentrations at 3 days was 70%. Within the control group, babies not exposed to antidepressants tended to be born at a later median gestational age of 40 weeks and longer average length 51 centimeters (cm) versus those exposed to antidepressants averaging 39 weeks at birth and 49 cm in length. These results classified as a significant difference (Rampono et al., 2009). However, there were no significant differences in obstetric outcomes or neonatal outcomes including Apgar scores, weight, resuscitation, gender, or head circumference. Brazelton Neonatal Behavioral Assessment Scale (BNBAS) cluster scores varied significantly between case and controls in areas of habituation, social-interactive, motor, and autonomic clusters ($p<0.05$) which suggests less optimal functioning in infants exposed to antidepressant medications during pregnancy (Rampono et al., 2009).

As explained above, Wisner et al. (2009) also evaluated the fetal effects of SSRI exposure during pregnancy by assessing neonatal outcomes. Outcomes of the research focused on neonatal effects including, "Minor physical anomalies, maternal weight gain, infant birth weight, pregnancy duration, and neonatal characteristics" (Wisner et al., 2009, page 559). Results in this category of data found that of the 203 infants born, 30 (15%) had three or more physical malformations. However, depression, first-trimester nor continuous SSRI exposure showed any significant increase in proportion of infants with three or more anomalies. There were no major physical malformations observed in any of the infants. Neonatal birth weight (below 10th or above 90th percentile for gestational age), birth length, and head circumference did not differ across comparison groups. When comparing rate of preterm deliveries, both the group with continuous SSRI exposure and the group with continuous MDD resulted in over 20% of infants delivered preterm. In the other groups, preterm birth rates were between 4-9%. When adjusting for age and African American race, an increased relationship was found with

continuous SSRI exposure. In the adaptation category, there were no differences between vaginal versus surgical delivery rates, nor was there a difference in NICU admission rates (Wisner et al., 2009).

Theme C: antidepressant pharmacotherapy effects during lactation

A pooled research analysis conducted by Weissman et al. (2004) studied the plasma level transfer of SSRI medications from breastmilk to infants. This study included data collected from MEDLINE, Current Contents, Biological Abstracts, and PsycINFO beginning from 1996 and continuing through 2002 (Weissman et al., 2004). The results of this data collection and analysis found interesting correlations between different SSRI medications used in lactating mothers. First, results showed that fluoxetine use in breastfeeding mothers produced the highest serum percentage of 22% in infants as well as the highest mean standardized level. Citalopram was also found to produce higher infant serum levels. Paroxetine was the next SSRI to be elevated in infant serum, with one out of twenty-four studied infants resulting in an elevated portion level. These three SSRI's were found to have the highest portion of medication transferred from mother to infant through breastmilk. The study also found that infants who were exposed to nortriptyline, paroxetine (except for the one infant stated above) and sertraline seem unlikely to develop elevated plasma levels from breastfeeding (Weissman et al., 2004).

Theme D: non-pharmacotherapy treatment efficacy

A study completed by Alder, Urech, Fink, Bitzer, and Hoesli (2011) in a quasi-experimental trial sought to compare the effects of a single relaxation session with women experiencing high and low levels of anxiety in their third trimester of pregnancy. Before and after the session, anxiety levels, hypothalamus-pituitary-adrenal (HPA) axis and sympathetic adrenal-medullary (SAM) system activity levels were evaluated. The participant sample size was

thirty-nine healthy pregnant women over age eighteen. Treatment of anxiety included progressive muscle relaxation (PMR), guided imagery (GI), and passive relaxation/quiet resting (PR). Levels of epinephrine, norepinephrine, cortisol, and ACTH were measured to compare endocrine reactivity during the relaxation experiment. Results found that for patients with high or low anxiety levels, negative affect did not benefit differently in either group. Both groups did self-rate their relaxation as higher after the relaxation procedure for all time points measured at 1 minute, 10 minutes, and 20 minutes (Alder et al., 2011). Therefore, the relaxation procedure seems to benefit highly anxious women and low anxious women similarly.

Another quasi-experimental trial performed by Salehi, Pourasqhar, Khalilian, and Shahhesseini (2016) specifically focused on comparing the effects on anxiety of group cognitive behavioral therapy (CBT) to interactive lectures (IL) for women during their first pregnancy. The setting of the study was in northern Iran and included nulliparous women in their second trimester of pregnancy. Exclusion criteria were set and followed, resulting in a sample size of thirty-four women in each group- the CBT and IL groups, with 38 women in the control group receiving only prenatal care. The CBT group received four group counseling sessions with two sessions per week led by a trained midwife, psychiatrist, and a co-therapist. The IL group also completed four lectures with two per week. The control group completed standard prenatal care. The results of the study found that the group CBT showed improvements in anxiety compared to both the control and IL groups (P<.001). There was no significant difference found between state anxiety levels (P=0.079) or trait anxiety levels (P=0.069) in CBT versus IL treatment options (Salehi et al., 2016).

In another study completed by Van Lieshout, Yang, Haber, and Ferro (2017) assessed the effectiveness of group CBT in comparison to individualized CBT for women with perinatal

depression. The main outcome measured was the level of depressive symptoms as reported by the patient. The group CBT was conducted weekly with a two-hour timeslot. The study size was 34 individuals divided into seven separate CBT groups. 59% of the patients were not taking an antidepressant medication at the beginning of the study. The EPDS, Beck Depression Inventory II (BDI-II), social support evaluated through the Social Provisions Scale (SPS) and the quality of partner relationships was assessed using the Dyadic Adjustment Scale (DAS), and the quality of mother-infant bonding was measured using the Postnatal Bonding Questionnaire (PBQ). The results were quite positive, with statistically significant improvement across all study outcomes. 80% of women receiving the group CBT showed a clinically significant improvement in depressive symptoms over the 9-week therapy course. There were also improvements noted in social support, bonding between the mother and infant, and quality of the partner relationship (Van Lieshout et al., 2017).

A Cochrane Review completed by Dennis, Ross, and Grigoriadis (2007) evaluated the effects of psychosocial and psychological treatment methods on mothers and their families during pregnancy to treat antenatal depression. The search included data collected from the Cochrane Trials Registers, MEDLINE, EMBASE, and CINAHL in which all published, unpublished, and ongoing randomized controlled trials were selected. The ongoing trials included preventative psychosocial or psychological interventions with the aim of treating antenatal depression. Quasi-randomized trials were excluded from the analysis. Participants of the study were pregnant women completing nonpharmacologic treatment of depression. One study was conducted in the United States with a participant number of thirty-eight women (Dennis et al., 2007).

Results of the review were focused the effects on the mother. Maternal outcomes were evaluated immediately post-treatment which found that interpersonal psychotherapy when compared to parenting education programs did have a decreased risk of depressive symptoms. Both the Clinical Global Impression Scale and the Hamilton Rating Scale for Depression were used, with relative risk (RR) measured of 0.46 (CI_{95} 0.26-0.83) and 0.82 (CI_{95} 0.65-1.03) respectively. However, the authors concluded in their recommendations that due to the presence of only one adequate psychological or psychosocial trial of "antenatal depression," there is insufficient data to recommend that psychosocial interventions are superior to antidepressant medication treatment options (Dennis et al., 2007).

In summary, the review of literature has thoroughly evaluated the effectiveness of pharmacotherapy and, separately, the effects on both the fetus and the breastfeeding infant. Nonpharmacologic means of treatment have also been evaluated for effectiveness. Throughout the Discussion section below, further comparison of the current research will provide a focused view of the research questions.

Discussion

Throughout this research, it was interesting to note first the similarity of the studies in regard to the prevalence of prenatal depression. The average prevalence of prenatal depression is close to 15% and during the postpartum time up to one year after delivery, the incidence increases to almost 20% (Van Lieshout et al., 2017). According to the recommended treatment options, both pharmacological methods and psychosocial interventions such as cognitive behavioral therapies are available for patients. Below is a focused comparison of the current research specifically pertaining to this project's research questions.

In the pregnant and breastfeeding population, what is the efficacy of antidepressant medication treatment for patients diagnosed with depression and/or anxiety?

Although many studies are completed evaluating fetal effects of antidepressant medications, there is limited literature assessing the effectiveness of these medications during pregnancy. As stated above by Charlton et al. (2014), SSRI's are commonly prescribed as the antidepressant of choice in pregnant women, but discontinuation of antidepressants continues to occur. In fact, results from the study found that at least 40% of the women discontinued their SSRI prescriptions during pregnancy. According to the data, prescription levels dropped from 5.4% receiving an SSRI prescription prior to pregnancy to 2.3% of women receiving a prescription during pregnancy (Charlton et al., 2014). The other study pertinent to antidepressant effectiveness was completed by Wisner et al. (2009) who did find that the treatment with SSRIs showed higher mean levels of functioning when compared to either depression group with no SSRI exposure. These results correspond as well to the findings of postnatal depression studies evaluating the efficacy of antidepressants.

In the spectrum of postpartum women, the randomized controlled trial completed by Sharp et al. (2010) showed that antidepressant therapy appeared to be more beneficial in a quicker time-frame when compared psychosocial therapies such as listening services for PND. Results from this study showed that antidepressant medication tended to improve depressive symptoms quicker than the listening sessions. When comparing baseline EPDS scores to four weeks of treatment, 45% of women had significantly improved with antidepressant medication and only 20% showed significant improvement with the active listening therapy. However, at eighteen weeks, 62% of women had responded in the antidepressant category compared to 51% of women in the listening category (Sharp et al., 2010). The eighteen-week evaluation suggests that with continued therapy, the psychosocial sessions do seem to show significant improvements with a closer similarity to antidepressant treatment. In the Cochrane Review conducted by Molyneaux et al. (2014), although the participant number was low and there were limited studies available, results did suggest quicker response and remission rates in postnatal depression when using SSRIs compared to the usual psychological or social support treatment options. These findings do seem to agree with the findings from Sharp et al. (2010).

It is unfortunate that there is limited literature data available for this important topic. As common as it is to find research on antidepressant medications and effects, very few quality studies evaluate the psychological effects on the mother during pregnancy and in the postpartum stages. It would be beneficial if continued research assessed the responses of patients who are administered antidepressants throughout pregnancy and afterwards to evaluate the true benefit medications may have on psychological health.

In patients diagnosed with depression and/or anxiety, what are the fetal effects resulting from use of antidepressants during pregnancy?

As shown in the literature review above, there is a vast expanse of research available evaluating possible fetal effects from antidepressant medication exposure during pregnancy. Several studies sought to evaluate the qualities of placental transfer of medications, while other research assessed long-term effects such as motor control and autism correlations in children three years and older. Interestingly enough, the results of the various studies correlated in the fact that there were almost always noticeable clinical effects in offspring of mothers who used antidepressant medications during pregnancy.

First, the study completed by Handal et al. (2016) did show a slightly increased rate of fine motor impairment in children exposed to SSRI medication in utero compared with children not exposed. There also seemed to be an increased rate of delayed motor development in the SSRI exposure group when compared to controls (Handal et al., 2016). The other study evaluating long-term effects of antidepressant medication was completed in Sweden to assess the risk of autism in offspring. Rai et al. (2017) found that in the antidepressant exposure group, 4.1% of children were diagnosed with autism. In the comparison group of offspring from mothers who had a psychiatric disorder with no antidepressant use, 2.9% of children were diagnosed with autism. In the control group of mothers with no psychiatric disorders and no antidepressant use, the rate of autism diagnoses in offspring was 2.1%. Specifically, the research showed that antidepressant exposure increased a child's risk of diagnosed autism without an intellectual ability by an odds ratio of 1.57 (Rai et al., 2017). These two studies do agree and suggest that antidepressant medication use during pregnancy does have an increased risk of negatively affecting offspring when considering the risks of autism and motor control delays.

Several studies within this literature review focused on the effects of prenatal antidepressant medication use in relation to neonatal outcomes at delivery. First, Klieger-Grossman et al. (2012) evaluated SSRIs and bupropion use during pregnancy. Specifically, when studying escitalopram, results found that the rate of low birth weight (less than 2,500 grams) was 9.9% in infants exposed to escitalopram compared to 3.6% low birth weight rates in infants exposed to other antidepressants. Spontaneous abortions were found to be almost two times as frequent in the escitalopram and other antidepressant groups compared to the control group. Fortunately, there were no other noticeable differences in infant malformations, premature birth rates, stillbirths, or NICU admissions (Klieger-Grossman et al., 2012). Rampono et al. (2009) also tended to suggest that gestational age of infants and average length was different when comparing newborns exposed to antidepressants and those not. The control newborn group with no antidepressant exposure showed that the babies were born at an average gestational age of 40 weeks with an average length of 51 cm. Compared to the infants with antidepressant exposure, gestational age at birth was 39 weeks with an average length of 49 cm. Both of these results did classify as a significant difference. Interestingly, this study also found that there were not significant differences noted in obstetric outcomes or neonatal outcomes which correlated with Klieger-Grossman et al. (2012). Further in the study data shows that there were differences in the newborns exposed to antidepressants in areas of habituation, social-interactive, motor, and autonomic clusters to suggest decreased optimal functioning (Rampono et al., 2009). Hannerfors et al. (2015) found that CRH serum levels in pregnant women on SSRIs were increased associated with increased prenatal complications when compared to depressed women with no antidepressant medication use, with both a lower CRH serum level and less complications. The CRH level in untreated, depressed women was similar to healthy pregnant women (2015).

One study included in this research evaluated the effects of SSRIs and other antidepressant medications across the placenta during pregnancy and the effects on the fetus. Rampono et al. (2009) found that several SSRIs resulted in a higher level of metabolite and medication levels in the cord/maternal serum including escitalopram, fluoxetine, and fluvoxamine. The serum levels were less in the SSRIs sertraline, N-desmethylsertaline, and paroxetine being the lowest (Rampono et al., 2009). Although the serum levels were elevated and SSRI use was associated with earlier delivery dates and shorter average length when compared to the control group, it is difficult to evaluate what the specific effects of these elevated SSRI medication and metabolite cord serum levels have on the infant.

In breastfeeding patients diagnosed with depression, are there effects caused from the transfer of antidepressant medications from mother to infant during lactation?

There is limited research in the field of infantile effects from antidepressant medication exposure during the time of breastfeeding. Although the research question is broad, it was difficult to find specific studies that assessed infantile effects; rather the studies tended to evaluate the transferable qualities of antidepressant medications from mother to infant. One pertinent study included in this research was completed by Weissman et al. (2004) which evaluated the plasma transfer of SSRI medications from breastmilk to infants. Fluoxetine was found to have the highest serum percentage and the highest mean standardized level in infants after exposure through breastmilk. Citalopram was found to produce the next-highest levels. Paroxetine was third highest in transfer of medication, with one infant out of twenty-four with a positive level. The SSRI medications nortriptyline, paroxetine (except for the one infant above), and sertraline did not show a high risk of developing increased plasma levels from breastmilk. Unfortunately, this study did not evaluate the effects of these elevated serum levels, so further

research remains to be done in regards to the short and long-term effects on infants who are exposed to antidepressant medications during lactation.

In patients diagnosed with depression and/or anxiety during pregnancy and postpartum, what is the effectiveness of treatment options such as cognitive behavioral health therapy?

The literature available on behavioral health opportunities for management and treatment of depression in pregnancy and postpartum is broad, with thorough data including the type of therapy used and patient-related scores of depression and anxiety pre and post treatment. There did seem to be a common theme throughout the results suggesting that behavioral therapy, whether it be a group therapy or individual/partner-specific therapy is beneficial to mothers, both in the prenatal and postpartum timeframe. One very important benefit of psychosocial treatment is that it does not incur any possible negative effects on the fetus during pregnancy, which is frequently chief concern for expecting and breastfeeding mothers.

The research completed by Alder et al. (2011) found that a single relaxation session did seem to improve anxiety in pregnant women, but did not find a major difference of effect in highly anxious versus low anxiety women (Alder, et al., 2011). When considering the effects of CBT, several studies within this research project evaluated depression improvement both subjectively and objectively. Salehi et al. (2016) found that when comparing CBT to IL for women in their first pregnancy, CBT tended to have greater improvements in anxiety symptoms (Salehi et al., 2016). The study completed by Van Lieshout et al. (2017) went one step further and compared group CBT to individualized CBT. Results showed that both the group and individualized CBT showed significant improvement in patient symptoms, partner relationships, and mother-infant bonding (Van Lieshout et al., 2017). Van Lieshout et al. study results may suggest a safer method of depression treatment compared to pharmacological means and may still result in positive

improvement of depressive symptoms in pregnant and postpartum women. Both of these studies suggest that CBT is an effective option for treatment and management of anxiety and depression in pregnant women. In the review completed by Dennis et al. (2007), results showed that treatment of depression through interpersonal psychotherapy did have an increased benefit when compared to parenting education programs, but due to the limited data available, it was difficult for their conclusion to be complete because a comparison to antidepressant medication options was not included (Dennis et al., 2007).

When considering the above research findings and similarity of study results, the data seems to correlate and agree well. While there is a known advantage to antidepressant medication use, there are also recognized potential risks for the unborn infant throughout pregnancy and potentially during lactation. Also, as recognized above, there is research that suggests psychotherapy such as CBT which is proven to be beneficial for pregnant mothers as well as partners and possibly, the mother-infant bonding during postpartum. In the following section, there will be an evaluation of current practices compared to recent research in this challenging field of depression and anxiety during pregnancy and postpartum.

Application to Clinical Practice

As stated above in the Introduction, the standard of practice for the management of depression and anxiety in adults is antidepressant medication and CBT, which have both been shown to improve depression symptoms (National Guideline Clearinghouse, 2012). It is common for antidepressant medication to be prescribed during both pregnancy and postpartum because of the quicker response time and effectiveness. Other frequently used methods of treatment include psychosocial and behavioral therapy interventions, which are also included in top recommendations for treatment of depression and anxiety.

When evaluating current practice techniques for treating prenatal and postnatal depression and anxiety, several aspects of care must be considered. First, is the treatment plan going to be effective for the patient and will her symptoms improve? When considering this question, this literature review research tends to be in agreement that antidepressant medication, especially SSRIs, appears to have a quicker response rate in symptom improvement compared to nonpharmacologic methods such as CBT. When compared to symptom control of the anxiety and depression aspects of MDD, antidepressant medication has been shown to work within four weeks, whereas the psychosocial treatment methods seem to take longer for improvement, but then reach similar response rates after a longer period of time (Sharp et al., 2010). This evidence does agree with current recommendations that antidepressant medications are effective in treating depression and anxiety in relation to pregnancy and postpartum. For a woman not wishing to begin medication therapy for her depression or anxiety symptoms, both group and individual CBT sessions have been shown to provide benefits as well (Salehi et al., 2016).

The second question to consider when determining a plan of care for a pregnant or breastfeeding woman with depression is if the method of treatment will affect the growing fetus/

newborn infant in terms of delivery and development long-term. The research stated above in this literature review does agree that the drug and metabolites are passed to the fetus through the bloodstream and to the infant through breastmilk. The research tends to agree that use of antidepressant medications have an increased risk of an earlier delivery and smaller infants, but do not seem to change the maternal or neonatal outcomes during delivery. There does, however, appear to be long-term effects in offspring exposed to antidepressant medications in pregnancy. Unfortunately, the effects of these medications in breastmilk has not yet been evaluated thoroughly to understand what the long-term results may be. Further research remains to be completed in this area.

In the clinical setting, because research continues to suggest that both pharmacologic and nonpharmacologic methods of treatment for depression and anxiety are beneficial, the decision to begin antidepressant medication or psychosocial therapy must continue to be a discussion for the patient and practitioner. Considerations such as severity of symptoms, risk to the fetus or infant health, and long-term response rates of the treatment options should be evaluated. Several other aspects of the treatment plan that also play an important role in a patient's decision is the cost of the possible treatments and the availability of psychosocial interventions.

In conclusion, because depression and anxiety continue to be present in pregnancy and the postpartum time, medical recommendations for treatment and management need to be cognizant of both maternal symptom management and the fetal/breastfeeding infant effects. Through the evidence shown above in the literature review, while both medications and psychosocial treatment benefit the mother, current guidelines may need to be adjusted to better preserve the safety of the children exposed to antidepressant medications. As research continues to be ongoing in this topic of prenatal and postnatal mental health, practice standards may change

to ensure the safety of the fetus/infant is maintained while the mother is receiving appropriate

care for her psychological well-being.

References

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental

disorders, 5th edition. Arlington, VA: American Psychiatric Association.

Alder, J., Urech, C., Fink, N., Bitzer, J., & Hoesli, I. (2011). Response to induced relaxation

during pregnancy: Comparison of women with high versus low levels of anxiety. *Journal

of Clinical Psychology in Medical Settings, 18,* 13-21. https://dx.doi.org/10.1007/s10880-

010-9218-z.

Bardal, S.K., Waechter, J.E., & Martin, D.S. (2011). Psychiatry. *Applied pharmacology (*pp.

369-390)*.* St. Louis, MO: Elsevier/Saunders.

Brandon, A. R., Trivedi, M. H., Hynan, L. S., Miltenberger, P. D., Broussard Labat, D.,

Rifkin, J. B., & Stringer, C. A. (2009). Prenatal depression in women hospitalized for

obstetric risk. *Journal of Clinical Psychiatry, 69* (4), 635-643.

Charlton, R., Jordan, S., Pierini, A., Garne, E., Neville, A., Hansen, A…. de Jong-van den

Berg, L. (2014). Selective serotonin reuptake inhibitor prescribing before, during and

after pregnancy: A population-based study in six European regions. *BJOG, 122,* 1010–

1020. http://dx.doi.org/10.1111/1471-0528.13143.

Decherney, A. H., Nathan, L., Laufer, N., & Roman, A. S. (2013). CURRENT diagnosis &

treatment: Obstetrics & gynecology, 11th edition. McGraw-Hill.

Dennis, C.L., Ross, L. E., & Grigoriadis, S. (2007). Psychosocial and psychological

interventions for treating antenatal depression. *Cochrane Database of Systematic Reviews

2007, 3,* CD006309. http://dx.doi.org/10.1002/14651858.CD006309.pub2.

Handal, M., Skurtveit, S., Furu, K., Hernandez-Diaz, S., Skovlund, E., Nystad, W., &

Selmer, R. (2016). Motor development in children prenatally exposed to selective

serotonin reuptake inhibitors: A large population-based pregnancy cohort study. *BJOG, 123,* 1908-1917. https://dx.doi.org/10.1111/1471-0528.13582

Hannerfors, A., Hellegren, A., Schijven, D., Illiadia, S., Comasco, E., Skalkidou, A., …Sundstrom-Poromaa, I. (2015). Treatment with serotonin reuptake inhibitors during pregnancy is associated with elevated corticotropin-releasing hormone levels. P*sychoneuroendocrinology, 58,* 104-113. http://dx.doi.org/10.1016/j.psyneuen.2015.04.009.

Klieger-Grossmann, C., Weitzner, B., Panchaud, A., Pistelli, A., Einarson, T., Koren, G., & Einarson, A. (2012). Pregnancy outcomes following use of escitalopram: A prospective comparative cohort study. *The Journal of Clinical Pharmacology, 52,* 766-770. https://dx.doi.org/10.1177/0091270011405524.

Molyneaux, E., Howard, L.M., McGeown, H.R., Karia, A.M., & Trevillion, K. (2014). Antidepressant treatment for postnatal depression. *Cochrane Database of Systematic Reviews 2014, 9.* https://dx.doi.org/10.1002/14651858.CD002018.pub2.

National Guideline Clearinghouse. (2012). Guideline summary: Diagnosis and treatment of depression in adults: 2012 clinical practice guideline. *Agency for Healthcare Research and Quality.* Retrieved from https://www.guideline.gov.

Rai, D., Lee, B.R., Dalman, C., Newschaffer, C., Lewis, G., & Magnusson, C. (2017). Antidepressants during pregnancy and autism in offspring: population-based cohort study. *BMJ, 358*, j2811. https://dx.doi.org/10.1136/bmj.j2811.

Rallis, S., Skouteris, H., McCabe, M., & Milgrom, J. (2014). A prospective examination of depression, anxiety, and stress throughout pregnancy. *Women and Birth, 27,* e36-e42. https://dx.doi.org/10.1016/j.wombi.2014.08.002.

Rampono, J. Simmer, K., Ilett, K., Hackett, L., Doherty, D., Elliot, R… Forman, T. (2009).

Placental transfer of SSRI and SNRI antidepressants and effects on the neonate.

Pharmacopsychiatry, 42, 95-100. http://dx.doi.org/10.1055/s-0028-1103296.

Salehi, F., Pourasqhar, M., Khalilian, A., & Shahhosseini, Z. (2016). Comparison of group

cognitive behavioral therapy and interactive lectures in reducing anxiety during

pregnancy: a quasi-experimental trial. *Medicine (Baltimore), 95,* 43.

https://dx.doi.org/10.1097/MD.0000000000005224.

Sharp, D.J., Chew-Graham, C.A., Tylee, A., Lewis, G., Howard, L., Anderson, I. … Peters,

T.J. (2010). A pragmatic randomized controlled trial to compare antidepressants with a

community-based psychosocial intervention for the treatment of women with postnatal

depression: The RESPOND trial. *Health Technology Assessment 2010, 14* (43), 1-153.

https://dx.doi.org/10.3310.hta14430.

Van Lieshout, R., Yang, L., Haber, E., & Ferro, M. (2017). Evaluating the effectiveness of a

brief group cognitive behavioural therapy intervention for perinatal depression. *Archives

of Women's Mental Health, 20,* 225-228. https://dx.doi.org/10.1007/s00737-016-0666-9.

Weissman, A.M., Levy, B.T., Hartz, A.J., Bentler, S., Donohue, M., Ellingrod, V.L., &

Wisner, K.L. (2004). Pooled analysis of antidepressant levels in lactating mothers, breast

milk, and nursing infants. *AM J Psychiatry, 161,* 1066-1078. Retrieved from

https://ajp.psychiatryonline.org/doi/pdf/10.1176/appi.ajp.161.6.1066.

Wisner, K.L., Sit, D.K., Hanusa, B.H., Moses-Kolka, E.L., Bogen, D.L., Hunker, D.F….

Singer, L.T. (2009). Major depression and antidepressant treatment: Impact on pregnancy

and neonatal outcomes. *AMJ Psychiatry, 166,* 557-566.

https://do.doi.org/10.1176/appi.ajp.2008.08081170.