CRITICAL DETERMINANTS OF THE RISK-BENEFIT ASSESSMENT OF ANTIDEPRESSANTS IN PREGNANCY: PHARMACOKINETIC, SAFETY AND ECONOMIC CONSIDERATIONS

by

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A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy

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Untreated depression in pregnancy may result in adverse health outcomes to both the mother and her unborn child. Pharmacotherapy with antidepressants is the most common treatment option for depression; however, the decision to treat with medication becomes complicated by pregnancy. Risk benefit assessments are critical tools to guide the treatment decision. Factors that should be included in these analyses include the pharmacokinetics and pharmacodynamics of antidepressants in pregnancy and their maternal and fetal safety. The economic cost of untreated maternal depression is also important to keep in mind.

When the pharmacokinetics of the antidepressants venlafaxine and bupropion were studied in pregnancy it was found that the apparent oral clearance rate of bupropion was increased in late pregnancy when compared to early pregnancy \((p = 0.03)\). There was a trend for lower area under the curve for these medications when the third trimester was compared to the first trimester. When the metabolism of antidepressants was investigated using hair analysis it was found that there was increased metabolism in pregnancy when compared to the postpartum period for citalopram \((p = 0.02)\) but not venlafaxine \((p = 0.77)\).
Follow up of depressive symptoms throughout pregnancy identified that depression scores were highest in the first trimester of pregnancy, which may be due to concurrent nausea and vomiting of pregnancy. A meta-analysis of paroxetine use in early pregnancy demonstrated that there was no increased risk for cardiac malformations; case-control studies had an odds ratio of 1.18 (CI\textsubscript{95}: 0.88 – 1.59) while a weighted average difference of 0.3% was found in case-control studies (CI\textsubscript{95}: -0.1 – 0.7%, \( p = 0.19 \)) The direct medical costs incurred by the Ontario government due to discontinuation of antidepressant medications in pregnancy was estimated to exceed $20,000,000 CAD.

The management of depression in pregnancy with pharmacotherapy is an important and complex issue. My study documents the advantages of conducting risk benefit assessments for vulnerable populations such as pregnant women with depression.
ACKNOWLEDGEMENTS

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APA – American Psychiatric Association
AUC – area under the curve
$C_{\text{max}}$ – maximum concentration
DSM-IV – Diagnostic and Statistical Manual of Mental Disorders, fourth version
ECT – electroconvulsive therapy
EPDS – Edinburgh Postnatal Depression Scale
FDA – Food and Drug Administration
GFR – glomerular filtration rate
MDD – major depressive disorder
MDE – major depressive episode
NVP – nausea and vomiting of pregnancy
SSRI – selective serotonin reuptake inhibitor
SNRI – selective norepinephrine reuptake inhibitor
TCA – tricyclic antidepressant
1.1 Statement of the Problem

Major depressive disorder (MDD), commonly referred to as depression, is a chronic and recurrent mental illness. It is estimated that over 100 million people worldwide are currently suffering from depression; it is predicted that by 2012, depression will be the leading cause of disease in the world. ¹

Depression affects both men and women; women however are disproportionately affected by this disorder; the lifetime occurrence of major depression is approximately 2–3 times higher in women than in men, regardless of ethnicity.² Annually, between 7% and 13% of women worldwide experience MDD.³ Furthermore, depression is the leading cause of disease for women between 15 and 44 years of age which approximates a woman’s childbearing years.⁴ Therefore, it is not surprising then that depression is one of the most common conditions to complicate pregnancy.

In spite of the high morbidity associated with depressive illness and the additional risks that the illness may pose in pregnancy, many clinicians fail to recognize, diagnose, and offer appropriate treatment for depression during pregnancy. Depression is a chronic
illness that needs to be managed; pregnancy does not change the need for effective treatment

Pharmacotherapy is the most commonly used treatment modality for the management of depression in non-pregnant populations. However, no standard of care exits for the management of depression during pregnancy nor is there consensus among clinicians regarding the most appropriate and effective ways to manage the condition during this time. This lack of consensus or widely accepted guidelines leaves clinicians with difficult treatment decisions when caring for pregnant women with depression. Furthermore, risk is inherent in every treatment decision that clinicians make. In light of this, clinicians must weigh both the risks and benefits associated with each treatment option they consider. The factors that go into this analysis are very important as they will ultimately guide the treatment decision.

1.2 Goals and Objectives

The decision to treat depression with pharmacotherapy during pregnancy or leave it untreated is critical, as it carries with it multi-factorial risks and benefits for both the expectant mother and her fetus. This research sought to evaluate critical factors that should be included in individualized risk-benefit assessments that are necessary for making this clinical decision in pregnant and depressed women. This dissertation will examine the following four elements:
• Pharmacokinetics of antidepressants in pregnancy

• The course of treated depression in pregnancy

• The safety of antidepressants (paroxetine) in pregnancy

• The economics of untreated maternal depression

The specific objectives of this research are as follows:

1. To describe metabolic and pharmacokinetic changes during pregnancy for selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs) using blood sampling and hair analysis.

2. To evaluate depressive symptoms throughout pregnancy and the early postpartum period in women receiving antidepressant therapy

3. To evaluate the teratogenic risk of paroxetine after exposure in early pregnancy

4. To estimate the direct medical cost to the Ontario government resulting from antidepressant discontinuation in pregnancy

1.3 Study Hypotheses

It is hypothesized that:

1. Changes in drug metabolism will be seen during late pregnancy including increased apparent oral clearance rate and increased parent:metabolite ratios for SSRIs and SNRIs
2. Depressive symptoms, as measured by the Edinburgh Postnatal Depression Scale, will increase as pregnancy progresses if dose modifications are not made, due to the increased clearance of the antidepressant medications in late pregnancy.

3. Paroxetine is not teratogenic in humans.

4. Antidepressant discontinuation during pregnancy results in heavy costs to the health care system.
2.1 Pathophysiology of Depression

The exact etiology of depression is unknown, but there is strong evidence of a genetic predisposition for depression. Epidemiological studies have shown that approximately 40% - 50% of the risk for depression is genetic; the relative risk for the disorder is 1.5 – 3 times greater when a first degree biological relative is diagnosed with depression than when they are not. Biological, psychological and sociocultural factors have also been implicated in shaping this disorder; stress (acute and chronic) may also play an important role in the development of MDD.

Various theories exist that try to elucidate the biological origins of depression. The monoamine hypothesis of depression has been the leading theory for many years. It postulates that depression is caused by a deficiency in the biogenic monoamines, serotonin, norepinephrine and/or dopamine in synaptic clefts that results in interference to brain circuits involved in their signaling pathways. The serotonergic system is involved in modulating mood, appetite and sleep while norepinephrine plays a variety of roles including regulating emotions such as anxiety, aggression, pleasure and it is involved in the regulation of appetite, weight, sex drive, cognition and attention.
It is unlikely however that depression results solely from a depletion of monoamine transmitters. Stress and hormones that modulate the body’s response to stress also appear to be involved in the pathophysiology of MDD. The hypothalamic-pituitary-adrenal (HPA) axis becomes activated during periods of acute and chronic stress; current evidence suggests that increased levels of the glucocorticoid cortisol and corticotrophin-releasing factor (CRF) are linked to depression. It is proposed that the dysregulation of the HPA and hippocampus contribute to depression via hypercortisolism and enhanced hypothalamic CRF transmission.\textsuperscript{12, 13} Clinically, decreased activity of the HPA, including a reduction in CRF, has been found in patients that recovered from depression.\textsuperscript{14}

It should be kept in mind that depression is often comorbid with other psychiatric illnesses such as anxiety; depression can also occur in the context of other medical conditions such as diabetes, stroke, cancer and endocrine disturbances (i.e. hypothyroidism).

2.2 \textit{Clinical Presentation}

Depression is a complex and heterogeneous disorder. Depressive symptoms often present with varying degrees of intensity and duration. Consequently, MDD can be classified as mild, moderate or severe depending on the degree to which these symptoms impair an individuals daily functioning in their social and/or occupational settings.\textsuperscript{8}

Clinical depression is characterized by isolated or repeated major depressive episode(s) (MDE). A MDE is defined as a 2 week period or longer in which there is depression and/or a loss of interest or pleasure in usual activities.\textsuperscript{15} In addition to
prolonged depressed mood or loss of interest, the patient may also present with various clinical signs and symptoms of depression, which include but are not limited to anhedonia, significant fluctuations in weight, changes in appetite, insomnia or hypersomnia almost daily, fatigue, excessive or inappropriate feelings of worthlessness or guilt, diminished libido, observed psychomotor agitation/retardation, difficulty concentrating and recurrent suicidal ideations. An important caveat is that none of the above mentioned symptoms can be due to direct physiological effects of a substance or medical condition, be accounted for by bereavement, or meet the criteria for other psychiatric conditions.⁸ (Table 1)

**Table 1: Symptoms of Major Depressive Disorder**

<table>
<thead>
<tr>
<th><strong>PHYSICAL SYMPTOMS</strong></th>
<th><strong>PSYCHOLOGICAL SYMPTOMS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Appetite (increase or decrease)</td>
<td>Depressed mood</td>
</tr>
<tr>
<td>Sleep disturbances (insomnia or hypersomnia)</td>
<td>Loss of interest and/or pleasure in daily activities</td>
</tr>
<tr>
<td>Weight fluctuations</td>
<td>Suicidal ideation (recurrent)</td>
</tr>
<tr>
<td>Fatigue / Decreased energy</td>
<td>Guilt/Worthlessness</td>
</tr>
<tr>
<td>Psychomotor disturbances (agitation/retardation)</td>
<td>Hopelessness</td>
</tr>
<tr>
<td>Diminished concentration</td>
<td>Diminished libido</td>
</tr>
</tbody>
</table>
2.3 Depression in Pregnancy

It was once assumed that pregnancy was a time of emotional wellbeing for women, however, it is now known that pregnancy may act as a trigger for the return of depressive symptoms in women who are susceptible to the disorder. Many hormonal changes are associated with pregnancy including gradually increasing levels of estradiol, progesterone, CRF, corticotrophin and cortisol. Since CRF and estrogen are principal regulators of the HPA, their increased levels result in the increased secretion of cortisol, which as discussed above, is associated with vulnerability to depression.16

It has been estimated that as many as 30% of women suffer from some degree of depression during pregnancy. Some studies report the prevalence of depression in pregnancy to be between 25% and 35%, with approximately 10% of women meeting criteria for MDD.17 A recent meta-analysis estimated the disease burden of depression in pregnancy by trimester. It was found that rates in the first, second and third trimesters were 7.4%, 12.8% and 12.0% respectively.18

It is imperative that depression during pregnancy be recognized and managed in obstetric populations, as untreated depression is a significant risk factor for unfavourable pregnancy outcomes such as prematurity, low birth weight, increased admissions to neonatal care units and delays in cognitive and emotional development.19 Pregnant women with depression are also more likely to use alcohol or illicit drugs which poses further risks to the developing fetus.20 However, the unborn fetus in not the only one put at risk, there are risks to the mother that are associated with not treating depression in pregnancy, these include impaired self-care, failure to follow prenatal guidelines, suicidal
ideations, self-injurious behaviors, and lower than expected weight gain.\textsuperscript{20} In addition, it has been shown that women who are depressed during pregnancy are at a greater risk for post-partum depression.\textsuperscript{3} Consequently, the overall objective of treating depression in pregnancy is to maximize maternal health while minimizing the risk to the unborn fetus.

Unfortunately, depression often goes unrecognized and therefore untreated in the obstetric population for a variety of reasons including the overlap of the somatic symptoms of depression with those of pregnancy.\textsuperscript{21} For instance, sleep and appetite disturbance, diminished libido and low energy are symptoms of both conditions; this duplication of symptoms further impedes the accurate diagnosis of depression in pregnancy. Therefore, it is important to be aware of some of the distinguishing features of depression. The cognitive and affective aspects of depression such as anhedonia, excessive or inappropriate feelings of guilt and hopelessness and persistent thoughts of suicide or self-harm, allow symptoms of pregnancy to be discerned from those of depression. The symptoms of depression and pregnancy are most similar in the first and third trimesters of pregnancy.\textsuperscript{22}

2.4 Screening and Diagnosis

No reliable or practical biological marker currently exists that can predict those at risk for depressive disorders. At present, the diagnosis of depression is based upon a core set of clinical signs and symptoms exhibited by the patient. The Diagnostic and Statistical Manual of Mental Disorders, fourth version (DSM-IV) has put forth the following criteria for the diagnosis of depression: a person must have a MDE and display
five or more of the clinical symptoms described above.\textsuperscript{15} This is the most widely accepted and utilized criteria for the diagnosis of depression; this descriptive approach facilitates a reproducible diagnosis regardless of the clinical or cultural setting. The diagnosis therefore relies on both patient self-report regarding the duration and severity of their symptoms and the clinician’s observations of behavioral and functional impairment. The DSM-IV does not have explicit criteria for the diagnosis of antenatal depression, nor does it address the confounding effect of pregnancy symptoms on those used to determine depression.

The diagnosis of depression by clinicians is costly and time-consuming, thus lay – administered screening tools and patient self-report questionnaires have been developed to aid in the identification of depressive symptoms. It is important to note, that screening instruments and self-report questionnaires cannot diagnose depression, they can however, provide an indication of the severity of depressive symptoms. Patient’s scoring above the cutoff value of any particular scale, are more likely to be diagnosed with MDD as higher scores are regularly associated with more severe symptoms.\textsuperscript{23} Screening tools provide a simple mechanism to help increase the awareness of healthcare providers and aid in the early detection and diagnosis of depression.

Several factors need to be taken into consideration when deciding upon an appropriate instrument for screening; the characteristics of the population to be screened, the psychometric properties of the tool, how straightforward it is to use, time required to administer and score the questionnaire, and the actual cost of obtaining the measure. The Edinburgh Post Natal Depression Scale (EPDS), the Center for Epidemiologic
Studies Depression Scale (CES-D) and the Beck Depression Inventory (BDI) are screening instruments that have been commonly used to screen for depression in obstetric populations.

The EPDS was originally designed to detect post-natal depression, the scale has since been validated for use in obstetric populations. The EPDS focuses on the cognitive and affective aspects of depression rather than the somatic symptoms due to the overlap of physiological symptoms of depression and those of a typical pregnancy. The EPDS is a self-report scale that examines a person’s mood in the last week; the scale has been found to have a sensitivity of 86% and a specificity of 78%. The EPDS consists of 10 questions that are each assigned a score from 0 – 3; the maximum possible score is 30. A score above 12 is accepted to indicate probable depressive disorder. The EPDS is currently available in 23 languages.

The CES-D has not been validated for use in pregnancy; however, it has been extensively used for research on depression in pregnancy. It is a 20 item measure which examines mood in the past week. The total possible score is 60, with scores greater than or equal to 16 corresponding to depressive symptomology in the general population.

The BDI is a self-report questionnaire that has been validated for use in an obstetric population; however it was initially designed to evaluate the intensity of depression in a psychiatric population. The scale examines a person’s mood for the present day and consists of 21 items which include questions regarding the somatic symptoms of depression. The maximum possible score that can be obtained with this measure is 63; scores greater than or equal to 16 are indicative of depression.
Not surprisingly, it has been found that when the BDI and the CES-D have been used on symptomatic pregnant women they generate higher scores and have a larger proportion of false positives as the assessment by these scales relies in part on the somatic symptoms of depression.\textsuperscript{28-30} This has not been found when using the EPDS in a similar population. This illustrates that there are certain inherent limitations present with the use of any screening tool. Depression screening instruments are limited in that they are not able to address the degree of impairment caused by the condition, nor are they able to ascertain the duration of symptoms or if a co-morbid condition(s) exists. Therefore, if a positive result is produced by a screening measure, a clinical diagnosis should be made using DSM-IV criteria. Furthermore, depression may manifest itself differently depending on a person’s age, gender or cultural background\textsuperscript{23}; hence the value of sound clinical judgment should not be forgotten.

It may not be feasible to screen all obstetric patients for depression, but the literature suggests that certain women may be at higher risk for prenatal depression than others. This includes women with a history of depression, younger age, limited social support, living alone, a greater number of children, and comorbid illness; depression has also been shown to be negatively correlated with socioeconomic status (SES).\textsuperscript{17, 31} These women may benefit most from being screened for depression during the perinatal period. (Table 2)
Table 2: Risk Factors for Depression in Pregnancy

<table>
<thead>
<tr>
<th><strong>BIOLOGICAL</strong></th>
<th><strong>PSYCHOSOCIAL</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior history of depression or mood disorders</td>
<td>Unplanned pregnancy</td>
</tr>
<tr>
<td>Prior history of post-partum depression</td>
<td>Younger age</td>
</tr>
<tr>
<td>Prior history of premenstrual dysphoric disorder</td>
<td>Single motherhood</td>
</tr>
<tr>
<td>Family history of psychiatric illness</td>
<td>Limited social support</td>
</tr>
<tr>
<td></td>
<td>History of child abuse</td>
</tr>
<tr>
<td></td>
<td>Low level of education</td>
</tr>
<tr>
<td></td>
<td>Unemployment</td>
</tr>
<tr>
<td></td>
<td>Substance abuse and smoking</td>
</tr>
</tbody>
</table>

2.5 Treatment Modalities for Depression

2.5.1 Non-pharmacological options

Depression is associated with significant morbidity and an increased risk of mortality if left untreated; approximately 15% of patients with a mood disorder commit suicide, moreover, at least 66% of all suicides are preceded by depression. Fortunately, early identification and proper treatment significantly decrease the negative impact of depression in most patients. In obstetrics, there are two patients that must be taken into account when choosing treatment options; the mother and her developing fetus.
Treatment should ultimately resolve the mother’s condition without causing harm to the fetus.

Interventions that can be used to manage depression can take various forms such as light therapy, electroconvulsive therapy (ECT), psychotherapy or pharmacotherapy. Psychotherapy, pharmacotherapy and ECT have been shown to be the three most effective treatments for depression; these treatment modalities can be used alone or in combination with each other. Alternative treatments such as acupuncture, herbal remedies and guided imagery, do exist, however there is little to no scientific evidence that has established their efficacy and/or effectiveness. Factors that need to be taken into consideration when choosing a treatment option include, patient preference, compliance, and treatment and resource availability.

ECT in pregnancy is considered to be relatively safe; it has been used to treat severe, resistant depression in pregnant women for over 50 years. This treatment has been reported to be highly efficacious and low risk during all three trimesters of pregnancy and into the post-partum period. As with any treatment, there are potential risks associated with ECT during pregnancy; these include gastric reflux, aortocaval compression, spontaneous abortion, preterm labor and placental abruption. ECT is not a first-line treatment for depression in pregnancy due to the effectiveness and non-invasiveness of other methods.

Psychotherapy can take various forms including the two most commonly used, interpersonal psychotherapy (IPT) and cognitive-behavioral therapy (CBT). IPT is a structured therapy that seeks to improve an individual’s social interactions and coping skills for life transitions and conflict while CBT aims to modify negative cognitive
processes. One study found IPT to be effective at significantly improving mood in depressed pregnant women after 16 weeks of therapy. There is a lack of data on the effectiveness of CBT during pregnancy, although it has been shown to be useful for post-partum depression. It should be kept in mind, that the usefulness of psychotherapy can be limited by its high resource consumption and costs as well as the availability of skilled therapists to provide the service.

2.5.2 *Pharmacological Treatment*

Treatment with antidepressants is the most common form of therapy for depression regardless of pregnancy status; SSRI’s and SNRI’s are among the most widely used antidepressants as they have a better side effect profile than the older generation tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs). It has been demonstrated that many medications including antidepressants and their metabolites cross the placenta resulting in fetal exposure. The question then arises does fetal exposure equate to fetal harm? In the general population, the baseline risk for having a baby with a major malformation is 1% - 3%; this occurs purely by chance and is not the result of exposure to teratogenic agents. There is a growing body of clinical evidence regarding the relative safety of antidepressants in all stages of pregnancy. No association has been found between TCAs and major fetal malformations. A recent meta-analysis by Einarson et al. summarizes many of the studies undertaken to determine the safety of the newer antidepressants, including SSRI’s and SNRI’s, in pregnancy; these medications were not found to be associated with increased teratogenic risk. It is also reassuring to
note that *in utero* exposure to TCAs and fluoxetine have not been shown to effect the global IQ, language, temperament or behavioral development of children followed up to four years of age.\textsuperscript{41-43}

Concern still exists however, regarding the use of antidepressants during pregnancy as data has been published suggesting an increased incidence of persistent pulmonary hypertension (PPHN) in infants whose mothers used SSRI’s during late pregnancy (after 20 weeks)\textsuperscript{44} and an increased risk for cardiac malformations in infants exposed to paroxetine (Paxil\textsuperscript{TM}) during gestation;\textsuperscript{45} further research needs to be conducted in order to establish a causal relationship between SSRI medications and these negative outcomes.

Women that choose to continue using antidepressants during pregnancy may have infants that may be at risk for poor neonatal adaptation syndrome (PNA), a condition that results from the use of antidepressants (SSRIs) in late pregnancy. It is characterized by self-limiting symptoms such as jitteriness, irritability, hypoglycemia and respiratory distress; these symptoms typically appear within the first 48 hours after birth and resolve within two to four weeks after birth. The absolute risk for PNA ranges up to 30\%.\textsuperscript{46} It is important to note that no neonatal deaths have been reported in association with third trimester exposure to antidepressants.

Due to the complex and sometimes conflicting nature of the information available, many women who take antidepressants prior to conception are advised or choose to discontinue therapy upon confirmation of pregnancy due to perceptions of teratogenic risk.\textsuperscript{47} Discontinuation of antidepressant medication during pregnancy has been associated with adverse maternal consequences. In a preliminary study, it was
demonstrated that depressed women who abruptly discontinued their medication upon confirmation of pregnancy experienced both physical and psychological effects, including suicidal ideation.\textsuperscript{47} Cohen et al. have shown that women who discontinued antidepressant medications prior to conception or during early pregnancy had an increased risk for depressive relapse during pregnancy compared with women who maintained therapy throughout pregnancy.\textsuperscript{48} It has been shown that providing women with evidence-based counseling regarding the safety of medications in pregnancy is an effective means by which to lower fear of teratogenic risk and increase the likelihood of women maintaining needed pharmacotherapy during gestation.\textsuperscript{47, 49} It is important that depressed women who are planning or pregnant receive evidence-based information that will equip them to make a decision, along with their health-care provider, regarding their treatment options during this time; women have terminated otherwise wanted pregnancies due to fear and misinformation.

\textbf{2.5.3 Guidelines/position statements}

There is a dearth of guidelines or consensus statements specifically pertaining to the treatment and management of depression in pregnancy. A small section is devoted to this topic in the Practice Guidelines of the American Psychiatric Association (APA). These guidelines briefly touch upon three main treatment options for depression in pregnancy; psychotherapy, antidepressant medication and electroconvulsive therapy (ECT). The guidelines suggest that whenever possible a pregnancy be planned in consultation with a psychiatrist (or health care provider); this may not always be feasible
as up to 50% of pregnancies are unplanned. In regards to treatment, the guidelines advise that pregnancy, lactation or the desire to become pregnancy may be an indication for psychotherapy as an initial treatment. However it cautions that there may be the risk for delayed effectiveness and onset of symptom alleviation, thus these issues should be considered when choosing this as a treatment modality. Antidepressant treatment in pregnancy is recommended for women who have or are in remission from MDD, or for women who are on maintenance therapy and are deemed at high risk for reoccurrence of depression if pharmacotherapy is discontinued. In addition, if antidepressants are used during gestation, it is suggested that maternal weight gain be carefully monitored and that a gradual tapering off of medication be considered 10-14 days prior to the expected (or planned) date of delivery to circumvent any potential neonatal withdrawal symptoms. Antidepressant therapy may be resumed at the pre-pregnancy dose following delivery if the woman is deemed to be at risk from her MDD. The APA recommends ECT for patients who are unsuitable for or unresponsive to medication, who have MDD with psychotic features or who have an individual preference for this treatment modality after being informed about its risks and benefits in pregnancy.50

Establishing the safety of medications is often difficult as women of childbearing age are frequently excluded from participation in clinical trials due to concerns regarding potential teratogenicity, other adverse pregnancy outcomes and ensuing liability and litigation issues. As such, agencies such as the US Food and Drug Administration (FDA) warn against the use of all psychotropic drugs in pregnancy, since limited data is available from randomized controlled trials.4 This however creates further barriers to
treatment for women who become pregnant and require treatment for their depressive disorder.

In 2001, the Canadian Psychiatric Association in collaboration with the Canadian Network for Mood and Anxiety Treatments developed recommendations for the treatment of depression in pregnancy. They suggested that fluoxetine be the first line treatment, while citalopram, fluvoxamine, paroxetine and sertraline be second line treatments. Finally they recommended that TCAs, ECT, and interpersonal therapy be used as third line treatments for depression in pregnancy. However, it should be kept in mind that not all antidepressants are equally effective for everyone; there is variability in an individual’s response to different medications.

The American College of Obstetricians and Gynecologists recommend that the use of SSRIs to manage depression in pregnancy should be individualized based on the specific risks and benefits to the patient. It also cautions against the use of Paxil ® in pregnancy when possible, due to reports of potential increased risk for fetal cardiac defects, persistent pulmonary hypertension of the newborn (PPHN) and other negative effects.

These various position statements and guidelines demonstrate the lack of consensus regarding the best way to manage depression during pregnancy. Individual risk-benefit assessments must be undertaken to determine the best course of action for each patient.
2.6 Pharmacology of Antidepressants

Antidepressant medications can be classified into seven different classes depending on their mechanism of action. The tricyclic antidepressants (TCAs) and the monoamine oxidase inhibitors (MAOIs) represent the older generation of antidepressant medications while the newer generation includes the selective serotonin reuptake inhibitors (SSRIs), the serotonin-norepinephrine reuptake inhibitors (SNRIs), the norepinephrine-dopamine reuptake inhibitor (NDRI), the noradrenergic and specific serotonergic antidepressant (NaSSA) and the serotonin antagonist reuptake inhibitor (SARI). The newer generation of antidepressants are more commonly prescribed because of their more favourable side-effect and safety profiles. Globally, SSRI’s are the most widely prescribed antidepressant medication today; in Canada the SSRI’s accounted for 81% of the drugs used to treat depression in 2003. The focus of this section will be on SSRIs, SNRIs and NDRIs.

2.6.1 Selective Serotonin Reuptake Inhibitors

Mechanism of action

The serotonin transporter (SERT) is the molecular target of SSRIs. SERT is an integral membrane protein that acts as a pump and is responsible for the reuptake of serotonin (Figure 1) from the synaptic cleft into presynaptic cells; this reuptake effectively terminates serotonin’s neurotransmitter actions.
SSRIs exert their antidepressant action through selective binding to SERT. The binding of the drug serves to inhibit the reuptake of serotonin into serotonergic neurons. The initial result is increased availability of serotonin primarily in the somatodendritic area; reuptake of serotonin is also blocked to a lesser extent at the axon terminal. Chronic administration of SSRIs leads to the desensitization of the serotonin -1A autoreceptors found in the somatodendritic area of the neuron; this desensitization is a result of the sustained higher levels of serotonin. The result is that the desensitized serotonin-1A autoreceptor allows the serotonergic neuron to transmit neuronal impulses more readily, as it is less susceptible to inhibition by serotonin, and consequently more serotonin is released from the axon terminal. 53 It is of note that the onset of clinical action seen with these medications is also a delayed process.

Figure 1: Chemical structure of serotonin (5-HT)
Fluoxetine was the first SSRI to be introduced successfully into the market in 1986; it was marketed under the proprietary name Prozac® in North America. Fluoxetine is approved for several indications in the United States including major depressive disorder, obsessive compulsive disorder and panic disorder.\(^{54}\)

Fluoxetine is a 50/50 racemic mixture of R- and S- fluoxetine enantiomers; R- and S-enantiomers are equipotent at blocking serotonin reuptake. (Figure 2) Fluoxetine, however, is the least selective of all the SSRIs.\(^{55}\)

Fluoxetine undergoes first-pass metabolism and has an oral bioavailability of approximately 80%: peak plasma concentrations are reached within six to eight hours of administration. Fluoxetine is 95% plasma protein bound. Fluoxetine undergoes hepatic metabolism to a pharmacologically active metabolite called norfluoxetine; CYP2C9 and CYP2D6 play a major role in this metabolic conversion while CYP3A4 and CYP2C19 play lesser roles. The average terminal half-life of fluoxetine ranges between 24 and 96 hours; norfluoxetine has a more extensive half-life of 168 – 360 hours.\(^{56}\)

\[\text{Figure 2: Chemical structure of fluoxetine}\]
**Sertraline**

Sertraline was first introduced as part of the SSRI family in 1991 and marketed under the name Zoloft®. Sertraline is approved to treat major depressive disorder, panic disorder and obsessive compulsive disorder. This medication is marketed as a non-racemic mixture of the S-enantiomer (Figure 3).\(^{54}\)

After oral administration, sertraline is slowly absorbed from the GI tract resulting in an extended time to peak plasma concentrations (T\(_{\text{max}}\) = 6 – 8 hours). The oral bioavailability of sertraline is 44% and it is 98.5% plasma protein bound. The mean elimination half life of sertraline has been reported to be approximately 26 hours. Like other members of the SSRI family, sertraline undergoes hepatic metabolism. This process, which is in part mediated by CYP3A4, produces an pharmacologically active primary metabolite, desmethylsertraline. This metabolite however, has substantially less activity than the parent compound and is thought not to contribute significantly to the clinical effects of sertraline.\(^{57}\)

![Chemical structure of sertraline](image)

**Figure 3:** Chemical structure of sertraline
**Paroxetine**

Paroxetine was first released into the market in 1992 under the trade name Paxil®. Major depressive disorder, panic disorder, obsessive-compulsive disorder and generalized anxiety disorder are some of the indications it is currently approved to treat in the United States. It is marketed as a non-racemic mixture of the R-enantiomer (Figure 4).⁵⁸

Paroxetine is a potent serotonin reuptake blocker; however it is less selective than some of the other SSRIs (ie: sertraline and fluvoxamine). This drug undergoes extensive first-pass metabolism in the liver resulting in an oral bioavailability of ~ 64%. Peak plasma concentrations are achieved within five hours of oral dosing. Paroxetine is 93% plasma protein bound and has a mean elimination half-life of 21 hours. The metabolism of paroxetine occurs in the liver and is mediated in part by CYP2D6 which produces pharmacologically inactive metabolites.

![Chemical structure of paroxetine](image)

**Figure 4:** Chemical structure of paroxetine
Citalopram

Citalopram was first introduced into the United States market in 1998 as Celexa®. It is a racemic drug mixture with the S-enantiomer being the more potent form (Figure 5); the S-enantiomer is currently being marketed under the name Ciprolex®. Citalopram is approved to treat major depression, social anxiety disorder and panic disorder. 54

Citalopram undergoes hepatic first-pass elimination, however, this does not appear to affect the oral bioavailability of the drug which is 80%. Peak concentrations of citalopram occur approximately 2 – 4 hours after ingestion; it is 82% protein bound. The mean elimination half-life of citalopram is approximately 36 hours. Citalopram is metabolized by CYP2C19 and CYP3A4 producing the pharmacologically active major metabolite desmethylicitalopram; however, this metabolite plays a negligible role in the clinical activity of citalopram. 56

Figure 5: Chemical structure of citalopram
2.6.2 *Serotonin/Norepinephrine Reuptake Inhibitors*

*Mechanism of Action*

The SNRIs exert their pharmacological activity by blocking the reuptake of the monoamines, norepinephrine (NE) (Figure 6) and serotonin. Their sites of action are the serotonin and norepinephrine reuptake pumps on serotonergic and noradrenergic neurons. The blockade of the serotonin transporter by SNRIs results in the same cascade of events as outlined for the SSRIs in the above sections.

The norepinephrine transporter (NET) is located on the presynaptic terminal of the noradrenergic neuron. When SNRIs bind to the transporter they block norepinephrine reuptake, leading to increased levels of the neurotransmitter which eventually leads to the down-regulation of β-adrenergic receptors. 59

![Chemical structure of norepinephrine](image)

*Figure 6: Chemical structure of norepinephrine*
Venlafaxine was first introduced in 1993 under the brand name Effexor ® (Figure 7). It is marketed as a racemic mixture of its R- and S- enantiomers, both of which are pharmacologically active. Venlafaxine is indicated for major depression, social anxiety disorder, panic disorder and generalized anxiety disorder.  

Following oral administration, venlafaxine undergoes extensive first-pass metabolism; it is 45% bioavailable and 27% plasma protein bound. Peak plasma concentration are reached 2 hours after oral administration. The primary route of venlafaxine metabolism is via CYP2D6 producing the active metabolite O-desmethylvenlafaxine. Venlafaxine has an elimination half-life of 5 hours, while its active metabolite has a half-life of 11 hours. 

At low doses venlafaxine inhibits serotonin reuptake, while at medium to high doses it blocks serotonin as well as norepinephrine reuptake. At very high doses, venlafaxine shows weak interaction with dopamine receptors. 

Figure 7: Chemical structure of venlafaxine
Bupropion

Bupropion was first introduced into the market as an antidepressant in 1985 under the trade name Wellbutrin®; in 1997 it was also introduced as a smoking cessation agent under the name Zyban®. The exact mechanism of bupropion’s antidepressant activity is not known, but it appears to be mediated through its increased turnover of NE in the body and to a lesser extent the blockade of noradrenergic and dopaminergic receptors.\textsuperscript{59}

Bupropion is a racemic mixture (Figure 8). No bioavailability data exists for bupropion in humans; in animals bioavailability ranges from 5% - 20%. Bupropion is 84% plasma protein bound and produces peak plasma levels within two hours after oral administration. The mean elimination half-life of bupropion is approximately 21 hours. This drug is extensively metabolized to three active metabolites – hydroxybupropion, threohydrobupropion and erythrohydrobupropion; CYP2B6 plays a primary role in the formation of hydroxybupropion.\textsuperscript{61}

\begin{figure}[h]
\centering
\includegraphics[scale=0.5]{bupropion_structure.png}
\caption{Chemical structure of bupropion}
\end{figure}
2.7 Changes in metabolism of antidepressants in pregnancy

Physiological changes occur during pregnancy that can impact the way medications are handled by the body and ultimately their therapeutic effect. These physiological changes include an expansion of the plasma volume, a reduction in intestinal motility resulting in increased GI and intestinal emptying time, hypoalbuminemia, a reduction in gastric acid secretions resulting in an increased gastric pH, increased hepatic metabolism and renal clearance. Consequently the plasma levels of drugs may be decreased, absorption thus the onset of action of a drug may be delayed and protein binding may be decreased.

The increased metabolism of nicotine in pregnancy has been described by Dempsey et al.\textsuperscript{63}, this phenomenon has also been seen with cyclosporine in pregnancy.\textsuperscript{64,65} In addition, there have been reports of the need for an increase in the daily dosage of certain selective serotonin reuptake inhibitors (SSRIs) during pregnancy in order to keep depressive symptoms under control.\textsuperscript{66}

A review of the existing literature shows that the pharmacokinetics of antidepressant medications in pregnancy is not well studied. To date there have been two reports that described the pharmacokinetics of tricyclic antidepressants (TCAs) in pregnancy and three studies that examined the pharmacokinetics of the newer antidepressants in human pregnancy.

The two earliest reports described changes in blood levels of TCAs; the first describes two case reports and the second is a case series of eight women. The first case report discusses a woman on 175 mg of imipramine. Blood levels were obtained 6
months prior to conception and then again in the second and third trimesters in addition to in the post-partum period. The woman’s dosage was increased in the late stages of the second trimester and again in the third trimester in response to return of depressive symptoms. The second case report details nortriptyline levels for the same time course as the first patient. The patient’s pregravid dose of nortriptyline was 125 mg/day and was increased to 150 mg/day by the third trimester; the levels of the drug in plasma had dropped to almost half of the pre-pregnancy levels. The case series looked mainly at nortriptyline (6 out of 8 women); clomipramine and imipramine were also studied. Drug levels were obtained from plasma when the women were not pregnant and again in their third trimester of pregnancy. It was found that the final dose of medication required in pregnancy was 1.3 to 2 times greater than that required in the non pregnant state. Overall TCA levels decreased during pregnancy such that an increase in medication was required to attenuate depressive symptoms in both studies, thus suggesting altered pharmacokinetic parameters.

The first study examining the SSRIs, looked at various endpoints regarding the use of citalopram in pregnancy and lactation, including changes in citalopram concentrations during the second and third trimesters. The trough concentrations of 11 women taking 20-40 mg of citalopram were obtained at various time points; once in the second trimester, twice in the third trimester and four times in the early post-partum period. It was found that maternal trough concentrations of citalopram were low during pregnancy when compared to values from their depressed non-pregnant counterparts on similar dose regimens; one woman in the study had to increase her daily dose of medication.
The same research group then conducted a similar study in pregnant women who used 20 – 40 mg of fluoxetine to manage their depression. Blood samples were obtained once, late in the third trimester and four times in the early post-partum period. The trough concentration of fluoxetine was determined from these samples; eleven women completed the study. Again it was found that depressed pregnant women had considerably lower trough concentrations of fluoxetine than their non-pregnant counterparts taking similar doses; one patient required a dose adjustment to a higher level.\(^{70}\)

The third and most recent study examined women taking citalopram (n = 5) or sertraline (n = 6) during pregnancy.\(^{71}\) Eleven women participated in the study; the dose of their medication was documented across the pregnancy. Trough plasma levels were obtained at six time points: 20, 30 and 36 weeks of gestation, delivery and 2 and 12 weeks postpartum. The mean dose to corrected plasma concentration (L/D) ratios were used as a surrogate indicators of metabolism. Eighty percent of women taking citalopram showed increased metabolism between 20 weeks gestation and delivery, while 83% of women taking sertraline displayed the same pattern of metabolism. Some women developed increased depressive symptoms in the third trimester and had to increase their dosage accordingly.

To date, no study has been completed examining the full pharmacokinetic profile of antidepressants in pregnancy. These data would help inform the development of dosing regimens for pregnant women suffering from depression and thus play a key role in the risk benefit assessments clinicians must undertake with their patients.
Two studies were undertaken to investigate changes in antidepressant metabolism during pregnancy. The first study compared the pharmacokinetics of SSRIs in the first and third trimesters of pregnancy using blood while the second study examined the metabolic ratios of the parent compound (antidepressant) to its metabolite using hair analysis.

3.1 A comparison of pharmacokinetics and pharmacodynamics of venlafaxine and bupropion in the first and third trimesters of pregnancy

Pregnancy induced pharmacokinetic changes may affect the dose required to maintain effective therapy; these changes include expanded plasma volume, reduced plasma protein binding and increased cytochrome activity leading to higher clearance rates.\textsuperscript{62} If the need for dose increases during pregnancy goes unrecognized the depression may be subtherapeutically managed leaving the woman vulnerable to relapse.

Several studies have demonstrated pharmacokinetic changes of antidepressants during pregnancy. The tricyclic antidepressants are one example of medications that have been shown to require greater doses in pregnancy to remain effective,\textsuperscript{67,68} due to their increased metabolism by the cytochrome 2D6.\textsuperscript{72} Conversely, less drug may be required if
enzymatic activity of metabolizing enzymes is decreased, as is the case of CYP2C19 and the antimalarial drug proguanil.\textsuperscript{73,74}

However, when it comes to the SSRIs and SNRIs, there is a paucity of data regarding their pharmacokinetics in pregnancy. Two studies examined citalopram and fluoxetine in pregnancy and found low trough levels and increased metabolism of these medications during pregnancy.\textsuperscript{69,70} The objective of this study was to compare the pharmacokinetics and pharmacodynamics of individual patients in the first and third trimesters of pregnancy taking venlafaxine and bupropion.

**Methods**

**Subjects**

Women were recruited from the Motherisk program, a teratogen information service at the Hospital for Sick Children in Toronto, Ontario. Women calling the counseling line regarding the use of antidepressants in pregnancy were informed about the study and its requirements and asked to participate. Women in their first trimester (\(\leq 12\) weeks) who had a diagnosis of depression (either by a family physician or psychiatrist) and were currently on monotherapy for depression for greater than four weeks were included in the study. Antidepressants being used for indications other than depression, concurrent use of other psychoactive medications and gestation greater than 13 weeks were criteria for exclusion. The protocol for this study was approved by the Research Ethics Board of The Hospital for Sick Children in Toronto.
Blood Sampling Procedure

Women attended a clinic at the Hospital for Sick Children where the blood sampling was performed; they came once in the first trimester and once in the third trimester of their pregnancy. On each visit, serial blood samples were collected over a ten hour time period. Prior to the commencement of blood sampling, long term venous access via an indwelling catheter was established by a nurse and height and weight data were recorded. Women brought their prescribed antidepressant medication with them to the clinic; a single dose was taken with water in the clinic on the morning of the study.

Blood samples were drawn at nine different time points: before tablet administration, and then at 30min, 1hr, 2hr, 3, 4, 6, 8, 10 hr post ingestion. Five mL of blood was drawn on each occasion resulting in a total blood volume of 45 mL being collected per visit. Blood samples were immediately cooled and centrifuged using a refrigerated centrifuge, at 20,000 rpm for 10 minutes after collection. Plasma was stored at –80°C until assayed.

Women were given a diary at the outset of the study and asked to record all missed doses; pharmacy refill records were also checked to monitor adherence. In addition, we administered to the women the Edinburgh Postnatal Depression Scale.

Laboratory analysis

Plasma samples were thawed and 10% ascorbic acid was added to all samples to enhance the stability of the analytes. The stabilized samples and the deuterated internal
standards were then extracted using ethyl acetate at alkaline pH. All samples were
analyzed using tandem liquid chromatography/mass spectrometry/mass spectrometry
(LC/MS/MS) (Thermo TSQ Quantum), positive mode, using an ESI probe. A C18
Kromasil column 100x4.5mm (Chromatography Sciences Company) was used with a
mobile phase of ammonium acetate, acetonitrile and ascorbic acid. The calibration range
was 1-1000 ng/mL for both bupropion and venlafaxine.

Pharmacokinetic and Statistical Analyses

Pharmacokinetic parameters were calculated in Microsoft Excel 2003 using
Pharmacokinetic Functions. Paired t-test was used to compare pharmacokinetic
parameters in the first and third trimesters of pregnancy, as well as to compare the EPDS
scores. All statistical analyses were completed using the SPSS 15.0 for Windows
software package. Statistical significance was defined as p<0.05 for all tests.

Results

Five women participated in the pharmacokinetic study; 3 were on bupropion and
2 were taking venlafaxine. Demographic data are provided in Table 3.
Table 3: Demographic data for women participating in pharmacokinetic study

<table>
<thead>
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<th>MATERNAL CHARACTERISTICS</th>
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<tr>
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<td>(mean ±SD)</td>
</tr>
<tr>
<td><strong>PARITY</strong></td>
<td>(mean ±SD)</td>
</tr>
<tr>
<td><strong>WEIGHT (kg)</strong></td>
<td>(mean ±SD)</td>
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</table>

<table>
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<th>3&lt;sup&gt;rd&lt;/sup&gt; trimester</th>
</tr>
</thead>
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</tr>
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<td>150 mg</td>
</tr>
<tr>
<td>B2</td>
<td>300 mg</td>
<td>300 mg</td>
</tr>
<tr>
<td>B3</td>
<td>150 mg</td>
<td>150 mg</td>
</tr>
<tr>
<td><strong>Venlafaxine</strong></td>
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<td></td>
</tr>
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<td>75 mg</td>
</tr>
<tr>
<td>V2</td>
<td>375 mg</td>
<td>375 mg</td>
</tr>
</tbody>
</table>
**Bupropion**

The pharmacokinetic parameters of $T_{\text{max}}$, $C_{\text{max}}$, apparent oral clearance rate and area under the curve (AUC) and were calculated for bupropion. The mean time to maximum concentration in the first trimester was $2.3 \pm 1.5$ hrs compared to $1.67 \pm 1.2$ hrs in the third trimester ($p = 0.21$). Apparent oral clearance rate was significantly increased in the third trimester when compared to the first trimester ($p = 0.03$) while a trend for lower AUC was detected ($p = 0.15$); figures 9 and 10 display the results for clearance rate and AUC respectively. All women displayed reduced plasma concentrations of bupropion in the third trimester when compared to the first trimester, however these data did not reach statistical significance ($p=0.25$). When the ratio of bupropion:hydroxybupropion was compared in the first and third trimesters, no statistical difference was found ($p=0.76$). Individual participant concentration time curves are presented in Appendix 1. Women reported missing on average 1.5 doses of their medication during the study period; prescriptions were refilled on time.
**Figure 9**: Bupropion apparent oral clearance rate 1\textsuperscript{st} vs. 3\textsuperscript{rd} trimester (n = 3). B1, B2, B3 represents each patient.
Figure 10: Bupropion area under the curve 1\textsuperscript{st} vs. 3\textsuperscript{rd} trimester (n = 3)
**Venlafaxine**

In the first trimester, the mean time to reach maximum concentration was 4 ± 0 hrs in contrast to 5 ± 1.4 in the third trimester (p=0.50). There was an increase in the apparent oral clearance of venlafaxine, however because only two patients were involved in the study, no formal statistics were calculated. When the AUC of the first and third trimesters were compared, no significant differences were found; however one participant (V1) had doubled her dose by the third trimester. Figures 11 and 12 display these results. The venlafaxine:o-desmethylvenlafaxine ratios in the first and third trimesters were not significantly different. Individual participant concentration time curves are presented in Appendix 1.

**Depression Scores**

Depression scores for three women (2 taking bupropion and 1 taking venlafaxine) were available in the first and third trimesters. The mean EPDS scores in the first and third trimesters were 13.7 ± 9.4 and 7.7 ± 3.2 respectively (p= 0.25). Data is presented in Figure 13.
Figure 11: Venlafaxine apparent oral clearance rate 1\textsuperscript{st} vs. 3rd trimester (n=2)
Figure 12: Venlafaxine area under the curve 1st trimester vs. 3rd trimester (n = 2)
Figure 13: EPDS Scores – 1\textsuperscript{st} trimester vs. 3\textsuperscript{rd} trimester (n = 3)

EDINBURGH POSTNATAL DEPRESSION SCALE SCORES
1st trimester vs. 3rd trimester

Scores >12 indicate depressive symptoms
Discussion

To our knowledge, this is the first study to report pharmacokinetic parameters of bupropion and venlafaxine in pregnancy. These results suggest that the apparent oral clearance of bupropion and venlafaxine are increased by the third trimester and consequently the AUC and plasma concentrations are also decreased at this time; one woman required a dose increase by the third trimester. Pregnancy is accompanied with a variety of physiological changes that may alter a drugs pharmacokinetics and explain the above mentioned changes. It has been demonstrated that the activity of the metabolic enzymes CYP2D6, which metabolize venlafaxine, increases during pregnancy; no studies examining changes in CYP2B6 activity during pregnancy were found. Enhanced enzymatic activity may in part explain the lowered plasma concentrations seen in late pregnancy, in addition to an increased glomerular filtration rate which would facilitate more rapid elimination of any unchanged parent drug and its metabolites.

In both the venlafaxine cases, the venlafaxine: o-desmethylvenlafaxine ratio decreased from the first to the third trimester; indicating increased metabolism. In the bupropion participants however, there was no consistent trend; two women had decreased parent:metabolite ratios while one woman had an increased ratio when the first and third trimesters were compared. Although no studies have been found investigating CYP2B6 activity in pregnancy, it is known that CYP2B6 is highly polymorphic and that some of the variants are associated with lower enzyme expression/activity and thus a diminished capacity to metabolize substrates such as bupropion. These polymorphisms may account for some of the inter-individual variability seen in these participants.
It is important to determine if and how these changes in pharmacokinetic parameters in pregnancy translate clinically. In our study three women had their depressive symptoms monitored throughout their pregnancy using the EPDS; one woman taking venlafaxine had low scores during the entire study period, indicating no depressive symptoms throughout the pregnancy. The other two women on bupropion had scores indicating depression in their first trimester while in their third trimester their scores were below the cut off for depression; this is despite their plasma concentrations decreasing in the third trimester. Bupropion’s dose-response relationship is not clear, some studies have shown positive correlations while others have shown either no or inverse correlations. Moreover, late pregnancy is characterized by an upsurge in estrogen levels, which may mitigate depressive symptoms.

This pilot study is limited by its sample size. Yet, it clearly shows that the increased apparent clearance rate and falling levels in the third trimester do not necessarily translate to heightened depression. Hence, it is critical to monitor continuously the pharmacodynamics of the drugs and modify doses in response to worsening depressive symptoms and not kinetic changes.
3.2 Changes in antidepressant metabolism in pregnancy evidenced by metabolic ratios in hair: a novel approach

There is a paucity of data regarding the pharmacokinetics of SSRIs and SNRIs in pregnancy. This lack of data is in part due to the invasive nature of pharmacokinetic studies that would be required to collect serial blood samples over extended periods of time. One way to overcome these issues is to identify a biological matrix that can provide the same information without the prolonged time commitment or invasiveness of blood sampling.

Hair may serve as a non-invasive biological marker which allows monitoring of long term systemic exposures to medications and other substances. As hair grows at a rate of approximately 1cm per month, drug analysis in hair may allow for the identification of metabolic activity throughout gestation. This is in contrast to blood which can only provide information regarding drug concentrations at the time of sampling.

Our group recently described changes in the metabolism of nicotine to cotinine during pregnancy using hair analysis. The study was able to demonstrate that the ratio of hair nicotine:cotinine decreased significantly between the first and third trimesters of pregnancy, thus corroborating increased nicotine metabolism in late pregnancy.

In the present study we compared for the first time, antidepressant metabolism in early and late pregnancy to metabolism in the postpartum period (>2 months after delivery) in a cohort of depressed pregnant women receiving SSRIs or SNRIs. The primary objective was to determine whether the ratio of hair antidepressant: major metabolite changes in pregnancy.
Methods

The present study involved pregnant, depressed women consulting the Motherisk program regarding the use of antidepressant medications during pregnancy. The Motherisk program is a teratogen information service at the Hospital for Sick Children in Toronto, Ontario which provides counseling on the safety/risk of exposures during pregnancy and lactation. The protocol for this study was approved by the Research Ethics Board of The Hospital for Sick Children in Toronto.

Subjects

Women taking antidepressant monotherapy for depression and who had no other concurrent medical conditions or medication use at the time of their initial call were included in the study. Women were recruited in the first trimester of pregnancy (≤12 weeks) and followed throughout pregnancy and into the early post-partum period.

Hair Sampling

At approximately 6 weeks postpartum women were contacted by telephone and asked to provide a hair sample. A kit was subsequently mailed to each woman that included a detailed instruction booklet (with diagrams) describing how to cut the hair, an information sheet asking about the date the hair was cut and any chemical treatments the hair may have underwent and a sheet on which the hair was to be affixed delineating the
direction the hair should be placed in (i.e: scalp end and root end). A postage paid return envelope was also included in the package.

Hair samples were obtained from the vertex posterior of the scalp and placed in a clearly labeled envelope and stored at room temperature until ready for analysis.

**Hair Analysis**

Hair samples were prepared and analyzed using liquid chromatography – mass spectrometry-mass spectrometry (LC-MS-MS) using the methods of Thieme et al.\textsuperscript{80}; segmental analyses were performed on all hair samples. The mean concentration of parent compound and metabolite was found for each trimester and the postpartum period. The limit of detection for citalopram was 0.17 pg/uL while it was 0.33 pg/uL for fluoxetine, sertraline, and venlafaxine.

**Correction for Antidepressant Metabolites**

When calculating the antidepressant: major metabolite ratio, a correction had to be made to the metabolite concentrations in hair. The metabolites of venlafaxine, citalopram, sertraline and fluoxetine are eliminated primarily by the kidneys.\textsuperscript{60,57,81} During pregnancy the glomerular filtration rate (GFR) increases 40% to 65% above non-pregnant levels.\textsuperscript{82} This increase in renal clearance results in the metabolites being cleared more rapidly than in the non-pregnant state and therefore blood and hair concentrations would reflect not only increased formation rate but also increased
elimination. To correct for this increased clearance of metabolites, all 1st trimester and 3rd trimester metabolite values were corrected by 31% and 51% respectively to reflect the rates of increase in GFR. A mean non-pregnant GFR baseline of 96 mL/min was used.

Adherence

All women were asked to complete a ‘Missed Dose Diary’ for the duration of the study period; women recorded whenever they missed a dose and how long they did not take the medication for. Pharmacy records were also obtained to check antidepressant prescription refill history.

Statistical analysis

Paired Student t-tests were used to compare the antidepressant: metabolite ratios in the first trimester to the post-partum and the third trimester to the post-partum. All statistical analyses were completed using the SPSS 15.0 for Windows software package. Statistical significance was defined as p<0.05 for all tests.

RESULTS

Twelve women provided hair samples; nine women provided hair that was sufficiently long to encompass both the first and third trimesters of pregnancy. No
woman reported smoking or the use of alcohol or any illicit drug during pregnancy. Demographic data are presented in Table 4.

Citalopram doses ranged from 30 – 60 mg/day while venlafaxine doses ranged between 75 – 300 mg/day. The dose of sertraline was 75 mg/day while the dose of fluoxetine was 30 mg/day. Eight women remained on the same dose of medication throughout the pregnancy, while two increased their dose in the second trimester and 1 woman decreased her dose continuously throughout the pregnancy. One woman stopped her medication altogether by the second trimester and the subsequent elimination of the medication and its metabolite from the hair can be seen in Figure 14.

The mean ratio of citalopram: norcitalopram in the first trimester was 0.89 ± 0.26 versus 1.4 ± 0.24 in the postpartum period (p = 0.022). When the third trimester ratios were compared to those from the postpartum period a statistically significant difference was also seen; 0.9 ± 0.14 and 1.4 ± 0.24 respectively (p=0.048). The mean ratio of venlafaxine and its metabolite was 1.1 ± 0.4 and 1.03 ± 0.06 in the first trimester and postpartum period respectively (p = 0.77) while the ratio in the third trimester was 0.80 ± 0.20 and was not statistically significant when compared to the postpartum period (p = 0.19). No statistical analyses were conducted for sertraline or fluoxetine as we had only one patient on each medication. The sertraline: norsertraline ratio was 5.8 in early pregnancy and decreased to 3.5 in late pregnancy. A large difference was seen between the fluoxetine: norfluoxetine ratios in the first and third trimesters; 14 and 5.4 respectively. The mean ratio of parent compound to metabolite for each antidepressant is displayed in Figure 15.
Adherence data was available for 6 out of the 9 women; these participants filled their prescriptions on time and had an average of 2.6 missed doses during the study period.

**DISCUSSION**

To our knowledge, this is the first attempt to calculate antidepressant: metabolite metabolic ratios in hair in demonstrating pregnancy-induced changes in drug metabolism. Our results demonstrate that citalopram exhibits a consistent increased metabolism in pregnancy when compared to the postpartum period, while venlafaxine shows no such consistent difference in metabolism during these time periods, although there were documented individual cases with marked changes. Single cases support pregnancy induced metabolic changes for sertraline and fluoxetine.

Our results for citalopram support the findings of Heikkinen et al. who examined citalopram concentrations in blood during late pregnancy and compared them to levels in the postpartum period. Heikkinen et al showed that metabolite: parent ratios were significantly higher in pregnancy than in the postpartum (or conversely parent: metabolite ratios were lower in pregnancy than in the postpartum which is what was found in this study). A recent study by Sit et al. corroborated increased metabolism of citalopram in late pregnancy when they examined the blood levels of citalopram and its metabolite.
Venlafaxine is metabolized mainly by CYP2D6 which has been shown to be increased in pregnancy. Our results however, did not demonstrate a persistent increase in metabolism during gestation. To date there have been no systematic pharmacokinetic studies of venlafaxine in pregnancy.

When examining the older SSRI fluoxetine, one study showed that fluoxetine metabolism increased in late pregnancy this is similar to the enhanced metabolism seen in the one participant that took fluoxetine in our study.

This study was limited by its small sample size and the difficulty in obtaining hair samples of sufficient length to encompass an entire pregnancy. Further studies are needed to explore the utility of this type of analysis for examining metabolic changes of medications in pregnancy.

Ethically, the use of hair overcomes a major difficulty associated with conducting repeated pharmacokinetic studies using blood. Moreover, even under ideal conditions, one can expect one measurement per trimester, whereas hair provides a continuous account of the drug: metabolite ratio. Hair analysis offers a novel, non-invasive way to study the metabolism of antidepressant medications in pregnancy. It is important that variations in drug metabolism during pregnancy be considered as these changes may necessitate a dosage adjustment to ensure that therapeutic failure does not occur during pregnancy.
Table 4: Demographic data for women participating in hair analysis study (n= 12)

<table>
<thead>
<tr>
<th>Maternal Characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ±SD)</td>
<td>34.3 ± 4.3</td>
</tr>
<tr>
<td>Gravidity (mean ±SD)</td>
<td>2.5 ± 1.3</td>
</tr>
<tr>
<td>Parity (mean ±SD)</td>
<td>0.9 ± 0.9</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>83%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>8%</td>
</tr>
<tr>
<td>Oriental-Asian</td>
<td>8%</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>33%</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>8%</td>
</tr>
<tr>
<td>Sertraline</td>
<td>8%</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>50%</td>
</tr>
</tbody>
</table>
**Figure 14:** Hair profile of participant who discontinued antidepressant medication (citalopram) after 1st trimester.
Figure 15: Comparison of antidepressant metabolite ratios in hair - 1st and 3rd trimesters and postpartum
Screening for and managing depression during pregnancy is essential, since untreated depression can have adverse maternal and neonatal outcomes. Women who are depressed during pregnancy tend to have a poor nutritional status, have inadequate prenatal care, are more likely to smoke and abuse alcohol and other substances, and are also at risk for having suicidal ideation. In addition, perinatal depression is a strong predictor of postpartum depression. Adverse neonatal outcomes of maternal depression include higher rates of preterm delivery and lower birth weight and consequently higher likelihood of admissions to neonatal intensive care units. Delays in cognitive and emotional development have been seen in infants cared for by depressed mothers.

Much of the scientific literature on depression in women has focused on postpartum depression and its prevention or treatment, with antenatal depression often looked at as a predictive factor for postpartum depression. However, there is a paucity of data regarding the effectiveness of antidepressants during pregnancy, with few studies prospectively and longitudinally examining the course of treated depression in pregnancy. Currently, the most widespread and accepted treatment for the management of depression is the use of antidepressants such as selective serotonin reuptake inhibitors (SSRIs). The relative safety of antidepressants, including SSRIs, has been documented in pregnancy;
an increased risk for major birth defects has not been found when these medications are used during gestation.\textsuperscript{89-96} However, concern still exists regarding the use of antidepressants during pregnancy as data has recently been published suggesting an increased incidence of persistent pulmonary hypertension (PPHN) in infants whose mothers used SSRI’s during late pregnancy (after 20 weeks)\textsuperscript{44} and an increased risk for cardiac malformations in infants exposed to paroxetine (Paxil\textsuperscript{TM}) during gestation\textsuperscript{25-29, 97}; further research needs to be conducted in order to establish a causal relationship between SSRI medications and these negative outcomes. Due to the complex and sometimes conflicting nature of the information available, many women who take antidepressants prior to conception are advised or choose to discontinue therapy upon confirmation of pregnancy due to perceptions of teratogenic risk.\textsuperscript{47}

Discontinuation of antidepressant medication during pregnancy has been associated with adverse maternal consequences. In a preliminary study, our group demonstrated that depressed women who abruptly discontinued their medication upon confirmation of pregnancy experienced both physical and psychological effects, including suicidal ideation.\textsuperscript{47} More recently, Cohen et al. have shown that women who discontinued antidepressant medications prior to conception or during early pregnancy had an increased risk for depressive relapse during pregnancy compared with women who maintained therapy throughout pregnancy.\textsuperscript{48} The Motherisk Program has shown that providing women with evidence-based counseling regarding the safety of medications in pregnancy is an effective means by which to lower fear of teratogenic risk and increase the likelihood of women maintaining needed pharmacotherapy during gestation.\textsuperscript{47, 49}
The primary objective of this study was to determine the effectiveness of maintaining antidepressants during pregnancy, as measured by symptoms of depression, anxiety, irritability and stress, following reassuring counseling on the fetal safety of these medications.

METHODS

Recruitment of Subjects and Counseling Provided

Women were recruited for this study from the Motherisk program, a teratogen information service, at the Hospital for Sick Children in Toronto, Ontario, between July 2004 and October 2005. Evidence-based information was provided to the women in our study regarding the risks and benefits of the particular antidepressant they were taking.

During the initial telephone contact an intake form is completed which collects demographic information, medical and obstetrical histories as well as details regarding the exposure and concurrent exposures that are recorded on a standardized questionnaire. Details about the exposure include duration, timing in pregnancy, dose, frequency and medical indication for drug use. Following completion of the intake form, the counselor refers to a ‘Motherisk Statement’ which is a standardized compilation of all the relevant literature that has been reviewed and summarized regarding the particular drug of inquiry. The information is explained to the caller in terms that they are able to understand, as well as whether or not the drug may increase the baseline risk for birth defects above the population rate of 1 – 3%. Callers are never advised as to what medication to take or
alternative therapies as this is not part of our mandate. For these questions they are referred back to their health care provider.

For this study, when pregnant and depressed women called Motherisk, based on the existing scientific literature, including two meta-analyses,\textsuperscript{98,40} they were advised that the use of antidepressants including SSRIs did not increase the baseline risk for birth defects above 1\%--3\% which is expected in the general population. Women were also advised of the possibility of the baby experiencing poor neonatal adaptation syndrome with the use of an SSRI in late pregnancy. This study was conducted prior to the release of the data regarding SSRI’s and PPHN, therefore women did not receive this information as part of their counseling. Finally, women were advised about the risks associated with untreated depression; these risks include poor prenatal care, increased risk for suicidal ideation, low birth weight and preterm delivery.\textsuperscript{20,19} After the counseling was provided, women were informed about the present study and offered the opportunity to participate. Once verbal consent was obtained by Motherisk counselors over the telephone, the study coordinator contacted the women at a later date to initiate study. Women who were in their first trimester of pregnancy (≤12 weeks), had been diagnosed with depression (either by a family physician or psychiatrist) at the time of call, and who were taking antidepressant medications were eligible for inclusion in the study. Women who were beyond the first trimester of pregnancy (>12 weeks), who were taking antidepressants for indications other than depression, or who were concurrently taking other psychoactive medications, were excluded. The protocol for this study was approved by the Research Ethics Board of The Hospital for Sick Children in Toronto.
Study Procedures and Rating Instruments

Women participated in four telephone interviews which were conducted in the first (0--12 weeks), second (16--22 weeks), and third trimesters (32--38 weeks) as well as the post partum period (beginning at 6--8 weeks postpartum, based on the expected date of confinement). Four instruments were administered to each participant during each phone call: the Edinburgh Postnatal Depression Scale (EPDS), the Goldberg Anxiety Scale, the Perceived Stress Scale (PSS) and the Born-Steiner Irritability Scale.

The EPDS consists of 10 questions, each of which is assigned a score from 0--3, so that the maximum possible score is 30.\(^9\) Women who scored 13 or higher on the EPDS (scores greater than or equal to 13 are consistent with depressive symptoms) or who gave a positive answer to the question regarding self-harm on the EPDS, were asked permission to share the results with their current physician. Physicians were informed of these results via a faxed letter.

The Goldberg Anxiety Scale has 9 potential questions to help identify pathological anxiousness; the first four items are a screen; if response on those items is positive, there are an additional five items to be answered. Anxiety scores can range from 0--9; scores greater than or equal to five are considered clinically significant. The scale has been found to have a specificity of 91% and a sensitivity of 86%.\(^1\)

The Born-Steiner Irritability Scale is a new tool that consists of five items that look at annoyance, anger, tension, hostile behaviour, and sensitivity in the past week. Irritability scores can range from 0--18; scores greater than 12 would be indicative of
clinically significant irritability (Born L, Koren G, Lin E, et al., unpublished data). The use of the scale has been piloted over the telephone.

A link between depression and chronic stress has been proposed. The Perceived Stress Scale (PSS) is an instrument that is commonly used as a global measure of perceived stress. The scale was originally created as a 10 item questionnaire, but a shortened 4-item version is also available, which was used in this study. Items are given a score from 0 to 4 for a possible maximum total score of 16 on the 4-item version. The 4-item version of the scale has been successfully used in obstetric populations. The scale has been piloted for use over the telephone. All scales and intake forms used in the study can be found in Appendix 2.

Statistical Analysis

Depression, anxiety, irritability, and stress scores as measured by their respective scales were analyzed using General Estimation Equations (GEE); time was used as the factor (i.e.: trimesters 1, 2, 3 and the postpartum period) and scores were assumed to follow a normal distribution. The significance level was set at 0.05 for all tests. SAS statistical software was used to analyze the data.

RESULTS

The demographic characteristics of the 58 women enrolled in this prospective interventional study are presented in Table 5. Of the 58 women, 8 (14%) were smokers who consumed a median of 8.5 cigarettes per day; none of the women reported alcohol
consumption during pregnancy. In all, 38 women completed the study with at least three out of four follow-ups. Women who did not complete 75% of the follow-ups included 5 women who had miscarriages (9%) and 11 women who were lost to follow-up (19%); there were no differences between women who remained in the study and women who miscarried or were lost to follow up in terms of age, gravidity, or parity. However, the women who were lost to follow up were statistically more depressed at the time of enrollment than those who remained in the study (EPDS score of 10.8 vs. 7.6 respectively, \( p = 0.03 \)); however the mean EPDS scores for both groups were below the cut off for depression at the time of enrollment.

At the outset of the study, all 58 women were taking antidepressants; 8 (14%) women discontinued their antidepressant medication at some point during the study period, with 2 (3%) stopping medication by the second trimester, 4 (7%) stopping medication by the third trimester, and the 2 (3%) discontinuing medication in the postpartum period; the reasons for discontinuation of medication were not disclosed by all participants. Of the 38 women who completed 75% of the follow-ups, 18 remained on the same dose of medication, while the dose was increased in 5 women and decreased in 8 women; 2 women switched medications during the study period. Six of the 8 women who stopped their medication belonged to the group of women who completed three out of four follow-ups.

Depression scores were highest in the first trimester and decreased as pregnancy progressed (Table 6). No statistically significant differences were found between the EPDS scores at any point during the study (\( p = 0.118 \)). In general, a change in the dose of the antidepressant medication did not have a large effect on the change in EPDS score
The rates of depression per trimester and in the postpartum are reported in Table 7; in the first trimester, the group of women who chose to discontinue their medication had the highest rate of depression.

No trimester-dependent changes were found in measures of anxiety, irritability or stress. Anxiety scores were similar across the trimesters, with a mean of 3.5 in the first trimester, 3.3 in the second, 3.0 in the third and 2.8 in the postpartum period (p = 0.390). Irritability levels also remained steady throughout the study period, with mean scores of 3.3, 3.5 and 3.3 in the first three trimesters, respectively, and a mean score of 3.8 in the postpartum period (p = 0.375). Stress scores followed a similar trend with no large changes seen during pregnancy; mean scores were 4.4, 3.9 and 4.2 in the first three trimesters, respectively, and 4.6 in the postpartum period (p = 0.477) (Table 8).

**DISCUSSION**

In this prospective study, we followed pregnant women who received evidence-based counseling concerning the safety of antidepressant medications in pregnancy and the risks of untreated depression and who were treated for depression with antidepressant medications throughout their pregnancy and into the early postpartum period. Our results indicate that treating depression with antidepressants during pregnancy and the early postpartum period is effective as depressive symptoms did not reemerge for the majority of women who continued to use pharmacotherapy during pregnancy. Overall, among treated women, depressive symptoms lessened as pregnancy progressed, with the largest difference being seen between the first and the third trimesters.
Other earlier attempts to assess the course of depression during pregnancy have been reported in a few studies. One prospective study of 119 women had results similar to ours, in that women with depression during the first trimester exhibited fewer depressive symptoms as pregnancy progressed into the second and third trimesters, while a second study found that levels of depression were highest during the third trimester. However, neither of these studies reported if the women were on antidepressant medication and, if so, if the dosage of medication was adjusted during the study period.

A more recent prospective study by Cohen et al., in which medication status was reported, found that depressed women who maintained their course of pharmacotherapy during pregnancy had better outcomes than depressed women who discontinued their medication prior to or during early pregnancy; women who discontinued their antidepressants had significantly higher rates of depressive relapse than women who continued taking medication, thus providing further evidence to support the continuation of antidepressant therapy during pregnancy.

In our study, the women who discontinued medication (most discontinued by the third trimester) did not show depressive relapse even though they had the highest rate of depression during the first trimester. Our numbers, however, were small and discontinuation was defined as stopping therapy at any point during our study; therefore, our limited sample was not able to show the same trend found by Cohen et al. A longer follow-up period may have revealed a higher rate of depressive relapse in women who discontinued their medication as antidepressant medication can take several weeks to be completely cleared from the body. The rate of discontinuation for women studied by
Cohen was 32%, whereas in our study the discontinuation rate after counseling was 14 %, suggesting that counseling may be an effective intervention option when attempting to help women continue pharmacotherapy during pregnancy. However, it should be noted that the Cohen et al. study did not report if the women in their study received any counseling and, if so, what they were advised.

In our study, women were adequately treated with pharmacotherapy ensuring that they did not have to further adjust their dose, depression decreased as pregnancy progressed, with a large difference being seen between the first trimester and the early postpartum period. Postpartum depression may begin within the first 24 hours after birth and can occur anytime within the first year after delivery, so continued monitoring of depressive symptoms would be beneficial to ensure that there is not a late onset of postpartum depression.

The present study is one of the first to examine how anxiety, irritability, and stress changed during the course of pregnancy in depressed women. Levels of anxiety were low throughout the study period, the mean anxiety score in each trimester did not exceed the cut off of 5, which would indicate a clinically important condition. Depression and anxiety are commonly found as comorbid conditions. Antidepressants are not only used to treat depression but anxiety as well, so it is not surprising to find low levels of depression and anxiety in the same cohort. In addition, it has been postulated that the hormonal changes that are associated with pregnancy have anxiolytic properties, lending further support to the findings of reduced anxiety during this time. Irritability scores were also found to be very low in our sample; irritability is commonly a prominent symptom in female mood disorders. The relationship between depression and stress is not
clear, however, one is believed to exist. Physiologically the changes that are seen in the stress hormone systems under chronic stress are similar to those observed in depression. In our study both the depression and the stress scores were found to be low in treated women. Studies have shown significant comorbidity between depression and anxiety. The fact that treatment with antidepressants, mainly SSRIs and SNRIs, during pregnancy appears to control symptoms of depression as well as anxiety is therefore reassuring.

Overall, this study did not find any differences in depression, anxiety, irritability or stress scores when pregnant women taking antidepressant medication were followed throughout pregnancy and into the early postpartum period. This may be due to the limited sample size collected, however, as this was an exploratory study and differences that may exist might be determined using a larger sample size and a control group in future studies.

In light of the recent data regarding the safety of SSRI’s in pregnancy, there has been an increased volume of calls to the Motherisk Program regarding these medications and their potential risks. It is important to be aware of the potentially negative effects that scientific data and medical information released in mass media may have on women treated with these medications. A study that was published in response to Health Canada’s 2004 warning regarding SSRI’s in pregnancy demonstrated such effects; many women reported being anxious after hearing/reading the advisory and some women went as far as to discontinue their antidepressant medication because of it. As such, women currently calling the Motherisk Program are informed about existing studies as well as the recent concerns surrounding PPHN and SSRI’s in late pregnancy and cardiac
malformations in infants exposed to paroxetine (Paxil),\textsuperscript{44,111} however the data is also contextualized with negative trials so that they can better understand the minimal size of risks if they exist (i.e.: risk in general population compared to the risk after exposure to medication). As always, women are advised to discuss the information they receive with their physician and weigh the risks and benefits of continuing therapy with their current medication against the risks and benefits of discontinuing therapy, so that both maternal and fetal health can be optimized.

In summary, the treatment of perinatal depression is very important to the well being of mothers and their children. Antidepressants that have been shown to be non-teratogenic offer a safe and effective way to manage depression in women during pregnancy. Continuation of pharmacotherapy during pregnancy resulted in low levels of depression. Irritability, anxiety, and stress scores were also low throughout pregnancy.
**Table 5**: Demographic data of women enrolled in longitudinal depression study in pregnancy (n = 58)

<table>
<thead>
<tr>
<th>Demographic Data</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (Yrs)</strong></td>
<td>31.3 ± 6.0</td>
</tr>
<tr>
<td><strong>Gravity</strong></td>
<td>2.6 ± 2.0</td>
</tr>
<tr>
<td><strong>Parity</strong></td>
<td>1.0 ± 1.3</td>
</tr>
<tr>
<td><strong>Medication</strong></td>
<td></td>
</tr>
<tr>
<td>Bupropion</td>
<td>2</td>
</tr>
<tr>
<td>Citalopram</td>
<td>21</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>5</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>7</td>
</tr>
<tr>
<td>Sertraline</td>
<td>6</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>18</td>
</tr>
<tr>
<td><strong>Number of Weeks into Pregnancy</strong></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td></td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; Interview</td>
<td>6.8 ± 2.3</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; Interview</td>
<td>17.6 ± 1.8</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; Interview</td>
<td>35.9 ± 1.7</td>
</tr>
<tr>
<td><strong>Number of Weeks Postpartum</strong></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td></td>
</tr>
<tr>
<td>4&lt;sup&gt;th&lt;/sup&gt; Interview</td>
<td>8.7 ± 2.6</td>
</tr>
</tbody>
</table>
Table 6: Mean scores from depression, irritability, anxiety and stress scales by trimester (N = 38)

<table>
<thead>
<tr>
<th></th>
<th>1&lt;sup&gt;st&lt;/sup&gt; Trimester</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; Trimester</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt; Trimester</th>
<th>Post-partum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EPDS</strong>&lt;br&gt;Mean ± Sd</td>
<td>7.6 ± 4.1</td>
<td>6.5 ± 4.5</td>
<td>5.6 ± 3.4</td>
<td>5.7 ± 5.4</td>
</tr>
<tr>
<td><strong>Born-Steiner Irritability Scale</strong>&lt;br&gt;Mean ± Sd</td>
<td>3.3 ± 2.1</td>
<td>3.5 ± 2.5</td>
<td>3.3 ± 2.0</td>
<td>3.8 ± 3.0</td>
</tr>
<tr>
<td><strong>Goldberg Anxiety Scale</strong>&lt;br&gt;Mean ± Sd</td>
<td>3.5 ± 2.9</td>
<td>3.3 ± 3.1</td>
<td>3.0 ± 2.7</td>
<td>2.8 ± 2.6</td>
</tr>
<tr>
<td><strong>Perceived Stress Scale</strong>&lt;br&gt;Mean ± Sd</td>
<td>4.4 ± 3.1</td>
<td>3.9 ± 2.8</td>
<td>4.2 ± 2.4</td>
<td>4.6 ± 3.2</td>
</tr>
</tbody>
</table>
Table 7: Percentage of women with depressive symptoms by trimester

<table>
<thead>
<tr>
<th></th>
<th>1&lt;sup&gt;st&lt;/sup&gt; Trimester EPDS Score &gt; 12</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; Trimester EPDS Score &gt; 12</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt; Trimester EPDS Score &gt; 12</th>
<th>Post-partum EPDS Score &gt; 12</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No Dose Adjustments (N= 18)</strong></td>
<td>6%</td>
<td>6%</td>
<td>0% (n= 14)</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Increased Dose (N= 5)</strong></td>
<td>20%</td>
<td>40%</td>
<td>20%</td>
<td>40%</td>
</tr>
<tr>
<td><strong>Decreased Dose (N = 10)</strong></td>
<td>20%</td>
<td>0%</td>
<td>0% (n= 5 )</td>
<td>0% (n= 7)</td>
</tr>
<tr>
<td><em><em>Stopped Medication</em> (n= 8)</em>*</td>
<td>50%</td>
<td>0% (n= 6)</td>
<td>0% (n= 5)</td>
<td>0% (n= 4)</td>
</tr>
</tbody>
</table>

*Note: The numbers are not the same as some women did not complete follow-ups in all trimesters.
Figure 16: Change in Dose versus Change in EPDS Score

1st Trimester compared to 3rd Trimester: Change in Dose vs. Change in EPDS Score

-15
-10
-5
0
5
10
-5.00 -4.00 -3.00 -2.00 -1.00 0.00 1.00 2.00 3.00 4.00 5.00

Change in antidepressant dose (mg/kg)

Change in EPDS Score

Stopped Medication
Unchanged dose
Increased Dose
Decreased Dose
The previous study explored depression across pregnancy in a cohort of women who were pregnant and depressed. A limitation of that study, however, was that it did not include any control groups. The lack of control groups did not allow the questions which are addressed in this chapter to be answered. The present study uses the same methodology employed in the previous study, but incorporates two control groups; a depressed control group that is not pregnant and a pregnant control group that is not depressed. The primary objective of this study was to evaluate the course of treated depression during pregnancy and determine if pregnancy affects depressive symptoms by examining depressive symptoms over time in three groups of women. The hypothesis was that depressive symptoms in the two control groups would be relatively stable across time while symptoms in the depressed and pregnant group would increase as pregnancy progressed.

METHODS

All women were recruited from the Motherisk program at the Hospital for Sick Children in Toronto, Ontario between November 2005 and June 2007. Three groups of women were enrolled in the study; i) pregnant and depressed ii) pregnant and non-depressed iii) not pregnant and depressed.

The inclusion criteria for the first group of women were as follows: first trimester of pregnancy (< 12 weeks), a diagnosis of unipolar depression (either by a family
physician or psychiatrist) at the time of call, and treatment with antidepressant monotherapy. Women calling about non-teratogenic and non-psychoactive medications were enrolled in the pregnant and non-depressed group. They had to be in their first trimester of pregnancy (\( \leq 12 \) weeks) at the time of call and could not have a diagnosis of depression. The depressed and non-pregnant group was recruited by searching the Motherisk database and contacting women who had previously called the program regarding antidepressant therapy in pregnancy. Women who had placed a call between January 2004 and December 2005 were contacted. Women were included if they were still currently taking antidepressant monotherapy for unipolar depression, were not currently pregnant and were not planning a pregnancy within the next year. Women were excluded if they were no longer taking antidepressant medication or if they were taking antidepressants for indications other than depression; concurrent psychoactive medications, a current pregnancy or planning a pregnancy in the next year were additional reasons for exclusion.

Women were matched for maternal age (\( \pm 2 \) years), gestational age at time of call (\( \pm 2 \) weeks), smoking and alcohol status, and number of years depressed (\( \pm 4 \) years) (where possible). The protocol for this study was approved by the Research Ethics Board of The Hospital for Sick Children in Toronto.

All women participated in four telephone interviews during the first (0--12 weeks), second (16--22 weeks), and third trimesters (32--38 weeks) and the post partum period (beginning at 6--8 weeks postpartum, based on the expected date of confinement); the depressed non-pregnant group was contacted at time intervals that mimicked this schedule. Four instruments were administered to each participant during each phone call:
the Edinburgh Postnatal Depression Scale (EPDS), the Goldberg Anxiety Scale, the Perceived Stress Scale (PSS) and the Born-Steiner Irritability Scale.

Depression, anxiety, irritability, and stress scores as measured by their respective scales were analyzed using General Estimation Equations (GEE); time was used as the factor (i.e.: trimesters 1, 2, 3 and the postpartum period) and scores were assumed to follow a normal distribution. The significance level was set at 0.05 for all tests. SAS statistical software was used to analyze the data.

RESULTS

In total 97 women were enrolled in the study, and their demographic data are presented in Table 8. Data were analyzed for the 73 women who finished the study with at least three out of the four follow-ups complete; reasons for withdrawal from the study are detailed in Table 9. There were no statistically significant differences between the women who remained in the study and those that did not in terms of age, gravidity, parity, nausea and vomiting status and depression score upon enrollment.

Of the women that remained in the study, 10% of depressed-pregnant women discontinued their antidepressant medication at some point during the study period compared to no discontinuations in the depressed control group. Twenty-three percent of the depressed-pregnant women increased their dosage at some point during the study while 6% decreased their dosage, compared to 18% and 12% of women in the depressed control group respectively; there were no statistically significant differences between these groups.
When the nausea and vomiting status of women in the depressed-pregnant group was compared to that of the non-depressed-pregnant group at the time of first call, no statistically significant difference was found between the groups.

Analysis of depression scores among the three groups revealed that the depressed groups (pregnant and non-pregnant) had scores that were highest upon enrollment and subsequently declined over the study period; the pregnant non-depressed group had consistent depression scores across the study period. When the mean depression scores from all four time points were compared, the scores of the depressed pregnant group were significantly higher than those of the pregnant non-depressed group (7.26 ± 0.64 vs. 5.01 ± 0.69 respectively; p = 0.02). The same result was also found when the mean depression scores of the depressed non-pregnant group were compared to those of the non-depressed pregnant group (7.66 ± 0.88 vs. 5.01 ± 0.69 respectively; p = 0.02).

When groups were examined separately, the depressed-pregnant group had significantly higher depression scores in their first trimester when compared to their postpartum period (9.32 ± 6.42 vs. 6.29 ± 4.33; p = 0.04). At no time during the study did the depression scores in the pregnant non-depressed group or the depressed non-pregnant group differ significantly. Data are displayed in Figure 17.

All groups had mean depression scores below the cut-off for depression (EPDS > 12) at all time points during the study. The proportion of women with EPDS scores indicative of depression is displayed by trimester and group in Table 10. Significantly more women in the depressed groups (pregnant and non-pregnant) had EPDS scores greater than 12 in the first trimester (χ² = 7.71, p = 0.02); there were no differences among the remaining time points.
When irritability scores were examined, it was found that the depressed pregnant group had significantly higher overall mean scores of irritability during the study than the pregnant non-depressed group (4.78 ± 0.83 vs. 2.88 ± 0.91; p = 0.003). When irritability scores were analyzed over time within each group, no significant differences were found in any group at any time point during study. Results are displayed in Figure 18. Overall, mean anxiety scores were found to be significantly higher in the depressed groups (pregnant = 3.57 ± 0.64 and non-pregnant = 3.56 ± 0.90) when compared to the pregnant non-depressed group (2.16 ± 0.7); p = 0.004 and 0.02 respectively. Analysis of anxiety scores over the study period revealed that there were no statistically significant differences within any of the groups at any time period. Mean Goldberg anxiety scores were not above the clinically significant cut-off of 5 for any of the study groups; scores are displayed in Figure 19.

When mean perceived stress scores were examined, the depressed groups (pregnant = 5.49 ± 0.83 and non-pregnant = 5.06 ± 1.17) had significantly higher overall mean scores than the pregnant non-depressed group (3.2 ± 0.92); p < 0.001 and p = 0.01 respectively. Analysis of stress scores over time within each group revealed that the depressed non-pregnant group had significantly higher stress scores at the time of first call when compared to their scores at the third and fourth calls (6.94 ± 3.19 vs. 4.25 ±2.79; p = 0.01) and (6.94 ± 3.19 vs. 3.88 ± 2.92; p = 0.02) respectively. Stress scores are displayed in Figure 20.
DISCUSSION

This comparative study followed three groups of women over time and measured symptoms of depression, irritability, anxiety and stress. The results indicate that treatment with antidepressants provides effective relief from depressive symptoms during pregnancy and the early post-partum period for a majority of women. This confirms the results of the previous study in which depression scores were also maintained below the depressive cut-off throughout the study period for depressed, pregnant women treated with antidepressants. In addition, the same trend seen in the previous study was corroborated in this study, in which depression scores were highest in the first trimester and subsequently declined as pregnancy progressed and entered the post-partum period. Furthermore, in the current study, both the depressed groups (pregnant and non-pregnant) displayed their highest depression scores during the first call and their lowest scores during the fourth call. However, the depression scores between the first and fourth calls for the depressed non-pregnant group did not reach statistical significance ($p = 0.08$), this may be due to the insufficient sample size of this group to answer this question.

When comparing the percentage of women displaying depressive symptoms at each call, the proportions were very similar between the two depressed groups except at the 2nd call. Thus, results from this study suggest that between 10% - 30% of women still experience depressive symptoms even when treated with antidepressants, therefore there is a need to monitor depression regardless of pregnancy status.

These results also suggest that women with depression are more likely to have depressive symptoms in the first trimester of pregnancy than pregnant women without a
history of depression, however this may be due to the depression itself and not the pregnancy as the depressed non-pregnant group also had high levels of depression at the time of the first call. Furthermore, pregnant women who are treated for depression do just as well as their non-pregnant depressed counterparts, showing that depression can be effectively managed with medication during pregnancy, treatment appears to be as effective for pregnant and non-pregnant women.

Low levels of anxiety were seen throughout the study in all three groups; however, the depressed groups did display higher anxiety scores than the non-depressed group which is not surprising as depression and anxiety are often co-morbid conditions. The low anxiety scores found in the depressed groups may have been a result of the antidepressant medications they were taking as some of the medications also have anxiolytic properties. Low irritability and stress scores were also found in all study groups.

The limited sample size of the depressed non-pregnant group is a limitation of the study. Recruiting and retaining these participants in a longitudinal study was more difficult than recruiting participants for the pregnant groups, perhaps because they were less invested and motivated to remain in the study than their pregnant counterparts. Another limitation of the current study is that the Motherisk population that participants were recruited from is a self-selected group that is usually well educated and of higher socio-economic status and thus the findings may not be generalizable to all populations.
CONCLUSION

Pregnant women with depression that are treated with antidepressants appear to display depression scores which are similar to depressed women that are not pregnant and similarly treated with antidepressants; non-depressed pregnant women have lower depression scores than both groups. Depression can be effectively managed with antidepressants during pregnancy. These data do not suggest that there is an overall worsening of depression symptoms in pregnancy and support a need for individual monitoring.
Table 8: Demographic data of women enrolled in the comparative study

<table>
<thead>
<tr>
<th></th>
<th>Depressed and Pregnant N = 41</th>
<th>Pregnant and Non-Depressed N = 34</th>
<th>Depressed and Non-Pregnant N = 22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Maternal Age (yrs)</td>
<td>32.5</td>
<td>34.1</td>
<td>34.2</td>
</tr>
<tr>
<td>Gravidity</td>
<td>2.5</td>
<td>2.1</td>
<td>1.9</td>
</tr>
<tr>
<td>Parity</td>
<td>1</td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td>Gestational Age at Enrollment (wks)</td>
<td>7.9</td>
<td>8.2</td>
<td>N/A</td>
</tr>
<tr>
<td>Antidepressant Medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion</td>
<td>4</td>
<td>N/A</td>
<td>1</td>
</tr>
<tr>
<td>Citalopram</td>
<td>13</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>3</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>4</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>1</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Sertraline</td>
<td>2</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>14</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>% Report Smoking</td>
<td>17</td>
<td>6</td>
<td>14</td>
</tr>
</tbody>
</table>
Table 9: Reasons for withdrawal from the comparative study

<table>
<thead>
<tr>
<th></th>
<th>Depressed and Pregnant N = 41</th>
<th>Pregnant and Non-Depressed N = 34</th>
<th>Depressed and Non-Pregnant N = 22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous Abortion</td>
<td>2</td>
<td>5</td>
<td>n/a</td>
</tr>
<tr>
<td>Elective/Therapeutic Abortion</td>
<td>2</td>
<td>0</td>
<td>n/a</td>
</tr>
<tr>
<td>Fetal Death</td>
<td>1</td>
<td>0</td>
<td>n/a</td>
</tr>
<tr>
<td>Became Pregnant During Study</td>
<td>n/a</td>
<td>n/a</td>
<td>2</td>
</tr>
<tr>
<td>Lost to Follow-up</td>
<td>5</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
Figure 17: EPDS depression scores across pregnancy in the 3 study groups

- Scores > 12 indicate depressive symptoms
- p = 0.04

Depressed & Pregnant: n=31
Healthy Control: n=26
Depressed Control: n=16

* indicates statistical significance at p = 0.04
Table 10: Percentage of women with depressive symptoms by trimester and group

<table>
<thead>
<tr>
<th></th>
<th>1&lt;sup&gt;st&lt;/sup&gt; Trimester</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; Trimester</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt; Trimester</th>
<th>Post-partum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Depressed and Pregnant</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N = 31)</td>
<td>32%</td>
<td>10%</td>
<td>10%</td>
<td>6%</td>
</tr>
<tr>
<td><strong>Pregnant and not depressed</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N = 26)</td>
<td>4%</td>
<td>8%</td>
<td>0%</td>
<td>4%</td>
</tr>
<tr>
<td><strong>Depressed and not pregnant</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N = 16)</td>
<td>31%</td>
<td>25%</td>
<td>6%</td>
<td>0%</td>
</tr>
</tbody>
</table>
Figure 18: Born-Steiner irritability scores across pregnancy in the 3 study groups
Figure 19: Goldberg anxiety scores across pregnancy in the 3 study groups

Anxiety scores > 5 clinically significant
Figure 20: Perceived stress scores across pregnancy in the 3 study groups
CHAPTER 5

EARLY GESTATIONAL EXPOSURE TO PAROXETINE AND THE RISK OF CARDIAC MALFORMATIONS: A META-ANALYSIS


One of the principal reasons for the discontinuation of necessary medications in pregnancy is fear of harming the developing fetus, in particular the fear of using a teratogenic medication. Therefore, it is imperative that the safety of medications commonly used in pregnancy be determined so as to protect the health of both the mother and her developing child.

Mood disorders, including depression and anxiety, are commonly treated with selective serotonin reuptake inhibitors (SSRIs) antidepressants. These disorders often begin during the childbearing years, therefore it is not uncommon for women to be receiving pharmacotherapy for these conditions when they become pregnant. Various drug utilization surveys from Europe found that between 0.2% and 2.8% of pregnant women received a prescription for an antidepressant during early pregnancy; a recent study from the US found that approximately 8% of pregnant women were dispensed antidepressants during pregnancy. Consequently, fetal exposure to these medications occurs frequently in the course of treating antenatal mood disorders.

Early studies examining the use of SSRIs in pregnancy did not demonstrate an increase above the baseline risk for major malformations of 1% - 3% in the general population. More recently, however, several studies have reported an association between SSRIs and an increased risk for major malformations. Paroxetine (Paxil®) in
particular was singled out as a medication of concern.\textsuperscript{111,120-122} In late 2005, GlaxoSmithKline (the manufacturer of paroxetine), the US Food and Drug Administration (FDA) and Health Canada issued warnings regarding the possible risk for cardiac malformations in infants exposed to this medication during the first trimester. These warnings were based on findings that were unpublished at the time.\textsuperscript{111} Subsequently, a debate has arisen surrounding the safety of paroxetine in the first trimester of pregnancy.

In a meta-analysis of the first few studies, we found an apparent increased risk of cardiac malformations associated with paroxetine.\textsuperscript{45} It has long been acknowledged that bias against the null hypothesis may lead to early publication of ‘positive’ studies and a delayed and partial publication of ‘negative’ studies. Since our original study, a number of additional studies have been published, increasing the overall sample size and enabling more accurate estimation of potential fetal risk.

The objective of this study was to systematically review the current literature and summarize the existing data to ascertain whether first trimester exposure to paroxetine is in fact associated with an increased rate of cardiac defects. Such analysis is of utmost importance in counseling and managing women who need SSRIs in pregnancy.

**Methods**

**Data Sources**

A literature search was conducted between January 1985 and November 2007 using the MEDLINE, EMBASE, REPROTOX, Scopus, and Biological Abstracts...
databases. The following terms were used in the search strategy: pregnancy outcome, congenital or fetal AND anomalies, malformations, cardiac/heart defects, AND selective serotonin reuptake inhibitors, paroxetine and Paxil®. Additional articles and abstracts were identified by examining the references of retrieved articles, proceedings from meetings of professional societies (e.g., in the fields of teratology, obstetrics, psychiatry, pediatrics) and Internet websites.

**Study Selection**

We sought to retrieve all studies reporting the risk of cardiac malformations after *in utero* exposure to paroxetine. Studies in any language that met the following criteria were included in the analysis: reported first trimester (0-14 weeks gestation) exposure to paroxetine and included a comparison group of pregnant women unexposed to paroxetine. Case-control studies and cohort studies were both accepted for analysis as long as the populations from which they drew their study and control groups were similar. Review articles, case reports, editorials, studies without a comparison group and studies that did not specifically report cardiac defects were rejected from the analysis. The inclusion and exclusion process was carried out by two reviewers who independently evaluated the articles for acceptance into the study. A third reviewer acted as an adjudicator for any unresolved disputes.
Data Extraction

The reviewers extracted the following data from the included studies into 2x2 tables: the numbers of infants born with cardiac malformations (exposed and not exposed to paroxetine in the first trimester) and the number of infants without cardiac malformations (exposed and not exposed to paroxetine in the first trimester). Again, a third reviewer was used to resolve disagreements in the data. The 27-item checklist developed by Downs and Black\textsuperscript{15} was used to assess the quality of the included articles and abstracts. The quality score was expressed as a percentage of the applicable items presented in the article. Here too, two reviewers assessed quality with discrepancies settled first through consensus, then adjudication by a third judge, if needed.

Statistical Analysis

Case-control and cohort studies were analyzed separately, due to their inherent methodological differences. Data from case-control studies were combined into a summary odds ratio using a random-effects meta-analysis, which weights by both within study variance and between study variance.

For cohort studies, we calculated rates of cardiac malformations for exposed and non-exposed infants. The effect size of interest was the difference between rates in exposed and non-exposed infants. Rate differences were combined across cohort studies to yield a weighted average rate difference, along with its standard error. For all analysis, we considered outcomes for live births only.
As quality assurance measures, we first assessed for the presence of heterogeneity of effects using chi-squared tests. Since those tests are weak, we used a liberal cutoff for the p-value of 0.10. We also calculated the $I^2$ value, which is the proportion of between study variance due to study differences as opposed to random error. Publication bias was assessed using a funnel plot and by calculating tau values according to the Begg-Mazumdar test.

Results

Overall 21 relevant studies were identified in the literature search. Of those 21, a total of 12 studies were rejected either because they were review articles, editorials or they did not provide specific information regarding cardiac defects in the exposed and non-exposed groups. Therefore, 9 studies were included in the analysis, of which 6 were cohort studies and 3 were case-control studies (Table 11). Six studies had comparison groups consisting of women exposed to antidepressants other than paroxetine, while three studies used women exposed to known non-teratogenic medications as a control group.

When we examined the case-control studies for evidence of heterogeneity of effects, the chi-squared value was not significant ($\chi^2=0.91$, df=2, $P=0.64$) and the $I^2$ value was zero, suggesting that results could reasonably be combined. There were too few studies for a funnel plot; however, the Begg-Mazumdar test found a small non-significant coefficient ($\tau=-0.33$, $P=0.60$).

The three case-control studies examined more than 30,000 women and produced a non-significant summary OR of 1.18 (CI$_{95\%}$: 0.88-1.59) (Figure 21). With this OR, it would require an additional 170,351 patients to achieve statistical significance.
No heterogeneity of effects was detected among the six cohort studies ($\chi^2=4.97$, df=5, $P=0.419$; $I^2=0$); therefore, results were considered combinable. The funnel plot was symmetrical with no evidence of publication bias; the Begg-Mazumdar test similarly found a small and non-significant coefficient ($\tau=0.33$, $P=0.60$) suggesting a lack of publication bias.

When the cohort studies were analyzed, the rates of cardiac malformations were 1.14% in the 3428 infants exposed to paroxetine and 1.09% in the 62,981 controls. These two rates both fall within the 95% confidence interval (0.7% to 1.2%) for the population at large, as reported by Hoffman and Kaplan. The weighted average difference in cardiac malformation rates between the paroxetine exposed and non-exposed groups was very small (0.3%) and non-significant (-0.1% to 1.7%; $P=0.19$). Figure 22 displays the results. We had sufficient power to find significance at a rate as low as 1.26% (note that the upper 95% limit of the population rate is 1.19%).
<table>
<thead>
<tr>
<th>Study</th>
<th>Publication Year</th>
<th>Type of Publication</th>
<th>Study Design</th>
<th>Control Group</th>
<th>Quality Score (%)</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cole et al.</td>
<td>2007</td>
<td>Journal Article</td>
<td>Retrospective cohort</td>
<td>Other SSRI or other antidepressant *</td>
<td>93</td>
<td>USA</td>
</tr>
<tr>
<td>Davis et al.</td>
<td>2007</td>
<td>Journal Article</td>
<td>Population-based retrospective cohort</td>
<td>No antidepressant exposure †</td>
<td>73</td>
<td>USA</td>
</tr>
<tr>
<td>Einarson et al.</td>
<td>2007</td>
<td>Abstract</td>
<td>Cohort study</td>
<td>No antidepressant exposure †</td>
<td>73</td>
<td>Australia, Canada, Germany, Italy, Switzerland, USA, Sweden</td>
</tr>
<tr>
<td>Källén et al.</td>
<td>2007</td>
<td>Journal Article</td>
<td>Prospective, registry</td>
<td>Other SSRIs or other antidepressants *</td>
<td>73</td>
<td>Sweden</td>
</tr>
<tr>
<td>Malm et al.</td>
<td>2005</td>
<td>Journal Article</td>
<td>Population-based cohort</td>
<td>No drug purchased</td>
<td>93</td>
<td>Finland</td>
</tr>
<tr>
<td>Wichman et al.</td>
<td>2007</td>
<td>Abstract</td>
<td>Retrospective chart review</td>
<td>Other SSRIs or other antidepressants *</td>
<td>70</td>
<td>USA</td>
</tr>
<tr>
<td>Alwan et al.</td>
<td>2007</td>
<td>Journal Article</td>
<td>Case-control</td>
<td>Other SSRIs or other antidepressants *</td>
<td>93</td>
<td>Canada, USA</td>
</tr>
<tr>
<td>Berard et al.</td>
<td>2007</td>
<td>Journal Article</td>
<td>Case-control</td>
<td>Other SSRIs or other antidepressants *</td>
<td>93</td>
<td>Canada</td>
</tr>
<tr>
<td>Louik et al.</td>
<td>2007</td>
<td>Journal Article</td>
<td>Case-control</td>
<td>Other SSRIs or other antidepressants *</td>
<td>87</td>
<td>Canada, USA</td>
</tr>
</tbody>
</table>

Table 11: Summary of studies included in the Paxil meta-analysis
Figure 21: Case-control studies: odds ratio meta-analysis plot (random effects)
Figure 22: Cohort studies: meta-analysis plot (per 100 births)
Discussion

Upon examination of the results of the present meta-analysis, consisting of 9 studies, it appears that there is no increased risk for cardiac defects associated with paroxetine use in early pregnancy. The rate of congenital heart defects found in this study (1.14% and 1.09% respectively) closely approximate those rates found in the general population (0.7% -1.2%).

In 2002, Hoffman and Kaplan summarized all of the incidence rates of malformations that had been reported in the literature. They aggregated data from thousands of births and all types of malformations. There were 43 studies that reported on cardiac outcomes. Across those studies, the rate of cardiac malformations was 0.96% (CI: 0.73%-1.19%). These values therefore represent what one would expect in the general population. It is interesting that our estimates of cardiac defects fell within this range for both the exposed and comparison groups. The two distributions overlapped almost entirely.

A previous meta-analysis conducted by our group appeared to show an association between first trimester exposure to paroxetine and congenital heart defects. However, that apparent association disappeared in the current study when a larger sample size was available. The rates of malformations are almost identical between groups and both fall within what would be expected in the (non-exposed) general population.

There is strong evidence on the eagerness of some authors to report significant results; seldom do they acknowledge the possibility that their findings may merely be false positives due to random sampling. This bias against the null hypothesis stems from
the early publication of ‘positive’ results and the delayed, or no publication of ‘negative’ results due to the ‘file drawer syndrome’. 142, 143

It is of great importance that the debate surrounding the potential teratogenicity of paroxetine be resolved, as the impact of the uncertainty surrounding the safety of the medication can have adverse effects on pregnant women who require treatment for mood disorders during pregnancy. Paroxetine is one of the most commonly prescribed medications in North America; in Canada it is the most prescribed antidepressant while in the US it is the third most frequently prescribed antidepressant. 127, 144 Since the warnings regarding the potential risk for an increased rate of birth defects with the use of paroxetine in early pregnancy were issued by the US and Canadian regulatory agencies, some women who were taking paroxetine prior to these warnings discontinued their medication, as previously occurred when similar warnings were issued.110 It has been well established that discontinuation, especially abrupt discontinuation, of antidepressants in pregnancy may lead to relapse of the initial psychiatric condition, suicidal ideation and other potentially seriously side effects including postpartum depression.47, 48

Based on systematic review of all available data, there is no evidence to support early fears that paroxetine exposure in the first trimester is associated with an increased risk of cardiac malformations. This evidence-based information will assist women, together with their physicians and other health care providers, to make an informed decision regarding the use of paroxetine during pregnancy. The risks and benefits associated with antidepressant therapy during pregnancy should always be assessed on a case-by-case basis.
Major depressive disorder is a chronic and recurrent mental illness. Canadian statistics indicate that 4 – 5% of the population suffer from major depression during any given year\(^1\) and that one in five Canadians will experience mental illness during their lifetime.\(^2\)

Depression is the leading cause of chronic disease in women between 15 and 44 years of age, overlapping with a woman’s childbearing years.\(^3\) Furthermore, pregnancy represents a time in which women are more vulnerable to the onset of depression or its reemergence. However, all too often women who have been diagnosed with depression prior to pregnancy and have commenced pharmacotherapy to manage their condition, decide on their own or on the advice of their physicians or other health care providers, to discontinue or decrease antidepressant therapy due to fears of teratogenicity when pregnancy is confirmed.\(^4\) Once antidepressant medication is discontinued, many women do not replace it with other forms of treatment (i.e. psychotherapy). The end result is that these women are untreated or sub-therapeutically treated during pregnancy and are at a high risk for the return of depressive symptoms.\(^5\)

The goal of pharmacotherapy during pregnancy is to optimize both maternal and fetal health. Risks and benefits have to be considered in managing and not managing depression with medication during pregnancy; these risks and benefits must be weighed

---

1. Major depressive disorder is a chronic and recurrent mental illness. Canadian statistics indicate that 4 – 5% of the population suffer from major depression during any given year and that one in five Canadians will experience mental illness during their lifetime.

2. Depression is the leading cause of chronic disease in women between 15 and 44 years of age, overlapping with a woman’s childbearing years. Furthermore, pregnancy represents a time in which women are more vulnerable to the onset of depression or its reemergence. However, all too often women who have been diagnosed with depression prior to pregnancy and have commenced pharmacotherapy to manage their condition, decide on their own or on the advice of their physicians or other health care providers, to discontinue or decrease antidepressant therapy due to fears of teratogenicity when pregnancy is confirmed.

3. Once antidepressant medication is discontinued, many women do not replace it with other forms of treatment (i.e. psychotherapy). The end result is that these women are untreated or sub-therapeutically treated during pregnancy and are at a high risk for the return of depressive symptoms.
carefully when deciding what course to take. The extent and severity of a woman’s depressive symptoms must be taken into consideration, as well as her history of depression; women with a depressive history appear to be at high risk for recurrent depression during pregnancy, particularly as a consequence of antidepressant discontinuation. 22

Once a woman discontinues her antidepressant medication, the possibility of the depressive disorder reemerging is very real. Generally depression reemerges gradually over weeks. 149 A recent large, multi-center study has found that 68% percent of women who discontinued their medication just prior to pregnancy or in the early stages of their first trimester, had a depressive relapse during their pregnancy and that they relapsed at a rate that was five times greater than women who remained on medication during pregnancy. 48

The potential risks of treating depression with medication may theoretically include fetal risks such as morphological malformation, neurobehavioural complications and direct toxicity, while risks to the mother of taking the medication include the various side effects of the medication itself. 150 Benefits include restoring maternal mental health, decreasing or alleviating depressive symptoms and a return to normal functioning.

The risks of not treating depression for the mother include: impaired self-care, failure to follow prenatal guidelines, suicidal ideations, self-injurious behaviour, lower than expected weight gain. Pregnant women with depression are more likely to use alcohol or illicit drugs 20 which poses further risks to the fetus. If antidepressant medication is abruptly discontinued, severe side effects may occur in both the mother and fetus. Children born to depressed mothers are more likely to be premature, of low birth
weight, have had an admission to the neonatal unit, have growth retardation and delays in cognitive and behavioural development. 19

The Canadian Health Care System: A Brief Overview

The Canadian health care system known as Medicare is a publicly funded, privately administered system that is founded on the principles of universal care, portability, comprehensiveness, accessibility and public administration of care (Table 12). 151 Medicare consists of a group of provincial/territorial health insurance plans in which medical care is free to all Canadian citizens at the point of service; each province/territory funds and administers its own health care system thus each insurance plan may differ slightly. Despite this autonomy, all provincial and territorial health insurance plans operate within the context of national standards and guidelines set by the federal government in the Canada Health Act.

In Ontario, the Ministry of Health and Long Term Care (MOHLTC) administers the provincial health insurance plan known as the Ontario Health Insurance Plan (OHIP) on a non-profit basis. The provincial legislation upon which OHIP is founded is the Ontario Health Insurance Act. All Canadian citizens, permanent residents, landed immigrants and convention refugees are eligible to receive OHIP if Ontario is their principal and permanent place of residence. 152 The MOHLTC also regulates and finances general hospitals, long-term care facilities such as nursing homes and emergency health services and operates psychiatric hospitals and medical laboratories. Ontario spends approximately 42% of its annual budget on health care; $37.9 billion CAD was allotted for health care in the 2007-2008 provincial budget. 153
Mental illnesses such as depression are a public health concern as they carry with them large economic and societal costs. Mental disorders have been shown to place a large financial burden on the Canadian health care system; in 1998 the economic costs of mental illnesses was estimated at $14 billion CAD. It is critical to understand the ways in which mental illnesses, particularly during pregnancy, contribute to the overburdening of the health care system.

The goal of this study is to estimate the direct medical costs resulting from cessation of antidepressant pharmacotherapy during pregnancy; it will be examined from the viewpoint of the public payer (Government of Ontario’s Ministry of Health and Long Term Care). The paper will limit its scope to women diagnosed with and treated for depression with antidepressant medications prior to confirmation of pregnancy and who subsequently discontinued their medication upon verification of pregnancy status.

**METHODS**

*Assumptions*

The present examination limited itself to the direct medical costs that would be incurred by Ontario’s MOHLTC due to untreated depression in pregnancy. The following assumptions were made when estimating the cost of untreated depression during pregnancy; all pregnancies resulted in single births (this may slightly overestimate the actual number of depressed women during pregnancy); women were established on their antidepressant medication and would have continued treatment if not for the fact that they had become pregnant (ie. discontinuation was not due to reasons such as side effects)
A study conducted by the Joint Canada/United States Survey of Health reported that Canadians and Americans had similar rates of major depression; approximately 12% of women of childbearing age in Canada and the United States experienced major depression.\textsuperscript{154} Throughout this analysis, we assume that rates of depression reported in U.S studies are comparable to Canada.

\textit{Sources}

To estimate the rate of diagnosed but untreated depression in pregnancy that resulted from discontinuation of medication the following values had to be determined; the number of pregnancies in Ontario in a given year, the rate of depression during pregnancy, the rate at which depression is treated with antidepressants and the rate at which treatment is withdrawn in pregnancy. Data from scientific peer-reviewed studies were also used as reference values.

\textit{Pregnancies in Ontario}

Between July 1, 2006 and June 30, 2007 there were 134,141 live births in Ontario, Canada (Statistics Canada). It should be noted that this figure may slightly underestimate the number of pregnant women as it does not include women who miscarried or experienced other events resulting in fetal loss.
Rate of Depression During Pregnancy

A recent meta-analysis that utilized data from the international literature, reported that the rates of diagnosed depression during pregnancy were 7.4% in the first trimester, 12.8% and 12.0% in the second and third trimesters respectively. In order to estimate the overall percentage of women that suffer from depression during pregnancy, the mean rate was found (10.7%) from the rates of depression per trimester.

Antidepressant Discontinuation in Pregnancy

This study considered only women who discontinued their antidepressant medication after confirming pregnancy; these women were otherwise committed to continuing their medication if not for the fact that they became pregnant. It was found that in 2002, 89% of people with diagnosed depression were treated with antidepressant medication. The discontinuation rate of antidepressants in the adult literature has been reported between 28% and 44%. The rate of antidepressant discontinuation in pregnancy was estimated using pooled data from three studies looking at this phenomenon in which 34% of women were found to discontinue their medication during pregnancy. A 68% relapse rate of depression after cessation of antidepressant therapy has been reported.
Maternal Use of Health Care System

It has been shown that depressed individuals utilize the health care system more than their non-depressed counterparts;\textsuperscript{157} therefore pregnant women with untreated depression who experience depressive relapse would be expected to use more health care services than depressed women maintaining treatment. In terms of maternal health, the use of the health care system will be examined in the following areas: physician visits (general practitioners and psychiatrists) and hospitalizations due to depression. In terms of fetal health/outcomes the use of the health care system by depressed mothers will be examined in the following areas: hospitalization due to preterm delivery and hospitalization due to low birth weight.

General practitioners (GPs) play a critical role in the delivery of mental health care; quite often they are the sole provider of mental health services for a large proportion of the Ontario population; they also deliver care in conjunction with a psychiatrist to a smaller number of patients. Psychiatrists offer more specialized mental health care, however they are not accessed as frequently as family physicians for various reasons. A study looking at the utilization of physician services for mental health (1992-1993 data) found that 75.5\% of mental health users used only GPs while 8.7\% of users accessed services from GPs in conjunction with psychiatrists, and 10.2\% used psychiatrists alone; women of child bearing age were more likely to utilize GPs together with psychiatrists.\textsuperscript{158}

In 2000, Canadians made 7.8 million consultations with office-based physicians for depressive disorders. Canadian adults visited GPs an average of 3.9 times a year\textsuperscript{159} while adults with mental illness made an average of eight visits per year to GPs and
approximately 5.5 visits per year to psychiatrists (2000-2001 data). Lin et al. found that people who used both GPs and psychiatrists, averaged between 3 - 4 more visits than the combined averages of people visiting either just GPs or psychiatrists. The Lin et al. report also produced data detailing the most common fee code categories physicians (GPs and psychiatrists) submitted to OHIP regarding mental health care in Ontario (1992-1993 data).

In 1999, the hospitalization rate for Canadian women with major depressive disorder between the ages of 15 and 44 was 0.12%; The average length of stay in a Canadian hospital due to major depressive disorder was 15.2 days (1999 data). The average cost of an admission to a hospital (acute and psychiatric) in 2002-2003 was $5568 CAD for depression.

Utilization of Health Care Services by Infants Born to Depressed Mothers

Depression in pregnancy has been associated with adverse neonatal outcomes such as low birth weight (LBW) and preterm delivery. Low birth weight refers to neonates who weigh less than 2,500 grams at birth. Preterm delivery is defined as birth before 37 weeks of pregnancy; approximately 1 in 13 births are preterm. Low birth weight and preterm deliveries are often associated with each other; sixty percent of low birth weight infants are born preterm. Preterm and low birth weight infants place a greater burden on the health care system than healthy normal weight full term babies because they generally require longer hospital stays at birth, admissions to neonatal care units, are hospitalized more frequently and for longer durations of time during the first year of life and are more likely to experience developmental delays, however, the costs of chronic
health problems that develop as a result of preterm and low birth weight gestations are not being estimated in this analysis.

The rate of preterm delivery is approximately 8% in the general population; it has been found that depressed women have approximately a 13% rate of preterm delivery. Applying this rate to the population of depressed women who discontinued their antidepressant medication during pregnancy in Ontario, it can be predicted that 384 of these women would have preterm deliveries.

The cost of preterm deliveries depends on the degree to which the infant is born premature; the more premature the infant the more costly they are. The mean cost of the initial admission at birth was determined by Petrou et al. to be £5064 which converts to approximately $10,080 Canadian dollars, while the mean cost of readmissions to the hospital during the first year of life totaled £6639 (approximately $13,215 CAD).

About 12% of births are low birth weight; depressed women have an increased risk of delivering low birth weight babies (RR = 1.6). That means that approximately 567 low birth babies would be born to the depressed cohort in Ontario. It has been estimated that the mean hospital costs associated with the delivery of each low birth weight infant are $33,970 U.S; this converts to $34,310 CAD. The additional costs incurred by the health care system during the first year of life of LBW infants was also determined; the incremental cost for each LBW infants was $24,687 US or $24,937 CAD.

Cost estimates for preterm delivery and low birth weight were determined from studies not performed in Canada and therefore not in Canadian dollars. As such, a transferability checklist was used (employing the method of Boulenger et al.) to
ensure that the studies from which the estimates were taken were appropriate for use in
the current population. The checklist in its original form consists of 42 questions,
however a sub-checklist of 16 ‘essential’ items was found to be more concise; both
checklists were validated. There are four possible responses that can be given for each
question; yes (score =1), partially (score = 0.5), no/no information provided (score = 0) or
not applicable. The transferability score is reported as a percentage; it is calculated by
summing the scores and dividing them by 16 and multiplying by 100. If an item in the list
is not applicable to the study under review, the denominator is reduced by the number of
non-applicable items and the score is subsequently generated from the remaining items.
The Petrou et al. study had 12 applicable questions and received a transferability score of
71% while the Schmitt et al. study had 11 applicable questions and received a score of
77%; the Lewit et al. study had 13 applicable questions and received a transferability
score of 76%. An arbitrary cut-off score of 70% was used to represent an acceptable
transferability score; no standard cut-off levels have been reported in the literature.

Costs Associated with Continuing Antidepressant Therapy During Pregnancy

To obtain a more accurate estimate of the cost of untreated depression during
pregnancy, the direct medical costs associated with continuing antidepressant therapy
during pregnancy must also be considered. Potential adverse events associated with the
use of newer generation antidepressants (i.e.: SSRI’s, SNRI) are usually minor and
include GI disturbances such as nausea and diarrhea, sexual dysfunction (decreased
libido) and CNS effects such as anxiety, sedation and headaches. These side effects
usually subside within the first few weeks of therapy and do not normally require medical intervention. More serious but rare adverse events include bleeding events (0.63 per 1000 patient months of treatment), cardiovascular effects (rate = 0.0003%) and serotonin syndrome (0.5 – 0.9 cases/ 1000 patient months of treatment). Because the rates of serious adverse events were so low (< 0.5 women who continued antidepressant therapy during pregnancy), the medical costs associated with these events were assumed to be negligible.

However, one additional cost must also be calculated as infants of women who continue to use antidepressants during pregnancy may be at risk for poor neonatal adaptation syndrome (PNA), a condition that results from the use of antidepressants (SSRIs) in late pregnancy. It is characterized by self-limiting symptoms such as jitteriness, irritability, hypoglycemia and respiratory distress; these symptoms typically appear within the first 48 hours after birth and resolve within two to four weeks after birth. It is important to note that no neonatal deaths have been reported in association with third trimester exposure to antidepressants.

Using the upper end of the range for the absolute risk of PNA, it is estimated that 30% of infants would be affected by PNA subsequent to maternal use of antidepressants in late pregnancy. Using this rate, it would therefore be expected that 2529 infants in this analysis would be expected to experience PNA; this was calculated using the number of pregnant depressed women in Ontario who did not discontinue antidepressant therapy, assuming they used antidepressant medication throughout their entire pregnancy including the third trimester (n=8431).
While there is no current consensus on the management of PNA, supportive care in a special care nursery for a minimum of 48 hours is often provided. In Canada the hourly cost associated with being in a special care nursery is $25.90 CAD.\textsuperscript{176}

**RESULTS**

It was estimated that 2953 women in Ontario discontinued their antidepressant medication in pregnancy and consequently suffered depressive relapse; the calculation is illustrated in Figure 23.

**Maternal Health Care Costs**

Using the data on physician visits and the OHIP Schedule of Benefits and Fees (Schedule of Benefits for Physician Services 2006) and applying these numbers to the current population of interest (n = 2953), the average number of physician visits was determined and subsequently the cost produced by these visits (refer to Table 13). The ensuing calculations determined that a total cost of $1,277,198 CAD would be incurred by the MOHLTC due to physician services sought by pregnant and depressed women no longer receiving antidepressant therapy.

To describe the cost due to hospitalizations, the hospitalization rate for Canadian women of childbearing age with depressive disorder (0.12\%) was applied to the number of pregnant and depressed women in Ontario (n=2953); approximately 3.5 depressed and pregnant women would be admitted to a general hospital due to depression (assuming
they are not hospitalized for pregnancy related complications). An estimated $19,488 would therefore be spent on hospitalizations due to depression in pregnancy.

**Infant Health Care Costs**

The total cost of caring for preterm infants born to depressed mothers in the first year of life was estimated to be $8,945,280 CAD. Given that 60% of low birth weight infants are born preterm, it is assumed that the cost of these infants would be included in the above calculation. Therefore the cost of caring for the remaining 40% of low birth weight infants (n=227) during the first year of life would be an estimated $13,449,069 CAD.

**Total Cost to Ontario Health Care System**

Totaling the above estimates, the overall cost to the MOHLTC resulting from the discontinuation of antidepressants during pregnancy would be $23,691,035 CAD/yr, with the majority of costs resulting from the care of preterm/low birth weight infants.

However the cost associated with continuing antidepressant therapy during pregnancy must also be taken into consideration. The direct medical cost associated with continuing antidepressant therapy throughout gestation would be the cost of caring for infants born with PNA. It was assumed that all infants that displayed PNA required care in a special care nursery for 48 hours; the resulting cost was estimated at $3,144,053 CAD. This cost must then be subtracted from the overall cost to the MOHLTC of not
treating depression during pregnancy ($23,691,035 CAD) resulting in a net cost of $20,546,982 CAD/yr.

DISCUSSION

Depression is a major public health issue given its prevalence in North American society and the ensuing health care costs. Depression is a treatable disease and as such can be actively managed in most depressed populations, particularly vulnerable populations such as pregnant women. It was estimated that $20,546,982 CAD is spent annually on untreated maternal depression. Not only does depression carry with it economic consequences, more importantly it interferes with the quality of child-rearing, maternal responsiveness to infants and other elements essential for optimal child development.

There are several limitations to this analysis. It is important to keep in mind that this estimate only included the direct costs due to medically diagnosed depression that went untreated. As previously stated, only 50% of depression is diagnosed therefore there is utilization of the health care system for depression that goes undiagnosed; depression may manifest itself as other somatic symptoms that are treated instead of the depression itself. Consequently, this would lead to an underestimation of the direct costs associated with untreated depression during pregnancy as some depressed women are using the system more than the average person but are not identified as sufferers of depression.

Another consideration is that depressed women who do not receive treatment during pregnancy may end up excluding themselves from health care altogether, the
literature shows that these types of women have poor prenatal care and as such their pregnancy outcomes are also poor; the resulting outcomes of their pregnancies may be an additional burden on the health care system.

It should also be recognized that depressed women are more likely to smoke and to use alcohol and other illicit substances, which can result in poor pregnancy outcomes (i.e. fetal alcohol syndrome, additional low birth weigh infants); the costs of outcomes such as these were not factored into the analysis. Another factor to consider is the use of allied health professionals such as social workers and psychologists; these health care providers are not covered by OHIP outside a primary care setting, and would only be paid for by the government if women received social assistance (i.e. welfare). The number of pregnant and depressed women receiving social assistance or referred to an allied health professional was not available and therefore the final cost to the MOHLTC may be underestimated.

The risks of untreated depression does not end with birth; perinatal depression is one of the best predictors of depression during the post-partum period. Depressed mothers have been found to have unfavourable patterns of health care utilization for their babies in early infancy. They may be more likely to seek care for their infants in emergency departments and have children who are hospitalized. These additional services would add to the estimated costs for the MOHLTC. This analysis only examined direct medical costs, but future analyses ought to consider the broader societal perspective which would include indirect costs as well as the direct costs incurred from untreated depression to patients and their families. Factors such as time lost from work,
loss of income, years of life lost and number of deaths could then be taken into consideration.

An estimated $20,546,982 CAD is spent annually in Ontario on untreated maternal depression. Depression is a treatable disease and therefore safe treatment options for the management of this condition during pregnancy should be actively explored as treated depression may translate into cost savings for the Ontario government that can then be passed on and used in other priority areas.
Table 12: Five Principles of the Canadian Health Care System

<table>
<thead>
<tr>
<th>FIVE PRINCIPLES CANADIAN HEALTH CARE SYSTEM FOUNDED ON</th>
<th>DEFINITION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Universal Care</strong></td>
<td>Those entitled to and insured by the provincial/territorial health insurance plans are entitled to health coverage on uniform terms and conditions.</td>
</tr>
<tr>
<td><strong>Portability</strong></td>
<td>The health insurance plan must cover insured persons when they move to another province or territory within Canada and when they travel abroad. Limits exist to the coverage provided by provinces/territories when care is obtained outside of Canada on a non-emergency basis.</td>
</tr>
<tr>
<td><strong>Comprehensiveness</strong></td>
<td>All insured health services (as outlined in the Canada Health Act) provided by hospitals and physicians must be covered by provincial and territorial insurance plans.</td>
</tr>
<tr>
<td><strong>Accessibility</strong></td>
<td>Provinces/territories must ensure that all insured persons have reasonable access to medically necessary hospital and physician services without financial or other barriers.</td>
</tr>
<tr>
<td><strong>Public Administration of Care</strong></td>
<td>Provincial and territorial health insurance plans must be administered and operated by public authorities on a not-for-profit basis; the authority’s records and accounts are publicly audited.</td>
</tr>
</tbody>
</table>

Ref: 179
Table 13: Estimated cost of physician services incurred by pregnant women with depression who discontinued antidepressant therapy

<table>
<thead>
<tr>
<th>Health Care Provider</th>
<th>Number of Annual Visits</th>
<th>Type of Visit</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP</td>
<td>17836</td>
<td>Individual Psychotherapy</td>
<td>$514,725</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Counselling</strong></td>
<td>$358,695</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Other</strong></td>
<td>$55,140</td>
</tr>
<tr>
<td>GP + Psychiatrist</td>
<td>4367</td>
<td>Individual Psychotherapy (Psychiatrist)</td>
<td>$90,999</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Individual Psychotherapy (GP)</td>
<td>$46,272</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>In-patient Assessments/Consultations (Psychiatrist)</strong></td>
<td>$33,343</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Psychiatric Care (In-patient) (Psychiatrist)</td>
<td>$27,340</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Other</strong></td>
<td>$44747</td>
</tr>
<tr>
<td>Psychiatrist</td>
<td>1656</td>
<td>Individual Psychotherapy (Psychiatrist)</td>
<td>$59,836</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Psychiatric Care (In-patient) (Psychiatrist)</td>
<td>$25,513</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Other</strong></td>
<td>$20,588</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>23859</strong></td>
<td></td>
<td><strong>$ 1,277,198</strong></td>
</tr>
</tbody>
</table>

*All figures based on an n = 2953 (women in Ontario with depressive relapse due to discontinuation of antidepressants)

** Other – visits not specified, therefore categorized as a general visit

*** Other – visits not specified, therefore categorized as a general visit. Half of visits attributed to GPs and half to psychiatrists
Figure 23: Estimating the number of women in Ontario with depressive relapse due to discontinuation of antidepressants in pregnancy

- 134,141 births in Ontario (2006-2007)
  - X 10.7% (rate of diagnosed depression in pregnancy)
- 14,353 depressed, pregnant women in Ontario
  - X 89% (rate of treatment with antidepressants)
- 12774 pregnant women treated for depression in Ontario
  - X 34% (discontinuation rate of antidepressants in pregnancy)
- 4343 pregnant women discontinued antidepressants in Ontario
  - X 68% (rate of relapse upon discontinuation)

2953 pregnant women in Ontario with depressive relapse due to discontinuation of antidepressants
7.1 Summary and Overall Discussion

Depression is a complex and multi-faceted disease and consequently so is its treatment, particularly in vulnerable populations such as pregnant women. In the absence of widely accepted guidelines, the clinical decision on how to manage depression during pregnancy is extremely difficult as risks present themselves in both treating and not treating the condition. To overcome this gap, my dissertation focused on risk-benefit assessments as an aid in the decision making process. Factors that should be considered in these types of analyses include changes in the pharmacokinetics of medications during pregnancy, alterations in pharmacodynamic response and the relationship between them. If medications are to be used effectively in pregnancy, their safety in the mother and fetus must also be assessed. In addition, it is important to consider the burden untreated depression during pregnancy can have on the health care system.

The six studies presented in this dissertation provide further insight into the above mentioned factors. The first study found that the apparent oral clearance rates of bupropion and venlafaxine were increased in late pregnancy. The study exploring the metabolism of antidepressants using hair analysis demonstrated that there was increased metabolism in pregnancy when compared to the post-partum period for citalopram but not for venlafaxine. When depressive symptoms were followed across pregnancy, depression scores had a trend of decreasing as pregnancy progressed. In the meta-analysis examining paroxetine and the risk of cardiac malformations, no increased risk for cardiac
defects was found after gestational exposure to the medication. The economic analysis estimated that the direct medical cost of antidepressant discontinuation in pregnancy in Ontario was approximately $20,546,982 CAD/yr.

The results of the pharmacokinetic studies of antidepressants in blood and hair demonstrated that in late pregnancy metabolism and apparent oral clearance rate for many agents are increased leading to lowered plasma levels. The decrease in plasma levels due to increased metabolism in late pregnancy has been described with citalopram, fluoxetine and sertraline; increased metabolism and glomerular filtration rate in pregnancy are likely to play a role in these decreases, as GFR is a major elimination route for some active metabolites. In previous studies, some patients with decreased plasma levels required an increase in dosage to alleviate depressive symptoms. In our pharmacokinetic study, we found that women did not require an increase in dose as depression scores either decreased during pregnancy or remained steady, despite increased metabolism and decreased levels. This can be explained by several different mechanisms which act in parallel.

In general, SSRIs have been shown to exhibit flat dose response curves, such that doses beyond the minimum effective dose do not achieve a greater clinical response while the incidence of adverse events may increase. In our study, the patient on venlafaxine had decreased plasma levels of the medication in the third trimester, however her depression scores in the third trimester were well below the cut off for depressive symptoms and not significantly different from those seen in the first trimester. Similarly, participants in our study displayed decreased depression scores in late pregnancy despite decreased AUC and increased apparent oral clearance rates. Moreover, some SSRIs and
SNRIs (e.g. fluoxetine, venlafaxine) are metabolized to active metabolites; hence increased metabolism in late pregnancy and decreases in parent drug levels do not necessarily mean less active drug.

This apparent dissociation between the pharmacokinetics and pharmacodynamic response of some antidepressants in pregnancy is important because it speaks to the necessity of managing pregnant and depressed women on an individual case by case basis. This strongly calls for a need for depressive screening during pregnancy in routine clinical practice; this would help to determine and monitor depressive symptoms without constant and resource demanding therapeutic drug monitoring. One study found that 20% of women screened while waiting for prenatal care visits displayed depressive symptoms and only 14% of those women were receiving any formal treatment for the condition. 177 Screening would therefore provide an opportunity to detect prenatal depression and mitigate preventable adverse events. It is important to keep in mind however, that screening tools such as the EPDS are not diagnostic, they only measure depressive symptomology. Furthermore, interpretation of these scales must be done with caution as the sensitivity and specificity of the measure varies when different cut-off points are used. Clinical assessment should be used to validate the findings of screening instruments and determine remission or relapse of depression.

Other potential factors that could be playing a role in the varied pharmacodynamic responses observed in our studies include increased estrogen levels in late pregnancy. Estrogen is known to exert effects on several neurotransmitter systems in the central nervous system including the serotonergic system and may be able to act synergistically with antidepressants to decrease depressive symptoms. 180,181 Due to its
neuromodulatory effects, estrogen has been investigated as an adjunct therapy for depression.  

It was hypothesized that depressive symptoms would increase as pregnancy progressed due to the increased clearance rate of antidepressant medications. However, the results from our longitudinal study of depression in pregnancy showed the opposite; there was a trend for depressive symptoms to be highest in the first trimester and decrease as pregnancy progressed. Nausea and vomiting of pregnancy (NVP), which affects up to 60 – 80% of pregnancies, may have a major influence on the reporting of depressive symptoms. Several studies have found an association between depression and the severity of NVP. Symptoms of NVP peak during gestational week nine and then decrease as pregnancy progresses, this would coincide with the temporal pattern of depressive symptoms seen in our study. As such, physiological factors such as nausea and vomiting of pregnancy must be considered when assessing depression in pregnant women and determining the appropriate treatment.

The use of pharmacological treatment for depression during pregnancy requires that medications be shown to be non-teratogenic or have minimal risks involved. Once scientific concerns regarding relative safety are allayed, there still remains a very important factor that must be addressed – perceptions of teratogenic risk. Perceptions by prescribing physicians and expectant mothers will ultimately affect the treatment decision; inadequate treatment of maternal disease or termination of otherwise wanted pregnancies are not uncommon outcomes when perceived risk is high. It has been shown that women and their health care providers often overestimate the teratogenic risks
associated with medication consumption in pregnancy;\textsuperscript{188} this may lead to underutilization of necessary drugs in pregnancy.

Furthermore, a study comparing women taking antidepressants in pregnancy to women using non-psychiatric medications (antibiotics and gastric drugs) in pregnancy found that women taking antidepressants were more likely to discontinue their medication than women on non-psychiatric drugs even after they had been advised about the relative safety of the medications in pregnancy.\textsuperscript{49} Discontinuation of antidepressant therapy in pregnancy has been shown to lead to depressive relapse in a large proportion of women when compared to women who maintained therapy throughout gestation.\textsuperscript{48}

The stigma attached to mental disorders such as depression should not be ignored; it may leave women more likely to avoid treatment during pregnancy. One of the drawbacks to improperly managed depression is that depressed patients have been shown to utilize the health care system more than their non-depressed counterparts.\textsuperscript{157} This may lead to increased health care expenditures particularly in systems that are publicly funded with universal health care insurance. The economic impact of the illness is an important consideration that should also be addressed when conducting risk benefit assessments in pregnant and depressed women.

Several strengths exist in the research presented here, these include new pharmacokinetics data on antidepressants never studied before in pregnancy, and the novel application of hair analysis to monitor metabolism of antidepressants in pregnancy. Meta-analysis is a powerful epidemiological approach that allows for the analysis and synthesis of available data to determine pregnancy outcomes in populations with limited sample sizes such as pregnant women, where it is unethical to conduct randomized trails
to ascertain teratogenicity. The teratogenicity data on paroxetine in pregnancy was reassuring and therefore has the potential to combat negative and alarming information found in the lay media that may affect treatment decisions of physicians prescribing the medication to women in pregnancy and a woman’s willingness to take the medication.

Limitations of the research presented include restricted sample sizes in the pharmacokinetic studies using blood and hair and a reduced sampling time in the blood pharmacokinetic study resulting in an incomplete pharmacokinetic profile. The economic analysis would have been strengthened by the inclusion of a comparison group of non-depressed pregnant women.

7.2 Conclusion

Depression in pregnancy is a serious public health issue as it adversely affects both the expectant mother and her developing fetus. Deciding how to manage the illness during pregnancy is difficult, and this treatment decision is affected by various factors. Risk benefit assessments are critical tools when attempting to decide on a course of clinical action. Pharmacokinetic and pharmacodynamic information on antidepressant medication in pregnancy as well as the safety of the medication during gestation are essential components in risk benefit assessments for pregnant, depressed women.

In conclusion, a unified approach to the analysis of determinants affecting depression in pregnancy and its treatment was presented. Some of the results such as the meta-analysis and cost-analysis, have direct impact on patient care, whereas other approaches such as hair metabolism analysis are novel translational methods that should be further explored.
7.3 Future Research

Further study is required in regards to various hurdles in treating depression in pregnancy. It would be useful to have more safety data on the new and emerging antidepressant therapies in pregnancy, as well as their pharmacokinetic profiles in pregnancy. Additional investigation into the dose-response relationship of antidepressants in pregnancy are necessary as it is important to address whether titrating dose will indeed affect the desired response to a medication. It is essential that depression be identified in obstetric populations not only as a preventive measure for postpartum depression, but as a routine practice to ensure healthy pregnancies. The feasibility of this type of screening and the best tools to identify women at risk for depression in pregnancy has to be more clearly elucidated. Further study into the economic consequences of untreated depression in pregnancy is also required; indirect medical costs such as time lost from work, loss of income, years of life lost and number of deaths need to be investigated.
References


111. GlaxoSmithKline Medicine. Updated preliminary report on bupropion and other antidepressants, including paroxetine, in pregnancy and the occurrence of cardiovascular and major congenital malformation [Clinical Trial Register Website]. 2007.


CONCENTRATION – TIME CURVES FOR BUPROPION AND VENLAFAXINE
Bupropion
Subject B2

Bupropion 1st & 3rd trimesters
(normal plot)

- Bupropion (1st tri)
- Hydroxybupropion (1st tri)
- Bupropion (3rd tri)
- Hydroxybupropion (3rd tri)
Subject B3

Bupropion 1st & 3rd trimesters
(normal plot)

Bupropion 1st & 3rd trimesters
(normal plot)

Bupropion (1st tri)  Hydroxybupropion (1st tri)
Bupropion (3rd trimester)  Hydroxybupropion (3rd tri)
Venlafaxine

Subject V1

*Note: dose increase by 3rd trimester
Subject V2

Venlafaxine 1st & 3rd trimesters
(normal plot)

Venlafaxine (1st tri) O-desmethyl venlafaxine (1st tri) Venlafaxine (3rd tri) O-desmethyl venlafaxine (3rd tri)
FORMS FROM LONGITUDINAL STUDY OF DEPRESSION IN PREGNANCY
INTAKE FORM: PATIENT DEMOGRAPHICS (ASKED ONLY ON FIRST CALL)

GROUP:

☐ Study
☐ Control Group 1
☐ Control Group 2

PATIENT NAME: ____________________________________________________________

D.O.B: _____________________________________________________________________

HEIGHT: _____________________________________________________________________

TELEPHONE NUMBER: _______________________________________________________

ADDRESS: ___________________________________________________________________

PHARMACY NAME AND PHONE #: _____________________________________________

DOCTORS NAME AND ADDRESS (IF APPLICABLE) _________________________________

* REMIND PATIENT THAT ALL INFORMATION THEY ARE PROVIDING IS CONFIDENTIAL AND THAT IF THEY DO NOT FEEL COMFORTABLE ANSWERING ANY OF THE FOLLOWING QUESTIONS THEY ARE NOT REQUIRED TO DO SO

MARITAL STATUS

☐ Single
☐ Married
☐ Common Law
☐ Divorced
☐ Widowed
☐

EDUCATION

What was the last level of education you completed?

☐ Elementary
☐ Secondary (high school)
☐ Post-secondary (college, university)
What was the last level of education your spouse/partner completed?

- Elementary
- Secondary (high school)
- Post-secondary (college, university)

**ETHNICITY**

Would you mind telling me how you would describe yourself based on the following choices?

- Caucasian
- Black
- First Nations/Native Canadian
- Indo-Asian
- Oriental-Asian
- Hispanic
- Other

**OCCUPATION AND ANNUAL INCOME**

Could you please tell me your occupational status?

- Employed full time
- Employed part time
- Unemployed
- Student
- Full time homemaker
- Disability

What is your occupation? ________________________________

What is your annual income?

- Less than $20 000
- Between $20 000 - $40 000
- Between $40 000 - $60 000
- Between $60 000 - $80 000
- Greater than $80 000

What is your child’s father’s annual income?

- Less than $20 000
- Between $20 000 - $40 000
- Between $40 000 - $60 000
- Between $60 000 - $80 000
- Greater than $80 000
HISTORY OF DEPRESSION

♦ How did you find out that you were depressed?

☐ Self-diagnosis
☐ General Practitioner
☐ Psychiatrist
☐ Other

♦ When were you first diagnosed as clinically depressed?

Date: ________________________________

♦ Have you ever been hospitalized for your depression?

☐ No
☐ Yes

If yes when and for how long? ________________________________

♦ When did you first start taking antidepressant medication?

Date: ________________________________

♦ When did you start taking the antidepressant medication that you are currently on?

Date: ________________________________
PHARMACODYNAMICS OF DEPRESSION

PATIENT ID# __________________________

CALL 1  2  3  4  (circle one)

PATIENT NAME: ______________________________________________________

DATE OF CALL: __________________________________________________________

DATE OF NEXT CALL: _____________________________________________________

GROUP:

☐ STUDY    GEST. AGE (WKS): ________    WEIGHT (LBS) ________

☐ CONTROL GROUP 1    GEST. AGE (WKS): ________    WEIGHT (LBS) ________

☐ CONTROL GROUP 2    N/A    WEIGHT (LBS) ________

General Questions

* TO BE ASKED TO STUDY GROUP ONLY

♦ Are you experiencing any nausea and/or vomiting associated with pregnancy?

☐ No

☐ Yes (mild ____ , moderate ____ , severe ____)

* TO BE ASKED TO STUDY GROUP AND CONTROL GROUP 2 ONLY

DRUG & CURRENT DOSE: ________________________________________________

IS THIS THE DOSE YOUR MD PRESCRIBED TO YOU?

☐ YES

☐ NO

☐ MORE

☐ LESS
ARE YOU TAKING THE DRUG AS OFTEN AS YOUR MD TOLD YOU TO?

☐ YES
☐ NO
☐ MORE
☐ LESS

♦ Do you have any side effects from your antidepressant medication?

☐ No
☐ Yes

If yes, what do you do about them? (ie: skip dose?)
_____________________________________________________
________________________________________________________

♦ Are you currently receiving any other form of treatment aside from your medication for your depression (ie. psychotherapy, ECT, St. John’s Wort)?

☐ No
☐ Yes

If yes, what type? ____________________________

How often? ________________________________

♦ Have you had any periods of low mood since we last spoke?

☐ No
☐ Yes

If yes, when? ____________________________

For how long? ________________________________

Reason (if applicable) (i.e: death in family) ________________________
EDINBURGH POSTNATAL DEPRESSION SCALE (EPDS)

1. I have been able to laugh and see the funny side of things.
   - As much as I always could
   - Not quite so much now
   - Definitely not so much now
   - Not at all
   Score: _______

2. I have looked forward with enjoyment to things.
   - As much as I ever did
   - Rather less than I used to
   - Definitely less than I used to
   - Hardly at all
   Score: _______

3. I have blamed myself unnecessarily when things went wrong.*
   - Yes, most of the time
   - Yes, some of the time
   - Not very often
   - No, never
   Score: _______

4. I have been anxious or worried for no good reason.
   - No, not at all
   - Hardly ever
   - Yes, sometimes
   - Yes, very often
   Score: _______

5. I have felt scared or panicky for not very good reason.*
   - Yes, quite a lot
   - Yes, sometimes
   - No, not much
   - No, not at all
   Score: _______

6. Things have been getting on top of me.*
   - Yes, most of the time I haven’t been able to cope at all
   - Yes, sometimes I haven’t been coping as well as usual
   - No, most of the time I have coped quite well
   - No, I have been coping as well as ever
   Score: _______

7. I have been so unhappy that I have had difficulty sleeping.*
   - Yes, most of the time
   - Yes, sometimes
   - Not very often
   - No, not at all
   Score: _______
8. I have felt sad or miserable.*
   o Yes, most of the time
   o Yes, quite often
   o Not very often
   o No, not at all
   Score: ______

9. I have been so unhappy that I have been crying.*
   o Yes, most of the time
   o Yes, quite often
   o Only occasionally
   o No, never
   Score: ______

10. The thought of harming myself has occurred to me.*
    o Yes, quite often
    o Sometimes
    o Hardly ever
    o Never
    Score: ______

TOTAL SCORE: ______________

SEND DOCTOR A LETTER: YES ___  NO ___
BORN-STEINER IRRITABILITY SCALE

Check the item that best describes how this patient has been feeling in the past week.

1. ANNOYANCE
   This item covers a feeling of being easily annoyed or bothered, less patient or tolerant. The patient may endorse being short-tempered, that little things bother her. At the most extreme, she may fly off the handle over any external stimuli.

   Mostly patient and tolerant  ______  0
   Sometimes lost patience over small things ______ 1
   Temper often flared ______ 2
   It felt like everything was annoying all of the time ______ 3

2. ANGER
   This item includes feeling angry or mad, i.e., a strong and pervasive feeling of displeasure. The patient may feel constantly angry at herself or at others. At the more extreme, the patient may report experiencing fury or rage.

   Did not feel angry at all ______ 0
   Felt angry occasionally ______ 1
   Often felt downright mad ______ 2
   Mostly felt full of rage ______ 3

3. TENSION
   This item covers feeling tense, on edge, touchy, hyper or agitated. The patient may report feeling stressed, worried or unsettled. At the more extreme, she may indicate feeling cranky or explosive.

   On most days felt quite relaxed ______ 0
   Occasionally felt on edge ______ 1
   Felt stressed about things quite a bit ______ 2
   Often felt very tense ______ 3
BORN-STEINER IRRITABILITY SCALE

4. HOSTILE BEHAVIOUR
The patient describes speaking with her voice raised, in a sharp, curt or harsh manner. She often snaps or yells. She says things she doesn’t mean, and may be critical or sarcastic of others. There is a tendency to blame other for perceived wrongs. She may have angry facial expressions or body behaviours. The patient may be confrontational and frequently argue with others.

For the most part was pleasant when talking to others _______ 0
Spoke sharply to people now and then _______ 1
Sometimes was verbally harsh _______ 2
Often got into shouting fights _______ 3

5. SENSITIVITY
The patient may endorse a heightened awareness of noise or (physical) touch. Ask the patient about each item:

a) Jumpy when touched by someone _______ 3
b) It seemed like people’s voices were much louder than usual _______ 3

TOTAL SCORE: _______
GOLDBERG ANXIETY SCALE

Score 1 point for each “Yes”

1. Have you felt keyed up, on edge?  
   Yes _____  No _____

2. Have you been worrying a lot?  
   Yes _____  No _____

3. Have you been irritable?  
   Yes _____  No _____

4. Have you had difficulty relaxing?  
   Yes _____  No _____

(If “yes” to two of the above, go on to ask)

5. Have you been sleeping poorly?  
   Yes _____  No _____

6. Have you had headaches or neck aches?  
   Yes _____  No _____

7. Have you had any of the following: trembling, tingling, dizzy spells, sweating, urinary frequency, diarrhea?  
   Yes _____  No _____

8. Have you been worried about your health?  
   Yes _____  No _____

9. Have you had difficulty falling asleep?  
   Yes _____  No _____

TOTAL SCORE: _______
PERCEIVED STRESS SCALE – 4 ITEM

**Instructions:** The questions in this scale ask you about your feelings and thoughts during the last month. In each case, please indicate with a check how often you felt or thought a certain way. Items 2 and 3 are the positively scored items (therefore reverse code).

1. In the last month, how often have you felt that you were unable to control the important things in your life?
   ____ 0 = never _____ 1 = almost never _____ 2 = sometimes _____ 3 = fairly often
   _____ 4 = very often

*2. In the last month, how often have you felt confident about your ability to handle your personal problems?
   ____ 0 = never _____ 1 = almost never _____ 2 = sometimes _____ 3 = fairly often
   _____ 4 = very often

*3. In the last month, how often have you felt that things were going your way?
   ____ 0 = never _____ 1 = almost never _____ 2 = sometimes _____ 3 = fairly often
   _____ 4 = very often

4. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?
   ____ 0 = never _____ 1 = almost never _____ 2 = sometimes _____ 3 = fairly often
   _____ 4 = very often

**TOTAL SCORE:** ________
HOSPITAL FOR SICK CHILDREN ETHICS APPROVAL FORMS
Research Ethics Board (REB)

The REB is organized and operates according to the principles and practices stated in the Declaration of Helsinki, the Canadian Tri-Council Policy Statement (1998), ICH/GCP guidelines and Division 5 of the Food & Drug Regulations, Health Canada

SickKids

Approval & Terms of Agreement

Investigators:
Dr. Gideon Koren, L.O'Brien, A.Einarson, L.Born

Project title:
Pharmacodynamics and Pharmacokinetics of Antidepressants in Pregnancy

File number: 1000008054

Protocol Version Date: August 2005
Consent & Assent form version date: October 13, 2005
Investigator’s Brochure version date: N/A

Level of Continuing Review: II D

I agree to carry out the proposed research involving human subjects in accordance with the protocol approved by the REB using the approved consent form. I shall notify the division/department head and the REB prior to implementing any amendments in the protocol and of any deviations, adverse or unexpected events as soon as possible. I certify that the research contract and corresponding protocol are consistent (where applicable) and will inform the contract manager of any proposed amendments.

Signature of Primary Investigator ____________________________ DATE Oct 25/2005

I approve of this research protocol, agree to share responsibility for its proper conduct, and will ensure that the REB is notified of concerns, as appropriate.

Signature of (Division/Department Head) ____________________________ DATE 10/25/2005

The REB of the Hospital for Sick Children has reviewed and approved the above-named project.