ILLICIT DRUG USE DURING PREGNANCY AND ITS RELATIONSHIP TO NEONATAL OUTCOMES AMONG HEPATITIS C POSITIVE WOMEN IN BRITISH COLUMBIA

by

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ABSTRACT

OBJECTIVES: To investigate the relationship between stimulant and/or opiate drug use during pregnancy, and adverse neonatal outcomes in Hepatitis C positive women.

METHODS: HCV positive pregnant women in British Columbia who consented to participate in a prospective, cohort study were enrolled in the HCV Vertical Transmission Study. A baseline questionnaire sought information on sociodemographic characteristics, substance use, obstetrical and medical history, and sexual behaviour. Follow-up questionnaires collected details on delivery and neonatal outcomes. The adverse neonatal outcomes of interest, for this analysis, were prematurity, low birth weight, low Apgar score, and admission to a neonatal intensive care unit. Required variables were extracted from the primary study dataset. The secondary analysis included descriptive, univariate, and multi-variable statistical techniques to address the above stated objectives.

RESULTS: Data from 136 women and their infants were analyzed for this study. Fifty-three (39.0%) of the women gave birth to infants that suffered an adverse neonatal outcome. Approximately half (49.6%) of the cohort used stimulant drugs during their pregnancy, 35.9% used opiates, and 68.4% smoked cigarettes. Concurrent substance use was very common among these women. Current stimulant use (p<0.01), current opiate use (p<0.001) and current tobacco use (p<0.01) were associated with adverse neonatal outcome. Opiate use during pregnancy remained significant with adverse neonatal outcome after adjusting for stimulant use, tobacco use, age, aboriginal ethnicity, and gravidity. An odds ratio 5.52 (95% Confidence Interval: 1.82, 16.76) was determined through multi-variable analysis.
CONCLUSION: Pregnant women living with HCV in British Columbia report high use of stimulants, opiates, and tobacco during their pregnancies. The infants of these women also suffer high incidences of adverse neonatal outcomes. When a wide range of substances, obstetrical risk factors, and lifestyle characteristics were considered, the use of opiates during pregnancy was determined to be the strongest predictor of a poor neonatal outcome. Women who use opiates during their pregnancy are at increased risk of delivering an infant who will experience an adverse neonatal outcome.
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CHAPTER 1 – INTRODUCTION

Illicit drug use is recognized as a major epidemic that causes avoidable mortality and morbidity. It is a problem that persists despite education, law enforcement, and other anti-drug efforts. In the province of British Columbia alone there are between 170 and 200 deaths annually from injection drug overdose, making it among the leading causes of death for individuals aged 30-49 years. The burden of this problem does not end there. Of more than 15,000 injection drug users in British Columbia, a substantial proportion will be women in their reproductive years. Due to the highly addictive nature of illicit drugs, some of these women will continue to use drugs during their pregnancies. Most estimates report maternal drug use to be in the range of 3-4% of all pregnancies. The use of illicit drugs during pregnancy has the potential to harm both the pregnant woman and her baby.

1.1 SIGNIFICANCE OF THESIS RESEARCH PROJECT

This research examines the relationship between drug use during pregnancy and adverse neonatal health outcomes in HCV positive women. The research identifies additional risk factors for these adverse outcomes that include concurrent substance use, the use of other non-illicit substances, obstetrical history, and infectious diseases. The project also includes a component that describes the sociodemographic characteristics, medical history, and sexual behaviour of HCV positive pregnant women in this province.

Various studies in the United States have previously examined the issue of drug use in pregnancy. To date no data related to this issue in British Columbia have been examined and, in fact, few Canadian studies exist. The differences between Canada and
the US, in their health care systems and approaches to illicit drugs, dictates the need for Canadian-based research to aid in the planning of health care, prevention and education in our country. The fact that the demographic profile of childbearing women in Canada, and more specifically in BC, is distinct from that of the US, further highlights that studies, specific to the women in this province, are necessary.

In general, the components of this thesis will enhance the current body of knowledge and provide additional evidence to support or refute the association between drug use in pregnancy, and the effects of this behaviour on the health of newborns. More specifically, it will provide health related data that is representative of the situation and population in British Columbia. It is hoped that this research will direct the allocation of resources that will lead to effective interventions and improvements in the care of drug-addicted pregnant women in BC. The ultimate aim is the reduction of adverse health outcomes experienced by the infants born to these women.

1.2 STUDY OBJECTIVES

The main objective of this research was to measure the impact of drug use on adverse pregnancy outcomes among women who are Hepatitis C positive. This thesis, therefore, was comprised of two primary objectives.

The first objective was to investigate the relationship between stimulant drug use during pregnancy and adverse neonatal outcomes. The second objective was to investigate the relationship between opiate drug use during pregnancy and adverse neonatal outcomes. These objectives were carried out while controlling for other known risk factors such as concurrent substance use, obstetric history, and sociodemographic
characteristics. The main outcome considered for these objectives, adverse neonatal outcome, was determined by the incidence of the following indicators of neonatal health: premature birth; low infant birth weight; low Apgar score; or admission to a neonatal intensive care unit. Sub-analyses include describing the sociodemographic profile, obstetric and medical history, and sexual behaviour of those HCV positive pregnant women who report drug use during their current pregnancy.

1.3 SUMMARY

The Hepatitis C Vertical Transmission Study, based at the Children’s and Women’s Health Centre of British Columbia, was initiated to study specific objectives related to HCV infection during pregnancy and disease transmission to the infant. It has provided a unique opportunity to study illicit drug use during pregnancy and the effect of this behaviour on neonatal outcomes. This thesis project was undertaken to study this issue in BC by addressing the above stated objectives.
CHAPTER 2 – BACKGROUND

2.1 INTRODUCTION

The issue of drug use during pregnancy and its effect on the neonate is a complicated one. There are many factors, outside of maternal drug use, that may influence an infant’s health; these include obstetrical history, infectious diseases, and genetic factors. In addition, women who use drugs have complex issues. Their illicit drug use often goes hand-in-hand with the use of other substances such as alcohol and tobacco that, if used during pregnancy, are known to have detrimental effects on the fetus. Drug users are also at increased risk of acquiring sexually transmitted infections, which may put their infants at increased risk of poor neonatal outcomes. This chapter will review the current literature related to drug use during pregnancy and the effects on the neonate. It will also provide the relevant background related to the use of other substances, and infectious diseases that may also lead to adverse pregnancy outcomes.

The first section in this chapter will define, and then present rates of selected obstetric and neonatal outcomes. The second section will review studies that have examined the issue of drug use in pregnancy and its effect on the neonates. The third section is related to tobacco, alcohol, and marijuana use, and in particular the effects of these substances on neonatal outcomes. The fourth section will focus specifically on hepatitis C. It will provide a brief review of this infection, its’ relation to drug users, and how it affects pregnancy outcomes. Finally, the fifth section focuses on the effect of various sexually transmitted infections on neonatal health.
2.2 NEONATAL OUTCOMES

2.2.1 DEFINITIONS

The brief glossary below provides definitions for some relevant obstetrical and neonatal terms:

**Abruptio placentae**
A disorder of pregnancy in which the placenta prematurely separates from attachment to the wall of the uterus; marked by hemorrhage, pain, and fetal distress.\(^{12}\)

**Apgar score**
The infant is evaluated at 1, 5 and 10 minutes post-delivery and is assigned a score out of two for each of the following: heart rate, respiratory effort, muscle tone, reflex irritability, and colour. A score of 10 is the highest possible and indicates an infant in the best condition. The Apgar score is the standard method of assessing a baby at delivery.\(^{13}\) In general, a total score below 7 indicates distress.\(^{12}\)

**Gravidity**
The number of pregnancies a woman has ever had, including her current pregnancy.\(^{12}\)

**Low Apgar score**
Infant receives a score of less than 7 at 5 minutes post-delivery.\(^{13}\)

**Low infant birth weight (LBW)**
Infant is born with a weight of less than 2500 g, irrespective of the gestation period.\(^{14}\)
Intrauterine growth restriction (IUGR)
Fetal size is less than 10\textsuperscript{th} percentile, by ultrasound measurement.

Neonate
An infant from birth to four weeks (birth to 28 days).\textsuperscript{12}

Neonatal intensive care unit (NICU)
Hospital unit designed for special care of the seriously ill, premature, or very low birth weight newborn.\textsuperscript{12}

Oligohydramnios
Abnormality of pregnancy characterized by an insufficient or decreased volume of amniotic fluid surrounding the fetus.\textsuperscript{12,14} Less than 10\textsuperscript{th} percentile of amniotic fluid index.

Polyhydramnios
Abnormality of pregnancy characterized by an excess volume of amniotic fluid surrounding the fetus.\textsuperscript{12,14} More than 90\textsuperscript{th} percentile of amniotic fluid index.

Preterm birth or prematurity
Infant is born prior to 37 weeks gestational age; that is 36 weeks 6 days, or less.\textsuperscript{13,14} A premature infant is usually of low birth weight.\textsuperscript{12}

Special nursery hospitalization
Premature infants often require special care that is provided in the neonatal intensive care unit.\textsuperscript{12}
2.2.2 PREVALENCE OF SELECTED NEONATAL OUTCOMES IN BRITISH COLUMBIA

Table 2.1 provides the rates of selected neonatal outcomes for British Columbia.

<table>
<thead>
<tr>
<th>Neonatal outcome</th>
<th>British Columbia Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prematurity</td>
<td>7.0\textsuperscript{15}, 9.1\textsuperscript{16}</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>5.3\textsuperscript{15}, 5.5\textsuperscript{16}</td>
</tr>
<tr>
<td>Low Apgar score</td>
<td>1.3\textsuperscript{16}</td>
</tr>
<tr>
<td>NICU admission*</td>
<td>11.0\textsuperscript{**16}</td>
</tr>
</tbody>
</table>

*Level II & III NICU admissions
**# of admissions/total # births; not # of newborns admitted/total # births

2.3 ILLICIT DRUG USE AND NEONATAL OUTCOMES

2.3.1 OPIATES: OPIOID AND HEROIN USE

A. PREVALENCE OF USE IN PREGNANCY

With the rise of the drug epidemic in the 1960s prenatal care providers began to see an increase in the number of women that used illicit drugs during their pregnancies. Years before the rise of cocaine use, heroin addiction in pregnancy was identified as a matter of concern. In the subsequent decades, studies have estimated that the use of opioids by expectant women ranges from 0.3% to 3.9%\textsuperscript{3-7}.

B. MECHANISM OF ACTION

Opioids are natural or synthetic derivatives of the poppy plant. Opium is the actual resin from poppies, heroin a semisynthetic derivative, and methadone a completely synthetic opioid\textsuperscript{17}. Although they differ in chemical structure the pharmacological
properties of these opiates are the same.\textsuperscript{17} Most opioids can be ingested; however, opium and heroin are also smoked, and morphine and heroin can be injected.\textsuperscript{18}

Opioids act by binding to endogenous opioid receptors in the central nervous system, autonomic nervous system, smooth muscle and vasculature.\textsuperscript{18,19} The effect is to decrease the release of noradrenalin producing a euphoric effect. Opioids also cause a release of dopamine providing added positive reinforcement.\textsuperscript{18} In addition to euphoria, opiates cause respiratory depression, and peripheral vasodilation.\textsuperscript{17} Heroin, like all opiates including methadone, rapidly crosses the placenta and, therefore, illicit use results in both maternal and fetal addiction.\textsuperscript{18,20} Any subsequent withdrawal of the drug by the mother then causes the fetus to undergo simultaneous withdrawal.\textsuperscript{18,20} Reported maternal effects of withdrawal include uterine irritability, and preterm labour and delivery.\textsuperscript{18,20,21}

C. EFFECTS OF USE DURING PREGNANCY ON NEONATAL OUTCOMES

There are many studies reporting neonatal outcomes from opiate exposure in utero but the usefulness of their results is often limited by the shortcomings of the study. Several early studies related to fetal opiate exposure were conducted without the use of a drug-free control group while other authors failed to include a statistical analysis of their data.\textsuperscript{22-26} A number of later studies did carry out statistical analyses and they have been summarized in Table 2.2.\textsuperscript{27-38}
<table>
<thead>
<tr>
<th>Adverse neonatal outcome studied</th>
<th>Studies finding statistically significant difference</th>
<th>Studies finding no difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prematurity</td>
<td>Lam et al 1992&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Gillogley et al 1990&lt;sup&gt;27&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Little et al 1990&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Keith et al 1989&lt;sup&gt;31&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Oro et al 1987&lt;sup&gt;32&lt;/sup&gt;</td>
<td>Kandall et al 1977&lt;sup&gt;35&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Ostrea et al 1979&lt;sup&gt;33&lt;/sup&gt;</td>
<td>*Kandall et al 1977&lt;sup&gt;35&lt;/sup&gt;</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>Lam et al 1992&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Gillogley et al 1990&lt;sup&gt;27&lt;/sup&gt;</td>
</tr>
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<td>Ostrea et al 1979&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Keith et al 1989&lt;sup&gt;31&lt;/sup&gt;</td>
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<td>Connaughton et al 1977&lt;sup&gt;34&lt;/sup&gt;</td>
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<td>Stimmel et al 1976&lt;sup&gt;36&lt;/sup&gt;</td>
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<td></td>
<td>*Stimmel et al 1976&lt;sup&gt;36&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Naeye et al 1973&lt;sup&gt;37&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Low Apgar score</td>
<td>Ostrea et al 1979&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Fulroth et al 1989&lt;sup&gt;30&lt;/sup&gt;</td>
</tr>
<tr>
<td>Special nursery hospitalization</td>
<td>Lam et al 1992&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Keith et al 1989&lt;sup&gt;31&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

* Methadone exposure

In addition to narcotic withdrawal syndrome, among the most commonly recognized neonatal complications are prematurity, and low birth weight. In terms of prematurity, the results are equivocal. Many studies found significant differences between their groups<sup>28,29,32,33</sup> while equally as many studies did not.<sup>27,31</sup> For low birth weight, the majority of studies did report significant differences between study and comparison groups<sup>28,33,34,36-37</sup> while only a few found no differences.<sup>27,31</sup> It is important to note, however, that of those finding significant differences most did not consider or control for other factors that might have affected the outcome, such as maternal tobacco or alcohol use, or the use of other drugs.<sup>27</sup> In the study by Gillogley et al, when they controlled for prenatal care, smoking and prior preterm delivery, the authors did not find any significant differences for prematurity or low birth weight.<sup>27</sup>
With regard to Apgar scores, two studies found a significant difference between opiate exposed infants and the control group, while Ostrea et al were not in agreement with this finding. Again, the analyses of these studies did not control for other risk factors.

In summary, a number of studies examining opiate exposure during pregnancy have been conducted. However, most of the research regarding adverse neonatal outcomes, such as prematurity and low birth weight, employed only a univariate approach. The authors of these studies often concluded their research by recognizing that the relationship between opiate use and neonatal outcomes was confounded by other socioeconomic and behavioural risk factors, in particular the concurrent use of tobacco and/or other illicit drugs. Unfortunately, when researchers recognized the need for multi-variable analysis a rise in cocaine use and its subsequent use during pregnancy took the forefront. Thus, the need for multi-variable approaches to examine the neonatal effects of in utero opiate exposure still remains.

2.3.2 STIMULANTS: COCAINE AND AMPHETAMINE USE

A. PREVALENCE OF USE IN PREGNANCY

A sharp reduction in the price of cocaine in the 1980s saw a shift in popularity toward this drug. The use of cocaine to produce a state of euphoria continues, and its highly addictive properties mean women often fail to discontinue use even after learning they are pregnant. Various studies in the United States have estimated maternal cocaine use during pregnancy to be between 0.7% and 18%. The prevalence of cocaine use during pregnancy in Canada is not known but a Toronto study, that included three hospitals, found the overall incidence of cocaine exposure to be 6.25%. The prevalence of
amphetamine use during pregnancy has not been as well studied; estimates of 0.2% and 0.66% have been reported.\textsuperscript{3,7}

B. MECHANISM OF ACTION

Cocaine can be snorted, injected or smoked as freebase or crack.\textsuperscript{21,38,41} Its' effect is to block the reuptake of norepinephrine and dopamine resulting in a euphoric state. This inhibition of reuptake results in vasoconstriction, hypertension and tachycardia because of rising norepinephrine levels and activation of the sympathetic nervous system.\textsuperscript{19,41-44} Vasoconstriction in a pregnant woman will lead to a decrease in placental blood flow and a subsequent decline in oxygen transfer to the fetus. Increased uterine tone can result from the elevated sympathetic output.\textsuperscript{21,41} Since cocaine readily crosses the placenta, fetal effects of the drug are often observed in addition to the maternal effects.\textsuperscript{41,42,44} The more commonly reported maternal and fetal effects of prenatal cocaine use include premature labour and delivery, low birth weight, fetal distress, fetal growth retardation, and fetal death.\textsuperscript{19,38,42-44}

Amphetamines, like cocaine, can be taken orally, sniffed, or injected, and have a stimulatory affect on the central nervous system.\textsuperscript{38,45} There are limited studies on the effects of amphetamine use on the neonate, and any poor outcomes observed may be due to other lifestyle factors.\textsuperscript{38,45}

C. EFFECTS OF USE DURING PREGNANCY ON NEONATAL OUTCOMES

With the rise in the use of cocaine as a recreational drug came a rise in the number of studies examining adverse neonatal outcomes from in utero cocaine exposure. The majority of the studies in the 1980s and early 1990s found differences between study and
comparison groups for prematurity \cite{27,30,32,46-56} and low birth weight. \cite{11,27,47,49,51,52,56,57} The results, however, are equivocal with some studies reporting contrary results for these outcomes. \cite{31,46,58,59} A summary of these studies is presented in Table 2.3. The table also shows there are studies that have reported conflicting results for low Apgar score and special nursery hospitalization. As with the studies related to opiate exposure during pregnancy, however, most of these studies failed to control for confounders. The influence of other risk factors already known to be associated with these outcomes, such as smoking with low birth weight, were not considered and an independent association cannot be established.
Table 2.3: Summary of studies examining neonatal outcomes from in utero cocaine exposure

<table>
<thead>
<tr>
<th>Neonatal outcome</th>
<th>Studies finding statistically significant difference</th>
<th>Studies finding no difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prematurity</td>
<td>Datta-Bhutada et al 1998(^{46})</td>
<td>Richardson et al 1999(^{58})</td>
</tr>
<tr>
<td></td>
<td>Rosengren et al 1993(^{47})</td>
<td>Keith et al 1989(^{31})</td>
</tr>
<tr>
<td></td>
<td>Calhoun et al 1991(^{48})</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cohen et al 1991(^{49})</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dombrowski et al 1991(^{50})</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kelley et al 1991(^{51})</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phibbs et al 1991(^{52})</td>
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</tr>
<tr>
<td></td>
<td>Gillogley et al 1990(^{27})</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mastrogiannis et al 1990(^{53})</td>
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<td></td>
<td>Fulroth et al 1989(^{30})</td>
<td></td>
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<td></td>
<td>Little et al 1989(^{54})</td>
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<td>Neerhof et al 1989(^{55})</td>
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<td></td>
<td>Chouteau et al 1988(^{56})</td>
<td></td>
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<td></td>
<td>Oro et al 1987(^{32})</td>
<td></td>
</tr>
<tr>
<td>Low birth weight</td>
<td>Singer et al 1994(^{57})</td>
<td>Richardson et al 1999(^{58})</td>
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<td>Rosengren et al 1993(^{47})</td>
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<td></td>
<td>Cohen et al 1991(^{49})</td>
<td>Chazotte et al 1991(^{59})</td>
</tr>
<tr>
<td></td>
<td>Kelley et al 1991(^{51})</td>
<td>Keith et al 1989(^{31})</td>
</tr>
<tr>
<td></td>
<td>Phibbs et al 1991(^{52})</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gillogley et al 1990(^{27})</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chouteau et al 1988(^{56})</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frank et al 1988(^{40})</td>
<td></td>
</tr>
<tr>
<td>Low Apgar score</td>
<td>Calhoun et al 1991(^{48})</td>
<td>Chazotte et al 1991(^{59})</td>
</tr>
<tr>
<td></td>
<td>Cohen et al 1991(^{49})</td>
<td>Mastrogiannis et al 1990(^{53})</td>
</tr>
<tr>
<td></td>
<td>Keith et al 1989(^{31})</td>
<td>Little et al 1989(^{54})</td>
</tr>
<tr>
<td>Special nursery hospitalization</td>
<td>Calhoun et al 1991(^{48})</td>
<td>Chazotte et al 1991(^{59})</td>
</tr>
<tr>
<td></td>
<td>Phibbs et al 1991(^{52})</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neerhof et al 1989(^{51})</td>
<td></td>
</tr>
</tbody>
</table>

There are a number of studies that have attempted to control for the influence of maternal risk factors, as well as prenatal alcohol and tobacco use, through matched or multi-variable analyses.\(^{10,21,58,62}\) They are improvements on the univariate approach to in utero cocaine exposure employed by the studies mentioned above; these studies are
summarized in Table 2.4. Of the studies presented here, two that used multi-variable analyses found an association between prematurity and cocaine use (OR 13.40, 95% CI 1.23-145.0; RR 3.4, 95% CI 2.9-4.0)\textsuperscript{62,63} while two others, that matched for various confounders, found significant differences between their groups (p<.05 and p<.0005).\textsuperscript{61,64}

Similarly, two studies using multi-variable analyses reported associations with low birth weight (RR 1.59, 95% CI 1.03-2.43; RR 4.4, 95% CI 3.7-5.2)\textsuperscript{60,62}, and two others, that matched for certain risk factors, found significant differences between exposure groups (p<.05 and p<.005).\textsuperscript{61,64} Of note, a meta-analysis, that included results from six studies examining low birth weight, reported a pooled estimate of the random effects relative risk of 1.77 (95% CI 1.15-2.71).\textsuperscript{65} The studies included in this meta-analysis had adjusted for tobacco use and presented results for ‘any’ prenatal cocaine exposure. Two studies examining low Apgar score that reported no significant findings are also presented in Table 2.4.\textsuperscript{60,61} Although the studies in Table 2.4 considered maternal factors as well as tobacco and alcohol use, the difficulty in determining an independent association between the adverse neonatal outcomes and prenatal cocaine use still persists. These studies did not consider the influence of other illicit drugs that could potentially have effects on neonatal outcomes. In fact, the number of studies that have considered illicit drug use in addition to other risk factors are few.
Table 2.4: Summary of studies that adjusted or matched for maternal factors, tobacco use & alcohol use when examining neonatal outcomes from in utero cocaine exposure

<table>
<thead>
<tr>
<th>Neonatal outcome</th>
<th>Studies</th>
<th>Results RR/OR (95% CI) or p-value</th>
<th>Controlled or matched variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prematurity</td>
<td>Shiono et al 1995(^{10})</td>
<td>OR 1.3 (0.9-2.0) p&lt;.05</td>
<td>T, A, M, P, MA, MR, income, BMI, LBW, STIs, age 1st</td>
</tr>
<tr>
<td></td>
<td>Kliegman et al 1994(^{62})</td>
<td>OR 13.40 (1.23-145.0)</td>
<td>T, A, PC, P, MA, MR, Preterm</td>
</tr>
<tr>
<td></td>
<td>Handler et al 1991(^{53})</td>
<td>RR 3.4 (2.9-4.0) p&lt;.0005</td>
<td>T, PC, G, MA, MR, hospital</td>
</tr>
<tr>
<td></td>
<td>*MacGregor et al 1987(^{54})</td>
<td></td>
<td>Matched for T, P, MA, SES</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>Sprauve et al 1997(^{60})</td>
<td>OR 1.59 (1.03-2.43)</td>
<td>T, A, PC, MW, MA, PC, Preterm</td>
</tr>
<tr>
<td></td>
<td>Shiono et al 1995(^{10})</td>
<td>OR 0.7 (0.4-1.3) p&lt;.05</td>
<td>T, A, M, P, MA, MR, income, BMI, LBW, STIs, age 1st</td>
</tr>
<tr>
<td></td>
<td>Kliegman et al 1994(^{62})</td>
<td>OR 9.90 (0.53-184.0)</td>
<td>T, A, PC, P, MA, MR, Preterm</td>
</tr>
<tr>
<td></td>
<td>Handler et al 1991(^{53})</td>
<td>RR 4.4 (3.7-5.2) p&lt;.005</td>
<td>T, PC, G, MA, MR, hospital</td>
</tr>
<tr>
<td></td>
<td>*MacGregor et al 1987(^{54})</td>
<td></td>
<td>Matched for T, P, MA, SES</td>
</tr>
<tr>
<td>Low Apgar score</td>
<td>Sprauve et al 1997(^{60})</td>
<td>OR 1.34 (0.57-2.30) NS</td>
<td>hypertension, abruption, FGR</td>
</tr>
</tbody>
</table>

T=tobacco; A=alcohol; M=marijuana; PC=prenatal care; P=parity; G=gravidity; MA=maturity age; MR=maternal race or ethnicity; SES=socioeconomic status; BMI=body mass index; LBW=prior low birth weight baby; Preterm=prior preterm birth; age 1st=age at 1st intercourse; hospital=location of delivery hospital; FGR=fetal growth restriction

NS=not significant

*no multi-variable analysis
The 1994 study by Richardson et al controlled for other illicit drug use, as well as tobacco and alcohol, and reported that cocaine use was not associated with either prematurity or low birth weight. These results confirmed those from an earlier study by Hadeed et al who found no significant difference between groups for prematurity. However, even though these latter researchers excluded subjects that had used other illicit drugs and/or alcohol, they did not consider tobacco use. A study by Miller et al in 1999 did adjust for both tobacco and alcohol use as well as opiate use. The results of this later study, therefore, were able to support the lack of association found by Richardson et al for prematurity, and low birth weight with maternal cocaine use. Miller et al reported odds ratios and 95% confidence intervals of 0.6 (0.2 - 1.9) for prematurity and 1.2 (0.4, 3.6) for low birth weight.

In contrast, Kistin et al found relative risks (95% CI) for prematurity, and low birth weight of RR 4.0 (2.3-7.0), and RR 5.3 (3.0-9.3) respectively. They dealt with the confounding effects of other illicit and non-illicit substance use by excluding any mother that was a user of heroin, amphetamines, marijuana, tobacco and/or alcohol. This association between maternal cocaine use, and prematurity and low birth weight is supported by the results of another study. Bateman et al found that the risk of both prematurity and low birth weight were almost doubled in the cocaine exposed group with odds ratios and 95% confidence intervals of 1.94 (1.21-3.11) and 2.10 (1.23-3.67) respectively. The results of these studies are summarized in Table 2.5.

Studies by Eyler et al and Cherukuri et al also reported significant results for prematurity and low birth weight from maternal cocaine use. Although both of these
studies excluded concurrent users of other illicit drugs neither considered tobacco use. Similarly, Forsyth et al examined NICU admissions as a result of cocaine use during pregnancy, but failed to account for maternal tobacco use. Therefore, the usefulness of the results from these studies is limited and they are not included in Table 2.5.
Table 2.5: Summary of studies that adjusted for tobacco and alcohol use as well as other illicit drugs when examining neonatal outcomes from in utero cocaine exposure

<table>
<thead>
<tr>
<th>Neonatal outcome</th>
<th>Studies</th>
<th>Results RR/OR (95%CI)</th>
<th>Controlled variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prematurity</td>
<td>Miller et al 1999(^69) Kistin et al 1996(^68) Richardson et al 1994(^66) Bateman et al 1993(^70)</td>
<td>OR = 0.6 (0.2,1.9) RR = 4.0 (2.3,7.0) NA OR = 1.94 (1.21,3.11)</td>
<td>Op, T, A, M, PC, P, MA, MR, LBW, STIs, Abuse G, MA, MR; excluded heroin, Amph, T, A, M T, A, M, other illicit drugs; excluded &lt;18 yrs, no PC</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>Miller et al 1999(^69) Kistin et al 1996(^68) Richardson et al 1994(^66) Bateman et al 1993(^70)</td>
<td>OR = 1.2 (0.4,3.6) RR = 5.3 (3.0,9.3) NA</td>
<td>Op, T, A, M, PC, P, MA, MR, LBW, STIs, Abuse G, MA, MR; excluded heroin, Amph, T, A, M T, A, M, other illicit drugs; excluded &lt;18 yrs, no PC</td>
</tr>
</tbody>
</table>

Op=opiates; Amph=amphetamines; T=tobacco; A=alcohol; M=marijuana; PC=prenatal care; P=parity; G= gravidity; MA=maternal age; MR=maternal race or ethnicity; LBW=prior low birth weight baby; STIs=sexually transmitted infections; Syp=syphilis. Abuse=physical and/or sexual abuse
NA=no association
In summary, there are some studies that have employed a multi-variable approach to maternal cocaine use and the neonatal outcomes prematurity, low birth weight, low Apgar score and special nursery hospitalization. Of those that have attempted to adjust for confounders, however, few have considered the influence of concurrent drug use and the results from these studies remain equivocal. Additional research that controls for other illicit drug use, and tobacco use as well as obstetric and maternal factors is required to support or refute the association between in utero cocaine exposure and neonatal outcomes.

2.3.3 MULTIPLE SUBSTANCE USE

The above review mentioned that abusers of one illicit drug are often multiple substance users, concurrently indulging in more than one other licit or illicit substance. These substances may include cigarettes, alcohol and/or other drugs of abuse. This poly-drug use holds true for pregnant users as well, with several studies finding that pregnant women who use one illicit drug are also using one or more other substances.\(^4,6,11,29,30,55,74\)

For example, a study by Frank et al found that 14% of pregnant cocaine users were also opiate users and that 9% of pregnant cocaine users were found to be using 'other illicit drugs'.\(^11\) In another study, Zuckerman et al found that 22% of those using cocaine during pregnancy also used opiates.\(^6\) Hence, the need to consider concurrent drug use in any analysis that examines the effects of a specific drug on an outcome.
2.4 TOBACCO, ALCOHOL AND MARIJUANA

2.4.1 ILLICIT DRUG USE AND THE USE OF OTHER SUBSTANCES

As discussed above, the concurrent use of other substances by pregnant drug users is not uncommon. In fact, many pregnant users continue to consume alcohol, smoke tobacco and use marijuana. One study found that 9% of cocaine users consumed two or more alcoholic drinks per day whereas only 2% of the non-users consumed the same number of drinks.\textsuperscript{11} Similarly, 31% and 28% of cocaine users smoked more than one pack of cigarettes per day and smoked marijuana three or more times per week, respectively. This was compared to 7% smoking more than one pack of cigarettes per day and 5% smoking marijuana three or more times per week, in the non users group.\textsuperscript{11}

2.4.2 EFFECTS OF USE DURING PREGNANCY ON NEONATAL OUTCOMES

A. TOBACCO

It is estimated that between 12% and 20% of pregnant women smoke and the adverse outcomes related to this behaviour are well documented.\textsuperscript{16,75-77} Among the maternal complications associated with smoking during pregnancy are spontaneous abortion, premature rupture of membranes and preterm delivery.\textsuperscript{12,16,76-78} In addition, there are many complications faced by the neonates who have been exposed to tobacco in utero. These include increased incidence of intrauterine growth restriction, low birth weight, and stillbirth or perinatal death.\textsuperscript{12,16,21,76-78}

B. ALCOHOL

Although alcohol is a well-recognized teratogen, it is still estimated that approximately 15% of pregnant women drink alcohol.\textsuperscript{16,21,79,80} Of those, between 1% and
3% are frequent or binge drinkers consuming more than 7 drinks per week.\textsuperscript{21,79} Alcohol abuse during pregnancy can result in birth defects and mental retardation as well as spontaneous abortion, preterm labour, and growth deficiencies.\textsuperscript{12,21,81-83}

C. MARIJUANA

Data from the Ottawa Prenatal Prospective Study estimated that 20% of women use marijuana during the year prior to their pregnancy with only about half of them discontinuing use after learning they were pregnant.\textsuperscript{84} Other studies confirm the percentage of women using marijuana during pregnancy may be in the range of 10-30%.\textsuperscript{6,85-89} The effects of marijuana use during pregnancy are not as well studied or reported as other illegal substances. There are, however, some studies that have linked intrauterine growth retardation, preterm labour and preterm birth with marijuana use during pregnancy while others have found no association.\textsuperscript{6,79,85-87,89-91}

2.5 HEPATITIS C

2.5.1 A BRIEF REVIEW OF HEPATITIS C

A. RISK FACTORS AND DISEASE TRANSMISSION

Infection with hepatitis C is contracted through contact with infected blood or body fluids.\textsuperscript{92} The virus is communicated from an infected host to a susceptible host via direct contact with body fluids, or indirect contact via biological products including blood, serum, or organs.\textsuperscript{92,93} Modes of direct contact include sexual transmission and vertical transmission. Transmission via sexual contact represents a fairly low-risk route of infection and accounts for only approximately 2.5% of cases.\textsuperscript{94,95} The risk of perinatal
infection is also relatively low. Higher rates of both sexual and vertical transmission have been observed in individuals who are co-infected with HIV.

The highest rates of infection for hepatitis C via indirect contact are associated with individuals that receive contaminated blood, blood products or organs, and individuals exposed to contaminated needles and medical equipment. In countries such as Canada, however, the implementation of modern blood screening techniques have now virtually eliminated the risk of acquiring HCV via blood/blood product transfusion. Sharing needles or drug paraphernalia is now the most common route of infection in Canada and many other developed countries.

Other modes of transmission via contaminated objects include tattoo or piercing equipment, or personal hygiene items that could have traces of contaminated blood, such as razors or dental floss. Indirect contact via breastfeeding has also been implicated as a mode of transmission; however, the evidence regarding this route, as a means of communicating the virus, is unresolved.

B. VIRAL AGENT, DIAGNOSIS AND CLINICAL MANIFESTATIONS

Hepatitis C infection is caused by an enveloped RNA virus in the Flaviviridae family. It was first recognized in 1989, and therefore, identification of the virus is relatively recent. Since widespread screening is not currently recommended in Canada, diagnosis of hepatitis C infection may be suspected from presentation of symptoms, physical examination, or a history of risk taking behaviour. Such suspicions may be confirmed by serologic assays since antibodies to the proteins of HCV permit diagnosis of infection.
Within its human host, the hepatitis C virus may manifest itself in two stages of disease progression: acute and chronic. Acute disease is not usually symptomatic but may be characterized by anorexia, vague abdominal discomfort, nausea, vomiting, and jaundice in 5-25% of newly infected individuals. Only about 20% of individuals, asymptomatic or symptomatic, will spontaneously clear the virus. This means that 75-85% of infected individuals will suffer long-term infection and progress to a chronic disease state. Of those individuals with chronic infection, a large proportion (10-25%) will develop chronic liver disease, which may progress to cirrhosis or sometimes even carcinoma over multiple decades.

C. HCV PREVALENCE IN CANADA

Since many HCV infected individuals experience no symptoms of disease, and widespread screening does not exist, there is a proportion of individuals in the population who are unaware of their infection. Therefore, even though hepatitis C has been deemed a nationally reportable disease in Canada, the prevalence of this illness in our country is not known. It has been estimated, however, that the prevalence in the general Canadian population is 0.81% or approximately 251,000 people. Twenty to twenty-five percent of the reported cases of hepatitis C in Canada occur in BC.

2.5.2 ILLICIT DRUG USERS AND HEPATITIS C

The tie between illicit drug use and hepatitis C infection is evident. In developed countries where blood product screening exists, injection drug use is the primary route of HCV transmission. In Canada, approximately 75% of prevalent infections and the majority of new cases are now attributed to injection drug use. Therefore, it is not
surprising that intravenous drug users, as a group, have the highest prevalence of HCV infection.\textsuperscript{108}

Long-term surveys of adult injection drug users have consistently shown HCV prevalences in the range of 70-90\%.\textsuperscript{109-114} Some studies have even reported that six months after initiating injection drug use, the prevalence rate of infection exceeds 75\%.\textsuperscript{114,115} More specifically, in a cohort of Vancouver injection drug users the prevalence of HCV was found to be 87\% and the annual incidence to be 26\%.\textsuperscript{98,104,116}

The prevalence of HCV among non-intravenous drug users is far less frequently reported. Woodfield et al reported the prevalence of anti-HCV antibodies among those who administer drugs via oral and/or nasal routes to be approximately 5\%; considerably lower than that of intravenous users.\textsuperscript{117,118} This lower rate is consistent with the fact that intranasal cocaine use cannot be unequivocally implicated as an independent risk factor.\textsuperscript{97,114}

2.5.3 \textbf{EFFECTS OF HEPATITIS C INFECTION ON NEONATAL OUTCOMES}

\textbf{A. SEROPREVALENCE}

The seroprevalence of hepatitis C in pregnancy has been reported to be between 1-4\%; however, higher rates have been observed for women in high-risk categories, including intravenous drug users.\textsuperscript{119-124} In British Columbia, the overall HCV rate, determined by an anonymous seroprevalence study, was found to be 1.17\% while the rate among women residing in the Lower Mainland was as high as 1.9\%.\textsuperscript{125}
B. VERTICAL TRANSMISSION

Although the reported rates are varied, it is recognized that vertical transmission of the hepatitis C virus from mother to infant does occur. Transmission rates from zero to 36 percent have been reported; however, the average rate in healthy women is between 5 and 6 percent. The unpublished rate of transmission from the HCV Vertical Transmission Study is 2.7%.

C. NEONATAL OUTCOMES

There are limited studies that have considered obstetrical and/or neonatal complications in HCV-infected women. From the available data, however, there is no indication that HCV infection during pregnancy causes an increased risk of adverse outcome other than vertical transmission of the virus. More specifically, studies have found no differences in mean birth weight, gestational age at delivery, or mean Apgar score.

2.6 SEXUALLY TRANSMITTED INFECTIONS

2.6.1 ILLICIT DRUG USE AND SEXUALLY TRANSMITTED INFECTIONS

It is well recognized that there is a link between illicit drug use and the incidence of sexually transmitted infections (STIs). Individuals who use drugs, whether they are injection or non-injection drugs, are at increased risk of acquiring STIs through high-risk sexual behaviours. The tendency of drug-using individuals to engage in this type of high risk behaviour can be largely explained by the addictive nature of illicit drugs. Most individuals quickly become addicted and also soon lack the economic means to sustain such a habit. Consequently, they resort to the exchange of sex for money or
In addition, some illicit drugs may have more direct influence on behaviour including sexual disinhibition. Regardless of the reasoning, illicit drug use often results in the participation of risky sexual behaviours, including an increased number of sexual partners, and thereby leads to an increased risk of STIs.

### 2.6.2 EFFECTS ON OBSTETRIC AND NEONATAL OUTCOMES

There are many sexually transmitted infections (STIs) that are recognized to have an affect on pregnancy and/or neonatal outcomes. Some of the most common are considered below.

#### A. CHLAMYDIA

The organism responsible for chlamydia infection is *Chlamydia trachomatis*. Any infant exposed to chlamydia during a vaginal delivery is at a 5-15% risk of pneumonitis, as well as a 15-25% risk for conjunctivitis, an eye infection which can lead to blindness. Other conditions possibly associated with prenatal chlamydia infection include spontaneous abortion, premature rupture of membranes, preterm labour and low birth weight.

#### B. GONORRHEA

Pregnant women infected with *Neisseria gonorrhoeae*, are at an increased risk for spontaneous abortions, premature rupture of membranes, preterm labour and delivery.

#### C. GENITAL HERPES

The herpes simplex virus (HSV-2) is the organism responsible for genital herpes. Spontaneous abortion, birth anomalies, or intrauterine growth restriction can occur if
intrauterine HSV infection occurs during pregnancy. The neonates of infected mothers are also at risk of acquiring the infection during a vaginal delivery; therefore, delivery by caesarean section is usually recommended for mothers with symptomatic genital herpes. Without antiviral therapy, infection in the neonate is associated with infant morbidity as well as mortality.

D. GENITAL WARTS

Human papillomavirus (HPV) infection, in the genital area, is characterized by visible single or multiple warty growths. Infants exposed to HPV during delivery are at risk of acquiring laryngeal papillomatosis.

E. SYPHILIS

The syphilis bacterium, *Treponema pallidum*, is the cause of syphilis and untreated infection has well-recognized adverse effects on pregnancy outcome. Congenital syphilis can cause spontaneous abortion, prematurity, stillbirth, growth restriction, neonatal morbidity and mortality.

F. TRICHOMONIASIS

Trichomoniasis is caused by infection with the *Trichomonas vaginalis* protozoan. Maternal trichomoniasis infection is a recognized cause of premature rupture of membranes, preterm delivery and low birth weight.

G. HEPATITIS B VIRUS

The most prevalent adverse pregnancy outcome associated with hepatitis B virus infection is the vertical transmission of HBV to the neonate. There is also some
evidence to indicate that if the acute severe phase of HBV infection occurs during the third trimester of pregnancy, then there is an increased risk of preterm delivery.\textsuperscript{147}

H. HUMAN IMMUNODEFICIENCY VIRUS

Like HBV infection, the primary risk to a neonate of an HIV infected mother is vertical transmission of the virus, and its' associated morbidity and mortality.\textsuperscript{147,166,167} Evidence related to the effect of infection on pregnancy outcome is varied; some results show that mothers with advanced HIV may have higher incidences of prematurity, low birth weight, and still-births.\textsuperscript{161,166-168}

I. SUMMARY

A number of sexually transmitted infections have been implicated as risk factors for various obstetrical and neonatal complications including prematurity, preterm labour/delivery, and low birth weight.

2.7 SUMMARY

In summary, when one considers studying neonatal outcomes the task is always a complicated one. There are many variables, such as obstetrical history, that must be taken into account. Furthermore, when examining a study population such as illicit drug users the task becomes all the more complex. Illicit drug use is linked to other behaviours and health issues that potentially pose an increased risk to the infant. It is necessary, therefore, to consider these additional factors when studying illicit drug users and outcomes in their neonates. This thesis will examine the effects of stimulant as well as opiate drug use on specific neonatal outcomes while controlling for concurrent tobacco and/or other illicit drug use.
CHAPTER 3 - METHODS

3.1 PRIMARY STUDY SETTING – The Hepatitis C Vertical Transmission Study

Of 141,000 HCV infections that have been reported in Canada, British Columbia accounts for 20-25% of these reported infections. Our province, therefore, provides a unique opportunity to study Hepatitis C infection. The seroprevalence in pregnant women in BC is estimated at 1-2%. Hepatitis C is the most common blood-borne infection complicating pregnancy in Canadian women. Yet there remain many unanswered questions regarding this infection in pregnancy, and the factors affecting vertical transmission. The objectives of the Hepatitis C Vertical Transmission Study, therefore, were to determine the vertical transmission rate of hepatitis C in British Columbia and to identify the specific maternal, virologic, and pre, peri, and post partum factors associated with the vertical transmission of this infection.

The Children’s and Women’s Health Centre of British Columbia is the largest obstetrical facility in Canada and provides an ideal setting for a large, prospective cohort study on perinatal hepatitis C infection. The Hepatitis C Vertical Transmission Study was funded by Health Canada and based at the C&W Health Centre of BC. It enrolled HCV positive pregnant women from throughout the province, beginning in September 2000 until September 2003. Due to the high seroprevalence of HCV positivity among intravenous drug-users, this cohort included a large sub-group of drug-users from the downtown Eastside of Vancouver. Thus, identification of HCV positive pregnant women led to the enrollment of a sub-sample of women who admitted using drugs during
their current pregnancy. Therefore, while addressing the needs of the primary study, this cohort also provided the opportunity to study this sub-population and the objectives outlined for this thesis.

3.2 STUDY SAMPLE SELECTION AND STUDY ACTIVITIES

HCV positive women were identified through a linked database system between Canadian Blood Services (CBS) and the Public Health Information System (PHIS) at the British Columbia Centre for Disease Control (BCCDC). The database linkage identified 547 women with reported, confirmed HCV infection who were or became pregnant over the study period. Hepatitis seropositivity was determined by two sequential enzyme immune assays (EIA). The physicians, of acknowledged HCV positive pregnant women, were sent a package containing study information, including a letter of invitation and consent form for the patient. Other recruitment methods included physician referrals and in-person recruitment as well as a website and posters. Those women who consented to participate were enrolled in the Hepatitis C Vertical Transmission Study and contacted by the study coordinator. A detailed questionnaire, administered by the study nurse, collected information on demographics, obstetrical/gynaecological and medical history, behavioural/risk factor history, and sexual history. This baseline questionnaire was administered antenatally and the subjects were followed through delivery and for 18 months post-partum. Post-partum follow-up questionnaires gathered information related to delivery, neonatal and pediatric details. Chart reviews were used to collect data when necessary. A summary of the four questionnaires utilized is provided in Table 3.1 and the full questionnaires are included in the Appendices.
Table 3.1: Summary of baseline and follow-up questionnaire content

<table>
<thead>
<tr>
<th>Section</th>
<th># of Questions</th>
<th>Type of Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Questionnaire</strong></td>
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<td></td>
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<tr>
<td>Demographics</td>
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<td>Age, marital status, ethnicity, education, employment, income</td>
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<td>Obstetrical/Gynaecological</td>
<td>22</td>
<td>Early/late pregnancy complications, STI during pregnancy, previous pregnancy outcome/mode</td>
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<td>Medical History</td>
<td>20</td>
<td>Medical problems, HCV/HIV/Other hepatitis diagnoses, liver disease diagnoses</td>
</tr>
<tr>
<td>Behavioural/Risk Factors</td>
<td>40</td>
<td>Blood/blood product exposure, injection drug use history, occupational/household exposure</td>
</tr>
<tr>
<td>Sexual History</td>
<td>39</td>
<td>Sexual partner history, STD history, sexual relations for drugs/money, high risk sexual practices</td>
</tr>
<tr>
<td><strong>Maternal Data Questionnaire</strong></td>
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<tr>
<td>Baseline Characteristics</td>
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<td>Gravity, parity, LMP, date of HCV diagnosis</td>
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<tr>
<td>Prenatal Tests</td>
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<td>Rh status, amniocentesis, HBV, HIV, Syphilis, Varicella</td>
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<td>Antenatal Infections</td>
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<td>Candida, bacterial vaginosis, CMV, genital herpes</td>
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<tr>
<td>Prescription medications</td>
<td>2</td>
<td>Antiretroviral therapy, other medications</td>
</tr>
<tr>
<td>Substance Use</td>
<td>2</td>
<td>Tobacco/alcohol, other drugs</td>
</tr>
<tr>
<td>Laboratory Results</td>
<td>17</td>
<td>HIV RNA, CD4 count, HCV RNA, HCV PCR, ALT</td>
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<tr>
<td>Antenatal Complications</td>
<td>12</td>
<td>Hypertension, weight gain, antepartum hemorrhage</td>
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<td><strong>Delivery Data Questionnaire</strong></td>
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<td></td>
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<tr>
<td>Pregnancy Outcome</td>
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<td>Delivery date, outcome, gestational duration</td>
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<tr>
<td>Delivery Information</td>
<td>12</td>
<td>Labour details, mode of delivery, delivery complications</td>
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<tr>
<td>Postpartum Follow-up</td>
<td>3</td>
<td>Length of hospital stay, complications</td>
</tr>
<tr>
<td>Neonatal Information</td>
<td>13</td>
<td>Birth weight, cord blood gases, Apgar scores, defects</td>
</tr>
<tr>
<td>Medical Problems</td>
<td>3</td>
<td>Prematurity, jaundice, sepsis, viral infection</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>1</td>
<td>Breastfeeding infant, maternal medications</td>
</tr>
<tr>
<td><strong>Pediatric Data Questionnaire</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infant Health</td>
<td>4</td>
<td>Skin problems, ENT problems, GI problems</td>
</tr>
<tr>
<td>Virology</td>
<td>4</td>
<td>HIV culture, HIV PCR, HCV PCR, HCV Ab</td>
</tr>
<tr>
<td>Laboratory Results</td>
<td>6</td>
<td>AST, ALT, PTT, PT, Bilirubin, Albumin</td>
</tr>
</tbody>
</table>
3.3 DATA MANAGEMENT

Data collected for the Hepatitis C Vertical Transmission Study was verified, coded, entered, and stored in a relational database created using Microsoft Access software. All personal identifying information of each mother and infant was removed from this database.

This thesis analysis utilized the data collected for the primary study. For the purposes of data preparation and cleaning, the dataset was imported into Microsoft Excel. Subjects with non-singleton pregnancies were excluded from the analysis. As well, some mothers had more than one pregnancy during the study period and enrolled twice. In order to maintain an independent sample, data for only the second pregnancy was included in this thesis study.

Variables were chosen based on the literature review for this project. Many variables were used directly from the database while it was necessary to modify or combine others to produce a needed variable. Newly created variables and those requiring further definition are included in Section 3.4.

3.3.1 STATISTICAL SOFTWARE

All data analysis for this thesis was carried out using S-Plus 6.1 Statistical Software.

3.4 VARIABLES AND VARIABLE DEFINITIONS

3.4.1 MAIN OUTCOME VARIABLE

The main outcome variable and its response categories are presented in Table 3.2.
ADVERSE NEONATAL OUTCOME: positive response for this summary measure was determined by a positive response for any of the following outcomes:

- **Premature delivery**: infant is born prior to 37 weeks gestational age
- **Low birth weight**: infant is born with a weight of less than 2500 g
- **Low Apgar score**: infant receives a score of less than 7 at 5 minutes post-delivery
- **NICU admission**: infant is admitted to neonatal intensive care unit post-delivery

### 3.4.2 MAIN EXPLANATORY VARIABLES

Table 3.3 presents the main explanatory variables with their corresponding response categories.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Response Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DRUG USE VARIABLES</strong></td>
<td></td>
</tr>
<tr>
<td>Current stimulant use</td>
<td>Yes</td>
</tr>
<tr>
<td>Current opiate use</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Table 3.2: Description of main outcome variable

<table>
<thead>
<tr>
<th>Variable</th>
<th>Response Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse neonatal outcome</strong> summary measure based on the following outcomes:</td>
<td>YES</td>
</tr>
<tr>
<td>Premature delivery</td>
<td>Yes</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>Yes</td>
</tr>
<tr>
<td>Low Apgar score</td>
<td>Yes</td>
</tr>
<tr>
<td>NICU admission</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Definitions for the main explanatory variables are presented here.

CURRENT STIMULANT USE: mother reported use of any of the following after the date of her last menstrual period (LMP):

- Crack cocaine
- Nasal cocaine
- Ecstasy (MDMA)
- Crystal meth
- Amphetamines (Speed)

CURRENT OPIATE USE: mother reported use of any of the following after the date of her LMP:

- Heroin
- Morphine
- Opium
- Talwin/Ritalin

3.4.3 COVARIATES

Table 3.4 presents other explanatory and descriptive variables and their corresponding response categories.
Table 3.4: List of additional explanatory and descriptive variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>Response Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OTHER SUBSTANCE USE</strong></td>
<td></td>
</tr>
<tr>
<td>Current methadone use</td>
<td>Yes</td>
</tr>
<tr>
<td>Current marijuana use</td>
<td>Yes</td>
</tr>
<tr>
<td>Current other illicit drug use</td>
<td>Yes</td>
</tr>
<tr>
<td>Current tobacco use</td>
<td>Yes</td>
</tr>
<tr>
<td>Average # cigarettes/day</td>
<td>Continuous</td>
</tr>
<tr>
<td>Alcohol use over past year</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>SOCIODEMOGRAPHIC CHARACTERISTICS</strong></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Continuous</td>
</tr>
<tr>
<td>Aboriginal ethnicity</td>
<td>Yes</td>
</tr>
<tr>
<td>Less than high school education</td>
<td>Yes</td>
</tr>
<tr>
<td>Yearly gross household income &lt; $30,000</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>REPRODUCTIVE/OBSTETRIC HISTORY</strong></td>
<td></td>
</tr>
<tr>
<td>Gravidity</td>
<td>1</td>
</tr>
<tr>
<td>Prior preterm birth (&lt; 37 weeks)</td>
<td>Yes</td>
</tr>
<tr>
<td>Pregnancy complication in current pregnancy</td>
<td>Yes</td>
</tr>
<tr>
<td>Sexually transmitted infection during current pregnancy</td>
<td>Yes</td>
</tr>
<tr>
<td>Type of delivery</td>
<td>Vaginal</td>
</tr>
<tr>
<td><strong>MEDICAL HISTORY</strong></td>
<td></td>
</tr>
<tr>
<td>HBV diagnosed</td>
<td>Yes</td>
</tr>
<tr>
<td>HIV diagnosed</td>
<td>Yes</td>
</tr>
<tr>
<td>HCV PCR positive</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>SEXUAL BEHAVIOUR</strong></td>
<td></td>
</tr>
<tr>
<td>Age at first intercourse</td>
<td>Continuous</td>
</tr>
<tr>
<td># partners in past year</td>
<td>Continuous</td>
</tr>
<tr>
<td># partners in lifetime</td>
<td>Continuous</td>
</tr>
<tr>
<td>Engaged in high risk sexual behaviour</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Explanatory variables needing further definition and definitions for newly created explanatory variables are presented here.
CURRENT OTHER ILLICIT DRUG USE: mother reported use of any of the following after the date of her LMP:

- Acid/LSD
- PCP
- Mushrooms
- Mescaline

CURRENT METHADONE USE: mother reported use of methadone after the date of her LMP.

PREGNANCY COMPLICATION IN CURRENT PREGNANCY: includes occurrence of any of the following during the pregnancy:

- Oligohydramnios
- Polyhydramnios
- Intrauterine growth restriction
- Abruptio placentae
- Hypertension

SEXUALLY TRANSMITTED INFECTION DURING CURRENT PREGNANCY: includes any of the following:

- Syphilis
- Chlamydia
- Other STI
- Gonorrhea
- Genital warts
- Genital herpes
- Trichomonas

ENGAGED IN HIGH RISK SEXUAL BEHAVIOUR: one or more of the following were reported:

- Sexual contact with gay/bisexual men
- Sex with someone with genital herpes or who had genital sores
- Sex with a male or female prostitute
- Ever been paid or received money for having sex
- Ever given or received sex for drugs
3.5 OVERVIEW OF METHODOLOGICAL APPROACHES

3.5.1 DESCRIPTIVE ANALYSES

Frequencies and percentages are used to describe the cohort as a whole as well as for the two groups: mothers with infants who suffered an adverse outcome versus mothers whose infants had no adverse outcome. Summary statistics and appropriate graphical representations were produced for descriptive and exploratory purposes.

3.5.2 UNIVARIATE ANALYSES

Explanatory variables were compared for those with infants who suffered an adverse outcome versus those with infants who had no adverse outcome. As appropriate, t-tests or Wilcoxon Rank Sum were used to compare continuous variables. Chi-square or Fisher’s exact test were used for categorical variables. Crude odds ratios and 95% confidence intervals were computed for all categorical variables.

3.5.3 MULTI-VARIABLE ANALYSES

Multi-variable logistic regression was used to investigate the association between current stimulant and/or current opiate drug use during pregnancy and the likelihood of an adverse neonatal outcome. Other explanatory variables found significant in the univariate analyses as well as potential confounders and interaction terms were also considered in the regression analysis. Significance of individual regression estimates was tested by Wald statistics. A critical value of 3.84 at α=0.05 was used. Where appropriate, the likelihood ratio test was used was used for the comparison of regression models, and the change in the log odds ratio was compared when considering the influence of potential confounders. Beta coefficients, standard error, and Wald statistics
as well as odds ratios with their 95% confidence intervals were reported for the regression models. The odds ratio is the measure of the association between the independent variables and the dependent variable.

The assumptions made for the model to be valid were that all observations are independent, observations are measured without error, inclusion of all higher order terms, and variance is predicted by the model.\textsuperscript{169}

3.6 ETHICAL CONSIDERATIONS

Ethical approval was received from the University of British Columbia Clinical Ethical Review Board, and Children’s and Women’s Health Centre of BC for the primary study. An amendment, submitted for the secondary analysis comprising this thesis, was also approved by both review boards.

3.7 SUMMARY

The Hepatitis C Vertical Transmission Study database offers an appropriate data source for the analyses described in this thesis. It is an excellent data source providing detailed histories for a challenging cohort of pregnant drug users and non-users. As well, it is a source of prospectively collected data related to the pregnancies, deliveries and post-partum health of infants born to these women.
CHAPTER 4 – RESULTS

4.1 DESCRIPTIVE AND UNIVARIATE ANALYSES

The Hepatitis C Vertical Transmission Study enrolled 154 patients. Five subjects were not included in the primary dataset because of early withdrawal from the study or refusal to sign the consent form. This thesis study then excluded two patients with non-singleton pregnancies as well as the data for six subjects that corresponded to patients with double enrollment. Neonatal outcome data was not available for 5 additional entries. Data from 136 women and their infants were analyzed.

4.1.1 NEONATAL OUTCOMES

Fifty-three (39.0%) of the infants born to women in the study cohort had an adverse outcome, as defined for this study. Eighty-three (61.0%) of the infants had no adverse outcome. The results for the neonatal outcome data are presented in Table 4.1. There were three stillborn births (2.2%) and one intrauterine death (0.7%). Among the women in the cohort, 17.6%, 13.2%, 5.9%, and 26.5% had infants born prematurely, infants born with low birth weight, infants receiving a low Apgar score at 5 minutes, and infants admitted to the neonatal intensive care unit, respectively. Of those infants admitted to NICU, the median length of stay was 5.5 days (range 1.0 – 69.0). Fourteen infants (10.3% of the cohort) were born small-for-gestational-age (SGA). The adverse neonatal outcome group had nine SGA babies while the group with no adverse outcomes had five SGA babies. In addition, twenty-one infants that had an adverse outcome suffered from substance withdrawal syndrome; that is 15.4% of the cohort. Interestingly, thirteen (9.6%) of those infants without an adverse outcome also experienced some level of substance withdrawal syndrome.
Table 4.1: Neonatal outcome details for the cohort (n=136)

<table>
<thead>
<tr>
<th>Outcome Variable</th>
<th>Adverse Outcome n (% of cohort)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Outcome</td>
<td>53 (39.0)</td>
</tr>
<tr>
<td>Stillborn</td>
<td>3 (2.2)</td>
</tr>
<tr>
<td>Intrauterine death</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Prematurity</td>
<td>24 (17.6)</td>
</tr>
<tr>
<td>Low Birth Weight</td>
<td>18 (13.2)</td>
</tr>
<tr>
<td>Small for Gestational Age</td>
<td>14 (10.3)</td>
</tr>
<tr>
<td>Low Apgar Score</td>
<td>8 (5.9)</td>
</tr>
<tr>
<td>Neonatal Intensive Care Unit Admission</td>
<td>36 (26.5)</td>
</tr>
<tr>
<td>Of those admitted to NICU, median (days) length of stay in NICU</td>
<td>5.5</td>
</tr>
<tr>
<td>Range (days)</td>
<td>(1.0 - 69.0)</td>
</tr>
<tr>
<td>Substance withdrawal syndrome</td>
<td>21 (15.4)</td>
</tr>
</tbody>
</table>

4.1.2 SOCIODEMOGRAPHIC CHARACTERISTICS

The mean age of this cohort of women was 30.2 ± 5.54 years. The mean age for the adverse outcome group was 30.2 ± 5.44 years while the mean age for the group with no adverse neonatal outcome was 30.1 ± 5.63 years. There was no significant difference in age between the two groups. Comparisons between the groups for other sociodemographic characteristics revealed no significant differences in aboriginal ethnicity, education level or yearly household income less than $30,000/year. The frequencies and percentages for the sociodemographic characteristics of the cohort, as well as the two groups of interested are presented in Table 4.2. Crude odds ratios and 95% confidence intervals are also found in this table.
Table 4.2: Univariate results for sociodemographic data for those women with an infant with an adverse outcome versus those whose infants had no adverse outcome

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cohort n (%)</th>
<th>Adverse Outcome n (%)</th>
<th>No Adverse Outcome n (%)</th>
<th>Crude Odds Ratio</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (years)</td>
<td>30.2</td>
<td>30.2</td>
<td>30.1</td>
<td></td>
<td></td>
<td></td>
<td>0.932</td>
</tr>
<tr>
<td>Std deviation</td>
<td>5.5</td>
<td>5.4</td>
<td>5.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aboriginal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>33(25.4)</td>
<td>15(30.0)</td>
<td>18(22.5)</td>
<td>1.5</td>
<td>0.66</td>
<td>3.29</td>
<td>0.339</td>
</tr>
<tr>
<td>No</td>
<td>97(74.6)</td>
<td>35(70.0)</td>
<td>62(77.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; High school education</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>47(41.2)</td>
<td>20(47.0)</td>
<td>27(38.0)</td>
<td>1.4</td>
<td>0.66</td>
<td>3.05</td>
<td>0.372</td>
</tr>
<tr>
<td>No</td>
<td>67(58.8)</td>
<td>23(53.5)</td>
<td>44(62.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;$30,000 yearly income</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>83(74.8)</td>
<td>33(85.0)</td>
<td>50(69.0)</td>
<td>2.4</td>
<td>0.89</td>
<td>6.60</td>
<td>0.079</td>
</tr>
<tr>
<td>No</td>
<td>28(25.2)</td>
<td>6(15.4)</td>
<td>22(30.6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Percentages based on valid data. Range of missing values (0.0 - 18.4%)

4.1.3 SUBSTANCE USE

Illicit and non-illicit substance use among this group of women was common. In fact, 49.6%, 35.9%, and 19.5% admitted use, during their pregnancy, of stimulants, opiates, and other illicit drugs, respectively. While a large proportion of women continued to smoke during their pregnancy (68.4%), prenatal use of marijuana (22.6%) and alcohol (23.9%) were not as heavy. Table 4.3 summarizes substance use among the cohort as well as for the two groups of interest: those women whose infants experienced an adverse outcome versus those whose infants did not.

Significant differences were found between those women whose infants had an adverse outcome and those whose infants did not for stimulant use (p<0.01), opiate use
(p<0.001) as well as methadone use (p<0.001). Almost two-thirds (64.0%) of the mothers of infants with an adverse outcome admitted to the use of stimulants during their pregnancy while only 40.0% of the mothers of the infants without an adverse outcome reported such use. With respect to opiate use, 57.1% of the adverse neonatal outcome mothers admitted use compared to 22.8% of the no adverse neonatal outcome mothers. A significant difference (p<0.01) was also found between the two groups for tobacco use, 83.0% versus 59.0%. However, there was no significant difference for the average number of cigarettes smoked per day by the women in each group. No significant differences were found between the groups for other illicit drug use, marijuana use, or alcohol use. Crude odds ratios and 95% confidence levels for this data are presented in Table 4.3.
Table 4.3: Univariate results for substance use data for those women with an infant with an adverse outcome versus those whose infants had no adverse outcome

<table>
<thead>
<tr>
<th>Substance Used</th>
<th>Cohort n (%)</th>
<th>Adverse Outcome n (%)</th>
<th>No Adverse Outcome n (%)</th>
<th>Crude Odds Ratio</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Current stimulant use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>62 (49.6)</td>
<td>32 (64.0)</td>
<td>30 (40.0)</td>
<td>2.7</td>
<td>1.27</td>
<td>5.59</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>No</td>
<td>63 (50.4)</td>
<td>18 (36.0)</td>
<td>45 (60.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Current opiate use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>'46 (35.9)</td>
<td>28 (57.1)</td>
<td>18 (22.8)</td>
<td>4.5</td>
<td>2.09</td>
<td>9.78</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>82 (64.1)</td>
<td>21 (42.9)</td>
<td>61 (77.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Current methadone use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>45 (33.3)</td>
<td>28 (53.9)</td>
<td>17 (20.5)</td>
<td>4.5</td>
<td>2.11</td>
<td>9.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>90 (66.7)</td>
<td>24 (46.2)</td>
<td>66 (79.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Current other illicit drug use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>25 (19.5)</td>
<td>12 (23.5)</td>
<td>13 (16.9)</td>
<td>1.5</td>
<td>0.63</td>
<td>3.65</td>
<td>0.353</td>
</tr>
<tr>
<td>No</td>
<td>103 (80.5)</td>
<td>39 (76.5)</td>
<td>64 (83.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Current marijuana use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>28 (23.1)</td>
<td>12 (25.5)</td>
<td>16 (21.6)</td>
<td>1.2</td>
<td>0.53</td>
<td>2.93</td>
<td>0.619</td>
</tr>
<tr>
<td>No</td>
<td>93 (76.9)</td>
<td>35 (74.5)</td>
<td>58 (78.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Use of alcohol over past year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>32 (23.9)</td>
<td>12 (23.5)</td>
<td>20 (24.1)</td>
<td>1.0</td>
<td>0.43</td>
<td>2.20</td>
<td>0.940</td>
</tr>
<tr>
<td>No</td>
<td>102 (76.1)</td>
<td>39 (76.5)</td>
<td>63 (75.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Current tobacco use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>93 (68.4)</td>
<td>44 (83.0)</td>
<td>49 (59.0)</td>
<td>3.4</td>
<td>1.46</td>
<td>7.86</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>No</td>
<td>43 (31.6)</td>
<td>9 (17.0)</td>
<td>34 (41.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avg # cigarettes/day among those currently using tobacco</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (# cigarettes)</td>
<td>10</td>
<td>15</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td>0.122</td>
</tr>
<tr>
<td>Range (# cigarettes)</td>
<td>1.0 - 40.0</td>
<td>1.0 - 30.0</td>
<td>1.0 - 40.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Percentages based on valid data. Range of missing values (0.0-11.0%)
Table 4.4 provides further detail regarding the substance use patterns of the women in this cohort. It highlights the exclusive and concurrent use of stimulants and opiates. The groups that used both stimulants and opiates, or neither stimulants nor opiates represent the two largest groups in the cohort. In fact, very few individuals, only four, restricted their drug use to opiates during their pregnancy.

<table>
<thead>
<tr>
<th>Substance used</th>
<th>Cohort n(%)</th>
<th>Adverse Outcome n(%)</th>
<th>No Adverse Outcome n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulants only (No opiates)</td>
<td>20 (16.4)</td>
<td>5 (4.1)</td>
<td>15 (12.3)</td>
</tr>
<tr>
<td>Opiates only (No stimulants)</td>
<td>4 (3.3)</td>
<td>3 (2.5)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Both stimulants &amp; opiates</td>
<td>39 (32.0)</td>
<td>24 (19.7)</td>
<td>15 (12.3)</td>
</tr>
<tr>
<td>Neither stimulants nor opiates</td>
<td>59 (48.4)</td>
<td>15 (12.3)</td>
<td>44 (36.1)</td>
</tr>
</tbody>
</table>

Percentages are for valid data. Missing values 10.3%.

Similarly, there are few individuals who used opiates without the use of methadone, and even fewer who were exclusively maintained on methadone. A larger percentage of the cohort reported the use of both opiates and methadone during their pregnancy. The data for the exclusive and concurrent patterns of opiate and methadone use in this population are presented in Table 4.5.

<table>
<thead>
<tr>
<th>Substance used</th>
<th>Cohort n(%)</th>
<th>Adverse Outcome n(%)</th>
<th>No Adverse Outcome n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opiates only (No methadone)</td>
<td>12 (9.4)</td>
<td>5 (3.9)</td>
<td>7 (5.5)</td>
</tr>
<tr>
<td>Methadone only (No opiates)</td>
<td>9 (7.1)</td>
<td>4 (3.2)</td>
<td>5 (8.2)</td>
</tr>
<tr>
<td>Both opiates &amp; methadone</td>
<td>33 (26.0)</td>
<td>22 (17.3)</td>
<td>11 (8.7)</td>
</tr>
<tr>
<td>Neither opiates nor methadone</td>
<td>73 (57.5)</td>
<td>17 (13.4)</td>
<td>56 (44.1)</td>
</tr>
</tbody>
</table>

Percentages are for valid data. Missing values 6.6%.
4.1.4 OBSTETRICAL HISTORY

The obstetrical history for the two groups of women was considered in the univariate analysis. There were no statistically significant differences in the gravidity of women in the groups. Similarly, there was no difference in the number of prior preterm births the women in the adverse neonatal outcome group had experienced compared to the women in the no adverse neonatal outcome group. With regard to the current pregnancy of the women, there were no statistically significant differences between the comparison groups for incidence of a pregnancy complication. Comparisons between the two groups for other obstetrical variables, including incidence of a sexually transmitted infection during the current pregnancy and type of delivery also found no statistically significant differences. These results as well as crude odds ratios and 95% confidence intervals are presented in Table 4.6.
Table 4.6: Univariate results for obstetrical history data for those women with an infant with an adverse outcome versus those whose infants had no adverse outcome

<table>
<thead>
<tr>
<th>Obstetric History</th>
<th>Cohort n (%)</th>
<th>Adverse Outcome n (%)</th>
<th>No Adverse Outcome n (%)</th>
<th>Crude Odds Ratio</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gravida</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 2</td>
<td>117 (87.3)</td>
<td>47 (90.4)</td>
<td>70 (85.4)</td>
<td>1.6</td>
<td>0.53</td>
<td>4.87</td>
<td>0.395</td>
</tr>
<tr>
<td>1</td>
<td>17 (12.7)</td>
<td>5 (9.6)</td>
<td>12 (14.6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior preterm birth (&lt; 37 wks)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>12 (9.8)</td>
<td>7 (15.2)</td>
<td>5 (6.6)</td>
<td>2.5</td>
<td>0.76</td>
<td>8.57</td>
<td>0.208</td>
</tr>
<tr>
<td>No</td>
<td>110 (90.2)</td>
<td>39 (84.8)</td>
<td>71 (93.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy complication in current pregnancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>26 (19.4)</td>
<td>14 (27.5)</td>
<td>12 (14.5)</td>
<td>2.2</td>
<td>0.94</td>
<td>5.33</td>
<td>0.065</td>
</tr>
<tr>
<td>No</td>
<td>108 (80.6)</td>
<td>37 (72.6)</td>
<td>71 (85.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STI during current pregnancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>33 (25.6)</td>
<td>16 (32.0)</td>
<td>17 (21.5)</td>
<td>1.7</td>
<td>0.77</td>
<td>3.82</td>
<td>0.184</td>
</tr>
<tr>
<td>No</td>
<td>96 (74.4)</td>
<td>34 (68.0)</td>
<td>62 (78.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of Delivery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal</td>
<td>91 (67.4)</td>
<td>38 (73.1)</td>
<td>53 (63.9)</td>
<td>1.5</td>
<td>0.72</td>
<td>3.28</td>
<td>0.266</td>
</tr>
<tr>
<td>C-section</td>
<td>44 (32.6)</td>
<td>14 (26.9)</td>
<td>30 (36.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Percentages based on valid data. Range of missing values (0.7 - 10.3%)

4.1.5 MEDICAL HISTORY

The data analyzed included medical history variables that could potentially have some influence on the outcome of infants born to women in the cohort. This data included the number and percentage of women that had been diagnosed with HIV, whether the women were HCV PCR positive, and if they had been diagnosed with HBV. No statistically significant differences were found for any of these variables. The univariate results for the medical history data are presented in Table 4.7.
Table 4.7: Univariate results for medical history data for those women with an infant with an adverse outcome versus those whose infants had no adverse outcome

<table>
<thead>
<tr>
<th>Medical History</th>
<th>Cohort n (%)</th>
<th>Adverse Outcome n (%)</th>
<th>No Adverse Outcome n (%)</th>
<th>Crude Odds Ratio</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV diagnosed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>19 (14.0)</td>
<td>10 (18.9)</td>
<td>9 (10.8)</td>
<td>1.9</td>
<td>0.72</td>
<td>5.07</td>
<td>0.188</td>
</tr>
<tr>
<td>No</td>
<td>117 (86.0)</td>
<td>43 (81.1)</td>
<td>74 (89.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV PCR positive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>102 (76.1)</td>
<td>39 (75.0)</td>
<td>63 (76.8)</td>
<td>0.9</td>
<td>0.40</td>
<td>2.04</td>
<td>0.809</td>
</tr>
<tr>
<td>No</td>
<td>32 (23.9)</td>
<td>13 (25.0)</td>
<td>19 (23.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV diagnosed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>19 (14.3)</td>
<td>9 (17.3)</td>
<td>10 (12.4)</td>
<td>1.5</td>
<td>0.56</td>
<td>3.95</td>
<td>0.425</td>
</tr>
<tr>
<td>No</td>
<td>114 (85.7)</td>
<td>43 (82.7)</td>
<td>71 (87.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Percentages based on valid data. Range of missing values (1.5 - 4.4%)

4.1.6 SEXUAL BEHAVIOUR

The sexual behaviour of the women was compared for those with an infant with an adverse outcome versus those whose infants had no adverse outcomes. The median age at first sexual intercourse was the same for both groups of women, 15.0 years. There were no significant differences found, between the two groups of interest, for the number of sexual partners in the past year or in a subject’s lifetime. The data and comparisons presented for these two “number of sexual partner” variables was computed after removal of an extreme outlier from the dataset; one individual answered 500 to 2000 partners in an 18 month period. Similarly, there was no significant difference between the adverse outcome group and the no adverse outcome group for the number of individuals that reported engaging in high risk sexual behaviour. The data for these sexual history
variables are summarized in Table 4.8. The crude odds ratio for the variable engaged in high risk sexual behaviour was 2.0 (95% CI: 0.89, 4.73).

Table 4.8: Univariate results for sexual behaviour data for those women with an infant with an adverse outcome versus those whose infants had no adverse outcome

<table>
<thead>
<tr>
<th>Sexual History</th>
<th>Cohort n (%)</th>
<th>Adverse Outcome n (%)</th>
<th>No Adverse Outcome n (%)</th>
<th>Crude Odds Ratio</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at first sexual intercourse</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (years)</td>
<td>15.0</td>
<td>15.0</td>
<td>15.0</td>
<td></td>
<td></td>
<td></td>
<td>0.111</td>
</tr>
<tr>
<td>Range (years)</td>
<td>4.0 - 25.0</td>
<td>4.0 - 19.0</td>
<td>7.0 - 25.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># partners in past year</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
<td></td>
<td></td>
<td></td>
<td>0.057*</td>
</tr>
<tr>
<td>Range</td>
<td>1.0 - 6.0</td>
<td>2.0 - 6.0</td>
<td>1.0 - 6.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># partners in lifetime</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>15.0</td>
<td>20.0</td>
<td>10.5</td>
<td></td>
<td></td>
<td></td>
<td>0.170*</td>
</tr>
<tr>
<td>Range</td>
<td>2.0 - 100.0</td>
<td>3.0 - 100.0</td>
<td>2.0 - 100.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Engaged in high risk sexual Behaviour</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>70 (63.1)</td>
<td>30 (73.2)</td>
<td>40 (57.1)</td>
<td>2.0</td>
<td>0.89</td>
<td>4.73</td>
<td>0.091</td>
</tr>
<tr>
<td>No</td>
<td>41 (36.9)</td>
<td>11 (26.8)</td>
<td>30 (42.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Percentages based on valid data. Range of missing values (0.0 - 18.4%)
*p-value with extreme outlier removed

4.1.7 SUMMARY

The univariate analyses identified four variables with significant results. The variables current stimulant use, current opiate use, current methadone use, and current tobacco use all yielded significant p-values from chi-square analyses.
4.2 MULTI-VARIABLE ANALYSES

All the variables that were significant in the univariate analyses were initially considered for the multi-variable analysis. In addition, other variables of interest considered for the multi-variable analysis included: age, aboriginal ethnicity, gravidity, and incidence of a pregnancy complication. The inclusion of these variables was dictated by those considered in other studies, as presented in the literature review of this thesis, or by their clinical significance. Aboriginal ethnicity was of particular interest since this study and its' data reflected a study population with a different ethnic distribution than that of past studies. The pregnancy complication variable was considered because of its' potential influence on an adverse outcome as well as the fact that its' p-value (p=0.065) approached significance. The variables to be considered for the multi-variable analysis are listed in Table 4.9.

<table>
<thead>
<tr>
<th>Significant Variables</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current stimulant use</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Current opiate use</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current methadone use</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current tobacco use</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other Variables of Interest</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy complication</td>
<td>0.065</td>
</tr>
<tr>
<td>Gravidity</td>
<td>0.395</td>
</tr>
<tr>
<td>Age</td>
<td>0.932</td>
</tr>
<tr>
<td>Aboriginal ethnicity</td>
<td>0.339</td>
</tr>
</tbody>
</table>
4.2.1 MULTI-VARIABLE LOGISTIC REGRESSION

Multi-variable logistic regression was carried out to identify risk factors associated with an adverse neonatal outcome.

The logistic regression model (Model 1) included all the variables from Table 4.9 as predictor variables, and the summary measure adverse neonatal outcome as the dependent variable. Univariate Wald test statistics were considered to determine the significant variables in the model. A critical value of 3.84 at α=0.05 was used. The coefficient estimates, Wald statistics, and odds ratios with 95% confidence intervals, for Model 1, are presented in Table 4.10.

<table>
<thead>
<tr>
<th>Variable</th>
<th>beta Coefficient</th>
<th>Standard Error</th>
<th>Wald Test Statistic</th>
<th>Adjusted Odds Ratio</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>-3.573</td>
<td>1.546</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current stimulant use</td>
<td>-0.080</td>
<td>0.596</td>
<td>0.02</td>
<td>0.92</td>
<td>0.29</td>
<td>2.97</td>
</tr>
<tr>
<td>Current opiate use</td>
<td>1.105</td>
<td>0.663</td>
<td>2.78</td>
<td>3.02</td>
<td>0.82</td>
<td>11.07</td>
</tr>
<tr>
<td>Current methadone use</td>
<td>0.835</td>
<td>0.559</td>
<td>2.24</td>
<td>2.31</td>
<td>0.77</td>
<td>6.89</td>
</tr>
<tr>
<td>Current tobacco use</td>
<td>0.456</td>
<td>0.587</td>
<td>0.60</td>
<td>1.58</td>
<td>0.50</td>
<td>4.99</td>
</tr>
<tr>
<td>Pregnancy complication</td>
<td>0.681</td>
<td>0.543</td>
<td>1.57</td>
<td>1.98</td>
<td>0.68</td>
<td>5.73</td>
</tr>
<tr>
<td>Age</td>
<td>0.027</td>
<td>0.045</td>
<td>0.35</td>
<td>1.03</td>
<td>0.94</td>
<td>1.12</td>
</tr>
<tr>
<td>Aboriginal ethnicity</td>
<td>0.166</td>
<td>0.497</td>
<td>0.11</td>
<td>1.18</td>
<td>0.45</td>
<td>3.13</td>
</tr>
<tr>
<td>Gravidity</td>
<td>1.140</td>
<td>0.843</td>
<td>1.83</td>
<td>3.13</td>
<td>0.60</td>
<td>16.31</td>
</tr>
</tbody>
</table>

4.2.2 COLLINEAR VARIABLES

A. PREGNANCY COMPLICATION

Of interest in Model 1 is the variable pregnancy complication and its’ potential relationship to substance use. It was suspected that this variable may represent an...
intermediary variable between substance use and adverse neonatal outcome, and thus, its' inclusion as an explanatory variable may be inappropriate. To investigate this further a sub-analysis was carried out. The potential relationship between pregnancy complication and substance use was confirmed by the results of an additional univariate analysis. Opiate use was associated (p<0.05) with pregnancy complication in a chi-square analysis. The results of a logistic regression model using pregnancy complication as the dependent or outcome variable support this finding and are presented in Table 4.11 below.

Table 4.11: Logistic regression results for model using pregnancy complication as outcome variable

<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta Coefficient</th>
<th>Standard Error</th>
<th>Wald Test Statistic</th>
<th>Adjusted Odds Ratio</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>-1.836</td>
<td>0.325</td>
<td>3.85</td>
<td>2.47</td>
<td>1.00</td>
<td>6.10</td>
</tr>
<tr>
<td>Current opiate use</td>
<td>0.905</td>
<td>0.461</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The results of this sub-analysis and the relationship between pregnancy complication and opiate use, suggest that pregnancy complication should be excluded from the final model. In a decision to exclude this variable, a comparison of the full model (Model 1) to a reduced model (excluding pregnancy complication) was carried out. Using the likelihood ratio test, it was determined there was no advantage to including pregnancy complication in the model. The reduced model was as good as the full model (p>0.001). A comparison of the log odds ratio for the adjusted and unadjusted models also suggests that excluding this variable results in a better model. The log odds ratio comparison revealed that inclusion of the variable pregnancy complication led to a greater than 10% change for all other explanatory variables.
B. METHADONE USE AND OPIATE USE

The relationship between opiate use and methadone use was also considered. It is clear from Table 4.12, that opiate use and methadone use are associated in univariate analysis. It is also evident from this data that the majority of women in this study that used methadone had also used opiates at some point during their pregnancy. Since the data for the timing of opiate versus methadone use was not available, what is important is the fact that they ‘currently’ used opiates or used opiates during their pregnancy. This may mean that the association of methadone with adverse neonatal outcome in the univariate analysis is actually driven by the subjects’ opiate use. The highly correlated relationship between current opiate use and current methadone use dictated that methadone use be removed from the model. The likelihood ratio test (p>0.001) and a comparison of the log odds ratio for the adjusted and unadjusted model (>10% change in predictor variables) supported this decision.

<table>
<thead>
<tr>
<th>Current opiate use</th>
<th>Current methadone use</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
<td>33</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>NO</td>
<td>9</td>
<td>73</td>
<td></td>
</tr>
</tbody>
</table>

C. STIMULANT USE AND OPIATE USE

It is evident from Table 4.4, and Table 4.13 below that the variables opiate use and stimulant use are also highly correlated. Based on the \textit{a priori} objectives of this study, however, it was determined that neither of these variables should be excluded from the
logistic regression model. Excluding one of these substance use variables would have meant the omission of a main explanatory variable, and that a key risk factor remained unexplained.

Table 4.13: Univariate comparison of opiate use with stimulant use

<table>
<thead>
<tr>
<th>Opiate vs. Stimulant Use</th>
<th>Current stimulant use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>YES</td>
</tr>
<tr>
<td>Current opiate use</td>
<td></td>
</tr>
<tr>
<td>YES</td>
<td>39</td>
</tr>
<tr>
<td>NO</td>
<td>20</td>
</tr>
</tbody>
</table>

p<0.001

4.2.3 INTERACTION TERMS

As previously discussed, a number of substances included in this model may have been used concurrently. In fact, as suggested by the data in Table 4.4, concurrent use of stimulants and opiates is especially prevalent among the women in this cohort. For these reasons, it was necessary to investigate the relationship between the substance use variables further. To this end, a number of interaction terms were introduced into the model. All possible two-way interaction terms for current stimulant use, current opiate use, and current tobacco use as well as a three-way interaction term were considered. None of the interaction terms were found to be significant and therefore, none were included in the model.

4.2.4 FINAL MODEL

The final model for predicting neonatal outcome is as presented in Table 4.14. Current stimulant use, current opiate use, current tobacco use, age, aboriginal ethnicity, and gravidity are included as explanatory variables for the dependent variable adverse
neonatal outcome. The regression coefficients obtained through the logistic regression “indicate the effect of an individual variable on the log odds of the outcome event with all the remaining variables held constant. The coefficient denotes the magnitude of the increase or decrease in the log odds produced by one unit change in the value of the regressor variable”.

From the model, current opiate use is independently associated with adverse neonatal outcome, odds ratio 5.52 (95% CI: 1.82, 16.76). For tobacco use during pregnancy, an odds ratio of 2.27 (95% CI: 0.79, 6.58) was observed; however, this association was not statistically significant. A non-significant result was also observed for current stimulant use. Moreover, the effect of stimulant use during pregnancy appears to be protective OR 0.69 (95%CI: 0.23, 2.08). Age, aboriginal ethnicity, and gravidity were not significant in the final model. The number of events per variable for this model was 7.5 EPV.

Table 4.14: Multi-variable logistic regression results for final model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta Coefficient</th>
<th>Standard Error</th>
<th>Wald Test Statistic</th>
<th>Adjusted Odds Ratio</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>-3.745</td>
<td>1.460</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current stimulant use</td>
<td>-0.369</td>
<td>0.562</td>
<td>0.43</td>
<td>0.69</td>
<td>0.23</td>
<td>2.08</td>
</tr>
<tr>
<td>Current opiate use</td>
<td>1.708</td>
<td>0.567</td>
<td>9.08</td>
<td>5.52</td>
<td>1.82</td>
<td>16.76</td>
</tr>
<tr>
<td>Current tobacco use</td>
<td>0.822</td>
<td>0.542</td>
<td>2.30</td>
<td>2.27</td>
<td>0.79</td>
<td>6.58</td>
</tr>
<tr>
<td>Age</td>
<td>0.047</td>
<td>0.043</td>
<td>1.18</td>
<td>1.05</td>
<td>0.96</td>
<td>1.14</td>
</tr>
<tr>
<td>Aboriginal ethnicity</td>
<td>0.180</td>
<td>0.451</td>
<td>0.16</td>
<td>1.20</td>
<td>0.49</td>
<td>2.89</td>
</tr>
<tr>
<td>Gravidity</td>
<td>0.830</td>
<td>0.767</td>
<td>1.17</td>
<td>2.29</td>
<td>0.51</td>
<td>10.32</td>
</tr>
</tbody>
</table>

A regression model using the alternate explanatory variables, # partners in past year, HIV diagnosis, and STI during current pregnancy is also included here for comparative purposes. As with the model presented above, opiate use remained
significant in the model with a similar odds ratio. There was little change in the odds ratios for the variables stimulant use and tobacco use. See Table 4.15.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta Coefficient</th>
<th>Standard Error</th>
<th>Wald Test Statistic</th>
<th>Adjusted Odds Ratio</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>-1.812</td>
<td>0.742</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current stimulant use</td>
<td>-0.849</td>
<td>0.686</td>
<td>1.54</td>
<td>0.43</td>
<td>0.11</td>
<td>1.64</td>
</tr>
<tr>
<td>Current opiate use</td>
<td>1.698</td>
<td>0.687</td>
<td>6.11</td>
<td>5.46</td>
<td>1.42</td>
<td>21.00</td>
</tr>
<tr>
<td>Current tobacco use</td>
<td>0.959</td>
<td>0.550</td>
<td>3.04</td>
<td>2.61</td>
<td>0.89</td>
<td>7.67</td>
</tr>
<tr>
<td># of partners in past year</td>
<td>0.142</td>
<td>0.279</td>
<td>0.26</td>
<td>1.15</td>
<td>0.67</td>
<td>1.99</td>
</tr>
<tr>
<td>HIV diagnosed</td>
<td>0.634</td>
<td>0.696</td>
<td>0.83</td>
<td>1.89</td>
<td>0.48</td>
<td>7.38</td>
</tr>
<tr>
<td>STI during current pregnancy</td>
<td>-0.155</td>
<td>0.565</td>
<td>0.08</td>
<td>0.86</td>
<td>0.28</td>
<td>2.59</td>
</tr>
</tbody>
</table>

4.3 POWER

Power is the probability of rejecting the null hypothesis when \( H_0 \) is false.\(^{171}\) Or in other words, the ability of a study to demonstrate an association if one exists.\(^93\) The observed power for this study for current stimulant use and adverse outcome was computed to be 0.69. The observed power for current opiate use was computed to be 0.97.

In order to achieve a power of 0.80 for stimulant use and adverse outcome, and based on the proportions observed in this study, one would need a sample size of at least 61 subjects in the adverse neonatal outcome group. This thesis study was limited by the sample size available from the primary study.
CHAPTER 5 – DISCUSSION AND IMPLICATIONS

5.1 SUMMARY OF FINDINGS

The HCV Vertical Transmission study database has provided detailed insight regarding substance use, obstetrical and medical history, and a wide range of lifestyle characteristics among a group of hepatitis C positive pregnant women. In particular, this data highlights the fact that these pregnant women, living in British Columbia, report high use of stimulants, opiates, methadone, and tobacco during their pregnancies as well as high levels of concurrent substance use. The data also reveals that the infants of this group of women suffer high incidences of adverse neonatal outcomes.

When comparing those women with an infant with an adverse outcome versus those with no adverse neonatal outcome, it is clear that substance use is an important risk factor for poor outcome in neonates. In fact, the crude odds ratios (95% CI) for stimulant use, opiate use, methadone use, and tobacco use are 2.7 (1.27, 5.59), 4.5 (2.09, 9.78), 4.5 (2.11, 9.71), and 3.4 (1.46, 7.86) respectively. In interpreting these univariate results it is important to recognize that concurrent use of these substances is extensive among this group of women. Employing a multi-variable approach is necessary. Such an approach is, however, complicated by the number of variables that may influence adverse neonatal outcomes as well as the relationships between these various explanatory variables.

Of interest in this analysis, was the role of the variable pregnancy complication. In the univariate analysis this variable approached significance as a risk factor for an adverse neonatal outcome and thus, this variable was originally included as an explanatory variable. However, the potential link between opiate use and various
pregnancy complications raised the question of whether this variable could possibly be an intermediary or alternate outcome variable. An analysis of the association of opiate use with pregnancy complication confirmed the relationship between these two variables and the variable pregnancy complication was excluded from the final model.

The methadone use variable was also of particular interest in determining the final model. Efforts are often made to prescribe methadone to opiate users. These efforts are particularly important during pregnancy since regular methadone maintenance may help stabilize the often-chaotic lifestyles of drug users. In the case of pregnant women, this may lead to more regular prenatal care. However, for this study the timing of methadone use was not recorded and therefore, one cannot confidently separate those individuals that may have achieved a less chaotic lifestyle. Furthermore, since the majority of methadone users had admitted use of opiates during their pregnancy it is possible that the association of methadone and adverse outcome is in fact, driven by the use of opiates. Since methadone use and opiate use were potentially measures of the same risk, methadone use was excluded from the final model. In interpreting the association of opiate use with adverse neonatal outcome, however, one must still be aware of the potential influence of methadone. Since a substantial number of opiate users were prescribed methadone in efforts to ensure more regular prenatal care and better outcomes for their infants, the odds ratio observed for opiate use may in fact, underestimate the true association with adverse neonatal outcome.
Perhaps the most notable finding of this study is the fact that current opiate use remained independently associated with adverse neonatal outcome in the multi-variable analysis, OR 5.52 (95% CI: 1.82, 16.76). That is, women who continue to use opiates during their pregnancy are at a 5.52 increased odds of delivering a baby who will experience an adverse neonatal outcome. These results support the findings of past researchers who have found statistically significant differences in adverse neonatal outcomes between their study and comparison groups.\textsuperscript{28,29,32-34,36-37} These past studies did not, however, employ multi-variable approaches. Therefore, this analysis offers additional insight by providing a measure of the association between opiate use and adverse neonatal outcome. Clearly the effects of opiate use during pregnancy are of grave concern to the neonates of these women.

The results of this study establish that opiate use is clearly predictive of adverse outcome, however, the review provided in this thesis and the univariate analysis led to the \textit{a priori} expectation that stimulant use and tobacco use would also prove independently associated in a multi-variable model. Bearing in mind that the result is non-significant, the odds ratio for stimulant use is counter-intuitive and suggests a protective effect OR 0.69 (95% CI: 0.23, 2.08). This is consistent with the results of Richardson et al and Miller et al who reported no association of cocaine use with prematurity or low birth weight.\textsuperscript{66,69} In fact, Miller et al report results of similar magnitude which are also non-significant. They present an odds ratio for cocaine use and prematurity of OR 0.6 (95% CI 0.2, 1.9), and for cocaine use and low birth weight of 1.2 (0.4, 3.6), both adjusted for other risk factors including opiates, tobacco, maternal race, maternal age, and parity.\textsuperscript{69} In contrast, Bateman et al adjusted for a similar list of risk factors and found odds ratios
(95% CI) of 1.94 (1.21, 3.11) and 2.10 (1.23, 3.67) for prematurity and low birth weight respectively.\textsuperscript{70} Kistin et al reported considerably higher relative risks (95%CI) of 4.0 (2.3, 7.0) for prematurity and 5.3 (3.0, 9.3) for low birth weight. These latter two studies adjusted for maternal race, maternal age, and gravidity, and excluded all subjects that had used heroin or tobacco.\textsuperscript{68}

One possible explanation for the results of this thesis analysis is that there were too few subjects reporting exclusive use of stimulants or opiates to appropriately control for the separate effects of these substances. In fact, there were only 4 subjects that reported using opiates without the concurrent use of stimulants. This extensive overlap in stimulant use and opiate use may have resulted in a model that is able to estimate the overall effect on adverse neonatal outcome but is not able to accurately determine the contribution made by each individual substance variable.

Furthermore, although the collinearity of the stimulant and opiate use variables presented challenges for this analysis, it is an important finding that such a large proportion of women used both substances during their pregnancy. High rates of concurrent drug use are recognized throughout the literature and this study confirms this behaviour among pregnant women in the province of British Columbia. In light of this, it is clear that concurrent use must be appropriately accounted for when educating female drug-users as well as in detoxification efforts. It should also be a consideration for future research.

The odds ratio (95%CI) observed for tobacco use and adverse neonatal outcome was 2.27 (0.79, 6.58). This indicates that women who smoke during pregnancy are at
increased odds of having an infant with an adverse neonatal outcome; however, the result is not statistically significant. This finding is consistent with the well-documented increased risk of prematurity and low birth weight among smokers.\textsuperscript{172-178} The non-significance of the result is likely related to insufficient power.

5.2 UNIQUE CONTRIBUTIONS

There are several studies using a multi-variable approach to determine the association between cocaine use during pregnancy and adverse neonatal outcomes. However, none of these studies published results for opiate use during pregnancy and such outcomes. Consequently, this study makes a very unique contribution by presenting a measure of the association between opiate use and adverse neonatal outcome.

This thesis study has also provided several other unique contributions. Among the studies related to maternal drug use during pregnancy and adverse neonatal outcomes, there are few studies that have been conducted in Canada and, at the time of this thesis literature review, none in British Columbia. Most studies have been conducted in the USA. When one considers the differences the health care systems and approaches to illicit drug use it is evident that a study conducted in Canada will provide our health care workers with additional insight when caring for their patients. It will also provide policy makers with a Canadian perspective of this health care issue so they can be confident their decisions are appropriate for our nation's population.

Not only is this study unique in its study setting, but the study population is distinct from that of past studies. The HCV Vertical Transmission Study offered the opportunity
to study neonatal outcomes in a population of pregnant women living with Hepatitis C; a population that may have special medical concerns during pregnancy.

This thesis is also unique with respect to the extensive list of patient characteristics that were considered as risk factors for adverse neonatal outcomes. Few studies have considered such a comprehensive set of patient attributes. Inclusion of all these factors clearly illustrates that the complexity associated with this outcome measure has been recognized by this study. A neonate's health can be affected by a variety of exposures and maternal characteristics and thus, the need to account for multiple substance use in addition to demographic and obstetrical characteristics.

5.3 STUDY LIMITATIONS

5.3.1 UNAVAILABLE EXPLANATORY VARIABLES

The secondary analysis for this thesis project was limited to the data collected by the primary study questionnaire. Although the Hepatitis C Vertical Transmission Study provided a rich data source, some additional explanatory variables would have enhanced the analyses described above.

A. SUBSTANCE USE DETAILS

A measure to assess the amount and frequency of drug use throughout pregnancy would be particularly useful in enhancing this analysis. Detail of this level would allow a dose-response relationship to be established. Demonstrating such a relationship, that as the dose of drug exposure increases the risk of adverse outcome increases, would provide very strong evidence for a causal relationship.\footnote{In addition, timing of drug use, for example identifying the trimester of use, would also be informative. The developmental}
stage at which the drugs were used may play an important role in the outcomes observed. As well, timing of use would allow a distinction to be made between women who continued their drug-using habits, versus those who ceased using or successfully maintained a methadone program.

B. PREGNATAL CARE AND NUTRITION

Prenatal care and adequate nutrition during pregnancy are both important factors that may have some influence on neonatal outcomes. Therefore, questions to establish that adequate care and nutrition were received would also provide valuable data and useful additions to the list of explanatory variables.

5.3.2 EXTERNAL VALIDITY

The primary study was designed to capture the population of HCV positive pregnant women in our province. It is from this population that the sub-population of current drug-using women was identified. Since a proportion of drug-using women may not seek any prenatal care until the onset of labour, this cohort likely represents more stable drug-using pregnant women. It is reasonable to assume that the sub-group in this study would be comprised of those women with less extreme drug-using habits who have at least sought some health care during their pregnancy as opposed to some women who have such chaotic lifestyles that they would not be able to access any health care or this study. Therefore, any estimates of association between drug use and outcomes presented in this thesis are more likely to underestimate rather than overestimate the association.

It is also important to note that this cohort captures only those women who are concurrently HCV infected. For this reason, the studies comprising this thesis may not be
generalizable to the entire population of drug-using pregnant women. However, the prevalence of HCV positivity among (intravenous) drug-users is approximately 80% and therefore, identification of HCV positive pregnant women is likely to capture a large proportion of those women who use drugs during their pregnancy.\textsuperscript{104} Nonetheless, this study will be biased to include women who have been involved in injection drug use, while drug using women who have never injected may not be represented.

5.3.3 SELF-REPORT AND RECALL BIAS

A large proportion of the information collected for this study was ascertained by self-report and therefore, is subject to the honesty of the participants in reporting their answers. Of particular concern is the truthfulness of participants regarding their drug use history during pregnancy. The potential for these types of untrue responses have, however, been minimized by efforts to ensure confidentiality and anonymity, and by the nature of the relationship between the study nurse and the women. In addition to collecting data, the study nurse acts as a counselor and advocate, and thus promotes a strong relationship of trust with the participants. This relationship is demonstrated by the high retention rates achieved for this challenging cohort.\textsuperscript{179}

Self-reported drug history is also subject to recall or reporting biases due to memory failure.\textsuperscript{93} This may be due to the effects of the drugs used or a result of the time that may have elapsed since the event. Time elapsed makes it more difficult to remember exact dates and may result in drug use that occurred during pregnancy being reported as prior to pregnancy.
5.3.4 SAMPLE SIZE

The sample size of this analysis was restricted to the number of participants that were enrolled in the primary study. Furthermore, the analysis for this thesis identified two groups of women from the original study cohort. Since this identification was guided by responses of self-reported drug use from the original questionnaire, it was subject to missing and ambiguous responses that further reduced the sample size.

Small sample size has several implications. First, it will result in a loss of power to the study; that is, the probability that the null hypothesis will be rejected if it is in fact false. This affects the ability of the study to demonstrate an association if one exists. Secondly, small sample size may yield a smaller number of outcome events. The number of events per variable needs to be considered in the multi-variable analysis and a smaller number may require restriction of the number of variables that can be entered into the model.

For this analysis, the number of outcome events at the onset of the study was 53; however, due to missing data the number of outcome events retained in the multi-variable analysis was only 45. Therefore, the number of explanatory variables that could be introduced was limited by the small sample size and subsequent reduced number of adverse events. However, with only 45 events the model was still able to include all the predictor variables that were significant in the univariate analysis as well as additional demographic and obstetric variables of interest.
5.3.5 COLLINEARITY

The main study variables in this analysis, stimulant use and opiate use, demonstrated a collinear relationship, primarily a result of high rates of concurrent substance use. This analysis was a secondary analysis and was, therefore, restricted to the data from the primary study. Little could be done to rectify the collinearity between these variables, unless important predictors had been omitted. Future studies should be aware of the potential relationships between explanatory variables. It is likely, however, that little can be done to resolve this issue since it is dependent on the study population and the extent to which they use substances concurrently. High rates of concurrent substance use are well recognized among illicit drug users as previously discussed in the literature review of this thesis.

5.4 IMPLICATIONS

This study provides evidence that the infants of pregnant drug users suffer increased adverse neonatal outcomes. The results of this study, therefore, reinforce the importance of services to reduce drug use among drug-addicted mothers. Among the facilities that offer services and care to pregnant women with substance use problems is Fir Square; a combined care unit at BC Women’s Hospital that is staffed by specially trained doctors and nurses. Its initiatives aim to reduce drug use and improve perinatal outcomes, and include a harm reduction approach that facilitates access to methadone maintenance programs. This study highlights the need for continued government support of such programs as well as improved efforts to increase awareness in the community about the services offered.
In addition, this study serves as a reminder that concurrent substance use is high among substance-using pregnant women, including those in our province. Thus, social workers and health care providers, in BC, need to consider multiple substance use while continuing their efforts to reduce drug use and improve the health of these mothers and their babies.

5.5 FURTHER RESEARCH

While the results of this study are interesting continued research in the area is necessary. From the study limitations described above, it follows that any subsequent studies should address these limits. A prospective cohort study with an increased sample size would be an ideal follow-up to this thesis study. A larger study sample would provide increased power for the study as well as allow for additional sub-analyses, particularly on the individual neonatal outcomes. A study that provides additional data regarding drug use details would enhance the analysis and offer a means of establishing a dose-response relationship. As well, inclusion of a method to assess the validity of self-reported answers would be useful; for example, using urine samples to detect drug use.

5.6 CONCLUSIONS

This study has provided a comprehensive descriptive profile of pregnant women living with hepatitis C in British Columbia. This profile includes patterns of illicit and licit substance use, sociodemographic characteristics, obstetrical and medical data, and sexual behaviour. These women report high concurrent use of stimulants and opiates during their pregnancies, and have high incidences of adverse neonatal outcomes. Furthermore, opiate use during pregnancy is independently associated with adverse neonatal outcome when adjusted for stimulant use, tobacco use and other demographic
and obstetrical variables. Women who use opiates during their pregnancy are at an increased risk of having an infant who will suffer an adverse neonatal outcome. Finally, this study highlights the importance of further study to support these results, and recommends that the relationships between opiate use and other substances be carefully considered in the design of future studies.
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HCV QUESTIONNAIRE

Subject code: ___________ Date of interview: ___________ (DD/MM/YY)

I would like to ask you a number of questions about yourself and your pregnancy, including general information and medical history. In order to determine any possible factors that may be involved in transmission of hepatitis C from mother to infant and also to identify potential factors that may have been involved in your infection, I would like to ask detailed questions regarding any possible drug use exposure, about other possible sources such as tattooing and details about types of sexual exposure. Some of these questions may seem completely unrelated to you, but all study participants will be asked the same questions. Some of these questions may make you uncomfortable, so I want you to know that you are free to refuse to answer any of them at any stage. This interview should take approximately 30-60 minutes, depending on any questions you may have. (interviewer make note of questions either not asked or not answered)

SECTION A

Demographics

In the following section I will be asking you some general questions about your background. If you are uncomfortable with any of the questions, please let me know and we can skip a question or stop at any time.


4. "How would you describe your current marital status?"
1. Single 4. Separated
2. Married 5. Widowed
3. Divorced 6. Living with partner > 1 year

5. Ethnic group: "How would you describe your ethnic background?"
1. Caucasian
2. Black
3. South Asian
4. Asian
5. Hispanic
6. First Nations/aboriginal (please indicate one of the following)
   - Status
   - Non-status
   - Metis
   - Inuit
   - Other - specify ___________
7. Other - specify _______________________

6. Place of birth:
   1. Canada
   2. USA
   3. Caribbean
   4. Central/South America
   5. Western Europe
   6. Eastern Europe
   7. Africa
   8. Asia
   9. Australia/Pacific Islands
   10. Other - specify

7. If born outside of Canada, year of arrival in Canada: __________

8. Postal code (first 3 letters) ___________

9. Occupation: current _______________________
   Ever _______________________

10. Age when stopped fulltime attendance in school: ______

11. Last education completed:
   1. Grade/elementary school
   2. High school
   3. College/university: years completed ______

12. Yearly gross household income
   1. $<10,000
   2. $10,000 - 30,000
   3. $30,000 - 50,000
   4. $>50,000

13. Social assistance/welfare
   No _______________________
   Yes - category (i.e. disability) _______________________

### SECTION B

**Obstetrical - Gynaecological History**

In this section I would like to ask you some questions about your current pregnancy, past pregnancies, and your gynaecological history. If you are uncomfortable with any of the questions, please let me know and we can skip a question or stop at any time.

1. LMP __________ (DD/MM/YY) Sure __________
2. Cycle length _______________________
3. Date of positive pregnancy test __________ (DD/MM/YY)
4. Did you have pre-pregnancy counselling? Yes No
5. Did you take folic acid prior to conception? Yes No

6. Current gestational age: ________ wks
11. IVF? 1. Yes 12. No
13. When is your expected delivery date? __________ (DD/MM/YY)
14. If this is not your first pregnancy, describe each pregnancy outcome, starting with most recent:

<table>
<thead>
<tr>
<th>Preg. No.</th>
<th>Outcome</th>
<th>Gest. (wks)</th>
<th>Date (MM/YY)</th>
<th>Mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>currently preg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>live birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>induced abortion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>neonatal death (&lt;28 days pp)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>stillbirth (&gt;= 20 wks gest)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>spontaneous abortion (&lt; 20 wks)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>tubal or ectopic pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>hydatidiform mole</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(G _____ P _____ L _____ SA _____ TA _____ )

15. If you have any other children, please answer the following for each child, starting from the oldest:

(it may be useful to ask the woman the date/year that she was diagnosed with HCV at this point)

**CHILD #1**

- Date of birth: __________ (DD/MM/YY)
- Gender: __ Male __ Female
- Before or after HCV diagnosis? __ before __ after
- Mode of delivery: __ SVD __ IVD 
  - forceps
  - scalp monitor
  - elective CS - reason:
  - emergency CS - reason:
- Breast fed? __ Yes ___ No
- Tested for HCV? __ No __ Yes - date/result: __________________________
- Other problems?

**CHILD #2**

- Date of birth: __________ (DD/MM/YY)
- Gender: __ Male __ Female
- Before or after HCV diagnosis? __ before __ after
- Mode of delivery: __ SVD __ IVD 
  - forceps
  - scalp monitor
  - elective CS - reason:
  - emergency CS - reason:
- Breast fed? __ Yes ___ No
- Tested for HCV? __ No __ Yes - date/result: __________________________
- Other problems?

**CHILD #3**

- Date of birth: __________ (DD/MM/YY)
- Gender: __ Male __ Female
- Before or after HCV diagnosis? __ before __ after
- Mode of delivery: __ SVD __ IVD 
  - forceps
  - scalp monitor
  - elective CS - reason:
  - emergency CS - reason:
- Breast fed? __ Yes ___ No
Tested for HCV?  No  Yes - date/result: ________________________________
Other problems? ______________________________________________________________________

**CHILD #4**

Date of birth: ______________ (DD/MM/YY)  Gender:  ____ Male  ____ Female
Before or after HCV diagnosis?  ____ before  ____ after
Mode of delivery:  ____ SVD  ____ IVD
  ____ forceps  ____ scalp monitor
  ____ elective CS - reason: ____________________________________________
  ____ emergency CS - reason: _________________________________________
Breast fed?  Yes  No
Tested for HCV?  No  Yes - date/result: ________________________________
Other problems? ______________________________________________________________________

16. Do you plan to breastfeed this child?  Yes  No
   If no, reason for not breastfeeding?  HCV status  ____ Personal__________

17. Early pregnancy complications:
   1.  ____ Nausea/vomiting
   2.  ____ Bleeding
   3.  ____ Infection

18. Late pregnancy complications?
   1.  ____ Gestation hypertension
   2.  ____ Gestational diabetes
   3.  ____ Preterm labor
   4.  ____ Premature cervical dilation
   5.  ____ Rupture of the membranes
   6.  ____ Growth problems of the baby
   7.  ____ Too little fluid around the baby
   8.  ____ Too much fluid around the baby
   9.  ____ Placental abruption
  10.  ____ Placenta previa
  11.  ____ Other________________________

19. Did you have any of the following?
   1.  ____ Maternal serum screening - date __________ (DD/MM/YY)
   2.  ____ Amniocentesis - date __________ (DD/MM/YY)
   3.  ____ Chorionic villus sampling - date __________ (DD/MM/YY)

20. Did you have prenatal ultrasound yet?  Yes  No
   Date  Place  Findings
   1.  ___________________  ___________________  ___________________
   2.  ___________________  ___________________  ___________________
   3.  ___________________  ___________________  ___________________
   4.  ___________________  ___________________  ___________________

21. Have you had any of the following infections in pregnancy?
   1.  ____ Urinary tract infection
   2.  ____ Yeast infection
   3.  ____ Bacterial Vaginosis
   4.  ____ Trichomonas
   5.  ____ Chlamydia
   6.  ____ Gonococcal
   7.  ____ Syphilis
   8.  ____ Genital Warts
   9.  ____ Herpes
  10.  ____ Other________________________
22. Beginning with the most recent, list the different kinds of BIRTH CONTROL methods you have used. Give the total number of months used for each method.

<table>
<thead>
<tr>
<th>Specify: (BCP/IUD/cap/etc)</th>
<th>Method</th>
<th>Months used</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
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</table>

**SECTION C  
Medical History**

*In this section I would like to ask you some questions about your medical and health history. If you are uncomfortable with any of the questions, please let me know and we can skip a question or stop at any time.*

1. Do you have any medical problems that we should be aware of?
   1. _____ Hypertension
   2. _____ Diabetes
   3. _____ Others ____________________________

2. Have you had any operations?  
   Yes  No

3. Did you have any complications from surgery?  
   Yes  No
   If yes, details: ____________________________

4. Do you currently take any medications?  
   1. _____ Prescription ____________________________
   2. _____ OTC ____________________________
   3. _____ Herbal? ____________________________
   4. _____ Other: ____________________________

5. Are there any diseases that run in your family? (provide details of what and who)
   _______________________________________
   _______________________________________
   _______________________________________

6. Does anyone in your immediate family have HCV infection? (who)
   _______________________________________
   _______________________________________

7. "What year did you receive your first HCV+ test?": __________
8. "What was the reason that you had the test?":
1. _____ jaundice
2. _____ pregnancy
3. _____ transfusion history
4. _____ unexplained hepatitis
5. _____ high risk behaviour - specify
6. Other

9. Estimated year of infection: __________
10. Year of jaundice illness: __________
11. Current treatment?

12. "Have you ever been diagnosed with any of the following?":
1. _____ HBV
2. _____ HAV
3. _____ HTLV
4. _____ Other - specify

13. Have you ever been tested for HIV? Yes No
14. Have you ever had a positive HIV test? Yes No
15. Date: ________________
16. If yes, have you ever had treatment for your HIV? Yes No
17. Are you currently on medication for your HIV? Yes No
18. Details:

19. "Have you ever been diagnosed with any other type of liver disease, such as:"
1. _____ Drug/medication etiology
2. _____ gallstones
3. _____ autoimmune
4. _____ alcohol-related
5. _____ other - specify

20. If "yes" to #4 above, can you describe for me your alcohol-related medical history? (narrative):

---

SECTION D

Behavioural / risk factors

In this section, I would like to ask you about some of the lifestyle practices and known risk behaviours that have been linked to hepatitis C transmission. If you are uncomfortable with any of the questions, please let me know and we can skip a question or stop at any time.

1. Have you ever smoked cigarettes? Yes No
2. If yes, how old were you when you started? __________
3. Do you still smoke? Yes No
4. If no, how old were you when you quit? __________
5. What is the average number of cigarettes you smoke(d) per day? __________
6. What has been your usual use of each of the following during the past year:

1. Beer (12 oz bottles per week)

2. Wine (4 oz glasses per week)

3. Liquor (1.5 oz drinks per week)

7. "Have you ever had a blood transfusion?" Yes No

8. If yes, for each transfusion:

   Date (DD/MM/YY) # units

   ______________________  ______________________
   ______________________  ______________________
   ______________________  ______________________
   ______________________  ______________________

9. Have you ever been a blood donor? Yes* No

10. Dates: ______________________

    ______________________

* NOTE: It is standard practice to request permission from HCV+ blood donors to notify the Canadian Blood Service

11. Have you ever been hospitalised, had a major accident, or had surgery (including c-sections)?

    Yes No

    Date Location Reason

    ______________________  ______________________  ______________________
    ______________________  ______________________  ______________________
    ______________________  ______________________  ______________________
    ______________________  ______________________  ______________________

12. Have you ever had hemodialysis? Yes No

13. Years ______________________

14. Are you or have you ever been a health care worker? Yes No

15. Have you ever had a needlestick injury? Yes No

16. If yes, date(s): ______________________

17. Have you ever had any other type of potential exposure to another person's body fluids (i.e. sputum or vomit, exposures to eyes, contact with broken skin)? No Yes

18. If yes, please describe and date(s):

19. Have you ever had any other type of potential exposure to another person's body fluids through any other type of work (i.e. sputum or vomit, exposures to eyes, contact with broken skin)?

    No Yes

20. If yes, please describe and date(s):

21. Are you aware whether or not your mother is infected with hepatitis C? Yes No
22. "Have you ever experimented with or used injection drugs?" Yes No
23. If yes, have you ever shared needles?

# of years using:
1. ______ < 1 year  
   3. ______ 6 - 10 years  
   5. ______ > 20 years  
2. ______ 1 - 5 years  
   4. ______ 11 - 20 years

24. What, if any, of the following drugs have you used?
1. ______ Crack cocaine (dates: ________________)
2. ______ nasal cocaine (dates: ________________)
3. ______ Subcutaneous (skin popping) drugs (dates: ________________)
4. ______ Heroin (dates: ________________)
5. ______ Other ____________________________ (dates: ________________)

25. Do you have any tattoos or body branding? Yes No

26. If yes, were they done at a licensed tattooing facility? Yes No

27. Other location: ______________________________

28. Dates: ______________________________

29. Have you ever had any body piercing? Yes No
30. ______ ears only
31. ______ other - specify ______________________________
32. Dates: ______________________________

33. Have you ever had acupuncture? Yes No
34. Dates: ______________________________

35. Have you ever had a medical injection in a developing country? Yes No
36. If yes, country ________________
37. Dates: ______________________________

38. Are you aware of any members in your household that are infected with HCV? Yes No
39. If yes, what is your relationship to this person? ______________________________

40. Have you shared with household members:
1. ______ Toothbrush?
2. ______ Razor?

---

SECTION E
Sexual history

In the next section, I would like to ask you some questions about your sexual practices. I know that these questions may make you feel uncomfortable or embarrassed, but all study participants will be asked these questions because they can be related to information about hepatitis C transmission. I want to remind you that all the information you share is confidential and that you are free to refuse to answer any questions that make you uncomfortable.

1. Are you currently in a sexual relationship(s)? Yes No
2. If yes, length of current relationship ____________________
3. Do you have any children? **Yes**  **No**  

<table>
<thead>
<tr>
<th>Ages:</th>
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5. Any children with HCV? **Yes**  **No**  

6. How would you describe your sexual orientation?  
1. **Heterosexual**  
2. **Gay/lesbian**  
3. **Bisexual**  
4. **Transsexual/transgender**  
5. **Other**  

7. How many sexual partners have you had in the past year?  
1. **none**  
2. **one**  
3. **2 to 5**  
4. **6 to 10**  
5. **more than 10**  
6. **not sure**  

8. How many sexual partners have you had in the past five years?  
1. **none**  
2. **one**  
3. **2 to 5**  
4. **6 to 10**  
5. **more than 10**  
6. **not sure**  

9. How many sexual partners have you had in the past 10 years?  
1. **none**  
2. **one**  
3. **2 to 5**  
4. **6 to 10**  
5. **more than 10**  
6. **not sure**  

10. How many sexual partners have you lived with in the past year?  
1. **one**  
2. **two**  
3. **more than two**  

11. How many sexual partners have you lived with in the past five years?  
1. **one**  
2. **two**  
3. **more than two**  

12. How many sexual partners have you lived with in the past 10 years?  
1. **one**  
2. **two**  
3. **more than two**  

13. How many sexual partners have you had in your lifetime?  

14. How old were you when you first experienced sexual intercourse?  

15. How long have you been in your current sexual relationship?  

16. Have you ever had sex with someone you know has used injection drugs? **Yes**  **No**  

17. Have you ever had sexual contact with gay/bisexual men? **Yes**  **No**  

18. Have you ever had sex with someone with genital herpes or who had genital sores? **Yes**  **No**  

19. In the past 12 months have you had sex with someone whose sexual background whose sexual background you don't know? **Yes**  **No**  

20. In the past 12 months have you had sex with anyone who may be at an increased risk for getting AIDS, HIV or Hepatitis infections from their sexual practices or other high risk activities? **Yes**  **No**  

21. Have you ever had any sores or ulcers on your penis/vagina or genital area? **Yes**  **No**  

22. Have you ever had any of the following:  
1. **syphilis**  
2. **gonorrhea**  
3. **genital herpes**  
4. **chlamydia**  
5. **genital warts**  
6. **any other sexually transmitted disease - specify**
23. Have you ever had sex with someone who you knew had hepatitis C? Yes No

24. Have you ever had sex with a male or female prostitute? Yes No

25. Have you ever paid or received money for having sex? Yes No

26. Have you ever given or received sex for drugs? Yes No

I would now like to ask a few questions about the specifics of sexual practices. Again, if any of these questions make you uncomfortable feel free to skip questions or stop at any time.

27. Do you or your live-in sexual partner use a condom? Yes No

28. If yes, what proportion of the time?
   1. _____ all of the time
   2. _____ most of the time
   3. _____ some of the time
   4. _____ never

29. Do you use a condom when you have sex with a partner you are NOT living with? Yes No

30. If yes, what proportion of the time?
   1. _____ all of the time
   2. _____ most of the time
   3. _____ some of the time
   4. _____ never

31. Have you ever participated in oral sex? Yes No
   1. _____ active
   2. _____ passive
   Within the past year? Yes No

32. Have you ever participated in anal sex? Yes No (if "NO," skip the following question regarding fisting)
   1. _____ insertive ("top")
   2. _____ receptive ("bottom")
   33. Within the past year? Yes No

34. Have you ever participated in fisting? Yes No
   1. _____ active
   2. _____ passive
   35. Within the past year? Yes No

36. Have you ever participated in oral-anal sex ("rimming")? Yes No
   1. _____ active
   2. _____ passive
   37. Within the past year? Yes No

38. Is there any other information about your history that we have not asked about that you think may be important for our study?

39. What have you been told about the transmission of hepatitis C from mother to infant?
APPENDIX 2:
HEPATITIS C VERTICAL TRANSMISSION STUDY MATERNAL FOLLOW-UP QUESTIONNAIRE

Study ID Number: [Redacted]

HCV Vertical Transmission Study
Maternal Data Form

Date of completion: (MM/DD/YY): [Redacted]

Maternal data form completed by: [Redacted]

Section A: BASELINE CHARACTERISTICS

1. Gravity: [Redacted]
2. Parity: [Redacted]
3. Date of last menstrual period (MM/DD/YY): [Redacted]
4. Estimated date of conception (MM/DD/YY): [Redacted]
5. Gestational age (in weeks) at study enrolment: [Redacted]
6. Date of HCV diagnosis (MM/DD/YY): [Redacted]

Section B: TESTS PERFORMED DURING PREGNANCY

1. Rh: [Redacted] positive [Redacted] negative
2. Amniocentesis [Redacted] yes [Redacted] no
   • If yes, when was this test performed? at _____ weeks.
     Reason(s): [Redacted]
Were any abnormalities indicated? □ yes □ no  
If yes, specify:  

3. Additional information about tests performed during pregnancy  

4. Hepatitis B (antibody +) □ yes □ no  
Hepatitis B (sAg+) □ yes □ no  
If yes, was it treated? □ yes □ no  
Year of diagnosis:  
Comments:  

5. HIV (antibody +) □ yes □ no  
If yes, is it being treated? □ yes □ no  
Year of diagnosis:  
Comments:  

6. RPR (Syphilis) □ yes □ no  
If yes, is it being treated? □ yes □ no  
Year of diagnosis:  
Comments:  

7. Varcella (Chicken Pox) □ yes □ no  
If yes, is it being treated? □ yes □ no  
Year of diagnosis:  
Comments:  

**Section C: ANTENATAL INFECTIOUS DISEASES**  

1. Candida (vaginal) □ yes □ no  
If yes, was it treated? □ yes □ no  
Year of diagnosis:  
Comments:  

99
2. Bacterial Vaginosis □ yes □ no
   • If yes, was it treated? □ yes □ no Year of diagnosis: □ □ □ □
   Comments: ____________________________

3. CMV □ yes □ no
   • If yes, was it treated? □ yes □ no Year of diagnosis: □ □ □ □
   Comments: ____________________________

4. Genital herpes □ yes □ no
   • If yes, was it treated? □ yes □ no Year of diagnosis: □ □ □ □
   Comments: ____________________________

5. Other Antenatal infectious diseases? □ yes □ no
   • If yes, specify (i) ____________________________
     Was it treated? □ yes □ no Year of diagnosis: □ □ □ □
     Comments: ____________________________
     • If yes, specify (ii) ____________________________
       Was it treated? □ yes □ no Year of diagnosis: □ □ □ □
       Comments: ____________________________
     • If yes, specify (iii) ____________________________
       Was it treated? □ yes □ no Year of diagnosis: □ □ □ □
       Comments: ____________________________
   • Additional information about antenatal infectious diseases
     _______________________________________
     _______________________________________
     _______________________________________
Section C: PRESCRIPTION MEDICATIONS

1. Is this patient currently being treated for HIV infection? □ yes □ no

   • If yes, complete the following section

**ANTIRETROVIRAL THERAPY (for those with HIV infection only)**

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Gest. Age at start</th>
<th>Gest. age at stop</th>
<th>Dose/freq</th>
<th>Toxicities</th>
<th>Adherence code</th>
<th>Comments</th>
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2. Is this patient taking any other significant prescriptions or over the counter medications? □ yes □ no

   • If yes, complete the following section

**OTHER PRESCRIPTION/OTC MEDICATIONS**

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Gest. age at start</th>
<th>Gest. age at stop</th>
<th>Dose/freq</th>
<th>Toxicities</th>
<th>Comments</th>
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</table>
Section D: OTHER SUBSTANCES

1. Does this patient use tobacco or alcohol? □ yes □ no
   • If yes, complete the following section.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Check all that apply</th>
<th>Gest. age at start</th>
<th>Gest. age at stop</th>
<th>Amount per day/week</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Alcohol:</td>
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<td>• Beer</td>
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<td>Tobacco</td>
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</table>

2. Any additional information about prescription or non-prescription drugs used during this pregnancy?:

__________________________________________________________________________
__________________________________________________________________________
__________________________________________________________________________
__________________________________________________________________________
__________________________________________________________________________
### Section E: LABORATORY RESULTS

<table>
<thead>
<tr>
<th>Date (MM/DD/YY)</th>
<th>Gestational Age (weeks)</th>
<th>CD4 count</th>
<th>HIV RNA (copies/ML)</th>
<th>HGB</th>
<th>WBC</th>
<th>Platelets</th>
<th>AST</th>
<th>ALT</th>
<th>AST</th>
<th>Alk Phosph</th>
<th>GGT</th>
<th>Bilirubin</th>
<th>PT, PTT</th>
<th>Alb</th>
<th>PT, PTT</th>
<th>Alb</th>
<th>HCV RNA</th>
<th>HCV PCR</th>
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### Section F: ANTENATAL COMPLICATIONS

1. Has this patient experienced any antenatal complications? □ yes □ no
   - If yes, complete the following section.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Check all that apply</th>
<th>Gest. age at onset (weeks)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gest. diabetes</td>
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<tr>
<td>Hypertension</td>
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<td>Poor weight gain</td>
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<td>Oligohydram.</td>
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<td>IUGR</td>
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<tr>
<td>Abruption</td>
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<td>Preterm labour</td>
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<td></td>
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<tr>
<td>PTD</td>
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<td></td>
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<tr>
<td>Premature ROM</td>
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<tr>
<td>Antepart. Hem.</td>
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<tr>
<td>Hyperemesis</td>
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<tr>
<td>Cholestasis</td>
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</table>

2. Has this patient experienced any other significant antenatal complications?
   □ yes □ no
   - If yes, complete the following section.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Gest. age at onset (weeks)</th>
<th>Comments</th>
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APPENDIX 3:
HEPATITIS C VERTICAL TRANSMISSION STUDY DELIVERY FOLLOW-UP QUESTIONNAIRE

Study ID Number ________________

HCV Vertical Transmission Study
Delivery Data Form

Date of completion: (MM/DD/YY): ____________

Delivery data form completed by: ________________

Section A: PREGNANCY OUTCOME

1. Date of delivery (or termination of pregnancy): (MM/DD/YY): ____________

2. Outcome:
   - [ ] Live birth
   - [ ] Spontaneous abortion
   - [ ] Therapeutic abortion
     Reason: ______________________________________
   - [ ] Intrauterine death
   - [ ] Still born

3. Duration of gestation period (in weeks) ____________

4. If abortus or stillborn - Pathology report results:
   ______________________________________________________________________
   ______________________________________________________________________
   ______________________________________________________________________
   ______________________________________________________________________

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Section B: DELIVERY INFORMATION (LIVE BIRTH)

1. Gestational age at delivery (weeks): __________

2. Location (hospital) of delivery: ________________________________
   • Maternal health record number: ________________________________
     (Unit number of hospital)

3. PHN: ________________________________

4. Labour
   □ yes □ no
   If yes, total length of labour (in hours) __________
   Rupture of membranes: ______ hours prior to delivery
   Mechanism of labour: □ spontaneous □ induced
   Monitoring during labour: fetal scalp electrode
     □ yes □ no
     fetal scalp sampling □ yes □ no
   Non reassuring fetal monitoring: □ yes □ no
   If yes, explain: ___________________________________________

   • Vaginal delivery: □ yes □ no
     If yes, was it? □ vaginal, vertex □ vaginal, breech
     Assistance: □ forceps - type________________________ □ vacuum

   • Caesarean Section □ yes □ no
     □ Booked/elective C/S, □ Emergency C/S
     Reason for C/S: □ OB indications □ HIV indications □ Choice
     Estimated Blood Loss: □ <500 ml □ 500-700 ml □ >700 ml

   • Were prophylactic antibiotics used? □ yes □ no
9. Analgesia/anaesthesia: [ ] anaesthetic [ ] epidural [ ] General [ ] regional [ ] spinal

10. Were there any complications? [ ] yes [ ] no

If yes, complete the following section.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Check all that apply</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal fever</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meconium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemorrhage</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

11. Placental pathology:

- Did this patient receive any Intrapartum ART? (HIV co-infected only) [ ] yes [ ] no
  
  If yes, complete the following questions.
  
  IV AZT: hours prior to delivery: ________________
  
  Other intrapartum ART? [ ] yes [ ] no
  
  If yes, specify: ____________________________________________
  
  Time of last ART(routine) dose prior to delivery: ________________

**Section C: POSTPARTUM FOLLOW UP**

1. Date of discharge: (MM/DD/YY): ________

2. Number of days in hospital: [ ]

3. Were there any complications? [ ] yes [ ] no
   
   If yes, complete the following section.
<table>
<thead>
<tr>
<th>Complication</th>
<th>Check all that apply</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPH - delayed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other med. Compl.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Episiotomy compl.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febrile (&gt;38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mastitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound hematoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound infection</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3. Were there any other complications? □ yes □ no
   If yes, specify: ____________________________________________

Section C: NEONATAL INFORMATION (DELIVERY TO ONE MONTH)

1. Birth weight: ______ grams (1 oz = 28.4 grams)

3. Length (cm): __________

4. Head circumference (cm): ______

4. Cord blood gases: pH ______

5. Resuscitation? □ yes □ no
   If yes, explain ____________________________________________

6. Apgars: 1 minute ______
      5 minutes ______

7. Transfusion? □ yes □ no
   If yes, explain ____________________________________________
8. Birth Defects? ☐ yes ☐ no
   If yes, explain ________________________________________________________

9. Other neonatal complications? ☐ yes ☐ no
   If yes, explain ________________________________________________________

10. Neonatal ART started within 24 hrs (HIV coinfected only) ☐ yes ☐ no
    If yes, complete the following section.

    | Medication | Start date | Stop date | Dose/mode | Indication |
    |------------|------------|-----------|-----------|------------|
    |            |            |           |           |            |
    |            |            |           |           |            |
    |            |            |           |           |            |
    |            |            |           |           |            |

    • Were there any ART-related complications? ☐ yes ☐ no
      If yes, explain ________________________________________________________

11. Was this infant admitted to:
    ☐ Nursery: (#days) __________
    ☐ Observation nursery*, (non-acute) (#days) __________
    ☐ Long-term care*, (#days): __________
    ☐ Neonatal intensive care unit*, (#days) __________
    ☐ Roomed with mother (#days) __________
    Other Indication: ________________________________________ Days admitted: __________

12. Total Hospital stay: _____ days
13. Substance withdrawal syndrome □ yes □ no
   If yes, explain _______________________________________

   • Severity of withdrawal - □ mild □ moderate □ severe
   # wks ____________________
   Drug withdrawal therapy □ yes □ no
   If yes, specify _______________________________________

Section D: MEDICAL PROBLEMS

1. Did the infant experience any medical problems? □ yes □ no
   If yes, complete the following section.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Check all that apply</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prematurity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jaundice</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeding problems.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RDS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICH</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. Did the infant experience any other medical problems? □ yes □ no
   If yes, specify. _______________________________________

_________________________________________________________________
3. Was this infant discharged to: ☐ Parental home ☐ Foster home
☐ Sunny Hill (mother) ☐ Sunny Hill (Ministry)

Section E: BREAST FEEDING

1. Is this mother breast feeding her child? ☐ yes ☐ no
   If yes, complete the following section.
   (a) Maternal medications with BF? ☐ yes ☐ no
       If yes, specify: ________________________________

   (b) Infant side effects to medications? ☐ yes ☐ no
       If yes, specify: ________________________________

   (c) Formula feeding? ☐ yes ☐ no
       If yes, name: ________________________________
       Start date (MM/DD/YY): ________________________
       Stop date (MM/DD/YY): ________________________

   (d) Solids? ☐ yes ☐ no
       Start date (MM/DD/YY): ________________________
       Stop date (MM/DD/YY): ________________________

   (e) Feeding problems? ☐ yes ☐ no
       If yes, specify: ________________________________
       ________________________________
APPENDIX 4:
HEPATITIS C VERTICAL TRANSMISSION STUDY PAEDIATRIC FOLLOW-UP QUESTIONNAIRE

Infant Study ID Number: [Blank]

HCV Vertical Transmission Study
Paediatric Data Form

Date of data form completion: (MM/DD/YY): [Blank]

Paediatric data form completed by: [Blank]

1. Date of birth of infant (MM/DD/YY): [Blank]

Section A: INFANT HEALTH (Birth to 6 months)

   If yes, give details:

2. ENT problems? [Blank] yes [Blank] no
   If yes, give details:

3. GI problems? [Blank] yes [Blank] no
   If yes, give details:

   If yes, give details:
**Section B: VIROLOGY**

<table>
<thead>
<tr>
<th>Date (MM/DD/YY)</th>
<th>HIV Culture</th>
<th>HIV PCR</th>
<th>HCV PCR</th>
<th>HCV AB</th>
</tr>
</thead>
</table>

**Section C: LABORATORY RESULTS**

<table>
<thead>
<tr>
<th>Date (MM/DD/YY)</th>
<th>AST</th>
<th>ALT</th>
<th>PT</th>
<th>PTT</th>
<th>Bili</th>
<th>Alb</th>
</tr>
</thead>
</table>

AST = aspartate aminotransferase (normal values: 5-30 U/L)
ALT = Alanine aminotransferase (normal values: 5-35 U/L)
PT = Prothrombin Time (11.1-12.6 sec)
PTT = Prothrombin Time (27.1-33.2 sec)
Bili = Bilirubin (normal values: 0-1.3 mg)
Alb = Albumin (normal values: 3.2-5.0 g)
APPENDIX 5: THE HEPATITIS C VERTICAL TRANSMISSION STUDY GROUP

Team Leader:

Dr. Deborah Money, MD, FRCSC, Assistant Professor, Head, Division of Maternal Fetal Medicine Department of Obstetrics & Gynecology, U.B.C. At Children's & Women's Health Centre of B.C

Team Members:

Dr. Mark Bigham, MD, FRCPC, Medical Consultant, Canadian Blood Services
Dr. Kim Butt, MD, FRCSC, Perinatologist, Fredericton, New Brunswick
Ms. Lesley Cole, RN, BSN, Project Coordinator, Division of Maternal Fetal Medicine
Mr. Kevin Craib, BC Centre for Excellence in HIV/AIDS
Dr. Simon Dobson, Clinical Associate Professor, UBC, Department of Pediatrics
Dr. Patrick Doyle, Consult Pathologist, Division of Medical Microbiology and Infection Control
Dr. Mel Krajden, Associate Professor, UBC, Director, BC Centre for Disease Control
Ms. Fiona Liston, Project Coordinator, Division of Maternal Fetal Medicine
Dr. Paula Lott, Obstetrics & Gynecology Resident, UBC
Dr. Fergal Magee, Clinical Assistant Professor, UBC, Department of Pathology
Dr. Chester Morris, MD, M.Sc, Director, HIV/AIDS Programs, Millwood, Virginia
Dr. David Patrick, Associate Professor, UBC, Director, UBC Centre for Disease Control
Dr. Vesna Popovska, Research Program Coordinator, Division of Maternal Fetal Medicine
Ms. Valencia Remple, BSN, MScN, PHD Candidate, Research Program Coordinator, BCCDC
Dr. Rick Schreiber, Clinical Associate Professor, UBC, Department of Pediatrics
Dr. Chris Sherlock, MD, FRCPC, Full Professor, UBC, Head, Virology and Infection Control
Dr. Eric Yoshida, MD, MHSc., FRCP(C), Associate Professor, UBC, Medical Director, BC Transplant Society, Division of Gastroenterology