SUBSTANCE ABUSE IN CANADA

2013

Licit and Illicit Drug Use **during Pregnancy:** Maternal, Neonatal and Early Childhood Consequences

By Loretta Finnegan
With A Call to Action by Franco Vaccarino and Colleen Dell

Canadian Centre
on Substance Abuse
Centre canadien **de lutte contre les toxicomanies**

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Maternal, Neonatal and Early Childhood Consequences

Prepared for the Canadian Centre on Substance Abuse

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Foreword

Every two years, the Canadian Centre on Substance Abuse (CCSA) produces a new report in the *Substance Abuse in Canada* series, with each edition shedding much-needed light on an important drug- and alcohol-related issue. The current report is devoted to drug use during pregnancy—more specifically, the maternal, neonatal and early childhood consequences of using substances ranging from tobacco and alcohol, to marijuana, cocaine and heroin. Through this installment, we hope to bring the challenges faced by pregnant women "out of the shadows" so we can better meet their needs and those of their children.

While this latest report covers a variety of topics, an important aim for CCSA was to ensure that it summarizes the latest knowledge in the biomedical literature pertaining to drug use and abuse during pregnancy. Through the work of CCSA's Scientific Advisory Council (SAC) and the leadership of Dr. Franco Vaccarino, Professor of Psychiatry and Psychology at the University of Toronto, CCSA had the good fortune to connect with Dr. Loretta Finnegan, a world-renowned expert in the fields of women's health, pediatrics and perinatal addiction. Dr. Finnegan authored the report and took the lead in researching it. We are deeply grateful for her contributions and fortunate to have been able to draw on her decades of experience on this complex issue.

Women who use drugs, alcohol and tobacco already face many health and social challenges. These challenges are further compounded during pregnancy, when substance use can profoundly affect the earliest stages of human development and have adverse outcomes that carry into early childhood and beyond. Clearly, we know that drug use has impacts on many lives. During pregnancy it affects the lives of the mother and child. Drug use also affects — and is affected by — their family, the larger community in which they live and even society as a whole through interactions with our healthcare and social systems. This report explores the full spectrum of impacts.

One of the important — but arguably less broadly recognized — impacts pertains to the biomedical consequences of drug use and abuse during pregnancy. An important driver for this report was to ensure an up-to-date understanding of this area, as it is vital that professionals providing health care and support to pregnant women are well-informed about the latest evidence. This perspective is considered as part of the educational, motivational and tailored tool kit that treatment providers can employ to connect with women during their pregnancy — a period when women are more likely to seek care and support from the health community.

Pregnancy is also a period when women might be more motivated to address the potential harms associated with their drug use. Because of this potential, it was considered important that the report inform and educate treatment providers about what is happening biologically to the fetus. We also took care to provide information about the measures that can be taken on the part of a pregnant woman and her community to reduce the harms to both the mother and her fetus.

A further catalyst for the approach taken in the present report derives from learnings in the mental health field. The treatment provider can relay information to the mother on the biological context of substance use in pregnancy. This information can help prevent the mother feeling any sense of blame and judgment, which feeling could lead to her inaction.

The biomedical focus of the report did not permit a comprehensive, in-depth analysis of the many complex psychosocial factors associated with drug use during pregnancy. The report does, however, include an important chapter relating to psychosocial issues, as well as a section highlighting the value of a setting that provides a more holistic and comprehensive approach to care. This information on the setting for care underscores the importance of psychosocial themes such as those related to victimization that were included in the report. It also stresses the central role played by the family and community in any treatment response or prevention effort. The Call to Action found at the end of the report encourages ongoing efforts to integrate biomedical and psychosocial approaches to care for women's drug use, particularly during pregnancy.

Acknowledgements

To meet our goals of producing a report with a broad-based international perspective, the report was not designed to be country-specific or to focus only on the state of affairs in Canada, although it does highlight some Canadian data. For this reason, Dr. Finnegan, the report's author, was a strong fit in her capacity as a world expert and she has provided a comprehensive, globally relevant report on the impacts of drug use during pregnancy on the fetus and on the infant.

There are a number of actions we need to take to address the challenges. This report is an important reminder of the need to continue to build our knowledge base as it pertains to the Canadian context. Some of this work will involve closing gaps in the knowledge pertaining to Canada-specific issues and some of it will involve adapting the knowledge derived from the international context to a Canadian context. But by concentrating our efforts on the areas identified in the Call to Action — among them, ensuring clinicians and their clients have access to the latest evidence and adopting a more holistic and multidisciplinary approach to treatment and prevention — we will be able to bring real change to frontline practices and to community responses, and we will help countless lives in the process.

Beyond the invaluable work performed by Dr. Finnegan and Dr. Vaccarino, an initiative of this scope would not be possible without the contributions of many knowledgeable researchers and clinical experts. I would like to take this opportunity to thank the members of CCSA's SAC for their review of this report and their contributions to it; as well as Dr. Colleen Anne Dell, Research Chair in Substance Abuse at the University of Saskatchewan, who co-authored the recommendations outlined in the Call to Action chapter together with Dr. Vaccarino. I must also acknowledge the external reviewers who helped finalize the report, including Dr. Peter Selby, Clinical Director of the Addictions Program at the Centre for Addiction and Mental Health, and Dr. Gideon Koren, Director of the Motherisk Program at Toronto's Hospital for Sick Children. Finally, it goes without saying that CCSA is indebted to Dr. Amy Porath-Waller, Senior Research and Policy Analyst, for her exceptional leadership and management of this report together with Dr. Vaccarino, from inception to completion, and to everyone involved in the design and production of this report.

Their contributions were invaluable.

Rita Notarandrea
Deputy Chief Executive Officer
Canadian Centre on Substance Abuse

Foreword

Non-medical abuse of drugs can occur at any stage of life. When such exposure occurs during pregnancy and in the post-natal phase, it raises understandable concern about the impact on the health of the mother and child, as well as possible long-term consequences for brain development in the new infant. As individuals our concerns are immediate and heartfelt, and yet as a society we have in many respects turned a blind eye to this tragic state of affairs. Women in the greatest need, arising in part from a dependency on illicit drugs, often have limited options for the long-term care they require.

We can hope that publications such as this *Substance Abuse in Canada* report, which summarizes new and sophisticated research and clinical developments concerning maternal, neonatal and early childhood consequences of drug use during pregnancy, indicate that the tide is turning. Thanks to the efforts of a new cohort of researchers who appreciate the complex biological and social factors that give rise to addiction, there are real prospects for a much better scientific understanding of addiction as a chronic disorder that requires new and integrated treatment strategies for it to be addressed effectively.

The urgency to deal effectively with drug use during pregnancy arises from the widly appreciated position that most aspects of our health and well-being are shaped by events that influence biological and psychological development early in life. Indeed, it may be argued that a probing analysis of addiction from the perspective of human development holds the key to the eventual understanding of this disorder.

Paralleling these laudable long-term goals are many more immediate challenges such as:

- The gendered aspects of drug use during pregnancy with the attendant exacerbation of stigma;
- The relative impact of the adverse consequences of licit drugs such as alcohol and tobacco, as distinct from more high profile illicit drugs including cocaine, methamphetamines and heroin; and
- The compromised nutritional status of the mother and child during formative periods of development.

Clearly, simple approaches to this most complex form of human disorder are destined to failure.

The Canadian Institutes of Health Research and NeuroDevNet, a network of centres of excellence in brain development, recognize that complex medical conditions, including addiction and mental ill-health, can be best understood from a multidisciplinary perspective that recognizes the biological, social and environmental determinants of such disorders. Accordingly, we applaud the initiative of the Canadian Centre on Substance Abuse (CCSA) for its invaluable work bringing evidence-based knowledge about issues of critical importance to the health impacts of addiction to a broad cross-section of Canadian society.

For its part, the Institute of Neurosciences, Mental Health and Addiction remains committed to the support of research into all aspects of addiction, with the explicit goal of improving the understanding and treatment of substance abuse disorders in their many and varied forms. NeuroDevNet is very aligned with this stance and one of its key research projects is to understand how the fetus is impacted by exposure to ethanol and to diagnose and treat children who have been affected by ethanol during the early formation of the brain. It is clear that no level of embryonic exposure to ethanol or illicit drugs can be thought to be safe.

Hopefully, the combined goals of an informed society and a multipronged research effort committed to innovative strategies to address complex medical problems can improve the treatment of addiction in the near term for both mother and child alike.

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Introduction

Launched in 2005, the *Substance Abuse in Canada* series highlights key contemporary issues related to substance abuse along with specific areas for action in both policy and practice. Developed through analyses and reviews of the latest research evidence, each *Substance Abuse in Canada* report is intended for a broad audience that includes policy makers, program development personnel, researchers, educators and health professionals. Health journalists also make up an important readership of this report as they can help raise the public profile of the issues and help create the impetus for change.

This fourth *Substance Abuse in Canada* report addresses the medical and obstetrical consequence of drug abuse and dependency in pregnant women as well as the short- and long-term effects prenatal exposure to drugs can have on the development of their children. (Although we lack a large research portfolio in the area of childhood outcomes, studies indicate what can be expected when infants are exposed to drugs in utero.) This report also details the various treatment approaches essential to avoiding or reducing adverse outcomes in women who are pregnant and using substances and their infants, which includes comprehensive prenatal care and medication-assisted treatment. Finally, it concludes with a Call to Action that draws upon the themes explored throughout the earlier chapters.

It should be noted that this report is not meant to be a systematic review of this topic area; instead, it is intended to provide readers with a high-level overview of this important health issue. The next report in the *Substance Abuse in Canada* series, to be published this coming spring, is a companion to the current report. It will focus on influences in childhood and adolescence that can affect later life substance abuse and the implications an understanding of those influences has for prevention and treatment.

A stigmatizing issue

Women's drug abuse is a major public health problem in Canada and around the world. Too often have we heard dramatic statements from physicians and nurses about the growing numbers of pregnant women who use illicit substances, accompanied by descriptions of infants who suffer from prenatal exposure to drugs.

Women who use drugs—especially pregnant women—are more heavily stigmatized than their male counterparts. This stigmatization makes them generally reluctant to "emerge from the shadows" and seek help for their problems. Even when they do, they tend to face significant barriers to obtaining appropriate medical and obstetrical services, from misinformation to denial and even inaction on the part of healthcare professionals. Such attitudes need to change, especially given that substance dependence is considered a chronic, relapsing brain disease that should be evaluated and treated in the same way as any other chronic disease.

THE SERIES TO NOW

The first *Substance Abuse in Canada* report, *Current Challenges and Choices*, examined a variety of topics, including the prevention of alcohol problems, alternative sanctions for cannabis use and possession, drug-impaired driving, and the abuse and diversion of prescription medication.

The second report, *Focus on Youth*, looked at the prevalence of substance use and its associated harms among young people, exploring the underlying neurobiology of substance use in adolescence and identifying existing gaps in youth-centric services.

The third edition, *Concurrent Disorders*, focused on the co-occurrence of mental health and substance abuse problems, examining the interconnections between addiction and mental illness, the tremendous costs concurrent disorders places on Canada's healthcare system, and why treating these complex cases requires new and innovative approaches.

Addressing the complex challenges related to the causes and outcomes of drug dependency in pregnant women requires a broad understanding of not only the medical aspects of addiction but also its psychological and sociological elements. A multifactorial and multidisciplinary approach is therefore needed to help women break free from their addictions and prevent the occurrence of negative consequences for themselves and their offspring.

Addiction is just the beginning

Whether licit or illicit, psychoactive drugs act primarily upon the central nervous system, altering brain function and resulting in

changes in perception, mood, consciousness and behaviour. They provide pleasure and ameliorate pain. And they can also cause physical dependence and tolerance, with many individuals finding they need to increase their dosage over time to achieve the same effects.

Regardless of the pharmacological properties of the drugs used, the characteristics of the person taking them and the consequences of continued drug abuse combine to produce a multifactorial and exceptionally challenging condition for any individual, especially for pregnant women. Compulsive drug use is only part of the picture; factors such medical complications, family dysfunction, legal problems, educational deficits, low socioeconomic status, psychiatric disorders, social issues, and physical and sexual abuse can all be involved and affect the future development of the child.

Putting knowledge into practice

Although much progress has been made in the field of addiction medicine over the past few decades, the latest scientific advances have not yet been fully translated into real-world practice, where they are needed most. Continued attention to the most recent evidence-based studies is essential to providing the best possible care and support for women who are addicted and to assessing the overall immediate and long-term effects of in utero drug exposure in their children. We also need to increase funding as well as research and clinical capacity in the field to further define this complex issue.

TERMINOLOGY NOTES

Several of the terms used in this document have specific and distinct clinical significance, but to avoid repetition have been used as equivalents. Unless otherwise noted, the definitions below are based on those provided in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR).

- **Addiction:** Generally applied to patterns of heavy use of psychoactive drugs. While addiction has been replaced technically by the more specific term "substance dependence," it continues to be used widely. Addiction is generally thought of as compulsive use leading to physical symptoms of withdrawal when use is discontinued. For that reason, it is often equated with physical dependence.
- **Substance dependence*:** Also referred to as "drug dependence," this constitutes a cluster of cognitive, behavioural and physiological symptoms indicating continued substance use despite the occurrence of significant substance-related problems. It involves a pattern of repeated self-administration that usually results in tolerance, withdrawal and compulsive drug-taking behaviour.
- **Substance abuse*:** Also known as "drug abuse," this term refers to a maladaptive pattern of substance use resulting in recurrent and significant adverse consequences related to the repeated use of a drug. Substance abuse is not characterized in terms of tolerance and withdrawal; instead, it includes only the harmful consequences of repeated use (for example, when such use becomes physically hazardous; causes failure to fulfill obligations at work, school or home; or creates legal, social or interpersonal problems). Although it is often taken to also mean substance use, Jaffe (1985) clarifies that "drug abuse refers to the use, usually by self-administration, of any drug in a manner that deviates from the approved medical or social patterns within a given culture."
- **Withdrawal:** Withdrawal occurs when the chronic intake of a substance is abruptly discontinued.
- **Tolerance:** The need to use an increasing amount of a drug to attain the desired effects, or the decreased intensity in effects experienced with the continued use of the same amount of the substance.
- **Intoxication:** The development of a reversible, substance-specific syndrome during or after substance use. It becomes a clinical problem when significant maladaptive patterns of behaviour lead to distress and impairment.
- **Morbidity:** From the Latin word "morbidus" (meaning "sick" or "unhealthy"), this term refers to a state of disease or disability from any cause. It can be used to refer to the existence of any form of disease as well as the degree to which a disease affects an individual.

* The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) combines the DSM-IV-TR categories of "substance abuse" and "substance dependence" into a single disorder measured on a continuum from mild to severe (American Psychiatric Association, 2013).

As this report outlines, the best public health result for women who are pregnant and using substances and babies exposed to maternal drug use can be obtained only once the barriers to effective intervention have been removed, allowing women to finally receive the services they need in supportive, nonjudgmental and multidimensional treatment settings.

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1 Epidemiology of Maternal Drug Use

Epidemiology is the study of the distribution and determinants of health-related states or incidents—and is extremely important to consider when examining the issue of substance use and addiction. The epidemiology of drug use has typically focused on identifying specific risk factors at the following levels: individual (e.g., genetic factors, high-risk behaviours), family (e.g., child abuse), community (e.g., availability of drugs) and societal (e.g., policies, laws). Through the data gathered from this research, which includes cross-sectional studies, longitudinal studies and clinical experiments, a foundation has been created for better understanding the extent of drug use, abuse and dependence; informing basic, clinical, treatment and services research; and developing drug-prevention strategies (Compton et al., 2005).

1.1 Prevalence of drug use in pregnant women

1.1.1 Canada

Details on the epidemiology of drug use among pregnant women can be gleaned from a variety of sources. For example, there is the 2006–2007 Maternity Experience Survey, which surveyed Canadian women aged 15 and older who had a singleton live birth during a three-month period preceding the 2006 Census of Population. Its results revealed that 10.5% of women smoked cigarettes daily or occasionally during the last three months of pregnancy; 10.5% reported drinking alcohol during their pregnancy; and 1% used street drugs during pregnancy (Public Health Agency of Canada, 2009).

Data at the national level was also provided by the 2008 Canadian Perinatal Health Report, which found that 11% of pregnant women consumed alcohol and 13% smoked cigarettes during the past month. An additional 5% of pregnant women also reported illicit drug use during pregnancy. However, given the systematic under-reporting of substance abuse, the actual prevalence rates are probably higher (Ordean & Kahan, 2011).

The Canadian Community Epidemiology Network on Drug Use (CCENDU) is a surveillance project that promotes networking among Canadian agencies with common interests in local, national and international drug trends. In 2010, CCENDU partner agencies collected data on alcohol and drug use in seven cities across Canada, examining rates of substance use

At a Glance

- Epidemiology is the study of the factors related to and distribution of health-related states or incidents among different groups of people.
- Tobacco and alcohol are the most common substances used by pregnant women in Canada and the United States.
- The use of illicit drugs by pregnant women is comparatively lower than for tobacco and alcohol, yet still represents a significant percentage of use in Canada and the United States.
- Cannabis is the most common illicit substance used among pregnant women.
- Substances used during pregnancy vary by the race and ethnicity of women.
- Children of parents with untreated substance use disorders are at greater risk of developing their own substance-related problems later in life.

prevalence, treatment, enforcement, prevention, morbidity and mortality. Although information on pregnant women represented just a fragment of the data collected, the 2010 CCENDU site reports did include the following highlights:

- In Saskatoon, respondents reported observing an increase in the number of women using various substances (namely alcohol, cocaine/crack and cannabis) during pregnancy. Survey respondents also indicated a lack of services to support pregnant women with substance use issues.
- In Winnipeg, the rate of maternal alcohol consumption during pregnancy ranged from 10.7% to 12.5% for the years 2003 through 2006. During this same period, the average rate of maternal smoking during pregnancy was 21% (and as high as 43% in some of Winnipeg's 12 Community Areas).

In addition, a report from the Reproductive Health Working Group in Alberta indicated that 2.3% of women who gave birth to live infants in 2006 reported using street drugs while pregnant, with cannabis being the most commonly used substance (Porath-Waller, 2009).

With regard to the country's population as a whole, the 2011 edition of the Canadian Alcohol and Drug Use Monitoring Survey found that among Canadian women of childbearing age (i.e., 15–44 years), 76.7% reported past-year consumption of alcohol, nearly 11% reported past-year use of cannabis, and 2.1% reported past-year use of illicit drugs such as cocaine, ecstasy, speed, hallucinogens (including salvia) and heroin (Health Canada, 2012).

1.1.2 United States

In the United States, the 2010 National Survey on Drug Use and Health (NSDUH) found that 4.4% of pregnant women aged 15–44 reported illicit drug use[1] during the past 30 days. In contrast, the prevalence of illicit drug use among non-pregnant American women in the same age group was 10.9% (Substance Abuse and Mental Health Services Administration [SAMHSA], 2011).

In addition, the 2010 NSDUH also found that among pregnant women aged 15–44:

- 10.8% reported past-month alcohol use;
- 3.7% reported past-month binge drinking;[2]
- 1.0% reported past-month heavy drinking;[3]
- 10.1% reported binge drinking in the first trimester of pregnancy (i.e., during the embryonic and early fetal stages); and
- 16.3% reported past-month cigarette smoking (with even higher rates among pregnant women in the 15–25 age group, where 22.7% smoked cigarettes).

Marijuana is the most commonly used illicit drug among pregnant women. A review of NSDUH data from 2002 to 2007 found that 4.6% of women aged 18–44 reported past-month marijuana use during the first trimester, 2.9% reported use in the second trimester and 1.4% used marijuana in the third trimester of pregnancy (SAMHSA, 2009).

Data collected from NSDUH surveys conducted between 2002 and 2010 also indicate that substance use during pregnancy varies by race and ethnicity (SAMHSA, 2012a). Reviewers found that pregnant white women had higher rates of cigarette smoking (21.8%) than both pregnant African-American women (14.2%) and pregnant Hispanic women (6.5%). Levels of self-reported alcohol use were fairly similar between pregnant white women and pregnant African-American women (12.2% and 12.8%, respectively), while Hispanic women had the lowest rates of alcohol use during pregnancy (7.4%). Finally, African-American women were found to have the highest rates of illegal drug use during pregnancy (7.7%), followed by pregnant white women (4.4%) and pregnant Hispanic women (3.1%).

1.2 Prevalence of drug use in non-pregnant women with children

The children of parents with untreated alcohol use disorders are at far greater risk of developing their own problems with alcohol and other substances later in life (SAMHSA, 2012b). Therefore, for the purposes of developing appropriate prevention and treatment strategies, it is also important to look into the prevalence of drug use among women who are no longer pregnant but still have children living in their households. According to a review of NSDUH from 2005 to 2010, approximately 7.5 million American children under the age of 18 (or 10.5% of all children) lived with a parent who had experienced an alcohol use disorder in the past year (SAMHSA, 2012b). Of these children, 6.1 million lived with two parents (with either one or both experiencing an alcohol use disorder in the past year) and the remaining 1.4 million children lived in a single-parent household.

Using data from the 2003 NSDUH, Simmons and colleagues (2009) sought to identify maternal risk factors by examining the prevalence of past-year illicit drug abuse or dependence among American women with children less than 18 years of age. They found that approximately 2% of the mothers reported illicit drug abuse or dependence, with these women more likely to be unmarried, have stress in their lives, have poorer health status and meet criteria for mental illness. Similarly, studies on female substance abuse treatment patients have found that women tend to have lower education levels and employment rates than men as well as a lower average age at admission into treatment. These characteristics generally lead to a lack of preventive and treatment services (Gomberg, 1993; Chou, 1994).

[1] Illicit drugs include marijuana, cocaine (including crack), heroin, hallucinogens, inhalants and the non-medical use of prescription psychotherapeutics.
[2] Binge drinking is defined as having five or more drinks on the same occasion at least once during the past 30 days.
[3] Heavy drinking is defined as having five or more drinks on the same occasion five times or more during the past 30 days.

LAUREN

Lauren is 17 and lives in Toronto. She has a younger brother and sister, both by different fathers. Her mother is addicted to crack cocaine. When Lauren was 10, her stepfather began sexually abusing her. He was also physically abusive of Lauren and her mother. It took Lauren a long time to summon the courage to tell her mother about her stepfather's late-night visits to her bedroom—and when she did, her mother did nothing about it. At just 12, she started drinking alcohol and smoking cigarettes as a way to escape. At 14, she ran away. Without a job, and resolved not to return home, she ended up living on the street. That's where she met 25-year-old Eric.

Lauren felt he genuinely cared for her: he provided her with food and clothes, and would listen to the stories of her abusive home life. As their relationship deepened, he convinced her to let him rent her a room at a hotel. Lauren became very attached to Eric. She believed they loved each other and felt indebted to him, so when he asked her to help pay for the room through prostitution, she agreed. That began years of working on the street, accompanied by cycles of abuse. Lauren became addicted to heroin and cocaine, and also used marijuana and amphetamines. She continues to depend on drugs to cushion the pain of her daily life.

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2 Medical and Obstetrical Consequences of Drug Use in Women

When non-medically prescribed drug use or abuse occurs in pregnant women, considerable morbidity can be expected for both the mother and her offspring. In particular, illicit drug use during pregnancy places the mother at increased risk of a variety of obstetrical complications, which are listed below according to time in the pregnancy:

- Early pregnancy loss;
- Abruptio placentae (premature detachment of the placenta from the wall of the uterus);
- Amnionitis (inflammation of the amnion, the thin membrane surrounding the fetus that contains the amniotic fluid);
- Intrauterine growth restriction;
- Placental insufficiency;
- Septic thrombophlebitis (a condition characterized by a venous clot, inflammation and infection);
- Pre-eclampsia (a sudden rise in blood pressure, excessive weight gain, generalized edema, proteinuria, severe headache and visual disturbances);
- Eclampsia (convulsions or coma occurring with pregnancy-associated high blood pressure);
- Late intrauterine death;
- Premature labour;
- Premature rupture of membranes; and
- Postpartum hemorrhage.

This chapter outlines the specific medical and obstetrical outcomes associated with the use of several different types of drugs, including opioids, cocaine, amphetamines, methamphetamines, cannabis, tobacco and alcohol.

2.1 Opioids

Opioids generally refer to morphine-like synthetic narcotics (e.g., heroin, methadone, oxycodone, propoxyphene) that produce the same effects as drugs naturally derived from the opium poppy (e.g., opium, codeine, morphine), which are collectively referred to as opiates. As pain relief is among these effects, opioids are some of the most common drugs taken during pregnancy. Although the onset and intensity of the effects will vary based on how the drug is taken and its formulation, all opioids have the potential for overdose, abuse, dependence and addiction.

Incidence of opioid abuse has been increasing at an alarming rate, especially among teens and young adults. In fact, the number of Americans abusing prescription medications has more than

At a Glance

- Women generally progress more quickly than men into alcohol dependence and other related medical problems, such as circulatory disorders, cirrhosis of the liver and hypertension, and have a higher rate of premature death.
- Women are also at greater risk of experiencing severe cocaine-related health problems compared to men.
- Women who abuse opioids may progress more quickly to addiction than men.
- Pregnant women with opioid addictions tend to seek out prenatal care late in pregnancy or not at all.
- Substance use during pregnancy increases the risk of various medical and obstetrical complications, such as early pregnancy loss, premature labour and postpartum hemorrhage.
- Amphetamines may reduce the production of breast milk and can be transmitted to the baby by nursing mothers.
- Heavy use of cannabis has been linked to decreased fertility among both women and men and an increased risk for a failed pregnancy.
- Tobacco smoking is associated with cancers of the ovaries and cervix, which may cause concern for a woman's reproductive health.
- Smoking can cause significant health risks for an infant and child, both in utero and postnatally through exposure to second-hand smoke.

doubled over the past decade, with more than 1.9 million new non-medical users aged 12 years or older of prescription pain relievers reported in 2012 alone (Substance Abuse and Mental Health Services Administration, 2013). Research has also shown that women who abuse opioids may progress more quickly to addiction than men. For instance, women are more likely than men to become addicted to heroin within one month of initial exposure (Hernandez-Avila, 2004). Women also escalate their use of heroin more rapidly and tend to become addicted within a shorter period of time (Anglin et al., 1987).

Opioid abuse can have a number of severe neurological consequences. Heroin, for example, has been shown to have negative effects on brain function, affecting attention span, memory and verbal fluency (Guerra et al., 1987; Kamboj et al., 2005). Studies have also found that heroin abusers exhibit impaired verbal function, visual-spatial analysis, impulse control and mental planning (Lee & Pau, 2002; Prosser et al., 2006; Davydov & Polunina, 2004). Such effects can seriously affect a person's ability to care for his or her own health and, in the case of pregnant women, for newborn children.

The chaotic lives of opioid-abusing women (e.g., sharing unclean needles for injection, turning to theft or prostitution to support their addictions) and the frequent lack of consistent prenatal care put them at risk of a variety of medical problems during pregnancy. In particular, heroin-abusing women may suffer from conditions such as anemia, bacteremia, septicemia, bacterial endocarditis, cellulitis, endocrinopathies, hepatitis, phlebitis, pneumonia, tetanus, tuberculosis, urinary tract infections and a number of sexually transmitted infections. Miscarriages are also prevalent in untreated heroin-addicted women. As well, the nutritional deficiencies resulting from the many medical complications associated with opioid use, overdose and withdrawal can be problematic for the developing fetus (Finnegan, 1976, 1981; Finnegan & Kandall, 1992, 2008, 2010). For example, intrauterine passage of meconium (a substance in the fetal gastrointestinal tract composed of mucous, bile salts and cellular debris) can occur as a sign of fetal distress. This distress might be related to the repeated exposure of the fetus to opioid withdrawal as well as the effects of withdrawal on placental function (Center for Substance Abuse Treatment, 2005; American Congress of Obstetricians and Gynecologists [ACOG], 2012).

Pregnant women with opioid addictions tend to seek prenatal care late in pregnancy (or not at all, arriving at the emergency department already in labour); miss their appointments; experience poor weight gain; or exhibit signs of sedation, intoxication or erratic behaviour. On physical examination by the physician, signs of opioid use might include track marks from intravenous injection, lesions from subcutaneous injections ("skin popping"), abscesses or cellulitis. Positive results of blood tests for human immunodeficiency virus (HIV) or hepatitis can also indicate substance abuse (ACOG, 2011a, 2012).

Additional risk factors that can alert obstetricians or family physicians to maternal drug abuse include an unexplained history of obstetrical or neonatal problems, homelessness, having a partner who is a drug user, a family history of drug abuse and a history of treatment with prescription drugs for chronic pain (Alto & O'Connor, 2011).

2.2 Cocaine

Cocaine use appears to affect women in different ways than men. First, women tend to use cocaine earlier in their patterns of concurrent addictions and move more quickly from their introduction to cocaine into abuse (Griffin et al., 1985; Mendelson et al., 1991; Haas & Peters, 2000). Women are also more likely than men to experience severe health problems related to cocaine use. It has been shown that chronic cocaine use can lead to potentially fatal myocardial alterations such as cardiac hypertrophy, fibrosis (scarring) and microangiopathy (Karch, 2005). Smoking crack cocaine produces more prolonged cardiovascular effects as well as higher cocaine plasma concentrations in women than in men (Evans et al., 1999). Women are also more likely to report headaches and trips to the emergency room following crack cocaine use (Dudish & Hatsukami, 1996).

Women's menstrual cycles affect how they experience the subjective effects of cocaine. The mood-altering effects of cocaine are experienced more strongly during the follicular phase of their menstrual cycle, when estrogen is high but progesterone is low. Later, in the luteal phase of the cycle when progesterone is higher, the effects of cocaine are not felt as strongly. It is suggested that progesterone plays a significant role in dampening the physical reaction to cocaine (Sofuoglu et al., 1999).

Cocaine use during pregnancy is associated with many adverse outcomes. For example, cocaine use can cause miscarriages in up to 38% of early pregnancies—most likely because of an increase in maternal plasma norepinephrine, which increases uterine contractility, constricts placental vessels and decreases blood flow to the fetus (Schempf & Strobino, 2008). In addition, placental abruption (the separation of the placenta from the uterus wall) accounts for up to 15% of the adverse effects experienced when cocaine is used during pregnancy—and is the primary reason why the incidence of stillbirth in cocaine-abusing mothers is 8% greater than that of the general population. More common with cocaine binging than with regular use, placental abruption is thought to be caused by vasospasm (the constriction of blood vessels) and hypoxia (decreased oxygen transfer to the tissues) of the placental bed (Bhuvaneswar et al., 2008; Schempf & Strobino, 2008).

Because cocaine stimulates uterine contractility, there is also an increased risk of premature rupture of membranes and preterm labour or delivery, conditions that affect 17–29% of pregnancies of cocaine-abusing women. Intrauterine growth restriction and low birth weight can be found in 22–34% of all infants exposed to cocaine in utero, secondary to the constriction of the uterine blood vessels that leads to intermittent hypoperfusion (a decrease in circulation of blood to the tissues) of the uterus and placenta. In addition, appetite is significantly suppressed by cocaine, contributing to poor maternal and fetal nutrition (Schempf & Strobino, 2008).

Clinicians should observe pregnant cocaine users for hypertension, hyperthermia (greatly increased body temperature), abdominal pain and increased heart rate—and in the case of heavy cocaine use, arrhythmias, myocardial infarction, respiratory failure, stroke and seizures (National Institute on Drug Abuse, 2010). Hyperthermia mediated by vasoconstriction (constricted blood vessels) or the hyper-metabolic state of cocaine use may also be observed; this should be considered an effect that might counteract the expected physiologic vasodilatation (and normal lowering of blood pressure) from increased levels of progesterone. Hyperthermia from multiple causes (including pyelonephritis and other infections) has been linked with prematurity, low birth weight and, in rare cases, fetal death (Bhuvaneswar et al., 2008).

Migraine headaches, which become more prevalent during pregnancy generally, are also more common among cocaine users. Dyspnea (shortness of breath) during pregnancy, owing to a decreased lung tidal volume from the compression of the lower lung fields by the expanding uterus, can also be indicative of so-called "crack lung" or pneumonitis in a cocaine user—a condition characterized by fevers, pulmonary infiltrates and leukocytosis (Bhuvaneswar et al., 2008).

2.3 Amphetamines

Commonly used as drugs of abuse, amphetamines are powerful central nervous system stimulants with a profound ability to increase wakefulness and focus. Amphetamines also increase the rate of release of neurotransmitters such as norepinephrine, serotonin and dopamine. (At the same time, they also inhibit re-uptake of these neurotransmitters.) Drugs in the amphetamine family can serve a variety of traditional medicinal purposes; methylphenidate, for example is a very effective treatment for attention deficit hyperactivity disorder.

As with cocaine, women experience the euphoric and addictive effects of amphetamines more strongly during the early follicular phase of their menstrual cycles. Women in one study also reported craving and enjoying the effects of amphetamines more during the early phases of menstruation, particularly in times of high estrogen levels (Justice & deWit, 1999).

Amphetamine use, particularly among young pregnant patients, appears to be increasing (Cox et al., 2008). However, it does not seem to be associated with any consistent increase in congenital abnormalities above the background 3% population risk. Furthermore, there is no evidence of a consistent syndrome associated with first trimester amphetamine use (Smith et al., 2006; Briggs et al., 2008).

That said, amphetamines have been found to inhibit the release of prolactin, potentially reducing a mother's supply of breast milk (Anderson, 2010). In addition, the concentration of amphetamines found in breast milk is 2.8 to 7.5 times higher than those found in maternal plasma, with infants who ingest the breast milk of women using amphetamines exhibiting increased irritability and agitation (Briggs et al., 2008; American Academy

of Pediatrics Committee on Drugs, 2001). Amphetamines purchased illegally often contain a mixture of substances with unpredictable harmful effects on the woman and her infant; therefore, women who are actively using amphetamines should not breastfeed.

2.4 Methamphetamines

Methamphetamine is a more potent stimulant drug than its parent compound, amphetamine. It is the only illegal drug that can be easily made from legally obtained ingredients such as pseudoephedrine. Its widespread availability is fuelled by a lower cost compared to other illicit drugs of abuse as well as its ability to be produced in both large and small clandestine laboratories (Good et al., 2010; ACOG, 2011b).

The consequences of long-term abuse of methamphetamines—in particular, crystal meth and speed—include addiction, anxiety, confusion, insomnia, memory loss, weight loss, severe dental problems, depression and violent behaviour (Winslow et al., 2007). Long-term users can also display psychotic symptoms such as paranoia, delusions, and visual and auditory hallucinations—and these symptoms can persist for months or years after a person has stopped using the drug. Brain-imaging studies of long-term methamphetamine users have shown severe structural and functional changes in the areas of the brain associated with emotion and memory (ACOG, 2011b).

Methamphetamine addiction can be especially harmful to the pregnant woman and her baby, with a 2005 study by the University of Toronto finding that taking just one dose of methamphetamine during pregnancy can have dire consequences for the baby (Adlaf et al., 2005).

Of the various conditions associated with methamphetamine use, most worrisome for pregnant women are increased blood pressure and heart rate; exhaustion; poor personal and dental hygiene; mental disorders such as psychosis and depression; and decreased cognitive abilities (e.g., memory, judgment, reasoning, verbal learning). Pregnant methamphetamine users also tend to have a decreased appetite, which can lead to poor nutrition.

A study conducted by Good and colleagues (2010) in California examined the demographic characteristics and clinical morbidity of 276 methamphetamine-exposed pregnancies compared to 34,055 control patients in the general obstetric population in a tertiary care, academic medical centre. Factors that were significantly associated with methamphetamine use were:

- Age younger than 20 years;
- Non-Hispanic white ethnicity;
- Married;
- Preterm delivery;
- Low Apgar scores; and
- Caesarean delivery.

The women using methamphetamines were also more likely to be unemployed, use other abusive substances and have higher rates of domestic violence when compared with the control population.

2.5 Cannabis

Three products can be derived from the cannabis plant (*cannabis sativa*): marijuana, which is made from dried flowers and leaves; hashish, which is made by drying and pressing the plant's resin into small blocks; and hash oil, the most potent of the three, which is a thick oil obtained from hashish.

The terms "marijuana" and "cannabis" are most frequently used to refer to this drug, which is used to heighten perception and affect a person's mood. Its pharmacologically active ingredient, delta-9-tetrahydrocannabinol (THC), influences brain chemistry in a way similar to alcohol, affecting memory while slowing thinking and reflexes. Long-term effects of marijuana use may include decreased motivation as well as harmful effects on the brain, heart, lungs and reproductive system. People who smoke marijuana are also at increased risk of developing cancer of the head and neck (Diplock & Plecas, 2009).

Heavy use of marijuana has been linked to decreased fertility in both men and women. In females, there is evidence that cannabis use might disrupt the menstrual cycle. In males, cannabis is thought to decrease sperm quality and testosterone levels. These factors can make it difficult for a woman to become pregnant when either partner is using marijuana (National Cannabis Prevention and Information Centre [NCPIC], 2011).

More alarmingly, a number of studies suggest that marijuana is a teratogen (i.e., something that can hinder the normal growth and development of a fetus) and that intrauterine exposure to cannabis might result in risks for the fetus. THC is known to pass from the mother to the fetus through the placenta and can be

DIANE

Diane's parents often fought, not only verbally but physically as well. One night during a particularly intense confrontation, Diane's father accidentally killed her mother. Diane was two. She and her sisters were entrusted to the care of their maternal grandmother, who lived in a small house with Diane's aunts. Growing up, Diane gradually became aware that her grandmother and aunts engaged in prostitution; her older sisters were eventually recruited as well. When Diane was 12, her sisters began grooming her to follow in their footsteps, assuring her she could make lots of money. Afraid and anxious, Diane ran away from home. She lived on the streets, stealing to subsist and getting clothes and food from friends when they were able to provide them. More than once, guys tried to convince her to engage in prostitution, but she resisted.

Vaughn, a 27-year-old in the periphery of her social circle, was especially persistent. One night after Diane had been binge drinking with her friends, he injected her with heroin and posted explicit pictures of her on the Internet. After that episode, he used threats and humiliation to force her to perform sexual acts, keeping her locked up in an apartment for several months until she finally relented and agreed to work the streets.

Today, Diane is addicted to heroin and pregnant, unsure who is the father. She has ulcers and abscesses from injecting heroin under her skin, and she has been treated for gonorrhoea. She is very worried about how her drug addiction will affect her unborn baby—and feels hopeless about ever escaping the life she's caught in.

found in the newborn's body for up to a month after a single use. As such, the fetus is affected by any amount of marijuana taken by the pregnant woman, placing it at greater risk for potential complications. In addition, any form of smoking can disrupt the supply of oxygen and nutrients to the fetus, which can result in restrictions to the growth of the fetus (including overall length, foot length, head size and body weight) and, in rare cases, premature birth, miscarriage and stillbirth (NCPIC, 2011).

A study conducted by El Marroun and colleagues (2009) examined the relationship between maternal cannabis use and fetal growth until birth in a population-based sample. Approximately 7,452 mothers in the Netherlands had fetal growth determined by ultrasound measures during the early, middle and late stages of pregnancy. Birth weight was also recorded. This study showed that, compared to non-exposed fetuses, maternal cannabis use during pregnancy was associated with growth restriction during mid- and late pregnancy as well as newborns with lower birth weights and smaller head circumferences. The growth reduction was most pronounced for fetuses exposed to continued maternal cannabis use during pregnancy, suggesting a dose-response relationship. Paternal cannabis use was not associated with fetal growth restriction.

A large international study of more than 3,000 pregnant women in Australia and New Zealand detailed the most common risk factors for preterm birth. Among the factors delineated was that women who used marijuana prior to pregnancy more than doubled their risk of premature birth (Dekker, 2012). Similarly, a 2006 study conducted by Vanderbilt University Medical Centre in Tennessee showed that women who smoke marijuana are at greater risk for a failed pregnancy because the drug can upset the chemical balance necessary for the safe passage of the embryo from the fallopian tube down to the uterus, potentially resulting in an ectopic (tubal) pregnancy or miscarriage (Dey et al., 2004).

2.6 Tobacco

The causal link between cigarette smoking and lung cancer has been well established: almost 80% of all lung cancer deaths in female smokers are attributable to smoking and, by 1987, lung cancer had surpassed breast cancer as the leading cause of cancer-related deaths in American women (Office on Smoking and Health, 2001; Parkin et al., 2005; Centers for Disease Control and Prevention, 2006).

Research also suggests women are more susceptible than men to the cancer-causing compounds found in tobacco smoke. A study of lung cancer patients in Poland revealed that women developed lung cancer at younger ages despite consuming fewer cigarettes per day and smoking for a shorter duration than men (Radzikowska et al., 2002). This is supported by the finding that the gene for the gastrin-releasing peptide receptor (which, when activated, has a demonstrated association with the proliferation of bronchial cells) is located on the X chromosome (Shriver et al., 2000). Similarly, females' pulmonary systems may be more swiftly compromised by long-term smoking, putting women smokers at greater risk of death due to chronic obstructive pulmonary disease (Jonas et al., 1992).

For women who are pregnant or planning to become pregnant, cancers of the reproductive system associated with smoking must be considered a significant health concern. Studies have suggested that tobacco use is associated with a higher incidence of both ovarian and cervical cancers. Cigarette smoking, however, also appears to interact with women's systems in unique ways, possibly reducing the risk of endometrial cancer and causing other estrogen-associated effects (Kay et al., 2010). In studies that controlled for the effect of human papillomavirus (HPV) infection (a recognized cause of the majority of cervical cancers), tobacco use was found to increase the risk of cervical cancer among women who were already HPV-positive. Tobacco use was also a more significant risk factor for cancer of the cervix than other environmental risk factors such as diet, sexual history and oral contraceptive use (Plummer et al., 2003).

A direct relationship between cigarette smoking and breast cancer has not been clearly established, with many studies failing to find tobacco use to be a significant risk factor for the disease (International Agency for Research on Cancer, 2004). Other evidence, however, suggests such as association may exist; in four of eight case-control studies reviewed in Japan, moderate or strong associations between smoking and breast cancer risk were observed (Nagata et al., 2006). More recently, Gaudet and colleagues (2013) analyzed data from a large cohort of American women and conducted a meta-analysis of their results with those published from 14 other cohort studies. Their findings suggest that active smoking is associated with increased risk for breast cancer among women who initiated smoking before their first birth.

Overall, women who begin smoking at an early age and continue at high doses throughout their childbearing years are not only at higher risk for smoking-related diseases—their smoking could also result in significant health implications for the infant and child (both in utero and through exposure to second-hand smoke).

2.7 Alcohol

In general, women tend to progress more quickly than men into alcohol addiction and the development of the physiological consequences of alcohol abuse (Orford & Keddie, 1985; Randall et al., 1999; Diehl et al., 2007). There is also considerable evidence that women move more quickly from first use to addiction (Kay et al., 2010).

In addition, medical problems associated with alcohol use progress more swiftly in women. Female alcoholics have 50–100% higher rates of premature death than male alcoholics, with more female alcoholics dying from circulatory disorders and cirrhosis of the liver than their male counterparts (Ashley et al., 1977; Hill, 1982). Even with shorter durations of heavy drinking than their male counterparts, women have comparable incidence rates of diseases associated with alcoholism such as ulcer disease, gastrointestinal hemorrhage, liver disease, hypertension, obesity, anemia and malnutrition (Ashley et al., 1977).

Many women begin to use and abuse alcohol starting in their teenage years. By the time they reach the end of their childbearing years they will have caused considerable damage to their bodies and, potentially, those of their unborn children.

For more details on the obstetrical effects and early childhood outcomes of alcohol use during pregnancy, please refer to the section on fetal alcohol spectrum disorder in Chapter 4.

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3 Psychosocial Issues and Victimization in Pregnant Women Using Drugs

To address the issue of substance abuse in pregnant women, it is first necessary to understand why these women turn to alcohol and other drugs in the first place. The reasons, not surprisingly, are many. Among them are psychosocial issues and histories of victimization, both of which can prevent or make it extremely difficult for women to access the services and supports that would otherwise help them and prevent adverse consequences for their developing children.

3.1 Psychosocial issues

It is estimated that two-thirds of women with substance abuse problems also have concurrent mental health problems, with drug-dependent and alcohol-using women often manifesting psychiatric conditions such as anxiety, depression, post-traumatic stress disorder (PTSD) and panic disorder. And because pregnant women are susceptible to tremendous emotional changes, pregnancy is a time of heightened vulnerability to the exacerbation of pre-existing psychiatric condition (Cox et al., 1979; Evans et al., 2001).

Numerous studies in medical literature describe the co-occurrence of substance abuse and psychiatric disorders; for instance, the 2009 volume of this *Substance Abuse in Canada* series, *Concurrent Disorders*, describes the many ramifications of concurrent disorders.

3.1.1 Depression and anxiety

Based on the available data, affective disorders such as depression and anxiety are among the most common forms of mental illness in substance-abusing women. In a retrospective chart review of 276 opioid-dependent pregnant women, 42% had a diagnosis of depression and 42% had an anxiety disorder (Wachman et al., 2010). Another study of 174 opioid-dependent pregnant women conducted by Benningfield and colleagues (2010), who used cross-section data collected as part of the Maternal Opioid Treatment: Human Experimental Research (MOTHER) Study, found that more than 60% exhibited symptoms that resulted in a positive screen for one or more psychiatric diagnoses. Specifically, 48.6% endorsed symptoms of a mood disorder and 40% endorsed symptoms of an anxiety disorder at some point in the past 30 days. In addition, nearly one-third (32%) of the women reported symptoms consistent with major depressive disorder and 16% reported symptoms consistent with PTSD.

The study by Benningfield (2010) also found that the women with psychiatric co-morbidities had higher degrees of medical and social impairment than those without additional psychiatric diagnoses.

At a Glance

- About two-thirds of women with substance abuse problems have co-occurring mental health problems, such as depression, anxiety and post-traumatic stress disorder.
- A large proportion of women with substance abuse problems are also victims of physical abuse and sexual assault. Such victimization has been linked with various mental health outcomes, suicide and low self-esteem.
- Untreated psychiatric and substance use disorders can have negative health consequences for both the mother and child and can result in poor parenting, and child neglect or abuse.

Unless promptly and appropriately diagnosed and treated, depression can increase a pregnant woman's risk of:

- Pre-eclampsia (Kurki et al., 2000);
- Low infant birth weight and delivery complications (Steer et al., 1992);
- Poor weight gain and postpartum depression (Gotlib et al., 1989);
- Suicide (Lindahl et al., 2005); and
- Decreased maternal responsiveness, resulting in impairment of the infant's socio-emotional functioning and development (Weinberg & Tronick, 1998).

Women with low self-esteem who lack attachment to their unborn children during pregnancy also have a higher risk of developing postnatal depression (Priel & Besser, 1999), while women who suffered from depression during or after pregnancy have a greater prevalence of future depressive episodes (Beck, 2001).

It has also been shown that women suffering from depression tend to seek prenatal care on a less frequent basis (Kelly et al., 1999) and are more likely than non-depressed women to use alcohol, cigarettes and other drugs during pregnancy (Zuckerman et al., 1989).

A study by Cormier and colleagues (2004) looked at the physical and mental health consequences of alcohol and drug use by Canadian women and several subgroups of women, including elderly women, Aboriginal women and pregnant women. Among those who reported heavy drinking, 25.7% had felt sad or depressed in the previous two weeks. In addition, 15% of heavy-drinking women reported visiting a mental health professional in the previous 12 months and 18.6% had seriously considered committing suicide. Of the women who had considered suicide, 37.3% had attempted to take their own lives.

Exacerbation of such psychological problems can occur with the use of stimulants, especially among women. A study by Wisniewski and colleagues (2006) established an association between illicit drug use and higher concentrations of cortisol, which may lead to more depressive symptoms. This study found that among heroin and cocaine users, the association was more pronounced in women—and that female users with elevated cortisol concentrations were significantly more depressed than other participants in the study. (It should be noted that this mechanism is not yet fully understood because it is unknown whether high cortisol levels precede depression or are an associated effect.)

3.1.2 Other disorders

Depression and anxiety are not the only psychiatric conditions linked to substance-using women. The U.S. National Violence Against Women Survey (Tjaden & Thoennes, 2000) found that female crime victims suffering from PTSD are 17 times more likely to have major drug abuse problems than the general population. The study also revealed that individuals with a history of PTSD symptomatology make use of substance abuse inpatient services more frequently than their non-PTSD counterparts. The co-occurrence of substance abuse and PTSD can therefore predict a more severe course than would ordinarily be the case with either disorder alone (Tjaden & Thoennes, 2000).

A high correlation also appears to exist between eating disorders and substance abuse. As many as 55% of bulimic women are reported to have drug and alcohol use problems, while 15–40% of women with drug abuse or alcohol problems have been reported to have eating disorder syndromes, usually involving binge eating (Gosnell & Krahn, 2010).

3.1.3 Detection and treatment of psychosocial issues

Using a medical record review in conjunction with validated psychiatric screening instruments, Kelly and colleagues (1999) assessed the detection and treatment of psychiatric disorders and at-risk substance use among pregnant women receiving prenatal care in California. They found that nearly 40% of the women had high levels of symptoms associated with psychiatric disorders or substance use (or both at the same time). Approximately 20% of the women met screening criteria for drug or alcohol use either before or during pregnancy, and among the women who screened positive for alcohol or substance use, more than half met the criteria for a depressive disorder.

That said, Kelly's team cautioned that the population studied, which was derived from a university-based obstetrics clinic serving low-income minority women, may not accurately reflect the prevalence of mental illness and substance use among the general population of pregnant women. Despite this caveat, the data from Kelly's team do suggest that a substantial number of women cared for in an obstetrical setting suffer psychiatric or substance use disturbances during pregnancy. Their results also demonstrate that under-recording of such disturbances is not limited to hospital discharge records: it exists throughout prenatal care and is accompanied by low documented rates of mental health and substance use evaluation and treatment.

Given that untreated psychiatric and substance use disorders during pregnancy can have negative consequences for both maternal and infant health (Zuckerman et al., 1989; Steer et al., 1992; Weinberg & Tronick, 1998), the high frequency of such disturbances, combined with the low rate of detection and treatment by healthcare providers, is a serious concern for pregnant women in obstetrical settings (Kelly et al., 1999).

3.2 Victimization

Many addicted women share a history of past or current physical abuse and sexual assault, with numerous reports in the United States and Canada linking victimization and drug abuse (Zilberman et al., 2003; Finnegan & Kandall, 2008).

A review by Cormier and colleagues (2004) reported that a large proportion of women with substance use problems are victims of domestic violence, incest, rape, sexual assault and childhood physical abuse (Ouimette et al., 2000; Brems et al., 2002; Freeman et al., 2002; Simpson & Miller, 2002). Among women in the general population, such victimization has been associated with a number of adverse health outcomes, including PTSD, depression, anxiety, suicidal behaviour and low self-esteem (Briere & Runtz, 1993; Kolko, 1996). Among those in treatment for substance use problems, women who have been abused are more likely than non-abused women to suffer from depression, suicidal ideation, low self-esteem and PTSD (Gil-Rivas et al., 1996; Daley & Argeriou, 1997; Guitierres & Todd, 1997; Najavitis et al., 1997; Kang et al., 1999; Coker et al., 2002).

In a study of women entering a Philadelphia drug abuse treatment centre, 83% came from households in which parents used drugs, 67% had experienced sexual assault and 60%

BRIDGET

Bridget was born to an alcoholic mother, Maggie, who had been abused as a child and did not want a daughter of her own. Exasperated with Maggie's bitterness and drinking, Bridget's father eventually left the family. Bridget wasn't fed or bathed regularly by her mother, though she did receive caring treatment from her grandmother, who took Maggie in whenever she went on a prolonged binge.

Bridget was naturally pretty and grew into a beautiful girl, but remained introverted and unhappy. She was never very interested in her studies and fell in with the wrong crowd at school. She began to smoke cigarettes and marijuana at the age of 12, and was drinking excessively by 14. A year later she had a baby. The infant seemed fine at birth, though somewhat small—likely because of Bridget's drug and alcohol use during pregnancy. Because of Bridget's drug history and inability to care for her child, the baby was placed in foster care. Bridget was allowed occasional visits but seldom made them because of her addicted lifestyle.

Bridget's ongoing victimization, psychosocial disturbances and substance abuse prevented her from ever holding a job or building a stable environment around herself. By the time she was 26 she had had four miscarriages, a second baby—born preterm—and a stillbirth. Her second surviving child was also placed in foster care. As a result of her life experience, Bridget now suffers from depression and post-traumatic stress disorder, and is unaware of any supports or services that could help.

had been physically assaulted (Finnegan et al., 1991). Another U.S.-based study compared the characteristics of out-of-treatment, homeless, crack-using, African-American women with those of women who were not homeless to determine the risks and protective factors differentiating the two groups (Wechsberg et al., 2003). Its results showed that homeless women not only reported psychologically painful histories and currently stressful lives, but were also more likely to have experienced childhood abuse and to use additional drugs besides crack.

Data collected from substance use treatment centres in Canada corroborate the high rates of victimization among substance-abusing women reported in the United States. In a sample of 98 substance-abusing women from nine treatment centres across Ontario, Cormier (2000) found that 85.7% had been victimized. Specifically:

- 56.1% reported current physical abuse;
- 45.4% reported current sexual abuse;
- 56.1% reported childhood physical abuse; and
- 56.3% reported childhood sexual abuse.

Similarly, a treatment facility for substance-abusing women in Vancouver reported that 65% of its patients had been physically assaulted as adults and 38% had been sexually assaulted as adults, while 47% had experienced physical violence during childhood and 53% reported childhood sexual abuse (Poole, 2000).

3.2.1 Intimate partner violence

In 2000, women in the United States experienced 4.8 million instances of intimate partner-related physical assaults and rapes (Tjaden & Thoennes, 2000). In 2005, a total of 1,181 women were murdered by an intimate partner (Bureau of Justice Statistics, 2005). An association between alcohol abuse and intimate partner violence exists, with considerable evidence linking intimate partner violence and alcohol use by the perpetrator (Kantor & Straus, 1989; Miller et al., 1989; Leonard & Senchak, 1996; Kyriacou et al., 1999; O'Farrell, 1999; Caetano et al., 2001).

At the same time, a correlation between intimate partner violence and alcohol use by the victim has also been identified (Kantor & Straus, 1989; Toman & Rosen, 2001). For example, Miller and colleagues (1989) surveyed alcoholic and non-alcoholic women and found that alcoholic women had higher levels of spousal violence in their lives. In addition, an analysis of forensic data from intimate partner-related homicides detected alcohol in 45% of victims and in 70% of suspects (Slade et al., 1991). It is important to be aware of this association so that signs of possible intimate partner violence among women who abuse alcohol—as well as signs of alcohol abuse in women who have experienced intimate partner violence—can be identified (Kay et al., 2010).

Tuten and colleagues (2004) evaluated the impact of partner violence on psychosocial and psychiatric functioning in pregnant, drug-dependent women at treatment enrolment. Abused pregnant women presented with more severe alcohol, family and social problems as well as greater rates of psychiatric problems and medical co-morbidity than those who were not abused. The partners of the abused women also had greater rates of alcohol and illicit drug use in comparison to the partners of non-abused women. These data suggest that treatment protocols should address the women's relationships with their partners, especially when substance abuse and violence issues surface.

3.2.2 Sexual abuse

Sexual abuse (in particular, childhood sexual abuse) is also common among women seeking treatment for drug abuse, with some studies indicating that up to 70% of women in treatment report victimization prior to the age of 11. One such study of drug use among women who became pregnant before reaching the age of 18 found that 32% had a history of rape or incest and that those women had lower self-esteem and used more drugs than non-victims (National Institute on Drug Abuse, 2010).

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4 Outcomes of Newborns of Pregnant Women Using Drugs

The key to having a healthy baby is a healthy pregnancy without medical or obstetrical complications. Unfortunately, such an outcome is unlikely if the mother uses substances while pregnant and does not receive treatment.

As stated in Chapter 2, illicit drug use during pregnancy places the mother at increased risk of a variety of complications, most of which can have adverse effects on the health of the newborn. In addition, the psychosocial and victimization issues discussed in Chapter 3—mental illness, physical and sexual abuse, family dysfunction—can all have serious outcomes for the newborn, including poor parenting, failure to thrive, child neglect, child abuse, abandonment and even death. These complex issues must be addressed to effectively help pregnant women using drugs and their unborn children.

4.1 Drug-related medical complications in newborns

Approximately 3% of the 4.1 million women in the United States of childbearing age who abuse drugs are believed to continue their drug use during pregnancy (Iqbal et al., 2002). Clearly, drug abuse among pregnant women and the resulting neonatal morbidity are very significant clinical and social problems.

4.1.1 Heroin

Low birth weight and prematurity are the two most prominent medical issues seen in the newborns of heroin-abusing women. Conditions such as asphyxia neonatorum (respiratory failure due to inadequate intake of oxygen before, during or just after birth), intracranial hemorrhage, nutritional deprivation, hypoglycemia (low blood sugar), hypocalcemia (low blood calcium), septicemia (blood-borne infection) and hyperbilirubinemia (jaundice) should also be anticipated in heroin-exposed babies.

Infants born to women undergoing methadone treatment for heroin addiction, however, are more likely to have higher birth weights and a decreased incidence of premature birth. Medical issues in infants born to heroin-abusing women generally reflect the amount of prenatal care received by the mother; whether the mother suffered obstetrical or medical complications during the pregnancy; and whether the fetus was exposed to multiple drug use, which can produce an unstable intrauterine milieu that can be further complicated by symptoms of withdrawal and overdose in both the woman and the fetus (Finnegan & Kandall, 2005).

At a Glance

- The use of drugs during pregnancy can lead to fetal growth restrictions such as reduced length, head circumference and birth weight, and medical complications such as preterm birth and infections.
- Pregnant women with opioid dependence who are undergoing methadone maintenance treatment are more likely to give birth to infants with higher birth weights and are less likely to experience premature birth than opioid dependent women who are not under methadone maintenance.
- Smoking tobacco during pregnancy can have harmful effects on fetal development and can result in reduced birth weight and sudden infant death syndrome. Smoking can also be linked to behavioural disorders such as attention deficit hyperactivity disorder, conduct disorders, and externalizing and internalizing behavioural problems.
- Exposure to alcohol in utero can result in a wide range of negative outcomes collected under the umbrella term fetal alcohol spectrum disorder, including fetal alcohol syndrome (FAS). FAS can be categorized by facial abnormalities, growth deficiencies and damage to the central nervous system. It is estimated that FAS occurs at a rate of one to two cases per 1,000 live births in Canada.
- Infants born to chronic opioid users are frequently born with a dependency to such drugs and experience withdrawal after the opioids cease to be administered following birth. The resulting effects are known as neonatal abstinence syndrome (NAS), which has a negative impact on vital bodily functions such as feeding, elimination and sleeping. Recent Canadian estimates suggest that 0.3% of infants are born with NAS.
- NAS caused by exposure to opioids can be treated using a number of different medications, although most UK and US physicians use morphine or methadone. Accompanying measures can be used to create a supportive, comforting environment for the infant and enhance the relationship between the mother and baby.

In another study, women with positive urine toxicology for either heroin or methadone (mostly women receiving methadone treatment and prenatal care) were compared to non-drug-using women. Its results showed a non-significant birth weight decrement of 130 grams but no statistical difference in low birth weight, preterm birth or gestational age (Gillogley et al., 1990).

During a study of pregnant women using drugs in Philadelphia conducted by Connaughton and colleagues (1977), neonatal morbidity was experienced by approximately 75% of the infants born to heroin-using women without prenatal care and methadone-treated women with suboptimal prenatal care. Neonatal problems were somewhat decreased in infants born to methadone-treated women, with hospitalizations averaging 17 days compared to the 27-day stays seen with the infants of heroin-abusing mothers. The main reason for prolonged hospitalization among methadone-exposed babies was neonatal abstinence syndrome. Babies exposed to heroin, meanwhile, suffered from a variety of medical problems primarily related to premature birth.

Infants of heroin-abusing women also have an increased risk of mortality owing to the absence of prenatal care and the concomitant complications resulting from that lack of care. For example, in a sample of 10 preterm heroin-exposed babies whose mothers did not attend prenatal care or addictions services, postmortem examinations revealed lesions in the infants' brains. These lesions were postulated to have occurred during maternal episodes of withdrawal or overdose, which caused a lack of oxygen to the fetal brains (Rorke et al., 1977). Mortality rates can be decreased if mothers enrol in methadone treatment, receive prenatal care and seek out comprehensive services for their opioid addictions (Finnegan et al., 1977).

4.1.2 Cocaine

Although in utero exposure to stimulants such as cocaine has been widely studied, confounding variables such as a lack of prenatal care and the mother's use of marijuana, opioids or alcohol have caused opposing opinions as to their effects upon newborn babies.

The general consensus is that maternal cocaine use can lead to shortened gestation as well as restricted fetal growth. It has been shown that cocaine intake can cause a rise in norepinephrine,[4] which can cause contractions of the uterus that, in turn, increase the incidence of precipitous labour and preterm births. Cocaine also causes constriction of blood vessels in the uterus and placenta, which can lead to reduced fetal nutrition resulting in poor fetal growth (Finnegan et al., 1992). In studies conducted during the surge of cocaine use in the United States in the 1980s, babies exposed to cocaine were commonly reported to have low birth weight, premature gestation or intrauterine growth restriction (Livesay et al., 1987; Chouteau et al., 1988; Handler et al., 1991; Kliegman et al., 1994).

Because a wide range of factors can contribute to decreased fetal growth and gestation, it is important for studies to control for concurrent use of other substances as well as other medical and socio-demographic factors. With this in mind:

- Eyler and colleagues (1998) controlled for associated substance use (alcohol, marijuana and tobacco) and documented a reduction in head circumference in cocaine-exposed newborns;
- Bandstra and colleagues (2001) studied 253 infants born to African-American women in Miami and found evidence supporting a pattern of cocaine-associated symmetric intrauterine growth restriction (i.e., affecting both birth weight and head circumference); and
- Scafidi and colleagues (1996) looked at reduced head circumference in preterm infants, with the data suggesting maternal cocaine use is associated with symmetric growth restriction.

Data on the relationship of cocaine to human malformations can be characterized as inconsistent. Numerous studies have reported on a variety of abnormalities in infants exposed to cocaine in utero (Bingol et al., 1987; Chasnoff et al., 1988; Hoyme et al., 1990; Lipshultz et al., 1991). However, Martin and colleagues (1992) did not find an increase in congenital malformations attributable to vascular disruption based on 1968–1989 data from the Metropolitan Atlanta Congenital Defects Program. Similarly, Rajegowda and colleagues (1991)

[4] Both a hormone and a neurotransmitter, norepinephrine is secreted by the adrenal medulla and the nerve endings of the sympathetic nervous system to cause blood vessel constriction and increases in heart rate, blood pressure and blood-sugar level. Its primary function is to help maintain a constant blood pressure by stimulating certain blood vessels to constrict when blood pressure falls below normal.

found no increase in congenital urogenital abnormalities in 1,324 cocaine-exposed infants when compared to 18,028 reportedly drug-free controls. The same lack of association was also found by Hadeed and Siegel (1989) and Zuckerman and colleagues (1989).

In general, there is a lack of definitive evidence linking cocaine to any effects on the developing fetus apart from the growth restriction mentioned above. A Canadian research team (Graham et al., 1991) reported that despite a growing number of studies investigating the effects of maternal cocaine use, a homogeneous pattern of fetal effects has not been established and there is little consensus on the adverse effects of the drug. In their meta-analysis of 20 studies of cocaine-using pregnant women, very few adverse reproductive effects could be shown to be *significantly* associated with cocaine use by poly-drug users when compared to control groups of poly-drug users who did not use cocaine. When the control groups consisted of women who did not use any drugs, the poly-drug users who also abused cocaine had a comparatively higher risk of miscarriage. Comparisons between women who only used cocaine to those who did not use drugs also revealed a higher risk for in utero death and genito-urinary tract malformations in the cocaine-exposed infants, most likely because of cocaine-induced constriction of the placental blood vessels. However, no statistical link could be found between prenatal cocaine use and premature delivery, low birth weight or congenital heart defects.

The results from the meta-analysis by Graham and colleagues (1991) also suggest that confounding factors such as the use of alcohol, tobacco or other drugs might actually account for the fetal growth restriction and prematurity commonly ascribed to cocaine. Women who use cocaine tend to smoke more cigarettes than those who use other illicit drugs and are also more likely to drink alcohol and take other drugs. As such, it can be difficult to determine which specific drug or combination of drugs causes these medical complications.

As part of the Motherisk program at Toronto's Hospital for Sick Children, women are counselled on pharmacological risks during pregnancy. Koren and colleagues (1992) reported that although cocaine exposure early in pregnancy was not associated with a markedly increased risk of congenital malformations, the physician's perception of a high risk of cocaine-related abnormalities resulted in the termination of many otherwise wanted pregnancies. Counselling of pregnant women as to the actual risk of congenital malformations resulted in a decrease in both risk perception and the tendency to terminate the pregnancy (Koren et al., 1993). At the present time, mothers should be informed that cocaine use might increase the risk of congenital malformations in their fetuses; however, confirmatory studies looking at cause and effect are needed.

4.1.3 Amphetamines and methamphetamines

Amphetamine use during pregnancy has been associated with a high perinatal mortality rate; reductions in birth weight, length and head circumference; associated congenital malformations; poor feeding; seizures; and abnormal neurological signs, muscle tone, drowsiness and cry patterns (Eriksson et al., 1978, 1981; Oro & Dixon, 1987; Smith et al., 2003).

The Infant Development, Environment and Lifestyle (IDEAL) Study looked at the effects of prenatal methamphetamine and poly-drug exposure on neonatal growth (Smith et al., 2006). It included 1,618 infants, 84 of whom were exposed to methamphetamine and 1,534 who were unexposed. Both groups included infants prenatally exposed to alcohol, tobacco or marijuana. In general, mothers in the methamphetamine group tended to be younger, poorer and less educated than those in the unexposed group. They also drank and smoked more frequently, were more likely to have no partner, had fewer prenatal care visits and began prenatal care at a later gestational age.

FETAL GROWTH RESTRICTION

Why does methamphetamine cause fetal growth restriction? One reason is that it can cause both maternal and fetal blood vessel constriction, restricting nutrient delivery to the fetus and contributing to high fetal blood pressure that can result in decreased hemoglobin oxygen-carrying capacity.

Sources: Burchfield et al., 1991; Stek et al., 1995.

After adjusting for covariates, infants in the methamphetamine-exposed group were 3.5 times more likely to be small for gestational age (SGA) compared to the unexposed group. (SGA is usually defined as having a birth weight below the tenth percentile, which puts the newborn at increased risk of morbidity and mortality.) In addition, mothers who used tobacco as well as methamphetamine were nearly two times more likely to deliver SGA babies (Smith et al., 2006).

GABRIELLE AND BABY JACQUES

Gabrielle and Jean-Paul met at university in Vancouver. They were relatively good students, though their weekends were usually a blur because of excessive drinking and some drug use at parties. For both of them, alcohol was their drug of choice. Shortly after graduating, the two were married and they each obtained good jobs as a result of the influence of Gabrielle's father, a well-connected politician. Jean-Paul became a junior architect and Gabrielle an assistant in a major advertising firm. As at school, they performed well during the week, but their weekends were occupied with binge drinking.

While they'd planned to get established before having a baby, Gabrielle was pregnant by age 25. She knew alcohol was incompatible with a healthy fetal outcome, but her nine-year habit of weekend binge drinking was well established. Jean-Paul did not want to stop drinking or be forced to drink alone, so Gabrielle convinced herself that the risk was greatest with daily consumption and reserved her drinking for weekends.

Baby Jacques was delivered at 38 weeks. Gabrielle was surprised by his small size. He was jittery, he didn't nurse well and he didn't look like either Gabrielle or Jean-Paul: he had a small head with thin lips, an upturned nose and small, wide-set eyes. A doctor explained to Gabrielle and Jean-Paul that these were all signs of fetal alcohol spectrum disorder, of which Jacques had an extreme form. He said Jacques would most likely have decreased intellectual functioning in addition to vision, hearing and behavioural problems as a result of his exposure to alcohol in utero.

Because preliminary growth data after one year of the study reported an increased incidence of SGA in methamphetamine-exposed infants, the IDEAL team continued to enrol subjects after its initial report was published in 2006. A second report on the complete data set was released in 2010, this time including 204 infants exposed to methamphetamine and 3,501 who were not.

One of the more surprising findings was that methamphetamine-using mothers gained more weight than those in the unexposed group. To further study this point, the IDEAL team compared weight gain between mothers who reported methamphetamine use during the first or second trimester only to those who also reported use during the third trimester. It was found that women who quit using the drug earlier in gestation gained 10.4 pounds more than those who continued to use throughout their pregnancy, suggesting the anorexic effects typically associated with methamphetamine occur only with continuous use and that a rebound in maternal weight might be possible if the mother discontinues use.

In its expanded study (Nguyen et al., 2010), the IDEAL researchers found that although the infants in the methamphetamine group were born slightly earlier than those in the unexposed group, both groups had a term mean gestational age. While no significant differences were found in birth weight, the incidence of SGA was higher in the exposed group. They also reported a low incidence of the maternal complications known to cause SGA; of the 204 women in the exposed group, none of the nine mothers diagnosed with diabetes or chronic hypertension delivered SGA infants, while only two of the 10 diagnosed with pre-eclampsia delivered SGA infants. Finally, in contrast with the initial study, the team did not find that co-exposure to methamphetamine and maternal smoking resulted in significantly decreased neonatal growth.

It should also be noted that the increased incidence of SGA and fetal growth restriction associated with prenatal methamphetamine exposure might pose long-term health risks for the newborn, including coronary heart disease, stroke, diabetes and hypertension during adulthood (Barker et al., 1993). Nguyen and colleagues (2010) therefore recommended further longitudinal studies of the methamphetamine-exposed infants involved in the IDEAL Study to fully ascertain whether they are at increased risk for future growth abnormalities or other medical problems.

4.1.4 Cannabis and tobacco

The effects of heavy cannabis smoking include reduced fetal growth, preterm birth and an increase in neonatal tremors and startle responses. The Ottawa Prenatal Prospective Study, a major Canadian study that collected data on a wide range of pre- and postnatal outcomes following exposure to cannabis and tobacco smoke, also showed that in utero exposure to marijuana can affect an infant's ability to respond to visual stimulation (Fried, 1995; Fried et al, 1983).

With regard to maternal tobacco smoking, a study by Godding and colleagues (2004) demonstrated the following outcomes:

- Birth weight is reduced by approximately 150–200 grams for every pack of cigarettes smoked during pregnancy;
- Maternal tobacco smoking of long duration is linked to increased rates of abruptio placentae, placenta previa (where the placenta is inserted partially or wholly in the lower part of the uterus), placental infarcts (interrupted blood supply to the placenta) and other placental changes caused by blood vessel constriction; and
- Delivery of oxygen to the fetus is adversely affected by the elevated levels of carbon monoxide in the mother's blood.

In addition, hypertonia (increased muscle tone) has been reported in infants born to tobacco-smoking mothers. Increased rates of hospitalization and death in children up to five years of age, primarily from respiratory disorders such as bronchiolitis and pneumonia, have also been reported in infants born to smokers. Mild neonatal abstinence syndrome can also occur in infants exposed to heavy maternal smoking during pregnancy (Godding et al., 2004).

As reviewed by Abbott and Winzer-Serhan (2012), maternal smoking during pregnancy can have deleterious effects on fetal development as well as long-term adverse consequences on postnatal development and maturation of several organ systems. Low birth weight, sudden infant death syndrome (SIDS), behavioural disorders including attention deficit hyperactivity disorder (ADHD), externalizing and internalizing behavioural problems, and conduct disorders in children have all been linked to prenatal exposure to tobacco smoke.

4.2 Fetal alcohol spectrum disorder

Alcohol use during pregnancy is one of the leading preventable causes of birth defects and developmental disabilities (Centers for Disease Control and Prevention [CDC], 2012). Yet while the effects of prenatal exposure to alcohol have been known for centuries, they were not actually documented in the medical literature until 1968, with fetal alcohol syndrome (FAS) first identified in 1973 (Calhoun & Warren, 2007).

A diagnosis of FAS requires the presence of all three of the following diagnostic criteria:

- Facial anomalies or abnormalities;
- Growth deficiency; and
- Central nervous system (CNS) damage or dysfunction.

It should be noted that while confirmed prenatal alcohol exposure can strengthen the evidence for diagnosis, it is not necessary in the presence of the above criteria.

In the decades following the identification and definition of FAS, it has since become clear that even if a person does not meet all of the FAS criteria listed above, he or she can still experience a vast spectrum of physical, mental, behavioural and learning disabilities, all with potential lifelong implications. As a result, the term "fetal alcohol spectrum disorder" (FASD) is now used as a non-diagnostic umbrella term to include the wide range of negative outcomes that can occur in individuals exposed to alcohol during pregnancy, including FAS (Bertrand et al., 2004).

Although the term FASD is not intended for use as a clinical diagnosis, diagnostic guidelines have been developed to describe many of the effects of prenatal exposure to alcohol. For example, designations have been defined for many of the disorders that fall under the FASD umbrella, including FAS, partial fetal alcohol syndrome (PFAS), fetal alcohol effects (FAE), alcohol-related birth defects, alcohol-related neurodevelopmental disorder (ARND), static encephalopathy/alcohol exposed and neurobehavioural disorder/alcohol exposed (Bertrand et al., 2004; Hoyme et al., 2005; Astley, 2006; Astley et al., 2009; Olson et al., 2009). In general, individuals diagnosed with FAS are typically more impaired than those with other disorders under the FASD umbrella (Fryer et al., 2007; Olson, King & Jirikowicz, 2008; Chasnoff et al., 2010).

4.2.1 Prevalence of FASD

In Canada, it is estimated that FAS occurs at a rate of one to two cases per 1,000 live births (Roberts & Nanson, 2000) and that an FASD occurs in approximately nine of every 1,000 live births (Public Health Agency of Canada, 2003). These rates are believed to be even higher in Canada's Aboriginal communities (Canadian Paediatric Society, 2002), with some statistics suggesting rates anywhere from 25 to 200 instances of FAS or FASD per 1,000 live births in isolated northern communities (Masotti et al., 2003). It has been noted, however, that Canadian studies of the prevalence of FAS/FAE have focused primarily on Aboriginal communities where alcohol abuse and dependency are known to be high, raising concern that the high prevalence rates of FAS/FAE found in these communities will be used to describe rates in the general Aboriginal population (Tait, 2003a; Dell & Roberts, 2006). The lack of epidemiological data regarding other populations in Canada also makes it difficult to determine whether or not Aboriginal women are at greater risk than other groups (Dell & Roberts, 2006).

In the United States, the prevalence of FAS is estimated at 0.5 to two cases per 1,000 live births. Other FASD disorders are believed to occur approximately three times as often as FAS, with signs of FASD present in 2–5% of young children across the U.S. school population (Department of Health and Human Services, 2005). A slightly lower rate was found by May and Gossage (2001), who showed that FASD is estimated to affect at least 1% of all live births in the United States.

FASD has been linked to patterns of alcohol consumption that produce high blood-alcohol concentrations. In particular, studies conducted on animals have found that binge drinking (for women, this is typically defined as four or more drinks on a single occasion) is especially dangerous to fetal brain development, even if the total amount of alcohol consumed is less than the amount consumed in a more continuous drinking pattern (Maier & West, 2001).

Data from the 2007–2008 Canadian Community Health Survey indicated that the national prevalence of alcohol consumption during pregnancy was 5.8% (Thanh & Jonsson, 2010). In the United States, rates of alcohol use and binge drinking among women aged 18–44 were derived from self-reported data taken from the 2006–2010 Behavioral Risk Factor Surveillance System. Overall, 7.6% of pregnant women reported past-

month alcohol use. Although the prevalence of binge drinking is much lower among pregnant women (1.4% compared to 15.0% of non-pregnant women), pregnant women who did report past-month binge drinking did so with similar frequency (an average of three times per month) and intensity (an average of six drinks on a single occasion) as non-pregnant women (CDC, 2012).

4.2.2 Outcomes of FASD

Multiple studies have shown that even low levels of prenatal exposure to alcohol can have adverse effects on fetal development. What's more, these effects are dose-dependent, meaning heavier maternal alcohol consumption is associated with more severe outcomes (Olson, King & Jirikowicz, 2008; Olson et al., 2009; Riley, Mattson & Thomas, 2009). Although there is consensus on the adverse effects of heavy maternal drinking over an extended period of time during pregnancy, the issue of whether adverse effects are associated with low to moderate levels of drinking continues to be controversial (Abel, 2006).

There is also a marked variability in FASD-related outcomes, even among heavy drinkers. This variability can be explained by differences in consumption patterns and timing of exposure in addition to other factors such as maternal health, genetic background and interactions with other substances (Abel, 2006; Olson, King & Jirikowicz, 2008; Guerri, Bazinet & Riley, 2009).

The three most prominent outcomes of FASD are facial abnormalities, growth deficiencies and damage to the CNS. Facial abnormalities associated with FASD include a shorter distance between each end of the eye-socket opening, a thin upper lip and a lack of skin-fold indentation between the nose and upper lip (also known as smooth or indistinct philtrum) (Astley, 2006; Astley et al., 2009). FASD-related growth deficiencies are considered to exist if pre- or postnatal height or weight is at or below the 10th percentile at any point in time (Bertrand et al., 2004).

Damage to the CNS, however, represents the most devastating consequences of prenatal alcohol exposure (Astley, 2006; Guerri et al., 2009; Riley, Mattson & Thomas, 2009) and generally persists throughout the affected person's lifespan (Bertrand et al., 2004). FASD-related CNS dysfunction can include any combination of the following abnormalities:

- Structural, including reduced head circumference or brain abnormalities such as reduced size of the corpus callosum (the thick band of nerve fibres dividing the left and right sides of the brain);
- Neurologic, including motor problems or seizures not resulting from postnatal insult; and
- Functional, including substandard cognitive functioning in various domains.

General mental ability

Prenatal exposure to alcohol can result in impairments to an individual's general mental ability, including a lack of general proficiency in learning, reasoning, abstract thinking and the processing of complex information efficiently and accurately (Gottfredson, 2008). In fact, impaired general mental ability constitutes the central cognitive impairment related to—and the most devastating consequence of—prenatal alcohol exposure (Kodituwakku, 2007; Riley, Mattson & Thomas, 2009).

Intellectual disability is seen in approximately 25% of individuals with an FASD (Bertrand et al., 2004; Streissguth et al., 2004). While FASD is fully compatible with average and above-average intellectual functioning—IQs as high as 126 have been found in people with FASD (Streissguth et al., 2004)—it does not mean there is no impairment in cognitive functioning. And because general mental ability does not include the full spectrum of cognitive abilities (Gottfredson, 2008; McGrew, 2009), it does not capture the full range of cognitive deficits caused by an FASD (Bertrand et al., 2004; Hoyme et al., 2005).

THE EFFECTS OF PRENATAL ALCOHOL EXPOSURE ON INTELLECTUAL FUNCTIONING

The mean IQ in individuals with FAS is in the low 70s for those with facial anomalies and in the low 80s for those without facial anomalies.

Source: Riley, Mattson & Thomas, 2009.

Non-verbal learning disability, for example, is among the cognitive deficits not accounted for by general mental ability. A number of studies (Don & Rourke, 1995; Tsatsanis & Rourke, 2008; Rasmussen & Bisanz, 2009) have shown that the non-verbal learning disabilities commonly found in individuals with FASD include:

- Poor coordination and motor slowness, often more marked on the left side of the body;
- Deficiencies in visual-spatial skills and visual spatial memory;
- Relative deficiencies in mechanical arithmetic in contrast with verbal skills such as word decoding, spelling, vocabulary and rote verbal memory;
- Difficulty dealing with cause-and-effect relationships;
- Deficiencies in the appreciation of incongruities (e.g., humour);
- Deficiencies in non-verbal problem solving, concept formation and hypothesis testing;
- Difficulty with more complex verbal material and written text (e.g., material that is abstract or inferential);
- Notable difficulty adapting to novel or complex situations; and
- Deficiencies in the capacity to benefit from feedback in novel or complex situations.

Combined, these impairments contribute to deficits in skills related to social perception, judgment and interactions, making it practically impossible for the individual to adapt to novel interpersonal situations (Eme & Millard, 2012).

Executive functions

Executive functions such as response inhibition and working memory represent a class of higher-order cognitive abilities that allow for strategic planning, impulse control, cognitive flexibility and goal-directed behaviour (Weyandt, 2009). Because executive functions facilitate behavioural and affective regulation (Barkley, 2006; Nigg, 2006), major life problems can occur as a result of impaired executive functions (Vaurio, Riley & Mattson, 2009).

For example, it is estimated that 95% of individuals with ADHD have impaired executive functioning (Barkley, 2006). Although individuals diagnosed with FASD account for just 2% of all individuals with ADHD (Nigg, 2006), ADHD is the most frequent neuropsychiatric presentation of an individual with FASD, with rates ranging from 60% to 95% (Streissguth et al., 1996; Burd et al., 2003; Fryer et al., 2007; O'Malley, 2007; Herman, Acosta & Chang, 2008; Astley et al., 2009). The impairment of executive functions can therefore account for many of the social, legal, substance use and mental health problems typically faced by individuals with FASD (Vaurio et al., 2009).

4.2.3 Diagnosis, treatment and prevention of FASD

Although its consequences are devastating, FASD is a completely preventable condition. According to Dr. Ann Streissguth, a researcher who has dedicated her life to the effects of alcohol on fetuses, newborns, children and adults, "the most outstanding characteristics of [FASD] are bad judgment and the inability to make the connection between an act and its consequences" (Streissguth et al., 2004). There is a pressing need to foster greater public awareness of FASD and its effects, part of which involves the development of practical guidelines for diagnosis, treatment and prevention. Fortunately, medical professionals, parents, educators, advocates and government agencies have all worked to produce such material in recent years.

Published in 2003 through funding from the Alberta FAS Initiative, the Alberta Clinical Practice Guidelines contain a number of recommendations to help physicians, midwives and other healthcare professionals reduce the incidence of FASD. In particular, they call for increased screening for alcohol consumption during pregnancy, greater awareness of the link between alcohol use and FASD, and productive dialogue and action between practitioners and their patients (and when possible, their partners) (Alberta Clinical Practice Guidelines Program, 2003).

In 2005, a subcommittee of the Public Health Agency of Canada's National Advisory Committee on FASD reviewed, analyzed and integrated the existing approaches to the diagnosis of FASD-related disabilities with the aim of reaching an agreement on a national diagnosis standard applicable to Canadians of all ages (Chudley et al., 2005). Because such diagnosis necessitates a multidisciplinary approach, the resulting guidelines—the first of their kind in Canada—are organized into the following seven categories:

- Screening and referral;
- Physical examination and differential diagnosis;
- Neurobehavioural assessment;
- Treatment and follow-up;
- Maternal alcohol history in pregnancy;

- Diagnostic criteria for FAS, PFAS and ARND; and
- Harmonization with Institute of Medicine and 4-Digit Diagnostic Code[5] approaches.

These Canadian guidelines were developed in parallel and in consultation with a U.S.-based committee charged with the same task. In its report, the National Center on Birth Defects and Developmental Disabilities at the U.S. Centers for Disease Control and Prevention stated that because the challenges related to FASD prevention, diagnosis and intervention are constantly evolving, more research is needed to determine whether tools such as brain imaging, biomarkers and DNA micro-array techniques could enhance the accuracy and reliability of alcohol-related diagnoses and treatment (Bertrand et al., 2004). The guidelines featured in this report are intended to help facilitate the training of healthcare professionals, improve access to diagnostic services and facilitate referral to treatment for people affected by FASD.

Most recently, Canada's Low-Risk Alcohol Drinking Guidelines (Butt, Beirness, Gliksman, Paradis & Stockwell, 2011) address alcohol use during pregnancy simply by stating that the safest option during pregnancy or when planning to become pregnant is to not drink alcohol at all. Ultimately, with greater public awareness and recognition of the adverse effects of FASD, it is hoped that pregnant women will be more likely to heed the warnings and choose to abstain from alcohol—not only during pregnancy, but also when they are planning to become pregnant.

With respect to culturally appropriate guidelines for Aboriginal women, the Society of Obstetricians and Gynaecologists of Canada prepared a policy statement in 2001 to guide professionals in addressing Aboriginal health concerns, including FASD (Smylie, 2001). In a report prepared for the Aboriginal Healing Foundation, Tait (2003b) suggested best practices from an Aboriginal perspective, proposing alternative practices that are aligned with the culture and fit with the reality in which Aboriginal peoples live in Canada. The report gives particular attention to the role of residential schooling, concluding that the widespread use of alcohol and other substances among many residential school survivors can be attributed to that traumatic experience.

4.3 Neonatal abstinence syndrome

Infants of chronic opioid users are frequently born with a passive dependency on the drugs used by their mothers. With their low molecular weight and lipid solubility, opioids can pass easily from the mother to the fetus through the placenta; once the drugs accumulate in the fetus, equilibrium is established between the maternal and fetal blood. Disruption of the transplacental passage of drugs when the umbilical cord is cut at birth terminates the drug supply to the baby, potentially resulting in the development of symptoms of abstinence or withdrawal. Affecting the central nervous, autonomic nervous, gastrointestinal and respiratory systems, this constellation of symptoms constitutes a multisystem disorder called neonatal abstinence syndrome (NAS).[6]

NAS is a serious medical condition because it affects the vital functions that permit growth and normalcy—feeding, elimination and sleep, for example. Moreover, the symptoms can mimic other neonatal conditions such as infection, hypoglycemia, hypocalcemia and intracranial hemorrhage, all of which can be life threatening or lead to other major problems. If untreated, NAS can cause death because of excess fluid loss, high temperatures, seizures, respiratory instability, aspiration of fluid into the lungs or the cessation of breathing. However, with current medical knowledge about drug abuse during pregnancy and newborn care, no infant should die as a result of NAS.

4.3.1 Prevalence of NAS

In 2009–2010, 0.3% of all infants born in Canada had NAS, with affected newborns staying in acute care facilities for an average of 15 days after birth (Canadian Institute for Health Information [CIHI], 2012). The incidence of NAS in Ontario, as reported by CIHI, has increased from 1.3 cases per 1,000 births in 2004 to 4.3 cases per 1,000 births in 2010 (Dow et al., 2012).

In the United States, a study of 7.4 million discharges from 4,121 hospitals across the country found that between 2000 and 2009, the number of mothers using opiates increased from 1.19 to 5.63 per 1,000 hospital births per year. NAS was diagnosed at a rate of 3.39 per 1,000 hospital births per year; in 2009, an estimated 13,539 newborns (or approximately

[5] The 4-Digit Diagnostic Code is used for diagnosis, screening and surveillance in clinics throughout Canada and the United States (Chudley et al., 2005).
[6] There are two types of NAS: prenatal, which is caused by the discontinuation of drugs taken by the pregnant mother; and postnatal, which is caused by the discontinuation of drugs given directly to the infant (Hall et al., 2007). Only prenatal NAS will be discussed in this report.

one infant born each hour) showed signs of withdrawal or abstinence. Newborns with NAS were 19% more likely than all other hospital births to have low birth weight and 30% more likely to have respiratory complications. These babies also tended to have greater feeding difficulties and more frequent seizures (Patrick et al., 2012).

While the length of hospital stay for NAS-diagnosed newborns remained relatively unchanged from 2000 to 2009 (approximately 16 days), the charges for these stays increased from $39,400 to $53,400, which is nearly six times the cost of non-NAS hospital births (Patrick et al., 2012). These data speak to the significant burden drug abuse places not only on the health of the mother and her child but also on hospital staff and resources—not to mention the costs incurred at the national level.

4.3.2 Onset and severity of NAS

At birth, most infants exposed to opioids appear physically and behaviourally normal. Symptoms of NAS typically appear shortly after birth and up to two weeks later, with the majority exhibited within the first 72 hours of life (Finnegan, 1988; Finnegan & Kandall, 2005; Hudak & Tan, 2012). This timing is because most opioids are short-acting and therefore not stored by the fetus in appreciable amounts. (Methadone, however, is longer-acting; therefore, the occurrence, timing and severity of NAS symptoms for babies withdrawing from methadone are more variable.) Acute symptoms can persist for several weeks, whereas subacute symptoms (e.g., irritability, sleep problems, hyperactivity, feeding problems, hypertonia) can persist for up to four to six months (Franck & Vilardi, 1995; Coyle et al., 2002).

The type of pain medication and anesthesia received by the mother can also influence the onset of NAS symptoms, with epidural anesthesia generally resulting in fewer problems for both mother and child. In addition, poor nutritional status and illness in the baby can result in a later onset of NAS because the infant is slower to excrete the drugs (Finnegan et al., 1975; Finnegan & Kandall, 2005).

The maturity of the infant is another important factor influencing the onset of NAS symptoms. In full-term infants, NAS onset is earlier and the symptoms can be more severe. Preterm babies, on the other hand, tend to have a later onset and less severe symptoms, likely because of the developmental immaturity of the preterm nervous system or the reduced total drug exposure in shortened gestations (Doberczak et al., 1991).

Why is there so much variability in the expression of NAS? It has been suggested that the rate of decline in a newborn's drug plasma level from the first day to the fourth day of life influences the severity of abstinence symptoms (Doberczak et al., 1993; Rosen & Pippenger, 1976). Essentially, the faster a baby excretes the pharmacological agent, the faster the onset of NAS symptoms.

As with the variability in the onset of NAS, the pattern of the syndrome can take several different courses. It can be mild and transient, delayed in onset, have a stepwise increase in severity, be intermittently present, or have a biphasic course that includes acute neonatal symptoms followed by improvement and then an exacerbation of the acute symptoms (Finnegan et al., 1975).

4.3.3 Symptoms of NAS caused by exposure to opioids

In general, NAS resulting from opioids is characterized by signs of CNS hyperirritability, gastrointestinal dysfunction, and respiratory and autonomic nervous system symptoms.

Central nervous system

Tremors, high pitched crying, hypertonia, irritability, increased deep tendon reflexes and an exaggerated startle reflex are all characteristic of neonatal abstinence. An exaggerated rooting reflex and a voracious appetite manifested as sucking of fists or thumbs are also common, yet when feedings are administered the infant may have extreme difficulty because of an uncoordinated sucking and swallowing mechanism. Kron and colleagues (1976) found that both heroin- and methadone-exposed infants showed reductions in sucking rates and pressures, disordered sucking organization and a reduction in the amounts of nutrient consumed. As a result of these issues, an infant affected by NAS can be challenging to feed except by a very skilled neonatal nurse.

Seizures represent perhaps the most dramatic CNS manifestation of NAS. Fortunately, they are not the most prominent of the symptoms. However, because they may be subtle or confused with exaggerated tremors, the reported incidence of seizures varies, ranging from 1% (Finnegan, 1986) to 5.9% (Herzlinger et al., 1977) to 7.8% (Kandall et al., 1983) of newborns exposed to heroin or methadone during pregnancy. Certain practices used in the treatment of NAS, such as tightly swaddling the infant in a darkened room, can also make it difficult to observe seizure movements.

CELESTE AND BABY SARA-ANN

Celeste is 26 years old and newly married to her husband, Chris. Both had lucrative jobs and were building strong careers when two things happened: Celeste had a serious automobile accident and, during her evaluation in the hospital, she was told that she was pregnant.

For the severe back injury she suffered in the accident, Celeste was placed on oxycodone. Her pain was intense and, because she was in the first trimester of pregnancy, she had the discomforts of nausea and vomiting to contend with as well. Although she felt poorly, she continued to work—not only because she needed the money, but also because she did not want to jeopardize her position. She escalated her dose of medication, quickly finding that she had to take progressively more pills to achieve the same effect. Her doctor told her to wean off the medication to avoid becoming addicted, but did not explain how to do so safely. Celeste ended up with multiple prescriptions, one from her obstetrician and another from her family physician.

As the pregnancy progressed Celeste's pain worsened, so she continued taking oxycodone until baby Sara-Ann was born. Concerned about the effect her use of pain medication would have on the newborn, Celeste spoke to her obstetrician, who in turn consulted a neonatologist. By this point, Sara-Ann was already showing signs of neonatal abstinence syndrome, which can occur when newborns stop receiving doses of drugs via their mother in utero. She was actively monitored to determine if treatment would be necessary. On her second day of life, Sara-Ann's symptoms reached a critical level and she was given morphine drops to relieve them. Because the baby was otherwise healthy, after two weeks of treatment the doctor was able to start weaning her off morphine. Celeste and Chris took Sara-Ann home by three weeks of age, and Celeste enrolled in a drug treatment program to deal with her addiction to prescription medications.

Gastrointestinal system

Regurgitation, projectile vomiting and loose stools are all gastrointestinal manifestations of NAS. Dehydration because of poor intake, coupled with increased losses from the gastrointestinal tract, can cause excessive weight loss, electrolyte imbalance, shock, coma and even death. Babies with mild NAS not requiring treatment can lose about 4% of their birth weight, regaining it by the seventh day of life. Newborns displaying more severe abstinence lose more weight and do not regain their weight until an average of two weeks after birth, suggesting that timely and appropriate pharmacological control of abstinence, combined with the provision of extra fluids and calories to offset the weight loss, are important in the management of NAS (Weinberger et al., 1986).

Although babies that exhibit mainly gastrointestinal symptoms might not meet the criteria for pharmacological treatment of their symptoms, it is still extremely important for these babies to be monitored following discharge from the hospital because of the potential for water losses and poor intake, both of which can lead to dehydration.

Respiratory system

Respiratory symptoms caused by NAS can include excessive secretions and nasal stuffiness, sometimes accompanied by retractions between the ribs of the chest wall, intermittent cyanosis (blue colouring of the lips and fingertips) and apnea (cessation of breathing) (Finnegan, 1980). Severe respiratory distress occurs most often when the infant regurgitates, aspirates and develops aspiration pneumonia. Infants with acute heroin withdrawal were found to have increased respiratory rates, leading to hypocapnia (a state of reduced carbon dioxide in the arterial blood) and an increase in blood alkalinity during the first week of life (Glass et al., 1972). Surprisingly, the incidence of respiratory distress syndrome is actually decreased in NAS-affected infants, possibly because of chronic intrauterine stress, accelerated heroin-mediated maturation of lung function or perhaps both (Glass et al., 1972). This decrease, however, is just one benefit among a long list of adverse effects resulting from intrauterine heroin exposure.

Autonomic nervous system

Autonomic nervous system signs seen during abstinence include sneezing, yawning, skin color changes (mottling) and water loss caused by increases in temperature and the shedding of tears. In addition, Behrendt and Green (1972) found that approximately 40% of low-birth-weight infants born to heroin-addicted mothers had spontaneous generalized sweating. In comparison, this condition appeared in less than 1% of healthy low-birth-weight babies.

4.3.4 Symptoms of NAS caused by exposure to other drugs

Even though opioid-related NAS produces the most dramatic effects in newborns and their mothers, anti-depressants, sedative-hypnotics, alcohol and tobacco have all been identified as causes of NAS (Finnegan et al., 1975; Finnegan & Kandall, 2005; Weiner & Finnegan, 2010).

Cocaine

Although neurobehavioural symptoms in cocaine-exposed babies can include tremors, lethargy intermittent with irritability, abnormal cry patterns, poor sucking, hypertonia, abnormal sleep patterns and poor interactions with caretakers, NAS does not generally occur in babies exposed to cocaine in utero. Askin and Diehl-Jones (2001) defined these effects not as “true” NAS but rather neurotoxicity with under-aroused neurobehavioural function. Moreover, symptoms of irritability in these infants are difficult to separate in the context of other factors from which they suffer, such as prenatal exposure to other drugs used together with cocaine (Askin & Diehl-Jones, 2001; Bada et al., 2002).

Antidepressants

Selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, paroxetine, sertraline, citalopram, escitalopram and fluvoxamine are the most frequently used drugs to treat depression and other mood and behavioural disorders. Infants exposed to SSRIs during the last trimester of pregnancy can exhibit the full range of NAS-related CNS signs (e.g., irritability, seizures), respiratory signs (e.g., increased respiratory rate, nasal congestion), gastrointestinal symptoms (e.g., diarrhea, feeding difficulty) as well as motor signs (e.g., agitation, tremors, hypertonia), fever and hypoglycemia (Haddad et al., 2005). A decrease in maternal SSRI use during the third trimester can lower the neonatal risk of developing NAS; however, this needs to be balanced against the harmful effects of untreated depression during pregnancy, which can include a lack of attention to prenatal care and continued illicit drug use.

The onset of SSRI-related NAS symptoms ranges from several hours to several days after birth, usually resolving within two weeks. Symptoms are more commonly reported among infants exposed to fluoxetine and paroxetine.

Sedative-hypnotics

Sedative-hypnotics such as benzodiazepines (i.e., diazepam) and barbiturates can also cause NAS. Because these agents have a longer half-life, withdrawal might not start until after the infant has been discharged from hospital. In study by Seligman and colleagues (2008) on the maternal variables predicting length of treatment for NAS in methadone-exposed newborns, it was found that later gestational age and concomitant maternal benzodiazepine use is associated with longer treatment durations. These results indicate that maternal poly-drug abuse can increase the severity of NAS.

Tobacco and alcohol

Infants born to heavy cigarette smokers have been found to demonstrate increased signs of stress and abstinence (Law et al., 2003). Among babies exposed prenatally to alcohol, NAS symptoms are usually seen within the first 24 hours of life and are especially reported in those with signs of FAS. In addition, these newborns have also been shown to exhibit irritability, tremors, seizures, abdominal distension and opisthotonus (severe hyperextension and spasticity in which the baby's head, neck and spinal column enter into an "arching" position).

Volatile substances

Volatile substances cover a wide range of easily obtained products such as gases, glues and aerosols that, when inhaled, make people feel uninhibited, euphoric and dizzy—and can even result in death due to these substances' effects on the heart. Researchers from the University of Manitoba studied infants of mothers who were volatile substance abusers to determine if they were at risk for an abstinence syndrome (Tenenbein et al., 1996). They found that there is indeed an identifiable volatile substance abuse abstinence syndrome in newborns and that a characteristic chemical odour in either the newborn or the mother is a marker for its occurrence.

4.3.5 NAS as a side effect of opioid therapy

NAS is a potential side effect of medications provided for the treatment of opioid dependence in pregnant women. In general, when pregnant women are receiving methadone treatment for heroin abuse, their exposed babies have about a 60% chance of developing NAS (Finnegan & Kandall, 2005).

For many years, the dose of methadone was considered linked to the severity of NAS. Numerous studies have looked into this issue (Dryden et al., 2009; Lim, et al., 2009; Wouldes & Woodward, 2010), with some finding that the greater the dose of methadone, the greater the severity of NAS. However, an equal number of reports have found no correlation between methadone dose and NAS severity. Cleary and colleagues (2010) conducted a meta-analysis of 67 studies (29 of which met the criteria for inclusion) to help settle this debate. They concluded that the severity of NAS symptoms does not appear to differ according to whether mothers are on high- or low-dose methadone maintenance therapy.

Buprenorphine, an opioid partial agonist, is another effective medication for the treatment of opioid abuse, with numerous studies in Europe and the United States reporting its efficacy among pregnant women. In Canada, buprenorphine-naloxone is available for the treatment of opioid dependence; however, this formulation is contraindicated during pregnancy due to its naloxone component. (As discussed further in Chapter 5, although plain buprenorphine can be accessed through Health Canada's Special Access Program, logistical issues make it impractical to use in pregnant opioid-dependent women in Canada.)

NAS has been reported in varying degrees and incidence in relation to buprenorphine use. While studies have showed minimal abstinence symptoms from buprenorphine alone, those studies that included other drug use indicated significant NAS occurrence. In several well-controlled studies, the occurrence, duration and severity of NAS from buprenorphine administration were found to be less than methadone-related NAS (Fischer et al., 1998, 2006; Fischer, 2000; Johnson et al., 2003; Lacroix et al., 2004; Jones et al., 2005, 2010; Lejeune et al., 2006).

For more information about the use of methadone and buprenorphine in the treatment of opioid dependence in pregnancy, please refer to Chapter 5.

AGONIST AND ANTAGONIST DRUGS

For drugs that are site-specific, actions initiated can be agonist, antagonist or a combination of both. Agonists initiate activity in the cell; the opioids with the greatest potential for abuse are full agonists such as morphine, heroin, and oxycodone. Antagonists (such as naloxone) act in the opposite way, blocking cellular activity. Drugs such as buprenorphine, meanwhile, provide a mixture of the two effects.

4.3.6 Assessment and diagnosis of NAS symptoms

Many different variables can affect the level of fetal drug exposure, including:

- The amount and purity of the drugs taken by the mother;
- The length of drug use and the mother's drug metabolism; and
- The individual kinetics of placental drug transfer.

Because of these variables, it is not yet possible to predict at birth whether a baby will develop NAS or, if developed, whether that NAS will be of a mild, moderate or severe degree. Therefore, careful assessment and diagnosis of newborns exposed to drugs in utero is the only way to determine if they will develop symptoms and warrant subsequent treatment.

One way to identify infants at risk for NAS is through the use of a toxicology screening protocol at birth. In some centres, meconium toxicology screens are used. Meconium is the first intestinal discharge of the newborn infant. Consisting of epithelial cells, mucus and bile, it also includes any drugs the fetus was exposed to from about the twentieth week of gestation (Finnegan & Kandall, 2005).

Newborns can also be assessed for symptoms of NAS using a neurological examination such as the Brazelton Neurobehavioral Scale of Infant Development or the Neonatal Intensive Care Unit (NICU) Network Neurobehavioral Scale (NNNS). The NNNS provides a comprehensive assessment of neurological integrity and behavioural function, examining neurobehavioural organization, neurological reflexes, motor development, active and passive tone, and signs of stress and withdrawal in drug-exposed infants. Yet while the Brazelton Neurobehavioral Scale and the NNNS can yield valuable information, both require specialized training and certification to be used effectively (Lester & Tronick, 1993).

It has been suggested that the sex of the infant might play a role in predicting NAS severity, with past studies showing an increased vulnerability to adverse outcomes among males. However, a study by Unger and colleagues (2011) looking at sex-based differences in birth weight and length, head circumference, and NAS duration and severity found that while males had a significantly higher birth weight and head circumference, there were no significant sex-related differences for NAS development, severity, duration or medication administered. This study concluded that a similar postnatal vulnerability exists for both males and females, suggesting that factors other than sex are the major determinants of clinically significant NAS (Unger et al., 2011). Similarly, no differences were found in another study that examined the need for NAS treatment, length of treatment and peak dose of medication required in male and female newborns (Holbrook & Kaltenbach, 2010).

Symptom severity score sheets

Because not all drug-exposed newborns experience abstinence symptoms, routine prophylactic treatment is not recommended for NAS. Close observation of clinical symptoms is therefore very important; the use of a semi-objective symptom severity score sheet allows for the accurate evaluation of signs and symptoms, avoids unnecessary treatment of mildly affected infants and provides a methodology for the effective tapering of medications.

A number of scoring tools have been developed and reported in the pediatric literature (Lipsitz, 1975; Green & Suffit, 1981; Finnegan, 1986; Zahorodny 1998). One of these is the Finnegan Neonatal Abstinence Score, a comprehensive tool recommended by the American Academy of Pediatrics for measuring the onset, progression and diminution of symptoms of abstinence (Hudak & Tan, 2012).

The Finnegan Neonatal Abstinence Score measures 21 signs and symptoms that have been reported in infants with neonatal abstinence, including high-pitched crying, tremors, increased muscle tone, regurgitation, rapid respirations, poor feeding, poor sleep and loose stools (Finnegan, 1986). A relative weight based on a postulated relationship to outcomes of newborn morbidity is assigned to each sign and symptom, with pharmacological treatment provided according to the severity of the score. The score is then used to monitor the infant's clinical response to the treatment and the amount of medication necessary to control the symptoms. Infants are evaluated on a regular basis throughout each day; with more severe symptoms, the infant is evaluated more frequently until stabilization of NAS occurs (Finnegan & Kaltenbach, 1992).

ARLENE AND BABY ANNIE

At the age of 13, Arlene started using heroin. Now 32, she continues her habit and smokes a pack of cigarettes a day. After a series of miscarriages and elective abortions, she recently became pregnant. This time she decided to keep the baby because she cares about the father, Derek. While Derek uses alcohol and cocaine excessively, he too wants to have the baby.

Five months into her pregnancy, Arlene considered seeing a doctor but didn't because she had not stopped using heroin. At seven months, she went into labour. Derek took her to the hospital and Arlene delivered Annie, a preterm and growth-restricted baby weighing just 1,500 grams (a little over three pounds). Annie had difficulty breathing and very low calcium and sugar levels in her blood. Within the first day of life, she had seizures, which the doctors attributed to a brain hemorrhage resulting from preterm birth. Because of Arlene's recurrent heroin use, which was inconsistent in both frequency and dose, her fetus had likely experienced equally recurrent episodes of abstinence (deprivation of drugs) and overdose. Baby Annie was very sick and needed antibiotics and treatment in the neonatal intensive care unit.

After three months in hospital, Annie finally recovered. Although Arlene and Derek said they loved her, they did not seek treatment for their drug and alcohol problems. They came occasionally to the nursery to see Annie but were usually high or disruptive; on several occasions they had to be escorted out by security. As a result, Annie was placed in a foster home for medically disabled children. Her doctors believe she has little chance of experiencing normal growth and development.

THE FINNEGAN NEONATAL ABSTINENCE SCORE

With proper training, healthcare professionals can use this tool to:

- Accurately assess infants for the presence of abstinence signs and symptoms;
- Implement appropriate examination techniques to evaluate infants for clinical signs and symptoms of abstinence; and
- Document clinical signs and symptoms of withdrawal.

Source: D'Apolito & Finnegan, 2010.

4.3.7 Medical treatment of NAS

A number of different medications can be used by clinicians to treat NAS, including opioids (e.g., morphine, methadone, buprenorphine), phenobarbital and clonidine. Once the infant is clinically stabilized on a medication (based on decreasing abstinence scores), the total daily dosage can be lowered by 10% each day. Based on pharmacokinetic studies, the duration of treatment, although variable, is typically longer following in utero methadone exposure compared to heroin exposure (Finnegan & Kaltenbach, 1992).

Regardless of the medication used, after cessation of treatment the infant should be monitored in the hospital for rebound abstinence symptoms for at least two days (Finnegan & Kaltenbach, 1992; Kandall, 1999).

Opioids

Based on numerous clinical studies and the assumption that opioid exposure is best treated with another opioid, preparations such as morphine and methadone have become the treatment of choice for NAS (Jackson et al., 2004).

The American Academy of Pediatrics recommends methadone for the treatment of NAS and data are available regarding its efficacy and safety (Isemann et al., 2011). Because methadone's long-acting properties can cause doses to be incorrectly calculated, caution must be exercised; the current recommendations by the American Academy of Pediatrics suggest carefully outlined regimens for orally administered methadone or morphine (Lainwala et al., 2005).

In 2012, the Neonatal Abstinence Work Group developed a set of clinical practice guidelines for Ontario focusing on NAS resulting from opioid dependence. These guidelines provide evidence-informed recommendations for the screening, assessment and medical treatment of NAS (Dow et al., 2012).

When used during treatment, morphine has been found to reduce bowel motility and loose stools in addition to facilitating feeding and interpersonal interaction. At the same time, it can also cause respiratory depression, hypotension, delayed gastric emptying, loss of bowel motility and urinary retention. The majority of practitioners use phenobarbital as a second drug if morphine treatment does not adequately control the signs of abstinence (Sarkar & Donn, 2006; O'Grady et al., 2009).

Langenfeld and colleagues (2005) compared the efficacy of oral morphine to an alcoholic mixture of tincture of opium in the treatment of exposed infants. They found morphine to be better for treating neonatal abstinence because it avoided the unwanted effects of the alcoholic extracts while enabling better weight gain in the newborns.

In comparing the effects of phenobarbital and morphine hydrochloride, Ebner and colleagues (2007) found that infants receiving morphine required a significantly shorter mean duration of treatment (9.9 days) than those treated with phenobarbital (17.7 days), concluding that morphine is the preferable treatment for newborns with NAS.

With buprenorphine being used more frequently by pregnant women undergoing treatment for opioid dependence, researchers in Philadelphia studied the feasibility of using buprenorphine to treat NAS. A randomized comparison trial of sublingual buprenorphine versus a neonatal opium solution showed a non-significant reduction in length of treatment and duration of hospitalization in the buprenorphine group. While buprenorphine therapy was well tolerated by the infants, administration was challenging because the medication is best absorbed when placed under the tongue (Kraft et al., 2008).

Phenobarbital

Phenobarbital is a nonspecific CNS depressant that offers the advantage of a broad spectrum of sedation in cases of maternal poly-drug abuse, controlling symptoms of irritability and insomnia in 50% of infants regardless of the mother's choice of drug. However, its usefulness is limited because it does not control non-CNS signs such as loose stools, depresses sucking and,

in larger doses, can depress respirations. Phenobarbital might also mask the severity of NAS symptoms. Infants need to be closely monitored for the possibility of over-sedation; however, if physicians properly monitor the blood level of the phenobarbital, there should be no cause for alarm when using this medication for the treatment of NAS (Weiner & Finnegan, 2010).

Coyle and colleagues (2002) tested the hypothesis that treatment of NAS with a combination of phenobarbital and a diluted tincture of opium (DTO) was superior to treatment with DTO alone. They found that the combined use resulted in shorter hospital stays and less severe symptoms.

A study of neonatal seizures by Kandall and colleagues (1983) observed that 11% of infants treated with phenobarbital developed seizures. The authors postulated that phenobarbital dosages used to control abstinence were not adequate to protect against seizures in the face of enhanced methadone clearance induced by phenobarbital. Therefore, it can be concluded that an opioid is more effective in relieving the symptoms of NAS and that prompt treatment with adequate dosages likely adds to the success of treatment with avoidance of seizures (Finnegan et al., 1975; Finnegan & Kandall, 2005).

In two searches of the Cochrane Controlled Trials Register, Osborn and colleagues (2002, 2005) examined the effectiveness and safety of opioid treatment compared to the use of sedatives and supportive care. In the first search, which included five studies with 285 infants meeting inclusion criteria, they concluded there is no evidence that phenobarbital (compared to supportive care alone) reduces treatment failure; however, it might reduce the daily duration of supportive care needed. From the second search, which included seven studies with 585 infants meeting inclusion criteria, they concluded that opiates (compared to supportive care alone) appeared to reduce both the time needed to regain birth weight and the duration of supportive care, but increased the duration of hospital stay. When compared to phenobarbital, opiates might reduce the incidence of seizures but there is no evidence of effect on treatment failure, further illustrating the superiority of opioids for the treatment of NAS.

Clonidine

The American Academy of Pediatrics also recommends clonidine, an α2-adrenergic receptor agonist that can be used in combination with an opioid or other drug in older children and adults to reduce symptoms of autonomic overactivity such as rapid heart rate, hypertension, sweating, restlessness and diarrhea (Gold et al., 1978; Hoder et al., 1984).

Experience with clonidine as a primary or a complementary treatment of NAS is limited but promising. In a randomized controlled trial, Agthe and colleagues (2009) compared the efficacy and safety of treating NAS with DTO plus oral clonidine versus DTO plus a placebo in 80 infants with prenatal exposure to methadone, heroin or both. While the combination therapy significantly reduced the median length of treatment, more infants in the DTO/clonidine group required resumption of DTO after initial discontinuation. In addition, the mean total dose of morphine over the treatment course was about 60% lower in the DTO/clonidine group. No clinically significant differences in feeding, weight gain or loss, heart rate or blood pressure were observed (Hudak & Tan, 2012).

Naloxone

The opioid antagonist naloxone is occasionally given to newborns having breathing problems to reverse the acquired effects of pain medications typically administered to the mother during labour and delivery. Because of its potential for precipitating severe abstinence symptoms, naloxone should not be given to newborns exposed to opioids in utero.

4.3.8 Supporting and caring for newborns with NAS

When drug abuse occurs during pregnancy, disturbances in mother-to-infant attachment can also occur. In the mother, there is anxiety over the infant's prognosis and the intervention of social authorities, possibly leading to further substance abuse. The separation of mother and infant due to the need for NAS treatment will also disrupt the attachment process. In addition, certain characteristics in the mother (e.g., difficulties with relationships, low self-esteem, depression, ambivalence, sense of guilt, problems with paternity, lack of breastfeeding) can all contribute to difficulties with attachment. These can be exacerbated when the baby displays characteristics such as prematurity, infections and neonatal problems like NAS, all of which can cause the baby to be less responsive. Infants exposed to drugs in utero are also more irritable and tremulous and may not want to be held or cuddled, behaviours the mother might incorrectly interpret as signs of rejection (Weiner & Finnegan, 2010). As such, measures to enhance the relationship between mother and baby are essential.

When a baby is born to a mother known to be using methadone or heroin, it is usually separated from the mother and admitted to an intensive care nursery for observation. Concerned that this separation contributes to decreased maternal attachment and neonatal abandonment, Abrahams and colleagues (2007) from the University of British Columbia conducted a retrospective cohort study to compare NAS treatment and discharge outcomes of newborns who "roomed in" with their mothers to those who received traditional care in neonatal intensive care nurseries. They found that newborns who roomed in with their mothers were less likely to require treatment for NAS and were more likely to be discharged home with their mothers, concluding that rooming in might promote more effective mothering and reduce NAS prevalence and severity.

In all cases, it is important to create a supportive environment for the infant experiencing abstinence. The following techniques recommended by Weiner and Finnegan (2010) have all been proven helpful in calming the baby:

- Blanket swaddling when at rest and feeding;
- Non-nutritive sucking (e.g., with a pacifier);
- Demand feedings;
- Changes in position so that when the baby shakes, excoriation (irritation) of the skin does not occur;
- Frequent skin care and diaper changes to prevent infection from excoriated skin;
- Decreased stimuli in the hospital and/or home (e.g., a quiet, dimly lit room);
- Appropriate dressing to avoid overheating;
- Gentle handling; and
- Firm holding close to the body.

Caring for an infant with NAS can be challenging for many parents. During the hospitalization of the infant, nursing staff should take the opportunity to teach parents the supportive measures listed above. Parents should also be advised of the persistent signs of abstinence that can last for as long as six months, which can include constant sucking and exaggerated rooting reflex, sweating, sensitivity to sounds, lessened responsiveness to visual stimulation, high-pitched crying, irregular sleep patterns and loose stools. These symptoms will generally not need any intervention with medications but supportive measures are essential (Weiner & Finnegan, 2010).

As a result of the difficulties describe above, supporting the mother is equally important. Because the substance-using mother might not have all of the parenting skills expected of her, frustration leading to abuse of the infant could occur. Providing supportive care to the mother through an appropriate treatment program might prevent any untoward actions by the mother upon the baby (Weiner & Finnegan, 2010).

Breastfeeding enhances the infant's immune system as well as maternal-infant attachment. Because opioids pass to the nursing infant through the breast milk in very small amounts, breastfeeding does not affect the severity of the NAS nor does it achieve sufficient concentrations to serve as treatment for neonatal symptoms (McCarthy & Posey, 2000). However, as babies with NAS have difficulties coordinating their sucking and swallowing reflexes, breastfeeding can be very challenging.

There is a great deal of information available for the clinicians, parents and others who care for newborns experiencing abstinence symptoms, not only in the published literature but also in the numerous protocols and guidelines concerning the assessment and management of NAS. For example, British Columbia's Ministry of Children and Family Development has developed a resource for parents and caregivers on how to provide daily care for babies who have been prenatally exposed to alcohol or other drugs (Nelson et al., 2011). This resource is based on information collected from sources such as parents, caregivers, healthcare professionals and the published literature. Due to the availability of these kinds of resources and supports, there is no reason why babies affected by this condition should not be able to receive excellent care to treat and alleviate their symptoms.

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5 Comprehensive Treatment Approaches for Pregnant Women Using Drugs

Drug abuse and dependence are complex conditions that present a number of substantial challenges for the healthcare system. Addiction can be likened to other chronic, relapsing diseases, with acute aggravations of varying severity followed by periods of dormancy. In some cases, only minimal treatment is required; in others, more intensive treatment is needed.

For drug-dependent pregnant women and their unborn children, a treatment approach that combines comprehensive services, prenatal care and the stopping of illicit drug use is essential to avoiding negative outcomes. Fortunately, pregnant women, even those who are abusing drugs, generally want to do what's best for their babies. This makes pregnancy a period of opportunity to initiate changes in the mother's substance use patterns and steer her toward appropriate treatment services.

5.1 Comprehensive services

To lessen the risks associated with their high-risk pregnancies, women who abuse drugs should be given access not only to specialized, comprehensive medical and obstetrical care but also to addiction counselling and psychosocial supports. U.S. Public Law 102-321, enacted in 1993, dictates that substance-using pregnant women must have first priority for drug treatment and timely access to health care, and must be provided with appropriate child care and transportation assistance when receiving treatment (Finnegan & Kandall, 2005).

5.1.1 The evolution of the comprehensive services approach

U.S. Public Law 102-321 marked a significant change in attitudes toward women suffering from drug abuse and dependence. In his writings on the history of women and addiction, Kandall (2010) made a number of observations:

- The extent of female drug use has always been wider than acknowledged;
- Women were frequently inappropriately medicated or overmedicated by physicians and pharmacists, leading to substance abuse through self-medication;

At a Glance

- Comprehensive, multidisciplinary treatment services for pregnant women who abuse drugs have demonstrated numerous positive outcomes for the mother and baby, including adequate prenatal care, improved maternal nutrition, reduced risk of premature birth, and decreased maternal and infant morbidity and mortality.
- A comprehensive treatment approach is one that combines a variety of services including medical and prenatal care, addiction counselling, psychosocial supports, child care services and transportation assistance.
- The stigma associated with drug abuse, particularly among pregnant women, presents a significant barrier to accessing treatment.
- Supervised medication-assisted treatment is an effective component of a comprehensive treatment plan for pregnant women who abuse drugs. However, there is comparatively less research that has examined how a newborn is impacted by exposure to such treatment, which limits the ability to draw firm conclusions.
- Mothers undergoing medication-assisted treatment can breastfeed their babies except in certain circumstances when there is continued concomitant drug use or HIV positivity.

- Women are more vulnerable to social ostracism, vilification and prosecution because of their drug use; and
- Addicted women have typically been marginalized and politically ignored, resulting in them receiving little help for their substance abuse problems.

CREATING A NATIONAL PICTURE OF ADDICTIONS TREATMENT IN CANADA

Historically, there has not been a central place where Canadians could go for information about treatment services for substance use. As part of the National Treatment Strategy, an interactive map has been created to address this gap, providing information on:

- How treatment services for those suffering with substance abuse are organized;
- Provincial and territorial strategies for addressing substance use; and
- Treatment service summary data.

In addition, the National Treatment Indicators (NTI) project aims to provide a comprehensive picture of substance use treatment in Canada. The recently published National Treatment Indicators Report summarizes 2010–2011 jurisdictional-level data on treatment services across the country.

Both the map and the NTI report are available at www.nts-snt.ca.

In the 1970s, the women's rights movement created an atmosphere in which a more enlightened discussion of women and drugs could occur. This, in turn, enabled the development of a comprehensive model of care that could enable addicted women to receive medical, obstetric and psychosocial services under one roof (Finnegan et al., 1972). By 1975, the U.S. National Institute on Drug Abuse (NIDA) had launched innovative drug-treatment demonstration grants in six cities, all using pregnancy as the entry point. At the same time, programs such as the Family Center Program in Philadelphia, the Hutzel Hospital Program in Detroit and the Pregnant Addicts and Addicted Mothers Program in New York were pioneering efforts to provide pregnant and parenting women using substances with a network of comprehensive, inter-related services.

5.1.2 A "one-stop" approach to drug treatment

Philadelphia's Family Center, established in 1972 and still in operation today, has determined that the intertwining medical and psychosocial risk factors that typically characterize drug dependency during the perinatal period is best treated by a comprehensive, supportive and nonjudgmental approach. In particular, its approach encompasses the following:

- A wide range of treatment services (residential, outpatient, home-based, prison-based);
- Onsite methadone maintenance treatment and inpatient stabilization of opioid-addicted patients;
- Inpatient treatment of newborns exhibiting signs of withdrawal (through the Newborn Nursery Service at Thomas Jefferson University Hospital);
- Long-term residential drug treatment services (through My Sisters Place at Thomas Jefferson University Hospital);
- Family-based health care (obstetric, pediatric and general medical), which is made available to the baby, father, significant other, grandparents and whomever else the pregnant woman identifies as being important to her recovery;
- Multiple counselling and therapy modalities (individual, group and family);
- Counselling on sexual abuse and domestic violence;
- Services for children (day care, play therapy and parental training);
- Concrete services (transportation, housing and food);
- Educational training (job training and high school equivalency training);
- Advocacy services (legal, welfare and child protection); and
- Aftercare.

In addition, by providing all of these services from a single location, the Family Center Program makes it easier for pregnant women to access the multiple aspects of treatment, ultimately enhancing compliance with their treatment plans.

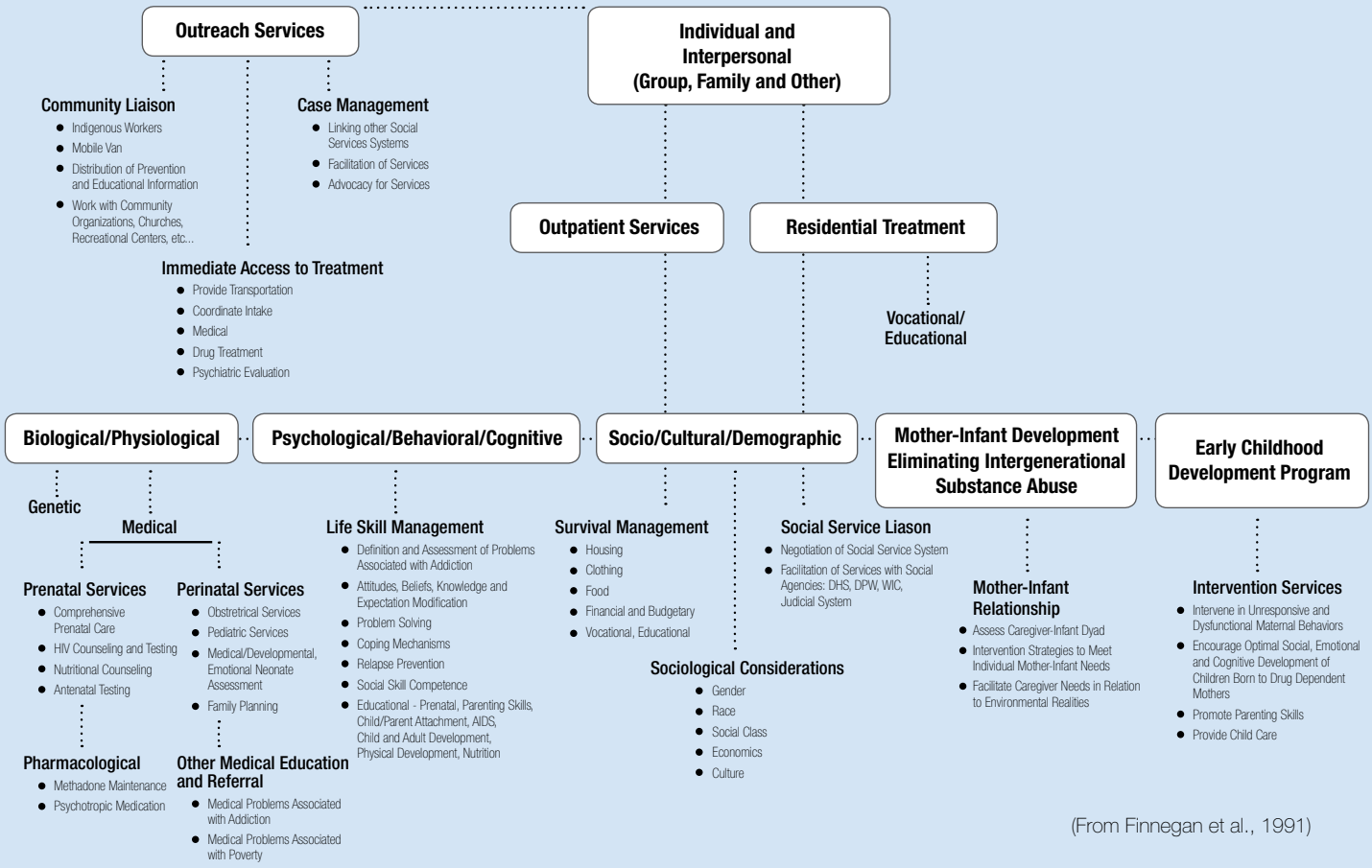
Comprehensive services like those offered by the Family Center Program require the collective effort of professionals from a multitude of disciplines, including physicians (e.g., addiction specialists, psychiatrists, obstetricians), pharmacists, nurses, social workers, psychologists, addiction counsellors and child development specialists. In addition, many of the activities designed to normalize the lives of the women enrolled in these kinds of programs are best accomplished in group settings that can address topics such as relapse prevention, life skills, problem solving, coping, parenting, child care and child development, women's health, neonatal abstinence, and anger and stress issues (Finnegan et al., 1991).

Because enrolment in a comprehensive services program typically lasts only three to six months prior to delivery, the aim of such programs is to reduce illicit drug use and enable a more stable life situation. Complete recoveries from drug dependence cannot be expected in such a short timeframe because treatment duration and intensity are both directly correlated to the recovery outcome. Women should therefore be engaged in treatment for an adequate period of time from pregnancy until the family is stable and safe. It is also important to reassess treatment needs periodically as multiple episodes of treatment might be necessary.

5.1.3 Outcomes of comprehensive services

Multiple studies have shown that comprehensive, multidisciplinary care for using drug pregnant women decreases illicit drug use, improves retention in treatment programs, increases the amount of prenatal care received, improves maternal nutrition, boosts maternal self-esteem, decreases maternal and infant morbidity and mortality, reduces the risk of premature birth, improves birth weights, creates home environments better suited for a newborn baby and enhances

Figure 1. Family Center schema for the treatment of drug dependency in the perinatal period and aftercare



(From Finnegan et al., 1991)

mother-child attachment (Finnegan et al., 1991). In addition, substance abuse treatment programs integrated with prenatal care have proven to be effective in reducing maternal and fetal pregnancy complications and costs (Finnegan et al., 1972, 1991; Armstrong et al., 2003).

Many programs have used treatment regimens similar to the one used by the Family Center Program over the years, with numerous studies finding that comprehensive services contribute to excellent outcomes for pregnant women and their babies. For example:

- Reporting on the outcomes of women enrolled in New York Medical College's Pregnant Addicts and Addicted Mothers Program, Green and colleagues (1979) found the number of prenatal visits correlated significantly with the newborn's gestational age at birth. They concluded that better neonatal outcomes occurred when the mother joined a comprehensive services program early in pregnancy and attended relatively often. Similar findings were also reported by Suffet and Brotman (1984). After providing pregnant addicts and their infants with comprehensive medical, counselling and child development services, they found the most favourable outcomes were directly related to the amount and duration of prenatal care.
- In the 1990s, Johns Hopkins University in Baltimore, Maryland, assessed its comprehensive services for pregnant women using drugs attending the Center for Addiction and Pregnancy, which combines the disciplines of pediatrics, addictions, obstetrics and family planning. The university found that it was able to improve both maternal and neonatal outcomes, with infants showing developmental indices within the normal range. Treatment costs were also reduced as a result of the mother having fewer medical complications and decreased infant morbidity (Jansson et al., 1996).
- The Toronto Centre for Substance Use in Pregnancy (T-CUP) is a family medicine program that uses the "one-stop access" model to provide comprehensive services, including addiction counselling and pre- and postnatal medical care, to pregnant women with a history of alcohol or drug abuse. In a retrospective chart review of 121 women who received care at T-CUP from August 2000 to January 2006, Ordean (2011) found positive maternal and infant health outcomes when the women had received comprehensive care, with approximately 75% of newborns discharged to home in the care of their mothers.

The comprehensive services model is also used outside of North America. From their review of the management of drug misuse in pregnancy, Day and George (2005) from the University of Birmingham in the United Kingdom noted that a range of service models have been developed in response to specific local needs and positive results have been achieved. For example, they found evidence that residential treatment programs that include facilities to admit children with their parents have improved rates of retention in treatment and higher abstinence rates (Hughes et al., 1995). They also found that the more comprehensive a residential program, the better the outcomes (Stevens & Arbiter, 1995). However, significant improvement in the health of opioid-dependent pregnant women and their babies can occur if they are monitored as outpatients by specialist obstetric units with expertise in managing substance use (Dunlop et al., 2003).

Day and George (2005) concluded that drug abuse is best managed through the development of a care plan that involves obstetric, neonatal and social services. They also noted that the predominantly negative attitudes toward pregnant women using substances must be taken into consideration, as these will have an impact on whether an individual seeks help and subsequently enters a treatment program.

In France, Brulet and colleagues (2007) evaluated the drug-using behaviour and pregnancy outcomes of 114 opioid-dependent women receiving multidisciplinary monitoring and psychosocial support at Montpellier University Hospital. Like the other studies mentioned above, their results also found that multidisciplinary prenatal care that included medical, social and psychological support decreased maternal and fetal risks during pregnancy.

5.1.4 Barriers to the delivery of comprehensive services

Although comprehensive service programs are becoming increasingly available, as of 2010 only 19 U.S. states had drug-treatment programs for pregnant women and only nine gave priority access to pregnant women. In addition, many of these programs frequently do not provide child care, do not account for women's family responsibilities or fail to provide affordable treatment (Guttmacher Institute, 2010). Under such restrictions, women who have not received treatment for drug dependence cannot be assumed to have rejected treatment (Flavin & Paltrow, 2010). Despite the many benefits associated with comprehensive services, it is evident that healthcare providers are still missing numerous opportunities to effectively intervene in the lives of pregnant women addicted to drugs.

For example, Mann and colleagues (1992) found that while services to 4,539 newborns prenatally exposed to drugs were provided by the State of Florida in 1990, an estimated 5,911 did not receive services because of an overburdened healthcare system and a failure to identify women in need of treatment. That said, the number of substance-abusing women identified during pregnancy increased markedly from 1989 to 1990; as more pregnant women were given appropriate prenatal care and referred for drug abuse treatment, low birth weight in newborns prenatally exposed to drugs decreased from 55% in 1989 to 26% in 1990.

Through personal interviews with 181 addicted women and a survey of 94 drug treatment programs in Washington, DC, Gershan (1995) examined the practices of prenatal care providers in detecting substance abuse among pregnant women and making referrals to treatment services. While a majority of the women (65%) had been asked about alcohol and drug use by physicians or nurses during their most recent pregnancies, 59% of those asked were not given any information about the effects of alcohol or drugs on pregnancy. More alarmingly, only 5% of those asked were referred to drug counsellors or treatment programs, even though 43% admitted to substance use and an additional 13% were using but did not admit it. Fortunately, with the increased availability of literature about drugs and pregnancy from government sources and advocacy groups, more healthcare professionals are now capable of providing information and making appropriate referrals.

Pregnant women can also be at increased risk of attrition. Putting pregnant women on a waiting list, for example, results in the loss of a critical opportunity to provide treatment; in many cases, women are more likely to deliver their babies before being enrolled in the treatment program. The effect of wait times on substance abuse treatment completion in 10,661 pregnant women was studied in Baltimore, Maryland. Analyzing the women's treatment admissions and discharges, the study found that shorter wait times are associated with increased treatment completion rates, especially in the ambulatory setting (Albrecht et al., 2011).

Stigma also presents a significant barrier to treatment. Women who feel guilt and shame about their substance use tend to have difficulty seeking and accessing the help they need. When they do reach out to healthcare professionals, women using drugs often encounter misinformation, denial, inaction and even punitive attitudes toward their substance use (Copeland, 1997; Grella, 1997; Health Canada, 2001; Poole & Isaac, 2001; Cormier et al., 2004).

In particular, Cormier and colleagues (2004) made a number of recommendations related to the treatment of women using drugs. One was to make treatment programming that addresses gender differences more easily accessible to women in Canada. Another concerned the blending of treatment for substance abuse, mental health and relationship violence, calling for linkages among these programs to be enhanced—or even integrated—to better address the interconnections among these health issues.

5.2 Prenatal care and the role of the obstetrician

Although they represent just one aspect of the comprehensive services model, obstetricians, gynaecologists and other healthcare providers (e.g., family physicians) have an important part to play in substance abuse treatment and intervention. They can influence the outcomes for pregnant women and their babies by providing appropriate information to encourage healthy behaviours, adhering to safe prescribing practices, and identifying and referring patients who are abusing drugs to addiction treatment professionals (American Congress of Obstetricians and Gynecologists [ACOG], 2006, 2011).

The role of the obstetrician is especially important given that substance-abusing women have considerable risk of maternal and fetal complications. Obstetricians should evaluate these

high-risk patients for poor maternal nutrition, intrauterine growth restriction, and poor placental perfusion and function. In the case of alcohol abuse, the possibility of fetal alcohol spectrum disorder accompanied by poor fetal growth and central nervous system abnormalities must be considered. Placental abruption and stillbirth are important additional considerations in the event of cocaine abuse (Keegan et al., 2010).

As part of its goal to improve awareness of the issues related to substance use during pregnancy, the Society of Obstetricians and Gynaecologists of Canada has developed the following evidence-based recommendations for screening and managing problematic substance use during pregnancy and lactation (Wong et al., 2011):

- All pregnant women of childbearing age should be screened periodically for alcohol, tobacco and prescription and illicit drug use.
- When testing for substance use is clinically indicated, urine drug screening is the preferred method.
- Because policies and legal requirements with respect to drug testing of newborns can vary by jurisdiction, caregivers should be familiar with the regulations in their region.
- Healthcare providers should employ a flexible approach to the care of women who have substance use problems and should encourage the use of all available community resources.
- Women should be counselled about the risks of periconception, antepartum and postpartum drug use.
- Smoking cessation counselling should be considered as a first-line intervention for pregnant smokers. Nicotine replacement therapy or pharmacotherapy can be considered if counselling is not successful.
- Methadone maintenance treatment should be the standard of care for opioid-dependent women during pregnancy. Other slow-release opioid preparations can be considered if methadone is not available.
- Opioid detoxification should be reserved for selected women because of the high risk of relapse to opioids.
- Opioid-dependent women should be informed that newborns exposed to heroin, prescription opioids, methadone or buprenorphine during pregnancy are monitored closely for symptoms and signs of neonatal withdrawal. Hospitals providing obstetric care should develop a protocol for assessment and management of newborns exposed to opioids during pregnancy.
- Antenatal planning for intrapartum and postpartum pain medication can be offered for all women in consultation with appropriate healthcare providers.
- The risks and benefits of breastfeeding should be weighed on an individual basis because methadone maintenance therapy is not a contraindication to breastfeeding.

5.2.1 Management of maternal nutrition

For many obstetricians, managing the nutritional intake of a substance-using pregnant woman can be particularly frustrating because it is often quite difficult to change a person's established behaviours. Even so, nutritional counselling from trained dieticians, frequent weight checks and fetal surveillance for intrauterine growth restriction should be incorporated into routine obstetrical care for substance-abusing mothers (Keegan et al., 2010).

Nutritional counselling

Pregnant women abusing drugs should be counselled on the importance of a balanced diet and should be given recommendations for caloric intake and appropriate weight gain. Because dietary allowances of most vitamins and minerals increase during pregnancy, prenatal vitamins and iron supplements should be included in the daily diet. Iron deficiency anemia is a common problem in substance-abusing pregnant women; therefore, an additional 60–120 milligrams of iron is recommended. Vitamin C and folic acid are also important supplements for pregnant women, regardless of substance-abusing status (Keegan et al., 2010).

Surveillance for intrauterine growth restriction and fetal weight

Alcohol and drug use are strongly associated with intrauterine growth restriction (ACOG, 2007). Because this is the case, surveillance for appropriate fetal growth and placental function is a critical component of care for pregnant women using drugs.

Recommendations regarding surveillance for fetal growth and placental function generally involve regular uterine fundal height[7] measurements and ultrasound evaluations, with particular attention paid to fetal head circumference and biparietal diameter (distance across the fetal head), abdominal circumference, amniotic fluid indices and Doppler velocimetry (measurement of the rate of blood flow through the umbilical artery). When intrauterine growth restriction is confirmed, the possibility of perinatal death or stillbirth becomes an important consideration. Although intrauterine growth restriction can almost never be reversed, careful surveillance is associated with a reduction in perinatal death (ACOG, 2007).

Non-stress testing, contraction stress testing and the biophysical profile are three common tests used by obstetricians to assess fetal well-being. Ultrasound measurements of the biparietal diameter and fetal head circumference, abdominal circumference and femur length provide the most accurate estimated fetal weight. These measurements should be taken every two to four weeks if intrauterine growth restriction is suspected (Keegan et al., 2010).

5.2.2 Delivery and labour

The timing of delivery can also be a challenge for obstetricians, who must carefully weigh the risk of prematurity versus the ongoing risk of intrauterine fetal death if poor fetal growth or placental insufficiency is suspected. Oligohydramnios or anhydramnios (a small amount or no amniotic fluid, respectively) as well as abnormalities in the uterine blood flow can all indicate the need for delivery. The complete absence of fetal growth observed in consecutive ultrasound evaluations two to four weeks apart can also provide a strong indication for the obstetrician to intervene with an early delivery (Keegan et al., 2010).

Management of the substance-using woman in labour can present additional challenges. Communication with the patient and management of anesthesia are of primary importance. Nurses, physicians and midwives must put the patient at ease and inform her of the potential for a variety of obstetric interventions, all of which will be done to maximize the likelihood of a positive outcome for her and her baby.

Establishing effective lines of communication with pregnant women using substances can be difficult, especially when they present in the labour area with erratic, bizarre, angry or uncaring behaviour (Byrne & Lerner, 1992). One reason why pregnant women might present such behaviour is because they have taken drugs prior to arrival to the labour suite. Cocaine and heroin users will frequently obtain drugs when labour begins, fearing that pain medication will not be offered or be inadequate. In these instances, obstetricians can establish a trusting relationship by speaking in a calm voice, using appropriate physical contact and employing soft lighting, all of which can be beneficial while trying to gain control of a potentially chaotic situation (Byrne & Lerner, 1992).

When a substance-abusing woman presents in labour, selecting the correct anesthesia or analgesia is particularly important. Various studies have delineated dangerous combinations of drugs of abuse and certain medications generally used for alleviating pain or anesthesia (Kuczkowski, 2003, 2005; Ludlow et al., 2007). For example:

- Tobacco use affects the pulmonary system by increasing sputum and secretion production and by impairing gas exchange;
- Cigarette smoking can affect liver enzyme function and alter the metabolism of the induction agents used for general anesthesia;
- Alcohol intoxication increases gastric acidity and diminishes the ability to protect the airway;
- The labouring patient with a history of opioid abuse can present with respiratory depression and arrest;
- Cocaine-induced thrombocytopenia (a decrease in the blood platelets that assist in clotting) can present a contraindication to regional anesthesia and analgesia;
- Central nervous system effects commonly observed in amphetamine users, such as increased alertness and euphoria, can make placement of regional anesthesia difficult;
- Patients presenting in labour with recent marijuana use often experience heart dysfunction and rapid heart rate;

[7] Fundal height is a measure of a pregnant woman's belly to see if the gestational age is compatible with the uterus size. A baby growing inside the womb of a pregnant woman will have a fundal height that matches closely (if not exactly) with the amount of weeks the mother has been pregnant. For example, a woman who is 33 weeks pregnant should have a fundal height measurement of 32–34 centimetres.

- Marijuana can increase the sedative and hypnotic effects of anesthetic agents; and
- Heavy marijuana use can impair lung function.

With the potential complications expected when administering anesthesia to pregnant women using drugs in labour, regional anesthesia is usually the best choice. Regional anesthesia is considered safe for alcohol-abusing patients as long as they do not suffer from an underlying neuropathy or clotting disorder. It is also safe for opioid abusers, who can have diminished anesthetic requirements. (Conversely, chronic opioid abusers can actually have increased tolerance and therefore require higher doses than anticipated.) However, both regional and general anesthesia can be complicated in cocaine users. Propofol, a commonly used medication in the United States, has been shown to be effective for the induction of anesthesia in cocaine-abusing mothers (Ludlow et al., 2007).

Unless there is a strong clinical indication to do so, pregnant women undergoing methadone maintenance therapy should not have their methadone withheld during labour because they will most likely experience withdrawal symptoms (Ludlow et al., 2007).

5.3 Contingency management

Stopping the use of illicit drugs is the best way to improve maternal and fetal health outcomes. Unfortunately, this is easier said than done. Individuals addicted to alcohol and other drugs often fail to stay off their drugs of choice because they will not go to or stay in treatment.

Contingency management is one approach that can be taken to improve patients' motivation to remain in treatment. First used in the addiction field in the 1960s, contingency management is based on the idea that behaviour is more likely to continue if it is reinforced. By systematically rewarding desired behaviours and withholding reinforcement of undesired behaviours, contingency management is an effective strategy for reducing the use of alcohol and other drugs, improving attendance of treatment programs and reinforcing treatment goals such as complying with a medication regimen or obtaining employment (Miller, 1975; Higgins et al., 1993; Higgins & Petry, 1999).

One form of contingency management is the token economy system, which has been shown to be successful with a diverse array of populations, including those suffering from addiction (Petry, 2001). Another is voucher-based contingency management, where patients earn vouchers (often exchangeable for prizes or program-specific privileges) contingent upon objectively verified abstinence or the achievement of specific behaviour-change goals (Petry et al., 2007; Stitzer et al., 2007). In a series of controlled clinical trials, the voucher-based approach was shown to be the most reliable method for producing abstinence in cocaine users (Lussier et al., 2006; Prendergast et al., 2007).

Contingency management has been effectively used to treat single-problem addictions as well as dual diagnoses (Drebing et al., 2007; Ghitza et al., 2008). Positive contingency rewards can also improve pregnancy outcomes; the 2010 Maternal Opioid Treatment: Human Experimental Research (MOTHER) Study found that escalating reinforcement procedures can help decrease drug abuse and increase outpatient attendance (Jones et al., 2010).

5.4 Medication-assisted treatment

Medication can become an essential part of an addict's ongoing treatment plan, enabling opioid-addicted individuals to regain control over their lives.

Because drug use changes the way the brain works (i.e., by causing compulsive behaviour focused on drug seeking and use), medical treatment for substance abuse must address these neurological changes to be truly effective. Medications developed to treat opioid addiction, such as methadone and buprenorphine, work through the same receptors in the brain as the addictive drug but are less likely to produce the harmful behaviours that characterize addiction. These medications work by either activating opiate receptors[8] in the brain but producing a diminished response, or by blocking these receptors and interfering with opioids' rewarding effects (National Institute on Drug Abuse, 2012).

Although both methadone and buprenorphine effectively suppress opioid use, it is important to note that neither medication is a "cure" for opioid addiction.

[8] Opiate receptors are proteins found in the spinal cord, brain and gastrointestinal tract. Opioids such as heroin, morphine and methadone bind to these receptors in the brain to reduce feelings of pain and cause feelings of euphoria.

RAMONA

Ramona, 28, had been dating Carlos for just over a year. He treated her well and had lots of money. Having grown up poor, she thought he would be a good man to marry. But she was unaware that Carlos' income came from dealing drugs. One night at a party, he cajoled her into snorting heroin. The only drug Ramona had tried in the past was marijuana. Although she didn't like heroin at first, after several hits she found she enjoyed the high—and that it pleased Carlos. Her occasional use became increasingly frequent, until she was using heroin every day. Her life began to change. She found it hard to get up for work. Her parents noticed a shift in her personality and that she had gained a lot of weight. Carlos became abusive; Ramona became depressed.

Then she discovered she was pregnant. Almost immediately, she sought to recover from her addiction because she was sick on a daily basis and about to lose her job. Fortunately, a friend referred her to a clinic that provided comprehensive services and methadone maintenance treatment for individuals dependent on heroin. After being evaluated for her addiction, psychiatric status and pregnancy, she was provided with high-risk obstetrical services, counselling and daily methadone. She could receive her methadone early in the morning and counselling after work twice weekly. She ended her relationship with Carlos, and is focusing on recovery and becoming a good parent.

5.4.1 Methadone

A synthetic opioid, methadone is used medically as an analgesic for managing severe chronic pain and, more pertinent to this publication, as a maintenance medication in patients with opioid dependency.

Methadone maintenance for opioid-dependent individuals began as a research project at the Rockefeller University in 1964 in response to the burgeoning post-war heroin addiction epidemic (Joseph et al., 2000). Since then, it has been rigorously tested and safely used to treat opioid addiction for more than 40 years.

Methadone works by blocking the craving for opioids (which is a major factor in relapse), suppressing the symptoms of opioid withdrawal for 24–36 hours and blocking the effects of administered heroin or other opioids (such as oxycodone). In addition, it does not cause intoxication or sedation, meaning it does not impair cognitive functions and has no adverse effects on mental capability or intelligence (Centers for Disease Control and Prevention [CDC], 2000). In a Cochrane review of 11 randomized clinical trials, methadone maintenance therapy appeared significantly more effective compared to non-pharmacological approaches in retaining patients in treatment and in the suppression of heroin use (Mattick et al., 2009). Enrolment in methadone maintenance treatment also has the potential to reduce the transmission of infectious diseases associated with heroin injection, including hepatitis and human immunodeficiency virus (HIV; Joseph et al., 2000).

Because methadone offers similar effects to heroin and morphine but without the same intensity, properly dosed patients can reduce or cease their use of these illicit substances completely. Daily methadone doses of 80 milligrams or more have been shown to exert a definite blocking effect on heroin craving, with the exact dose depending on a variety of individual factors. Provided the dosage is appropriate for a given patient, he or she can be maintained for years on methadone. Given that methadone is a corrective rather than a curative treatment for heroin addiction, it should be prescribed for an indefinite period of time (Joseph et al., 2000).

Some of the side-effects of methadone maintenance therapy can include sweating, constipation, sexual difficulties, drowsiness and weight change (Centre for Addiction and Mental Health, 2008; Bonhomme et al., 2012). An increase in methadone dosage may cause drowsiness for up to three days, making driving and other activities that require alertness potentially more hazardous (New Brunswick Addiction Services, 2005).

Regulation of methadone

In Canada, methadone is listed under Schedule I of *Controlled Drugs and Substances Act*. This means that, unless authorized, the possession, trafficking, importing and exporting of methadone are all illegal. To prescribe methadone for analgesia or for the treatment of opioid dependence, physicians must be exempted under Section 56 of the Act. The support of the physician's licensing body is also normally required.

British Columbia, Saskatchewan, Ontario and Quebec have their own provincial guidelines that should be followed by practitioners prescribing methadone in those provinces. Health Canada has also produced guidelines for methadone maintenance treatment to be followed by all other provinces (Health Canada, 2002).

In the United States, the *Controlled Substances Act* classifies substances according to their currently accepted medical use as well as their relative abuse potential and likelihood of causing dependence. Drugs in Schedules II–V, including methadone and other opioids such as morphine and oxycodone (all of which are listed under Schedule II), have some accepted medical use and may therefore be prescribed, administered or dispensed for medical use.

Methadone was approved by the U.S. Food and Drug Administration (FDA) in 1973 for medical use against heroin addiction and is currently the only opioid medication approved for medication-assisted treatment in pregnant women (CDC, 2000). The FDA has also established five categories (A, B, C, D, X) to indicate the potential of a drug to cause birth defects if used during pregnancy. (It should be noted that risks from pharmaceutical agents or their metabolites in breast milk are not accounted for in these categories). Although approved by the FDA, methadone is listed as a Category C pregnancy

drug, which states that although animal studies have shown an adverse effect on the fetus and there have been no adequate and well-controlled studies in humans, the potential benefits may warrant its use despite the risk.

In addition, methadone maintenance is considered so vital for the health of opioid-addicted pregnant women that U.S. federal regulations require these women be given preference for admission to methadone maintenance treatment and that arrangements be made for proper medical care during pregnancy (Institute of Medicine, 1995).

For a more detailed description of the various drug classifications and regulations used in the United States and Canada, please see the appendices.

Outcomes of methadone maintenance during pregnancy

Considered medically safe for pregnant women when used under proper supervision, methadone has long been the "gold standard" of treatment for opioid-dependent pregnant women (Dole & Nyswander, 1965; Joseph et al., 2000).

Among heroin-abusing pregnant women, various studies (Mitchell, 1993; Institute of Medicine, 1995; Center for Substance Abuse Treatment [CSAT], 2005) have shown methadone maintenance to:

- Reduce illegal drug use;
- Improve maternal nutrition;
- Increase the likelihood of prenatal care;
- Permit a more stable intrauterine environment for the fetus, decreasing the chances of fetal oxygen deprivation;
- Reduce the slowing of fetal growth and increase newborn birth weight;
- Stabilize the mother's daily routine, enhancing her ability to physically and psychologically prepare for birth;
- Reduce obstetrical complications;
- Help remove the opioid-dependent woman from the drug-seeking environment and eliminate related illegal behaviours (such as prostitution); and
- Offer an opportunity for these women to restructure their lives toward the goal of continued stabilization after pregnancy.

When coupled with comprehensive care, methadone maintenance for opioid-dependent pregnant women has been shown to reduce perinatal morbidity and mortality, largely due to reduced rates of low-weight births and improved treatment of maternal complications (Finnegan, 1991a; Jarvis & Schnoll, 1994; Finnegan & Kandall, 2005). A systematic review of randomized controlled studies of methadone treatment during pregnancy also revealed an approximate threefold reduction in heroin use and a threefold increase in treatment retention relative to non-pharmacologic treatment (Rayburn & Bogenshutz, 2004).

A recent Ontario study compared mortality rates of infants exposed to methadone to those of the general population using data from several provincial and national databases (Kelly et al., 2012). The authors concluded that children under the age of one year who were born to mothers on methadone maintenance therapy were not at increased risk for mortality.

Finally, mothers stabilized on methadone are more likely to retain custody because of the opportunities for child care, parenting education and life skills management offered at many methadone clinics that provide comprehensive services (CSAT, 2005).

Managing methadone dosage in pregnant women

Although the benefits are clear, methadone can be a potentially dangerous medication unless properly supervised. Therefore, it is highly controlled and pregnant women must make daily visits to an approved program to receive their medication dose, which will only suppress cravings for 24–36 hours. One of the most common side effects of methadone maintenance is neonatal abstinence syndrome (NAS) when the drug supply is interrupted at birth. (See Chapter 4 for a more in-depth discussion of NAS.) Fortunately, the risks to pregnant women and their unborn babies are few if the methadone dosage is properly managed.

Studies on the pharmacology of methadone in pregnant women revealed that plasma methadone levels during pregnancy show marked intra-patient and inter-patient variability (Pond et al., 1985). As pregnancy progresses, the same methadone dose produces lower blood methadone levels because of increased fluid volume, a larger tissue reservoir for methadone and altered opioid metabolism in both the placenta and the fetus. Because

women often experience symptoms of withdrawal during the later stages of pregnancy, dosage increases are required to maintain blood levels of methadone and avoid withdrawal symptoms (Whittmann, 1991).

Physicians have historically taken a low-dose approach to methadone treatment, basing maternal dosage solely on the need to decrease the incidence and severity of NAS without consideration of the pregnant woman's comfort. However, reduced methadone dosages may result in continued substance use with increased risks to both the pregnant woman and the fetus. Higher dosages for the pregnant woman (i.e., 50–150 milligrams per day), on the other hand, have been associated with increased weight gain, decreased illicit drug use, improved compliance with prenatal care and, in general, better neonatal outcomes (with the exception of the risk of NAS). Higher dosages early in pregnancy have also been associated with more normal fetal growth (Kandall et al., 1976).

Women receiving methadone prior to pregnancy will be initially maintained at their pre-pregnancy dosage. Pregnant women using heroin who are not yet on methadone when enrolling into treatment can be inducted onto methadone in an outpatient setting or, more preferably, admitted to hospital where they can be stabilized[9] on the medication within 48–72 hours. During the hospitalization, the health status of the pregnant women can be evaluated and they can be provided with treatments for any medical complications that exist. Given the adverse effects of poly-substance use on both maternal and fetal health, prenatal patients also need to be monitored for their use of other licit or illicit substances while receiving methadone.

Although methadone therapy has been used consistently in pregnancy for more than four decades, no randomized trials comparing dosing regimens have been published on which to base specific therapeutic recommendations. As such, clinicians tend to use dosages that are individually determined and intended to keep both the woman and fetus subjectively and objectively comfortable and medically stable.

Challenges related to methadone maintenance in pregnant women

Although methadone maintenance is an effective treatment for opioid-dependent pregnant women, it does present a number of challenges to these women and their healthcare providers. Compared to men, women are more likely to have:

- Total responsibility for child care;
- Lower socioeconomic status;
- Difficulty with transportation;
- Greater barriers to treatment entry and retention; and
- Different psychological, counselling and vocational training needs.

Once the baby is born, the daily trips to the methadone clinic might become cumbersome or the mother might not feel well enough to make the effort to attend treatment to receive her methadone dose, which could lead her back to illicit drugs. A great deal of support is therefore necessary from her family as well as medical staff to keep her involved in her treatment.

In addition, if the baby remains in the hospital for treatment of NAS, it is very important for the mother to visit daily to develop an attachment to the infant. Again, support systems are essential.

Broader issues of treatment access and regulation are also of significant concern. For example, in 1998, the U.S. National Institutes of Health (NIH) issued a consensus statement on the treatment of opioid addiction, recommending methadone maintenance as the standard of care for pregnant women with opioid addictions (NIH, 1998). In particular, the NIH made the following recommendations:

- Methadone maintenance coupled with relevant social, medical and psychosocial services has the highest probability of being the most effective of all treatments for opioid addiction;
- Opioid-dependent persons under legal supervision (e.g., probation, parole, in prisons) should have access to methadone maintenance treatment;

[9] Stabilization of patients onto methadone is a method of increasing the dose upward from a base level so that withdrawal is prevented in both the pregnant mother and the unborn baby.

- Political and medical leadership is needed to better educate the public and address the stigma and misunderstanding creating barriers to the expansion of methadone maintenance treatment;
- With better training of healthcare professionals and guidelines for accreditation, methadone could be prescribed and dispensed in a variety of medical settings, including physicians' offices, primary care centres and pharmacies; and
- Funding of methadone maintenance must be increased, with coverage for treatment of opioid addiction included in both public and private insurance.

Although some of the NIH recommendations have been successfully implemented, federal agencies in the United States are still working to set others in place. To follow up on their implementation, the Legal Action Centre (2011) prepared a report for the American Association for the Treatment of Opioid Dependence examining the availability of medication-assisted treatment in the U.S. criminal justice system. Although an estimated 65% of individuals in American prisons or jails have a substance use disorder, with a substantial number of these individuals (many of them women in their childbearing years) addicted to opioids, this report revealed widespread denial of access to medication-assisted treatment. The report's findings underline how access to treatment is not uniform across different sectors.

Some criminal justice agencies deny access to treatment according to a larger policy prohibiting the use of any prescribed controlled substance; however, such policies also are likely to violate the *Americans with Disabilities Act* or the *Rehabilitation Act* because of their disparate impact on opiate-addicted individuals in need of treatment. The failure to grant individuals who need treatment an exemption from such policies as a "reasonable accommodation" would also likely violate these anti-discrimination laws. And by forcing individuals receiving medication-assisted treatment to detoxify without appropriate medical supervision or delay provision of treatment, prisons and jails also risk violating the U.S. Constitution's Fourteenth Amendment Due Process Clause (Legal Action Center, 2011).

It is clear that methadone maintenance is subject to a number of difficult ethical questions. For instance, some claim that substituting a highly addictive drug with a strong medication is not an appropriate or healthy choice. And while there are many hurdles still to overcome with regard to methadone regulations, policies and practical considerations—not to mention the existing stigma and prejudice toward pregnant women receiving this form of treatment—treatment professionals, research scientists and thousands of formerly addicted individuals will attest to the fact that methadone is a safe and effective treatment.

5.4.2 Buprenorphine

Methadone has been the standard of care for opioid-dependent pregnant women for several decades. However, if methadone is refused, cannot be tolerated or is unavailable, medication-assisted treatment using buprenorphine—a semi-synthetic opioid agonist/antagonist—may be considered as long as informed consent is obtained and the physician clearly explains to the patient that there is limited clinical experience regarding the safety of its use during pregnancy when compared to methadone (CSAT, 2004).

Like methadone, buprenorphine treats opioid dependency by blocking the symptoms of withdrawal, and a number of studies in recent years have demonstrated its feasibility and effectiveness in the treatment of opioid-dependent patients. Through a review of the current evidence available on MEDLINE and the Cochrane Database of Systematic Reviews, Ducharme and colleagues (2012) from the McGill University Health Centre in Montreal found that buprenorphine has a long duration and less potential for abuse than methadone and for detoxification purposes is at least equivalent to methadone in terms of efficacy (Gowing et al., 2006). While they found that methadone has a slight advantage in terms of treatment retention, a stepped approach with initial use of buprenorphine followed by referral to methadone maintenance was also shown to be efficacious (Kakko et al., 2007). Citing the potential of buprenorphine to increase safety and treatment accessibility for opioid-dependent patients in Canada, Srivastava and Kahan (2006) from the Centre for Addiction and Mental Health (CAMH) suggested that buprenorphine might be a better initial choice for patients at greater risk of respiratory depression, such as the elderly or those taking benzodiazepines. However, in general, buprenorphine should be considered an alternative to methadone, not a replacement.

Side effects commonly seen with the use of buprenorphine include headaches, sweating, sleeping difficulties, nausea and

mood swings. Like other opioids, it has also been associated with serious (and potentially lethal) breathing problems, especially when combined with alcohol or depressants. These effects usually peak in the beginning of treatment and may last a number of weeks (CSAT, 2004).

Regulation of buprenorphine in Canada

Buprenorphine has been available for the treatment of opioid dependence in Canada since October 2007. However, only buprenorphine combined with naloxone in a 4:1 ratio is available for maintenance treatment; the buprenorphine mono-product is currently not marketed in Canada and is only available through the Health Canada Special Access Program for specific clinical situations, such as during pregnancy. The approval of buprenorphine-naloxone by Health Canada provided Canadian physicians with a long-awaited new treatment option for opioid-addicted patients. (At that time, buprenorphine had been available in the United States since 2000.) Since then, physicians who have received specialized training are allowed to prescribe buprenorphine from their offices without having to obtain the Health Canada exemption necessary to prescribe methadone (Hariri, 2008).

Although a specific license is required to prescribe methadone in Canada, physicians who wish to prescribe buprenorphine-naloxone must complete only a brief online training program. The continuing medical education (CME) course accredited by the College of Family Physicians of Canada is strongly recommended (Hariri, 2008). However, for physicians with less experience in treating opioid dependence, more exhaustive CME courses are also available (Ducharme et al., 2012). Clinical guidelines containing recommendations for the initiation, maintenance and discontinuation of buprenorphine treatment have also been prepared by organizations such as CAMH in Toronto (Handford, 2012) and the College of Physicians and Surgeons of Newfoundland and Labrador (2011). These guidelines will ultimately improve access to treatment and lead to safer prescribing and dispensing of buprenorphine across Canada.

Regulation of buprenorphine in the United States

Like methadone, buprenorphine has been classified as a Category C pregnancy drug by the FDA, meaning its potential benefits may outweigh the risk of birth defects. In addition, it is considered a Schedule III narcotic under the U.S. *Controlled Substances Act*, indicating moderate potential for abuse and a lower risk of causing physical and/or psychological dependence. Methadone, in comparison, is listed under Schedule II due to its higher potential for abuse. (For more information on these various drug classifications, please see the appendices.)

In 2000, the U.S. *Drug Addiction Treatment Act* expanded its clinical context of medication-assisted treatment to allow qualified physicians to dispense or prescribe approved Schedule III–V medications for the treatment of opioid addiction. Before this law came into effect, Schedule II treatments such as methadone could be dispensed only from a very limited number of addiction clinics. By making the less tightly controlled buprenorphine more readily available from the offices of specially trained physicians, patients now have greater access to the treatments they need. And as their therapy progresses, patients may even receive prescriptions for a take-home supply of the medication from their doctors. A database maintained by the Center for Substance Abuse Treatment (CSAT) helps patients locate qualified doctors across the United States (CSAT, 2004).

Under the *Drug Addiction Treatment Act*, the FDA originally approved two buprenorphine formulations for the treatment of opioid dependence:

- Buprenorphine hydrochloride (sold under the brand name Subutex®) was intended to be given during the first few days of treatment. Because of the possibility of diversion from its intended medical use, this product is no longer available except in a generic form.
- Buprenorphine hydrochloride plus naloxone hydrochloride (sold under the brand name Suboxone®) is currently prescribed for medication-assisted treatment. This drug is supplied in tablets of 2 milligrams and 8 milligrams, both which must be placed under the tongue to dissolve. Naloxone, an opioid antagonist and FDA Category C drug, has been added to guard against intravenous abuse of buprenorphine. Because both mother and fetus will be dependent on the opioids used by the mother, administration of naloxone could precipitate withdrawal in both (CSAT, 2004).

Although the FDA has not yet approved the use of buprenorphine in pregnant women (as of this writing, the approval process

JENNIFER

Jennifer, 19, attends a prestigious university in Montreal. Her father owns a restaurant and her mother is a lawyer. Both hard workers, they've been largely absent during Jennifer's teen years. To make up for it, they lavish her with money and gifts. For her last birthday she got a brand-new SUV.

Jennifer was interested in boys from a young age. Now she spends a fair amount of time on social media sites chatting with guys she doesn't know. Once she posted pictures of herself in her underwear, which led to an overwhelming number of inquiries and an invitation from one stranger to a party. She decided to go and ended up meeting other guys there with expensive cars and lots of cash. She really liked one of them: Tom. They started dating, and over time Tom convinced Jennifer he loved her and would take care of her. He asked her to move to New York with him. The idea was thrilling for Jennifer and, despite her parents' objections, she decided to go. Once there, Tom forced Jennifer to take a job stripping. She wanted to go home, but he became abusive and controlling, threatening to harm her family and forbidding her to contact them.

By this point, Jennifer was smoking marijuana daily. Tom introduced her to cocaine as well. When Jennifer got pregnant, Tom became angry and severely assaulted her. She was taken to the city hospital, where she explained to a social worker how she had ended up in this situation. She was released into the custody of her parents, who had not heard from her in over a year. Although supportive of Jennifer, they are worried about the health of their grandchild.

is still underway), women who are already on buprenorphine before becoming pregnant are allowed to continue treatment during pregnancy.

Although buprenorphine and buprenorphine-naloxone are less tightly controlled than methadone because of their lower potential for abuse and less dangerous consequences in overdose situations, the manufacturer of these drugs, in collaboration with the FDA and other agencies within the U.S. Department of Health and Human Services, has developed a comprehensive risk management program to deter abuse and diversion from their legitimate treatment use. This program involves educating physicians on the proper use of buprenorphine, the implementation of child-resistant packaging and close monitoring of drug distribution channels. Through its surveillance efforts, which include interviews with substance abusers and the monitoring of adverse event reports, the FDA is able to identify problems resulting from the availability of buprenorphine and, if necessary, take appropriate actions to protect public health (CSAT, 2004).

In addition, the provisions of the *Drug Addiction Treatment Act* include limits on the number of patients individual physicians are allowed to treat and special registration with the U.S. Drug Enforcement Administration for the use of buprenorphine, thus providing additional safeguards in the office-based treatment setting (CSAT, 2004).

Outcomes of buprenorphine maintenance during pregnancy

Buprenorphine has been used successfully in pregnant women for more than a decade, with numerous studies finding no adverse maternal effects and infants delivered both at term and with birth weights in the normal range. However, observations have varied concerning the frequency, intensity and duration of abstinence in newborns prenatally exposed to buprenorphine (Loustauneau et al., 2002).

International studies of more than 500 newborns exposed prenatally to buprenorphine found no increased risk of birth defects and reported low rates of premature birth (Fischer et al., 1998; Fischer, 2000; Johnson et al., 2001; Lejeune et al., 2001; Lacroix et al., 2004). In addition, buprenorphine treatment during pregnancy does not appear to have any greater risks to the mother or the fetus than treatment with methadone (Jones et al., 2005; Fisher et al., 2006).

A comparative, multicentre clinical study of 158 high-dose buprenorphine patients and 101 methadone maintenance patients in France by Lejeune and colleagues (2006) found no major difference between the two drugs in terms of overall maternal or infant outcomes. The only differences found were:

- A higher rate of prematurity in the methadone group (possibly explained by confounding factors such as the use of tobacco or other drugs); and
- A mean age at onset of NAS of 81 hours for the methadone group and 66 hours for the buprenorphine group.

They also observed that in utero exposure to buprenorphine resulted in NAS in more than 50% of exposed newborns. Overall, the onset and nature of buprenorphine-associated NAS were comparable but somewhat milder in intensity and shorter in duration than NAS associated with methadone (Lejeune et al., 2006).

Studies have shown that abstinence symptoms following buprenorphine exposure last for approximately 15–21 days, typically appearing within 12–24 hours of birth and peaking at 72–96 hours after birth. Concomitant nicotine exposure also appears to exacerbate the severity of buprenorphine-related NAS (Loustauneau et al., 2002).

5.4.3 Medication-assisted treatment and neonatal abstinence syndrome

Many of the available reports on the use of methadone and buprenorphine during pregnancy are limited in their significance because of confounding factors such as maternal use of alcohol and other drugs (the use of concomitant medication or abuse of other substances was rarely reported in detail), making it difficult to truly assess the impact of these medications (buprenorphine, in particular) on NAS frequency, intensity and duration. In addition, many reports were retrospective and had no appropriate control groups, or they examined treatment settings, dosages and exposure lengths too dissimilar to be accurately compared. Details were also lacking with regard to the treatment of NAS as well as the tools used to assess abstinence symptoms (Unger et al., 2010). More recent studies have therefore sought to clearly define the role of buprenorphine in comparison to methadone and to further delineate the effects of the two medications on exposed newborns, especially with regard to NAS.

In Sweden, Kakko and colleagues (2008) looked at the maternal buprenorphine and methadone dosages as well as the incidence, severity and duration of NAS in two consecutive case series of exposed newborns from 1982 to 2006. Measuring intrauterine growth, birth outcomes, malformations, neonatal adaptation, neonatal abstinence and infant mortality in 47 consecutive, prospectively followed buprenorphine-exposed pregnancies and 35 consecutive, retrospectively analyzed methadone-exposed pregnancies, it was found that buprenorphine treatment results in better birth weight (primarily due to longer gestation) and reduced incidence of NAS requiring pharmacological treatment when compared to methadone. Specifically, NAS occurred in 40.4% of the buprenorphine-exposed infants (with 14.9% requiring treatment) and 77.8% of those exposed to methadone (with 52.8% requiring treatment). And when buprenorphine treatment was started prior to pregnancy, NAS at any level was significantly less frequent than in women who initiated treatment after conception (26% versus 60%, respectively).

In Finland, Kahila and colleagues (2007) studied 67 women maintained on buprenorphine where tapering doses or even total abstinence was encouraged. This treatment approach resulted in an NAS incidence of 76%, with 57% of the infants requiring treatment. (Two sudden infant deaths also occurred.) The low-maintenance dose of buprenorphine was also linked to lower treatment retention rates and higher rates of illicit drug use, both of which are associated with increased NAS incidence and severity. The results of this study strongly suggest that pregnant women should be treated with dosages appropriate to their addiction. Concerns about the impact of higher dosages on NAS do not seem to be warranted based on clinical research data (Cleary et al., 2010).

The MOTHER Study

Given the previous studies examining the differences between methadone and buprenorphine with regard to NAS, NIDA funded an international, multi-site randomized clinical trial to investigate the safety and efficacy of maternal and prenatal exposure to methadone and buprenorphine. The Maternal Opioid Treatment: Human Experimental Research (MOTHER) Study involved 131 opioid-dependent pregnant women (73 on methadone and 58 on buprenorphine) who delivered their babies while retained in the study. Comprehensive care and contingency management was provided for all participants. The pregnant women were extensively evaluated throughout the study and their newborns underwent systematic assessment of NAS signs and symptoms using a modified Finnegan Neonatal Abstinence Score.

MOTHER's results showed that maternal outcomes in buprenorphine- and methadone-treated women did not differ significantly for any of the studied maternal outcomes, including weight gain, number of prenatal obstetrical visits, incidence of caesarean section, abnormal presentation, use of analgesia, positive drug screen for illicit opioids and medical complications at delivery. This suggests a similarity between the two medications with regard to their safety and efficacy in the treatment of opioid dependence in pregnant women (Jones et al., 2010).

The MOTHER Study also measured specific outcomes related to NAS. Again, the results showed no significant differences between buprenorphine and methadone with regard to the overall rate of NAS in which treatment was required, peak NAS score or the head circumference of the newborns. The study did find a reduction in the severity of NAS in buprenorphine-exposed newborns based on decreases in the three inter-related parameters: length of hospital stay, number of days required for treatment and the total amount of morphine needed to treat the NAS (Jones et al., 2010).

There were also considerable differences in the outcomes recorded among the three major site groups (urban United States, rural United States and Vienna, Austria). Specifically, total morphine administered for NAS varied from less than five grams to 34 grams and the total days of morphine administration varied from less than five to nearly 18 (Baerwert et al., 2012). As a result, further evaluation is required to make appropriate judgments from these data.

It is also worth noting that there was a non-significant (but potentially clinically important) difference in the proportions of mothers discontinuing from the study, with buprenorphine-exposed participants more likely than methadone-exposed participants to be dissatisfied with their medication (23% versus 2%, respectively). The study's buprenorphine-induction protocol may have been one of the factors that contributed to the markedly different attrition rates.

Questions and concerns about the MOTHER Study

Although the MOTHER Study has made an important contribution to the literature on opioid addiction during pregnancy, several questions remain about its clinical value and that of similar research studies. For example, to eliminate confounding in the results, MOTHER used stringent criteria for the inclusion of participants and excluded women using benzodiazepines and alcohol, both of which are quite prevalent in clinical populations of women using drugs. This prompted criticism from Newman and Gevertz (2011), who said the study lacked relevance to clinical decision making because its subjects were highly selected and atypical of real-world addiction medicine practice. They also claimed the protocol used in the study would be difficult to replicate in actual clinical practice and likely be unacceptable to the majority of patients. Additional concern was expressed over the need for the mothers to stay in hospital for stabilization onto the study medications and the need for the newborns to stay in hospital for observation for 10 days after birth even in the absence of NAS.

The degree of superiority of buprenorphine was also considered limited due to the fact that the three measures that decreased with buprenorphine exposure can all be influenced by non-pharmacological means. Newman and Gevertz (2011) concluded that more research is needed to guide clinicians in providing evidence-based care for opioid-dependent pregnant women.

In response to the concerns raised by Newman and Gevertz, Jones and colleagues (2012) wrote an editorial clarifying that because the MOTHER study was designed as an efficacy trial rather than an effectiveness trial, many of the limitations mentioned were not appropriate.

Among clinical service providers, another area of concern about the MOTHER Study was the safety of the fetus. McCarthy (2012) hypothesizes that intrauterine abstinence syndrome (IAS) can occur when pregnant women are inducted onto buprenorphine or when methadone tapering occurs, creating an adverse environment for the developing fetal brain that can result in long-term health effects. McCarthy claims MOTHER provided no protocol establishing the safety of going from illicit opioids directly to buprenorphine in an outpatient setting in which there is no fetal monitoring or immediate obstetrical aid should maternal or fetal distress occur during induction onto buprenorphine, creating a situation in which the development of IAS was inevitable. As such, McCarthy recommends that "better methods of detecting intrauterine withdrawal, including animal models of buprenorphine induction, need to be developed as well as evaluations of amniotic fluid catecholamines and glucocorticoids in order to delineate a guaranteed safety to the fetus" (McCarthy, 2012).

Despite these concerns, a considerable amount of useful information can still be derived from MOTHER's results. For full remission of opioid addiction to be sustainable postpartum and across the patient's lifespan, physicians cannot rely solely on medication. Instead, it is best to utilize a comprehensive treatment model that addresses the underlying multifaceted complexities within the pregnant woman's life (Finnegan, 1991b, 2010; Jones, Finnegan & Kaltenbach, 2012).

5.4.4 The need for a tailored treatment approach

Women who abuse drugs during pregnancy are not a homogeneous group. They enrol in treatment programs at varying times in pregnancy, use a wide range of drugs (some of which are more dangerous to the developing fetus than others) and have been abusing drugs for differing lengths of time. They also enrol in treatment with various amounts of trauma, mental illness and social problems. Determining the most appropriate medication for opioid-dependent pregnant women must therefore be made on a patient-by-patient basis, taking into consideration each woman's history of opioid abuse and dependence, medical circumstances, and previous and current treatment experiences and preferences.

A specific treatment plan should be developed that meets the individual needs of each woman, taking into account the risk-benefit ratio of the medication and involving priority order initiation so the issues most dangerous to both the mother and the fetus can be dealt with first. Although these treatment plans can be long and complex, with the dedication of the professional staff and the cooperation of the pregnant women, recovery is achievable.

Whether treated with buprenorphine or methadone, women should be encouraged to remain on their current medication when they become pregnant and not switch to the other. If stabilized on methadone, a pregnant woman should continue on methadone unless there is an appropriate clinical reason for change. Women who become pregnant on buprenorphine and are well stabilized should not be changed over to methadone under any circumstances. Transitioning from either medication to the other when stabilized can create the chance for withdrawal in both the women and the fetus with the potential to relapse to illicit opioid drugs (Jones, Finnegan & Kaltenbach, 2012).

However, because buprenorphine is not currently marketed in Canada and the safety of using naloxone during pregnancy has yet to be determined, the clinical practice guidelines for the use of buprenorphine-naloxone developed by the CAMH recommend that pregnant women receiving that formulation be switched to buprenorphine monotherapy (Handford, 2012).

Regardless of the medication taken, the dosage should be re-assessed periodically during pregnancy for adjustments, especially in the third trimester, to maintain medication plasma levels and thereby reduce (or eliminate) other drug use and maintain abstinence (Pond et al., 1985).

While randomized clinical trials, prospective and retrospective data have shown NAS to be less severe in infants exposed to buprenorphine compared to methadone, it should be remembered that NAS is an easily identifiable and treatable condition. NAS should therefore comprise only one aspect of the complete risk-to-benefit ratio that patients and physicians must consider when making medication decisions during pregnancy (Jones et al., 2010; Jones, Finnegan & Kaltenbach, 2012).

Medically supervised withdrawal

Although maintenance is the preferred treatment for pregnant women, some highly motivated women (or those facing logistical or geographic barriers preventing them from accessing medication-assisted treatment) may opt instead for medically supervised withdrawal (also known as detoxification) during pregnancy. In some cases, these women may have been stable on methadone and requested medical withdrawal before delivery; others may have simply refused to be maintained on methadone at all and want to be drug-free before delivery. Yet while medically supervised withdrawal remains a popular approach for the treatment of opioid-addicted pregnant women, research has consistently illustrated its limitations—most notably, high rates of patient attrition and relapse with the risk of infections, illicit drug use and criminality (Luty et al., 2003).

Medically supervised withdrawal from opioids is generally not recommended for pregnant women except in extraordinary circumstances, particularly because it is physically and emotionally stressful at a time when their energy needs to be conserved for pregnancy, recovery and care for the newborn child (Finnegan, 1991a; McCarthy, 2012). Adverse maternal and infant outcomes, including decreased gestational age and increased incidence of low birth weight, have been associated with medical withdrawal during pregnancy. Intrauterine fetal demise has also been documented, even when medical withdrawal is conducted under the most optimal conditions. Relapse is also prevalent following medical withdrawal, with women returning to illicit drug use at an incidence of 41–96 % (Jones et al., 2008).

The decision to attempt medically supervised withdrawal must therefore be made between the obstetrician, the pregnant woman and her counsellor. According to CSAT, if the decision is made to attempt a medical withdrawal regimen, it could be most safely accomplished during the second trimester (Mitchell, 1993). Although no controlled trials have been conducted to verify the proposed regimen, CSAT has advised that opioid withdrawal could be achieved through stabilization with methadone followed by a very gradual reduction of the methadone dosage. Fetal movement should be monitored twice daily and obstetrical stress tests should be performed at least twice weekly. Medically supervised withdrawal should be discontinued and no further decrease in methadone dosage should be ordered if the regimen causes fetal distress or threatens to cause preterm labour.

5.4.5 Breastfeeding while undergoing medication-assisted treatment

Health Canada, the American Academy of Pediatrics, the World Health Organization and many other major health authorities all agree that breast milk is the most complete form of nutrition for infants, with its mix of vitamins, protein and fat providing numerous benefits for health, growth, immunity and development.

In its report entitled *Breastfeeding and Maternal and Infant Health Outcomes in Developed Countries*, the U.S. Department of Health and Human Services summarized the results of a meta-analysis of the existing literature concerning breastfeeding and various infant and maternal outcomes. It found that babies that are breastfed typically have lower incidences, reduced risk and/or decreased severity of acute otitis media (middle ear infections), atopic dermatitis (a type of eczema), gastrointestinal infections, lower respiratory tract diseases, asthma, diabetes, childhood leukemia and sudden infant death syndrome (Ip et al., 2007).

The mother also benefits greatly from breastfeeding. The incidence of certain cancers (most notably, breast, uterine, endometrial and ovarian) is reduced in women who breastfeed. The physical closeness associated with breastfeeding is also essential to the mother's emotional health, helping to reduce feelings of anxiety and promoting a stronger maternal-infant attachment (Ip et al., 2007). The swaddling associated with breastfeeding may also help reduce NAS symptoms while contributing to greater bonding between mother and infant (ACOG, 2012).

Given the many positive outcomes associated with breastfeeding, for opioid-dependent women undergoing medication-assisted treatment, the decision to breastfeed their newborns is an extremely important one to make. But can the mother who is receiving treatment with methadone or buprenorphine safely breastfeed her baby?

Methadone and buprenorphine levels in breast milk

Methadone is detected in breast milk at very low levels. Studies have found the ratio of breast milk to maternal blood plasma concentrations to range from 0.05 to 1.2. Maternal doses of 25–180 milligrams of methadone produce very small quantities of the medication in the breast milk, providing approximately 0.05 milligrams per day of methadone to the baby (Wojnar-Horton et al., 1997; McCarthy & Posey, 2000).

In recent reports, breastfeeding has been shown to diminish the duration of methadone-associated NAS symptoms (Abdel-Latif et al., 2006; Jansson et al., 2008) not only due to the limited oral bioavailability of methadone but also through enhanced mother-child bonding (Lim et al., 2009). Yet even before these reports were published, most clinicians still felt comfortable recommending breastfeeding to methadone-treated mothers who expressed an interest in doing so, provided they were HIV negative, compliant with a treatment plan and did not use other licit or illicit drugs (American Academy of Family Physicians, 1996).

Buprenorphine is also detected in lactating women, passing into the breast milk at a plasma-to-milk ratio of approximately 1.0. Absorption of buprenorphine from breast milk is much less than other opioids; because buprenorphine is not absorbed well by mouth, infants are exposed to only 10–20% of the total buprenorphine available in the breast milk (Johnson et al., 2001, 2003; Lejeune et al., 2001; Loustauneau et al., 2002).

Studies have shown minimal effects on NAS in breastfed infants exposed to buprenorphine, most likely because of the drug's low oral bioavailability (Auriacombe & Loustauneau, 2001). The literature includes reports on approximately 40–50 women who were maintained on buprenorphine and who breastfed after delivery (Lejeune et al., 2001; Loustauneau et al., 2002; Johnson et al., 2003). These reports indicate that the buprenorphine present in breast milk does not appear to suppress NAS because it is not pharmacologically active in low doses. Additionally, NAS has not been observed after the cessation of breastfeeding by women maintained on buprenorphine (Loustauneau et al., 2002).

Recommendations and guidelines

Although the packaging on buprenorphine formulas Subutex®[10] and Suboxone® advise mothers treated with these medications not to breastfeed, CSAT states that any effects of these medications on the breastfed infant would be minimal and that breastfeeding is therefore not contraindicated. However, given the limited literature in this area, physicians are advised to use their professional judgment in their recommendations.

This statement was echoed by the American Congress of Obstetricians and Gynecologists, which said that although minimal levels of methadone and buprenorphine are found in breast milk regardless of the maternal dose, breastfeeding should be encouraged in patients who are not HIV positive, do not use additional drugs and have no other contraindications (ACOG, 2012).

[10] This formulation is not currently marketed in Canada.

The Vermont Buprenorphine Practice Guidelines from the Vermont College of Medicine provide more specific recommendations. If breastfeeding is declined by the mother, she should be placed on buprenorphine-naloxone immediately after delivery or continue methadone. If breastfeeding is accepted, the obstetrician should consult with the mother's pediatric provider to confirm they are aware of her medication-assisted treatment. If the newborn is not receiving methadone or morphine for NAS treatment, the mother can be placed on buprenorphine-naloxone. However, if the newborn is being treated with methadone or morphine for NAS, buprenorphine should be continued until the newborn is off medication or weaned from breast milk.

The clinical practice guidelines for the use of buprenorphine-naloxone developed by CAMH acknowledge that buprenorphine has been measured in maternal breast milk and suggest that breastfeeding can be considered only after weighing the risks and benefits of buprenorphine exposure (Handford, 2012).

Based on these recommendations, infants of mothers who are undergoing medication-assisted treatment should be able to benefit from the many advantages of breast milk, just like any other child. Moreover, the psychological benefits of breastfeeding are extremely important, especially in cases where opioid dependence complicates the pregnancy.

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6 Early Childhood Outcomes

The long-term development of children born to drug-dependent women is a significant concern, not only for the mothers of these children but also for the medical professionals involved in their care.

Substantial evidence has shown that the outcomes of early childhood development echo throughout an individual's entire life, meaning prenatal exposure to drugs can have long-lasting negative effects. For example, studies on the impact of prenatal stress suggest many of the biological factors acting on the fetus are associated not only with the development of cardiovascular and metabolic disorders during adulthood but also with a number of psychological abnormalities and behavioural disorders (Lester & Padbury, 2009).

Such findings have led to the development of theories such as the "fetal origins of adult disease," which postulates that a variety of common factors influence both intrauterine growth and adult physiological systems (Barker, 1992, 2002; Welberg & Seckl, 2001). The various environmental factors active during prenatal life serve to "program" an infant's developing systems. Prenatal exposure to drugs and alcohol is likely one of the many factors that can alter the typical "set points" for physiologic, metabolic and behavioural outcomes (Lester & Padbury, 2009).

As the outcomes of infants born to alcohol-abusing women were reviewed in Chapter 4, this section focuses primarily on how maternal opioid and cocaine use affects child development. For more information on the early childhood outcomes of infants prenatally exposed to cannabis, please refer to the review conducted by Porath-Waller (2009) on behalf of the Canadian Centre on Substance Abuse.

6.1 Challenges in assessing child development outcomes

Maternal drug use has long been associated with numerous long-term adverse effects on children exposed in utero. However, evaluating the direct impact of such drug use on childhood development can be challenging for a variety of reasons.

First, a number of studies (Kandall, 2010; National Institute on Drug Abuse [NIDA], 2011) have shown that early childhood development is dependent on a wide range of concomitant individual, family and environmental factors beyond prenatal drug use, including:

- Poverty and other socioeconomic disadvantages;
- The amount of prenatal and medical care received by the mother;
- Whether the pregnancy was wanted or unwanted;

At a Glance

- There are challenges associated with evaluating the direct effects of prenatal drug exposure on childhood development as it is influenced by a wide range of individual, familial and environmental factors.
- Although there are mixed reports as to whether prenatal exposure to cocaine is significantly associated with deficits in cognitive and motor development, such exposure has been shown to increase the risk of delays in language development.
- Supervised methadone maintenance treatment during pregnancy does not appear to negatively affect the development and cognitive functioning of children evaluated up to 4.5 years of age.
- Research on the effects of maternal opioid use during pregnancy on the postnatal growth and development of the child are limited and subject to various methodological limitations. There are reports suggesting that prenatal exposure to opioids increases the risk of neurodevelopmental impairment, however this finding is complicated by issues of poverty and the environment in which the child lives.

- The nutritional intake of the child;
- Medical illness and other inherent biological risk factors;
- The presence of sexually transmitted diseases;
- Pollution levels;
- Violent crime;
- Schooling and education;
- The amount of family and community support received; and
- The level of neglect and physical abuse experienced by the child.

Chronic maternal stress may also influence childhood development and is related to low birth weight and preterm birth with hypothesized pathways via neuroendocrine, immune and vascular mechanisms that may influence both the timing of delivery and utero-placental transfer of nutrients.

Second, even when looking at the issue of maternal substance use, there are a number of variables that make it difficult to come to definitive conclusions (Bada et al., 2002; Kandall, 2010). These include:

- Changes in maternal drug use patterns over time;
- Concomitant drug use (both licit and illicit), which can potentially confound a study's data;
- Judgmental questioning of the women studied, which may obscure actual drug use;
- "Objective documentation" not uniformly used to measure exposure;
- The ability of the physical and social environment to alter the effect of illicit drugs or treatment medications;
- Maternal drug dosages not being defined in many studies;
- Terms such as "drug exposed" and "drug affected" not being properly defined;
- Unequal examination of biological effects versus environmental effects; and
- The inability to maintain a cohort of children, meaning many studies include only a small number of subjects.

Because of the potential for all these factors to play a role in childhood development, a 2003 U.S. National Institute on Drug Abuse conference on placental biology and fetal development concluded that it is extremely difficult to determine if the detrimental effects seen in children exposed to drugs in utero are actually the result of poor maternal nutrition, stress, infection and poor prenatal care, all of which are common co-morbid factors in women using drugs (Thadani et al., 2004).

6.1.1 Myths and misconceptions

Because of the challenges mentioned above, studies examining the links between maternal drug use and early childhood development can have considerable limitations. Furthermore, published studies might report "facts" that have not necessarily been proven by sound research. All of this has contributed to a multitude of misconceptions on the development of children exposed prenatally to drugs (Evan B. Donaldson Adoption Institute, 1997). For example:

- *"Every child who is exposed to drugs and alcohol will have problems later in life."* Studies have shown that not all infants are negatively affected by prenatal drug exposure and that a variety of factors contribute to children's outcomes (Zuckerman, 1994).
- *"Children exposed prenatally to cocaine are severely and permanently brain damaged."* While neurobehavioural abnormalities have been reported in newborns exposed to cocaine, other studies have not reported such outcomes. Moreover, the problems observed do not equate with severe or permanent brain damage. In one study, no developmental differences were found in cocaine-exposed children compared to non-exposed children at both two and three years of age (Zuckerman, 1994).
- *"Children with FAS or FAE will not be able to succeed in school."* A diagnosis of FAS or FAE does not necessarily mean that a person will be unable to graduate from high school or attend post-secondary education (Kleinfeld, 1993).
- *"A positive environment can do little to promote the development of exposed children."* Research has shown that negative outcomes in drug-exposed children can actually be ameliorated by supportive home environments and quality parenting (NIDA, 2011). In a study of the developmental outcomes of children born to heroin-dependent mothers, Ornoy and colleagues (1996) found that any developmental delays were likely owing to severe environmental deprivation in the home and the fact that one or both parents were dependent on drugs, rather than prenatal drug exposure.

6.2 The Maternal Lifestyles Study

Given the common misconceptions regarding the development of children exposed to drugs in utero, it is critical that any research looking into this issue is appropriately designed and expertly conducted. One example of such research is the Maternal Lifestyles Study. Initiated in the early 1990s, this longitudinal study of cocaine and opioid exposure on neurodevelopmental outcomes used a large matched comparison cohort at four diverse sites: Brown University, the University of Miami, the University of Tennessee and Wayne State University. Its participants were mostly African-Americans receiving public assistance (Lester et al., 2002; Bada et al., 2005).

6.2.1 Developmental outcomes of infants

A total of 658 drug-exposed and 730 comparison infants were matched according to race, gender and gestational age. Exposure to drugs was determined by meconium assay and self-report. At one month corrected age,[11] infants were tested using the Neonatal Intensive Care Unit (NICU) Network Neurobehavioral Scale (NNNS) and an acoustical cry analysis. Both the exposed and non-exposed groups were compared, adjusting for the following covariates: alcohol, marijuana, tobacco, birth weight, social class and study site. Separate analyses were also conducted for levels of cocaine exposure.

On the NNNS, cocaine exposure was related to lower arousal, poorer quality of movement and self-regulation, non-optimal reflexes and higher rates of hypertonia (increased muscle tone), with most effects maintained after adjustment for covariates. Some effects were also found for opioids, alcohol, marijuana and birth weight (Lester et al., 2002).

With regard to acoustic cry characteristics, this study found that cocaine-exposed babies had a louder, higher-pitched cry with less resonance in the upper vocal tract. There was also more turbulence in the cries of heavily exposed infants. However, few cry effects remained after adjustment for covariates, suggesting they are not the result of cocaine use alone but most likely because of poly-drug use (Lester et al., 2002).

6.2.2 Developmental outcomes of toddlers

In addition to studying the growth and behavioural parameters of infants born to cocaine- and opioid-using mothers, the Maternal Lifestyles Study went on for many years, using a battery of developmental tests at various ages throughout infancy and childhood in a large cohort of children (Messinger et al., 2004). Specifically, it looked at childhood development across three domains:

- **Child:** Physiology, attention, temperament, social interaction, attachment, cognition, language, motor development;
- **Maternal:** Psychological distress, depression, self-esteem, attachment, parenting stress, IQ, drug history and use; and
- **Context:** Social class, neighbourhood, social support, home environment, social services, violence, acculturation.

At the ages of one, two and three years, 1,227 children from the longitudinal cohort were studied, 655 of whom were not exposed to cocaine or opioids in utero. Outcomes were measured using the Bayley Scales of Infant Development (BSID). While cocaine-exposed infants scored lower on the BSID Mental Developmental Index (MDI) (compared to those not exposed to cocaine) and opioid-exposed infants scored lower on the BSID Psychomotor Developmental Index (PDI) (compared to infants not exposed to opioids), these deficits were not notable when researchers controlled for birth weight and various environmental factors (Messinger et al., 2004).

WHAT IS THE NNNS?

Developed for the U.S. National Institutes of Health as part of the Maternal Lifestyles Study, the NNNS assesses both neurological integrity and behavioural function. It also documents the range of withdrawal and stress signs likely to be observed during the examination of drug-exposed infants. (Traditionally, scales that measure neonatal abstinence are treated separately from neurological and behavioural evaluations.)

Through this comprehensive approach, the NNNS allows for the creation of symptom-oriented intervention plans for drug-exposed infants. In addition, repeated observations can inform clinical practice while accommodating the dynamic nature of the developing child.

[11] Infants born prematurely were tested when they reached the specific ages of the study periods by adjusting their ages. For example, for the one-month examination, a 38-week-old infant was tested at six weeks of age after birth.

WHAT IS THE BSID?
Through a series of developmental play tasks, the BSID assesses the motor, language and cognitive development of infants and toddlers from one to 42 months of age. Raw scores are converted into two standardized scores: the MDI and PDI. These are used to determine the child's performance compared to typically developing children of the same age.

BSID scores can also be used to identify children who are developmentally delayed and chart a child's progress after the initiation of an intervention program. While, the BSID has poor predictive value and does not measure future ability, it is considered a good screening device for identifying children in need of early intervention.

6.2.3 Conclusions from the Maternal Lifestyles Study

Although the Maternal Lifestyles Study showed that significant mental, motor and behavioural deficits are not associated with cocaine and opioid exposure, it did conclude that the caregiving environment has a considerable impact on childhood development. Non-optimal environments can exacerbate neurobehavioural vulnerabilities, potentially turning the small differences in functioning caused by drug exposure into much larger deficits (Lester et al., 2002). The researchers also proposed that certain neurobehavioural characteristics could provide markers for later deficits, such as poor self-regulation in cocaine-exposed infants and the high-pitched, hyperphonated cries (cries with a qualitative break in the cry sound to a very high basic pitch) in cocaine, opioid or alcohol-exposed infants. Environmental risk may also interact with neurobehavioural risk; for example, lethargic infants might be more at risk of neglect and excitable infants might be more at risk of abuse.

Because cocaine can have latent effects that cannot be observed during infancy, it may be that cocaine affects areas of the brain that do not manifest until children are older. (Among adult cocaine users, the most common cognitive deficits are problems with executive function such as decision making, judgment and planning. The site of action for cocaine in the brain involves several areas thought to be instrumental in promoting these executive functions [Bolla et al., 1998; Breitner & Rosen, 1999].) Because cocaine's effects are so subtle among infants, especially when studied in the context of poly-drug use, Lester and colleagues (2002) recommended long-term follow-up of the children involved with the Maternal Lifestyles Study to determine whether the differences noted develop into clinically significant deficits.

6.3 Effects of cocaine exposure on child development

In addition to the Maternal Lifestyles Study, several other studies on the effects of prenatal cocaine exposure on cognitive, motor and language development have been published; however, they vary with regard to their methodological rigour.

6.3.1 Cognitive development

Frank and colleagues (2001) reviewed nine peer-reviewed studies published between 1992 and 2000, with five of the nine reporting no cocaine-related effects on mental or physical development. In the remaining studies, only subtle cocaine-related effects remained (none of which maintained their significance when controlled for multiple covariates), causing the reviewers to conclude the effects of cocaine exposure on child development were not discernible from the effects resulting from other contextual factors such as prematurity, assessment age and other prenatal drug exposures (Frank et al., 2001).

Larger prospective cohort studies, however, have suggested a more complex picture. For example, a pair of studies examining the effects of in utero cocaine exposure on the BSID MDI found lower overall scores as well as dose-dependent effects on infant development (Singer et al., 2001b; Lewis et al., 2004). Among cocaine-exposed preterm infants with very low birth weights, one study found a 10-point difference in mean MDI scores at three years of age (Singer et al., 2001b). Other longitudinal studies have shown more subtle effects of cocaine exposure on MDI scores (Behnke et al., 2002; Mayes et al., 2003). With an almost equal number of prospective studies reporting no cocaine-related effects on cognitive development after adjusting for covariates, it has been suggested that prenatal exposure to cocaine is simply a marker for subtle declines in MDI performance that might become less distinct with control for other variables such as low birth weight, exposure to human immunodeficiency virus (HIV), disruptions in maternal care, lower socioeconomic status and maternal vocabulary scores (Frank et al., 2001; Messinger et al., 2004).

GERALD

Gerald was born to Genevieve, who had been dependent on heroin and prescription opioids during her pregnancy. As soon as she realized she was pregnant, Genevieve enrolled in a comprehensive drug treatment program in Vancouver. The clinic was very user-friendly, with specific treatment plans dedicated to assuring healthy pregnancies and outcomes. She was prescribed methadone along with addiction counselling. She also attended numerous classes on mothering, child development and family management. The pregnancy went smoothly and Genevieve delivered a healthy baby boy.

Genevieve was told that 60 to 80% of babies exposed to methadone experience abstinence in the neonatal period, affecting their central nervous, gastrointestinal, respiratory and autonomic nervous systems. Gerald was at risk for this condition. On the second day of life, he began to demonstrate symptoms that required treatment. Although his withdrawal was fairly severe and prolonged, doctors were able to control the symptoms and eventually wean him off morphine, which had been used to relieve the symptoms resulting from his in utero exposure to methadone. Genevieve was very attentive to the baby while he was in the hospital and visited as often as she could. Gerald came home when he was four weeks old, still with some mild irritability but that resolved quickly.

Because Genevieve had received training in how to support him through his symptoms, Gerald did well. He met his developmental milestones at ages one, two and three. The parenting sessions Genevieve participated in during her treatment helped her parent her son and his three year-old sister successfully. She read to them daily and took them to children's events in the community. When Gerald reached the fourth grade, he was at the top of his class academically and had an outgoing personality. Genevieve was assured Gerald was headed for success in his future life.

6.3.2 Motor development

In general, prenatal cocaine exposure has not been shown to affect typical motor development as assessed by the BSID PDI. In the review conducted by Frank and colleagues (2001) cited earlier, only two of the studies showed significant cocaine-related effects on PDI scores. In the more recent review by Bandstra and colleagues (2010), only one study (Lewis et al., 2004) showed a direct cocaine-related effect on PDI scores among infants one to three years of age.

That said, several studies have found PDI scores to be affected by the timing and severity of the infant's cocaine exposure. For example, Richardson and colleagues (2008) found lower scores were predicted by maternal cocaine use during the second trimester, while Frank and colleagues (2002) demonstrated a significant relationship between low birth weight and lower PDI scores in the infants of mothers who reported heavy cocaine use. In a longitudinal analysis of global motor development from 1–18 months conducted by Miller-Loncar and colleagues (2005), it was shown that motor skills for cocaine-exposed infants were, on average, lower than the norm, with deficits most evident between the ages of one and four months. However, the infants studied recovered to normal motor function by approximately 18 months of age.

6.3.3 Language development

Prenatal cocaine exposure also presents a risk for language delays in early childhood. A longitudinal study of children through three years of age by Morrow and colleagues (2004) found that infants exposed to cocaine in utero had lower total language scores than their non-exposed counterparts. These results were partially mediated through fetal growth (Morrow et al., 2003). They also observed that increased levels of prenatal cocaine exposure were associated with increased deficits in expressive language functioning. Similarly, two studies conducted by Singer and colleagues (2001a, 2001b) showed that expressive language skills were more adversely affected in cocaine-exposed infants who had very low birth weights and that heavily exposed infants showed lower auditory comprehension and poorer overall language skills than those with lighter or no cocaine exposure.

It is thought that the mechanisms underlying this effect include disruptions in attentional processing through a direct impact on the fetus' monoaminergic neurotransmitter systems and by impairing the parent-to-child interactions critical to language development (Malakoff et al., 1999).

Because language development during early childhood is determined by many interacting genetic and environmental influences, from the clinicians' perspective, viewing prenatal cocaine exposure within the lens of cumulative risk may help to identify affected children in need of remediation. And moving forward, studying language development in cocaine-exposed children as they grow into adolescence will help shed light on the pathways linking language functioning to other social, academic and behavioural childhood outcomes (Bandstra et al., 2003).

6.3.4 Effects on older children

Although the evaluation of infants with prenatal drug exposure is essential to determining if early intervention is necessary, the follow-up of these children into adolescence is equally important. While longitudinal studies that evaluate children well into their teenage years are costly and difficult to conduct, several have been successfully accomplished.

The most prominent study of this kind was conducted by Lester and LaGasse (2010), who reviewed 42 studies conducted between 1996 and 2008. Their results suggest that prenatal cocaine exposure has a number of unique effects on children up to 13 years of age, including a variety of problems related to behaviour, attention, language and cognition. In addition, a dose-response relationship was associated with the resulting behavioural problems, indicating that heavier exposure to cocaine produces more substantial effects. They also found weaker evidence of adverse effects from prenatal cocaine exposure on IQ and overall academic achievement.

Some of the more specific findings reported by Lester and LaGasse (2010) include:

- Girls exposed prenatally to cocaine but not alcohol are more aggressive;
- Boys exposed prenatally to both cocaine and alcohol are more delinquent;
- Cocaine exposure is associated with both attention deficit hyperactivity disorder (ADHD) and oppositional defiance disorder; and

- Cocaine-exposed children were more likely to have smoked cigarettes by the age of 10½ years.

Because the studies reviewed had reasonably large samples and were adjusted for a variety of confounding variables, Lester and LaGasse (2010) suggest the effects noted are indeed "true" cocaine effects. Of the 42 studies reviewed, 20 were based on samples of more than 300 children, with all studies combined representing 14 different cohorts totalling 4,419 children. With such a large population, statistical control for many prenatal and postnatal confounding variables can occur.

It should be noted that not all of the studies reviewed evaluated the same areas. However, with the evaluations currently available, it is clear that children exposed to cocaine in utero should be assessed on a regular basis so that appropriate interventions can be provided, if necessary.

6.4 Effects of opioid exposure on child development

Few long-term studies of children exposed prenatally to opioids have been conducted, with the majority focusing on maternal methadone and heroin use (Hans, 1996). While there is great interest in studying the effects of buprenorphine or prescription opioids such as hydrocodone and oxycodone on early childhood development, no studies have yet been published on the effects of these drugs on the child after the neonatal period (Lester & LaGasse, 2010).

6.4.1 Methadone

Numerous short- and long-term research studies on the neurobehavioural and developmental outcomes of methadone-exposed children in the United States were published in the late 1970s and 1980s, including studies of cohorts of children from Chicago (Hans, 1989), Philadelphia (Kaltenbach, Graziani, & Finnegan, 1979; Kaltenbach & Finnegan, 1984, 1987, 1988, 1989), New York (Johnson, Diano, & Rosen, 1984; Rosen & Johnson, 1982), Detroit (Strauss, Lessen-Firestone, Chavez, & Stryker, 1979; Strauss & Reynolds, 1983) and Houston (Wilson 1989; Wilson, Desmond, & Wait, 1981; Wilson, McCreary, Kean, & Baxter, 1979; Lifschitz, Wilson, Smith, & Desmond, 1985). These studies evaluated children born to mothers undergoing methadone treatment for opioid dependency and compared their scores on the BSID to children born to women who were not drug dependent but were from comparable socioeconomic and racial backgrounds.

Although some differences between these two groups were observed among preschool children, in general, methadone-exposed infants functioned within the normal range of development up to two years of age. For example, Lifschitz and colleagues (1985) used a multifactorial analysis and found that, when sociodemographic, biological and health factors are taken into consideration, the outcomes of methadone-exposed children do not differ from those of other high-risk infants (based on variables identified as being predictive for cognitive performance, such as the amount of prenatal care, prenatal risk and conditions in the home).

During this period, few studies involved children older than two years of age. In Philadelphia, Kaltenbach and Finnegan (1989) evaluated methadone-exposed children at the ages of 3½ and 4½ years using the McCarthy Scales of Children's Abilities (MSCA) and a neurological examination. Their results compared favourably with a study done in Detroit (Strauss, 1979) that examined methadone-exposed children at five years of age. Both studies found no differences between the exposed and non-exposed comparison groups on the MSCA General Cognitive Index or any of the MSCA subscales, although the scores in Detroit were overall much lower than those reported in Philadelphia. This variation might reflect the large number of confounding variables present within opioid-dependent women, who frequently use other drugs, including alcohol and benzodiazepines, in addition to methadone.

WHAT IS THE MSCA?

The MSCA assesses the cognitive development and motor skills of children 2½ to 8½ years of age. A wide range of puzzles, toys and game-like activities is used to evaluate each child on five different scales:

- Verbal (comprehension and use of language);
- Quantitative (mathematical ability);
- Perceptual Performance (ability to conceptualize and reason without words);
- Memory (short-term recall of words, numbers, pictures and tonal sequences); and
- Motor (fine and gross motor coordination).

In addition to individual scores for each scale, the Verbal, Quantitative and Perceptual Performance scales are combined to yield the General Cognitive Index, an index of overall intellectual functioning expressed as a mental age equivalent between 1½ and 12½ years of age.

The results reported by Kaltenbach and Finnegan (1989) in Philadelphia differed from those reported by Wilson and colleagues (1979, 1981, 1989) in Houston, who noted differences between heroin-exposed children and those in three different comparison groups, including a drug environment group, a high-risk group and a socioeconomic group.

Maternal medical and obstetrical complications can also influence the child's outcome. However, the data reported by Kaltenbach and Finnegan (1989) suggest that methadone treatment during pregnancy, in the context of comprehensive services, does not impair the development and general cognitive functioning of children evaluated up to age 4½ years.

6.4.2 Heroin

In the review conducted by Lester and LaGasse (2010), some of the more notable studies on the effects of heroin on child development included:

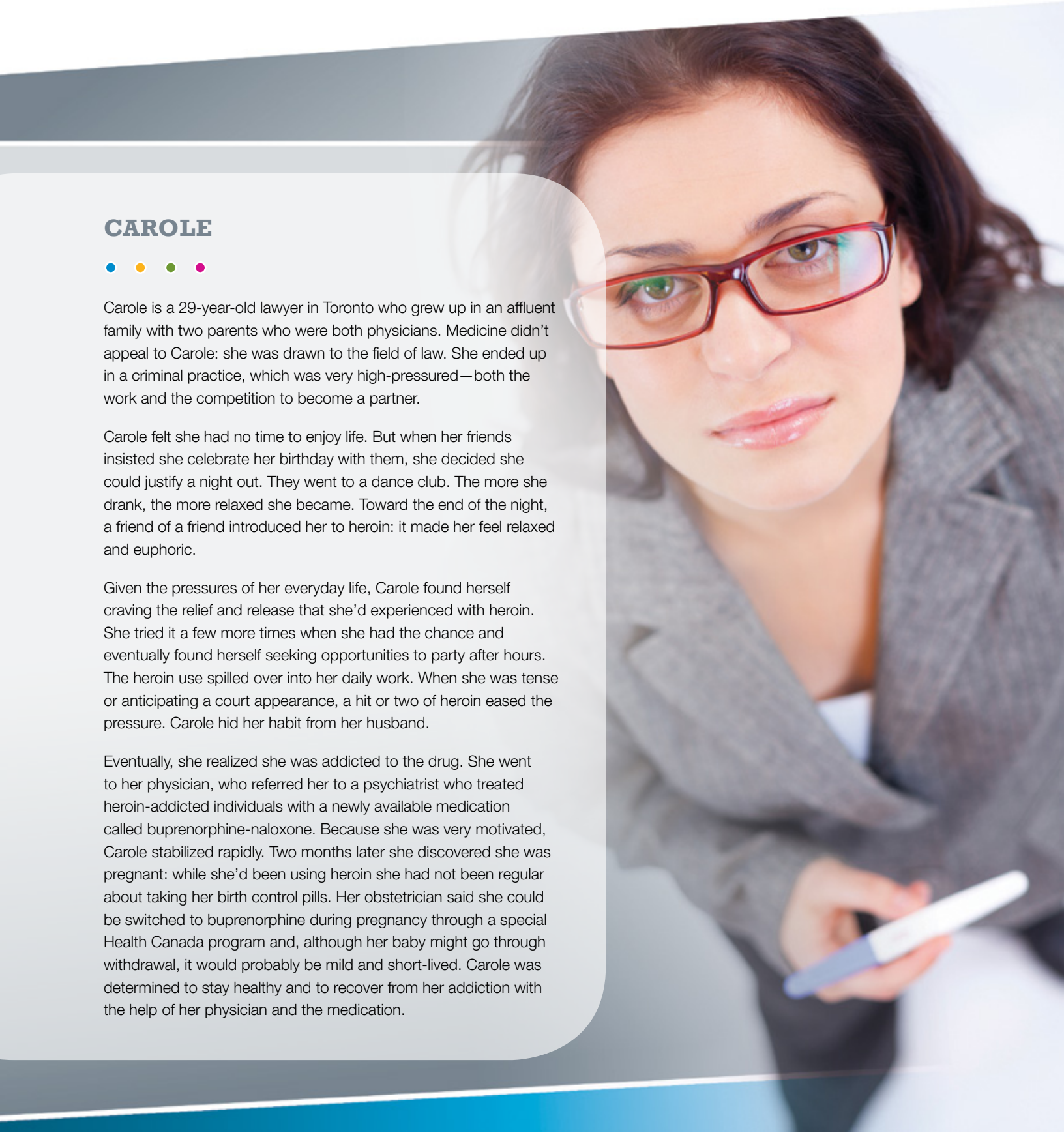
- Sowder (1980): In an evaluation of 126 children ranging in age from eight to 17 who were born to heroin addicts, this study found that school absence, academic failure and behavioural problems were more common in heroin-exposed children than in a comparison group of non-exposed children from the same neighbourhoods.
- de Cubas and Field (1993): In a study of 20 children aged six to 13 with prenatal exposure to methadone and a control group of non-exposed children, the researchers found no significant differences on cognitive tests (although methadone exposure was associated with lower IQ). The methadone-exposed children also tended to exhibit greater anxiety, aggression and rejection than those in the control group, and more behaviour problems were reported by the mothers of these children.
- Hans (1996): In a 10-year follow-up on 36 methadone-exposed children, this study found drug-exposed children made more errors on attentional (i.e., continuous performance) tasks and were somewhat more likely to receive ADHD and disruptive behaviour diagnoses when compared to a similar group of comparison children.

In addition to these findings, some studies have suggested that the chaotic lifestyle inherent with heroin use has as much of an effect on child development as in utero exposure to the drug itself. In such high-risk home environments, similar learning and behavioural problems have been reported in school-age children whether they were exposed to drugs in utero (Olofsson et al., 1983) or just living with drug-dependent parents without prenatal exposure (Nichtern, 1973; Hejanic, Barredo, Hejanic, & Tomelleri, 1979).

Conversely, in comparing the neurological and behavioural functioning of opioid-exposed children aged six to 15 to non-exposed children living with parents or caregivers who use opioids, Davis and Templer (1988) found the opioid-exposed children had perceptual, motor and attentional functioning impairments not seen in the non-exposed children. Similar results were found by Moe (2002), who evaluated 64 heroin-exposed children with minimal postnatal social risk and 52 comparison children using the MCSA at 4½ years of age. In this study, social risk was controlled by studying the children born to drug-using parents who were then placed in foster or adoptive care designed specifically for at-risk infants. Lower scores were found in the heroin-exposed children despite the minimal social risk.

Finally, a series of studies on the development of children aged five to 12 (Ornoy et al., 2001; Gogtay et al., 2004) found those born to and raised by their heroin-dependent parents had impaired verbal, performance, reading and mathematical skills. In comparison, children who were born to heroin-dependent mothers but adopted at a young age had normal intellectual and learning abilities with only some reduced function on performance IQ. A high rate of ADHD was reported in all children born to parents with heroin dependency, including those who were adopted; however, the highest rate was found among children who were raised at home by their heroin-dependent mothers.

Reports on the long-term effects of prenatal opioid exposure on postnatal growth and development are limited. As evident from these varying and conflicting findings, data can be difficult to interpret for a number of methodological reasons, including small sample sizes, poorly defined comparison groups and difficulty controlling for environmental variables (Bandstra et al., 2010). To further complicate the scarcity of literature, difficulties



CAROLE

Carole is a 29-year-old lawyer in Toronto who grew up in an affluent family with two parents who were both physicians. Medicine didn't appeal to Carole: she was drawn to the field of law. She ended up in a criminal practice, which was very high-pressured—both the work and the competition to become a partner.

Carole felt she had no time to enjoy life. But when her friends insisted she celebrate her birthday with them, she decided she could justify a night out. They went to a dance club. The more she drank, the more relaxed she became. Toward the end of the night, a friend of a friend introduced her to heroin: it made her feel relaxed and euphoric.

Given the pressures of her everyday life, Carole found herself craving the relief and release that she'd experienced with heroin. She tried it a few more times when she had the chance and eventually found herself seeking opportunities to party after hours. The heroin use spilled over into her daily work. When she was tense or anticipating a court appearance, a hit or two of heroin eased the pressure. Carole hid her habit from her husband.

Eventually, she realized she was addicted to the drug. She went to her physician, who referred her to a psychiatrist who treated heroin-addicted individuals with a newly available medication called buprenorphine-naloxone. Because she was very motivated, Carole stabilized rapidly. Two months later she discovered she was pregnant: while she'd been using heroin she had not been regular about taking her birth control pills. Her obstetrician said she could be switched to buprenorphine during pregnancy through a special Health Canada program and, although her baby might go through withdrawal, it would probably be mild and short-lived. Carole was determined to stay healthy and to recover from her addiction with the help of her physician and the medication.

associated with the studied population—in particular, high attrition rates and the lifestyle variability that characterizes the drug abuse culture—are prevalent (Hunt et al., 2008).

However, the studies available suggest that infants exposed to opioids in utero are at increased risk of neurodevelopmental impairment (Ornoy et al., 2001; Hunt et al., 2008). While the home environment clearly plays a significant role in the development of opioid-exposed children, the magnitude of its effect is still unclear (Ornoy et al., 1996, 2001; Hunt et al., 2008).

6.5 Prenatal drug exposure leading to addiction later in life

A common question about children exposed prenatally to drugs is whether they will be at greater risk for drug abuse and addiction when they grow older. Like the other developmental outcomes discussed in this chapter, the answer is not readily available. While prenatal drug exposure might lead to future drug problems, it is most likely that multiple factors influence or contribute to future drug use or addiction.

For example, in a systematic review of articles on the association between childhood sexual abuse and the development of substance-related disorders in adolescence or adulthood, Maniglio (2011) showed that while sexual abuse is definitely a risk factor for such disorders, it is not the only risk factor. Although this study had limitations, it is consistent with the fact that the majority of women who present to treatment centres have a history of sexual abuse. Maniglio's study therefore points out the importance of identifying childhood sexual abuse and providing appropriate interventions to help prevent future substance abuse.

6.6 Implications

When interpreting the effects of prenatal drug exposure on early childhood development, Bandstra and colleagues (2010) remarked that unlike traditional models of behavioural teratology (the study of congenital abnormalities), which are typically based on animal research with optimized control of the postnatal environment, real-world infants develop within very complex social and environmental conditions, all of which can influence functional and behavioural capacities. As such, it can be extremely difficult to determine the specific effects of drugs on the developmental process. Moreover, the environment can have a direct impact on the expression or magnitude of the effect of prenatal drug exposure.

Researchers agree that prenatal exposure to drugs is just one of the many factors than can influence a child's development. Many believe that the postnatal environment likely has a greater impact than prenatal drug exposure in determining a child's developmental outcomes, with the importance of responsive parenting well established (Bandstra et al., 2010). Multiple factors can moderate or mediate the effects of prenatal drug exposure on the caregiving attachment relationship and, ultimately, infant development. For example, cocaine-abusing mothers often use other substances and typically reside in high-risk environments characterized by poverty, poor nutrition, ongoing substance use and family instability. These factors, combined with prenatal drug exposure, can increase maternal stress and compromise the quality of the parenting—which, in turn, can have an adverse impact on infant development (Freier, 1994; Espinosa et al., 2001; Johnson, 2001; Eiden et al., 2006).

In addition to the teratogenic effects of drugs on development, it has been suggested that non-teratogenic effects might also exist. Lester and Padbury (2009) have presented a model in which drugs act as an intrauterine stressor that disrupts the neuroendocrine environment and genetic programming of fetal-placental development.

Based on these findings, existing intervention strategies developed for other at-risk children can offer guidelines for working with drug-exposed children and their families, potentially preventing or alleviating future developmental problems. In addition, specialized treatment programs supported by parent education services can help ameliorate the adverse effects of in utero drug exposure (Kronstadt, 1991; Twomey et al., 2010).

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JACQUELINE

Jacqueline was born in London, Ontario. Her mother, Joanne, had taken a number of drugs during her pregnancy including heroin, cocaine and benzodiazepines. She had also smoked tobacco and marijuana cigarettes. Joanne did not receive prenatal care or any addiction treatment until a few weeks before delivery, at which point she was placed on methadone. Jacqueline was born preterm and experienced a prolonged withdrawal, requiring hospital care for many weeks. Joanne visited regularly, carefully holding and feeding her, and was adamant about taking her baby home. She vowed to stay off street drugs, remain in treatment and provide a good home.

After Jacqueline's discharge, a social worker planned a series of follow-up visits. Joanne became quite anxious about these visits, worried Jacqueline might be taken away from her. She and her boyfriend, who was not Jacqueline's father, decided to move to Winnipeg. This disruption, combined with the poor conditions in which they lived after the move, brought considerable stress to their lives. Soon Joanne was using drugs again. She fed and bathed Jacqueline, but didn't stimulate or play with her. They never read books to her, the TV was on constantly and she had very few toys.

At four years of age, Jacqueline was taken to the doctor for a severe respiratory infection. The doctor observed her mother was depressed and discovered, in conversation, that she was consuming mood-altering drugs. On follow-up, when Jacqueline was physically better, the doctor noted the child was behind in her developmental milestones. She was referred to a clinic for evaluation and possible treatment. The cause of her slow progress could not be determined: it might have been because of her in utero drug exposure (which was complicated by withdrawal and overdose, leading to hypoxia), the environmental deprivation, or both. Jacqueline was referred to a guidance clinic to receive interventions for her developmental delay, while Joanne was referred to a drug rehabilitation clinic for her addiction.

7

A Call to Action

Because pregnancy is arguably one of the most developmentally complex periods for a mother and her child, the use of licit and illicit drugs, alcohol and tobacco during this time presents a number of unique health and social challenges. Fortunately, pregnancy can also offer a window of opportunity during which a woman's motivation for behaviour change—including her substance use patterns—may be heightened. To this end, it is vitally important that the professionals who provide health care to pregnant women are well informed of the latest clinical evidence and research.

Despite this need, the history of addictions research is one in which women (and particularly pregnant women) have largely been kept in the shadows. Most of the research that has been done has largely been androcentric in focus and, in many cases, has even been stigmatizing and accusatory toward women who use drugs. The recommendations presented here are aimed at bringing pregnant women affected by drugs, alcohol and tobacco out of the shadows and to situate their stories within the complex communities in which they live.

In particular, the present Call to Action identifies a pressing need for:

- A wider distribution and understanding of the latest biomedical research among treatment providers and their clients;
- A multidisciplinary approach to treatment, health promotion and prevention;
- A framing of the latest biomedical research in the Canadian context;
- More available therapies and a better understanding of their effects on the fetus;
- Increased efforts to reduce the stigma and discrimination faced by women who are pregnant and using substances; and
- A consideration of the evidence in this report within the context of specific populations.

7.1 Improving treatment provider and client education

Written with the treatment provider in mind, the aim of this report is to share the latest information on the medical and biological consequences of substance use during pregnancy. It should be seen as part of the educational and motivational toolkit that treatment providers can use to connect with women during their pregnancy, a period when they are most likely

At a Glance

- Healthcare providers require accurate information regarding the risks of substance use during pregnancy and concrete approaches for reducing the harms associated with this behaviour.
- Healthcare and substance use treatment providers should share information regarding the effects of substance use with women of a childbearing age to increase their awareness of the risks of such behaviour during pregnancy.
- Treatment interventions should be multifaceted and integrate biomedical and psychosocial approaches to care for and support pregnant women who use substances. Collaborations between professionals, family and community supports are integral to addressing the complexities of substance use.
- Clinicians and researchers should continue to investigate the effects of medication-assisted treatment for opioid dependence on pregnant women and infants.
- The stigma associated with substance use in general—specifically substance use during pregnancy and while parenting—must be addressed by all members of society. Framing addiction in the neurological context could help to reduce the media's propensity to sensationalize the plight of infants born with substance exposure and, in turn, improve awareness and understanding among the general public.
- Factors related to substance use during pregnancy such as ethnicity, income and geography should be explored by researchers to enhance the development of effective, tailored services for women and their children.
- The unique experiences of youth should be acknowledged, especially as drug use can affect the neurological pathways responsible for judgment and decision making, which are malleable until the mid-20s.
- Substance use can profoundly affect the earliest stages of human development and have adverse outcomes that carry into early childhood and beyond. Healthcare providers need to explore these issues more fully with their patients and provide unbiased, compassionate information to women of childbearing age and their partners.

to access healthcare supports and may be more inclined to address the potential harms associated with their substance use. In this context, it is important to underline the educational value of informing treatment providers about what is happening biologically to the fetus and to provide them with information about harm-reduction measures that can be taken by a pregnant woman and her community.

As has been demonstrated in the field of mental health, a non-judgmental treatment provider who can effectively relay information on the biological context of substance use during pregnancy can help prevent any sense of blame and therefore inaction on the part of the substance-using woman.

7.2 Adopting a multidisciplinary approach to treatment, health promotion and prevention

Data collected over the past several decades have consistently identified a high prevalence of psychosocial issues among women who abuse substances. Concurrent disorders and the issue of trauma can render women's care extremely complex at times, requiring a multifactorial response. A better understanding of these issues, which frequently are antecedents to substance use, is essential if treatment, prevention and health promotion efforts are to make a positive difference in the lives of women who use alcohol, drugs or tobacco during pregnancy.

While the biomedical focus of the report did not permit an in-depth analysis of the many complex psychosocial factors associated with substance use during pregnancy, the report does include an important chapter on psychosocial issues (Chapter 3), as well as an emphasis on the importance of a comprehensive care setting (Chapter 5). It is important to underscore the psychosocial themes such as those related to victimization that are included in this report and it is worth stressing the centrality of the family and community in any treatment response or health promotion and prevention effort.

To this end, this Call to Action encourages ongoing efforts to integrate biomedical and psychosocial approaches to care for and support pregnant women who use substances. While discipline- and profession-specific training is necessary, there is a serious need for a collaborative approach to training and professional development that integrates areas of expertise. Whether in hospitals, correctional facilities or community health services, our goal should be to approach pre- and postnatal support for women in a coordinated and integrated manner, regardless of the setting. In addition to the system-based benefits of such collaboration and integration, the learning of integrated knowledge in a consistent and supportive manner for women during pregnancy may represent a motivating influence on their personal health care.

There are several existing resources that can be adopted or tailored for those working with pregnant women, including the *Competencies for Canada's Substance Abuse Workforce* (www.ccsa.ca/Eng/Priorities/Workforce/Competencies) and the Trauma-informed Care Toolkit (www.cnsaap.ca/Eng/ProfessionalToolkits/Treatment_Issues/TraumainformedCare).

At the same time, it is important to recognize that community and clinical programs need to be scientifically supported and rooted in strong, research-based evidence, and this should be a key goal for all treatment, prevention and health promotion programming. We know from the literature that some of the most well-evaluated programs in Canada that address high-risk drug-involved women and their families do so through a one-stop, supportive and comprehensive service delivery model. In the future, it will be important to establish evaluative norms that would enable programs to be objectively evaluated against internationally accepted standards relating to the clinical, community and treatment literature.

7.3 Applying the evidence to the Canadian context

This report provides a comprehensive, global understanding of the key biomedical issues pertaining to the effects of substance use during pregnancy. It is not meant to focus on any one specific country. While it does highlight some Canadian data, it is not a report on the state of affairs in Canada per se. Moving forward, it will be important to identify gaps in the existing Canadian literature—as well as opportunities where we can draw greater understanding from the literature—to help provide further Canadian-specific context to some of the important themes outlined in this report.

It is worth noting that Canada has a National Treatment Strategy aimed at strengthening the services and supports available to those with substance use problems. A variety of national and regional organizations have also demonstrated leadership in

this area, including the Public Health Agency of Canada, the Canada Northwest FASD Research Network and the British Columbia Centre of Excellence for Women's Health.

NATIONAL TREATMENT STRATEGY

Canada's National Treatment Strategy is aimed at providing direction and recommendations to strengthen the services and supports available to Canadians with substance use problems. Implementation is currently underway for recommendations made in four key areas:

- Leadership;
- Knowledge exchange;
- Promoting a tiered model of services and supports; and
- System monitoring.

Source: National Treatment Strategy Working Group, 2008.

7.4 Gaining a better understanding of pharmacotherapies

We must continue to learn more about how the fetus responds to substance-related pharmacotherapies such as methadone and buprenorphine. There is therefore a strong need for clinicians to develop safe protocols to protect pregnant women and the fetus during treatment for opioid dependence. For clinicians, the best-known practice at this time is to assure a woman's comfort to prevent any cause for hypoxia (oxygen deprivation) in the fetus, such as when immediate abstinence occurs. (Maternal abstinence can cause fetal abstinence, which can cause hypoxia that contributes to intrauterine growth restriction.) In their efforts to do the very best for the pregnant woman, the fetus and the newborn, clinicians must use the best available medical, clinical and scientific knowledge.

In addition to clinical considerations, it is important to stress the need for more research in the pharmacotherapy field. While there are considerable data on the effects of opiate exposure in adults, including literature on methadone and buprenorphine use in pregnant women, more remains to be learned about the effects of exposure to opiate-based medications on the fetus and, in particular, the extended properties of these medications. In this regard, more research is encouraged on the similarities and differences in the effects of methadone, buprenorphine and buprenorphine-naloxone formulations on the developing fetus. Such research would create a greater understanding about the efficacy and safety of opiate-related treatments on the developing fetus, thereby strengthening the evidence-based framework for making decisions about the treatment choices available to pregnant women, so as to avoid obstetrical complications and help ensure the well-being of newborns.

7.5 Reducing the stigmatization of women who use substances during pregnancy

Most substance-using pregnant women face difficult social realities—challenges that can be worsened as they encounter stigma and discrimination within the healthcare system. These realities are depicted in the brief vignettes found in each chapter of this report, which present fictionalized accounts of what is happening in the field as experienced by both frontline healthcare workers and the women they care for. While recognizing that these vignettes represent only a snapshot of the full spectrum of clinical case contexts, they do capture some of the challenges experienced by community and healthcare workers in some settings. The information contained in this report provides a context for understanding the vignettes and illustrates why supporting pregnant women is the best available option.

It is important to point out that the media play a significant role in shaping society's perceptions of women who use substances during pregnancy and the resulting stigmatization of these women and their children. Specifically, the media have frequently used pejorative labels such as "addicted babies," "the littlest addicts," "crack babies," "meth babies" and "babies battling addiction" to describe infants exposed to drugs in utero. While attempts have been made to discourage the use of such terms by treatment providers and researchers alike, many are still picked up and reinforced by the general public.

Moving forward, efforts to explain the basis of addiction in brain-related terms might be helpful in addressing the use of such labels. The latest research suggests that addictions primarily reflect pathological disturbances to brain systems associated with reward and motivational processes; that is, severe alterations within systems that regulate our ability to identify which things to obtain and which to avoid. Viewing addictions and related harmful behaviours in this way frames them in health terms that are not dissimilar from other health issues.

By forcing an understanding of addiction that is grounded in basic health-related principles, such framing can provide an educational perspective that can help to overcome stigma. For example, by highlighting the neurobiological basis of

addiction, it becomes clear that babies cannot be "addicted"; instead, the passive transfer of drugs from mother to fetus creates in the newborn a physiologic dependence on the drugs used by the mother. This understanding illustrates not only the moral and ethical problems of pejorative labels, but also the inaccuracy of such labels given what we now know about the biological basis of addiction.

7.6 Meeting the needs of specific populations

Given the biomedical focus of this report, attention to specific populations, while noted, was not emphasized. However, because specific populations can present unique challenges as well as unique opportunities for support and treatment, diversity across social conditions and inequities such as income, race, geographic location, sexuality, disability, language, heritage and culture must be acknowledged.

Youth represent one such population. We need to better connect with the unique circumstances of youth, accounting for the full biopsychosocial continuum of specific youth populations. For example, at the social end of the continuum, young women may use substances to control their weight or body image. Recognizing this, it is worth thinking about what we can learn from the tobacco and alcohol industries with regard to the successful prevention and health promotion efforts that have been undertaken for a variety of age groups. At the biological end of the continuum, it is important to underline new knowledge derived from neuroscience indicating that the human brain is not yet fully developed during adolescence and the neural basis of executive function, which can affect judgment and choice, continues to develop through a person's mid-20s. We must also recognize that these life stages are not necessarily uniform from one young person to another. Both of these examples underline the importance of generating knowledge specific to the unique circumstances of distinct populations of youth.

In addition, the unique circumstances and backgrounds of women who use drugs, alcohol or tobacco during pregnancy need to be accounted for in any response. These circumstances include, for example, the historical impacts of colonization on the lives of First Nations, Inuit and Métis women in Canada. Aboriginal women experience some of the highest rates of poverty and interpersonal violence in Canada. For their healing, linkages with traditional culture and identity provide key support.

7.7 Conclusion

As a society, we need to continue to learn more about substance use, abuse and addiction generally, as is evident in the evolving definition of addiction presented in the most recent version of the *Diagnostic and Statistical Manual of Mental Disorders*. It follows that healthcare professionals must continually update their content-specific knowledge so they can best assist women experiencing substance-use challenges while pregnant and better understand the nature of substance use disorders and their related harms. In the context of this report, it is of particular interest to highlight the field of epigenetics, an emerging field that is helping to explain the interactions between nature and nurture. By providing a platform for understanding how environment and experience can modulate the expression of genetic and biology processes (e.g., explaining differences between identical twins despite their identical genetic make-up), the knowledge derived from epigenetics can help connect psychosocial and biomedical perspectives.

To meet the needs of women who use and become addicted to drugs, we need to continue our efforts to understand the multifactorial aspects of addiction and the effects of in utero exposure on offspring. Gaining this understanding will take many more dedicated researchers and clinicians, supportive infrastructures and a strong policy focus that recognizes the multidimensional nature of these challenges. Yet as we propose to find "solutions" to treatment and prevention, we must keep in mind that we also need to focus on what is actually working today. As new knowledge emerges in the field, we have the tendency to sometimes look at it as a "magic bullet" without keeping at the centre of our vision what is already known to be working. For example, because we already know that empowering women to make their own choices and "meeting them where they are at" is effective, this consideration should be at the forefront of any new knowledge as it is uncovered.

The most recent epidemiological data in Canada indicates a decline in substance use in both males and females. We also know that binge drinking has increased among college-aged women—and that the alcohol industry is increasingly marketing to this group and other women. And we also know that advances in the neurosciences are happening at lightning speed. Once again, it is important to know from all perspectives what is being uncovered to help contextualize what we are learning together in the research lab, the clinic, the classroom and the living room.

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Appendix A: U.S. Food and Drug Administration Pregnancy Categories

In 1979, the U.S. Food and Drug Administration (FDA) established five categories (A, B, C, D, X) to indicate the potential of a drug to cause birth defects if used during pregnancy. The placement of a drug into one of these categories is determined by the reliability of the drug's documentation as well as its risk-to-benefit ratio. It should be noted that these categories do not account for risks conferred by pharmaceutical agents or their metabolites in breast milk.

The FDA uses the following definitions for its pregnancy categories:

Category A: Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).

Category B: Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.

Category C: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Category D: There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Category X: Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

Appendix B: *Controlled Substances Act* (United States)

Signed into law in 1970, the U.S. *Controlled Substances Act* is divided into five schedules, with all pharmaceutical agents regulated under federal law classified according to their currently accepted medical use as well as their relative abuse potential and likelihood of causing dependence. Drugs listed in Schedule I have no currently accepted medical use and may not be prescribed, administered or dispensed for that purpose. Drugs in Schedules II–V, however, have some accepted use in treatment and may therefore be prescribed, administered or dispensed for medical use.

Some examples of the controlled substances in each schedule are as follows:

Schedule I: These substances have a high potential for abuse and no currently accepted medical treatment use. In addition, there is a lack of accepted safety for the use of these substances under medical supervision. Substances listed in Schedule I include heroin, lysergic acid diethylamide ("LSD"), cannabis, peyote, 3,4-methylenedioxymethamphetamine ("ecstasy") and methaqualone (Quaaludes®).

Schedule II: These substances have a high potential for abuse, potentially leading to severe psychological or physical dependence. While they do have a currently accepted medical treatment use, there may be severe restrictions on such use. Substances listed in Schedule II include morphine, methadone, hydromorphone, oxycodone (OxyContin®), cocaine, phencyclidine ("PCP"), amphetamine (Adderall®), methamphetamine, methylphenidate (Ritalin®) and barbiturates such as amobarbital and pentobarbital.

Schedule III: These substances have a lesser potential for abuse than those listed in Schedules I and II. Their abuse may lead to moderate or low physical dependence and/or high psychological dependence. Substances listed in Schedule III include buprenorphine, benzphetamine, ketamine, anabolic steroids such as oxandrolone, products containing less than 15 milligrams of hydrocodone per dosage unit (Vicodin®) and products containing not more than 90 milligrams of codeine per dosage unit (Tylenol® with codeine).

Schedule IV: These substances have a low potential for abuse relative to those listed in Schedule III. However, there is still the potential for physical or psychological dependence. Substances listed in Schedule IV include propoxyphene (Darvon®) as well as benzodiazepines such as alprazolam (Xanax®), diazepam (Valium®), clonazepam, clorazepate, lorazepam, midazolam, temazepam and triazolam.

Schedule V: These substances have a low potential for abuse relative to those listed in Schedule IV and consist primarily of preparations containing limited quantities of certain narcotics. Generally used for antitussive, antidiarrheal and analgesic purposes, substances listed in Schedule V include cough medicines containing not more than 200 milligrams of codeine per 100 milliliters or per 100 grams (Robitussin AC®, Phenergan® with codeine).

For a complete list of all of the substances included in each schedule of the *Controlled Substance Act,* please refer to the U.S. Food and Drug Administration's website at: http://www.fda.gov/regulatoryinformation/legislation/ucm148726.htm.

Appendix C: *Controlled Drugs and Substances Act* (Canada)

Passed in 1996, the *Controlled Drugs and Substances Act* is Canada's federal drug control statute. Repealing the previous *Narcotic Control Act* as well as parts of the *Food and Drug Act*, it establishes a series of schedules pertaining to the control of certain drugs, their precursors and other substances. The schedules outlined by the *Controlled Drugs and Substances Act* can be amended the Governor in Council as deemed necessary in the public interest.

Except as authorized under the regulations, no person shall:

- Possess a substance listed under Schedules I–III;
- Traffic in a substance listed under Schedules I–IV;
- Import or export a substance listed under Schedules I–VI; or
- Produce a substance listed under Schedules I–IV.

Some examples of the controlled substances in each schedule are as follows:

Schedule I

- Heroin
- Morphine
- Oxycodone
- Hydromorphone
- Codeine (when not in medication containing at least two other ingredients)
- Cocaine
- Methadone
- Buprenorphine
- Phencyclidine ("PCP")
- Ketamine
- Methamphetamine
- 3,4-methylenedioxymethamphetamine ("ecstasy")
- Amphetamine (Adderall®)
- 4-hydroxybutanoic acid ("GHB")
- Flunitrazepam (Rohypnol®)

Schedule II

- Cannabis and its preparations, derivatives and similar synthetic preparations (but not including non-viable cannabis seed or mature cannabis stalks without leaves, flowers, seeds or branches)

Schedule III

- Lysergic acid diethylamide ("LSD")
- Dimethyltryptamine ("DMT")
- Methaqualone (Quaaludes®)
- Mescaline
- Harmaline
- Methylphenidate (Ritalin®)
- Psilocin
- Psilocybin
- Some barbiturates, including pentobarbital and amobarbital
- Medications combining hydrocodone and acetaminophen (Vicodin®)

Schedule IV

- Anabolic steroids such as oxandrolone
- Benzodiazepines such as alprazolam (Xanax®), diazepam (Valium®) and triazolam
- Most other barbiturates, including those used as general anesthetics or considered to be mild hypnotics such as barbital, phenobarbital, sodium thiopental and mephobarbital
- Cathine

Schedule V

- Propylhexedrine

Schedule VI

- Synthetic and natural forms of precursors such as acetic anhydride, lysergic acid, norephedrine, piperidine, potassium permanganate, acetone, hydrochloric acid, sulphuric acid and toluene

For a complete list of all of the substances included in each schedule of the *Controlled Drugs and Substances Act,* please refer to the Government of Canada's website at http://laws-lois.justice.gc.ca/eng/acts/C-38.8.