Population-Based Outcomes of a Provincial Prenatal Screening Program: Examining impact, uptake and ethics

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ABSTRACT

The field of prenatal screening and diagnosis has developed rapidly over the past half-century, enabling possibilities for detecting anomalies in reproduction that were never before contemplated. A simple blood sample can aid in the identification of several conditions in the fetus early in the pregnancy. If a fetus is found to be affected by Down syndrome, anencephalus, spina bifida, or Edward's syndrome, a decision must then be made whether to continue or terminate the pregnancy. As prenatal screening becomes increasingly commonplace and part of routine maternal care, researchers are faced with the challenge of understanding its effects at the level of the population and monitoring trends over time. Greater uptake of prenatal screening, when followed by prenatal diagnosis and termination, has important implications for both congenital anomaly surveillance and infant and fetal mortality indicators. Research in Canada suggests that this practice has led to reductions in the congenital-anomaly specific infant mortality rate and increases in the stillbirth rate.(1, 2)

The current study is a population-based, epidemiological exploration of demographic predictors of maternal serum screening (MSS) and amniocentesis uptake, with special attention to variations in birth outcomes resulting from different patterns of use. To accomplish our objectives, multiple data sources (vital statistics, hospital and physician services, cytogenetic and MSS laboratory information) were compiled to create a comprehensive maternal-fetal-infant dataset. Data spanned a six-year period (2000-2005) and involved 93,171 pregnancies. A binary logistic regression analysis found that First Nations status, rural-urban health region of residence, maternal age group, and year of test all significantly predicted MSS use. Uptake was lower in women living in a rural health region, First Nations women, and those under 30 years of age. The study dataset identified ninety-four terminations of pregnancy following detection of a fetal anomaly (TOPFA), which led to a lower live birth prevalence of infants with Down syndrome, Trisomy 18, and anencephalus. While a significant increasing trend was observed for the overall infant mortality rate in Saskatchewan between 2001-2005, a clear trend in one direction or the other could not be seen in regards to infant deaths due to congenital anomaly.

First Nations status and maternal age were important predictors of both MSS and amniocentesis testing, and appeared to influence the decision to continue or terminate an affected pregnancy. The fact that First Nations women were less likely to screen (9.6% vs. 28.4%) and to have diagnostic follow-up testing (18.5% vs. 33.5%), meant that they were less likely to obtain a

prenatal diagnosis when the fetus had a chromosomal anomaly compared to other women (8.3% vs. 27.0%). This resulted in a lower TOPFA rate compare to the rest of the population (0.64 vs. 1.34, per 1,000 pregnancies, respectively) and a smaller difference between the live birth prevalence and incidence of Down syndrome and Trisomy 18 for First Nations women.

Women under 30 years of age were much less likely to receive a prenatal diagnosis when a chromosomal anomaly was present (18.4% vs. 31.8%). While risk for a chromosomal anomaly is considerably lower for younger mothers, 53.5% of all pregnancies with chromosomal anomalies and 40.7% of DS pregnancies belonged to this group.

Consistent with other studies pregnancy termination rates following a prenatal congenital anomaly diagnosis are high (eg. 74.1% of prenatally diagnosed Down syndrome or Trisomy 18 cases), but these rates may be misleading in that they are based on women who chose to proceed to prenatal diagnosis. The fact that two-thirds (67.3%) of Saskatchewan women who received an increased-risk result declined amniocentesis, helps to put this finding into context.

Strong surveillance systems and reasonable access to research datasets will be an on-going challenge for the province of Saskatchewan and should be viewed as a priority. Pregnancies and congenital anomalies are two particularly challenging outcomes to study in the absence of perinatal and congenital anomaly surveillance systems. Still pregnancies that never reach term must be accounted for, in order to describe the true state of maternal-fetal-infant health and to study its determinants. While our study was able to identify some interesting trends and patterns, it is only a snapshot in time. Key to the production of useful surveillance and evaluation is timely information. The current system is not timely, nor is it user-friendly for researchers, health regions or governments. Data compilation for the current study was a gruelling and cumbersome process taking more than five years to complete. A provincial overhaul is warranted in both the mechanism by which researchers access data and in the handling of data. The Better Outcomes Registry & Network (BORN) in Ontario is an innovative perinatal and congenital anomaly surveillance system worthy of modelling.(3)

Academic papers in non-ethics' journals typically focus on the technical or programmatic aspects of screening and do not effectively alert the reader to the complex and profound moral dilemmas raised by the practice. A discussion of ethics was felt necessary to ensure a well-rounded portrayal of the issue, putting findings into context and helping to ensure their moral relevance did not remain hidden behind the scientific complexities. Here I lay out the themes of

the major arguments in a descriptive manner, recognizing that volumes have been written on the ethics of both screening and abortion. A major ethical tension arising within the context of population based prenatal screening is the tension between community morality and the principle of respect for personal autonomy. Prenatal screening and selective termination have been framed as a purely private or medical matter, thereby deemphasizing the social context in which the practice has materialized and the importance of community values. I consider how a broader sociological perspective, one that takes into account the relevance of community values and limitations of the clinical encounter, could inform key practice and policy issues involving prenatal screening. It is my position that the community's voice must be invited to the conversation and public engagement processes should occur prior to any additional expansion in programming. I end with a look at how the community's voice might be better heard on key issues, even those issues that at first glance seem to be the problems of individuals. As Rayna Rapp (2000) (4) poignantly observed, women today are 'moral pioneers' not by choice, but by necessity.

By elucidating the effects of prenatal screening and the extent of the practice of selective termination in the province, the true occurrence of important categories of congenital anomalies in our province can be observed. Without this knowledge it is very difficult to identify real increases or decreases in fetal and infant mortality over time as the etiologies are complex. Evidence suggests a large and increasing impact of TOPFA on population-based birth and mortality statistics nationally, whereas in Saskatchewan the effect appears to be less pronounced. Appreciation of the intervening effect of new reproductive technologies will be increasingly important to accurate surveillance, research, and evaluation as this field continues to expand.

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DEDICATION

To my children, Lara, Tristan and Tyler, who inspire me daily

To those families experiencing the unimaginable loss of losing a child

DISCLAIMER

This Study is based in part on de-identified data provided by the Saskatchewan Ministry of Health. The interpretation and conclusions contained herein do not necessarily represent those of the Government of Saskatchewan or the Saskatchewan Ministry of Health.

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DEFINITIONS

Congenital anomaly - An abnormality of structure, function or body metabolism that is present at birth (even if not diagnosed until later in life) and results in physical or mental disability.[1]

Gestation - Development of the fetus from the first day of the last period until birth, 40 weeks.[2]

Infant mortality - Death in the first year of life (0-364 days)[3]

Live birth - "... the complete expulsion or extraction from the mother, irrespective of the duration of the pregnancy, of a product of conception in which, after the expulsion or extraction, there is breathing, beating of the heart, pulsation of the umbilical cord or unmistakable movement of voluntary muscle, whether or not the umbilical cord is cut or the placenta is attached."[4]

Medical abortion - A medical procedure (whether by drugs or surgery) meant to destroy the fetus or embryo. Also referred to as a termination of pregnancy, or therapeutic, surgical or induced abortion.

Neonatal - First 27 days after birth[3]

Postneonatal - 28 to 364 days after birth[3]

Prenatal - Before birth[2]

Spontaneous abortion - A clinically recognized natural pregnancy loss before the fetus is 20 weeks or weighs 500 grams.[5]

Stillbirth - "...the complete expulsion or extraction from the mother after at least 20 weeks' pregnancy, or after attaining a weight of at least 500 grams, of a product of conception in which, after the expulsion or extraction, there is no breathing, beating of the heart, pulsation of the umbilical cord or unmistakable movement of voluntary muscle."[2]

Termination of pregnancy for fetal anomaly - A medical abortion performed because of a known or suspected condition posing serious threats to the quality of life of the child and/or undesirable to the mother.

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[1] March of Dimes Resource Center. *Birth Defects*. 1998. (Available www.modimes.org).
[2] Tiran D. (1997). Midwives' Dictionary. (9th ED). London, UK: Bailliere Tindall.
[3] Public Health Agency of Canada. Canadian Perinatal Health Report - 2008 Edition. Ottawa 2008.
[4] Vital Statistics Act, 1995, Saskatchewan Government. (Available at http://www.qp.gov.sk.ca/documents/English/Statutes/Statutes/V7-21.pdf).
[5] Regan L, Ral R. Epidemiology and the medical causes of miscarriage. Baillieres Best Pract Res Clin Obstet Gynaecol 2000;14(5):839.

CHAPTER 1: INTRODUCTION

1.0 Introduction

The field of prenatal screening and diagnosis has developed rapidly over the past half-century, enabling possibilities for detecting anomalies in reproduction that were never before contemplated. Technology has made it possible to test a blood sample and identify several conditions in the fetus early in the pregnancy. Given more information about the health status of the fetus, women are able to make decisions not available to them in the past, including whether to continue or terminate pregnancies[6] affected by congenital anomalies. These new choices, and the act of choosing, are fraught with ethical and moral dilemmas. As prenatal screening becomes increasingly commonplace and part of routine maternal care, researchers are faced with the challenge of understanding its effects at the level of the population and monitoring trends over time. Greater uptake of prenatal screening, when followed by prenatal diagnosis and termination, has important implications for congenital anomaly (CA) surveillance and the interpretation of infant and fetal mortality outcomes. Pregnancies that never reach term must be counted in order to describe the true state of maternal-fetal-infant health and to study its determinants.

The national live-birth prevalence of important categories of congenital anomalies (including Down syndrome, hypoplastic left heart syndrome, neural tube defects, and limb reduction defects) have either declined or stabilized since the late 1980s.(5) Prenatal screening and the termination of pregnancies diagnosed with a CA have been shown in some countries to be responsible for this stabilization (6-10); however, little is known about its impact throughout Canada. To date, the published literature in Canada has examined the connection between prenatal diagnosis and the prevalence of neural tube defects in British Columbia and Ontario.(11, 12) Investigations by Liu, Wen, Joseph, and Kramer et al (1999-2002, 2013) (1, 2, 13-16) have also elucidated the relationship between pregnancy terminations following prenatal detection of an anomaly and trends in infant and fetal mortality. There is, however, a need for more research in Canada to examine the population impact of prenatal screening and diagnosis, across provinces and across population sub-groups. In particular, studies have not been able to directly link birth outcomes to information on prenatal screening and diagnosis, and reliance on birth and

[6] Termination of pregnancy is synonymous with therapeutic, surgical or medical abortion, or induced abortion.

death certificate data invariably leads to undercounting of pregnancy termination for reasons of a CA (1).

When delivered as intended, prenatal screening is optional and each adequately informed woman either accepts or declines testing from their physician or midwife. The reasons for choosing to screen or not to screen are as complex as each individual, but also depend on many cultural, programmatic and system-level factors.(7, 17, 18) As such, rates of uptake of prenatal screening vary widely by geographic location and correlate to client and physician characteristics and value systems. The fact that uptake differs across populations means that follow-up diagnostic testing and ultimately, termination of pregnancies for fetal anomaly[7] (hereafter abbreviated to TOPFA), will both occur at differential rates. It is these differences that may result in variations in key population health indicators like the infant and perinatal mortality rates and CA birth rates; all of which provide us with important information about infant and maternal health and the broader determinants of health of society as a whole.

The current dissertation research is unique in that to my knowledge it is one of the first instances within Canada to undertake a comprehensive examination of the direct link between prenatal screening uptake and outcomes at the population level, including the birth prevalence of major categories of CAs and infant and fetal mortality rates. The prevalence of screening at the population level is related to a number of factors, including access to services, physicians` support and knowledge of screening, and women's values, educational backgrounds, level of real and perceived risk, and culture.(4, 19-32) The outcomes are therefore hypothesized to vary according to geography, age, and ethnic group. Similar variations in mortality and CA birth prevalence are also anticipated.

In recent years the infant mortality rate (IMR) has come under greater scrutiny because technological changes and methodological limitations threaten its utility as a global indicator of health and wellbeing.(33-36) Such limitations may have even severed its connections to the broader determinants of health. Gortmaker and Wise (1997) argue health care technologies (eg. neonatal intensive care services and surfactant therapy) have "altered traditional pathways of social influence [and] plead for recognition among infant mortality specialists [for] an opportunity to expand their disciplinary embrace to include the social forces that shape both the dimensions of medical progress and differential access to the fruits of this technical struggle".(34

[7] The terms fetal anomaly and congenital anomaly are used interchangeably throughout.

p.158) Three main factors have led to the challenges around comparability of IMR across populations. First, an important methodological limitation relates to differences in birth registration practices across countries; second, a health system's ability to deliver and sustain very low birth weight and pre-term infants may increase the pool of infants with a high mortality risk; and third, prenatal screening and selective termination reduces the number of high-risk infants, albeit inconsistently, across population sub-groups and different countries.(13-16, 33, 36-38) All of these factors have the potential to modify the IMR, and sometimes, counterbalance one another. Consider the historically elevated IMR in the Aboriginal population. How much of the variation is due to the social determinants of health (eg. income, education, lower use of preventative health care) and how much is due to lower acceptance of prenatal screening by Aboriginal women and the subsequent lower rates of termination of pregnancy for fetal anomaly are important questions to parse through. While the causes of IMR are said to be strongly linked to factors affecting the health of entire populations, such as economic development, living conditions, social wellbeing, and environment (39), not enough attention has been given to its strong link to prenatal screening and the selective termination of pregnancies with congenital anomalies. The 2005 United Nations' *Human Development Report* goes as far as to state: "No indicator captures the divergence in human development opportunity more powerfully than child mortality".(40 p.4) Though customarily acclaimed as a critical population health indicator, doubt has been cast on the utility of IMR in cross-national comparisons, leading to second guessing its inclusion in key national health indicator reporting.(41) An important step is to better understand the IMR-prenatal screening link.

Insights into the determinants of infant and fetal mortality through research will help to better guide practice and policy making, which together can lead to improved overall health and wellbeing. By elucidating the effects of prenatal screening and the extent of the practice of selective termination, the true prevalence of CAs in our province will be made known. Without this knowledge we are not able to track real increases or decreases in CAs and sufficiently interpret trends in infant mortality over time. Answers to these research questions are crucial for accurate surveillance, research, and evaluation in our province.

Outside of ethics' journals, much of the peer-reviewed literature on the topics of prenatal screening and termination of pregnancy for fetal anomaly offers the impression that there is nothing morally contentious being discussed. By using medical terminology and phrasing,

researchers present the topic in a way that masks the many layers of moral complexity inherent in these practices. This is not necessarily intentional, but rather a function of the publication process and its disciplinary focus, strict space limits, complexity of the issue, and a lack of familiarity with the philosophy and ethics of science. Nonetheless, ethical considerations are a significant and indivisible aspect of prenatal screening, and as a result, the current project will bring to light some of the thorny ethical questions posed by pregnancy termination of affected fetuses. In doing so it presents a more comprehensive analysis of prenatal screening than before, which typically has focused on either epidemiological aspects or ethical aspects, but not both. Attention will be given to both the broader questions surrounding prenatal screening and connected to the more practical dilemmas confronting physicians, women and their families.

1.1 Study Objectives and Null Hypotheses for Quantifiable Outcomes

When conceptualizing the link between prenatal screening and population health outcomes, one must keep in mind the cascade of events potentially set in motion by the initial offer for screening by the physician or midwife. This process includes a series of decision steps, which may ultimately contribute to a different pregnancy outcome. The objectives for this study, similarly, follow a logic, starting with the investigation of factors that influence the decision to have the screening test, then diagnosis. When a diagnosis is made the next decision step is whether to terminate the pregnancy or continue; a step in the pathway that has important ramifications for the live birth rate of congenital anomalies (those subject to prenatal diagnosis), as well as for indicators of fetal and infant death. Each decision point in this pathway will be analyzed through the lens of person- and place-specific factors that may contribute to the outcome of interest.

My primary study objectives and their accompanying null hypotheses are as follows:

1. To examine the relationship between mother's region of residence, Registered Indian status, and age and utilization of prenatal screening and diagnosis.

   Ho: Uptake of MSS and follow-up diagnostic testing does not vary by mother's health region of residence, Registered Indian Status, or age group.

2. To study variations in pregnancy terminations for fetal anomaly by mothers' region of residence, Registered Indian status, and age.

Ho: Pregnancy terminations for congenital anomaly do not vary by mother's health region of residence, Registered Indian Status, or age group.

3. To determine if terminations of pregnancy for fetal anomaly have resulted in decreases in the number of live births with congenital anomalies between 2000-2005 that are screenable by the MSS program, in particular, chromosomal anomalies.

Ho: The live birth prevalence rates of Down syndrome and trisomy 18 have not changed between 2000-2005 as a result of terminations of pregnancy prenatally-identified through the Saskatchewan MSS program.

4. To determine if terminations of pregnancy for fetal anomaly have resulted in decreases in the stillbirth rate, the neonatal mortality rate, the congenital anomaly-specific infant mortality rate, or the overall infant mortality rate between 2001-2005.

Ho: The number of terminations of pregnancy for fetal anomaly has not changed the annual stillbirth, neonatal mortality, CA-specific infant mortality, or crude infant mortality rates between 2001-2005.

CHAPTER 2: LITERATURE REVIEW

2.0 Prenatal Screening

Prenatal screening has evolved considerably since the 1970s when maternal age was the only means available to identify pregnancies at increased risk for CA. At that time, women over the age of 35 could be offered amniocentesis; a procedure that is now known to carry a risk of miscarriage of 1 in 200 to 1 in 100, after adjusting for factors such as gestational age.(42) Prenatal screening was introduced with the hope of reducing the need for invasive testing (amniocentesis) and could also be used by women who might not otherwise opt for screening and would therefore lead to increased case ascertainment during the prenatal period. In the late 1980's alpha fetoprotein (AFP) in maternal blood was just starting to be used to predict neural tube defects in select Canadian sites.(43) By the late 1990's and early 2000's, the ""triple marker" screen became the tool routinely used. The name reflected its ability to integrate measures of three blood serum levels: beta chorionic gonadotrophin (hCG), unconjugated estriol (uE3), and AFP.(44)

As newer tests are being integrated into existing screening programs, the triple test has been largely replaced. Some of the newer screens include: *the quadruple test*, where dimeric inhibin A is added to AFP, hCG, and uE3 markers; *nuchal translucency* (NT) measurement where the nuchal fold (a marker for aneuploidy) is measured using ultrasound between 11-14 weeks; *first trimester screening* (FTS) where a NT measurement is combined with two maternal serum markers – hCG and Pregnancy Associated Plasma Protein A (PAPP-A); and *integrated prenatal screening* (IPS) where a NT measurement is combined with PAPP-A and second trimester MSS.(45, 46) Each test performs differently in terms of its detection and false-positive rates, with the newer tests performing better (on average) than the triple test. Further evolution of prenatal screening has resulted in a shift in the timing from the second to the first trimester.

Table 2.1 Prenatal screening modalities by time frame of introduction, conditions detectable and detection rate*

Time frame	Test Name	Methodology	Conditions detected	Performance (detection rate)†
1970s	Maternal age > 35 years	Amniocentesis is offered to all women over age 35	Most major chromosomal problems; many genetic disorders	30%-40%
1980s	Alpha fetoprotein (AFP) testing	AFP	Neural tube defects (NTD), Down syndrome (DS), Trisomy 18 (T18)	Women < 35: 85% NTDs, 60% DS, 60% T18.
1990s – 2000s	Triple marker test	human chorionic gonadotrophin (hCG), unconjugated estriol (uE3), and AFP	NTD, DS, T18	65%-75%
2000s	Quadruple test	Dimeric inhibin A + hCG, uE3, AFP	NTD, DS, T18	80%-90%
Mid-2000s	First trimester screening	Nuchal translucency (NT) (an ultrasound measurement of the nuchal fold taken between 11-14 weeks)	DS	70%
		Maternal serum markers - Pregnancy Associated Plasma Protein A (PAPP-A) and ß-hCG	NTD, DS, T18	60%
		NT + maternal serum markers ß-hCG and PAPP-A	NTD, DS, T18	80% - 90%
late-2000s	Combined first and second trimester screening (integrated)	NT + PAPP-A and second trimester MSS†	NTD, DS, T18	95%
		Integrated maternal serum screening†	NTD, DS, T18	85%
		Stepwise sequential maternal serum screening‡	NTD, DS, T18	80%

* Coory MD, Roselli T, Carroll HJ. Antenatal care implications of population-based trends in Down syndrome birth rates by rurality and antenatal care provider, Queensland, 1990-2004. The Medical journal of Australia. 2007 Mar 5;186(5):230-4.(46) †Screening is done in both the first and second trimesters, but a single risk estimate is reported to the expectant mother only in the second trimester.‡ Screening is done in both the first and second trimesters, and results of the first trimester are reported to the mother so she can act on them at the time. The detection rate depends on the sequence of tests used (an indicative figure is given here).
† At a false-positive rate of 5%.

The shift from age-based screening to population-based screening is an important one in the field's history. The former practice of offering amniocentesis only to women over the age of 35 allowed for the detection of up to 30-40% of all Down syndrome (DS) cases in the population.(47) By extending the offer of screening to all pregnant mothers, there is the potential to capture 85% or more of DS cases. In 2007, the Society of Obstetricians and Gynecologists of Canada (SOGC) modified its previous guideline to reflect this move towards a population-based approach and now recommends that all women be offered be offered maternal serum screening.(48) It is not yet known what impact expanded screening has had on the occurrence of these three conditions as far as numbers of children being born into the Canadian population. If one looks at the case of Tay-Sachs disease, the introduction of prenatal screening almost three decades ago has led to an estimated 90% decrease in the condition in Jewish populations in the United States and Canada.(49) Because Tay-Sachs is an always fatal neurodegenerative disease, the impact of screening is likely much greater than would be expected with the three conditions targeted through MSS.

Only a handful of conditions are routinely screened for during the prenatal period in Canada - Down syndrome, neural tube defects; and trisomy 18. It is important to note that while only a small number of conditions can be screened for, many more can be diagnosed through prenatal diagnosis, which is conducted through either amniocentesis or chorionic villus sampling (CVS). The number of genetic conditions that can be diagnosed prenatally grew from approximately 100 in 1993 to more than 1000 today.(50, 51) Cystic fibrosis (CF) screening is the newest condition for which a screening test has been developed, however in this case screening starts with the parents. Parents are offered screening for CF through a blood test, and if both are positive, then amniocentesis is offered. At present, the SOGC has recommended against population-based carrier screening for CF for all parents, but recommends offering screening only to parents believed to be at higher-risk.(52) While we do not know how many parents are screened for CF in Canada, 20 percent of pregnant women receiving prenatal care in the United States are screened for cystic fibrosis.(53) Another parameter of interest for some parents is fetal gender. The practice of aborting female fetuses is well-established in countries like India and China where male children are more highly valued and there are growing concerns about prenatal sex selection in the US and Canada. While viewed as morally reprehensible by most practitioners, and addressed by the SOGC in a recent policy statement declaring its non-support

for termination of pregnancy on the basis of gender (54), there is evidence that prenatal sex selection is occurring in Canada (55, 56).

The SOGC statement reads:

> **"**The Society of Obstetricians and Gynaecologists of Canada believes that medical technologies and/or testing for the sole purpose of gender identification in pregnancy should not be used to accommodate societal preferences. Testing may include but not be limited to diagnostic imaging, maternal biochemical testing, chorionic villous sampling, amniocentesis, and any pre-implantation genetic testing. Sex identification with the intent of minimizing genetic transmission of disease is generally well supported internationally, but measures that perpetrate discrimination are condemned. The SOGC does not support termination of pregnancy on the basis of gender."(54 p.909)

In countries where sex selection abortion is common, the male to female ratio is increasingly skewed and analysis by Statistics Canada has found this very phenomenon in Canadian cities with high immigrant populations.(55-58) It seems the long-awaited genomic era has arrived, accompanied by its impenetrable moral, social and legal controversies.

Attempts to enact legislation governing assisted reproductive technologies in Canada have been unsuccessful, leaving most of the conversation to happen in academic journals and ethical concerns to be managed through the guidelines and policies of professional organizations.(59) There is a curious lack of public discourse around prenatal screening and which conditions are acceptable for screening. Instead, professional bodies are leading the charge. These are the organizations whose members are responsible for delivering testing and performing termination of pregnancies, and therefore could be argued to have a vested interest in the normalization of prenatal screening and diagnosis. At the very least, they represent one particular viewpoint out of a multitude of voices that need to be heard, but have not yet been engaged. One explanation for the lack of public engagement is the contextual and psychological proximity between prenatal screening/diagnosis to fiercely debated topics including abortion, treatment of people with disabilities, eugenics, and limits to individual autonomy. Instead, the responsibility for such decisions has rested almost entirely on physicians and pregnant women.(4) Inevitable advances in genetics and screening techniques are likely to cultivate further moral, ethical and legal dilemmas about what limitations society ought to impose.

2.0.1 Maternal Serum Screening

Maternal Serum Screening (MSS) is a cluster of prenatal screening methods used to identify pregnant women whose fetuses have a greater likelihood of congenital anomalies and offer these women follow-up diagnostic testing. The term itself is often used to refer to the 'triple screen', but can be used more generally when speaking about prenatal screening programs that utilize many of the screening techniques previously described. By measuring the concentration of markers in maternal blood, an estimate is produced that tells each woman their probability of giving birth to an infant with any of these three conditions.(44) Since MSS is a screen and not a diagnostic test, women with results above the cut-off ("increased-risk") must undergo follow-up testing, such as a detailed ultrasound or a more invasive amniocentesis, to know for certain.

MSS generates probability estimates by comparing each woman's test result to the norms for the population. An estimate is calculated for each patient based on maternal age and the trivariate Gaussian frequency distributions from affected and unaffected pregnancies.(60, 61) Put another way, an individual woman's test result is compared to the values expected for women with normal pregnancies of the same gestational age, maternal age, ethnic background, diabetes status, body weight and parity. Other factors such as smoking and previous false positive findings may also affect test results, but are not always controlled for in every screening program. It is important to note that an increased-risk result in one laboratory will not necessarily be an increased-risk result in another due to different population norms. In Saskatchewan, up until mid-2009, the triple test was the primary screening technique offered throughout the province. This particular test is offered between 15 and 20 weeks gestation, but the ideal time to sample is between 16 and 18 weeks. Recently the provincial MSS program has added several techniques, including first trimester and integrated screens.

Several studies have been conducted looking at the once popular triple test and have shown differences in its performance across settings. The age, race and general health of pregnant women differ in each population in ways that affect the test's performance or its ability to accurately detect fetal anomalies.(60) Therefore it is vital that evaluations are done specifically looking at the population in which the screening program is being implemented. Studies have shown the triple test to have detection rates in the range of 48% - 91% (median 71%), with false-positive rates between 3% and 35% (median 5.6%), depending on the cut-off level used by the laboratory and the proportion of tests where the gestational age is confirmed by

ultrasound.(6, 10, 44, 61-77) Accurate gestational dating is a crucial factor in test performance (78), but can be a challenge in rural settings where this service is not always offered. Detection rates for the triple test rise, on average, from 59% without gestational dating to 69% with these scans.(67) In Britain, differences in age distributions across health districts led to significant variations in test performance, which means that a greater proportion of women in some districts would receive increased-risk results and be referred for an amniocentesis, even though all were offered the same test using the same risk cut-off level.(60) Studies have also shown detection rates to vary by as much as 39% between women age 35 and over and women under age 35, with false-positive rates being as much as 38% higher in women age 35 and over.(62, 66, 71, 72) The positive predictive value of screening is lower in populations where the prevalence of disease is lower (79), such as in younger women.

While the sensitivity and specificity of MSS varies according to both patient characteristics and the condition being screened, the overall high rate of false-positives is a concern for pregnant women and physicians. It is estimated that anywhere from 1 in 10 to 1 in 20 women being tested will receive an increased-risk result.(5) In reality, only 1-2% of women receiving an increased risk result will have a fetus affected by DS, NTD, or trisomy 18. Therefore women undergoing amniocentesis due to such results may be putting their pregnancies at-risk based on a mistaken indication of their personal risk; a fact that limits the usefulness of MSS testing in the clinical setting, especially for pregnant women who are mainly seeking assurance of their babies health (80).

MSS is voluntary and women are given the choice to accept or decline testing, and as a result, studies have found the uptake of MSS varies by maternal age, residence and ethnicity (62, 63, 81) Religious beliefs and education also appear to impact women's acceptance of prenatal screening.(82) The influence of socioeconomic factors on screening utilization are less well-understood. However, the uptake and offer of prenatal serum screening was found to be lower in mothers with lower education levels living in northern Ireland; in contrast, no differences in the offer or uptake of other prenatal screening tests was observed.(83) Due to a lack of evaluation and research, it is not known to what extent ethnicity, religion or other factors affect test utilization by pregnant women in Canada.

In Canada, prenatal serum screening, in one form or another, is offered by most provinces including British Columbia, Alberta (1991), Manitoba (1999), Quebec, Ontario (1993), Nova

Scotia, and Newfoundland. Once performed only on an ad hoc basis in Saskatchewan, MSS became available to all pregnant women throughout the province in May of 2001. Prior to its introduction, there was no coordinating body for prenatal testing throughout the province. Modeled after the Ontario MSS program, the Saskatchewan MSS program allows for the Provincial Laboratory in Regina to receive and examine all blood samples and return results to physicians. In addition, the program is responsible for the distribution of educational materials to physicians. The Saskatchewan MSS program underwent a process evaluation looking at program uptake and overall test performance for the purposes of program evaluation and planning. The current dissertation project built upon a similar dataset compiled for the MSS Evaluation (i.e. laboratory and cytogenetic data linked to hospital birth outcomes); however, my dissertation dataset has been expanded to include all pregnancy losses, stillbirths, births and deaths during a five-year time period. The value of adding all pregnancy outcomes is that it enables the evaluation of population effects, while the former is limited to the sub-group of women who were screened.

The literature indicates that the performance of MSS programs vary widely.(44, 62, 69, 70, 73, 77) The success of a population-based screening initiative may be largely affected by the social, demographic, environmental, and cultural characteristics of the population it serves. In Saskatchewan, there are certain unique circumstances that can be studied to gain a better understanding of people's use of prenatal screening tests, including the large aboriginal population, the rural nature of the province coupled with more limited health services in rural and remote centres, and the traditionally low uptake of prenatal diagnostic technologies. From a health services perspective, there are questions around the delivery of the program, which will help to determine its effectiveness, suitability, and accessibility in the province. From a population health perspective, there is the question of the screening program's impact at the level of the population and differential uptake along social, economic, and cultural lines. Very few prenatal screening programs, Saskatchewan’s included, have been evaluated for an impact at the population level, which presents an opportunity to gain a better understanding of the factors affecting program performance at the level of the population.

2.0.2 A Population Health Lens

Drawing from the population health philosophy, there is a basic question of the screening program's impact at the level of the population. As a strategic training fellow in the CIHR-funded Community and Population Health Research (CPHR) training program, students are encouraged to adopt a population health focus within their research. In the document *Taking Action on Population Health (*1998), the Health Promotion and Programs Branch of Health Canada emphasized that one guiding principle of a population health approach is "an increased focus on health outcomes and on determining the degree of change that can actually be attributed to our work."(84 p.1) Kindig and Stoddard (2003) also advocate "for the inclusion of outcomes and distributional considerations if a population health approach is to be useful in policy making" and contend, "without such a framework, advocacy and financial incentives can proceed independently of their impact."(85 p.382) This research fits well within a population health framework and is designed to contribute to the understanding of prenatal screening in this context. Aside from the quantitative component, the population health perspective challenges this research to go beyond the clinical, technical and individual ethical issues posed by prenatal screening, to incorporate a broader sociological lens.

2.1 Congenital Anomalies

The term "congenital anomaly" is used to describe an abnormality of structure or function present at birth.(86) Other synonymous terms may include: birth defects, congenital malformations, and congenital abnormalities. In 2004, 4.8% of Canadian children were born with a CA, although estimates at birth depend on the inclusion criteria and ascertainment methods used by each region.(37) Congenital anomalies encompass a range of conditions in the fetus that vary markedly in their clinical picture and prognosis, even for infants with identical diagnoses. For most CAs, the causes are unknown. It is estimated that approximately 15%-25% are due to genetic conditions (chromosomal and single gene causes), 8%-12% to environmental factors (maternal-related conditions, drug or chemical exposures), 20-25% to multifactorial inheritance, and causes for the remaining 40%-60% are unknown.(87) The most common types of CAs in Canada are musculoskeletal anomalies, congenital heart defects, and urinary system anomalies.(5) Over the past two decades fewer infants are dying as a result of CAs, however,

they still remain an important cause of infant mortality.[8] In 2004, congenital anomalies were responsible for 23.6% of all deaths in infants under the age of one year.(37)

2.1.1 Screenable Conditions

Maternal Serum Screening (MSS) is able to detect, with varying degrees of sensitivity and specificity, three categories of congenital anomalies: Down syndrome, neural tube defects, and trisomy 18. Other congenital anomalies, such as limb reduction and congenital heart defects, can be detected by specialized ultrasound during the second trimester. Below is a brief introduction to these three groups of screenable conditions.

Down syndrome (DS), also known as trisomy 21, occurs in approximately 1 in 800 live births in Canada and its risk increases with advancing maternal age (5). Significant variations in mental abilities, behavior and physical development exist between individuals with DS; each person has their own unique personality, capabilities and talents.(88) Most people with DS will have mild to moderate developmental delays, but fewer than 10% fall into the severe category. In terms of health conditions, it is estimated that 40% of individuals with DS will have a cardiac anomaly.(5) Advances in health care have led to substantial reductions in early life mortality risk and much greater survival overall. More than 90% of infants born with DS will survive to one year of age and 85% to at least age 10.(5) Life expectancy of people with DS is approximately 55 years, depending on the individual and other medical conditions.(88) In recent decades, people living with DS are increasingly participating in the workforce, attending post-secondary school and even getting married.

Considerable variation in the rate of DS exists across Canadian provinces and European countries, with rates in 2001 – 2004 (combined) ranging from 10.4 per 10,000 total births in Quebec, to 14.0 per 10,000 births in Saskatchewan, to 21.7 per 10,000 births in Prince Edward Island.(8, 37) Very little is known about the etiology of DS, other than the risk of having an affected child increases with age. Despite the fact that risk increases with age and the average age of mothers has dramatically increased in the last two decades, national rates of DS-affected live births remain relatively unchanged.(5) Evidence suggests that the live birth prevalence of Down syndrome has remained stable as a result of increased detection and termination of

[8] This fact may reflect increased use of prenatal screening/ diagnosis and pregnancy termination; an important focus of this research.

affected pregnancies.(6-8, 10) To date, very little has been published on CA rates and trends in Saskatchewan, including on DS.

Trisomy 18, or Edward's syndrome, is a chromosomal anomaly occurring in about 1 out of every 3,000 live births.(89) It is three times more common in girls than boys and is caused by an extra copy of chromosome 18. While it is a generally a very severe condition with marked and fatal co-conditions, the severity varies across cases. Some of the more commonly observed characteristics include heart defects, kidney abnormalities, omphalocele, esophageal atresia, clenched hands, delayed growth and developmental delays. Most infants with this condition die before birth, and of those surviving, an estimated 10% live longer than one year. Only about 10 people with trisomy 18 have been documented to live into the teenage years. Much of the prenatal screening outcomes research has focused on DS or neural tube defects, however this study will also consider trisomy 18.

Neural tube defects (NTD) are among the most common types of CA and involve malformations of the central nervous system.(1) Neural tube defects were the first screenable category of CA. Anencephalus, spina bifida, and encephalocele are all types of NTD, however, they vary quite notably in severity. The number of infant deaths due to NTD dropped dramatically in Canada between 1989 and 1999, from 11.1 per 10,000 total births to 5.6, with prenatal screening and selective termination being the most likely explanation.(5) While research has found that folic acid has a strong protective effect - if taken early enough in the pregnancy it can prevent up to 75% of cases – a national survey done in 1998 found limited awareness about its benefits among women of childbearing years.(90) As a result, in 1998, Canada implemented mandatory fortification of enriched flour and uncooked cereal grains with folic acid. Recent research has shown that this initiative has led to substantial reductions in the incidence of NTDs.(91-93)

2.1.2 Other Categories of Congenital Anomalies not Screenable by MSS

Most CAs cannot be screened for using a simple blood test, but some conditions are detected through ultrasound, which is really another form of prenatal screening. Examples of this include congenital heart defects, oral clefts, and limb reduction defects.

The most common category of CA is congenital heart defects (CHD), which occur in approximately 1 in 100 – 150 newborns.(5) Improvements in diagnosis and surgical treatment

have dramatically improved the prognosis of children with CHD by substantially reducing childhood mortality and morbidity. Still CHD is one of the most common causes of death due to CA in Canada. Similar to DS, older maternal age is a known risk factor, as well as paternal age. Evidence has also shown folic acid to be protective of CHDs.(94) In terms of detection, CHD is initially recognized through detailed ultrasound screening and followed-up by fetal echocardiography.(5) Over half of all severe CHDs are detectable when high-risk pregnancies are targeted; a rate typically lower than the three conditions screened through MSS. Rates of CHD in Canada rose from 1989 to 1999 from 82 per 10,000 total births (live and still births) to 104.(5) Increasing rates are thought to be partly the result of improved diagnostic capabilities (increase case ascertainment) and potentially to the shift in maternal age distribution. National data does not reflect the number of cases terminated following prenatal detection.

Orofacial clefting is another relatively common CA in Canada and is an important cause of child morbidity. Oral clefts are difficult to diagnose prenatally through ultrasound screening, which is the only method currently available.(5) Prenatal screening therefore has a very limited impact on prevalence rates and only detects cases where there is another associated CA. Having said that, most pregnancies that are terminated would not be terminated for an oral cleft only, but the fetus would typically have a cleft in addition to other CAs. Birth prevalence of cleft lip (CL), cleft lip with cleft palate (CL/P), and cleft palate (CP) vary across provinces and ethnic groups. One Saskatchewan investigation found the live birth prevalence of oral facial clefts to be higher in First Nations mothers.(95) From 1989 to 1999 the national total birth rate (including stillbirths, but not terminations) has remained quite stable.(5)

Lastly, limb reduction defects (LRD) are a rare form of CA characterized by total or partial absence of an arm or leg or part thereof.(5) Thalidomide is the most commonly known risk factor for LRD, but otherwise very little is known about their etiology. The rates of LRD declined significantly over time in Canada, from 4.8 per 10,000 total births in 1989 to 3.7 per 10,000 births in 1999.(5) Serious LRDs can be detected prenatally by second trimester ultrasound, with a detection rate between 20-60% depending on the type of defect and if there is another CA present.(1) Prenatal screening, when followed by selective termination for CA, has been shown to reduce the birth prevalence of LRD. For instance, statistics found 12.9 per 10,000 total births in Alberta had a LRD; a figure that increased to 14.1 per 10,000 when terminations were included.(1)

2.2 Termination of pregnancy for fetal anomaly and surveillance

Studies have shown that a significant proportion of pregnancies confirmed to have a CA through prenatal screening and/or diagnosis are terminated (table 2.2).(6, 11, 71, 96-100) The rate at which terminations for this reason occur will determine the population health impact, as measured by CA birth prevalence and infant and fetal mortality rates. Studies have shown that the occurrence of TOPFA has been shown to vary across geographically and according to the type of anomaly detected. In the case of Down syndrome, the proportion of prenatally diagnosed cases terminated was very high in countries like France (99.5%) (1997-1998) and Hawaii (84.0%) (1987-1996), while lower in Atlanta (26.4%) (1994-199) and Britain (43.7%) (1991-1999).(71, 97, 100, 101) The uptake of prenatal screening has remained low (less than 25%) in the Netherlands, however the rate of TOPFA appears to have offset the effect of increasing maternal age on national DS rates. Less is known about trends in TOPFA for various anomalies, however terminations of prenatally identified DS cases in South Australia increased from 7.1% in 1982 to 75% in 1996.(6) Geographical variations in TOPFA were evident.

Not a great deal is known about variations within Canada or the exact proportion of total pregnancies with DS or other CA types that have been terminated. A dated estimate by the Royal Commission on New Reproductive Technologies, back in 1993, estimated that 5% of fetuses with a CA were prenatally detected and 80% of these pregnancies were terminated.(102) A more recently published study in British Columbia (2006) found that out of the 124 prenatally detected cases of NTDs between 1997-1999, 73% were terminated.(11) As a result, the three-year NTD birth incidence fell by 60% from 1.16/1000 to 0.47/1000. Nova Scotia experienced a notable increase in the proportion of total NTD cases resulting in a TOPFA (49.2% in 1991-1994 to 73.5% in 1998-2000), although the number of cases diagnosed prenatally was not reported.(91) Those women who continue down the prenatal screening pathway in search of a definitive diagnosis will almost certainly have differing views on the practice of TOPFA (25, 80, 103), which explains the characteristically high rate of pregnancy termination following prenatal diagnosis. A high percentage of fetuses that are prenatally diagnosed with a CA and then terminated may have a relatively small impact on the overall population of infants born with CA, if the numbers opting for screening and diagnosis are small. Where the practice is bound to have the greatest population impact is in settings where screening rates are high, test sensitivity is high, and TOPFA is common. More research is necessary in Canada to determine the magnitude

of impact that pregnancy terminations have on CA live birth trends, and if differences can be found across population sub-groups.

Table 2.2 Percent of congenital anomalies diagnosed during pregnancy and percent terminated--by research study, date, region, and congenital anomaly type

Authors	Time Period	Region	Congenital Anomaly type	Findings
Chan et al (104)	1966-1991	South Australia	Neural tube defects	Live birth prevalence declined by 5.1% each year, with an 84% decrease from 1966 to 1991 (2.29/1000 live births and 0.35/1000 live births, respectively). Of all identified cases, 27.8% resulted in a pregnancy termination (35.3% of anencephaly cases; 22.1% of spina bifida cases). In women undergoing AFP screening or mid-trimester ultrasound, 99.0% of anencephaly and 75.7% of spina bifida cases were detected.
Cragan et al (105)	1985-1994	Arkansas (1985-89), California (1989-1991), Georgia (1990-91), Hawaii (1988-1994), Iowa (1985-1990), South Carolina (1992-93)	Anencephaly or spina bifida	The proportion of total NTD cases that were terminated ranged from 9% in Arkansas to 42% in Atlanta and Hawaii. In Atlanta, the percentage of NTD-affected pregnancies terminated was higher among white women. In Hawaii, the proportion of pregnancies that were terminated was higher among Asian women.
Forrester et al (100)	1987-1996	Hawaii	Ten selected anomalies	The following proportion of selected anomalies were prenatally diagnosed: anencephalus (87%), encephalocele (83%), gastroschisis (76%), spina bifida (62%), trisomy 18 (61%), omphalocele (60%), Down syndrome (43%), trisomy 13 (40%), cleft lip (14%), and cleft palate (0%). The proportion of pregnancies terminated after prenatal diagnosis: anencephalus (83.1%), encephalocele (54.3%), spina bifida (48.3%), trisomy 18 (68.3%), Down syndrome (84.0%), and trisomy 13 (62.5%).
Roberts et al (106)	1990-1991	Atlanta, GA	Neural tube defects	87 NTD cases were identified and 28 of those pregnancies were terminated (32.2%). The birth prevalence rate was 0.77/1,000 live births. The incidence rate was 1.13/1.000 live births. The proportion of cases that were terminated was higher for women aged 35 and over compared to those less than 35 years (RR=5.10; 95% CI 3.14-8.28), and lower for black women compared to white women (RR=0.33, 95% CI 0.16-0.66).

Authors	Time Period	Region	Congenital Anomaly type	Findings
Siffel et al(101)	1990-1999	Atlanta, GA	Down syndrome	The birth prevalence of Down syndrome was 10.1 per 10,000 live births from 1994-99. The incidence was 15.3 per 10,000 births during the same period. Of 526 identified cases, 139 (26.4%) were terminated.
Rankin et al (97)	1991-1999	Five British regions	All anomalies combined	Out of all cases, termination of pregnancies occurred in 43.7% of Down syndrome cases; 81.3% of neural tube defects cases; 16.6% of limb reduction defects; 65.8% of trisomy 18 cases.
Royal Commission New Reproductive Technologies (102)	1993	Canada	All anomalies combined	Out of the 5% of prenatally-diagnosed congenital anomaly cases, 80% were terminated.
Crider et al (107)	1994-2003	Atlantic, GA	Trisomy 13 and trisomy 18	70.8% of trisomy 13 and 76.1% of trisomy 18 cases were diagnosed prenatally. Of prenatally diagnosed cases, 60.8% of trisomy 13 and 59.7% of trisomy 18 cases were terminated. The rate of prenatal diagnostic testing was lower in non-Hispanic black women for both trisomy 13 (OR 0.24, 95% CI 0.08-0.78) and trisomy 18 (OR 0.32, 95% CI 0.14-0.69).
Van Allen et al (11)	1997-1999	British Columbia	Neural tube defects	124 out of 144 neural tube defect cases (86.1%) were diagnosed prenatally. Out of 124 prenatally-diagnosed neural tube defect cases, 73% were terminated.
Gameren-Oosterom et al(108)	1997-2007	Netherlands		The mean incidence of Down syndrome was 14.57 per 10,000 births, of which 85% were live births. Live birth prevalence remained unchanged (p=0.385 for trend), despite an increase in mean maternal age (p<0.001). Pregnancy terminations could not be directly captured, however, an increasing trend in the proportion of DS births before 24 weeks was observed (p=0.011).
Zlotogora et al (99)	1999-2000	Israel	Neural tube defects	90% of anencephaly cases among Jewish women were terminated compared to 59% among non-Jewish women. 73% of spina bifida cases among Jewish women were terminated during pregnancy compared to 43% among non-Jewish women. The birth prevalence of NTDs was higher among non-Jews (anencephaly 3.6/ 10,000 live births, spina bifida 5.9/10,000) than among Jews (anencephaly 1/10,000 live births, spina bifida 1.4/10,000 live births).

Authors	Time Period	Region	Congenital Anomaly type	Findings
Cheffins et al (6)	2000	South Australia	Down syndrome	Terminations of prenatally-diagnosed Down syndrome cases increased from 7.1% in 1982 to 75% in 1996.
Muller et al (71)	2002	France	Down syndrome	Of 54,321 patients with an increased-risk screening result in 1997 and 1998, 95% had follow-up diagnostic testing. 623 out of 626 (99.5%) of prenatally- diagnosed Down syndrome cases were terminated.
Boyd et al (109)	2002-2004	12 European countries	Down syndrome and neural tube defects	**Down syndrome cases:** Out of all prenatally diagnosed cases, the termination rate ranged from 73% - 100% (mean=88%) across 12 countries. When all CA were taken together (prenatally diagnosed and not), the termination rate ranged from 31% - 87% (mean=60%). **Neural tube defect cases:** Out of all prenatally diagnosed cases, the termination rate ranged from 0% -100% (mean=88%) across 12 countries. When all CA were taken together (prenatally diagnosed and not), the termination rate ranged from 0% - 92% (mean=77%).
Loane et al (8)	1990-2009	13 European countries	Down syndrome, Trisomy 18, and Trisomy 13	Proportion of all cases diagnosed prenatally ranged from less than 10% in Ireland to ~85% in France and Switzerland. Mode of diagnosis (ie. ultrasound, serum screening/combined screening, or invasive diagnostic testing) varied considerably by country. The pregnancy termination rates for congenital anomalies were highest in France (77.3% of all cases combined, not only those prenatally detected) and lowest in Ireland and Malta (0%).
Smith et al (98)	1998-2007	East Midlands and South Yorkshire regions of England	Nine selected congenital anomalies with poor prognoses	86% of affected fetuses were prenatally detected and diagnosis did not vary over time or by level of deprivation. The pregnancy termination rates for congenital anomalies were lower in the most deprived areas (63%) than in the least deprived (79%). The proportion of pregnancies terminated after prenatal diagnosis were as follows: anencephaly (88%), spina bifida (78%), hypoplastic left heart (56%), diaphragmatic hernia (29%), trisomy 18 (81%), trisomy 13 (83%).

2.2.1 Calculating the Birth Prevalence of Congenital Anomalies

When examining the occurrence of CAs in a given population, the live or total birth rate is often the statistic reported. Both are incomplete in so far as they do not capture all cases of CAs in the numerator and the denominator (refer to Table 2.3 below). The rate reported typically depends on the data that is available. In settings where a CA surveillance system is in place, CAs in the majority of pregnancies are captured, including terminations. This enables reporting on all CAs in live births, stillbirths, and terminations of pregnancy, which is the current gold standard. Using this information the birth incidence can be reported. Having said that, all CA rate calculations exclude from the denominator elective medical abortions that are not specifically for reasons of CA; a calculation that could lead to either over- or underestimates (depending on the CA risk of this population). The most important point here is that accurate CA surveillance requires as complete capture of all pregnancies as possible – something that is a challenge for jurisdictions that do not have high-functioning, well-designed CA surveillance systems.

Table 2.3 Methods for calculating congenital anomaly prevalence

Indicator	Numerator	Denominator	Limitations
Live CA birth prevalence	Live births with a CA	All live births	Excludes stillbirths + TOPFA
Total CA birth prevalence	Live births with a CA + stillbirths with a CA	All live + stillbirths	Excludes TOPFA
CA incidence	Live births with a CA+ stillbirths with a CA+ TOPFA	Live + stillbirths + TOPFA	Only includes TOPFA in the numerator and denominator and excludes abortions for non-CA-related reasons

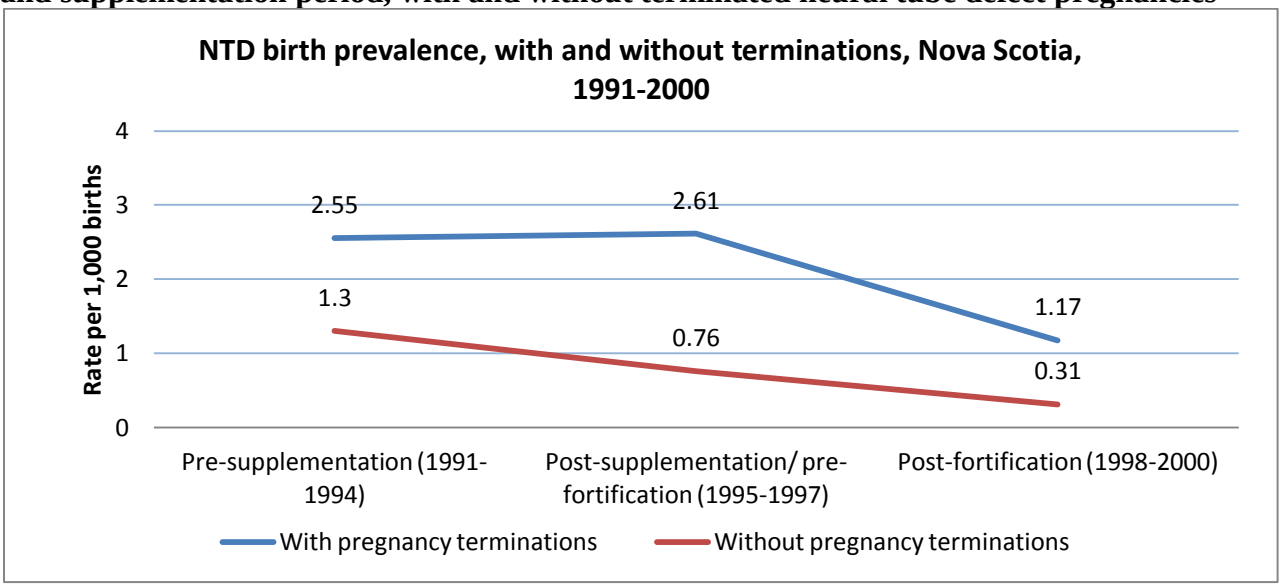
Studies have shown that decreases in the birth prevalence of CAs disappear or decrease when termination data are included in the analysis.(6, 8, 10, 110) This observation has significant implications for CA surveillance, especially when rates often only reflect live births or live and stillbirths combined. If true increases and decreases cannot be identified with confidence, research into the etiology of different CA types and tracking risk profiles of different populations will not be possible. The accurate and complete reporting of CAs is important to surveillance of birth outcomes and to the program and policy context surrounding screening programs and fetal-maternal health research.

2.2.2 Trends in neural tube defects and Down syndrome

Neural tube defects are commonly cited conditions where decreases in the birth prevalence have been observed nationally and internationally, but trends have been difficult to explain. In 1994, recommendations regarding folic acid supplementation (through vitamins) were introduced, then followed by a national policy on the mandatory fortification of grains products in November of 1998.(91) Initially increased folic acid consumption was presumed to be responsible for observed NTD reductions in Canada, but prenatal screening also became more common during this timeframe and soon became a competing explanation. A study by Van Allen et al (2006) in British Columbia found that declines in NTD birth rates between 1997-1999 were primarily attributable to prenatal screening and terminations.(11) Pregnancy termination following prenatal diagnosis reduced the three-year NTD incidence by 60% from 1.16/1000 to 0.47/1000. Later research revealed a more mixed picture however, when it comes to explaining declining NTD birth trends. In fact, it is not an either-or scenario, but rather both factors have played a role in reducing NTD birth rates. A study in Nova Scotia clearly illustrated a trend in falling NTD incidence owing to folic acid fortification– from 2.55 per 1000 births in the prefortification period (1991-1994) and 2.61 per 1000 births in the supplementation period (1995-1997), down to 1.17 per 1,000 births in the post-fortification period (1998-2000)(91); representing a 54% decrease over the 10-year period. These estimates included live births, stillbirths and termination of fetuses with an NTD. It is interesting to note the difference in calculated rates when terminations of pregnancy are excluded (done for illustration purposes), which is not an uncommon presentation of data in many jurisdictions. The 10-year NTD average incidence rate was 2.22 per 1,000 births when terminations were included and 0.89 per 1,000 when terminations were excluded; a 60% decrease over the time period. Therefore pregnancy terminations had a slightly greater impact on the birth prevalence of NTDs than folic acid fortification. In addition, when the rates exclude pregnancy termination data, the trending looks quite different and would have led to the erroneous conclusion that folic acid supplementation alone precipitated a 40% reduction in NTDs. Looking at the unchanged rates (when termination data was included: 2.55 vs. 2.61 per 1,000 births), this was not the case. Further evidence in support of folic acid fortification followed with a seven-province study spanning 1993 to 2002 that found a 46% reduction in NTD incidence (1.58 per 1,000 births pre-fortification to 0.86 during the full-fortification period, including termination of pregnancies for fetal anomaly).(93)

The magnitude of decrease was proportional to the prefortification baseline rate in each province, meaning that provinces with higher baseline rates like the Newfoundland and Labrador saw steeper declines than those with lower rates like British Columbia (a rate difference of 3.8 vs. 0.21 per 1,000 births, respectively). Geographical differences almost disappeared after fortification began. Similarly, a study done in the United States found that regional variations in the rates of NTDs were reduced or eliminated when pregnancy termination data was used in the analysis.(110)

Figure 2.1 Birth prevalence of neural tube defects in Nova Scotia by folic acid fortification and supplementation period, with and without terminated neural tube defect pregnancies*

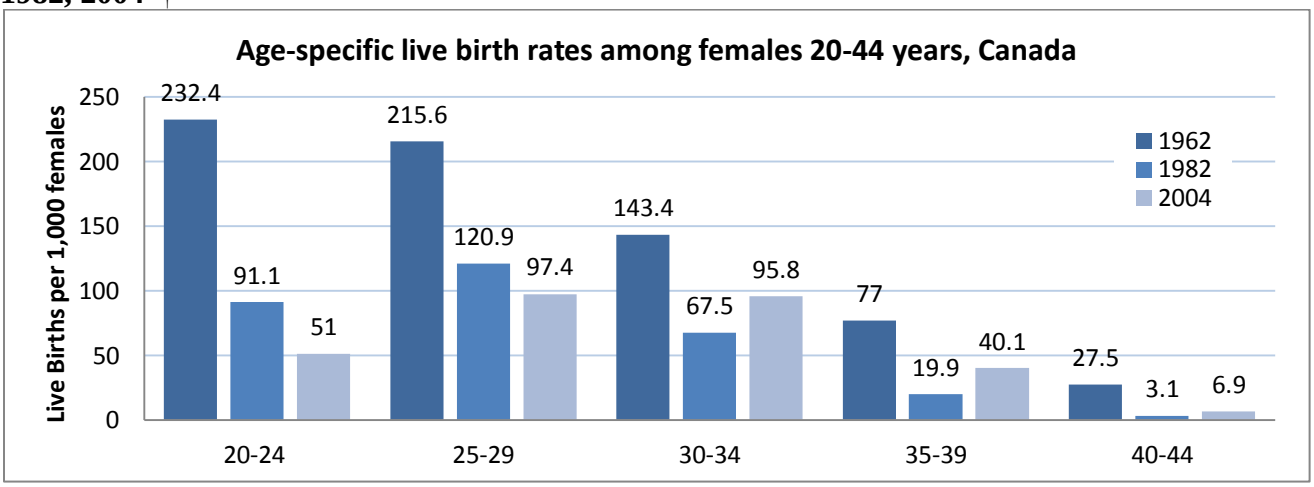


* Recalculated rates based on published figures from Persad VL, Van den Hof MC, Dube JM, Zimmer P. Incidence of open neural tube defects in Nova Scotia after folic acid fortification. CMAJ 2002 Aug 6;167(3):241-5.

While NTD rates have been on the decline, DS rates in Canada remain stable despite a dramatic shift in the maternal age distribution (See figure 2.2 below).(5) Maternal age is a well-established DS risk factor, with risk increasing incrementally up until age 35, then more sharply (see table 2.4 below).(111-113) Data on the birth incidence of DS in Alberta (1990-1998) show slightly different risk estimates than Bray et al's (1998) meta-analysis of nine published datasets (111), but portray a clear rate increase with maternal age.(5) Even though age is currently the only well-identified risk for DS, many cases occur in women younger than 35, reflecting the greater fertility of this group. Between 1980 and 2011, the proportion of women aged 30 and over who gave birth in Canada went from 21.5% to 51.2%.(5, 114) Saskatchewan has

experienced an increase in the proportion of births to mothers in this age group, however, they account for a much lower proportion of births. For instance, in 2011, 36.1% of live births in Saskatchewan were to women aged 30 and over compared to 51.2% nationally.(114) It is expected that an increase in live DS births would accompany such a large increase in the risk profile of Canadian mothers, however it did not (see Figure 2.3 below).

Figure 2.2 Age-specific live birth rates among females aged 20 – 44 years, Canada, 1962, 1982, 2004*†



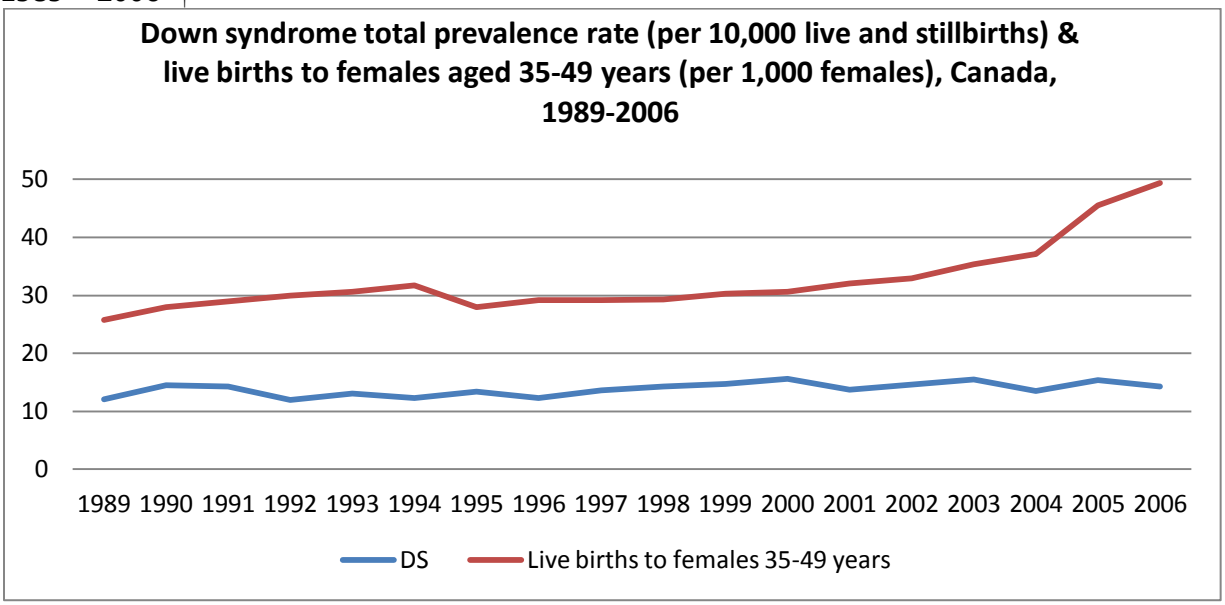
*Public Health Agency of Canada, 2008. Canadian Perinatal Health Report - 2008 Edition. Ottawa. † Statistics Canada, 2006. Births. Catalogue no. 84F0210XIE

Table 2.4 Estimated Down syndrome birth incidence by maternal age*†

Multi-centre study				Alberta	
Maternal age	**Odds**	**Rate per 1,000**	**Maternal age**	**Rate per 1,000**	**% of total DS cases**
16	1 in 1493	0.67	< 20	0.48	3.2
20	1 in 1445	0.69	20 – 24	0.67	12.5
25	1 in 1259	0.79	25 – 29	0.72	21.1
30	1 in 821	1.22	30 – 34	1.27	30.9
35	1 in 336	2.97	35 – 39	2.83	24.0
40	1 in 97	10.15	40 - 44	6.30	6.9
45	1 in 25	38.89	> 45	42.9	1.5
50	1 in 6	142.13			

*Health Canada, 2002. Congenital anomalies in Canada - A perinatal health report, 2002. Ottawa: Minister of Public Works and Government Services Canada. †Bray I, Wright DE, Davies C, Hook EB. Joint estimation of Down syndrome risk and ascertainment rates: a meta-analysis of nine published data sets. Prenatal diagnosis. 1998 Jan;18(1):9-20.

Figure 2.3 Down syndrome rates and fertility rates for females aged 35-49 years, Canada, 1989 – 2006*†

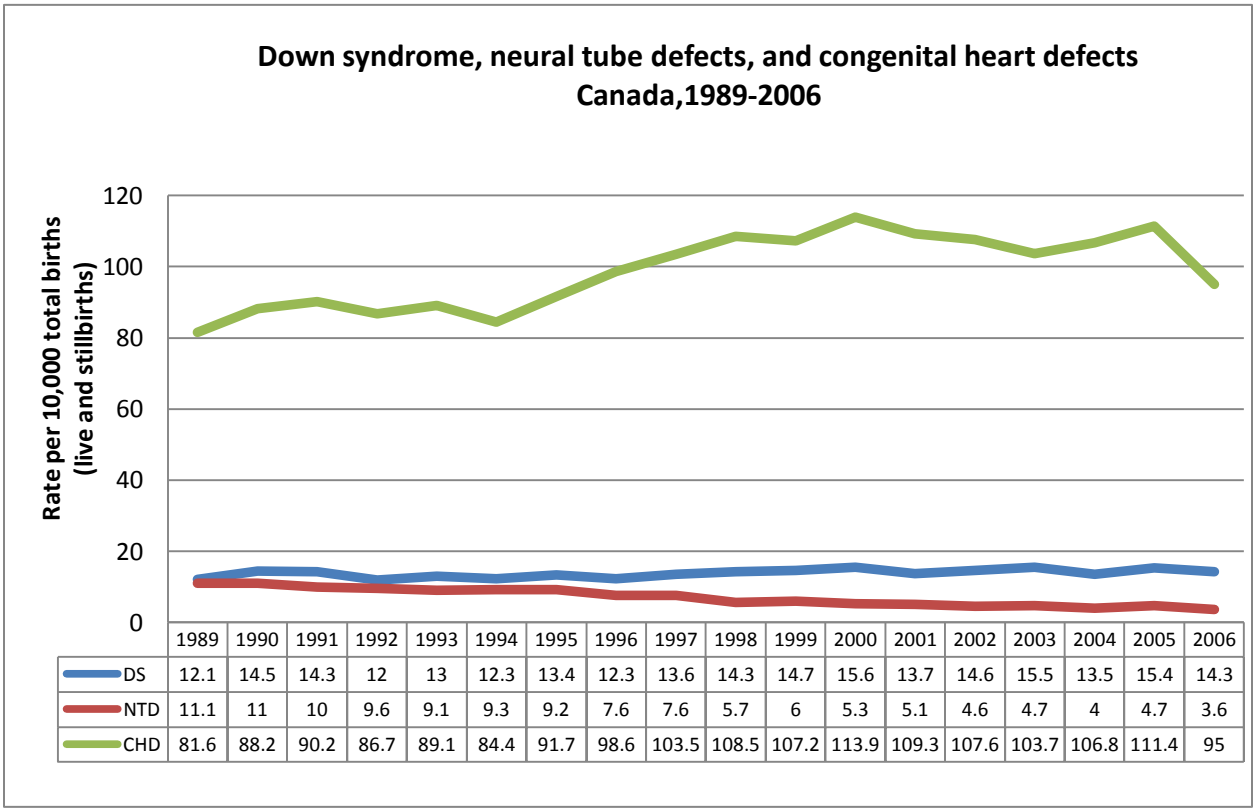


* Public Health Agency of Canada, 2008. Canadian Perinatal Health Report - 2008 Edition. Ottawa.

A similar phenomenon can be seen internationally in other developed countries. For instance, in Paris from 1981 - 2000 the proportion of women aged 35 and over giving birth increased markedly (11.1% to 26.1%); a trend that was accompanied by a rise in the DS incidence by 5% per year. Despite the substantial increase in the number of births to older mothers, the live birth prevalence of DS dropped 3% each year from 1981 to 2000, with a maternal age-adjusted decrease of 13% each year.(10) Accordingly the live birth prevalence fell from an estimated 10 to 5 cases per 10,000 births over the two decades, while the true birth incidence (terminations included) rose from 11 cases per 10,000 births in 1981 to 40 DS cases per 10,000 births in the late-90s. Interestingly, the proportion of DS cases diagnosed prenatally increased nine-times in women under the age of 38 (9.5% to 84.9%), and also increased in women aged 38 and over (59.1% to 95.4%). In general, the percentage of DS cases diagnosed prenatally in Paris is very high. Taken together, Khoshnood et al (2000) concluded that the shift towards screening women of all ages and France's national screening policy have had a substantial impact on prenatal detection and live DS birth rates in that country.(10) A study examining the population of France between 1997-1998 observed that 95% of women that received an increased-risk MSS result had follow-up diagnostic testing, with 99.5% terminating their pregnancy after receiving confirmation of Down syndrome.(71)

Similar trends have been observed in other countries. In South Australia use of maternal serum screening for Down's syndrome increased from 17% when introduced in 1991 to 76% of women who gave birth in 1996. Between 1982 to 1996 the overall birth prevalence of DS fell by 60% from 1.05 to 0.42 per 1,000 live births, in spite of a notable rise in maternal age.(6) As was the case in France, the drop in DS cases could be explained by an increase in the termination of pregnancies known to be affected by DS – from 7.1% of all cases detected in the population in 1982-86 to 75% in 1996. Most of this increase was found to be due to increased maternal serum screening use among younger women.(6) Neighbouring Queensland Australia also experienced a substantial drop in maternal age-adjusted rates of DS births from 2000 to 2004.(46) Interestingly, reductions in DS total prevalence were most pronounced in mothers receiving prenatal care from private obstetricians (-27.5%) and urban-residing mothers (-14.3%), as compared to rural-residing mothers (0.0%) or those receiving prenatal care from public hospitals (+2.9%).

Figure 2.4 Down syndrome, neural tube defect, and congenital heart defect rates, Canada, 1989 - 2006*



	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
DS	12.1	14.5	14.3	12	13	12.3	13.4	12.3	13.6	14.3	14.7	15.6	13.7	14.6	15.5	13.5	15.4	14.3
NTD	11.1	11	10	9.6	9.1	9.3	9.2	7.6	7.6	5.7	6	5.3	5.1	4.6	4.7	4	4.7	3.6
CHD	81.6	88.2	90.2	86.7	89.1	84.4	91.7	98.6	103.5	108.5	107.2	113.9	109.3	107.6	103.7	106.8	111.4	95

* Public Health Agency of Canada, Congenital Anomaly Surveillance System, 2012. Congenital anomaly national prevalence data, 1989-2006. Ottawa.

2.2.3 Data challenges in the ascertainment of pregnancy terminations for fetal anomaly

While there is reasonable evidence that the termination of affected pregnancies is responsible for declines in CA rates, particularly those amenable to screening, the shortage of Canadian research in this area limits what can be said about this relationship. Little is known about the magnitude of the impact that variations in screening/ diagnosis/ termination have on CA rates regionally and for different sub-groups (eg. those under and over age 35, Registered Indian compared to other women). In addition, the potential for undercounting TOPFA is significant and the relationship between screening uptake and population outcomes is largely unknown. There are three main reasons: (1) inability of traditional data systems to account for all CAs that are diagnosed prenatally and then terminated; (2) difficulties associated with the cross-linkage of screening and diagnostic information and birth outcome data; and (3) lack of published reporting on the topic. In most provinces without a CA surveillance system, like Saskatchewan, data on pregnancy termination is mainly captured by hospital separations in the Discharge Abstract Database (DAD), however detailed diagnostic data is not available on fetuses where an anomaly was detected.[9] As a result, the DAD must be linked with diagnostic data, typically held by cytogenetic laboratories and clinics. At the national level, the Canadian Congenital Anomalies Surveillance System (CCASS) faces noteworthy challenges that prevent accurate reporting of CA incidence. In the 2002 report, *Congenital Anomalies in Canada*, Health Canada notes that "one of the most significant limitations [of the CCASS] is the inability to monitor the impact of prenatal diagnosis on the birth prevalence of selected congenital anomalies ... directly limit[ing] an assessment of primary and secondary preventive strategies."(5 p.xiv) This is due to the fact that most jurisdictions do not report pregnancy losses with a gestational age less than 20 weeks (the criteria for stillbirth), which include earlier TOPFAs. The result is an underestimation of CA incidence, particularly for screenable conditions, and limited ability to interpret temporal and geographical patterns. Furthermore, cases that are diagnosed outside the hospital and those diagnosed in-hospital longer than 30 days after birth are also missed. The latter is due to the fact that CIHI no longer shares birth dates with CCASS, therefore follow-up of each infant was reduced from one-year to 30 days starting in 2001.(37)

[9] ICD-9 code 655and ICD-10-CA code O35 are most specific for neural tube defects (eg. O35.00 for fetal anencephaly), but are insufficient for the identification of cases of fetal Down syndrome (O35.1 chromosomal anomaly) or congenital heart defects (O35.9 fetal abnormality and damage, unspecified).

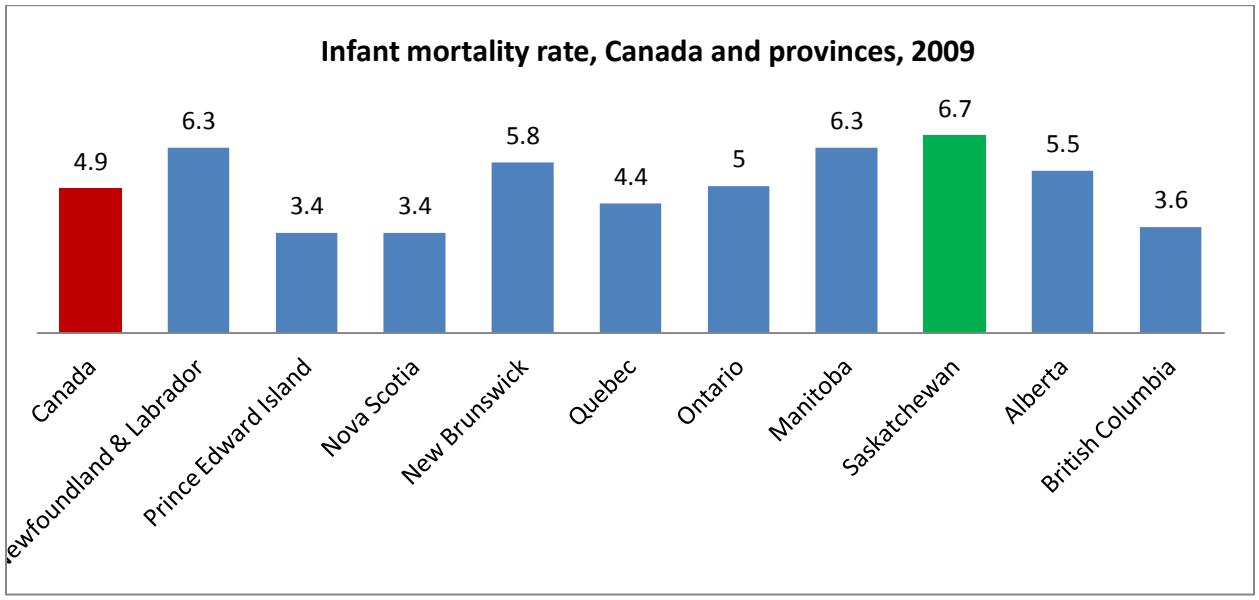
2.3 Infant Mortality Rates

The infant mortality rate (IMR), defined as the number of deaths in children under the age of one year per 1,000 live births in a calendar year, is a sensitive measure of population health in both developed and developing countries.(39) A well-established and often cited measure of wellbeing in society, the IMR is a reflection of a population's health, mortality, and health care system. In the Canadian Perinatal Health Report (2003), Shi Wu Wen states that "infant mortality has been considered the single most comprehensive measure of health in a society."(115 p.89) It has traditionally been viewed as a population health indicator that is responsive to structural factors such as economic development, sanitation, nutrition, inequality and environment.(39) Furthermore, it captures the health status of maternal and child populations and the multitude of factors that determine survival in the first year of life, including prenatal and postnatal nutrition, drug and tobacco use, medical care, and immunizations. While some have questioned the utility of the IMR as a measure of broader wellbeing, Reidpath and Allotey (2003) found a very high correlation between the disability adjusted life expectancy, a frequently used population health measure, and IMR in 180 countries.(39) An earlier study utilizing worldwide data on infant mortality from the United Nations demonstrated that the Human Development Index (HDI), and all of its individual components including life expectancy, literacy, and per capita gross domestic product, is a very powerful predictor of infant mortality rates.(116) The HDI accounted for 85-92% of the variance in infant mortality rates. This reinforces the IMR's ability to detect factors not only related to health in early life but also to the health of the entire population.

2.3.1 Infant mortality in Canada and Saskatchewan

Canada has experienced dramatic declines in infant death over the past century.(117) Despite its remarkable progress, Canada still has high rates in comparison to other Organization for Economic Co-operation and Development (OECD) countries. Canada's relative ranking on IMR fell to a ranking of 15th place out of 17 peer countries in 2006.(118) An important limitation to international comparisons is the lack of standardization of live birth and stillbirth registrations, which undermines the ability to compare fetal and infant mortality rates.(36) Within Canada, the IMR varies considerably across provinces and territories, with Saskatchewan having the highest rate in 2009 (see Figure 2.5).(119)

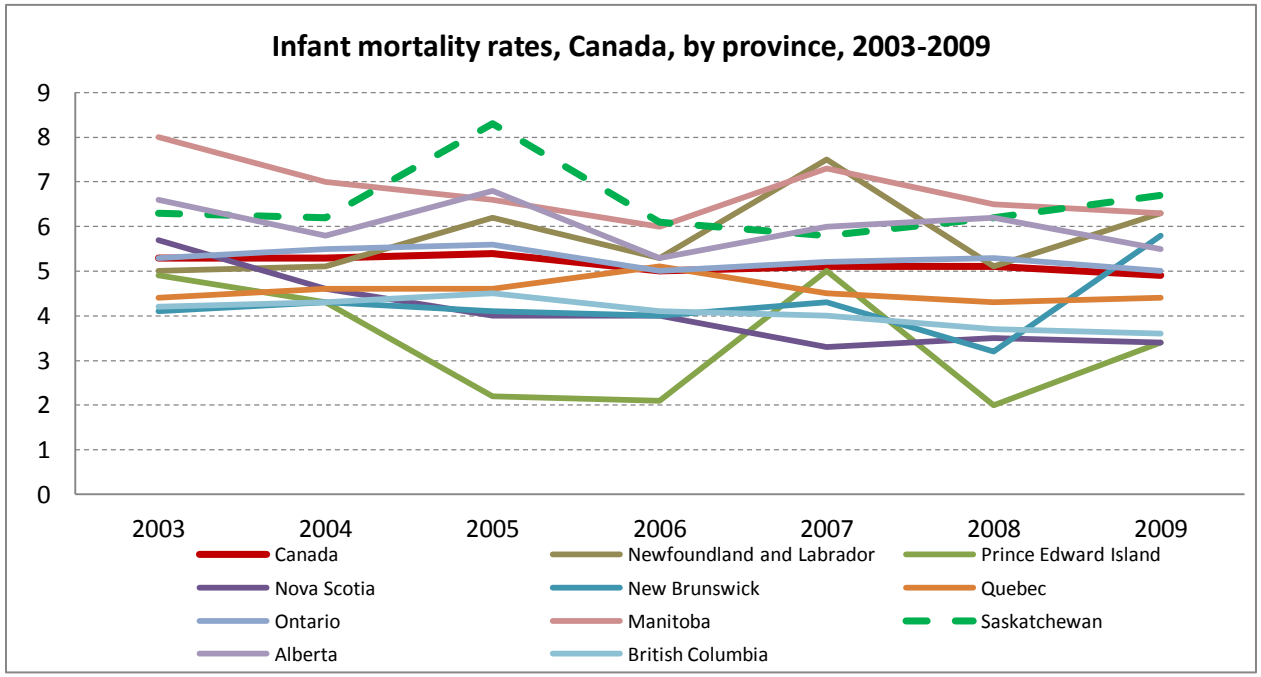
Figure 2.5 Crude infant mortality rates by province and Canada, 2009*



*Statistics Canada, CANSIM. Infant mortality rates by province and territory. Table 102-0504

Historically Saskatchewan has had one of the highest rates in the country. In recent years, Saskatchewan and Manitoba, and more recently Newfoundland and Labrador, have vied for this notorious distinction (figure 2.6).

Figure 2.6 Infant mortality rates by province, Canada, 2003-2009*



*Statistics Canada, CANSIM. Infant mortality rates by province and territory. Table 102-0504

Within the province, rates vary widely across health regions from as low as 3.7 deaths per 1,000 live births in the Cypress Health Region to as high as 11.4 and 15.3 in the Mamawetan Churchill and Athabasca Health Regions in 2001-05 (five-year averages).(120) Differences in social, economic and health care environments across health regions may explain some of this variation, but exact causal factors have not been fully explored.

Aboriginal ancestry and income are two interrelated risk factors that have been identified as impacting infant mortality. Disparities across ethnic and socioeconomic populations provide important insights into the nature and magnitude of inequity in our society. In Canada, the IMR among Aboriginal peoples has been reported as being twice as high as the rest of the population for the past century.(38, 121) Interestingly, however, statistics released from the First Nations and Inuit Health Branch (FNIHB) in 2000 noted a drop to 6.4 per 1,000 live births as compared to the national rate of 5.3 per 1,000 live births.(122) Similar to inconsistencies internationally in the documentation of births, evidence suggests underreporting of infant and fetal death in Aboriginal populations have an impact on IMR statistics, in particular for births at the borderline of viability.(123) A recent study done by the Joint Working Group on First Nations, Indian, Inuit, and Métis Infant Mortality disputes the IMR reported by FNIHB and concludes that available information demonstrates persistent and sizeable disparities.(38) Specifically, it found infant mortality rates in First Nations (Status Indians on-reserve), Status Indians living off-reserve and Inuit were 1.7 to more than 4 times higher than the overall Canadian and/or non-Aboriginal rates. The greatest disparity in infant mortality appeared during the postneonatal period, where death is often attributed to congenital conditions, sudden infant death syndrome, and infections. It has been hypothesized that some of the difference in IMRs across Aboriginal and non-Aboriginal populations is attributable to inadequate prenatal care, however, it is unclear what impact improved access to earlier prenatal care would have on infant mortality. Smylie (124) credits socioeconomic inequities as the source of the disparity, along with the distances needed to travel to receive adequate maternity care. Ethnic disparities in the United States have persisted in spite of improvements in prenatal care utilization by black and Hispanic women.(125)

Accurate documentation of Aboriginal ethnicity and capture of all births in this population is paramount to valid and reliable IMRs for Aboriginal populations in Canada. Following work done by the Joint Working Group on First Nations, Indian, Inuit, and Métis

Infant Mortality, Smylie, Fell, and Ohlsson (2010) comment on the need for better standardization and further research on this topic:

> "The calculation of accurate IMRs for Aboriginal populations in Canada is complicated by the lack of uniform and consistently available information regarding First Nations, Indian, Inuit, and Métis identity in Canadian birth and death registration databases. Our efforts at systematic review of the existing literature were limited by the paucity of publications in this area. There is a pressing need for more scholarly work, including the call for a more standardized approach to the collection of First Nations, Indian, Inuit and Métis birth and death data in the provinces and territories, particularly for non-Status Indians and Métis."(38, p.147)

The current research will help to broaden our understanding of infant mortality in Registered Indian populations in Saskatchewan and will shed light on the uptake and impact of prenatal screening and intervention in this population sub-group.

Despite the fact that significant progress has been made in Aboriginal peoples' overall health status, Aboriginal infant mortality rates remain higher than those for the rest of the Canadian population.(38) Elevated death rates in Aboriginal infants may be explained by socioeconomic risk factors, including poor housing conditions, communicable diseases, lower utilization of prenatal and medical care services, chronic disease, lifestyle factors (higher rates of obesity and smoking), and less frequent incorporation of preventative measures.(120, 125) One Canadian study documented an income gradient in an urban setting with the highest income levels having the lowest IMR and the lowest income levels having the highest IMR.(126) Given that both Aboriginal adults and children disproportionately experience poverty and low income in Canada, socioeconomic circumstances certainly will play some role in the higher mortality risk among Aboriginal infants, but the exact mechanism responsible for this association is not known. Differences in IMR across population sub-groups cannot be adequately explored without accounting for competing explanations such as uptake of prenatal screening and selective termination. Prenatal screening and pregnancy termination for fetal anomalies are believed to be much less common in Aboriginal women, while risk for some CAs to be higher; a difference that may explain disparities in infant death. No research has been done yet exploring the link between pregnancy termination for congenital anomaly and IMR with special attention to Aboriginal populations.

2.3.2 Reproductive Technologies and Congenital Anomaly-Specific Infant Mortality

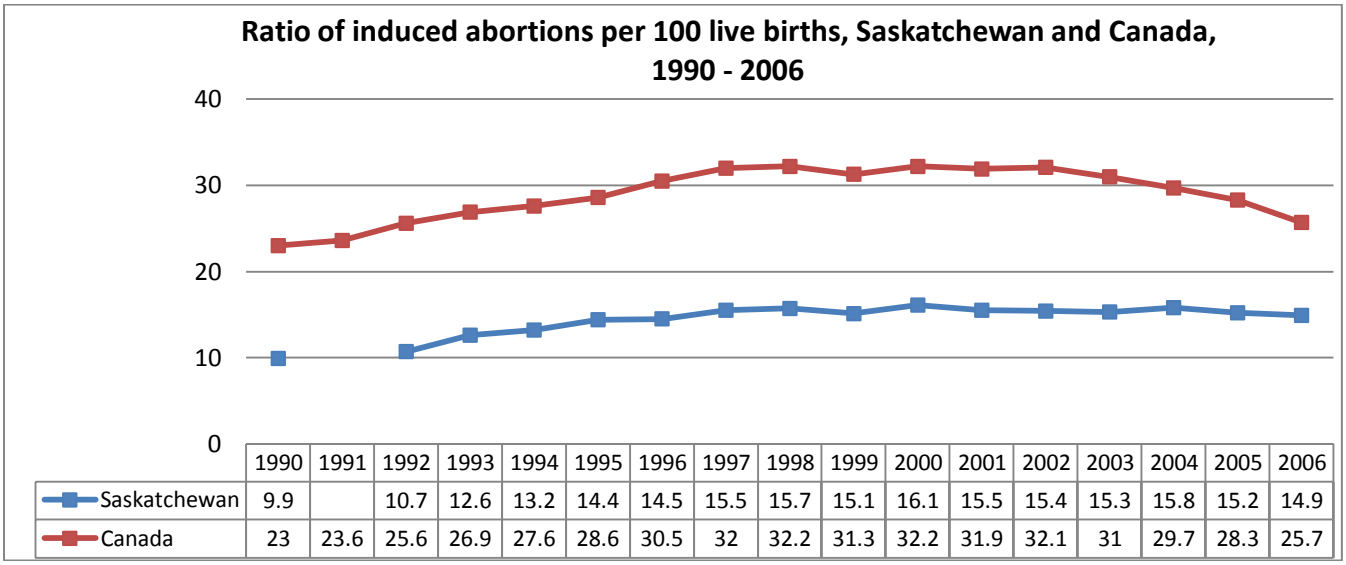
If lower rates of infant death are partially or largely explainable by increased prenatal screening/diagnosis and selective terminations, it is important that this link is well-understood. A body of research has begun to establish a clearer relationship between TOPFA and rates of fetal, neonatal, and infant mortality.(2, 14, 15, 98) Still studies have yet to establish TOPFA as a definitive cause of lowered rates of overall infant mortality, quantified its impact, or suggested what the rate would be if new reproductive technologies and pregnancy termination for this reason were not available. The quantification of impact will be necessary if we are to restore IMRs ability to reflect the true realities of populations. As Gortmaker & Wise (1997) explain, "mechanisms that traditionally defined infant mortality as a 'social mirror' (127) have been altered appreciably by rapid innovations in health services technology."(34 p.148) Such innovations, when accessed differentially by population sub-groups, have the ability to create or exacerbate apparent disparities in health indicators.

Pregnant women in Saskatchewan have traditionally been less inclined to utilize reproductive technologies and elective abortions.(102, 128) For instance, it is estimated that more than one in five pregnancies was terminated nationally in 2006, while one in eight was terminated in Saskatchewan.(128)[10] This apparent preference towards non-intervention could in fact explain the historically higher infant mortality rates – a central hypothesis of this research.[11] The decline observed nationally over the past three decades has been due, in part, to fewer infants dying from congenital anomalies, and there is evidence to point to TOPFA as the cause (1, 13-15, 37). A more nuanced understanding of this link is important to our understanding of regional variations and trends in prenatal testing and intervention.

[10] The Therapeutic Abortion Survey has notable limitations and the national figures provided are underestimates of the actual rate of induced abortions nationally. Some respondents, representing significant portions of the Canadian population, withhold their information. Since 2003, no information has been collected on Canadian residents who obtain an abortion outside of Canada. The figures also only include those abortions that occur either in hospital or clinic, and do not include other types of abortions (eg. pharmacological abortions).129. Canadian Institute for Health Information. Update to the Privacy Impact Assessment of the Therapeutic Abortions Database, 2003. March, 2011. In Saskatchewan, all information on therapeutic abortions occurring in hospitals is submitted. No abortions occur in clinics in Saskatchewan, therefore the provincial estimate is expected to be a better representation of the true incidence.

[11] It is also possible that factors other than personal values/preferences have contributed to the lower rate of abortions in Saskatchewan, such as low access. This possibility is discussed further in the discussion chapter.

Figure 2.7 Ratio of induced abortions per 100 live births, Saskatchewan and Canada, 1990 – 2006*



	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
Saskatchewan	9.9		10.7	12.6	13.2	14.4	14.5	15.5	15.7	15.1	16.1	15.5	15.4	15.3	15.8	15.2	14.9
Canada	23	23.6	25.6	26.9	27.6	28.6	30.5	32	32.2	31.3	32.2	31.9	32.1	31	29.7	28.3	25.7

*Statistics Canada. Induced abortions in hospitals and clinics, by area of residence of patient, Canada, provinces and territories, annual. CANSIM table 106-9013.

The primary causes of infant death have changed somewhat over time and are different for developing and developed countries. The history of infant death in Canada is not an uncomplicated one. Here congenital anomalies and immaturity have been the leading causes of death – accounting for approximately 55% of deaths in 2004.(37) One-quarter of infant deaths in Canada were due to CAs alone. Five year earlier CAs were the number one cause of infant death. While the national IMR has been in steady decline since the early 1960s, rates leveled out between 1991 and 1995, then dropped significantly in 1996 and 1997 despite increasing registration of births less than 500 grams.(15) The gains of 1991 – 1997 were mainly attributed to fewer SIDS deaths and deaths due to immaturity. Against the backdrop of these changes in infant mortality risk, the congenital anomaly-specific IMR in Canada steadily declined each year from 2.53 per 1,000 live births in 1985 to 1.06 per 1000 live births in 2005 (see figure 2.9).(130) Other developed countries have witnessed similar drops in CA-specific IMRs over the last two decades.(1, 131)

Studies by Wen, Liu, Joseph, Kramer et al have made significant contributions to the broader understanding of infant and fetal mortality trends due to congenital anomalies in Canada.(1, 2, 13-15) One of the earliest studies, by Wen et al (14) in 1999, found large interprovincial variations in infant mortality caused by cardiovascular system anomalies and anencephaly, whereas no variation was observed across provinces for chromosomal anomalies.

Infant mortality rates due to CA were also generally higher in Newfoundland, Saskatchewan and Alberta (1990-1995). This early piece of research, however, had two key shortcomings that call into question the inferences made. First, data on basic risk exposure (maternal age, in particular) was not available for analysis, which also varies by region. Because maternal age cannot be accounted for as an explanatory variable, it may be that some provinces have older maternal populations and therefore higher rates of particular CA types, which could alone increase the number of infants dying from a CA. Second, the results are purely correlational as the study was descriptive and did not explore causal links between prenatal screening, selective termination and cause-specific or overall IMR.

Using live birth and death databases for several Canadian provinces/territories (Ontario, Newfoundland, and British Columbia were excluded), Wen et al (13) analyzed trends in infant mortality due to congenital anomalies between 1981-83 and 1993-95. The researchers identified reductions in many major CA categories, but noted that the magnitude of decrease varied according to CA type. Decreases were largest for anencephaly (pre-folic acid supplementation and fortification), spina bifida, and digestive system, musculoskeletal, and cardiovascular anomalies.(13) An interesting discovery was that the proportion of infant deaths due to chromosomal anomalies, some of which are detectable through prenatal screening, rose from 7.5% (1981-83) to 13.0% (1993-1995); the authors point to increasing maternal age as a potential explanation. Infant deaths due to respiratory and urinary system anomalies did not show a significant decline, which makes sense given that these CA types are difficult to detect prenatally. Provinces and territories without widespread access to a provincial prenatal screening programs (at the time) were observed to have higher rates of infant deaths due to CA. For instance, compared with the province of Quebec, congenital anomaly-attributed infant mortality was statistically significantly higher in Newfoundland, Saskatchewan, and Alberta. These changes in cause-specific CA infant mortality strengthen the inference that prenatal screening and termination of pregnancies for CA are together responsible for observed declines and variations in IMR.

A 2002 study by Liu et al (15) found that the lowered IMR observed nationally in 1996 and 1997 was preceded by a rise in early fetal deaths (20-21 weeks) due to pregnancy termination or CA, suggesting a shift in the timing of death from infancy to the perinatal period. Both fetal death due to CA and fetal death due to pregnancy termination at 20 to 21 weeks

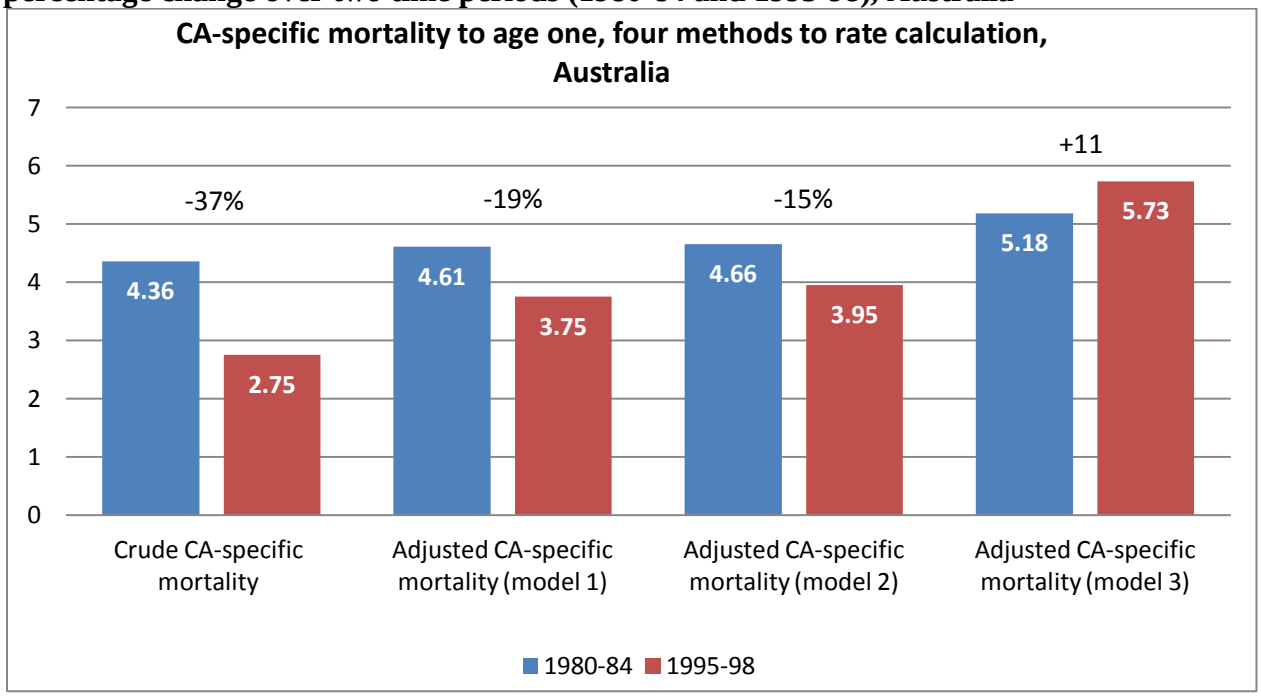
increased substantially between 1991-1998 (94% and 578%, respectively). It could also be seen that provinces and territories with higher rates of fetal death due to pregnancy termination and/or congenital anomalies at 20-23 weeks gestation had lower CA-specific IMR.(15) For example, in Saskatchewan the fetal death rate due to pregnancy termination/ congenital anomalies at 20 to 23 weeks' gestation was 16.7 per 100,000 fetuses at risk with a CA-specific IMR of 2.57 per 1000 live births, as compared to Nova Scotia where the fetal death rate was 131.4 per 100,000 fetuses at risk and the CA-specific IMR was 1.35 per 1000 live births. While this association was most evident for provinces like Saskatchewan, Newfoundland, Manitoba and Nova Scotia, it was questionable for Quebec, New Brunswick, and Prince Edward Island. Unless one simultaneously considers the incidence of fatal anomalies in each population, it is difficult to interpret aggregate trends. For instance, provinces with lower rates of neural tube defects will generally have a lower cause-specific IMR, as well as lower rates of fetal death due to pregnancy termination and/or CA for this reason. High rates of fetal death due to pregnancy termination, on the other hand, could theoretically reflect more terminations for Down syndrome, but this condition does not contribute significantly to death during the first year. Ideally, future studies can be designed to differentiate between pregnancy termination and etiological factors when examining the reasons for CA-related IMR.(15) While the study by Liu et al represents the most convincing piece of research on the TOPFA-IMR link to date, it utilized live birth and stillbirth databases only and provinces were not using a standard definition of stillbirth during the study period (1991-98), which means that a portion of pregnancy terminations for CA would have been missed. Because terminations of pregnancies for CA are often carried out before 20 weeks gestation, many cases would not be captured through the stillbirth data. An Australian study found that 79% of pregnancy terminations for CA were done before 20 weeks gestation.(131) In addition, while fetal deaths due to CA/termination were captured in the Liu et al (2002) study, identification of the reason for pregnancy termination (ie. CA type) was not possible.(15) While TOPFA was clearly a factor in the lower rates of infant deaths observed in some provinces, differences may have been due in part to maternal age distributions, other risk factors, or importantly, greater prenatal detection rates and therefore more fetal deaths being attributed to a CA. This is a challenge with grouping fetal deaths due to CA and TOPFA, and exemplifies the importance of having linked data on prenatal diagnosis and other demographics. Liu and his colleagues (2002) predicted that with the shift towards first-trimester screening and greater access to prenatal

diagnosis in rural communities, terminations of pregnancy for CAs would increase and subsequently CA-specific IMRs would decline further.(15) To adequately monitor and account for this mode of intervention, our data systems must be designed to accurately capture earlier terminations of pregnancy and work will need to be ongoing as prenatal screening/diagnosis practice continues to evolve.

Outside of Canada, Australia has witnessed a similar phenomenon where infant mortality rates due to CAs went from 4.36 per 1000 births in 1980-84 to 2.75 per 1000 births in 1995-98.(131) Bourke et al (2005) conducted one of the only studies designed to estimate the effect of pregnancy terminations for CA on mortality rates to one year of age over two decades (1980-1998).[12] Utilizing linked data from the Western Australian Birth Defects Registry, the proportion of pregnancy terminations for CA that would have resulted in a death before one year of age was estimated and adjusted death rates calculated. Experimenting with two new approaches for modeling this impact (in addition to the standard crude rate calculation), the researchers found significant differences in mortality rates to age one after adjusting for terminations of pregnancy for CA. The methods yielded important differences, showing changes ranging from a 37% reduction in mortality rates to age one to an 11% increase. Model one (1980-1998) and two (1980-84) calculated the proportion of births affected by a CA that resulted in a death by age one. These proportions were multiplied by the number of terminations in each CA category to estimate additional mortality to age one. Using an expert case review approach (model three), approximately half of the observed reduction in all-cause mortality to one year could be explained by the increase of terminations of pregnancy for CA.(102) Australia's supposed success in reducing mortality among CA live-born infants (to one year of age) was almost halved in the case of nervous system defects and increased substantially for chromosomal defects.

[12] Mortality rate to one year of age is different from the infant mortality rate in that it includes perinatal (stillbirths >=400 grams or of >= 20 weeks and live births dying within 28 days) and postneonatal (29 – 365 days) deaths. The advantage of this approach is that no time of death needs to be ascribed, in so far as determining the likelihood that each pregnancy termination might have resulted in a stillbirth, neonatal, or postneonatal death.

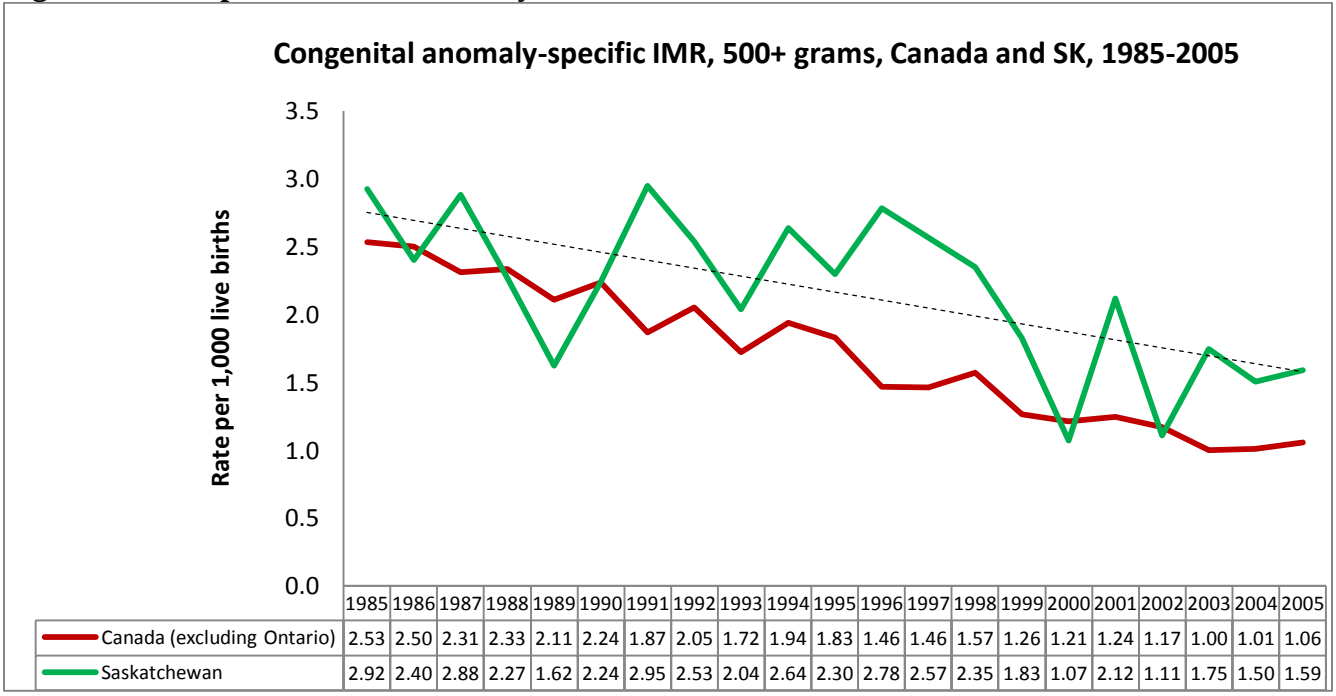
Figure 2.8 CA-specific mortality rates to age one, four methods to rate calculation, percentage change over two time periods (1980-84 and 1995-98), Australia*



* Bourke J, Bower C, Blair E, Charles A, Knuiman M. The effect of terminations of pregnancy for fetal abnormalities on trends in mortality to one year of age in Western Australia. Diatr Perinat Epidemiol. 2005 Jul;19(4):284-93.

In Saskatchewan congenital anomaly surveillance is poor. There is no provincial CA surveillance system in place, although Saskatoon Health Region implemented a pilot system, and the only provincial statistics publicly reported on CAs pertain to CA-related infant mortality. Changes in infant mortality due to CAs occurred somewhat sporadically from 1985-2005, although a general downward trend can be seen. From 1998-2005, the rate declined from 2.35 to 1.59 per 1,000 live births (-32.3%), which represented a larger decrease than the period from 1985-1998 (-12%). Overall, the CA-specific IMR in Saskatchewan decreased by 46% between 1985 and 2004, compared to a national decline of 58%. The Saskatchewan rate was also notably higher than the Canadian rates over time, including the most recent years. This data alone provides additional support for the TOPFA–IMR link, however lowered rates in Saskatchewan might have been due to other factors including fewer CA-affected pregnancies (eg. younger population of mothers, preconception preventive measures), improved medical care, and differences in the number of low birth weight births. Moreover the factors driving the Saskatchewan trends could differ from those observed nationally.

Figure 2.9 CA-specific infant mortality rates, Canada and Saskatchewan, 1985-2005*



	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
Canada (excluding Ontario)	2.53	2.50	2.31	2.33	2.11	2.24	1.87	2.05	1.72	1.94	1.83	1.46	1.46	1.57	1.26	1.21	1.24	1.17	1.00	1.01	1.06
Saskatchewan	2.92	2.40	2.88	2.27	1.62	2.24	2.95	2.53	2.04	2.64	2.30	2.78	2.57	2.35	1.83	1.07	2.12	1.11	1.75	1.50	1.59

* Public Health Agency of Canada, Congenital Anomaly Surveillance System, 2012. Congenital anomaly national prevalence data, 1989-2006. Ottawa.

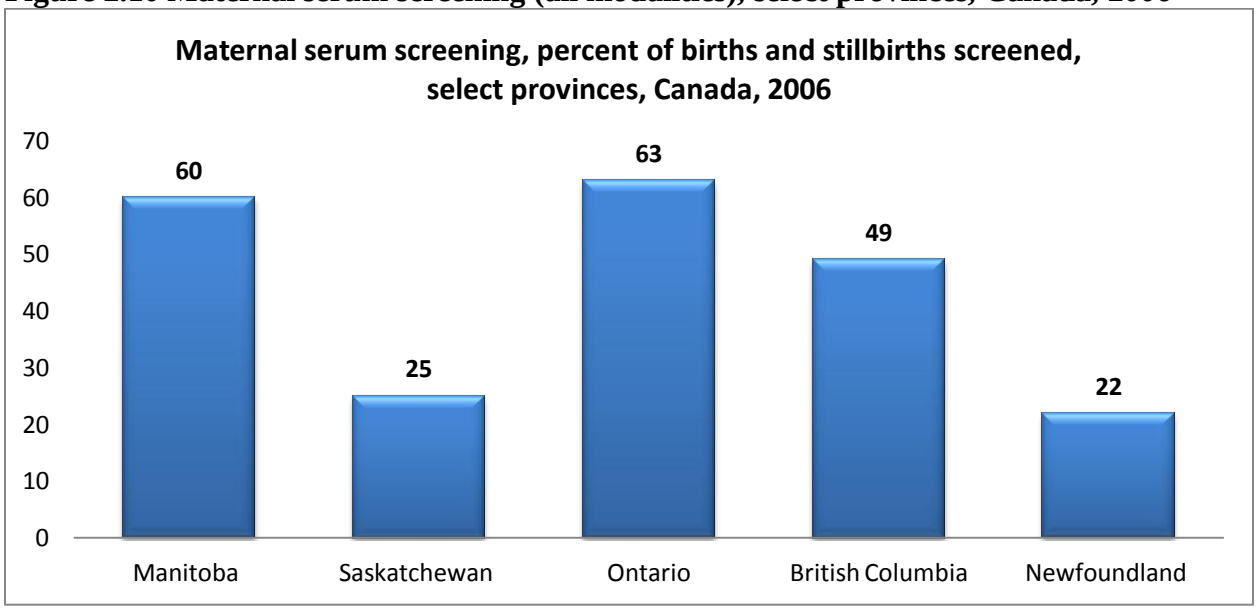
2.4 Predictors of Uptake of Prenatal Screening

Some women accept maternal serum screening (MSS) while others do not. Differences in patient characteristics, preferences, values, or some other structural barriers to MSS may explain variations in uptake. Evidence shows that personal characteristics such as maternal age, religious background, ethnicity, and geographic location all impact MSS utilization to some extent. In an audit of four East London hospitals, maternal age and ethnicity both significantly predicted uptake of MSS for Down's syndrome.(63) Women aged 37 or over at the time of delivery had the lowest uptake of serum screening, but were more likely to bypass serum screening and go directly to amniocentesis. Uptake of MSS in London was also higher among Caucasian (84%) women as compared to Bangladeshi (42%), Indian (74%) and Pakistani (75%) women (69). Religious background also appears to influence women's decisions. In one study conducted in Israel, Sher et al. (2002) found that substantially more non-religious women underwent prenatal diagnostic testing compared with more traditional, orthodox (religious), or ultra-orthodox women.(82) Shohat (2003) found use of MSS to be lower in the non-Jewish population, with the overall uptake of 20% remaining stable from 1996 through 2000 in Israel.(132) It is not known if ethnicity or religion is a factor in the decision-making of pregnant women in Canada. In fact,

there are no published studies that stratify MSS uptake for different ethnic groups within Canada or look at other predictors of uptake. Still there is the perception by Saskatchewan physicians that Aboriginal women in the province accept MSS less often than non-Aboriginal women.(32)

Uptake of prenatal screening has increased over time in many regions, although utilization can still vary widely within the same community. For instance, in London from 1990 - 1999 uptake ranged from 45-80% across hospitals.(63) Here in Canada, an Ontario study found an overall uptake of 48%, with rates being as high as 60% in Toronto and below 20% in Northern Ontario.(70) The same was seen in British Columbia where 45% of all pregnancies were screened in 2005, but rates varied from 84% in Vancouver to 29% in Vancouver Island and 28% for the rest of the province.(133) Nationally, Manitoba had the highest reported rate of uptake at 60% in 2006 whereas Saskatchewan and Newfoundland and Labrador had the lowest at just over 20%.(80, 134, 135) In 2006, uptake in Ontario sat at 63% and at 49% in BC.(133, 136) MSS experienced a dramatic increase in popularity in South Australia over a relatively short amount of time, rates jumping from 17% in 1991 to 75% in 1996.(25) In a study in France (1997-98), Muller et al (2002) found that 65% of all pregnant women in that country had MSS.(71)

Figure 2.10 Maternal serum screening (all modalities), select provinces, Canada, 2006



The way in which MSS is offered by each health system and provider characteristics have been shown to have some impact on utilization rates, however the relationship is not straightforward. Dormandy et al (2002) found a higher uptake of screening in hospitals in one

health region in England where serum screening was offered as part of the routine prenatal check as compared to those where a separate visit was required.(137) However, the type of screening test offered and whether or not a reminder notice was sent showed no effect. In Canada, research has shown that female physicians (compared to male) and obstetricians (compared to family physicians) were more likely to report offering screening to all patients.(21, 32)

Statistics on MSS uptake are made up of several groups of women including: those who accept, those who refuse (either directly to their care professional or by not presenting for the blood work), women who were never offered testing, and women presenting too late in their pregnancy for medical care and were therefore ineligible for screening. Research on this topic is extensive, spanning many countries, population sub-groups and three decades, and has identified several common themes about why or why not women have screening done. Reasons for screening included: to gain knowledge about the health of the fetus; being at increased risk of having a child with DS; did not know they could refuse screening; favourable characteristics of the screening test; trust in care professionals to offer only important tests.(25, 26, 30, 138, 139) Reasons for declining included: unfavourable characteristics of the screening test (eg. high false-positive rate; cannot detect all cases); not necessary/ personal risk perceived to be low; would not make a difference in the management of the pregnancy; opposition to abortion; anxiety/ uncertainty (and concerns about the impact of this stress on the baby); risk of fetal loss and harm during invasive follow-up testing; opposition to the medicalization of pregnancy; acceptance of / knowing persons with disabilities.(23-25)

Some women who receive "increased risk" serum screening results will decide to follow-up with prenatal diagnostic testing and some will not, depending on many factors relating to the mother's risk profile and values and preferences. Alberman et al (2003) found that more women under age 35 with a positive MSS result had prenatal diagnostic testing as compared to women aged 35 and over (58% and 41%); whereas a greater proportion of women aged 35 and older with a negative MSS result chose to have a diagnostic test (9% and 0.3%).(63) One study in Connecticut (1996) found that even though advances in screening had occurred, the proportion of DS cases detected during a 12-year period had not changed.(62) Ultimately, the decision to choose follow-up testing is based on a number of factors and appears to vary by geography and across population sub-groups (similar to prenatal serum screening). The overall impact of screening on CA detection requires uptake by a significant proportion of the population, test

sensitivity, and the decision to follow-up increased-risk results with diagnostic testing. To date, no studies have been published in Canada tracing uptake through the pathway from prenatal screen offer to acceptance of prenatal diagnosis and pregnancy outcome.

Women's decision to accept or reject testing does not necessarily offer much about her value and preferences or rationale. Based on the literature, a plethora of factors can play a role in uptake. For many women the goal of screening is to rule out any problems and receive reassurance of the baby's health, rather to intervene through abortion.(25, 80) By examining patterns of uptake of screening, diagnosis and pregnancy termination, some insights may be gained about the delivery and acceptance of new emerging reproductive technologies. However, more qualitative study and surveys will need to be done with Saskatchewan women themselves in order to know the exact reasons for choosing to screen or not to screen.

Differences in prenatal detection and termination of pregnancies affected by CAs have been shown to create disparities across socioeconomic and geographic groupings. One population-based study in Paris, France found that maternal occupation and place of origin had significant effects on the likelihood of a prenatal diagnosis of Down syndrome and on continuation of pregnancy after DS diagnosis.(31) Women in lower-status occupations were more than twice as likely, after controlling for age, to deliver a live-born infant with DS as women in the highest-status occupational category. This finding is consistent with research that has shown socioeconomic disparities in use of medical services generally, and prenatal testing in particular, in several countries.(34, 140-147) Khoshnood et al (2006) were the first to show that differences in the uptake of prenatal diagnostic testing by socioeconomic groups resulted in differences in live-birth DS prevalence; a finding that is due to the fact that women of lower SES were less likely to opt for screening/ diagnosis and were less likely to terminate a pregnancy when diagnosed with DS.(31) The study also found no difference in age-adjusted DS risk for women of different socioeconomic backgrounds. France has an active national policy targeting increased access to prenatal screening and a culture that favours pregnancy termination, which have together led to overall reductions in the live-birth prevalence of DS, perhaps making it a special case. A more recent study by Smith et al (2011) using data from the United Kingdom Fetal Anomaly Screening Program found that while antenatal detection rates were similar for pregnant women from different deprivation areas, the rates of TOPFA were lower in women from more deprived areas compared to those from less.(98) Differences in TOPFA led to

sizeable differences between deprivations areas in the live birth rate of CAs and neonatal mortality associated with nine of the anomalies studied. These observed disparities mean that families with fewer resources are more often taking on the responsibility for caring for, and advocating for, children with special needs.

2.5 Gaps in current research and surveillance

The greatest impediment to basic CA surveillance in Canada is the inability to accurately capture termination of pregnancies for CA, and the resulting underestimation of CA, which prevents systematic investigation of risk factors and trends in maternal, perinatal, and infant health. A strong national CA surveillance system would require the bringing together of data from multiple sources, which is complex and requires committed resources. The Canadian Congenital Anomaly Surveillance System (CCASS), the national surveillance database, does not capture data on early terminations of pregnancy for CA or those that occurred outside a hospital or other important risk factor information.[13] While it provides good quality information on CA live births and stillbirths, a significant proportion of CA pregnancies are spontaneously lost or terminated and therefore missed. According to Meschino (2007), a well-developed and functional CA surveillance system is integral to understanding the effectiveness of interventions (diagnosis, medical and surgical); helping to determine prognostic factors for many CA types; enabling us to better research CA etiology and tracking risk factor prevalence; and for exploring the impact of mode, timing, and location of delivery on morbidity and mortality of infants born with CAs.(148) Back in 2002, Alberta and Newfoundland were the only programs that collected elective pregnancy terminations less than 20 weeks and Newfoundland only captured those that are NTD-related.(5) In recent years investments have been made in provincial surveillance systems to enhance capacity for population-based reporting and data sharing agreements are in place (or underway) to enable many provinces/territories to contribute data to the CCASS. A standardized approach to collecting data across provinces (and even within provinces, as is the case in Saskatchewan) is necessary to render comparable statistics, addressing many of the limitations described.

[13] The CCASS is testing the linkage between mother and baby records and extending follow-up to two years. This linkage will provide data on maternal age, health conditions (diabetes, asthma), and drug usage (when recorded on the hospital record) (personal communication, Jocelyn Rouleau, Public Health Agency of Canada).

An estimated one in every five pregnancies in Canada was terminated in 2006.(128) Yet this population of pregnancies is routinely excluded from consideration when reporting provincial, national and international statistics on fetal mortality. Another important concern is that the *Therapeutic Abortion Database/ Survey*, the only source of abortion data nationally, has several data quality concerns that undermine its validity and reliability. Specifically, the data has incomplete demographic information; excludes out-of-country procedures after 2003; potentially double counts some records due to lack of identifiers; and several larger Canadian clinics have opted not to submit abortion data at all.(128) In addition, since 1999 Ontario has altered its method of capturing abortions and this has resulted in underestimates of about 5.4% each year provincially and 1% nationally. These are significant, and often underappreciated, omissions in the data used to conduct maternal and perinatal surveillance.

Another well-documented, although not-well-understood, challenge is the relatively common occurrence of spontaneous abortions (or "miscarriage"). Few surveillance systems worldwide track this pregnancy outcome, which may be due to the significant portion of cases that occur outside hospital and their uncertain significance as far as maternal and fetal/infant health. Typically spontaneous abortion is used as an outcome in itself, since testing of the fetus to identify causes is rare, and where known, is often not documented in hospital or physician databases. Still, spontaneous abortion, if used as part of an intentional surveillance program, can be used as a marker for teratogens in the environment, recognizing that many anomalies that appear among spontaneous abortions never or rarely appear in live births and the majority of anomalous conceptions are found in such cases.(149) Despite the lack of information available on this type of pregnancy outcome, many fetuses with a congenital anomaly are lost early. One study examining outcomes for 538 fetuses prenatally-diagnosed with trisomy 13 or 18 found that between 12 weeks gestation and term many ended in spontaneous abortion or stillbirth (49% and 72%, respectively).(150) In the case of CA surveillance and research, natural fetal loss (including both spontaneous abortion and stillbirth) and elective medical abortions are crucial to our understanding of the true occurrence of these outcomes.

2.5.1 A need for improved indicators

The advent of new prenatal screening technologies has the potential to mask real changes in infant and fetal death, thereby globally affecting these indicators. A solution proposed by both

Davidson et al. (2005) and van der Pal-de Bruin et al. (2002) is the use of "natural" or "adjusted" indicators of perinatal death.(151, 152) Specifically, terminations of pregnancy for fetal anomaly can 'artificially' reduce perinatal and infant mortality rates and give the illusion that progress has been made on etiological factors. An adjusted indicator could estimate mortality rates, under the hypothetical scenario that no TOPFA were performed.

The importance of revealing the natural IMR is that it offers a truer depiction of progress (or decline) in improving the social, economic, and health care environments that sustain and promote wellbeing of the population and for which the health and survival of infants is a key marker. As noted earlier, IMR is a valuable indicator of the health of the entire population. In terms of policy and surveillance, the lack of an adjusted IMR prevents decision-makers from accurately assessing the performance and policies of federal, provincial and regional/ community programs and broader health initiatives. It also leaves the door open for speculation that yearly fluctuations are due mostly or partly to prenatal screening and selective termination, without any definitive evidence to support or to dispute such a claim. It is unclear then if Saskatchewan's poor overall performance, as far as infant mortality, is the result of lower or declining quality of the social determinants of health or if it is linked to its historically lower uptake of prenatal screening and diagnosis as compared to other provinces. If the latter is the most responsible explanation, then the greater acceptance of prenatal screening and higher rates of termination of pregnancy for fetal anomaly in other provinces must not be mistaken for higher-quality social, economic, and health care environments which are the real determinants of lower IMR. In sum, the lack of clear understanding of the determinants of infant mortality in Saskatchewan blunts discussions around this topic and compromises the IMR's potential as a key indicator of a society's health-promoting circumstances.

Research has been done looking at changes in perinatal mortality (PMR) as a result of termination of fetuses with CAs. Van der Pal-de Bruin et al (2002) estimated the impact of prenatal terminations on the PMR using a calculated lethality for each CA in the hypothetical case that no pregnancy termination had been performed and was expressed in the natural PMR.(152) The study found large differences between European countries and regions in terms of the number of termination of pregnancies for CAs. The differences between the reported and natural PMR varied between 3.7 and 14.1 per 10,000 live and stillbirths. The difference was greater in regions where prenatal screening was more common. Here the emphasis on infant

mortality is largely due to the importance placed on the IMR as a global health indicator, as it is a much-more widely used indicator of general societal health and wellbeing. It is often used in health planning, evaluation, community research, and policy development.(34, 39, 41, 153) If a measure (ie. a TOPFA-adjusted IMR) could be developed that takes into consideration the population of vulnerable fetuses that have been removed by means of abortion, many of which would have been born alive, the validity and utility of the IMR would be strengthened. Ideally, the end result would be a single figure that is relatable in both policy and research contexts.

2.6 Ethics

Ethical inquiry has been incorporated into the current research for three reasons: (1) questions of ethics are valuable because they are socially relevant and intimately linked to the practice of selectively terminating pregnancies with CA; (2) the academic literature on prenatal screening often sidesteps the issues of ethics, addressing them separately as opposed to considering the interconnectedness of concepts; and (3) no ethical framework exists for future decision-making and policy around prenatal screening in Saskatchewan or Canada. An environmental scan (2002) was conducted on behalf of the CIHR Institutes' of Genetics and Health Services and Policy Research Joint Planning and Policy Committee on Health Services in Genetics.(154) The report commented on some of the shortcomings of research and policy-planning documents to date. "Many of the reports identified were theoretical or discursive in nature and varied in scope from highly specific to very general. The majority were rather general, and some focused on a particular issue or set of issues concerning genetics 'in society'. Most identified issues and concerns but few went beyond this in any useful way."(154) Alternatively, the committee developed a list of key questions on health services in genetics. In particular, there were questions concerning the impact of genetic testing and related health services on people and their families, society, health care providers, funders and industry, with attention to the broad range of factors that might modify such impact. The expectation for the current research is that it will go beyond describing the key ethical dilemmas around prenatal screening to offer some insights into how providers and policymakers might deal with such issues, whether or not a broader social consensus can be reached.

Despite its contentious nature, very little public dialogue has occurred around prenatal screening in Canada. The deeper one delves into the policy landscape, the more one recognizes

the need for greater engagement of a variety of affected stakeholders. Many have called attention to the widening gap between genetic advances and reproductive screening/diagnostic technologies and their application in clinical practice, yet not enough has been done on the policy front to attend to such disconnects. At the practice level, prenatal screening has raised concerns about everything from inadequate provider knowledge and education, lack of informed consent, lack of access to and inadequacy of genetic counseling, and poor test performance, to disparities in access and utilization between different groups of women. In terms of broader policy creation, there are questions about the limits of screening, its ethical basis and eugenic potential, implications for those living with disabilities, the question of personhood and the moral significance of the fetus, as well as who is driving the technology - mothers or industry or experts. There is an ever-widening gap between genetic knowledge and society's capacity to think through these new possibilities, but the need is growing for this type of thinking and a more applied ethics approach.

Emerging are the fields of Public Health Genetics and Community Genetics where numerous theories have been postulated about ways in which the gap between clinical medicine and public health interventions can be bridged.(155) However, debating the practicalities of implementing genetic medicine at the population level may be somewhat premature. What must be considered first, and articulated, is the foundation that these decisions ought to be based upon. Values are a critical building block of the 'translational highway' hoping to link clinical and public health genetics, and in fact, values must set the foundation.(155) In the United States, the National Human Genome Research Institute currently supports a scholarly program on the ethical, legal and social implications (ELSI) of genetics research. ELSI inquiry examines the values underlying the use of new genetic technology, ideally before it is in use. In 1999, the ELSI program was expanded to specifically address issues arising when genetics is used to advance the public's health; the results was Public Health ELSI (PHELSI). While there is some dialogue amongst Canadian ethics scholars on the social, legal, and ethical ramifications of prenatal screening, there is no parallel program in this country or mechanism for knowledge translation between new research and scholarship and decision-making.

Currently there are not any real limitations or laws setting parameters around termination of pregnancies, and a pivotal question arises: whose values will guide decisions about which terminations are morally acceptable, socially desirable and legally permissible? Arguably,

prenatal screening presents another case of science leading us and we are racing to catch up. Some have argued that the issue has quite successfully been framed as a purely private or medical matter, where the focus is on procedural solutions when substantive debate is actually what is required.(156) In Canada today, the Society of Obstetrics and Gynecologists of Canada (SOGC) along with the Prenatal Diagnosis Committee of the Canadian College of Medical Geneticists (CCMG) provide guidelines and recommendations on prenatal screening and diagnosis for practitioners.(52, 54, 157) However, some might argue that organizations whose professional bodies have a vested interest in promoting the uptake and spread of this technology and associated interventions should not be taking the lead on writing the best practice guidelines, or at minimum, that the views of those living with disabilities and intended users (women) should also be represented in such guidelines. In the absence of legislation or policies at the national or provincial level to guide current or future practice, there is a rather disjointed and vague decision-making landscape. However, legislation and public health policy can offer a variety of safeguards against potential misuses.(155) It is this lack of coherence and leadership that puts our society at risk for morally objectionable practices and increases the risk for an uninformed public to watch as a new reality around birth and genetics is fashioned and normalized.

Prenatal screening and termination of pregnancy for fetal anomaly continue to occur as though they are 'normal', or at least acceptable personal decisions, thereby demanding little attention. A better answer, it will be argued, is that the Canadian public is educated and consulted in a meaningful and deliberate way, where multiple voices guide public policy on these fundamental and monumental questions. On the face of it, Canadian society supports public participation and community involvement, yet the public has been left out of this key policy issue. Where prenatal screening is described in both academic and lay publications, the ethical issues raised are often given token recognition or left out entirely, unless debate occurs within a forum that specifically engages ethical issues. Up until recently, there has been no concrete attempt, or even plan, for engaging Canadians around discussions of values and morals. Questions of ethics have been broached in a limited way on broad topics relating to biotechnology through the Canadian Biotechnology Strategy, but prenatal screening was omitted from inquiry.(158) If not addressed, select groups of experts will carry on making all decisions about new and existing screening technologies for the whole of society. Ethical discussions will

continue to be restricted to the individual and the clinical encounter, where the historical roots and societal implication of this practice are decontextualized. Prenatal screening as it exists today, and as it is imagined for tomorrow, sets parameters around which human lives are optional and as such warrants a more open, encompassing, and transparent debate. The active engagement of an informed public will be essential if the positive potential of genomics is to be realized, while minimizing social harms.(155)

CHAPTER 3: METHODOLOGY

3.0 Study Design

In studying the relationship between maternal serum screening, pregnancy termination for CA, and live CA birth rates and infant mortality rates, multiple data sources were combined to create a comprehensive maternal-fetal-infant database. Most of the data spanned a six-year period (2000-2005) and individual level variables were drawn from the following sources: the provincial health administrative databases (hospital and physician services, person registry), provincial laboratory MSS data file, Vital Statistics, and cytogenetic laboratory data from the Saskatoon and Regina Qu'Appelle Health Regions. The study is a population-based, retrospective, cohort study. Saskatchewan women with a documented pregnancy were grouped either as exposed (i.e. those who underwent MSS) or unexposed (i.e. those who did not have MSS) and followed for a period of time to determine the incidence of prenatal diagnostic testing, TOPFA, and live born infants with congenital anomalies. In this context, prenatal screening/ diagnosis 'exposure' can involve three different tests (serum screening, ultrasound, and amniocentesis) and is best thought of as a pathway rather than a one-time event.

3.1 Study Population

The population-based cohort for this study includes all female residents, eligible for Saskatchewan Health benefits coverage, who either delivered a baby (live or stillborn), experienced a fetal loss (spontaneous abortion) or had a pregnancy termination (medical or therapeutic abortion) between January 1, 2000 and December 31, 2005, inclusive. Each woman was followed until her exit date from the cohort, which was the earliest of one of the following: pregnancy termination, fetal loss, stillbirth[14] or live birth[15]. Women were identified using the

[14] Stillbirth is defined under *The Vital Statistics Act, 2009* for the purpose of registering stillbirths in the Province of Saskatchewan as follows: "Stillbirth means the complete expulsion or extraction from the mother after at least 20 weeks' pregnancy, or after attaining a weight of at least 500 grams, of a product of conception in which, after the expulsion or extraction, there is no breathing, beating of the heart, pulsation of the umbilical cord or unmistakable movement of voluntary muscle." (p. 8, Vital Statistics Act, 1995, Saskatchewan Government; http://www.qp.gov.sk.ca/documents/English/Statutes/Statutes/V7-21.pdf)

[15] Live birth is defined under The Vital Statistics Act, 2009 for the purpose of registering live births in the Province of Saskatchewan as follows: “Live birth means the complete expulsion or extraction from the mother, irrespective of the duration of the pregnancy, of a product of conception in which, after the expulsion or extraction, there is breathing, beating of the heart, pulsation of the umbilical cord or unmistakable movement of voluntary

Vital Statistics live birth and stillbirth data, person registry, hospital separation, and physician services files as described below (See Appendix A). To link infant and mother records, each mother's health services number (HSN) was matched to the person registry system to obtain the family number, which was then used to obtain the infant's HSN.[16] In cases where the mother's HSN was not recorded on the birth registration record or where the infant's HSN was not found by this method, an iterative process of name, sex and date of birth matching was done to link moms and babies. All live born infants were followed for up to one year after their birth in order to capture all deaths in the first year of life (for IMR calculation) and to ensure high case ascertainment for all CA types.

3.1.1 Identification of births

Saskatchewan Health beneficiaries who delivered a live born or stillborn baby in Saskatchewan between January 1, 2000 and December 31, 2005 were identified using the Vital Statistics birth registration file. Vital Statistics birth and stillbirth registration data for out-of-province births and stillbirths to Saskatchewan residents were included where the data were available. Adoptions at birth were excluded because it is not possible to link the baby with his/her birth mother. However, the number of these instances would be relatively small. From 1999 to 2003, public adoptions dropped from 66 to approximately 20 per year.(159)

3.1.2 Identification of abortions

Saskatchewan Health beneficiaries who had a spontaneous, medical or "other" abortion during the study period of January 1, 2000 and December 31, 2005 were identified using hospital separation and physician services data. Spontaneous abortion subjects were identified as female Saskatchewan Health beneficiaries who had one or more physician service or hospital separation record with any of the following diagnostic or fee-for-service codes during the study period:

ICD-9 code	ICD-10-CA code	Fee-for-Service code
632 - missed abortion	O02.1 - missed abortion	350P - spontaneous abortion
634.x- spontaneous abortion	O03.x - spontaneous abortion	

muscle, whether or not the umbilical cord is cut or the placenta is attached." (p. 6, Vital Statistics Act, 1995, Saskatchewan Government; http://www.qp.gov.sk.ca/documents/English/Statutes/Statutes/V7-21.pdf)

[16]Records are only created for live and stillbirths, not for spontaneous or medical abortions. The exception is when a medical abortion is performed at or after 20 weeks or if the fetus weighed 500 grams or more.

Up until 2001/02 hospital services diagnoses in Saskatchewan were reported according to the International Classification of Diseases, Ninth Revision (ICD-9) coding scheme and procedures were coded according to the Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures (CCP) guidelines. In April 2002, all hospitals transitioned to using the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Canada (ICD-10-CA) guidelines, and procedures were recorded using the Canadian Classification of Health Interventions (CCI) coding scheme. While not all hospitals switched over at once, the extraction software used to identify codes is able to search for both ICD-9 and ICD-10-CA codes at the same time. Physician services data were coded using three-digit ICD-9 codes for the whole study period.

Elective abortion subjects were identified as female Saskatchewan Health beneficiaries who had one or more hospital separation record with any of the following ICD-9 or ICD-10-CA diagnostic codes during the study period. In Saskatchewan, medical abortions are performed as day surgery or inpatient procedures in a hospital; no Saskatchewan physician clinics performed medical abortions during the study period. Subjects who had a medical abortion in Saskatchewan were, therefore, identified only through the hospital separation data using the ICD-9 or ICD-10-CA codes listed below. Subjects who had a medical abortion outside Saskatchewan, on the other hand, were identified using both hospital separation data (using the codes listed below) and physician services data. Physician services data with the following ICD-9 and/or fee-for-service codes were used only to identify medical abortions performed outside Saskatchewan.

ICD-9 code	ICD-10-CA code	Fee-for-Service code
635.x - legally induced abortion	O04.x - medical abortion	50P - therapeutic abortion - first trimester 250P - medical abortion - second trimester

Within the International Classification for Diseases, there is a category for *other abortion.* Upon further examination, it appears that this code captures instances of self-inflicted abortions or spontaneous abortions following amniocentesis or trauma (eg. car accident). Because this category may include abortions relating to amniocentesis, these cases were included in the database and were matched against cytogenetic testing data to determine if these were pregnancy losses relating to prenatal diagnosis. Subjects having this type of abortion were

identified as female Saskatchewan Health beneficiaries who had one or more physician services or hospital separation records with any of the following diagnostic codes during the study period:

ICD-9 code	ICD-10-CA code	Fee-for-Service code
636.x - illegally induced abortion 637.x - unspecified abortion	O05.x - other abortion	n/a

The three types of abortion events (i.e., spontaneous, medical and other) were identified separately, then combined into a single "abortion event file" (see description below), and finally merged into the study`s Maternal-Fetal-Infant database. Spontaneous (SA), medical (MA) and other (OA) abortion records from the physician services and hospital separation data were processed separately using a "90-day rule" to collapse records into MA, SA, and OA episodes. The 90-day rule was applied as follows: if a woman had two or more physician service and/or hospital separation records for a given type of abortion within 90 days of each other, the record with the earliest service date was identified as the index date and all records for the same type of abortion (MA, SA, or OA) within 90 days following the index date were considered part of the same episode.

The resulting three abortion episode files (i.e., one file each for SA, MA and OA episodes) were then combined into a single abortion event file using a 90 day rule to collapse overlapping episodes. In these cases, flags on the subject file indicate that one or more abortion episode types were identified in the 90 day period following the "index abortion event". Flags identify the type of abortion, number of days after the index date and data source (physician service record vs. hospital separation record). These steps were determined to be the best possible approach to limiting the number of events missed, duplicated, or avoiding misclassification. Upon closer analysis of the three abortion categories and their occurrence in the data, the decision was made to rely primarily on the "index abortion event" and to also err on the side of over-inclusion of medical abortion cases, which meant recoding the index event if the second or third record was a medical abortion. Specifically, where there were both medical and spontaneous abortions codes or a medical and other abortion code (for one woman within 90 days), the diagnosis of a medical abortion was assumed to be correct. It appears that the category

"other abortion" may be used in error by physician clinics and most often likely relates to a spontaneous abortion.[17]

3.1.3 Study definition of medical abortion

For the purposes of the current study, the ascertainment of medical abortion cases was somewhat broader than the definition used by the National Therapeutic Abortion Database (CIHI). While the ICD diagnostic codes and CCP/ CCI procedure codes used to identify cases were nearly identical, the presence of a diagnostic code was used solely to identify abortions in the current study and a procedure code was not required. The type of intervention (eg. surgical, pharmaceutical) was not pertinent to the study hypotheses and reliance on diagnostic codes was meant to cast the net wider and detect more cases. In addition, the actual intervention or abortion procedure does not always occur on the same day as the completed abortion (eg. some women must present several times for induction, and are sent home, before the abortion is actually completed). Procedure codes were, however, extracted from the hospital and physician data and available for cross-matching. For the termination of pregnancy for fetal anomaly (TOPFA) cases, 93.6% (88/ 94) of abortion events had a matching medical abortion procedure code[18]. In addition, CIHI excludes hospital records where the specified intervention was cancelled, abandoned, performed previously or out of hospital; the current study did not make these exclusions, which could have resulted in a greater number of overlapping episodes, however, the impact of this on case ascertainment is expected to be small and will have benefits for capture of events.

Another methodological difference between the Therapeutic Abortion database (CIHI) and the current study is that CIHI retains the first abortion record (index event) and excludes all other codes of interest within 28 days, while here 90 days was used. The Manitoba Centre for Health Policy used 14 days. Here 90 days was seen to be a reasonable window given the healing time required (following a pregnancy loss or birth) before a subsequent pregnancy can occur and the time it takes for a woman to confirm a subsequent pregnancy. The likelihood is low that a

[17]The Manitoba Centre for Health Policy (MCHP) concurred with this assessment in their own work. Their recommendation was to consider omitting this code, however, it appears it is used much less often in Manitoba (perhaps partly because they were not using physician claims data in the work referenced, only inpatient hospitalizations).

[18] A limitation in the coding was the omission of three CCP procedure codes (used prior to 2001/02) and the grouping of another in a separate procedure group under "other obstetric-related procedures". This may account for the 6.4% without a procedure code (n=6).

unique, new pregnancy could be conceived, with the woman presenting for care at hospital or physician office for a second loss within 90 days of the first loss or pregnancy. In the extremely unlikely event that a second pregnancy was erroneously grouped with a previous pregnancy (and therefore misclassified), the effect on the independent and dependent variables should be negligible given that medical abortions following quickly after spontaneous abortions (or vice versa) would not have been eligible for maternal serum screening or diagnosis.

Looking at the index medical abortion cases in Table 3.1, there were 11,391 cases in total during the study period, with 372 of these cases having an "other" abortion code within 90 days (345, or 93%, of which were from physician data) and 644 having a spontaneous abortion code within 90 days (563, or 87%, of which were from physician data) that occurred within 90 days. For all medical abortion index cases, the woman was classified in the study as having a medical abortion. However, for the spontaneous and other abortion index cases where a medical abortion code followed within 90 days, the woman was reclassified as having a medical abortion (n=134; 122 of which were identified from the hospital data). This decision is largely due to lower confidence in the spontaneous and other abortion codes, and the fact that most of the overlapping medical abortion codes were identified in the hospital data, which is a more valid and reliable dataset as compared to physician services data.

Table 3.1 Type of abortion according to source of identification (physician services versus hospital file) and event order (index, second and third), 2000-2005 (pooled), Saskatchewan

	N (from physician services/ from hospital file)		
	Index Abortion event	**Second abortion event**	**Third abortion event**
Medical abortion	11391 (1103 / 10288)	280 - other (269 / 11) 625 - spontaneous (549 / 76)	92 - other (76 / 16) 19 - spontaneous (14/ 5)
Spontaneous abortion	8724 (3652 / 5072)	62 - medical (9 / 53) 2980 - other (2723 / 257)	5 - medical (1/ 4) 8 - other (8/ 0)
Other or unspecified abortion	3087 (2911 / 176)	67 - medical (2 / 65) 624 - spontaneous (319 / 305)	5 - spontaneous (4/ 1)

3.2 Data Sources

As described, there were five sources from which data were drawn for the current study. Vital Statistics birth and death registration data was used to identify live and stillbirths, as well as

infant deaths within the first year of life and causes of death. Data from inpatient hospital visits and day surgeries were used to capture pregnancy events such as medical and spontaneous abortions, as well as diagnoses. Physician services (or claims) data were scanned for fee-for-service and diagnostic codes (Table 3.3-3.4). Cytogenetics lab data reported laboratory results for amniocentesis tests for women from the study entry date to the exit date plus 90 days. The Provincial Laboratory provided a data file on all laboratory results for MSS tests completed between May 1, 2001 (program implementation) and March 31, 2005. When compiling the service data (ie. laboratory tests and physician services) for each subject, records were included when the service date fell within the study entry date and exit date. Vital Statistics, hospital, and physician services data were available for all six years of the study, while Cytogenetics data from Regina Qu'Appelle and MSS laboratory data were not (Table 3.2).

Table 3.2. Data inclusion by data source and year

Data source	Nature of data	2000	2001	2002	2003	2004	2005
Vital Statistics	Birth and death certificate information						
Hospital separations	Inpatient hospitalizations						
Physician services	Physician claims						
Cytogenetics laboratory	Amniocentesis details and results		RQHR October 1				
			SHR				
Provincial laboratory	MSS screening information and results		May 1				March 31

3.2.1 Creation of the Maternal-Fetal-Infant dataset

A comprehensive master file, the Maternal-Fetal-Infant dataset, was created using two subject files for women: one file relating to women who had birth events (live or stillbirths) and one file relating to women who had abortion events (spontaneous, medical or other) during the study period. Note that a woman may be included in the study more than once (e.g. for two or

more births, stillbirths, or abortion events). Women included in the study for more than one pregnancy had different study identification numbers assigned for each event to further protect confidentiality. For women, the study entry date was the latter of January 1, 2000 or health coverage initiation date up to December 31, 2005. Women exited the study on the date of the live birth, stillbirth, or abortion event. A baby subject file containing demographic and birth or stillbirth information for the live born and stillborn infants was also created. For babies, they enter the study on the date of their birth and are followed-up to either the date of death, date of emigration from the province, or one year after birth. For women, hospital separation, physician services, and MSS test data were compiled for the period of time they are included in the study. Amniocentesis data from the Cytogenetic Laboratories in the Saskatoon and Regina Qu'Appelle Health Regions was available from January 1, 2001 to December 31, 2005 and from October 1, 2001 to December 31, 2005, respectively. Amniocentesis data from Regina Qu'Appelle is missing from January through September of 2001 because cytogenetic testing was out-sourced to a lab in British Columbia during this time frame and data could not be located for this study. A flag was included on the mother's subject file to indicate a mother's Registered Indian status.[19] Mother's health region of residence was based on her home address as of December 31st of the year of the subject's study exit date. For babies, hospital separation, physician services and Vital Statistics data were compiled for the period beginning on the date of birth and ending on their study exit date. For babies whose study exit is due to death, all recorded causes of death were extracted from the Vital Statistics death registration file. In addition to deaths that occur in Saskatchewan, this file contains all deaths of Saskatchewan residents that occur in Alberta. If the death occurred in Alberta, the record will report underlying cause of death only. The database also includes a file derived from reciprocal billing hospital separation records, which reports fact and date of death for deaths of Saskatchewan Health beneficiaries occurring in hospitals outside Saskatchewan and Alberta.

3.2.2 Dataset strengths

Data collected through the provincial health databases will enable the study hypotheses outlined in Chapter 1 to be explored in detail. In general, this will include an examination of the

[19] For the current study, the Registered Indian flag is based on information in the Person Registry System. In the Person Registry, Registered Indians are those Saskatchewan Health beneficiaries registered under Section 6 of the Indian Act and assigned a ten-digit number in the Indian Registry and who self-identify to Saskatchewan Health.

screening program's general performance (detection rate, positive and negative predictive value, false-positive rate); outcomes of positive screening results (follow-up with amniocentesis, termination of pregnancy for fetal anomaly, and pregnancy loss due to invasive testing); distribution of MSS uptake across the province, over time, by ethnicity, age, and rural/remote/urban geographies; trends in the incidence and birth prevalence (live and total) of CA categories over time; and changes in infant and fetal mortality (overall and CA-specific). Because the dataset captures nearly most pregnancies, prenatal screening tests, and prenatal interventions for residents of Saskatchewan, the Maternal-Fetal-Infant database provides a unique opportunity for a population-based study of this nature. The linking of cytogenetic, laboratory, Vital Statistics, hospital, and physician data strengthens inferences that can be made regarding the causal pathway leading from prenatal screening through to pregnancy termination for CAs, which is a limitation of other research in this field. Equally important, the data captures pregnancy terminations and spontaneous losses at less than 20 weeks gestation where a CA was diagnosed using amniocentesis; a population missing from the Canadian Congenital Anomaly Surveillance System (CCASS) and omitted from several key studies on this topic.(5)

3.3 Study Variables

Diagnoses of interest were reported for both women and their babies by specific codes or a grouping of related codes. Table 3.3 below outlines some of the key variables and diagnostic codes used to capture the presence or absence of each condition (for more detail see Appendix B). Table 3.4 outlines the procedure codes used to capture relevant variables. Both hospital and physician databases were used to identify procedures of interest, therefore fee-for-service codes were identified in addition to CCP and CCI codes.

Table 3.3 ICD-9 and ICD-10-CA diagnostic codes of interest for infants and women

Category	ICD-9*	ICD-10-CA
Infants		
Severe neural tube defects: Anencephalus, craniorachischisis, iniencephaly, encephalocele	740.x, 742.0	Q00-Q01.x
Spina bifida (with or without hydrocephalus)	741.x	Q05.x
Down's syndrome - Trisomy 21	758.0	Q90.0-Q90.2; Q90.9
Edwards' syndrome - Trisomy 18	758.2	Q91.0-Q91.3
Congenital heart defects	745-747.x	Q20-Q28.x
Congenital malformations of genital organs	752.x	Q50-Q56.x
All other congenital anomalies of nervous system	742.1-742.9	Q02-Q04.x, Q06.x, Q07.x
All other chromosomal anomalies	758.1, 758.3-758.9	Q91.4-Q99.x
All other congenital anomalies	743-744.x, 748-751.x, 753-757.x, 759.x	Q10-Q19.x, Q30-Q45.x, Q60-Q89.x
Other conditions originating in the perinatal period - termination of pregnancy, fetus and newborn	779.6	P96.4
Fetus and newborn affected by other maternal complications of pregnancy - spontaneous abortion, fetus	761.8	P01.8
Stillbirth		P95
Women		
Stillbirth	656.4, V27.1, V27.3, V27.4, V27.6, V27.7	O36.42, O36.43, O36.49, Z37.1, Z37.3-Z37.4, Z37.6-Z37.7x
Non-viable pregnancy	630, 631, 633	O00.x, O01.x, O02.0, O02.8 - O02.9
Spontaneous abortion (miscarriage)	632, 634.x	O02.1, O03.x
Medical abortion	635.x	O04.x
Other abortion	636.x, 637.x	O05.x
Failed attempted abortion	638	O07.x
Continuing pregnancy after abortion or intrauterine death of one fetus or more		O31.1, O31.2
Antenatal screening & abnormal findings†	V26.3, V28.0-V28.2, V28.8-V28.9, V83-V84.x	O28.x, Z36.x, Z31.5

* Four digit ICD-9 codes are only available on the hospital file; physician file has only three digit diagnoses. Therefore, on the physician file, four digit codes were grouped (e.g., ICD-9 758.0 and 758.2 into 'all other chromosomal anomalies'; 761.8 and 779.6 into 'perinatal conditions'; 656.4 into 'all other pregnancy/childbirth complications'). † ICD-9 codes - flag that screening was done; ICD-10-CA codes - flag for abnormal findings..

Table 3.4 Hospital procedure codes and fee-for-service physician billing codes

Category	CCP	CCI	FSC
Women			
Stillbirth			241P
Spontaneous abortion			350P
Ectopic gestation removal	81.21, 86.3	5.CA.93.^^	48P, 248P
Medical abortion	86.4x, 87-87.2x	5.CA.88.^^, 5.CA.89.^^, 5.CA.90.^^	50P, 250P
Surgical repair of Fetus	87.56	5.FG-5.FM.^^	n/a
Amniocentesis	87.3	5.AB.02.^^	57P, 58P, 59P, 44W
Other diagnostic procedures related to pregnancy			40W, 47W, 48W, 41W, 45W, 46W, 446W, 50W
Women and infants			
Genetic assessment	n/a	n/a	5G, 7G, 9G, 11G, 13G, 38G, 39G, 40G, 50G

3.3.1 Identifying terminations of pregnancy for fetal anomaly (TOPFA)

Once data linkage was complete and the Maternal-Fetal-Infant database constructed, a new variable was created that captures terminations of pregnancy following a CA diagnosis (TOPFA). Identification of TOPFA cases was done by matching abortion status against amniocentesis testing and maternal serum screening, along with ICD codes on the hospital record. That is, TOPFAs were classified in situations where the mother either had MSS testing or amniocentesis prior to a medical abortion, to differentiate elective abortions from those done in response to a definite or probable diagnosis. The rationale is that women who have elective abortions would rarely, if ever, investigate their pregnancy for CAs. Due to the fact that medical abortions sometimes resulted in live or stillbirths, a more qualitative line-by-line review of the data was completed to look at all information available on each pregnancy.

Of the 94 pregnancies terminated following a CA diagnosis during the 6-year study period: 25 had medical abortion codes and an accompanying stillbirth record; 56 had medical abortion codes; ten had medical abortion codes and an accompanying live birth record; two were live births with a termination of fetus/newborn code; and two had multiple abortion codes (including spontaneous abortion codes on the hospital file and medical and other abortion codes on the physician file; both had amniocentesis tests). It is important to note that a fetus terminated by means of a medical abortion can meet the definition of a stillbirth or live birth under the Vital

Statistics Registration Act.[20] In the case of administrative datasets, the mothers will have a code for a medical abortion and there will also be a stillbirth or live birth record for the infant. Any abortion that results in a fetus that breaths or has a heartbeat, or where the abortion takes places at 20 weeks or when the fetus weighs 500 grams or more, must be registered as a birth under the Saskatchewan Vital Statistics Registration Act. Out of the 94 pregnancies resulting in a TOPFA, eight had termination of pregnancy, fetus, and newborn codes (P96.4 or 779.6). In all of the TOPFA cases the medical abortion code was the most responsible diagnosis at discharge (ie. not secondary, pre-admit comorbidity, post-admit comorbidity or optional).

3.3.2 Identification of congenital anomaly diagnosis using hospital and physician data

The current study drew from multiple data sources in order to best capture all CAs diagnosed in the pregnancy population. Because Saskatchewan does not have a provincial CA surveillance system, the administrative health databases were necessary for CA identification. Congenital anomaly diagnoses are mandatory codes that are entered into the hospital services file for inpatient hospitalizations (including following deliveries on the newborn's record) and day surgeries using standardized, international classification systems including the International Classification of Diseases 9th and 10th versions (Canadian). The Saskatchewan Medical Services files capture information about each patient visit to a physician`s office where one fee-for-service code and one ICD-9 diagnostic code is captured.[21] Bringing together information from multiple data sources enabled more complete case ascertainment, much like CA surveillance systems rely on the same, varied sources of information. Table 3.5 presents the results of a kappa analysis. Perfect agreement is not expected, nor desirable, given that physician services data was used in hopes of enhancing case ascertainment. Interpretation of the kappa values is as follows: poor (<0.20), fair (0.21 – 0.40), moderate (0.41 – 0.60), good (0.61 – 0.80), and very good (0.81 – 1.00).(160) All values were significant at the $p<.05$ level. The highest level of agreement can be seen between hospital and physician data for anencephalus/ encephalocele and circulatory system defects, where agreement was very good and good. Kappa values for spina bifida and congenital malformations of the genital organs demonstrate moderate agreement. Fair agreement was found for CAs involving the nervous system, chromosomal anomalies and other anomalies.

[20]See footnote 14 and 15 for the definition of live and stillbirths in the province of Saskatchewan.
[21] Visits to salaried physicians and those on alternate payment schemes who do not shadow bill are not captured in the data.

It is worth acknowledging that kappa is an imperfect measure due to its reliance on the prevalence of cases in each category.(160) Nonetheless, it is commonly used and seems to be the most appropriate approach for judging agreement. There were diagnoses where agreement could not be assessed (ie. Down syndrome). The coding of Down syndrome in physician records is such that cases could not be separated out from other chromosomal anomalies.[22] In the case of anencephalus, the condition is highly fatal and one would not expect cases to be seen in the community. In total, 3975 instances of CA were diagnosed in the physician data that would not have been picked up using hospital data alone; this represents 41.5% of total CAs identified in the study population.

Table 3.5 Total CA diagnosed in hospital separation and physician billing data, agreement between data sources, Saskatchewan, 2000-2005

CA type	Cases diagnosed in hospital data	Cases diagnosed in physician data	Additional cases diagnosed in physician data	Total cases	Kappa	P-value
Down syndrome	97	**	0	97	-	
Spina bifida	24	63	45	69	.414	.000
Anencephalus / encephalocele	10	**	1	11	.991	.000
Trisomy 18	9	**	0	9	-	
Circulatory	1400	1611	624	2024	.648	.000
Genital	537	538	294	831	.450	.000
Nervous	221	230	169	390	.268	.000
Chromosomal	62	165	132	194	.290	.000
Other	3248	4158	2710	5958	.358	.000
Total	5608	6766	3975	9583		

** Figures suppressed < 5

3.4 Canadian Institute for Health Information (CIHI) aggregate data request

Two codes are available in the ICD-9 and ICD-10-CA system that help to identify a TOPFA. These include: ICD-9 code 655 (known or suspected fetal abnormality affecting management of mother) and ICD-10-CA code 035 (maternal care for known or suspected fetal abnormality and damage). When one of these codes is coupled with a code for a medical

[22]In the medical services data, diagnoses are reported using only three digit (as opposed to four digit, as in the hospital file) ICD-9 codes. Therefore, on the physician file, this resulted in conditions such as encephalocele code 742.0 being grouped in "all other anomalies of the nervous system" (rather than with anencephalus) and Trisomy 21 (Down Syndrome) code 758.0 and Trisomy 18 code 758.2 being grouped into "all other chromosomal anomalies".

abortion a TOPFA is detected. The dataset for the current study did not contain the O35/655 codes, which is a noted limitation[23]. In an effort to address this information gap, and to validate the study dataset, a request for aggregate data from CIHI's data holdings was made (Appendix B). The request included all O35/655 codes co-occurring in the same episode as a medical abortion performed as an inpatient or day surgery admission, between 2000-2010, for all Saskatchewan residents cared for in any Canadian hospital. Data were drawn from the Discharge Abstract Database/ Hospital Morbidity Database (hospital inpatient) and the National Ambulatory Care Reporting System (day surgery). Gestational age of the fetus at the time of abortion was reported according to the following groupings: <11 weeks, 12-14 weeks, 15-19 weeks, and 20 weeks or more. If several abstracts for one patient met the selection criteria and occurred within 28 days, only the first one was retained to avoid counting the same termination of pregnancy multiple times.

3.5 Software

Both SPSS (version 17.0 and 21.0) and SAS (Enterprise Guide 4.1) were used for statistical data analysis. Microsoft Excel (2007) was used to create tables and figures.

3.6 Data analysis

3.6.1 Descriptive analysis

Descriptive analysis covered three general topic areas: (1) sample characteristics and pregnancy outcomes; (2) program performance indicators, (3) uptake of MSS and prenatal diagnostic testing; and (4) fetal and infant mortality rates. Examination of program-level indicators is useful to our understanding about the cause-and-effect relationship between prenatal screening/diagnosis and population outcomes. Most measures were further broken down according to urban/rural region, mother's age group, and Registered Indian status in order to further explore the contribution of these factors to the diagnostic pathway. Documenting the pathway between prenatal screening, follow-up prenatal diagnosis, and pregnancy termination for CA is an important component to establishing a link between the MSS program and birth outcomes. Figure 3.1 illustrates the prenatal screening-diagnosis pathway when using the triple marker screen. Table 3.7 below outlines the indicators of interest for each area of inquiry.

[23] During the initial request these codes were grouped into a 'pregnancy/childbirth complication' category in error. A request was made to the Ministry of Health to have these codes separated out, but it was denied.

Figure 3.1 Prenatal screening-diagnosis pathway

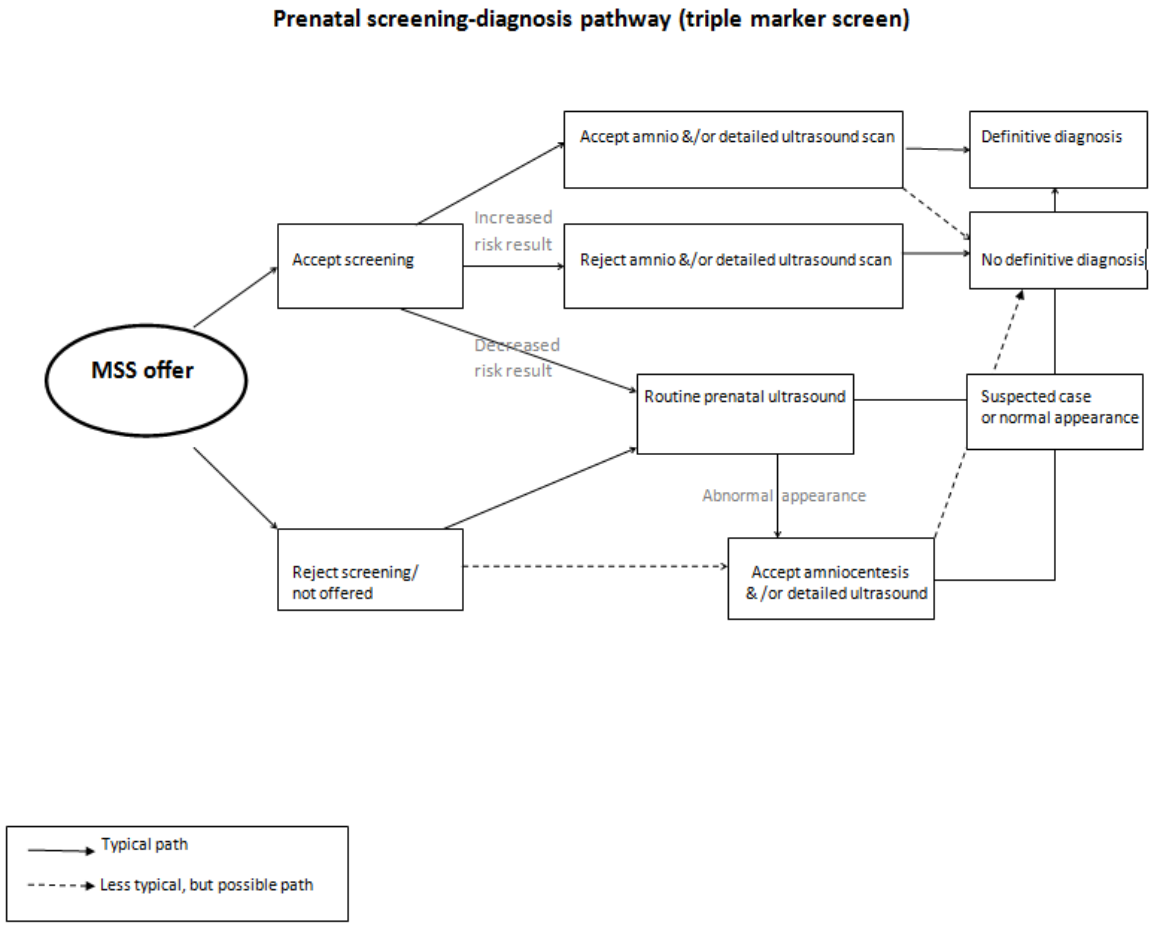


Table 3.6. Areas of analysis and related indicators

Program Performance	MSS and Amniocentesis Uptake	Population Outcomes
Detection rate (by screen category*) False-positive rate (by screen category*) Positive and negative predictive value (by screen category*) % dated via ultrasound Amniocentesis uptake CAs diagnosed by amniocentesis Pregnancy loss rate associated with amniocentesis % of pregnancies diagnosed with a fetal anomaly terminated	% utilization by geography, year of test, age group, and Registered Indian Status.	CA live birth prevalence CA total birth prevalence CA incidence Crude IMR CA-specific IMR Regular stillbirth rate Spontaneous stillbirth rate CA-specific neonatal mortality rate

* Down syndrome, Trisomy 18, neural tube defect

When studying CAs, prevalence has often been used as the measure of disease frequency instead of incidence.(5) This is largely because of the significant number of CA cases that go undetected due to early pregnancy loss, and in many jurisdictions, termination of CA-affected pregnancies. Case ascertainment in the current study is the highest that could be expected in a population-based study utilizing administrative health data, but information on the CA-status of spontaneous and elective abortions are still unknown. As described earlier (Chapter 2), there are three commonly used ways to calculate birth prevalence – live births only ("live birth prevalence"), live and stillbirths ("total birth prevalence"), or live and stillbirths and terminations of pregnancy for fetal anomaly ("birth incidence"). Despite the fact that some CA cases will be missed due to early pregnancy loss, the term "birth incidence" will be used over birth prevalence when describing results to denote the more complete inclusion of all possible known CA cases. Even with most diseases in children or adults, we often use the term incidence to describe all new cases in a given time period, recognizing that a certain percentage of cases always go undetected. Individuals may have more than one CA, therefore when calculating overall CA incidence and death due to CA, infants and fetuses with multiple CAs will be counted as one. However, when calculating the prevalence of specific CA types, infants with multiple CAs will be counted for each type of CA they are affected by.

3.6.2 Binary logistic regression analysis

3.6.2.1 Covariate identification for multivariate analysis

Bivariate analysis was used to determine which variables to include in the multivariate models. According to the standard approach, any variable with a p-value equal to or less than 0.25 would be included in multivariable analysis. Pearson’s chi-square test was used. Outcome variables were dichotomous – 'presence or absence of MSS testing' and 'amniocentesis performed - yes or no'. It is important to note that findings cannot account for the effects of age and other relevant factors, hence they were simply correlated with the outcomes and cannot indicate causal relationships. Bivariate analysis was only used for selecting statistically significant variables to be included in model building and multivariate analysis.

3.6.2.2 Model building strategy

Hosmer and Lemeshow's model building strategy was used to explore predictors of MSS uptake and amniocentesis testing.(161) In order to fit a best model for each, backward stepwise elimination was carried out manually using the 'enter' method. First, all relevant independent variables were entered into the model. These included factors that were significant ($p<.25$) in bivariate analysis and other biologically or clinically important factors. After fitting a model with all significant covariates, variables that were removed earlier from the model were re-entered to ensure they did not add to the model. The result was a main effects model where significant ($p<.05$) predictors remained. Next, all possible interaction terms were entered into the model one-at-a-time. The interaction terms were retained if the Wald statistic was significant at the $p<.05$ level. Confounding was assessed by comparing the ß values of important predictors in the reduced main effects model to those in a model including the potential confounder. A change greater than 20% in ß values between models was an indication of confounding, and hence the confounder would be retained in the model. Once the final model was constructed, it was assessed for goodness of fit using the likelihood ratio test.(162) Discriminative performance was assessed using the concordance (or c) statistic, which equals the area under the receiver operating characteristic (ROC) curve in the case of dichotomous outcomes.(163, 164) The c-statistic ranges from zero to one, with a value of one representing perfect prediction and a value of 0.5 representing chance prediction. A value between 0.7 and 0.8 is thought to demonstrate acceptable predictive performance. The Brier score was used to indicate overall model performance or calibration. Scores range from zero to one, with a lower score indicating less prediction error.(165) A value less than 0.25 represents an acceptable prediction error.

Pregnancies resulting in a live or stillbirth or those that were terminated for fetal anomaly (TOPFA) were included in a binary regression analysis to explore predictors of MSS uptake and prenatal diagnostic testing, while elective medical or spontaneous abortions were excluded. Spontaneous and medical abortions were excluded from this portion of the analysis due to the very low rate of uptake in pregnancies with such outcomes. The rationale for omitting these outcomes is based on the assumption that women with unwanted pregnancies are very unlikely to screen (figure 4.4) and therefore would create bias in the sample and a confounding effect that would complicate interpretation. Spontaneous abortions, by definition, occur early and testing is not offered until 15 weeks. It would have been ideal to include those spontaneous abortions that

qualified for screening (15-19 weeks), but information on gestational age for abortions was not available. Similarly, elective medical abortions are typically performed because a baby is not wanted (regardless of their CA status), therefore it stands to reason that very few of these women would want to know more about the fetuses' health. Due to the fact that month of pregnancy was not reported in the study dataset and MSS screening data was incomplete for 2001 and 2005, only a subset of pregnancies could be used for the current analysis (2002-2004). Nevertheless, a total of 35,527 pregnancies remained for analysis.

3.6.3 Infant mortality analysis

Analysis of infant deaths during the first year of life was undertaken to better understand the connection between the provincial MSS program, selective abortions and congenital anomaly trends in live born infants and as a cause of infant deaths. Cause of death information was obtained from the Vital Statistics death registration data. The Vital Statistics database includes all deaths that occur in Saskatchewan and deaths of Saskatchewan residents that occur in Alberta. If the death occurred in Alberta, the record reported the underlying cause of death only (i.e., multiple causes of death are not identified). The database also includes a file derived from reciprocal billing hospital separation records, which reports fact and date of death for deaths of Saskatchewan Health beneficiaries occurring in hospitals outside Saskatchewan and Alberta. The reasons for infant deaths were analyzed according to underlying (or primary) cause, as well as multiple (or contributing) causes. The World Health Organization defines underlying cause of death as "the disease or injury which initiated the train of events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury."(166 p.763) Information on other diseases or conditions leading to death are also important. On the Vital Statistics death registration file, up to 20 multiple causes may be reported for each case. Multiple causes are ". . .all those diseases, morbid conditions or injuries which either resulted in or contributed to death and the circumstances of the accident or violence which produced any such injuries.(166 p.763) For the current research, cause of death information was grouped according to the study's diagnostic categories, including CA (by type), conditions arising in the perinatal period, and 'other'. Perinatal conditions include complications of the placenta or umbilical cord, intrauterine hypoxia, and birth asphyxia. Conditions such as respiratory distress syndrome, SIDS,

infectious disease, cancer and unintentional and intentional injuries are captured in the 'other' category.

3.6.4 Assessing trends

Trends in both CA prevalence and incidence and infant and fetal mortality (figure 3.2) were assessed in a primarily descriptive manner, paired with the average annual percent change and chi-square test for trend. The average annual percent change allows one to see if the rate is increasing or decreasing and the magnitude of the change. The formula for average annual percent change is:

$$\frac{\left(\sum_{i=2}^{n} \frac{\text{Rate}_{\text{Year i}}}{\text{Rate}_{\text{Year i-1}}} - 1\right) \times 100}{n-1}$$

where n is the total number of years
Year 1 is the first year
Year n is the final year

In order to test for statistically significant trends, the chi-square test for trend was calculated using Epi Info™ (version 7.1.2). When working with rare events, and hence small numbers, the direction and size of differences (and their associated clinical and public health significance) may be viewed as important independent from their statistical significance.

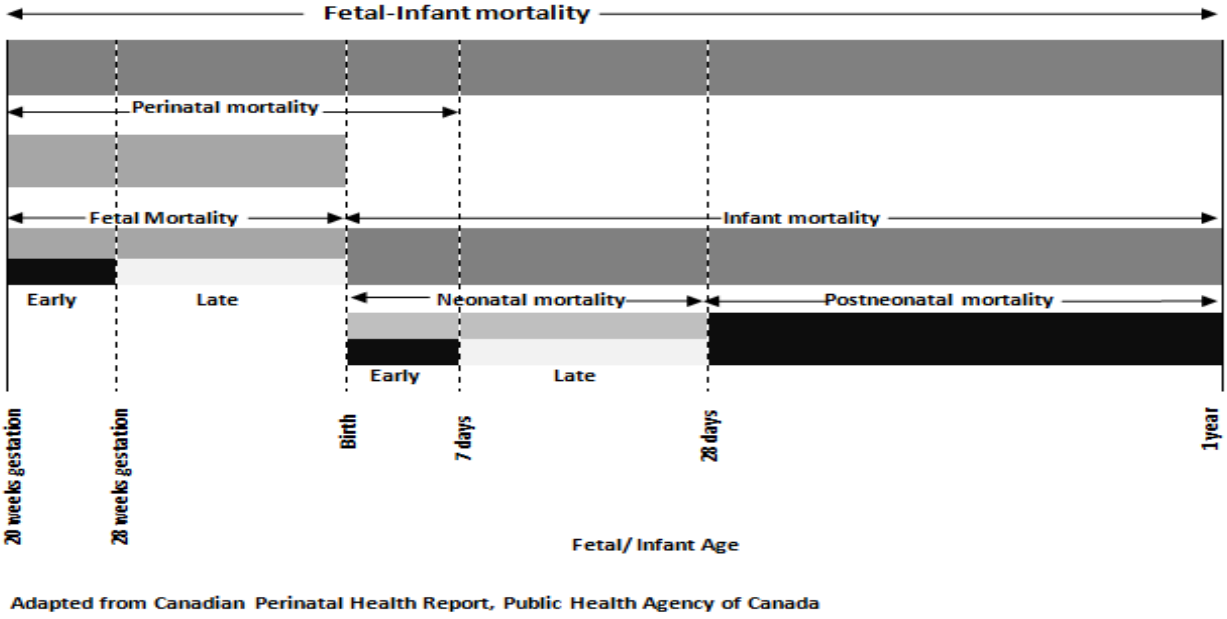
3.6.5 Tests of difference

To assess the statistical significance of a change in rate or of the difference between two rates (eg. between two population subgroups), the standard error of the difference between the two rates was calculated.(167)

$$\sqrt{\frac{p_1 q_1}{n_1} + \frac{p_2 q_2}{n_2}}$$

where p1 and p2 are the two rates to be compared (expressed as proportions) and q is 1-p.

Figure 3.2 Components of fetal-infant mortality (115)



Adapted from Canadian Perinatal Health Report, Public Health Agency of Canada

3.7 Study Ethics Approval

Formal ethics approval for this research was obtained from the Behavioural Research Ethics Board at the University of Saskatchewan (REB#B05-189) (Appendix C). The Data Access Review Committee (DARC) at the Ministry of Health reviewed the data request for issues related to confidentiality and privacy; approval was received April 2007. Operational approval was received from the Saskatoon Health Region for the use of cytogenetic laboratory data. All data was compiled by the staff at the Epidemiology and Research Unit at the Ministry of Health and subsequently de-identified such that the variables released for analyses off-site would not reasonably be expected to enable the identification of users or service providers.

CHAPTER 4: RESULTS

4.1 Descriptive Analysis

4.1.1 Characteristics of pregnancies in study population

A total of 93,171 pregnancy events were captured during the study period, involving more than 94,165 fetuses and infants.[24] Women may have been included in the study more than once, but multiple pregnancies were not linked, in order to better protect confidentiality. Using a variable that identified the number of times each woman was included in the study, it could be seen that there were 61,060 unique women: 37,308 (61.1%) women had one pregnancy included in the study; 17,154 (28.1%) had two; 5125 (8.4%) had three; and 1473 (2.4%) had four or more pregnancies included in the study.

Characteristics of the study population are presented in table 4.1. The majority of women were 34 years or younger (88.9%), however given the large study population, there were still 10,343 women aged 35 and over (11.1%). In terms of geographic location, women were spread across the province with 20.0% living in southern health regions (Cypress, Five Hills, Heartland, Sun Country, and Sunrise); 23.8% in Regina Qu'Appelle; 27.5% in Saskatoon; and 26.6% in northern health regions (Athabasca, Keewatin Yatthe, Kelsey Trail, Mamawetan, Prairie North, and Prince Albert Parkland). An estimated 21.7% of all pregnancies occurred in women of Registered Indian status.

The geographic distribution of births was slightly higher in the north (27.5%) and lower in the south (20.5%), which is consistent with the higher fertility rate in Aboriginal women and a somewhat older population in the south. A different geographic dispersal was seen for medical abortions, with almost two-thirds (63.7%) being performed on women who lived in the Saskatoon or Regina Qu'Appelle health regions. The proportion of elective medical abortions in First Nations[25] women was slightly lower than the overall proportion of pregnancies in this population (19.6% v. 21.7%, respectively; p=0.0001). Looking at cases of medical abortion where a fetal anomaly was diagnosed (TOPFA), few (12.8%) involved mothers of Registered Indian status.

[24] Information on plurality was only available for births not spontaneous or medical abortions, therefore this figure is an underestimate.

[25] The term First Nations will be used interchangeably with the term Registered Indian, recognizing that while all Registered Indian women are First Nations women, not all First Nations women are identified as such in this study (eg. Métis, Inuit).

Table 4.1 Demographic characteristics, by pregnancy outcome, Saskatchewan, 2000-2005 (n= 93,171)

n (%)	All pregnancies n=93,171	Live or Stillbirths n=70454	Medical abortions n=11,295	Spontaneous / other abortions n= 11,328	Termination of pregnancy for fetal anomaly n=94
Health Region of residence					
Southern regions	18648 (20.0)	14465 (20.5)	1843 (16.3)	2324 (20.5)	16 (17.0)
Regina Qu'Appelle	22150 (23.8)	15712 (22.3)	3668 (32.5)	2759 (24.4)	11 (11.7)
Saskatoon	25607 (27.5)	18964 (26.9)	3528 (31.2)	3097 (27.3)	18 (19.1)
Northern	24799(26.6)	19401 (27.5)	2251 (19.9)	3134 (27.7)	13 (13.8)
Regina Qu'Appelle & Saskatoon [†]	838 (0.9)	819 (1.2)	-	-	19 (20.2)
All rural regions [†]	868 (0.9)	851 (1.2)	-	-	17 (18.1)
Unknown/ suppressed [†]	261 (0.3)	242 (0.3)	5 (0)	14 (0.1)	-
Registered Indian Status of mother					
Yes	20197 (21.7)	15611 (22.2)	2218 (19.6)	2356 (20.8)	12 (12.8)
No	72974 (78.3)	54843 (77.8)	9077 (80.4)	8972 (79.2)	82 (87.2)
Age group of mother					
Under 25 years	35554 (38.2)	24924 (35.4)	6865 (60.8)	3747 (33.1)	18 (19.1)
25-29 years	27960 (30.0)	22511 (32.0)	2358 (20.9)	3063 (27.0)	28 (29.8)
30-34 years	19314 (20.7)	15717 (22.3)	1150 (10.2)	2424 (21.4)	23 (24.5)
35 years and over	10343 (11.1)	7302 (10.4)	922 (8.2)	2094 (18.5)	25 (26.6)

[†] For stillbirth events or where the baby died during the first year of life and for multiple pregnancies, RHAs were grouped more broadly; the two urban health regions (Regina Qu'Appelle and Saskatoon) were grouped into one and all other, rural regions into a second. Health region of residence was also suppressed for infants born with anencephalus/encephalocele, Down syndrome, trisomy 18 or spina bifida and for triplet pregnancies; these were grouped into the unknown category. Year of birth was suppressed for multiple pregnancies and where one or more baby had a diagnosis of anencephalus/encephalocele, Down syndrome, trisomy 18 or spina bifida and triplet pregnancies.

Table 4.2 enables a closer look at the distribution of pregnancy outcomes according to mother's age. More pregnancies in women aged 25-34 resulted in a birth than those in women who were younger or older. The proportion of medical abortions was highest in the 24 years and under age group with 19.3% of all identified pregnancies ended in this way, accounting for 60.8% of all abortions provincially during this time period. Medical abortion was least frequently seen in the 30-34 age group (6.0%). The reverse was true for TOPFAs, where the rate increased steadily with age. Medical abortion after a CA diagnosis was more common amongst the oldest age group (35 years and above), double the rate seen for women aged 30-34 (0.24% vs. 0.12%,

respectively). Spontaneous abortions were also twice as common in women aged 35 and over as compared to the youngest group (20.2% vs. 10.5%, respectively).

Differences across health regions and geographic groupings are of interest in so far as they suggest variations in access to health services, the health of the population, and potentially, value systems. A slightly higher percentage of pregnancies in the southern and northern regions of the province resulted in a birth than those in the urban regions. A contributing factor was the higher rate of elective medical abortions near cities. The percent of pregnancies in the rural north or south that ended by medical abortion was lower (9.1% and 9.9%, respectively) than women living in Saskatoon (13.8%) or Regina (16.6%). Rates of spontaneous abortions were similar across the regions. The higher rate of TOPFA in the 'Regina Qu'Appelle and Saskatoon' health regions (combined) and 'all rural regions' categories is due to the fact that, to protect confidentiality, the Ministry of Health suppressed the mother's health region of residence for twin or triplet pregnancies and those where a diagnosis of Down Syndrome, Edward's Syndrome, or neural tube defect was made.

Spontaneous and elective medical abortions were slightly less common in First Nations women when compared to the rest of the population, but there was not an appreciable difference. While TOPFAs were relatively uncommon events, they were almost twice as common in non-RI women as in RI women (0.11% vs. 0.06%, respectively).

Table 4.2 Number and rate per 100 pregnancies, by pregnancy outcome, according to women's characteristics, Saskatchewan, 2000-2005 (n=93,171)

n (%)	All pregnancies	Live or Stillbirths	Medical abortions	Spontaneous /other abortions	Termination of pregnancy for fetal anomaly
Age group of mother					
24 years & under	35554	24924 (70.1)	6865 (19.3)	3747 (10.5)	18 (0.05)
25-29 years	27960	22511 (80.5)	2358 (8.4)	3063 (11.0)	28 (0.10)
30-34 years	19314	15717 (81.4)	1150 (6.0)	2424 (12.6)	23 (0.12)
35 years and over	10343	7302 (70.6)	922 (8.9)	2094 (20.2)	25 (0.24)
Health region of residence					
Southern regions	18648	14465 (77.6)	1843 (9.9)	2324 (12.5)	16 (0.09)
Regina Qu'Appelle	22150	15712 (70.9)	3668 (16.6)	2759 (12.5)	11 (0.05)
Saskatoon	25607	18964 (74.1)	3528 (13.8)	3097 (12.1)	18 (0.07)
Northern regions	24799	19401 (78.2)	2251 (9.1)	3134 (12.6)	13 (0.05)
RQHR/SHR	838	819 (97.7)			19 (2.3)
All rural regions	868	851 (98.0)			17 (2.0)
Suppressed	261	242 (92.7)	5 (1.9)	14 (5.4)	-
Registered Indian Status of mother					
Yes	20197	15611 (77.3)	2218 (11.0)	2356 (11.7)	12 (0.06)
No	72974	54843 (75.2)	9077 (12.4)	8972 (12.3)	82 (0.11)

4.1.2 Birth outcome trends

The number of women experiencing a pregnancy each year remained quite stable across the study period (mean = 15,528). Table 4.3 provides data on the frequency of pregnancy outcomes (stillbirths, live births, spontaneous abortions, medical abortions, other abortions, and termination of pregnancy for fetal anomaly) from 2000 - 2005. The number of live and stillbirths varied slightly from year-to-year, with no discernible trend. Terminations of pregnancy for reasons of a fetal anomaly increased from two cases in 2000 to 20 in 2005. Spontaneous abortions declined from 2001-2003, then increased in 2004-05 to levels similar to 2000. The proportion of pregnancies ended by medical abortion was similar across all years (mean=1882/ year).

4.3 Pregnancy outcomes, number and percent of fetuses/infants according to outcome, annual, Saskatchewan, 2000-2005 (n= 94,165)*

Year	Stillbirth	Live birth	TOPFA	Spontaneous abortion	Medical abortion	Other abortion	Total fetuses/ infants
2000	68 (0.43)	11939 (75.6)	2 (0.01)	1426 (9.0)	1878 (11.9)	487 (3.1)	15794
2001	77 (0.49)	12018 (76.3)	7 (0.04)	1342 (8.5)	1857 (11.8)	452 (2.9)	15755
2002	83 (0.54)	11610 (75.8)	19 (0.12)	1321 (8.6)	1812 (11.8)	476 (3.1)	15325
2003	67 (0.43)	11834 (75.7)	23 (0.15)	1339 (8.6)	1854 (11.9)	520 (3.3)	15642
2004	80 (0.50)	11844 (74.7)	24 (0.15)	1410 (8.9)	1952 (12.3)	539 (3.4)	15856
2005	68 (0.43)	11815 (74.8)	20 (0.13)	1478 (9.4)	1889 (12.0)	533 (3.4)	15793
Suppressed	**	0	0	0	0	0	0
Total	444 (0.47)	71060 (75.5)	95 (0.10)	8316 (8.8)	11243 (11.9)	3007 (3.2)	94165

*Data was only available on plurality (or number of infants per pregnancy) for births and not abortions. ** Figure suppressed < 5.

Figure 4.1 Live births and total pregnancies, Saskatchewan, 2000-2005

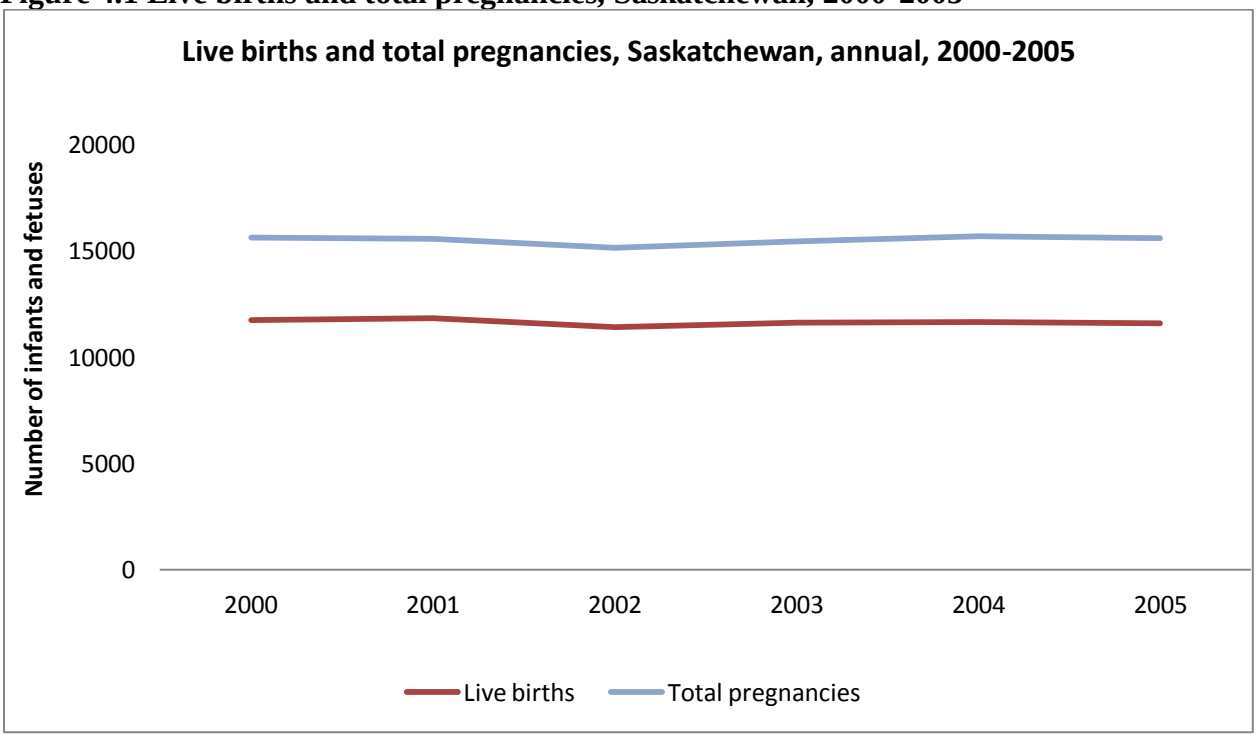
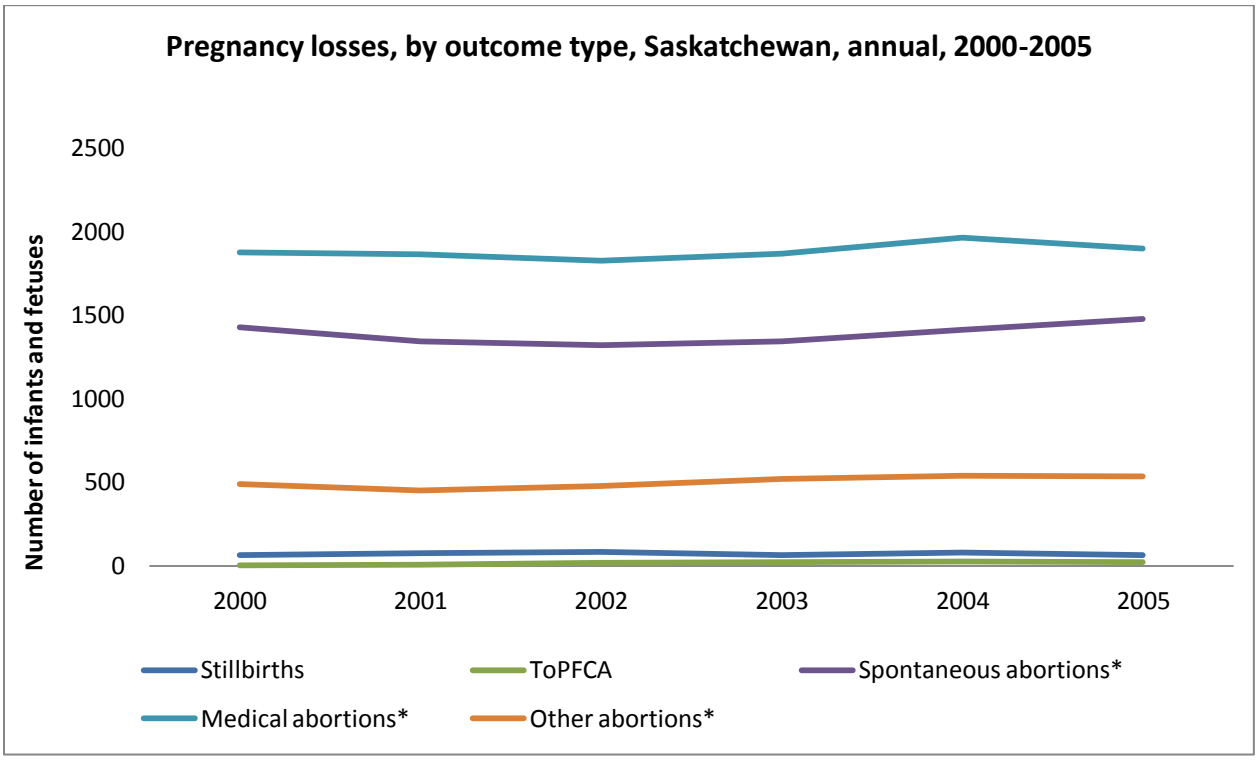


Figure 4.2 Pregnancy losses, Saskatchewan, 2000-2005



4.1.3 Characteristics of infants and fetuses in study population

Table 4.4 below provides information on the characteristics of both live and stillborn infants included in the study. Ideally, similar information would have been available for fetuses lost to spontaneous and medical abortion, however, data was not extracted from the 'Reproductive Abstract' portion of the DAD record and therefore information on gestational age, and plurality was not available. Of the 71,448 infants live born or stillborn, 48.9% of infants were female and 51.1% were male. Most were full-term (90.8%), singleton (94.5%) births. Birth weights were not normally distributed, with just 1.3% and 5.7% falling into the very low (<1500g) and low (<2500g) birth weight categories.

Table 4.4 Characteristics live or stillborn infants (n= 71448), Saskatchewan*

	Live or Stillbirths n (%)
Baby Sex	
Female	34971 (48.9)
Male	36476 (51.1)
Plurality	
Single	67534 (94.5)
Twins	1779 (2.5)
Triplets	84 (0.1)
Missing	2051 (2.9)
Gestational age at birth	
0-14 weeks	** (0.0)
15-20 weeks	28 (0.0)
21-27 weeks	435 (0.6)
28-33 weeks	1192 (1.7)
34-36 weeks	3609 (5.1)
37-41 weeks	63833 (89.3)
42 weeks+	1067 (1.5)
Missing	1283 (1.8)
Birth weight	
500 grams	125 (0.2)
500-999 grams	340 (0.5)
1000- 1499 grams	408 (0.6)
1500- 2499 grams	3175 (4.4)
2500- 3999 grams	55331 (77.4)
4000+ grams	11294 (15.8)
Missing	775 (1.1)

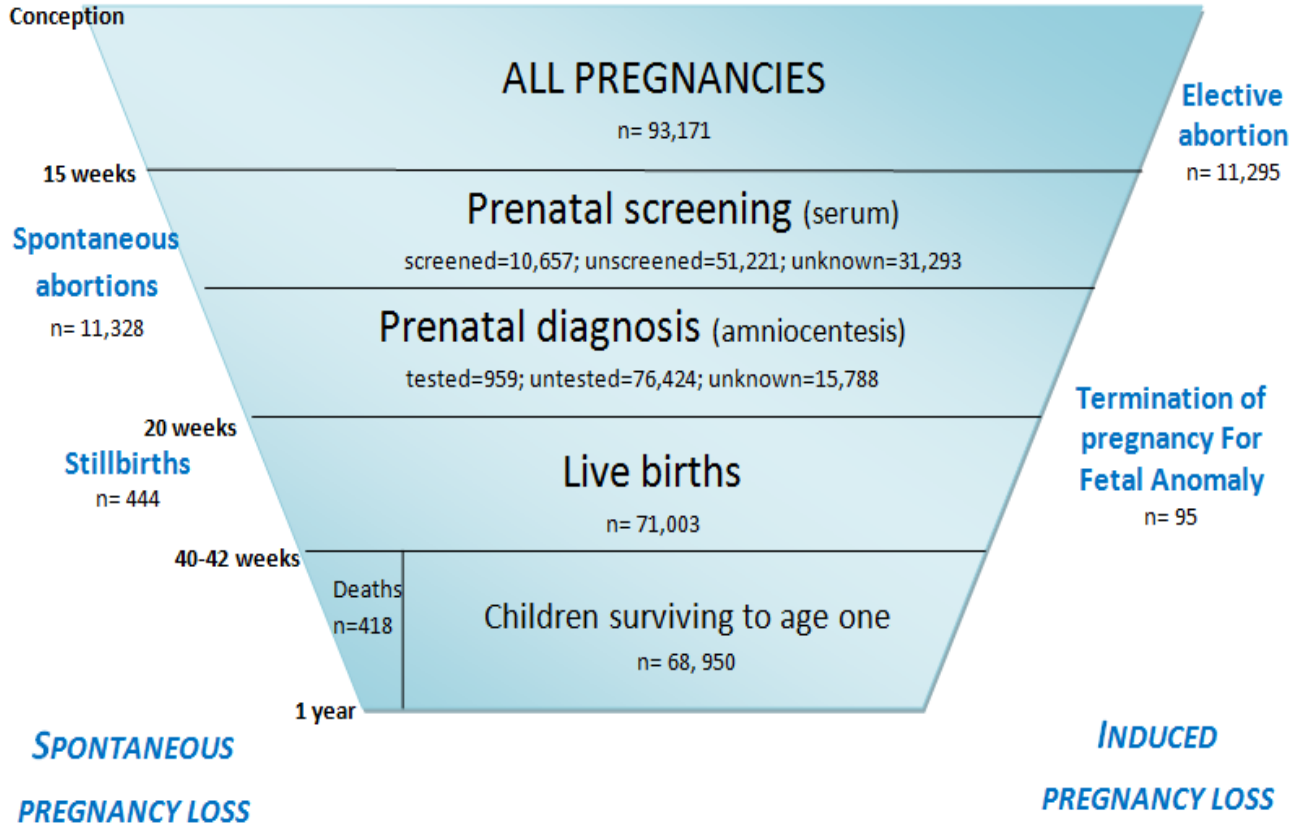
*Excludes TOPFA that were live born or stillborn
** Figure suppressed < 5

While Canadian statistics are showing significant trends towards delayed childbirth (37), the age distribution of Saskatchewan mothers who gave birth between the years 2000-2005 saw little change. The percent of mothers 30 years and over with a live birth increased from 31.4% in 2000 to 33.1% in 2005; all of the increase could be seen in the 30-34 age group. Nationally, this figure increased from 45.6% in 2000 to 48.9% in 2005, with increases in all age groups between 30-49 years.(114) The most recent estimate from Statistics Canada show this figure increased to 52.1% in 2011.

Figure 4.3 illustrates outcomes across the pregnancy continuum until one year of life, alongside the timing of prenatal screening options and diagnostic testing. In essence, a full cohort of pregnancies conceived will diminish in size due to a variety of natural and human initiated

factors that put fetuses at-risk of death. For the purposes of the study, loss-to-follow-up was shown too. From 2000-2005, there were 93,171 pregnancies identified (94,165 fetuses/ infants) through the Saskatchewan Ministry of Health's databases. Spontaneous abortions and stillbirths are two forms of unintended or natural pregnancy loss that affected 11,772 pregnancies (12.5%). Elective medical abortions and terminations of pregnancy for congenital anomaly ("intended pregnancy loss") collectively ended another 11,390 (12.1%). Three-quarters (75.4%) of all fetuses were born alive. Of these live births, 97.1% survived to one year of age, 0.6% died, and the outcome was unknown for the remaining 2.3% that were lost to follow-up.

Figure 4.3 Pregnancy continuum from conception to age one, by intervention status and outcome, 2000-2005 (pooled)



*Figures for live births, stillbirths, children surviving to one year, and ToPFA (where known) account for multiple fetuses, while other figures only count pregnancies. Information on plurality was only available for births. In total, there were 94,165 fetuses among 93,171 pregnancies.

4.1.4 Maternal Serum Screening Program

4.1.4.1 Test performance

Understanding the impact of the MSS program on commonly-used population health indicators is central to this research. As such, it is important to cultivate a better understanding of test performance and factors that predict uptake. Tables 4.5-4.7 below present the false positive, positive and negative predictive value, true positive, and detection rates for each of the three screenable conditions. All women in the study having a MSS test during the study period were included in these calculations. Uptake of MSS is explored in the section that follows.

A total of 9,791 pregnancies were screened for Down syndrome during this time period, of which, 745 had a result above cut-off. Of the 745 women screening-positive, 16 cases of Down syndrome were diagnosed. The false positive (type I error) rate was 7.5%. The detection rate was 69.6%, meaning that almost one out of every three cases of Down syndrome were missed during screening. Based on the positive predictive value, among women who received an increased risk result only 2.2% actually were carrying a fetus with Down syndrome. Based on the negative predictive value, among women who received a decreased risk result 99.9% did not have an affected fetus.

Table 4.5 Screening performance for Down Syndrome*

	Down syndrome diagnosed		False positive rate	Detection rate	Positive predictive value	Negative predictive value
Screening result	Yes	No	7.5%	69.6%	2.2%	99.9%
Negative	7	9039				
Positive	16	729				

* This crosstab excludes ~ 74 cases of abortion after the DS screen (10 positive and 64 negative screens) as these cases did not have outcome data. Of the 64 negative-screens, 44 were spontaneous abortions and 20 were medical abortions presumed to be TOPFAs. Of the 10 positive-screens, 8 were spontaneous abortions and 2 were medical abortions presumed to be TOPFAs. If we assumed that all TOPFA involved DS-affected fetuses, which is unlikely as 9 out of the 20 TOPFA cases screened positive for an NTD, the detection rate would be 37.2%, the negative predictive value would be 99.7%, and the false-positive rate and positive predictive value would remain unchanged.

There were 10,152 screening tests completed for the detection of neural tube defects. Of the 147 women screening at increased-risk, less than 5 cases were confirmed. Due to the missing information on NTD diagnoses, measures of test performance were not calculated. An apparently low detection rate would have been an artefact of the data, as many instances of NTD fetuses are lost before birth (whether by spontaneous abortion or termination), and could not be captured

due the absence of ultrasound diagnostic information and diagnostic coding of stillbirths (see Limitation section in Discussion Chapter for detailed discussion).

Table 4.6 Screening performance for Neural Tube Defect*

	Neural tube defect diagnosed		False positive rate	False negative rate	True positive rate	Detection rate
Screening result	Yes	No	-	-	-	-
Negative	12	9993				
Positive	**	144				

* The above data includes non-terminated pregnancies only. Cases of abortion were omitted (109 in total, of which 77 were negative and 32 were positive). Of the 77 screen-negative cases, 48 were spontaneous abortions and 29 were medical abortions presumed to be TOPFAs. Of the 32 screen-positive cases, 18 were spontaneous abortions and 14 were medical abortions presumed to be TOPFAs. ** Figure suppressed < 5.

There were 9,783 screening tests completed for the detection of trisomy 18. Of the 33 women receiving an increased risk result, less than 5 cases had documented diagnoses. Out of 6 cases of trisomy 18 diagnosed in the screening population, less than 5 cases were detected during screening resulting in a 66.7% detection rate. The false positive rate was very low (0.30%). Based on the positive predictive value, among women who received an increased risk result 12.1% actually were carrying a fetus with trisomy 18. Based on the negative predictive value, among women who received a decreased risk result 99.9% did not have an affected fetus.

Table 4.7 Screening performance for trisomy 18*

	Trisomy 18 diagnosed		False positive rate	Detection rate	Positive predictive value	Negative predictive value
Screening result	Yes	No	0.30%	66.7%	12.1%	99.9%
Negative	**	9748				
Positive	**	29				

*There were 54 cases of apparent abortions omitted because of lack of outcome data, of which 32 were negative and 22 were positive. Of the 32 negative, 22 were spontaneous abortions and 10 were medical abortions presumed to be TOPFA. Of the 22 positive screens, 19 were spontaneous abortions and another 3 were medical abortions presumed to be TOPFA. ** Figure suppressed < 5.

Accurate gestational dating is important to the accuracy of serum screening and can significantly lower the false-positive rate (168). Out of the 10, 657 women who had MSS during the study, 2501 (23.5%) had their pregnancy dated using ultrasound. Dating ultrasound is not available to all communities in Saskatchewan and may account for the lower rate.

4.1.4.2 Maternal serum screening uptake

Table 4.8 reports basic frequencies for study subjects who had MSS during their pregnancy. Screening spanned all age categories, but those in the 25-34 year group accounted for more than half of all screens (58.7%). A large percent of tests were drawn from women living in either Saskatoon or Regina Qu'Appelle health regions (62.2%) and the majority were not of Registered Indian status (91.3%). The annual volume of screens increased from 2001-2004. The MSS program was launched part way through 2001 (in May), only partly explaining the lower numbers for that year. The Maternal-Infant-Fetal dataset contained MSS data up to March 31st of 2005, therefore tests for the latter part of the year were not captured, explaining fewer tests that year (n=830). Sixty-three twin pregnancies had MSS, accounting for a very small portion of tested pregnancies (0.5%). Of the 10,657 women having MSS, 702 (6.6%) followed-up with an amniocentesis. The vast majority of screened pregnancies resulted in a live birth (98.1%).

Table 4.8 Demographic characteristics, women having MSS, Saskatchewan, 2001-2005 (n=10,657)

	MSS tested pregnancies
Mother's age group	
Under 25 years	2387 (22.4)
25-29 years	3353 (31.5)
30-34 years	2897 (27.2)
35 years and more	2020 (19.0)
Health region of residence	
Southern	2549 (23.9)
Regina Qu'Appelle	3481 (32.7)
Saskatoon	3040 (28.5)
Northern	1357 (12.7)
Regina Qu'Appelle/ Saskatoon	110 (1.0)
Rural regions	85 (0.8)
Registered Indian Status	
No	9730 (91.3)
Yes	927 (8.7)
Year of specimen collection	
2001	1126 (10.6)
2002	2548 (23.9)
2003	3034 (28.5)
2004	3065 (28.8)
2005	830 (7.8)
Missing	54 (0.5)

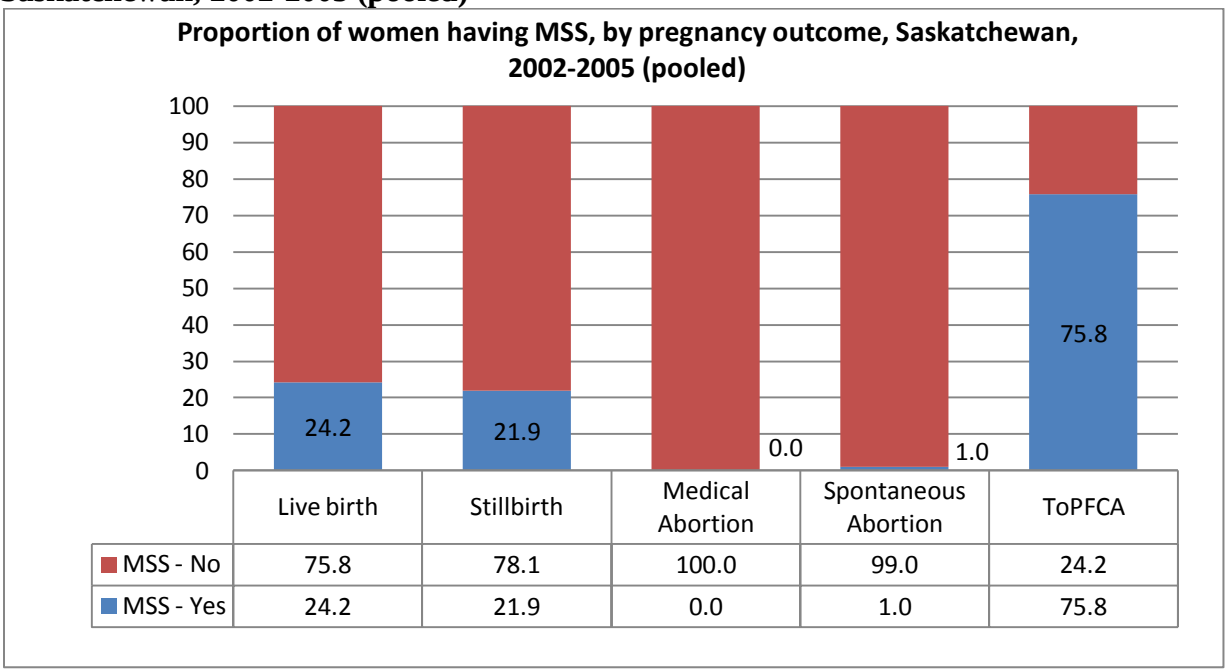
Year of birth or pregnancy loss	
2001	382 (3.6)
2002	2065 (19.4)
2003	3010 (28.2)
2004	3029 (28.4)
2005	2137 (20.1)
Missing	34 (0.3)
Plurality	
Single	10377 (97.4)
Twin	63 (0.5)
Multiple	** (0.0)
Missing	216 (2.0)
Amniocentesis completed	
Yes	702 (6.6)
No	9888 (92.8)
Missing	67 (0.6)
Pregnancy outcome	
Live birth	10455 (98.1)
Stillbirth	65 (0.6)
Spontaneous abortion	73 (0.7)
Medical abortion	** (0.0)
Termination of pregnancy for fetal anomaly	63 (0.6)

** Figure suppressed < 5.

The proportion of pregnancies having MSS testing varied according to pregnancy outcome. Only one pregnancy that ended in an elective medical abortion had MSS.[26] It was also very rare for pregnancies that ended by spontaneous abortion to have had MSS earlier in the pregnancy; an expected finding given that the triple test can only be offered between 15-18 weeks, at a time when many of these losses would have already occurred. Pregnancies that were aborted because of a known or suspected CA were most likely to have had MSS, with 67.0% (63/94) of TOPFA having had MSS. Serum screening is only but one step in the prenatal diagnostic continuum and it makes sense that most pregnancies where a fetus is diagnosed with an anomaly, then terminated, would have had MSS.

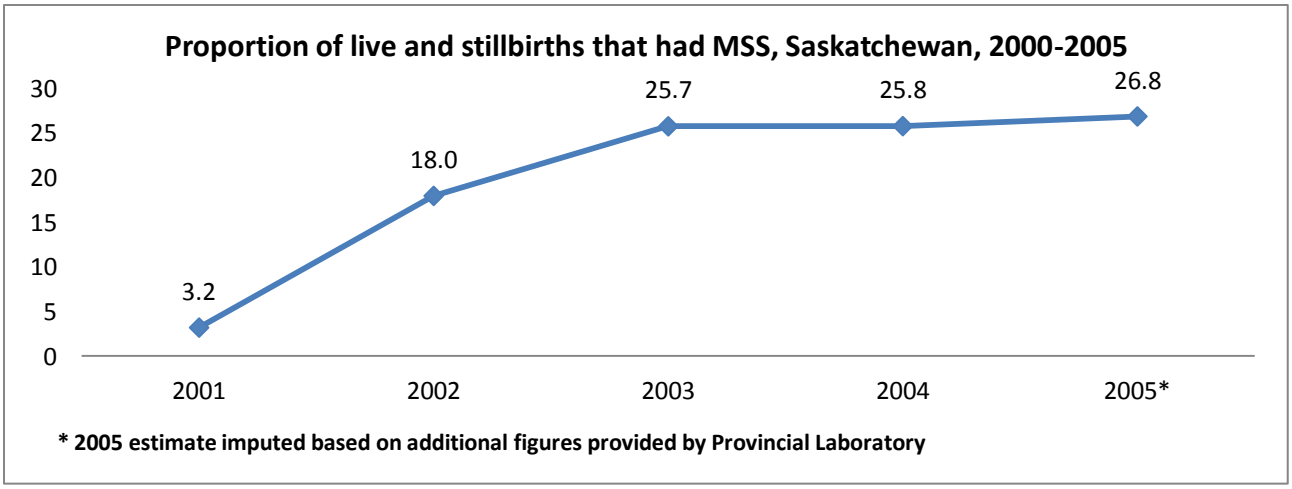
[26] The screening test was not processed as it was too early. There was no other codes indicating that diagnostic testing was performed or care codes suggesting investigation for anomalies. Hence the decision was not to designate as a TOPFA.

Figure 4.4 Proportion of women having MSS, by pregnancy outcome category, Saskatchewan, 2002-2005 (pooled)



Looking at MSS uptake over the study period, figure 4.5 shows the percent of live and stillbirths that had MSS each year. Utilization of this screening program increased substantially from 2001-2002, then leveled out in 2003-2005.

Figure 4.5 Proportion of live and stillbirths that had MSS, Saskatchewan, annual, 2000-2005*



***** The 2001 rate is low partly because MSS was not offered until May of that year. The data was not provided in a way that enabled me to determine which pregnancies would have been eligible (ie. which pregnancies were between 15-20 weeks at the time of program implementation).

4.1.5 Prenatal diagnostic testing

4.1.5.1 Descriptives

Cytogenetic laboratory data was obtained from the two tertiary hospitals in Saskatchewan where all samples, drawn for purposes of prenatal diagnostic testing, are sent. Data was available from January 1st 2001 - December 31st 2005 from Saskatoon's lab and from October 1st 2001 - December 31st 2005 from Regina's. In total, 959 pregnancies (1.0% of the study population) underwent prenatal diagnostic testing during this time. A large proportion of tests belonged to mothers living in the Saskatoon health region (41.2%), while fewer were performed on women from southern (15.2%) or northern (10.6%) health regions (see table 4.9). Most tests involved women aged 35 and over (68.6%) and women who were not of Registered Indian status (94.2%). The number of tests was lower in 2001 due to incomplete data from Regina's lab, but otherwise there was a slight decline in testing volume from 2002-2004. The lower testing number in 2005 is an artifact of data collection, since the study only captured pregnancies that resulted in an outcome in 2005, therefore pregnancies tested and that came to completion in 2006 were omitted. Most commonly amniocenteses were carried out between 15-20 weeks gestation (89.4%). The most common reasons given for testing were "advanced maternal age" (50.3%) or an abnormal MSS result (28.3%). As far as diagnosis, 91.0% of fetuses tested did not have a chromosomal anomaly. Another 7.4% had either Down syndrome, trisomy 18, or another chromosomal anomaly (detailed diagnoses not available). Testing was inconclusive or discontinued in 1.6% (16) of cases.

Table 4.9 Characteristics of women having prenatal diagnostic testing, Saskatchewan, 2001-2005 (n=959)

	n (%)
Age group:	
24 years and under	56 (5.8)
25-29 years	91 (9.5)
30-34 years	154 (16.1)
35 years and over	658 (68.6)
Health region of residence:	
Southern health regions	146 (15.2)
Regina Qu'Appelle health region	241 (25.1)
Saskatoon health region	395 (41.2)
Northern health regions	102 (10.6)
Unknown or broadly grouped	75 (7.8)

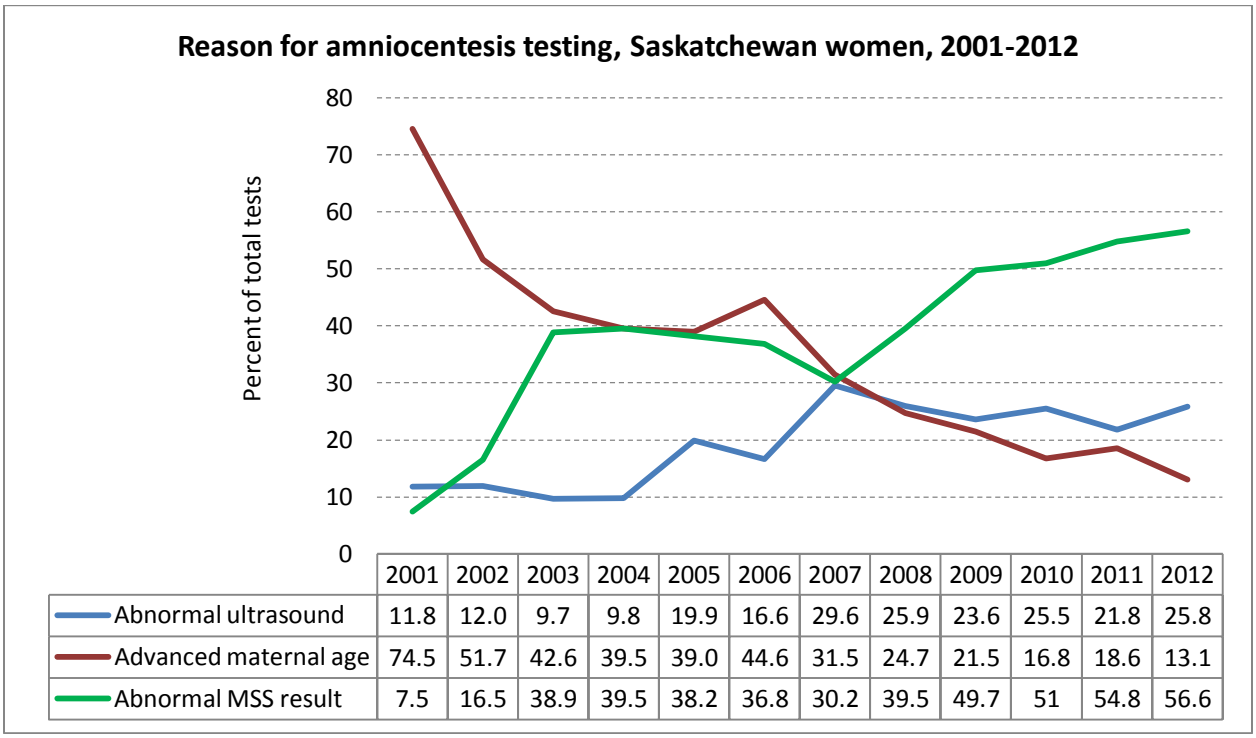
Registered Indian Status:	
No	921 (94.2%)
Yes	57 (5.8%)
Year of test*:	
2001*	159 (16.5)
2002	235 (24.5)
2003	215 (22.4)
2004	204 (21.3)
2005*	134 (14.0)
Missing	12 (1.3)
Parity:	
0	13 (1.4)
1	290 (30.2)
2	309 (32.2)
3	186 (19.4)
4 or more	118 (12.3)
Missing	43 (4.5)
Gestational age:	
12-14 weeks	** (0.3)
15-17 weeks	388 (61.6)
18-20 weeks	175 (27.8)
21-23 weeks	30 (4.8)
24-26 weeks	10 (1.6)
27-29 weeks	9 (1.4)
30-32 weeks	7 (1.1)
33 weeks and over	9 (1.4)
Missing	328
Reason for test:	
Abnormal ultrasound	118 (12.3)
Advanced maternal age	482 (50.3)
Abnormal MSS result	271 (28.3)
Risk of chromosomal anomaly	28 (2.9)
Fetal anomaly	23 (2.4)
Intrauterine fetal death	** (0.2)
Other or unspecified	32 (3.3)
Amniocentesis result:	
Trisomy 21	15 (1.6)
Trisomy 18	12 (1.3)
Other diagnosis	43 (4.5)
Normal	873 (91.0)
Inconclusive (eg. no growth, discontinued testing)	16 (1.6)

*2001 and 2005 figures for amniocentesis tests do not reflect all tests done in Saskatchewan for these years. Data from the RQHR lab went back to October 2001, which explains the lower overall number for that year. 2005 figures do not reflect tested pregnancies that did not result in an outcome during 2005, as our study was designed to capture abortions and births that occurred in 2005, not pregnancies.

4.1.5.2 Testing indication

Over the course of the study, the primary reason women chose amniocentesis shifted from "advanced maternal age" to abnormal MSS result. Test indication was documented by obstetricians and family physicians and included in the Cytogenetics lab file. In 2001, the year that the MSS program was launched in the province, 74.5% of tests were performed based on maternal age-associated risk and just 7.5% were due to an abnormal MSS result (figure 4.6). By 2005, advanced maternal age and abnormal MSS result accounted for an equal share of testing. Figure 4.7 supports this finding illustrating a notable drop in amniocentesis uptake in the oldest age group - from 79.5% of all tests involving mothers aged 35 and over in 2001 down to 63.2% in 2005. Women under age 29 accounted for an increasing proportion of amniocenteses over the study period (9.9% in 2001 and 20.6% in 2005). There was a slight increase in 2005 in the proportion of amniocenteses resulting from an abnormal ultrasound. The Cytogenetics Laboratory in Saskatoon was able to provide an update on amniocentesis testing in Saskatchewan, including the age of women being tested and the test indication. From 2006-2012, the proportion of testing done due to 'advanced maternal age' continued to fall (44.6% to 13.1%), while testing due to abnormal MSS results climbed (36.8% to 56.6%). Interesting to note is the increase in amniocenteses that are being performed as a result of abnormal findings during ultrasound. It does also appear that trends in low uptake of amniocentesis have continued as absolute numbers remained stable (mean=178), suggesting that the rate of TOPFA in Saskatchewan may be similar to the rate observed in the current study.

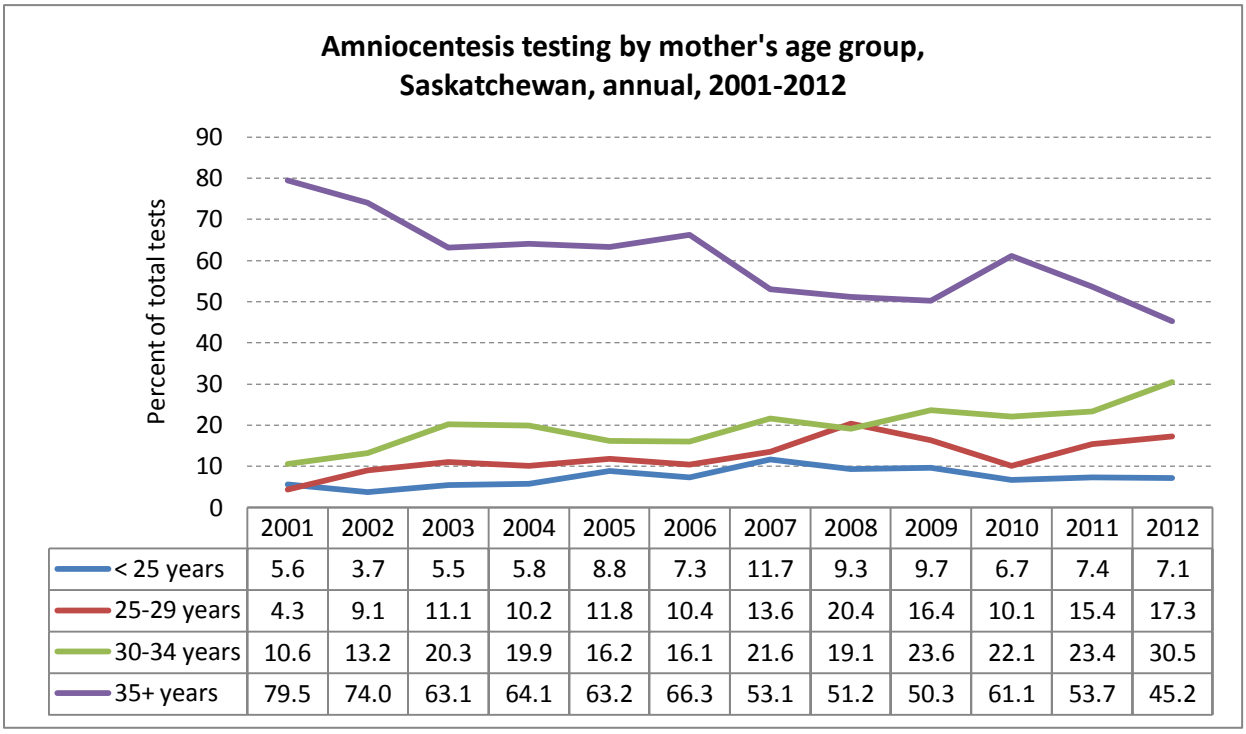
Figure 4.6 Main reason for amniocentesis, Saskatchewan, annual, 2001-2012*



	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Abnormal ultrasound	11.8	12.0	9.7	9.8	19.9	16.6	29.6	25.9	23.6	25.5	21.8	25.8
Advanced maternal age	74.5	51.7	42.6	39.5	39.0	44.6	31.5	24.7	21.5	16.8	18.6	13.1
Abnormal MSS result	7.5	16.5	38.9	39.5	38.2	36.8	30.2	39.5	49.7	51	54.8	56.6

* A data update for 2006-2012 was provided by the Cytogenetics laboratory, Saskatoon Health Region who now handles all testing in the province.

Figure 4.7 Proportion of amniocentesis by mother's age group, Saskatchewan, annual, 2001-2005



	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
< 25 years	5.6	3.7	5.5	5.8	8.8	7.3	11.7	9.3	9.7	6.7	7.4	7.1
25-29 years	4.3	9.1	11.1	10.2	11.8	10.4	13.6	20.4	16.4	10.1	15.4	17.3
30-34 years	10.6	13.2	20.3	19.9	16.2	16.1	21.6	19.1	23.6	22.1	23.4	30.5
35+ years	79.5	74.0	63.1	64.1	63.2	66.3	53.1	51.2	50.3	61.1	53.7	45.2

4.1.5.3 Use of maternal serum screening prior to testing

The expectation is that MSS results will facilitate women's decision-making about whether to follow-up with an invasive, diagnostic test, thereby reducing unnecessary risk to the fetus. Figure 4.8-4.9 show the uptake of prenatal diagnostic testing in women between the years 2002-2005 who had MSS and received an increased-risk result ("screen positive"), decreased-risk result ("screen negative"), or for cases where no result was generated.[27] Women who received a screen-positive result were much more likely than those who received a screen-negative or no result to follow-up with an amniocentesis (32.7%, 3.8%, and 8.3%, respectively). Table 4.10 breaks the information down further for each of the three screenable conditions, Down syndrome, NTD, and trisomy 18. Here it can be seen that 36.8% of women who screened-positive for DS opted for further testing, while 15.3% of women with a screen-positive for NTD and 32.7% of trisomy 18 did the same. Amniocentesis provides a definitive diagnosis for chromosomal anomalies and is a highly sensitive screening tool for NTD. Typically women who screen-positive for NTD are first offered high-resolution ultrasound, then amniocentesis, in order to obtain an amniotic AFP sample and acetyl cholinesterase measurements.(169,170) The amniotic fluid sample is then screened by the MSS program at the Provincial Laboratory to provide a risk estimate and is a highly accurate screen. Conversely, 1.3% of screen-negatives for DS opted for further testing, and 6.3% of NTD and 3.9% of trisomy 18 screen-negatives did the same.

[27] 2001 was excluded from analysis as amniocentesis data was missing from the Regina Cytogenetics Laboratory from January - September.

Figure 4.8 Amniocentesis testing by MSS uptake and screening result, all pregnancies, Saskatchewan, 2001-2004

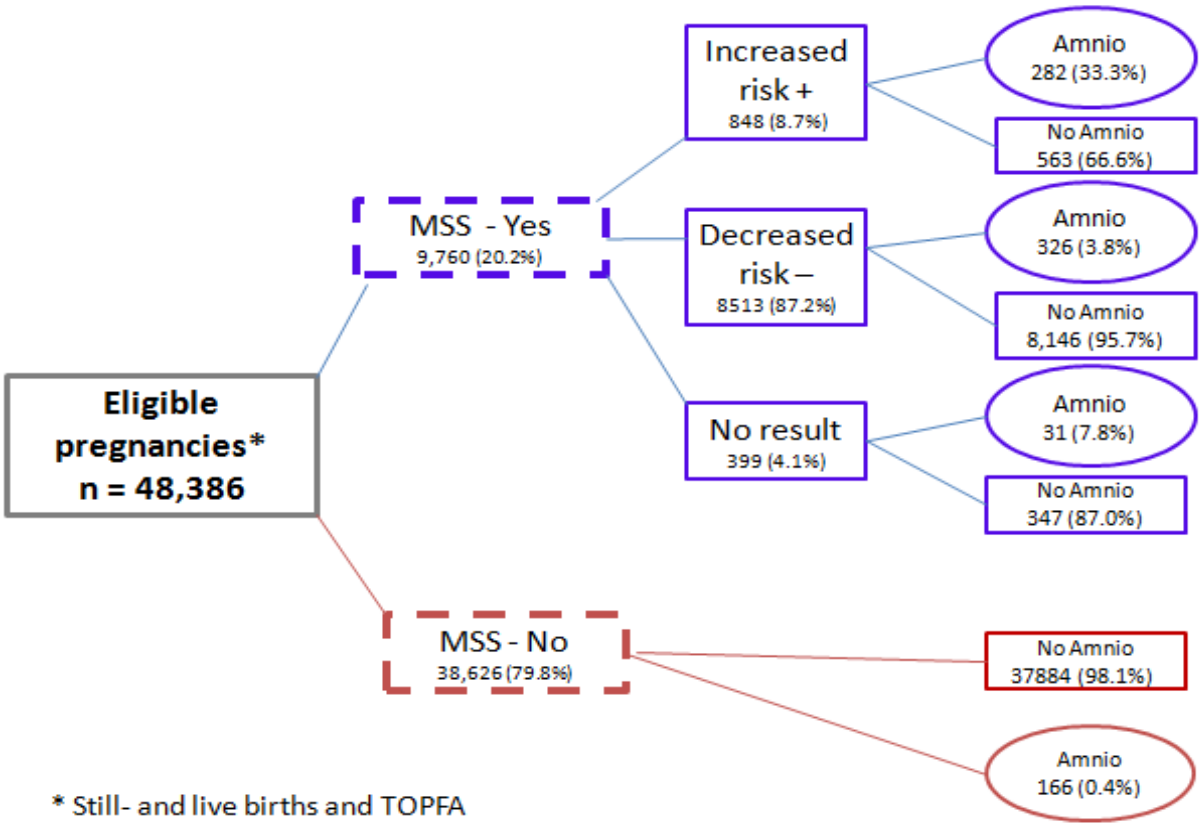


Figure 4.9 Amniocentesis uptake by screening result (all conditions combined), Saskatchewan, 2002-2005 (pooled)

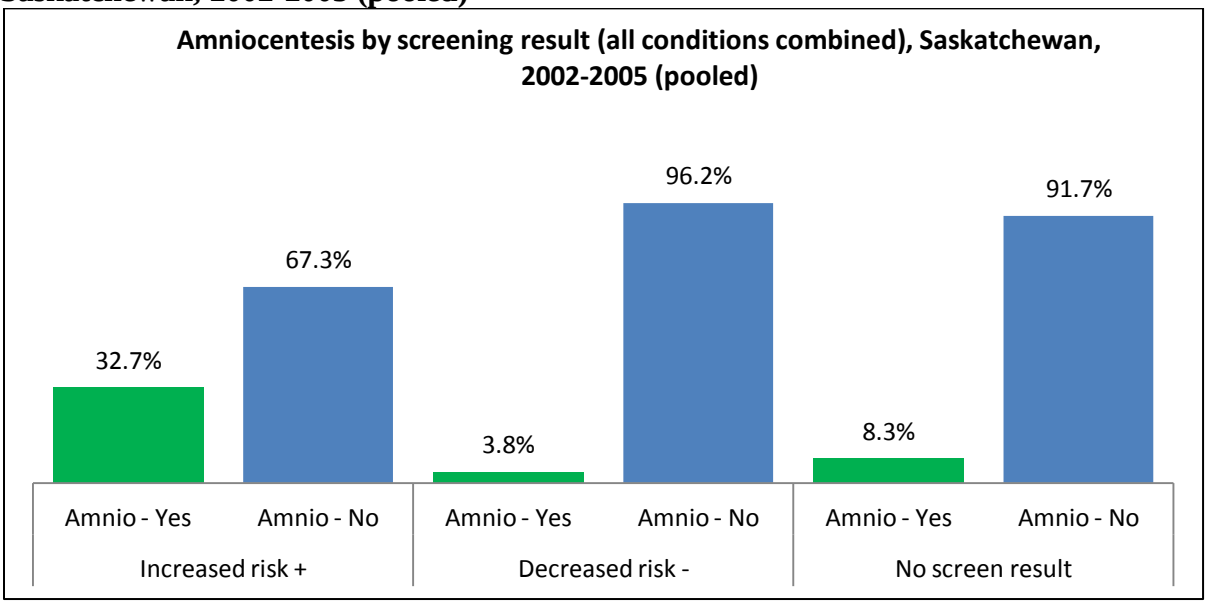
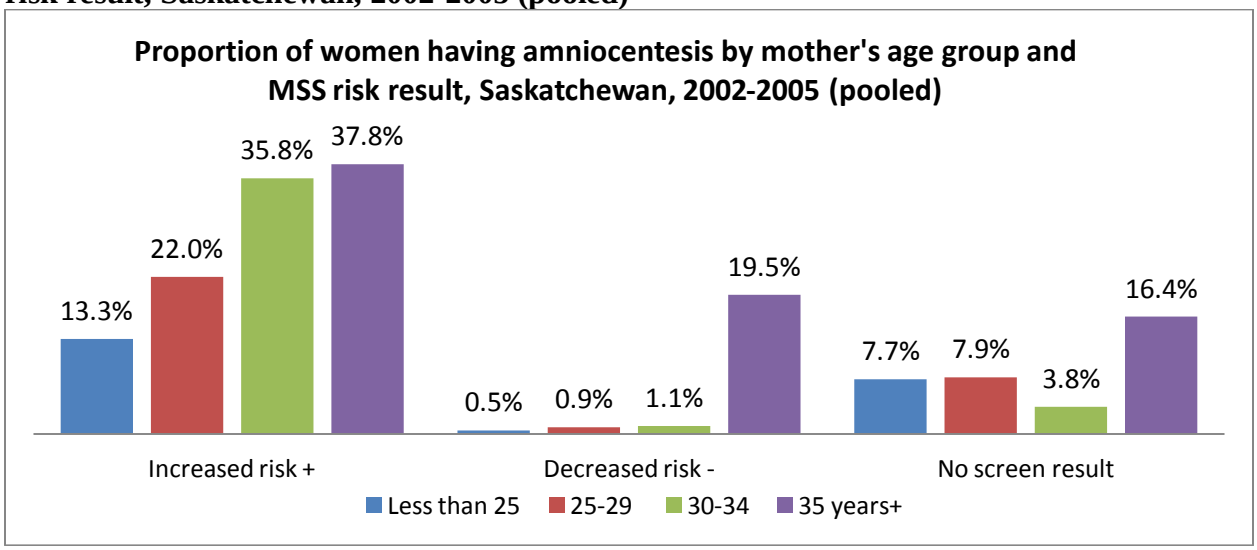


Table 4.10 Prenatal diagnostic testing according to MSS screening result, Saskatchewan, 2002-2005 (pooled)

Condition n (%)	Screening result	Amniocentesis	
		Yes	No
Down syndrome	Negative	118 (1.3)	8674 (98.7)
	Positive	270 (36.8)	463 (63.2)
Neural Tube Defects	Negative	607 (6.3)	9051 (93.7)
	Positive	24 (15.3)	133 (84.7)
Trisomy 18	Negative	372 (3.9)	9079 (96.1)
	Positive	16 (32.7)	33 (67.3)
All conditions combined (any)	Negative (to all 3)	353 (3.8)	8891 (96.2)
	Positive (to any of the 3)	313 (32.7)	645 (67.3)
	No result	36 (8.3)	398 (91.7)

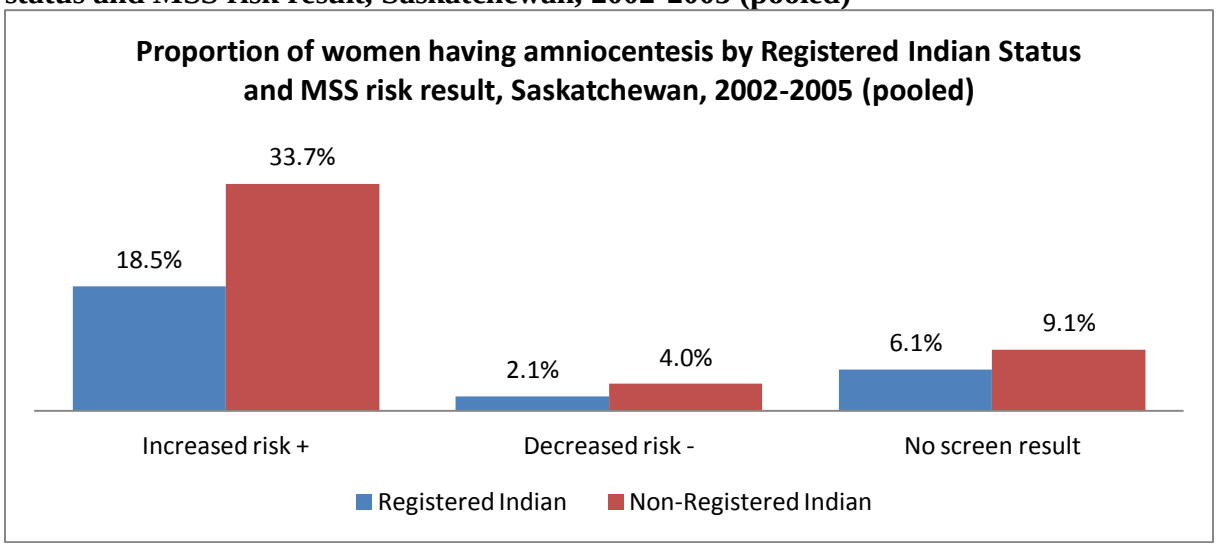
Figure 4.10 illustrates the moderating effect that age has on the association between MSS result and amniocentesis. While diagnostic testing is higher overall in mothers who received a screen-positive result, the uptake increases with age. Of women age 24 and under who received a screen-positive MSS result, 13.3% had an amniocentesis. Prenatal diagnostic testing was almost three times higher in the high age group (37.8%). A similar pattern could be seen for women who screened-negative. The rate of amniocentesis among the youngest women who received a screen-negative result was low (0.5%) compared to those in the 35 years and older age category (19.5%).

Figure 4.10 Proportion of women having amniocentesis by mother's age group and MSS risk result, Saskatchewan, 2002-2005 (pooled)



Registered Indian women were much less likely to opt for amniocentesis following a screen-positive or screen-negative MSS result. While 33.7% of non-Registered Indian women had an amniocentesis after receiving an increased risk result, just 18.5% of Registered Indian women had follow-up diagnostic testing.

Figure 4.11 Proportion of women having amniocentesis by mother's Registered Indian status and MSS risk result, Saskatchewan, 2002-2005 (pooled)



Pregnancy outcomes varied according to the diagnosis made through amniocentesis. The likelihood that a tested-pregnancy would result in a live birth was much higher if the result was "normal" than if a chromosomal anomaly was diagnosed.[28] Out of the 873 pregnancies where no chromosomal anomaly was diagnosed, 825 (94.5%) were live born. In the case of fetuses diagnosed with Down syndrome, trisomy 18, or another chromosomal anomaly, the proportion of live births was considerably lower (20.0%, 16.7% and 51.1%, respectively). For 'other chromosomal anomalies' some of this difference could be accounted for by a higher proportion of stillbirths. In the case of Down syndrome and trisomy 18, however, a large proportion of fetuses were taken by means of a selective abortion (73.3% and 75.0%, respectively). Because fewer 'other chromosomal anomalies' ended in TOPFA, this allowed for more spontaneous stillbirth losses.

[28] Not all data shown in table below due to small numbers.

Table 4.11 Pregnancy outcome by amniocentesis diagnosis (n=958), Saskatchewan, 2001-2005 (pooled)[29]

n (%)	Live birth	TOPFA	Total
Down syndrome and Trisomy 18	5 (18.5)	20 (74.1)	27
Other chromosomal anomaly	22 (51.2)	8 (18.6)	43
Normal	825 (94.5)	20 (2.3)	873

4.2 Multivariate Analysis

Binary logistic regression was used to further explore the differences between pregnancies that had MSS and those that did not, and pregnancies that had amniocentesis and those that did not.

4.2.1 Selection of variables for inclusion: MSS model

Using bivariate analysis, the following factors differed ($p<.25$) according to MSS use: mother's age, health region of residence, Registered Indian status, and year that the birth, abortion, or MSS test occurred. Looking in more detail at the distribution of MSS users and non-users according to each risk factor, some patterns were evident ($p<.000$). In terms of mother's age, the likelihood of having had MSS increased with age. This finding is not unexpected given that national guidelines up to 2007 recommended triple test screening primarily for women aged 35 and over.(48) Only 15.7% of the youngest age group had MSS, while 43.2% of the oldest did. A larger proportion of pregnancies in women residing in the urban health regions had MSS (30.0%) compared to those in rural settings (18.3%). MSS uptake was considerably less common in women of Registered Indian status (9.6% vs. 28.4%, respectively). MSS uptake was lower in 2002, during only the second year of the program, then held steady at 25.8% in 2003 and 2004.

[29] Portions of table suppressed due to small numbers, according to Saskatchewan Ministry of Health regulations.

Table 4.12 Covariates and MSS Uptake, 2002-2004

demographic characteristic	No	Yes	Total	Chi-square value (2-sided sig.)
Mother's age group				
Under 25 years	10428 (84.3)	1945 (15.7)	12373	1289.46 (.000)
25-29 years	8612 (75.7)	2757 (24.3)	11369	
30-34 years	5793 (71.4)	2179 (28.6)	8115	
35 years and more	2086 (56.8)	1536 (43.2)	3670	
Health region of residence				
Rural	14375 (81.7)	3228 (18.3)	17603	662.13 (.000)
Urban	12526 (70.0)	5379 (30.0)	17905	
Registered Indian Status				
No	19755 (71.6)	7851 (28.4)	27606	1195.38 (.000)
Yes	7164 (90.4)	757 (9.6)	7921	
Year of MSS test				
2002	9470(78.8)	2542 (21.2)	12012	93.00 (.000)
2003	8703 (74.2)	3024 (25.8)	11727	
2004	8746 (74.2)	3042 (25.8)	11788	

* If no MSS test, then year of birth/abortion was used.

4.2.1.1 Predictors of MSS uptake

The final main effects model (table 4.13) identified several predictors significant at the $p<.05$ level. When holding all other variables constant, health region of residence, age group, Registered Indian status, and year of MSS test remained significant predictors ($p<.000$) for MSS. As expected, the likelihood that one would have MSS increased with increasing age. Women belonging to the 35 years and over age group were more than three times as likely to have had MSS testing as compared to women in the youngest age category (OR=3.19, 95% CI 2.46-4.13). Non-First Nations women were more than three times as likely to screen as First Nations women (OR=3.26, 95% CI 2.81-3.79). The health region of residence variable was collapsed into a dichotomous rural-urban variable due to the difficulty placing cases broadly grouped by the Epidemiology, Research and Evaluation Unit (Ministry of Health) as a result of small sample concerns. The regression model found that women residing within Saskatoon or Regina Qu'Appelle Health Region boundaries were almost twice as likely to have MSS as those in rural or remote locales. The year that the pregnancy ended (whether by birth, stillbirth or abortion) or tested was shown to have a small impact on MSS uptake; women who were pregnant during the

latter two years were more likely to screen than those at the start of the study period, presumably due to increasing awareness of the screening program over time.

Significant interaction effects were found between age group and urban-rural region (p<.000); urban-rural region and Registered Indian Status (p=.004); and age and Registered Indian status (p=.019).

Table 4.13 Final main effects model which includes variables associated with MSS uptake

Variable (reference)	ß (S.E.)	Sig.	Odds Ratios	95% C.I. for Exp (ß) Lower	Upper
Age group					
24 years and under (ref)		.000			
25-29 years	.301 (.102)	.003	1.351	1.107	1.650
30-34 years	.338 (.123)	.006	1.401	1.102	1.782
35 years and over	1.161 (.132)	.000	3.193	2.467	4.133
Registered Indian (yes)	1.182 (.077)	.000	3.261	2.806	3.789
Urban-rural region (rural)	.690 (.084)	.000	1.993	1.692	2.348
Test year					
2002 (ref)		.000			
2003	.290 (.032)	.000	1.337	1.256	1.423
2004	.307 (.032)	.000	1.359	1.277	1.447
Age modified by region of residence		.000			
25-29 years*urban	-.048 (.069)	.485	.953	.833	1.090
30-34 years*urban	-.047 (.073)	.524	.954	.827	1.102
35 years and over*urban	.419 (.089)	.000	1.521	1.278	1.809
Urban-rural region by Registered Indian status					
Urban*non-RI	-.240 (.084)	.004	.786	.667	.928
Age modified by Registered Indian status		.019			
25-29 years*non-RI	.080 (.103)	.439	1.083	0.885	1.325
30-34 years*non-RI	.232 (.124)	.061	1.262	0.990	1.608
35 years and over*non-RI	-.258 (.135)	.056	0.772	0.593	1.006

4.2.1.2 Model diagnostics

To assess the goodness of fit of the model, the Hosmer-Lemeshow test was used. For the model presented in table 4.13, the chi-square statistic was 8.801 (p=0.359), showing no evidence of lack of fit. In addition, the likelihood ratio test was used to assess variables in the final model

against those in the preliminary main effects model. The log likelihood statistic was highly significant (LR=99.5 chi-square, 9 degrees of freedom = 49.76, p<0.005).This indicates that the final model was the better, more parsimonious model. As a result, the model is acceptable. The final model had a c-statistic of 0.677 (95% CI: 0.670, 0.683) and a Brier score of 0.000005 indicating acceptable discrimination and very low prediction error.

4.2.1.3 Interaction assessment

In the final model, three interaction terms (age*urban-rural region; urban-rural region*RI status ; and age*RI status) were found to be significant (p<.05). The predicted probabilities, calculated directly from the final regression model, are plotted below (figures 4.12-4.15). Error bars are included for each estimate providing the 95% confidence intervals. In addition, odds ratios for each level of effect were calculated manually to quantify the relationship (tables 4.14-4.16).(161)

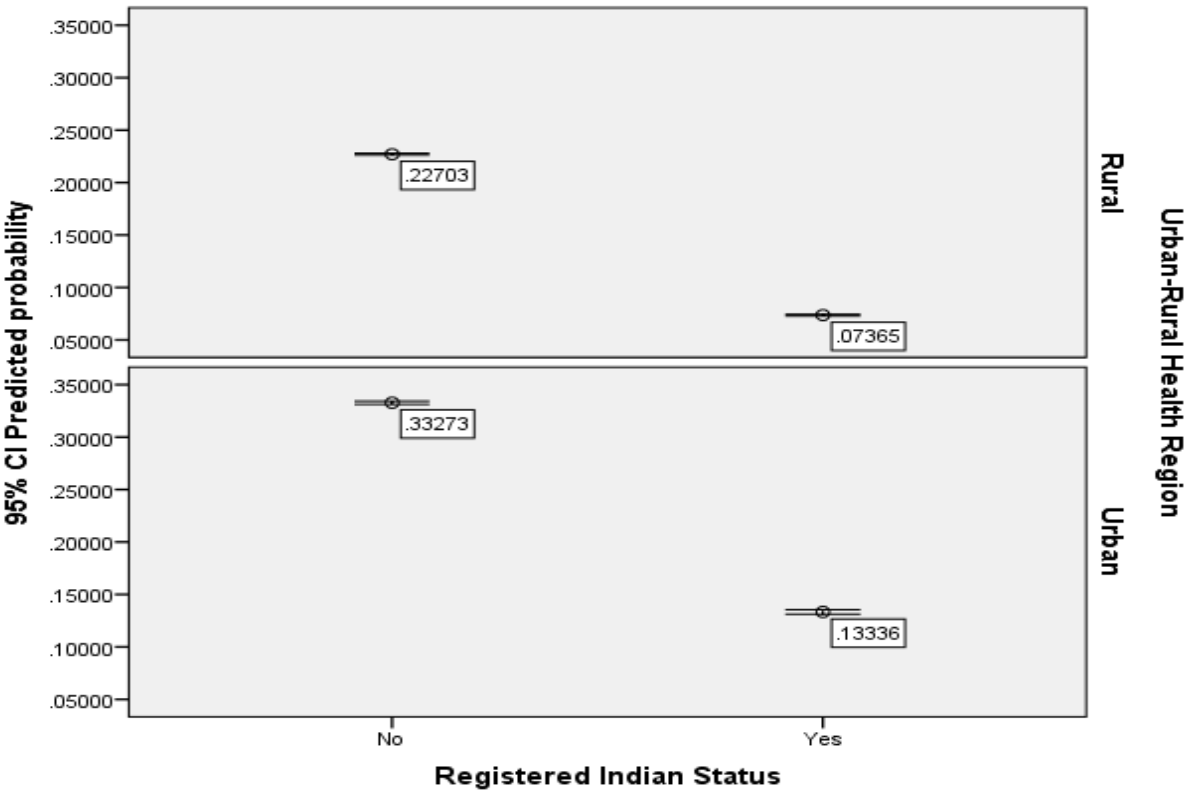
4.2.1.3.1 Registered Indian Status-Urban/Rural Interaction

Figure 4.12 shows the probability of women having MSS, according to whether they were Registered Indian or not and if they lived in an urban or rural health region. The probability of testing was higher in non-RI women living in an urban region (0.333) and lowest in RI women living in a rural region (0.736). Odds ratios for each level of effect were then calculated, along with 95% confidence intervals (table 4.12). Here it can be seen that among women living in an urban health region, those who were non-RI were 2.56 times more likely to have had MSS than those who were RI. In rural regions, the difference was greater, with non-RI women being 3.26 times more likely to have had MSS than RI women. Looking at RI women only, the effect of urban region is slightly larger than it is among non-RI women (1.99 vs. 1.57, respectively).

Table 4.14 Calculation of odds ratios for MSS uptake when interaction present

Effect	**Among**	**Odds Ratios**	**95% CI**
Urban-Rural Region*			
Urban	RI Status- No	1.57	1.24 - 1.98
Urban	RI Status- Yes	1.99	1.69 - 2.35
RI Status**			
RI Status- No	Urban	2.56	2.05 - 3.20
RI Status- No	Rural	3.26	2.81 - 3.79

Figure 4.12 Predicted probability of women having MSS by RI status and urban-rural health region, 2002-2004



4.2.1.3.2 Age-urban/rural interaction

Women living in an urban health region had higher MSS uptake than those in rural regions, for all age categories. Figure 4.13 plots the predicted probabilities of women having MSS, according to age and whether they lived in a rural or urban health region. The difference between the predicted probability that urban and rural women would have MSS increased with age (0.074, 0.092, 0.104, and 0.235, respectively). In women aged 35 and over, 53.1% living in an urban region had MSS, while only 29.6% of rural women in the same age group had screening. Looking at the youngest age category, 19.9% of women in the urban region had MSS compared to 12.4% of those in rural regions.

While uptake was highest in the 35 years and over age group, testing was substantially higher in urban compared to rural regions for this age group (OR=3.03, 95% CI 2.39 - 3.85) (table 4.15). In urban health regions the oldest age group was 4.85 times (95% CI 3.56-6.62) more likely to have MSS than the youngest. In rural regions, the oldest age group was 3.19 times (95% CI 2.47-4.13) more likely to have MSS than the youngest.

Figure 4.13 Predicted probability of women having MSS by age group and rural-urban health region, 2002-2004

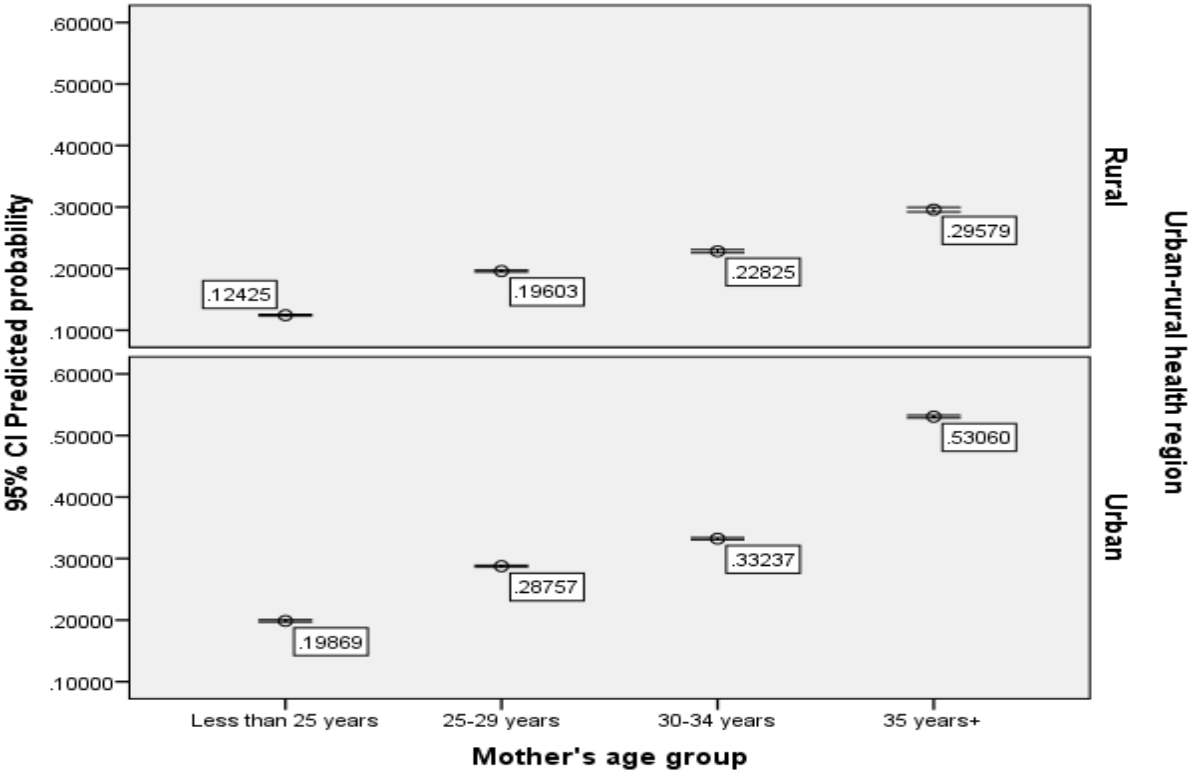


Table 4.15 Calculation of Odds Ratios for MSS uptake when interaction present

Effect	Among	Odds Ratios	95% CI
Age group			
35 years +	Rural	3.19	2.47 - 4.13
30-34 years	Rural	1.40	1.10 - 1.78
25-29 years	Rural	1.35	1.11 - 1.65
35 years +	Urban	4.85	3.56 - 6.62
30-34 years	Urban	1.34	1.01 - 1.77
25-29 years	Urban	1.29	1.01 - 1.64
Urban-rural health region			
Urban	35 years +	3.03	2.39 - 3.85
Urban	30-34 years	1.90	1.54 - 2.35
Urban	25-29 years	1.90	1.53 - 2.36
Urban	24 years & under	1.99	1.69 - 2.35

4.2.1.3.3 Age-RI status interaction

Registered Indian status was an influential factor as far as whether or not women had MSS, with uptake being higher in non-RI women for all age groups (figure 4.14). The increase in MSS uptake with each age category was comparably small for RI women under age 35. In the 35 years and older age group, MSS uptake was more than double in non-RI compared to RI women (OR= 2.52; 95% CI = 1.86-3.41) (table 4.16). The effect of non-RI status was greater in the younger age groups, for example, non-RI women in the 30-34 year age group were 4.11 times (95% CI 3.10-5.46) more likely to screen than RI women of the same age.

Figure 4.14 Predicted probability of women having MSS by age group and Registered Indian status, 2002-2004

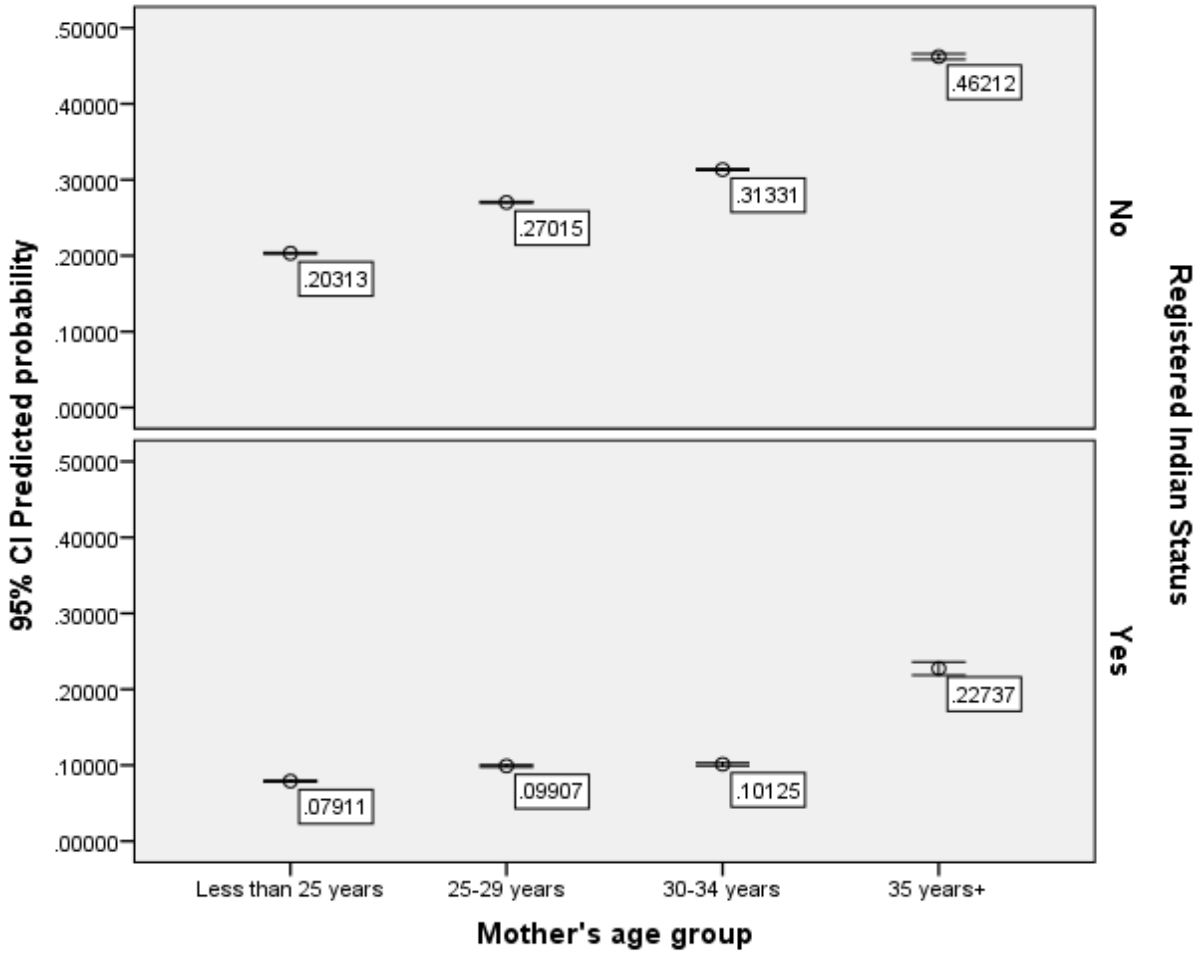
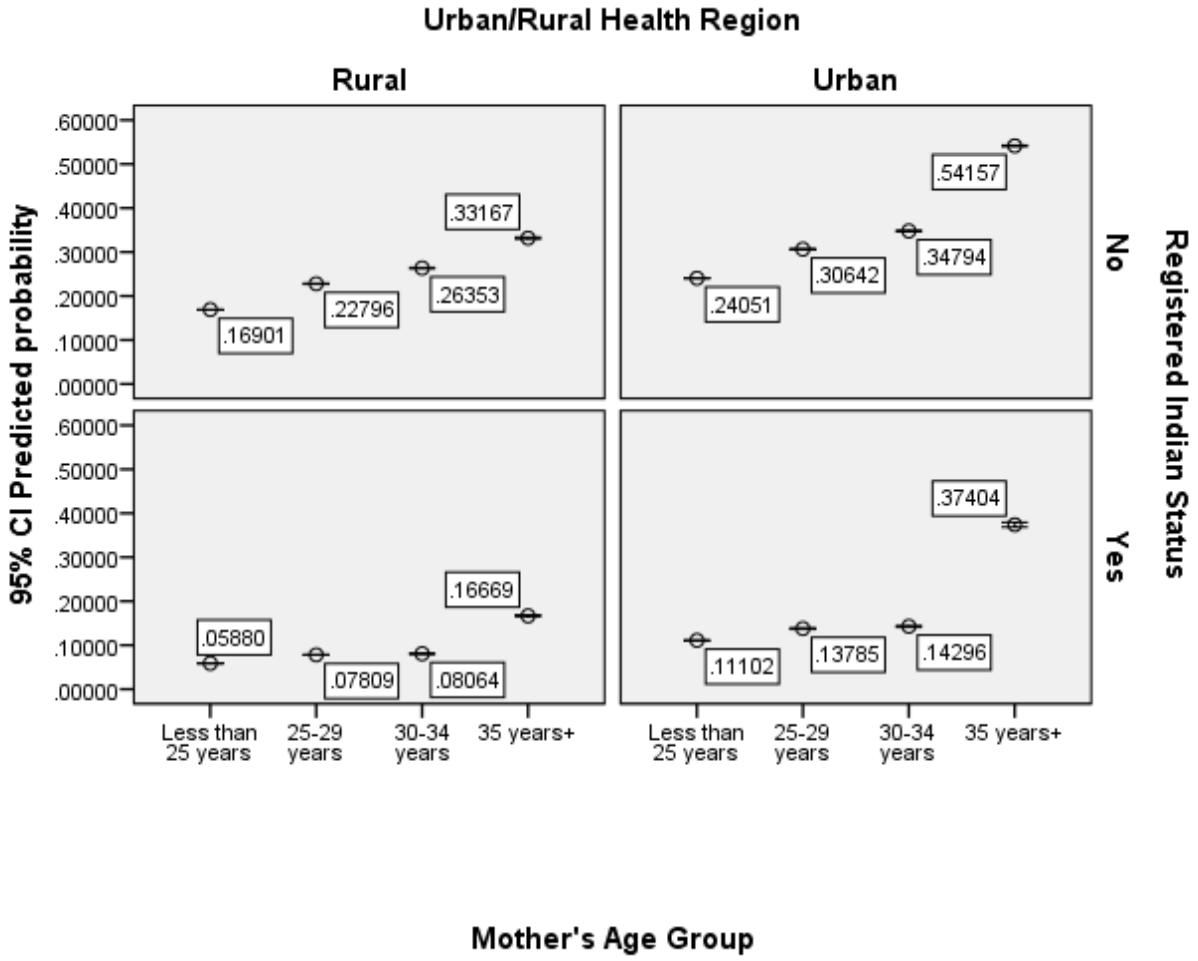


Table 4.16 Calculation of Odds Ratios for MSS uptake when interaction present

Effect	Among	Odds Ratios	95% CI
Age group			
35 years +	RI status	3.19	2.47 - 4.13
30-34 years	RI status	1.40	1.10 - 1.78
25-29 years	RI status	1.35	1.10 - 1.65
35 years +	Non-RI status	2.47	2.15 - 2.83
30-34 years	Non-RI status	1.77	1.26 - 2.48
25-29 years	Non-RI status	1.46	1.10 - 1.94
Registered Indian status			
Non-RI status	35 years +	2.52	1.86 - 3.41
Non-RI status	30-34 years	4.11	3.10 - 5.46
Non-RI status	25-29 years	3.53	2.84 - 4.39
Non-RI status	24 years & under	3.26	2.81 - 3.79

Figure 4.15 plots the relationship between all three variables contained in the statistically significant interaction terms, simultaneously illustrating the relationship between variables contained in the interaction terms and MSS. Particularly interesting is the very low probability of screening in RI women under age 35 living in a rural region and, by comparison, the much higher probability for non-RI women in the an urban region.

Figure 4.15 Predicted probability of women having MSS by RI status, urban-rural health region, and age group, 2002-2004



4.2.2 Selection of variables for inclusion: amniocentesis model

Table 4.17 presents chi-square analyses investigating patterns in prenatal diagnostic testing across geography, age groups, ethnicity, MSS testing status and result, and ultimately differences in pregnancy outcome for those deciding to have invasive testing. Due to missing data for the year 2000 and for the southern portion of the province in 2001, only pregnancies occurring from 2002-2005 were included in the present analysis. Amniocentesis was more than twice as common in urban mothers as compared to those living in a rural health region (2.6% vs. 1.0%, p<.000). Testing rates increased significantly (p<.000) with age, with 0.3% of mothers under 25 years having the procedure compared to 11.8% of those aged 35 and over. Amniocentesis uptake was more than four times higher in women not of Registered Indian status compared to those who were (2.2% vs. 0.5%, respectively). Women that had MSS were more likely to have amniocentesis than those who did not. Looking more closely at the influence of

MSS result, one-third of women (33.8%) who screened-positive had diagnostic testing compared to only 3.4% of those who screened negative. An interesting difference could be seen across pregnancy outcomes, with testing rates being the lowest in pregnancies that ended by a spontaneous or planned abortion (0.2% and 0.0%, respectively) and considerably higher in those that ended in stillbirth (7.6%). Amniocentesis is a risk factor for fetal loss and this finding will be examined in more detail.(171)

Table 4.17 Covariates and amniocentesis testing 2002-2004 (pooled)(n=35,527),

n (%)	Amniocentesis		Chi-square value (2-sided sig.)
	Yes	No	
Health region of residence:			
Rural	177 (1.0)	17426 (99.0)	125.254 (.000)
Urban	463 (2.6)	17442 (97.4)	
Age group:			
24 years and under	33 (0.3)	12340 (99.7)	2335.880 (.000)
25-29 years	62 (0.5)	11307 (99.5)	
30-34 years	113 (1.4)	8002 (98.6)	
35 years and over	432 (11.8)	3238 (88.2)	
Registered Indian Status:			
No	602 (2.2)	27004 (97.8)	100.665 (.000)
Yes	38 (0.5)	7883 (99.5)	
MSS screening result:			
No MSS/ result	129 (0.5)	27140 (99.5)	4751.542 (.000)
Negative	256 (3.4)	7248 (96.6)	
Positive	255 (33.8)	499 (66.2)	
Pregnancy outcome:			
Live birth	582 (1.7)	34659 (98.3)	2102.578 (.000)
Stillbirth	17 (7.6)	207 (92.4)	
Spontaneous abortion*	13 (0.2)	5598 (99.8)	
Medical abortion*	** (0.0)	5655 (100)	
Termination of pregnancy for fetal anomaly	41 (66.1)	21 (33.9)	

*Excluded from the logistic regression analysis, but figures reported here for reference. ** Figure suppressed < 5

4.2.2.1 Predictors of amniocentesis uptake

Binary logistic regression was used to further explore the differences between pregnancies that had an amniocentesis and those that did not. The final main effects model (table 4.18) identified several predictors significant at the $p<.05$ level. When holding all other variables constant, age group, Registered Indian status, urban or rural health region of residence, MSS

screening result, and ultimately, pregnancy outcome were all highly significant predictors of prenatal diagnostic testing ($p<.000$). Women aged 35 and over were six times more likely to have testing than those aged 24 and under (OR= 6.70, 95% CI 3.03-14.84), while women between the ages of 25-34 were no more likely than the youngest age group to have the procedure. Before adding the interaction terms to the final model, non-RI women were significantly more likely to have testing than RI women, but the effect became non-significant in the final model. Women living in an urban health region were more likely to screen than those in rural regions. The regression model shows that women's MSS result mattered as to whether or not they pursued diagnostic testing. While a positive MSS result was most strongly predictive of testing, women who received a negative MSS result were still more likely to have testing than those that did not have MSS. Due to the presence of interactions in the model, the main effects cannot be interpreted directly from the output below.

Significant interaction effects were found between age group and screening status ($p<.000$); urban-rural region and screening status ($p<.000$); and age and Registered Indian status ($p=.013$).

Table 4.18 Final main effects model which includes variables that are associated with having amniocentesis

	ß (S.E.)	S.E.	Sig.	Odds Ratios	95% C.I. for Exp (ß) Lower	Upper
Age group						
24 years and under (ref)			.000			
25-29 years	-.638	.561	.255	.528	.176	1.586
30-34 years	-.721	.709	.309	.486	.121	1.953
35 years and over	1.902	.406	.000	6.702	3.026	14.841
Registered Indian (yes)	-.573	.374	.125	.564	.271	1.173
Urban-Rural region (rural)	1.114	.205	.000	3.046	2.038	4.554
Screening status						
No MSS/ no result (ref)			.000			
Negative result	1.247	.538	.020	3.479	1.212	9.985
Positive result	5.268	.478	.000	194.007	76.046	495.299
Age modified by screening status			.000			
25-29 years*negative	1.260	.630	.045	3.526	1.026	12.119
25-29 years*positive	.541	.571	.343	1.718	.561	5.260
30-34 years*negative	1.256	.624	.044	3.511	1.034	11.917
30-34 years* positive	.933	.551	.091	2.542	.863	7.491
35 years and over*negative	1.064	.531	.045	2.899	1.024	8.206
35 years and over* positive	-2.236	.471	.000	.107	.042	.269
Urban-rural region modified by screening status			.000			
Urban*negative	-1.155	.251	.000	.315	.193	.515
Urban*positive	-.776	.272	.004	.460	.270	.784
Age modified by Registered Indian status			.013			
25-29 years*non-RI	.675	.626	.281	1.963	.575	6.699
30-34 years*non-RI	.939	.748	.209	2.558	.590	11.082
35 years and over*non-RI	1.551	.483	.001	4.714	1.830	12.145

4.2.2.2 Model diagnostics

To assess the goodness of fit of the model, the Hosmer-Lemeshow test was used. For the model presented in table 4.18, the chi-square statistic was 5.239 (p=0.631), showing no evidence of lack of fit. In addition, the likelihood ratio test was used to assess variables in the final model against those in the preliminary main effects model. The log likelihood statistic was highly

significant (LR=421.447 chi-squared, 9 degrees of freedom = 240.634, p<0.005). This indicates that the final main effects model was the better, more parsimonious model. As a result, the model is acceptable. The final model had a c-statistic of 0.838 (95% CI: 0.821 - 0.856) and a Brier score of 0.0000021 indicating excellent discrimination and very low prediction error.

4.2.2.3 Interaction assessment

In the final model, three interaction terms (age*screening status; urban-rural region*screening status; and age*Registered Indian status) were all found to be significant (p<.05). The predicted probabilities, calculated directly from the final regression model, are plotted for selected interactions below (figures 4.16-4.18). Error bars are included for each estimate providing the 95% confidence intervals. The probability of having had an amniocentesis increased with mother's age for all three screening categories (no MSS, negative, positive), but was considerably higher in pregnant women that received a screen-positive result (Figure 4.16). The groups with the highest mean predicted probability were women aged 30-34 years and women aged 35 and over who screened-positive (0.389 and 0.375, respectively). Pregnant women living in an urban health region were more likely to have had an amniocentesis than those living in a rural region, for all three screening statuses (figure 4.17). Among those receiving a screen-positive result, urban dwellers were more likely to have follow-up testing than women residing in rural regions (mean predicted probability of 0.366 vs. 0.271). While amniocentesis testing was more prevalent overall in non-Registered Indian women compared to Registered Indian women, the difference could not be seen for the youngest age group, widened with age, and was most pronounced in those 35 years and over (Figure 4.18). Testing was uncommon in women under 30 years in both RI and non-RI women.

Figure 4.16 Predicted probability of women having amniocentesis by screening status and mother's age group, 2002-2004

Figure 4.17 Predicted probability of women having amniocentesis by screening status and mother's health region of residence, 2002-2004

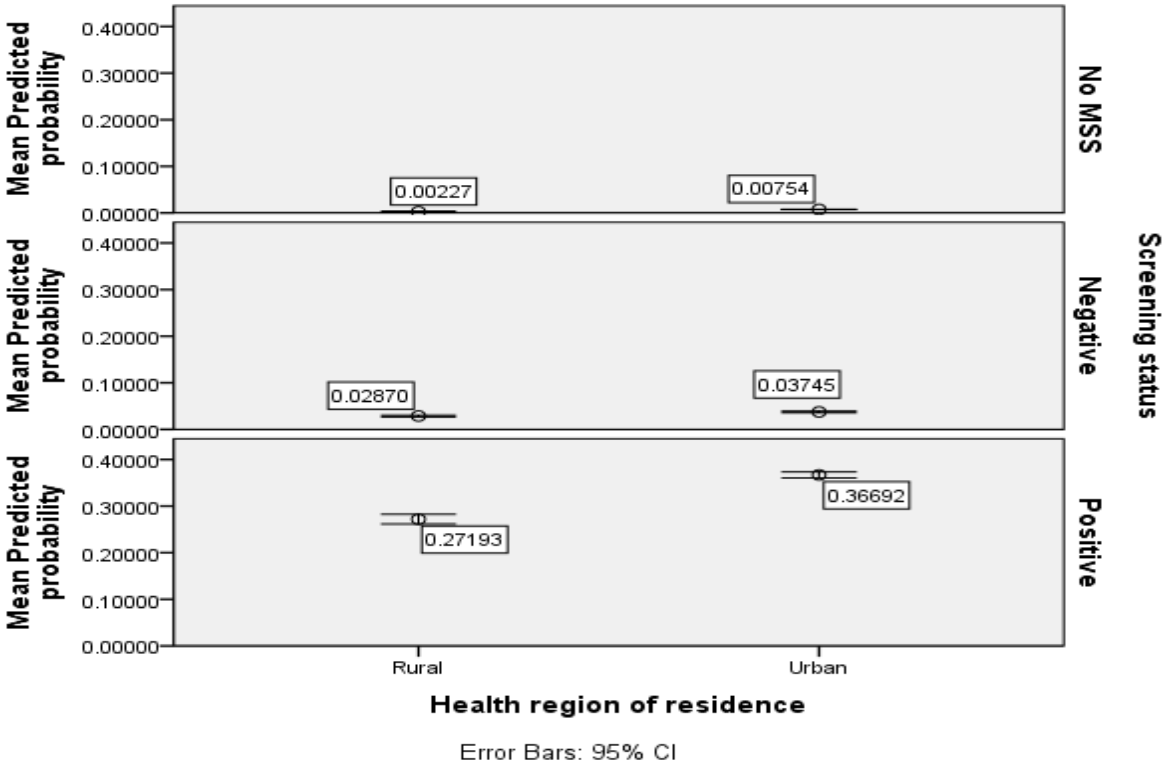
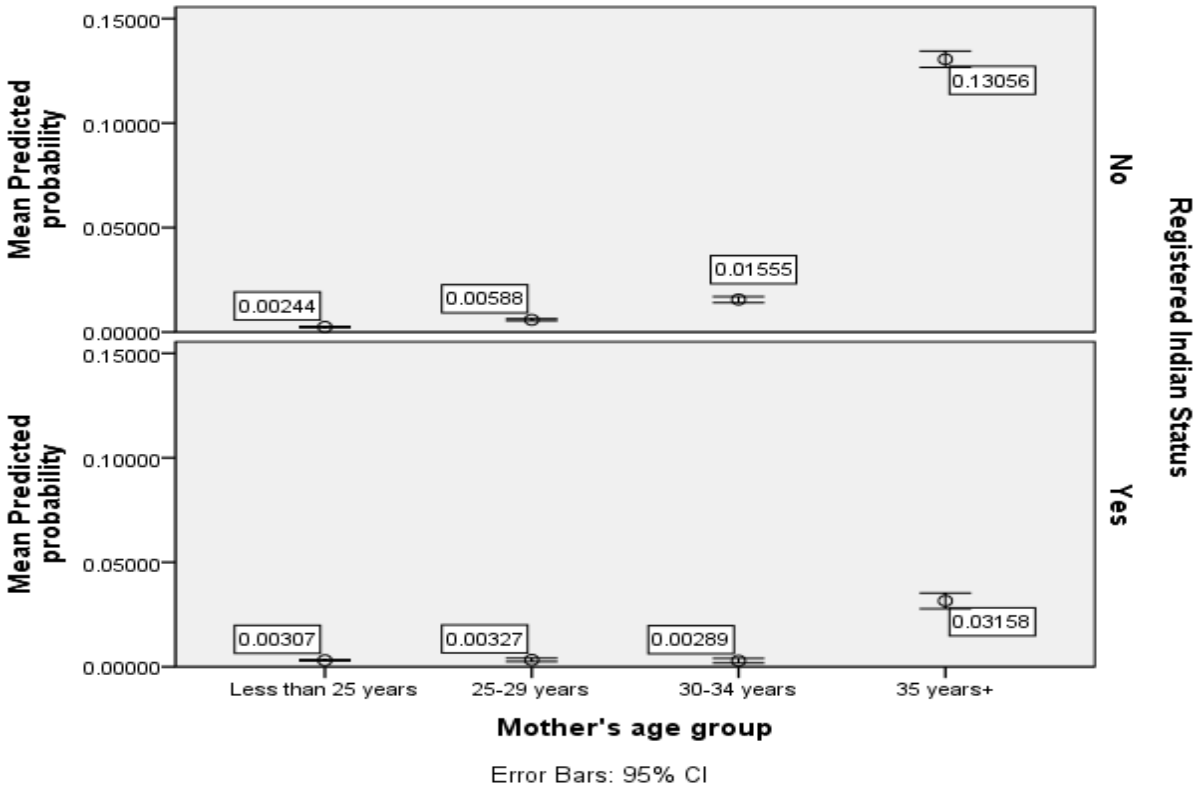


Figure 4.18 Predicted probability of women having amniocentesis by RI status and mother's age group, 2002-2004



4.3 Prenatal diagnosis of chromosomal anomalies

Antenatal detection of CA may differ depending on the extent to which women accept serum screening, the sensitivity of screening (both ultrasound and serum) for various conditions, rates of follow-up diagnostic, and the risk profile of women choosing to continue down the diagnostic pathway. Registered Indian women, younger women, and those living in a rural health region have been shown to be less likely to pursue these options. To assess differences in prenatal diagnosis across populations sub-groups, table 4.19 below presents the proportion of all chromosomal anomalies detected during pregnancy.[30] Prenatal detection of chromosomal anomalies was much lower in RI women compared to non-RI women (8.3% vs. 27.0% overall). Women in the 29 years and younger age group were also less likely to have received a diagnosis before delivery compared to those 30 years and over (18.4% and 31.8%).

[30] Data could not be analyzed according to rural or urban health region as this information was suppressed by the Ministry of Health for all conditions screenable by the MSS program.

Table 4.19 Number and proportion of cases prenatally diagnosed, by RI status and mother's age group, 2000-2005 (pooled)

Number of cases diagnosed prenatally / total number of cases (%)	**Down Syndrome**	**Trisomy 18**	**"Other" chromosomal anomaly**	**Overall**
Registered Indian status	(11.8)		(5.3)	(8.3)
Non-Registered Indian status	14/92 (15.2)	11/18 (61.1)	42/138 (30.4)	67/248 (27.0)
29 years & under	4/44 (9.1)	3/8 (37.5)	21/100 (21.0)	28/152 (18.4)
30 years & over	11/64 (17.2)	9/11 (81.8)	22/57 (38.6)	42/132 (31.8)
Total	15/108 (13.9)	12/19 (63.2)	43/157 (27.4)	70/284 (24.6)

*When either the numerator or denominator was less than 5 both were suppressed and only the proportion reported.

4.3.1 Amniocentesis-related fetal loss

There is general agreement that amniocentesis poses additional risk to the fetus, over-and-above the natural background risk associated with the final weeks and months of pregnancy, but the magnitude of excess risk has been debated.(171) The answer is important to informed decision making about both screening and prenatal diagnostic testing. All women with a pregnancy between 2002-2005 were grouped according to their amniocentesis status and pregnancy/birth outcomes were compared. Due to the absence of gestational age data for spontaneous abortions and for amniocentesis tests processed in the RQHR lab, only a crude assessment could be completed. The overall stillbirth rate was 2.22% (95% CI 1.3-3.5%) (19/854) and the total fetal loss rate was 4.0% (95% CI 2.7-5.4%) (34/869) in women having an amniocentesis. In those not having the procedure, the overall stillbirth rate was 0.61% (95% CI 0.5 - 0.7%) (279/45781). The total fetal loss rate could not be calculated for non-testers due to the absence of gestational age; the majority of losses occur before the pregnancy would be eligible for amniocentesis and this figure would be highly misleading. If only considering stillbirths at less than 24 weeks, as some studies have done (172), the rate was 0.95% (95% CI 0.4-1.9%) (8/843) for the amniocentesis group and 0.12% (56/45574) for the control group. Terminations of pregnancy for fetal anomaly were included in the denominators, as per the SOGC's suggestion, to ensure an accurate depiction of the true fetal loss rate.(171)

4.4 Congenital anomaly birth prevalence and incidence analysis

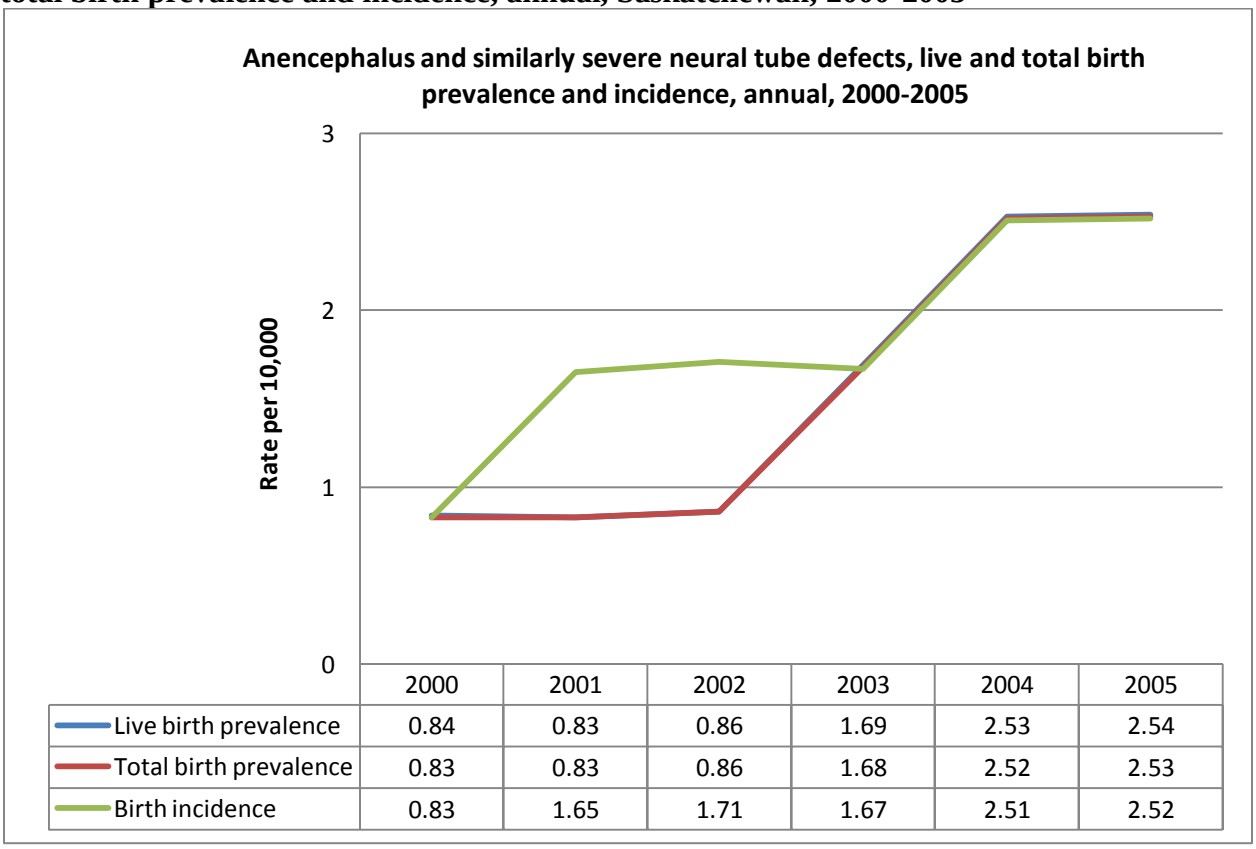
As described in section 2.2.1, birth prevalence and incidence rates for congenital anomalies can often portray a disparate picture. The magnitude of the difference and the pattern

will depend on the CA and the extent to which TOPFA are occurring in the population. It will also, as seen below, depend on the number of TOPFA cases that are stillborn or live born, as these will have been captured by standard CA rate calculations (ie. those where TOPFA are not included). Figures 4.19-4.21 present trends in CAs detectable through the provincial MSS program - anencephalus, Down syndrome, and trisomy 18. For each CA type, the live birth prevalence (cases diagnosed after delivery per 10,000 live births), total birth prevalence (cases diagnosed in stillbirths or live births per 10,000 live and stillbirths), and birth incidence (cases diagnosed in medical abortions or spontaneous abortions before 20 weeks gestation, stillbirths and live births per 10,000 live and stillbirths and early fetal losses tested by prenatal diagnosis) were calculated. Spontaneous and elective medical abortions were excluded from the denominator, unless having undergone prenatal diagnostic testing, due to the fact that their case status was unknown.

For two out of the five years studied, the live birth prevalence rate was notably lower than the incidence for severe NTDs (figure 4.19). During 2001 and 2002, the incidence rates were double the live birth prevalence rates. Overall, there was an annual average percent increase of 30% in the live birth prevalence of severe NTDs and 29.6% increase in the birth incidence. While the increases in both lines were notable, the trends were statistically non-significant ($p=0.15$ and $p=0.32$, respectively). Having said that, numbers were very small each year and therefore the power to detect a difference was low. In the case of Down syndrome, the live birth prevalence and incidence began to diverge in 2001, but the absolute difference between the rates held from 2003 onward (2.4 percentage points difference). The relative difference between the two rates decreased slightly between 2003 and 2005 (16.7% and 14.9%, respectively). An overall increasing trend was observed for Down syndrome rates in Saskatchewan, with the slope of the incidence line being slightly steeper than the live birth prevalence line. The average annual percent increase for the live birth line was 9.0% and 10.0% for the incidence line; the chi-square test for trend was non-significant ($p=0.28$) for the live birth prevalence rate and borderline non-significant ($p=0.09$) for the incidence rate. The incidence and birth prevalence rates of trisomy 18 varied considerably from year-to-year, as did the difference between the lines (figure 4.21). The largest difference in the live birth and incidence rates was in 2004 (0.84 vs. 4.19 per 10,000, respectively). The annual percent change for the live birth line was 45.3% and 83.9% for the incidence line, and the chi-square tests for trend were both non-significant ($p=0.77$ and $p=0.10$

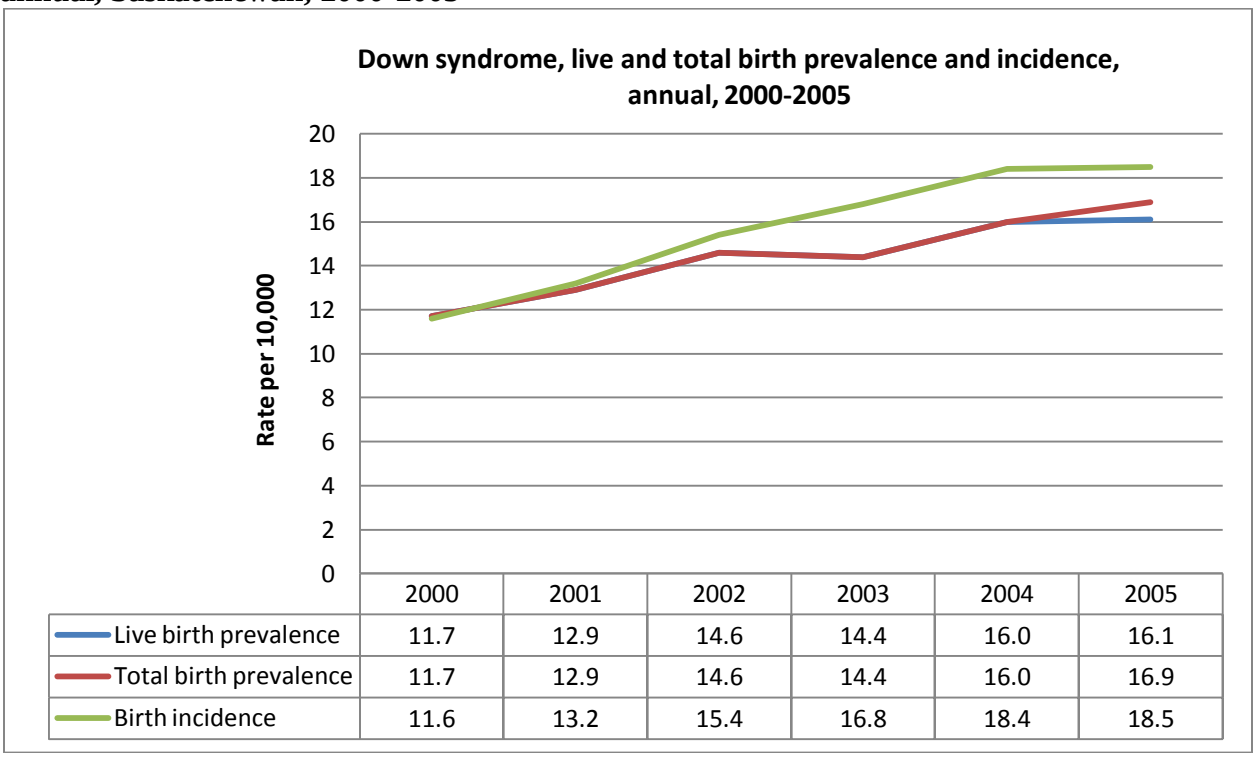
respectively). Anencephalus, Down syndrome, and trisomy 18 all increased over the six-year period studied. The total birth prevalence was almost identical to the live birth prevalence in the case of anencephalus and Down syndrome. In the case of anencephalus, the absence of diagnostic data on stillbirths likely accounts for the similarly in live and total birth prevalence rates in the population, given the known risk for stillbirth for this outcome. It is therefore likely that the total birth prevalence and incidence rates are underestimates of the true occurrence of severe NTDs in Saskatchewan. Similarly, the absence of cytogenetic laboratory data for 2000 and for the southern portion of the province for part of 2001 may have resulted in an underestimate in the birth incidence of Down syndrome and trisomy 18 for those two years.

Figure 4.19 Anencephalus and similarly severe neural tube defects, comparison of live and total birth prevalence and incidence, annual, Saskatchewan, 2000-2005*



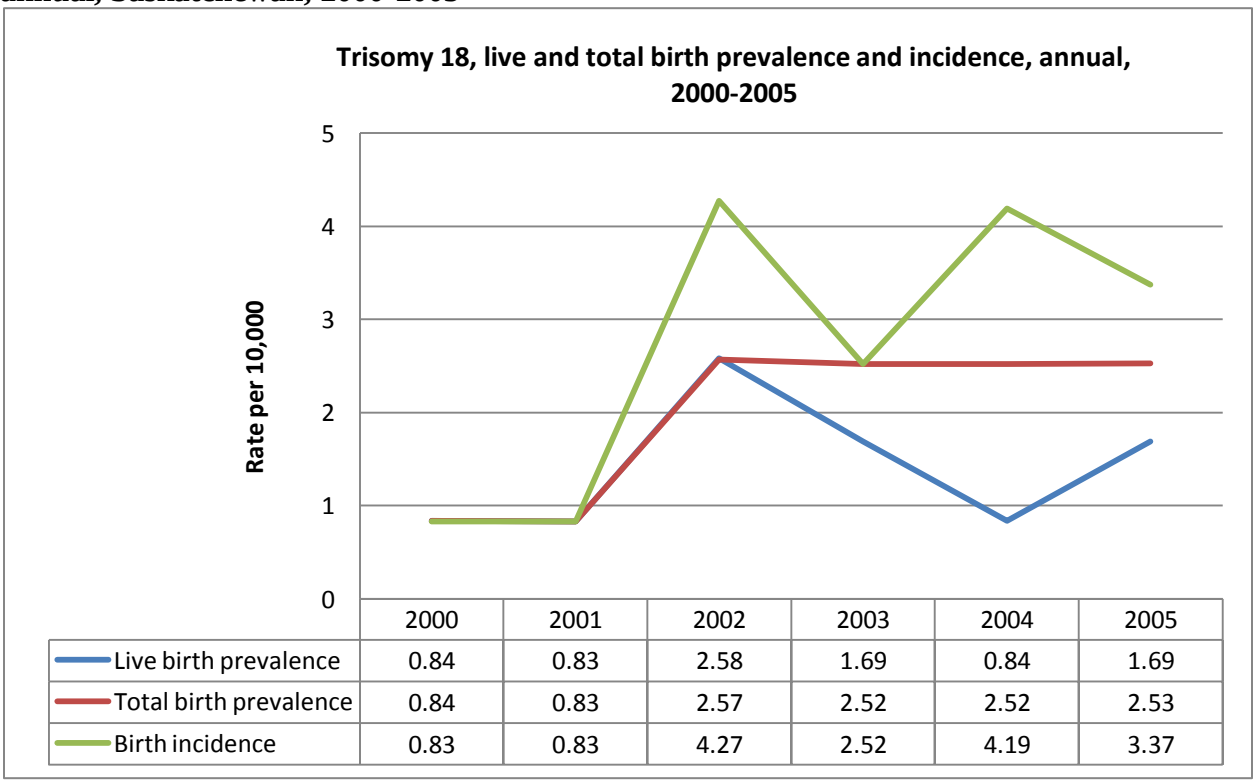
	2000	2001	2002	2003	2004	2005
Live birth prevalence	0.84	0.83	0.86	1.69	2.53	2.54
Total birth prevalence	0.83	0.83	0.86	1.68	2.52	2.53
Birth incidence	0.83	1.65	1.71	1.67	2.51	2.52

Figure 4.20 Down syndrome, comparison of live and total birth prevalence and incidence, annual, Saskatchewan, 2000-2005



	2000	2001	2002	2003	2004	2005
Live birth prevalence	11.7	12.9	14.6	14.4	16.0	16.1
Total birth prevalence	11.7	12.9	14.6	14.4	16.0	16.9
Birth incidence	11.6	13.2	15.4	16.8	18.4	18.5

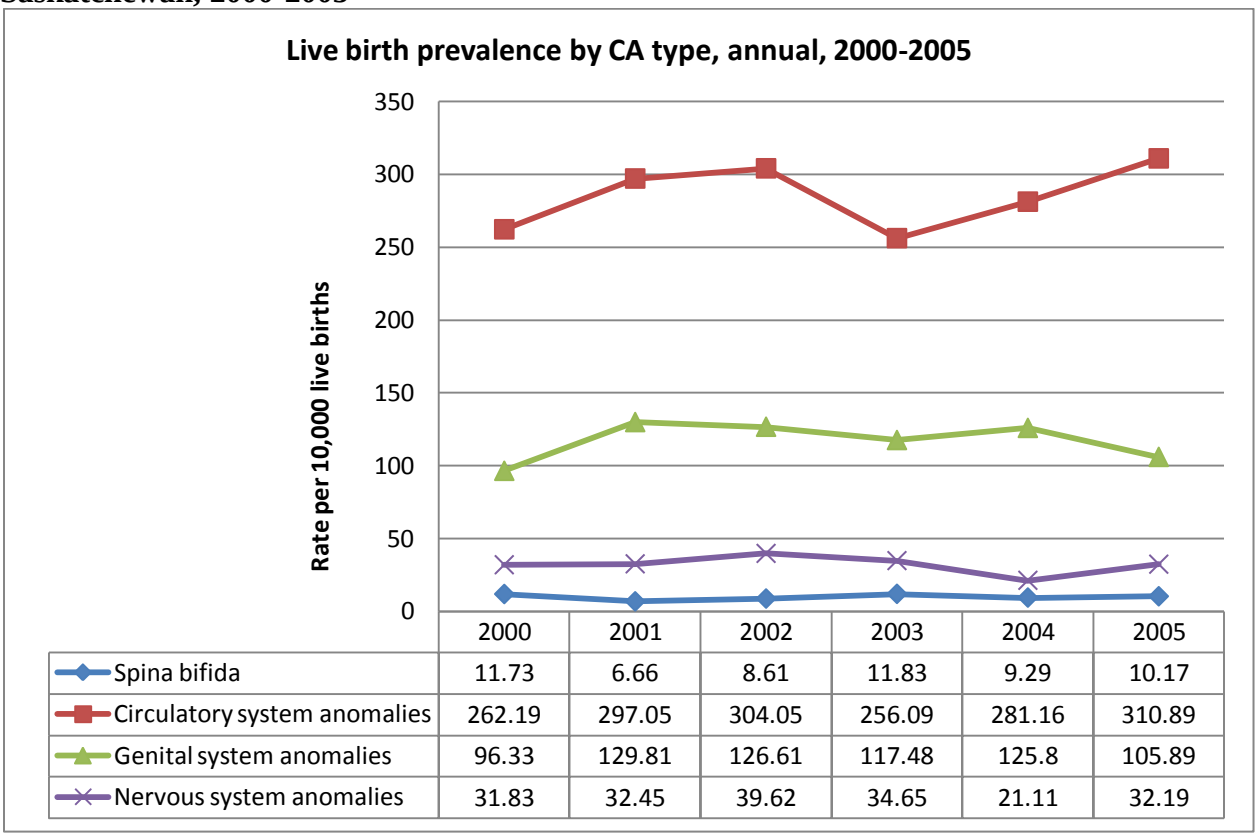
Figure 4.21 Trisomy 18, comparison of live and total birth prevalence and incidence, annual, Saskatchewan, 2000-2005



	2000	2001	2002	2003	2004	2005
Live birth prevalence	0.84	0.83	2.58	1.69	0.84	1.69
Total birth prevalence	0.84	0.83	2.57	2.52	2.52	2.53
Birth incidence	0.83	0.83	4.27	2.52	4.19	3.37

Diagnostic information was unavailable for conditions diagnosed by ultrasound that did not result in a live birth. As a result, only the live birth prevalence could be calculated for spina bifida and anomalies of the circulatory, genital, or nervous systems (figure 4.22). Circulatory system anomalies were by far the most common CA, followed by genital anomalies. While there were some notable year-to-year fluctuations, no clear trends could be seen. Spina bifida is a condition screenable by MSS and live birth prevalence rates are very likely impacted by the practice of TOPFA. While terminated cases could not be identified given the study limitations, there were 11 instances where a medical abortion was preceded by a 'positive' MSS result. These cases were very likely NTDs diagnosed by ultrasound, which would impact the rates of spina bifida and several NTDs reported here.

Figure 4.22 Live birth prevalence of select types of congenital anomalies, annual, Saskatchewan, 2000-2005



	2000	2001	2002	2003	2004	2005
Spina bifida	11.73	6.66	8.61	11.83	9.29	10.17
Circulatory system anomalies	262.19	297.05	304.05	256.09	281.16	310.89
Genital system anomalies	96.33	129.81	126.61	117.48	125.8	105.89
Nervous system anomalies	31.83	32.45	39.62	34.65	21.11	32.19

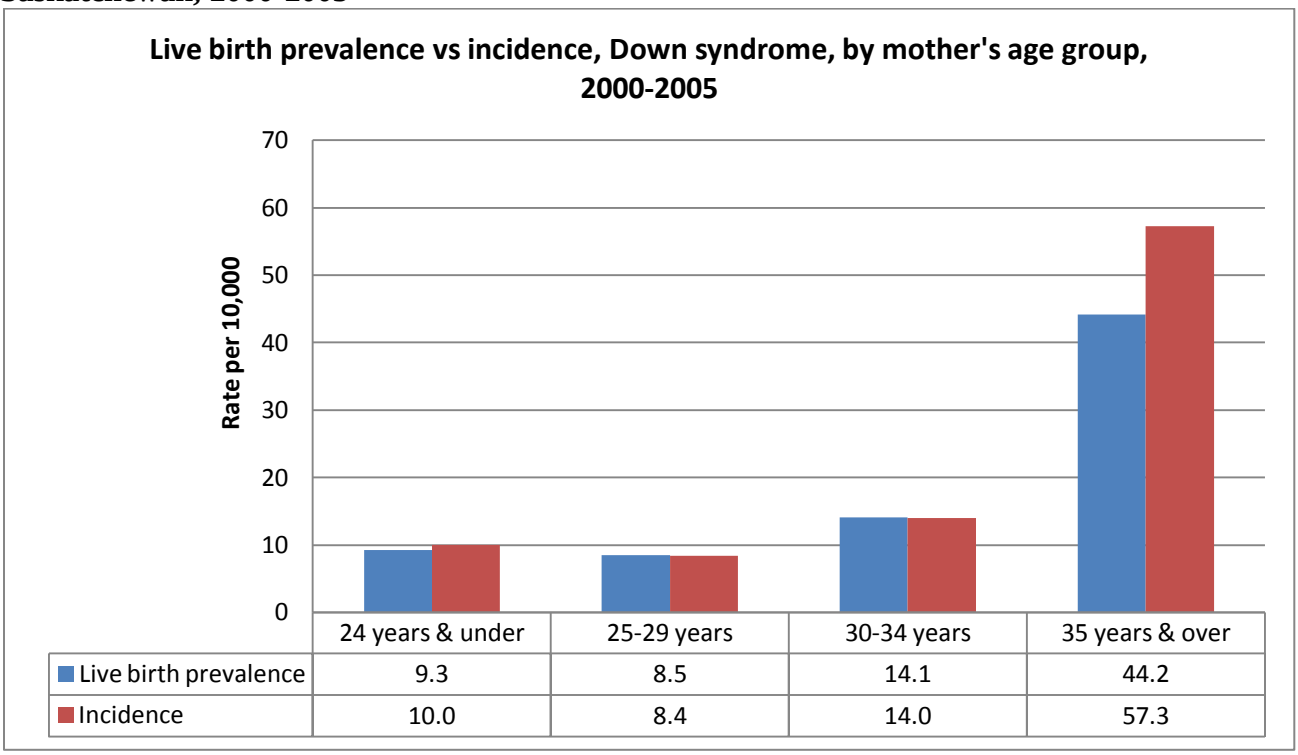
4.4.1 Population rates of chromosomal anomalies by mother's characteristics

Live birth prevalence and incidence rates of Down syndrome, trisomy 18 and "other chromosomal anomalies" were calculated and reported according to mother's age and Registered

Indian status to further explore differences in the termination of pregnancy (figures 4.23-4.28). For greater stability of estimates, data were pooled for all years due to the suppression of birth year for Down syndrome and trisomy 18 cases. These three CA types were selected due to the greater confidence in case ascertainment of chromosomal anomalies, because of access to cytogenetic laboratory data. Differences in the live birth and incidence rate varied according to CA type. For Down syndrome, the most notable difference was in the 35 years and over age group; the live birth prevalence was 44.2 per 10,000 live births and the incidence was 57.3 per 10,000 total births and pregnancies undergoing prenatal diagnosis. For trisomy 18, discrepancies between rates began earlier and could be seen in all but the youngest age group, but the difference was most pronounced in the oldest age category (8.2 vs. 2.8, respectively). For "other" chromosomal anomalies, the difference between the rates was similar across age groups.

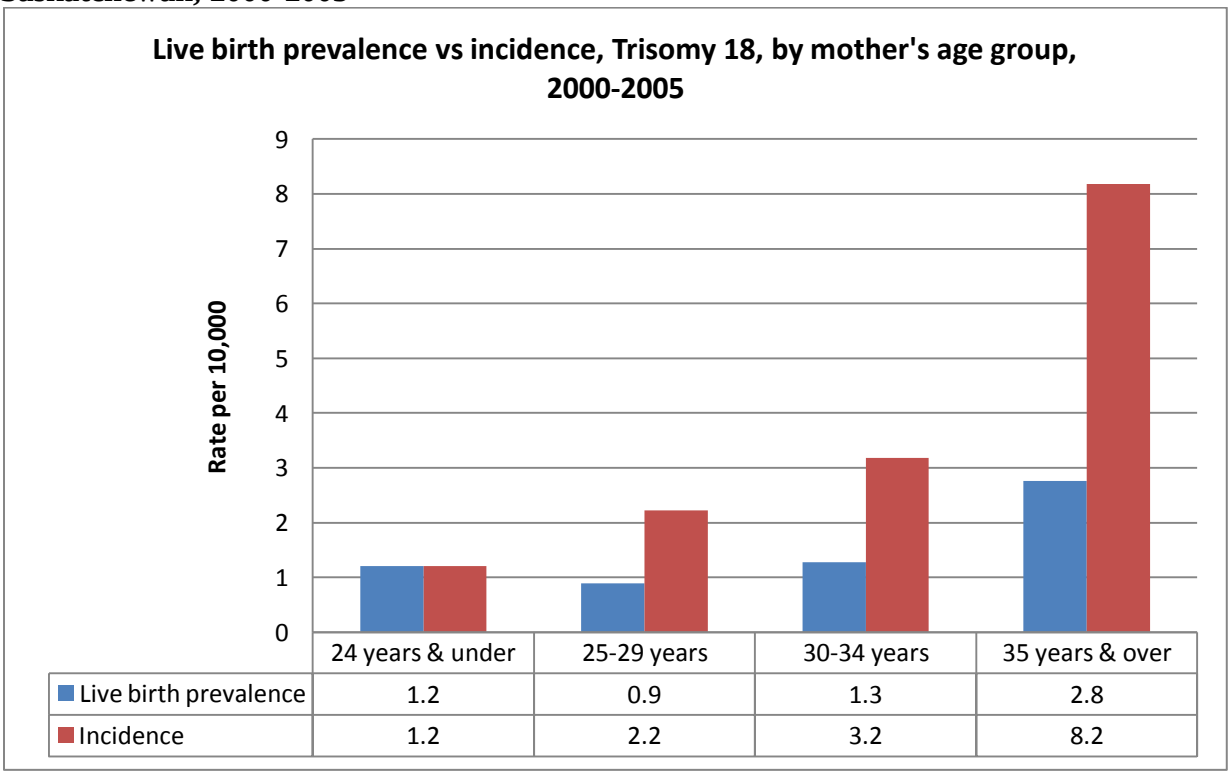
Differences were observed between the live birth prevalence and incidence of Down syndrome, trisomy 18 and "other" chromosomal anomalies according to Registered Indian status, albeit not as pronounced as those observed for maternal age. In the case of Down syndrome, the relative difference between live birth prevalence and birth incidence was smaller for Registered Indian (+5.2%) than for non-Registered Indian (+13.0%) women. Trisomy 18 incidence was twice the rate of live birth prevalence in non-RI women, however, no live birth cases were detected in the RI population and therefore a rate difference could not be calculated. Looking at 'other chromosomal anomalies', the rate difference was larger for non-RI compared to RI women (17.5% vs. 4.4%, respectively). A difference potentially due to the higher rates of amniocentesis testing in non-RI women compared to RI women, which increases the likelihood of identifying other chromosomal anomalies not screened for through MSS.

Figure 4.23 Live birth prevalence and incidence of Down syndrome by mother's age group, Saskatchewan, 2000-2005



	24 years & under	25-29 years	30-34 years	35 years & over
Live birth prevalence	9.3	8.5	14.1	44.2
Incidence	10.0	8.4	14.0	57.3

Figure 4.24 Live birth prevalence and incidence of trisomy 18 by mother's age group, Saskatchewan, 2000-2005



	24 years & under	25-29 years	30-34 years	35 years & over
Live birth prevalence	1.2	0.9	1.3	2.8
Incidence	1.2	2.2	3.2	8.2

Figure 4.25 Live birth prevalence and incidence of "other" chromosomal anomaly by mother's age group, Saskatchewan, 2000-2005

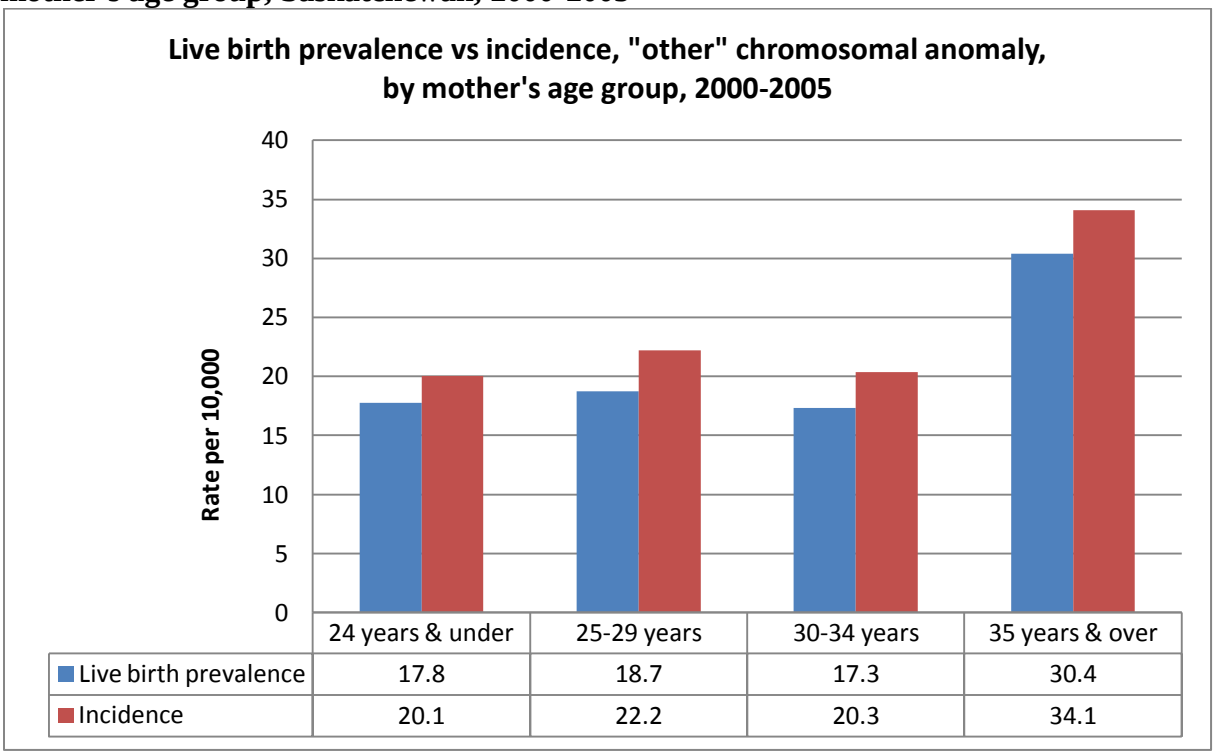


Figure 4.26 Live birth prevalence and incidence of Down syndrome by Registered Indian status, Saskatchewan, 2000-2005

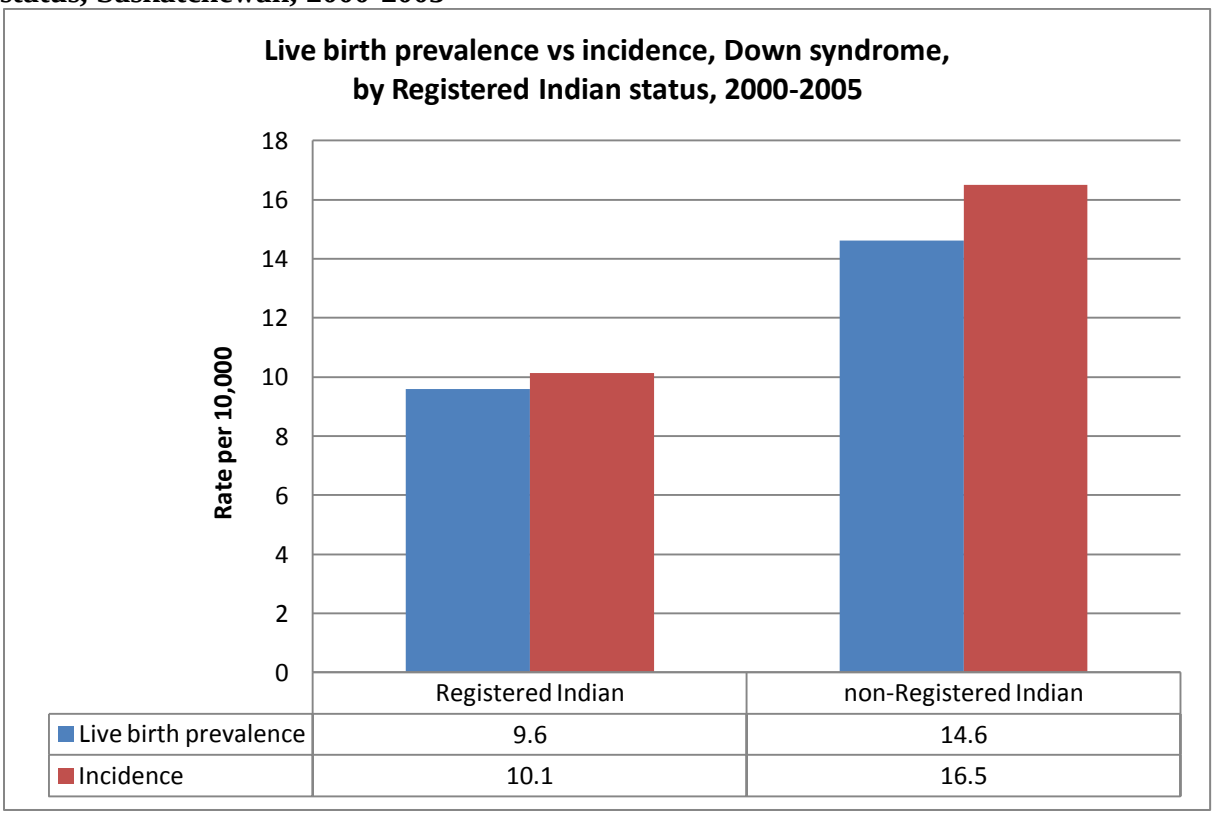


Figure 4.27 Live birth prevalence and incidence of trisomy 18 by Registered Indian status, Saskatchewan, 2000-2005

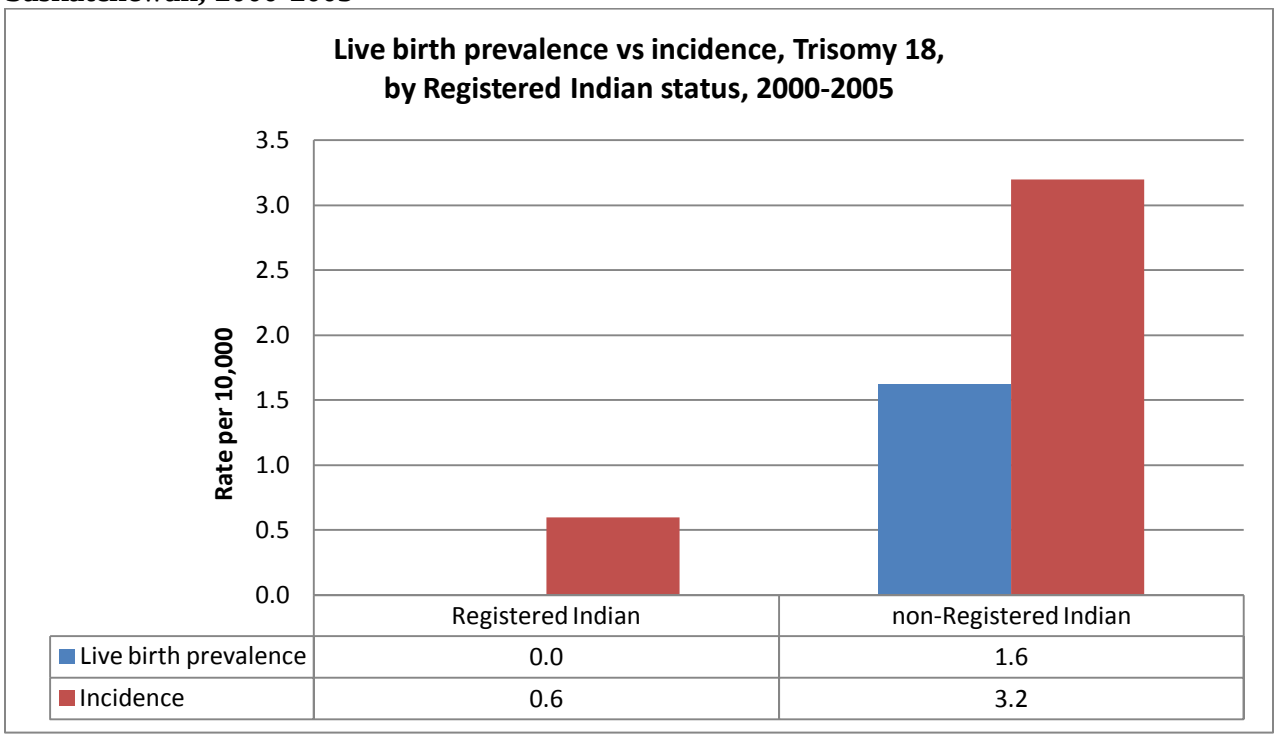
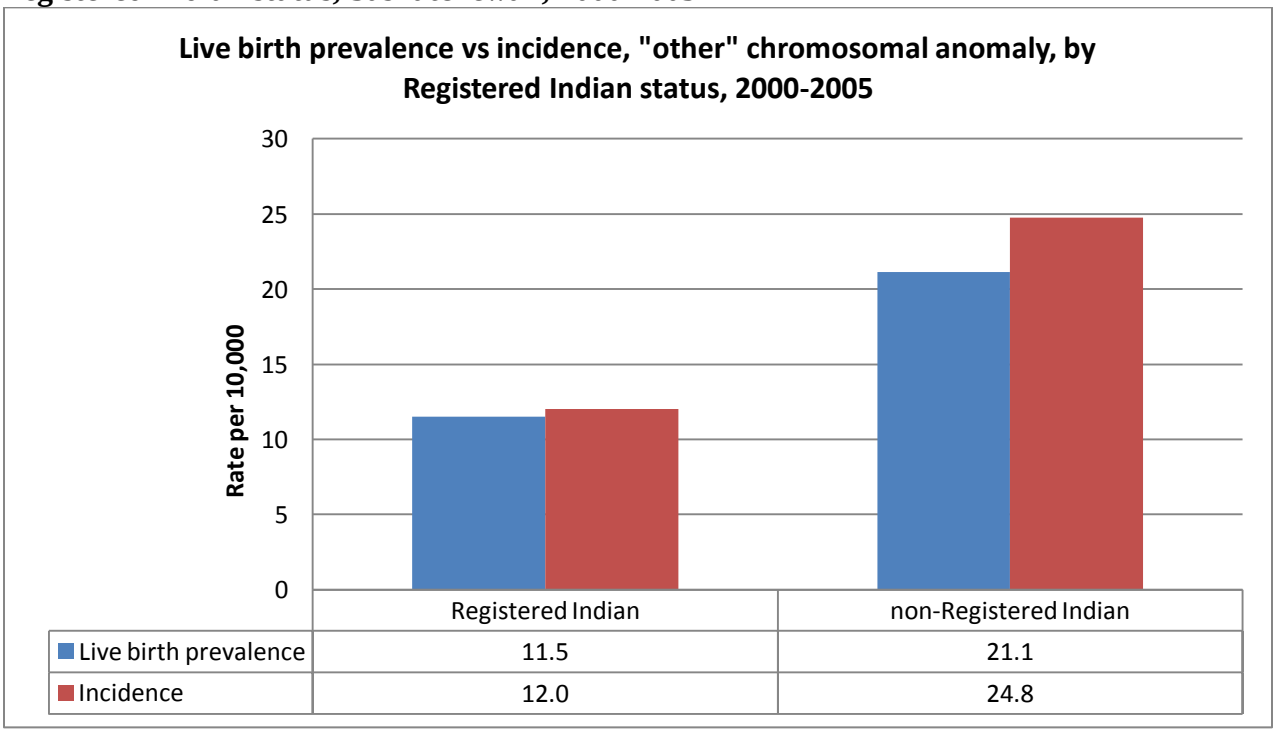


Figure 4.28 Live birth prevalence and incidence of "other" chromosomal anomaly by Registered Indian status, Saskatchewan, 2000-2005



4.5 Terminations of pregnancy for reason of congenital anomaly

4.5.1 Descriptives

The focal point of the current study was the identification of selective abortions performed following a CA diagnosis, to study the impact of this practice on population outcomes, and explore characteristics of pregnancies being ended in this manner. In total, 95 fetuses were taken by means of a TOPFA, involving 94 pregnancies. Table 4.20 presents information on key characteristics of these women and their fetuses. Women of all ages underwent TOPFA, with a somewhat higher percentage belonging to women aged 25-29 years; a difference that likely reflects the greater fertility of this population. Cases were split equally between urban and rural regions. While 21.7% of all pregnancies belonged to RI women (table 4.1), 12.6% of TOPFAs were performed on RI women. The number of cases was higher in 2003 - 2005 as compared to the first two years of the MSS program (2001-02). The majority of cases had MSS (67.4%) or amniocentesis (65.3%) earlier in the pregnancy. Of pregnancies undergoing amniocentesis (then followed by a TOPFA), almost one-third (32.3%) did not have a chromosomal anomaly, 22.6% returned no result or discontinued testing, and the remaining 45.1% had a chromosomal anomaly. When all diagnostic information was compiled for these cases, the most common known or suspected diagnoses were Down syndrome (15.8%), neural tube defect (14.8%), and other chromosomal anomaly (10.5%). In 46.3% of TOPFAs, the CA type was unknown. This is largely due to the absence of stillbirth diagnostic data and O35/655 codes from the mother's abstract. As far as timing of the abortions, selective terminations generally occurred later in the pregnancy than an elective abortion typically would; most were done between 15-23 weeks (82.1%), with 7 (10.5%) being carried out between 24-30 weeks gestation.

Table 4.20 Terminations of pregnancy for reason of fetal anomaly, Saskatchewan, 2001-2005 (n=95)

	n (%)
Mother's age group	
Under 25 years	18 (18.9)
25-29 years	29 (30.5)
30-34 years	23 (24.2)
35 years and more	25 (26.3)
Health region of residence	
Urban regions	47 (49.5)
Rural regions	48 (50.5)

Registered Indian Status	
No	83 (87.4)
Yes	12 (12.6)
Year of event	
2000	**
2001	7 (7.4)
2002	19 (20.2)
2003	23 (24.2)
2004	24 (25.3)
2005	20 (21.1)
Maternal Serum Screening completed	
Yes	64 (67.4)
No	31 (32.6)
Amniocentesis completed	
Yes	62 (65.3)
No	33 (34.7)
Amniocentesis diagnosis	
Trisomy 21	11 (17.7)
Trisomy 18	9 (14.5)
Other chromosomal anomaly	8 (12.9)
No chromosomal anomaly	20 (32.3)
No result/missing	14 (22.6)
Pregnancy outcome	
Live birth, followed by death	12 (12.6)
Fetal death >=20 weeks or 500g	25 (26.3)
Fetal death < 20 weeks or <500g	58 (61.1)
Confirmed or suspected diagnosis	
Down syndrome	15 (15.8)
Neural tube defect	14 (14.7)
Trisomy 18	9 (9.5)
Unknown*	44 (46.3)
Other chromosomal or congenital anomalies	13 (13.7)
Gestational age at termination	
15-20 weeks	45 (47.4)
21-23 weeks	33 (34.7)
24-30 weeks	10 (10.5)
Missing	7 (7.4)

***** Unknowns are presumed to be cases where a congenital anomaly was diagnosed (or suspected) by ultrasound (eg. spina bifida, anencephalus,cardiac abnormalities, urinary tract anomalies). Because ultrasound data is not available in a format that can be easily linked with administrative health databases, this information was not available. There were 6 cases where a fee-for-service billing code indicated an amniocentesis was performed, but there was no record (and therefore no diagnosis) in the data. It is possible that these were performed out-of-province.
**Figures suppressed <5

From 2001 to 2005 there were 70 chromosomal anomalies diagnosed through amniocentesis. Table 4.21 below reports the proportion of prenatally diagnosed cases that were terminated. Overall, the proportion of trisomy 18 (75.0%, 95% CI 42.8-94.5) and Down syndrome (73.3%, 95% CI 44.9-92.2) pregnancies terminated was much higher than for the 'other' chromosomal anomalies category (18.6%, 95% CI 8.4-33.4). Small numbers made interpretation difficult, in particular for RI women where the number of cases diagnosed during pregnancy was very small (<5). The number of prenatally diagnosed cases of Down syndrome and trisomy 18 was similarly small in younger women, making interpretation a challenge. Rate of TOPFA, for Down syndrome and trisomy 18 combined, was only slightly higher in women aged 30 and over (75.0%, 95% CI 50.9-91.3) compared to those 29 years and under (71.4%, 95% CI 29.0-96.3). For 'other' chromosomal anomalies, pregnancy termination was much less common in women aged 30 and over (33.3%, 95% CI 14.6-57.0) compared to those 29 years and under (4.5%, 95% CI 0.12-22.8). Data could not be reported according to urban and rural residence due to suppression of urban-rural status for live births with Down syndrome, neural tube defects, or trisomy 18.

Table 4.21 Number of chromosomal anomalies prenatally diagnosed and terminated, by CA type, by mother's age, RI status, and health region of residence, Saskatchewan, 2001-2005 (pooled)

TOPFA/ number prenatally diagnosed (%)	**Down syndrome**	**Trisomy 18**	**'Other' chromosomal anomalies**	**Total**
29 years & under	5/7 (71.4)		7/21 (33.3)	12/ 28 (42.9)
30 years & over	9/11 (81.8)	6/9 (66.7)	1/22 (4.5)	16/42 (38.1)
Registered Indian	**/**			**/**
Non-Registered Indian	10/14 (71.4)	8/11 (72.7)	8/42(19.0)	26/67 (38.8)
Total	75.0%	73.3%	18.6%	40%

** Figure suppressed < 5

Figures 4.29-4.34 present the TOPFA rates by RI status, maternal age, and urban-rural residence for all pregnancies[31], enabling comparisons across subgroups. Between 2001 and 2005, there were 1.19 pregnancy terminations for CA per 1,000 total pregnancies for the whole of Saskatchewan (95% CI 0.9-1.4), with the occurrence being half as common for women of RI status (0.64 per 1,000 total pregnancies, 0.3-1.0) compared to non-RI women (1.34, 95% CI 1.1-

[31] Note: Only pregnancies that had the potential to result in a TOPFA were included in the denominator (live births, stillbirths, or abortions that underwent prenatal diagnosis).

1.6). The difference between RI and non-RI women narrowed over the five-year period. The TOPFA rate was much higher in women aged 35 and over (2.78 per 1,000 pregnancies, 95% CI 1.8-4.1) compared to those 24 years and under (0.61 per 1,000 pregnancies, 95% CI 0.3-0.9); the rates rose with increasing age. Overall pregnancy terminations for fetal anomaly were more prevalent in women aged 30 and over from 2001-2005, however, rates increased from 2003-2005 in women under age 30. Rates were very similar in rural (1.44 per 1,000 pregnancies, 95% CI 1.0-1.9) and urban populations (1.32 per 10,000 pregnancies, 95% CI 0.9-1.7) (figure 4.33).

Figure 4.29 Rate of termination of pregnancy for fetal anomaly, number per 1,000 total pregnancies, Registered Indian and non-Registered Indian, Saskatchewan, 2001-2005 (pooled)

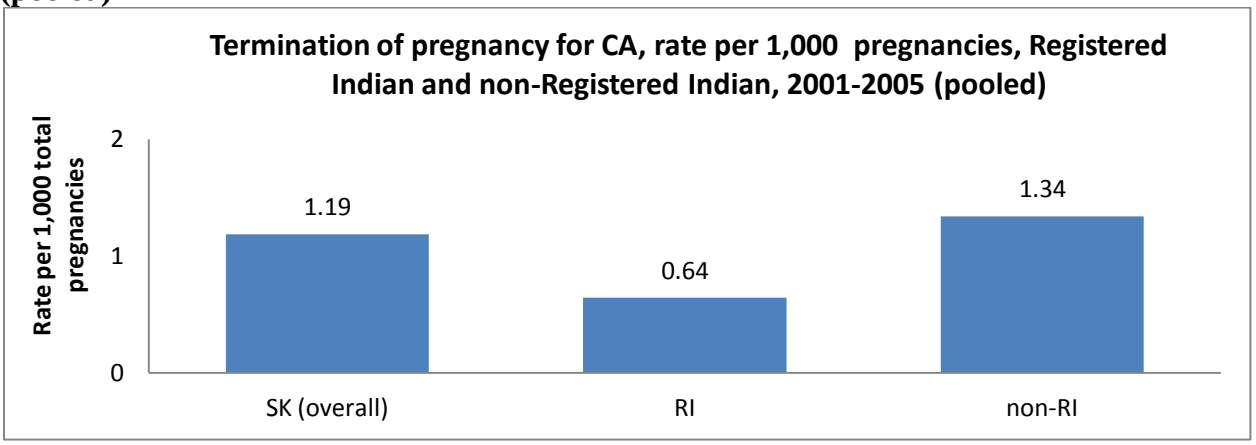


Figure 4.30 Rate of termination of pregnancy for fetal anomaly, number per 1,000 total pregnancies, Registered Indian and non-Registered Indian, annual, Saskatchewan, 2001-2005

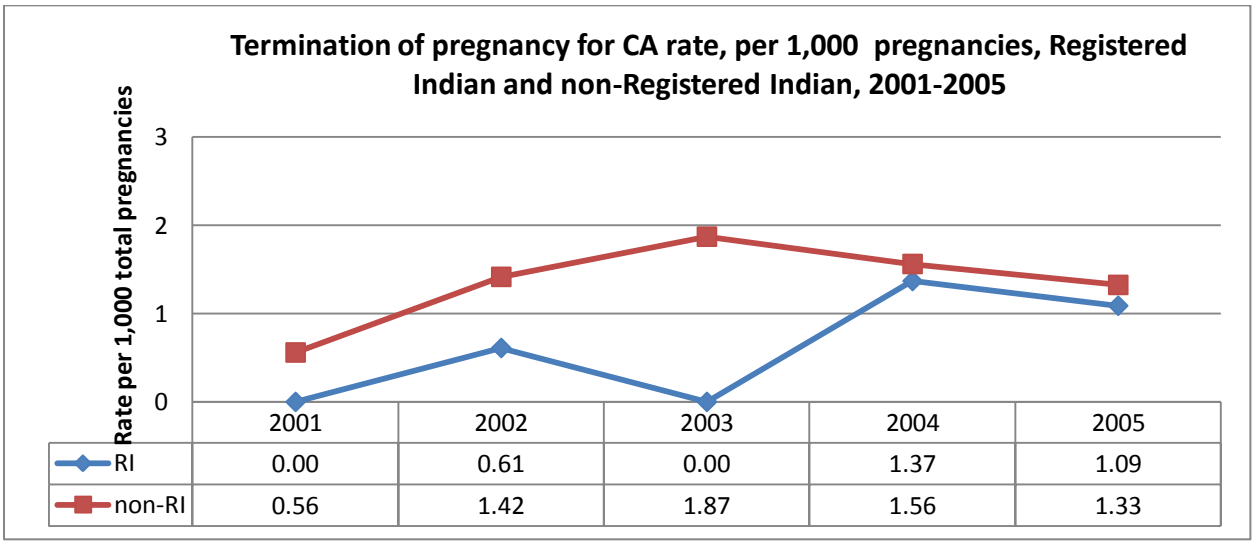


Figure 4.31 Rate of termination of pregnancy for fetal anomaly, number per 1,000 total pregnancies, by age group, annual, Saskatchewan, 2001-2005 (pooled)

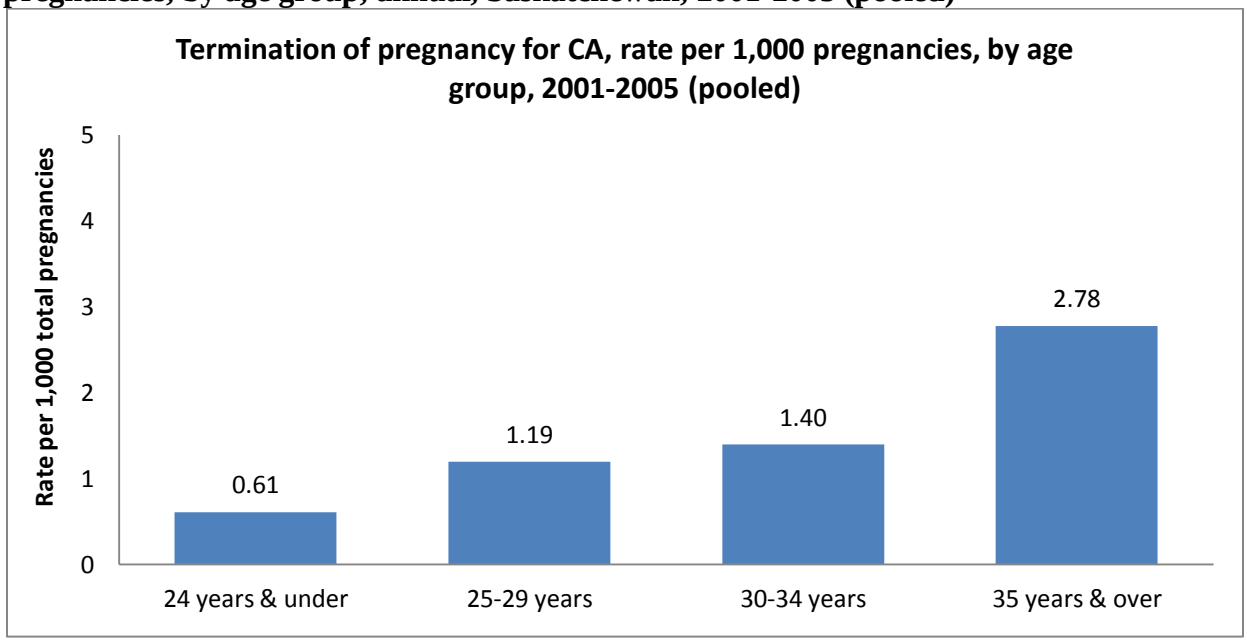
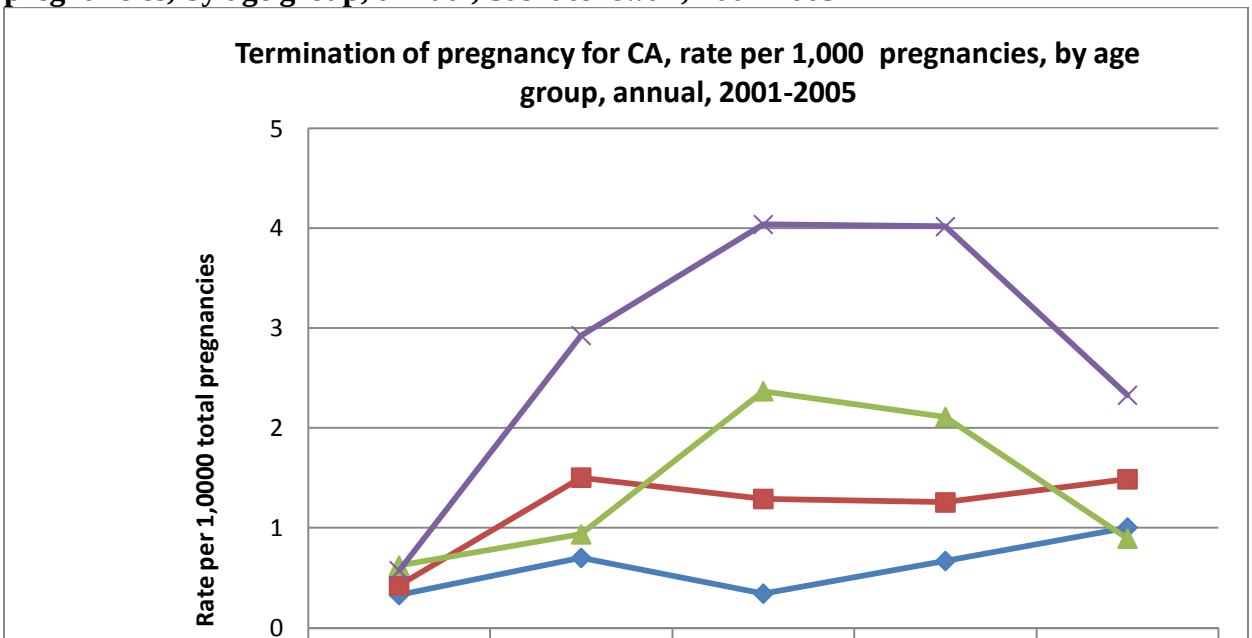


Figure 4.32 Rate of termination of pregnancy for fetal anomaly, number per 1,000 total pregnancies, by age group, annual, Saskatchewan, 2001-2005



	2001	2002	2003	2004	2005
24 years & under	0.33	0.70	0.34	0.67	1.01
25-29 years	0.43	1.50	1.29	1.26	1.49
30-34 years	0.62	0.94	2.37	2.11	0.89
35 years & over	0.57	2.93	4.04	4.02	2.33

Figure 4.33 Rate of termination of pregnancy for fetal anomaly, number per 1,000 total pregnancies, by rural-urban health region of residence, Saskatchewan, 2001-2005 (pooled)

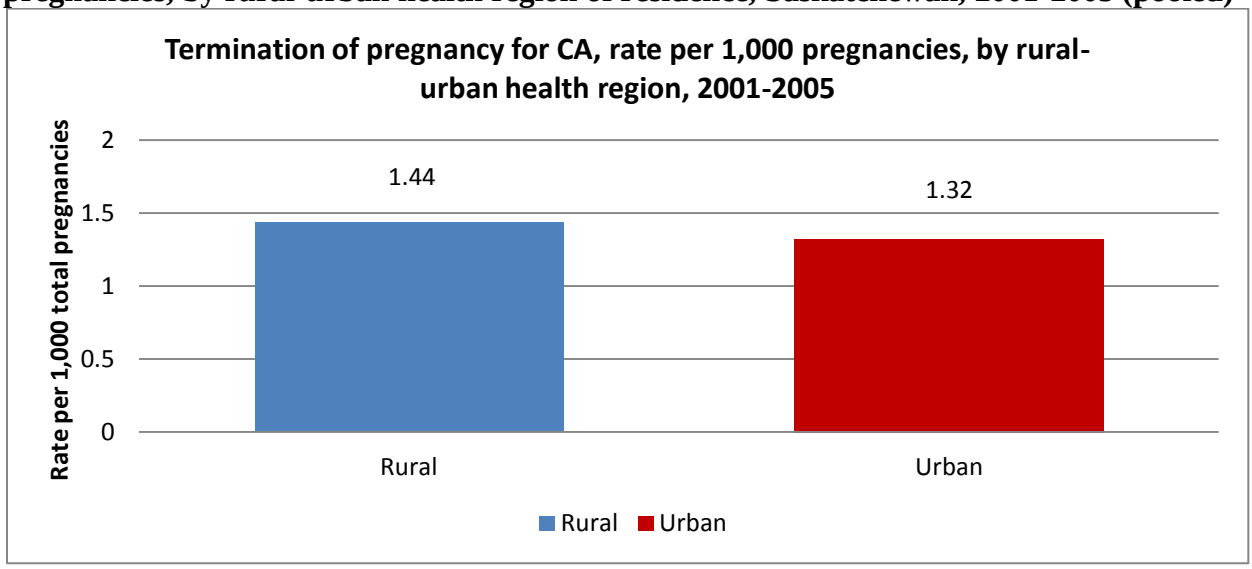
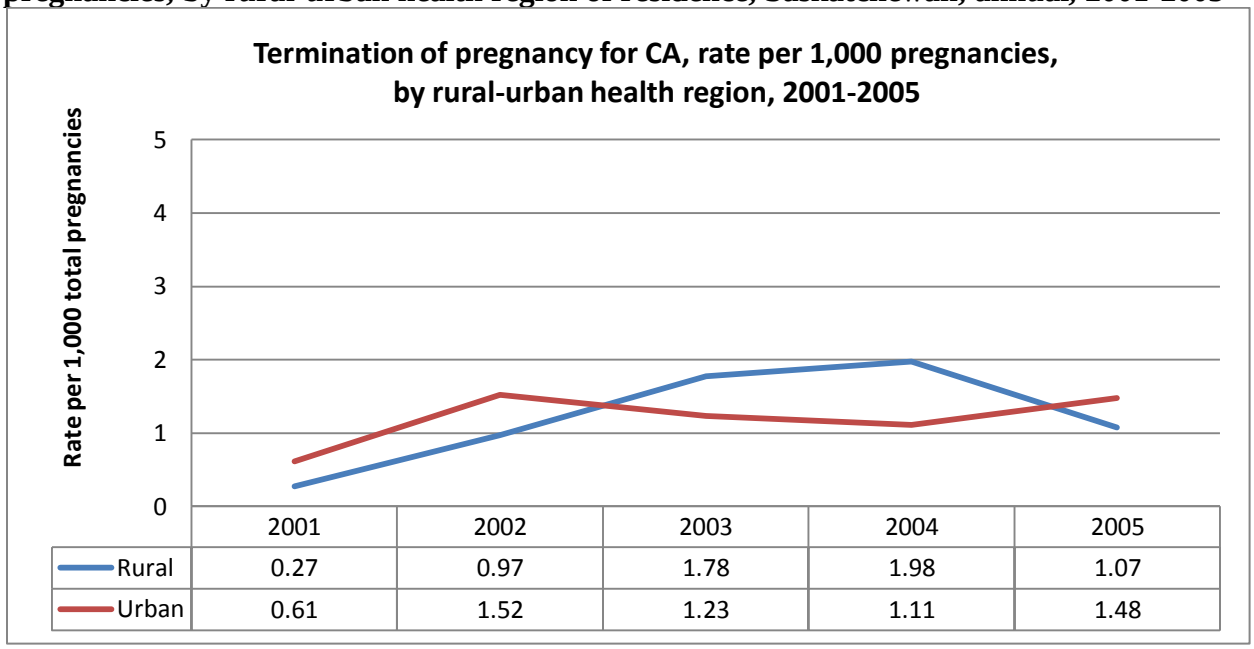


Figure 4.34 Rate of termination of pregnancy for fetal anomaly, number per 1,000 total pregnancies, by rural-urban health region of residence, Saskatchewan, annual, 2001-2005



	2001	2002	2003	2004	2005
Rural	0.27	0.97	1.78	1.98	1.07
Urban	0.61	1.52	1.23	1.11	1.48

4.5.2 Rates by gestational age

Recent evidence has shown that pregnancy termination rates vary by gestational age of the fetus at the time of diagnosis.(98) To test for a similar association in the Saskatchewan data, using all chromosomal anomalies diagnosed via amniocentesis, pregnancy termination rates were

calculated for three gestational age categories. Amniocentesis data from the Regina Qu'Appelle Health Region did not include gestational age; therefore the current analysis is limited to procedures performed in Saskatoon (n=660). Similar to findings from other studies, the pregnancy termination rate declined with increasing gestational age (chi-square = 44.86, p<.000). Upon closer inspection, the majority (81.3%) of the amniocenteses performed between 12-16 weeks were due to 'advanced maternal age', whereas abnormal ultrasound was the most common (83.6%) reason for having the procedure at 22 weeks or later. It must be noted that this analysis includes only women that received a diagnosis following amniocentesis, and not those cases where the anomaly was diagnosed using ultrasound only.

Table 4.22 Pregnancy termination for chromosomal anomaly, by gestational age at amniocentesis, 2001-2005

	Gestational age		
	12-16 weeks	**17-21 weeks**	**22 weeks or later**
Number of chromosomal anomalies diagnosed	12	24	8
Number of pregnancy terminations	7	10	**
Percent of pregnancies with anomaly terminated (95% CI)	58.3% (27.7-84.8)	41.7% (22.1-63.4)	<20.0%* (0.3-52.7)
Most common reason for amniocentesis (%)	81.3% - advanced maternal age	47.6% - positive MSS result	83.6% - abnormal finding on ultrasound

*Percent reported in general terms due to suppression of numerator **Figure suppressed < 5

Earlier pregnancy terminations for reasons of a CA (< 20 weeks) that do not meet the legal criteria for a stillbirth or live birth are often missed when surveillance or research relies solely on vital statistics records. In Saskatchewan, 58 TOPFAs (61.1%) were performed prior to 20 weeks (or before the fetus weighed 500 grams). Two sets of rates were calculated below in order to illustrate the difference one could expect to see if only using vital statistics records to identify cases (table 4.23): (1) TOPFA that resulted in a live or stillbirth (per 1,000 total births); and (2) all TOPFA including early terminations (per 1,000 total pregnancies).[32] The six-year rate for the TOPFA-live or stillbirths was 0.5 per 1,000 total births, while the total TOPFA rate was 1.3 per 1,000 total pregnancies.

[32] Total pregnancies includes all live and stillbirths, as well as pregnancies that underwent prenatal diagnostic testing. Spontaneous and other medical abortions that were not evaluated for a CA were not included in the denominator.

Table 4.23 Pregnancy termination for chromosomal anomaly, births versus all pregnancies, number and rate, Saskatchewan, annual, 2000-2005

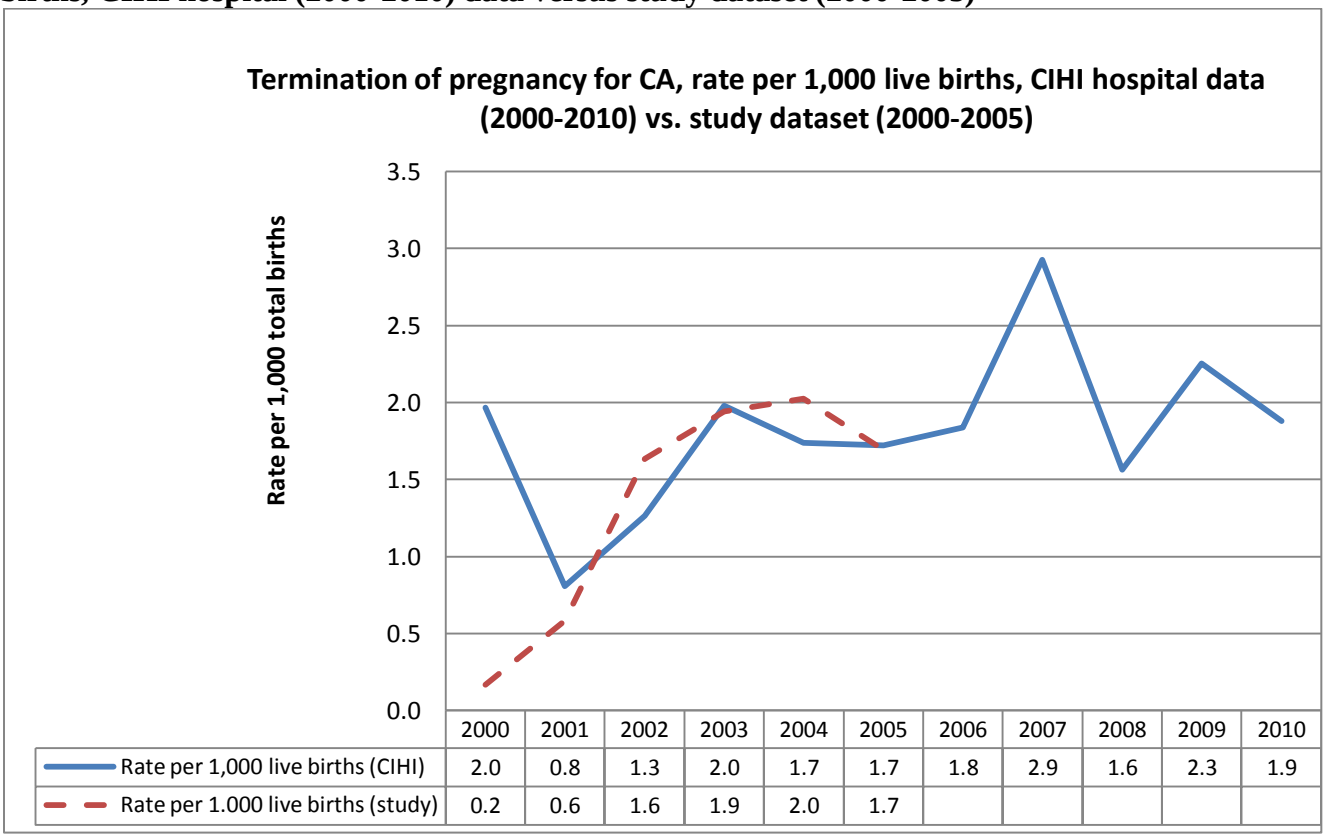
	2000	2001	2002	2003	2004	2005	6-year total (95% CI)
TOPFA- live or stillbirths	**	**	6	7	11	11	37
Rate per 1,000 total births	**	**	0.5	0.6	0.9	0.9	0.5 (0.4-0.7)
TOPFA- all pregnancies	**	7	19	23	24	20	95
Rate per 1,000 total pregnancies	**	0.6	1.6	1.9	2.0	1.7	1.3 (1.1-1.6)

** Figure suppressed < 5.

4.5.3 Comparing findings to aggregate data from the Canadian Institute for Health Information

Because the study dataset did not contain cytogenetics data for the year 2000 and part of 2001 was missing for Regina's laboratory, it was known that some cases of TOPFA would be missed. In addition, diagnostic data for non-chromosomal anomalies was not available for fetal losses, including pregnancy terminations. A special data request was made to the Canadian Institute for Health Information (see Methods chapter) in order to compare the number of TOPFA identified from each data source, despite the fact that the DAD itself may not have had perfect capture of cases during this time period. From 2000-2005, the study dataset identified 95 TOPFA cases, while the CIHI hospital data file reported 115 cases. As was expected, the largest difference could be seen in the year 2000 (24 cases in CIHI data vs. 2 in the study dataset), while agreement between the two datasets from 2001-2005 was very good. Beyond 2005, the CIHI data shows a slight upward trend, with rates varying year-to-year.

Figure 4.35 Rate of termination of pregnancy for fetal anomaly, number per 1,000 live births, CIHI hospital (2000-2010) data versus study dataset (2000-2005)



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Rate per 1,000 live births (CIHI)	2.0	0.8	1.3	2.0	1.7	1.7	1.8	2.9	1.6	2.3	1.9
Rate per 1.000 live births (study)	0.2	0.6	1.6	1.9	2.0	1.7					

4.6 Infant deaths

In total, 428 infant deaths occurred within our study population. A significant portion (42.3%) of deaths occurred to babies with mothers under age 25, however, a majority of births occurred in this age group as well (35.4%) (table 4.24). Fifty-one percent of babies dying lived in a rural or remote health region and 36.2% belonged to mothers of Registered Indian status. When considering that 22.2% of all births belonged to a RI mother, the proportion of infant deaths is overrepresented in the First Nations population, consistent with published research.(38) More than half (57.9%) of infants that died were of low birth weight (<2500g) and more than one-third (38.1%) of infants were extremely low weight (<1000g). More than half of infant deaths (61.2%) occurred within the first 27 days of life. An autopsy was performed in 139 (32.5%) of the death cases, but interestingly, only said to determine the cause of death in 40 of those cases.

Table 4.24 Infant death descriptives, Saskatchewan, 2000-2005 (n=428)

	n (%)
Mother's age	
Less than 25	181 (42.3)
25-29 years	130 (30.4)
30-34 years	76 (17.8)
35 years+	41 (9.6)
Plurality	
Twins (both died)	30 (7.0)
Twin (sibling survived)	26 (6.1)
Single	347 (81.1)
Missing or suppressed	25 (5.8)
RHA of residence	
RQHR/SHR	190 (44.4)
Rural health region	219 (51.2)
Suppressed	19 (4.4)
Mother's Registered Indian Status	
Yes	152 (36.2)
No	266 (63.8)
Birth weight	
500 grams or less	44 (10.3)
500-999 grams	119 (27.8)
1000-1499 grams	25 (5.8)
1500-2499 grams	60 (14.0)
2500-3999 grams	152 (35.5)
4000+ grams	20 (4.7)
Missing	8 (1.9)
Gestational age	
15-20 weeks	13 (3.0)
21-25 weeks	127 (29.7)
26-31 weeks	60 (14.0)
32-36 weeks	58 (13.5)
37 weeks +	157 (36.6)
Missing	13 (3.0)
Age at death	
0 days	153 (35.7)
1-6 days	73 (17.1)
7-27 days	36 (8.4)
28-365 days	166 (38.8)
Autopsy performed	
Yes	139 (32.5)
Used to determine cause of death	40 (9.3)
No	231 (54.0)
Missing	58 (13.5)

Year of death	
2000	57 (13.3)
2001	65 (15.2)
2002	60 (14.0)
2003	71 (16.6)
2004	75 (17.5)
2005	92 (21.5)
2006	8 (1.9)

From 2000-2005, the most common cause of death for infants under age one was "other causes" (45.0%), as per the current study definition (table 4.25). The second most common cause identified was "conditions arising in the perinatal period" (34.1%). Altogether, 20.8% (n=89) of infants who died had a CA listed as the underlying cause of death and an additional 4.4% (n=19) had a CA as one of multiple causes of death, meaning that one or more CA played a role in 108 (25.2%) infant deaths. In total, 310 of the 418 deaths (74.8%) did not identify a CA as a cause of death on the Vital Statistics registration. However, when taking a closer look into the hospital, amniocentesis, and physician services data, 72 of those 310 cases had a CA diagnosis including: 4 infants born with anencephalus or encephalocele, 24 instances of circulatory system anomalies, 17 with "other" CA types, and 21 with multiple anomalies. The contribution of these anomalies to death is unclear, but calls into question the documentation of CA as an underlying or multiple cause of death.

Table 4.25 Underlying cause of death, infant deaths (under 1 year of age), Saskatchewan, 2000-2005 (pooled)

Diagnostic category	Underlying cause of death, Vital Statistics n (%)
Congenital anomaly	89 (20.8)
Perinatal conditions	146 (34.1)
Other causes*	193 (45.0)
Total	428

*'Other causes' include reasons not related to congenital anomaly or conditions in the perinatal period.

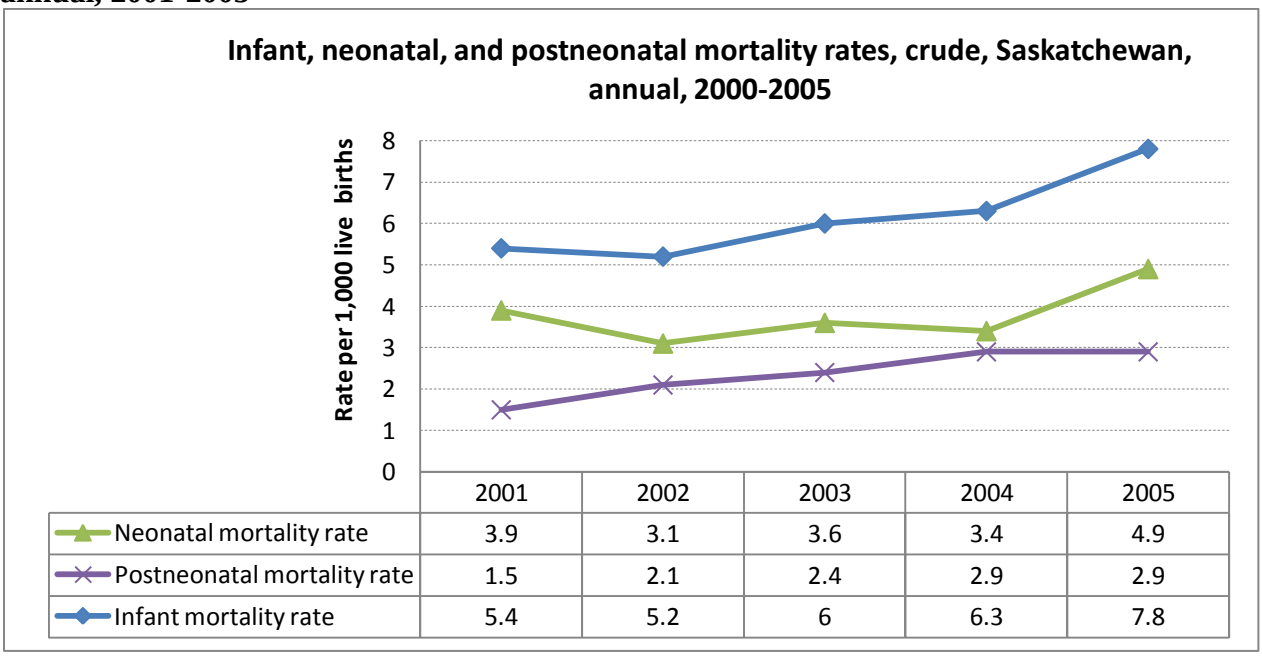
Overall congenital anomalies claimed a significant portion of infant lives (20.8%), but the contribution of any one category or type of CA was very small. Infant deaths due to anencephalus, spina bifida, Down syndrome, or trisomy 18 could not be reported on a year-to-year basis or even as a six-year pooled figure (for each individual category), due to the Ministry's 'small cell size' policy. Between 2000-2005, there were 12 infant deaths with one of the 'screenable conditions' as the primary cause (ie. anencephalus, spina bifida, Down syndrome,

or trisomy 18). The next most common categories of death involving a CA were: other chromosomal anomalies (n=8), circulatory system anomalies (n=13) and nervous system anomalies (n=12). A total of 44 infants died due to other types of CAs not named above.

4.6.1 Trends in infant and fetal mortality

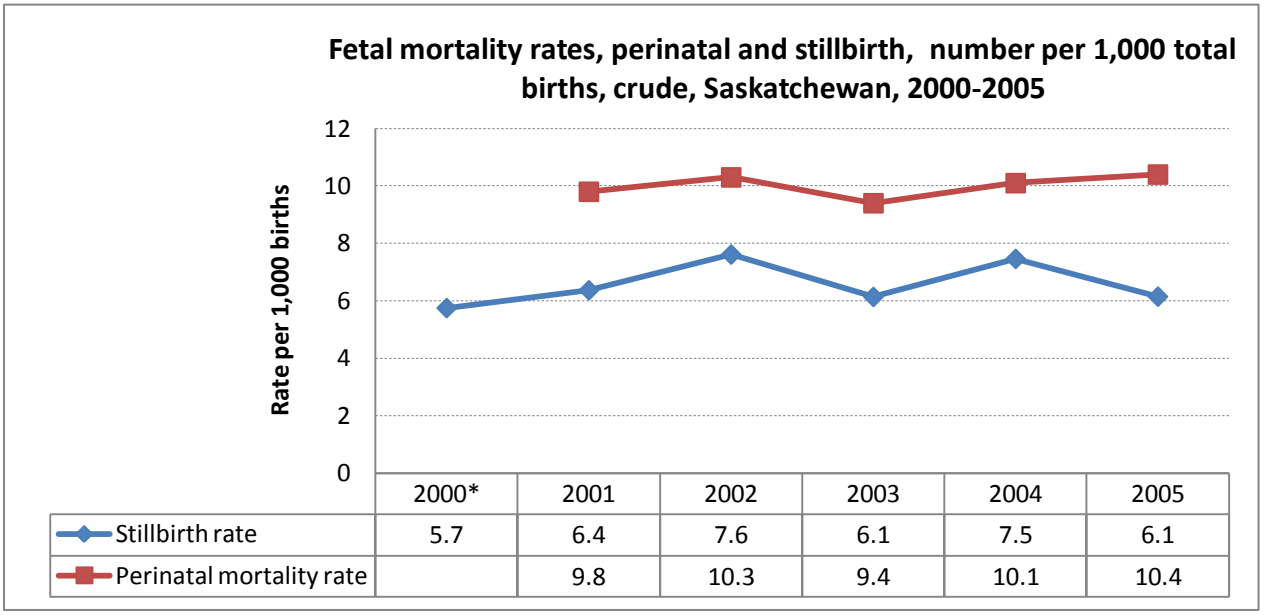
The year of death was reported for all infants who died in the study population; however, figures for the year 2000 were an underestimate given that babies born in 1999 were not included in the study. As such, analyses of infant death trends were limited to 2001-2005. Figure 4.36 illustrates trends in the crude infant, neonatal and postneonatal mortality rates across the study period. The infant mortality rate increased substantially during these five years, driven largely by an increase in postneonatal mortality from 2002-2005. The average annual percent change for the infant, neonatal, and postneonatal mortality rates were 10.0%, 8.5%, and 18.8%, respectively (chi-square test for trend p=0.01, p=0.21, and p=0.01). However, a 2005 spike in the number of neonatal deaths (3.4 per 1,000 live births to 4.9 per 1,000 live births) led to a 23.8% increase in the overall infant mortality rate above the 2004 rate. There were 58 neonatal deaths that year compare to the four-year preceding average of 42 deaths. Stillbirth and perinatal mortality (Figure 4.37) rates fluctuated year-to-year, with no clear trend observed.

Figure 4.36 Infant, neonatal, and postneonatal mortality rates, crude, Saskatchewan, annual, 2001-2005



	2001	2002	2003	2004	2005
Neonatal mortality rate	3.9	3.1	3.6	3.4	4.9
Postneonatal mortality rate	1.5	2.1	2.4	2.9	2.9
Infant mortality rate	5.4	5.2	6	6.3	7.8

Figure 4.37 Perinatal mortality and stillbirth rates, crude, Saskatchewan, annual, 2001-2005*



	2000*	2001	2002	2003	2004	2005
Stillbirth rate	5.7	6.4	7.6	6.1	7.5	6.1
Perinatal mortality rate		9.8	10.3	9.4	10.1	10.4

***** Perinatal mortality rate was not reported for the year 2000, due to the possibility that deaths to babies born in December of 1999 could have been missed. Given the study methodology, stillbirth capture would not have been affected.

4.6.2 Trends in congenital anomaly-related infant deaths

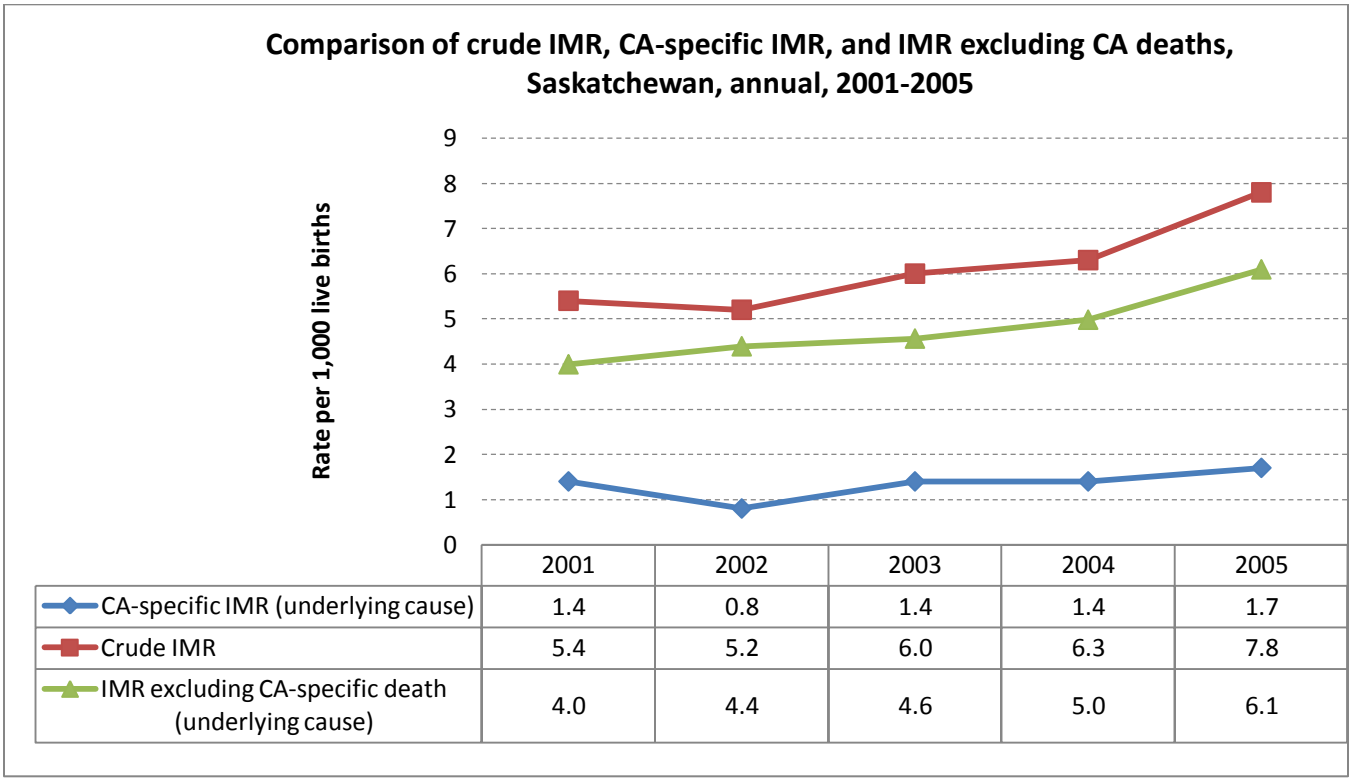
A total of 89 infants died as a result of a congenital anomaly, for an overall congenital anomaly-specific infant mortality rate of 1.25 per 1,000 live births. In order to investigate any changes in the contribution of CA-related deaths to overall infant mortality during the time period, the crude IMR is presented alongside two variations of CA-related infant mortality rates (figure 4.38): (1) CA-specific IMR and, (2) IMR excluding CA-specific death. The former is relevant to the current research as it may fluctuate due to TOPFA, while the latter will not. The CA-specific IMR experienced an annual average percent change of 13.4% over the five-year period, but the increase was not statistically significant (chi-square test for trend, p=0.31). However, in 2002 there was a 42.9% decrease in this rate (0.8 infant deaths per 1,000 live births compared to 1.4 deaths per 1,000 live births the year prior) (p=0.17). The 'IMR excluding CA-specific deaths' rose steadily and significantly over time from 4.0 per 1,000 live births in 2001 to 6.1 per 1,000 live births in 2005, representing an annual average percent change of 11.3% (p=0.01). Both CA-related and non-CA-related causes contributed to year-to-year variations in the crude IMR. For instance, fewer CA-related deaths in 2002 led to a slight decline (overall) that year, despite more non-CA deaths. In 2005, there was an increase in the number of neonatal

deaths (figure 4.36) and in non-CA deaths (table 4.26).[33] Looking at the proportion of infant deaths each year caused by a CA (figure 4.39), the figure varied from a high of 26.2% in 2001 to a low of 15.0% in 2002. The 2005 increase in the number of CA-related deaths was not apparent, as measured by proportion of deaths, due to the simultaneous increase in the number of non-CA deaths.

Table 4.26 Infant deaths, by congenital anomaly and non-congenital anomaly related causes, numbers and rates, Saskatchewan, annual, 2001-2005

	2001	2002	2003	2004	2005	Five-year total
Total infant deaths	65	60	71	75	92	363
Infant deaths **with** CA as underlying cause	17	9	17	16	20	79
Infant deaths **without** CA as underlying cause	48	51	54	59	72	284
Total births	12018	11611	11834	11845	11811	71058

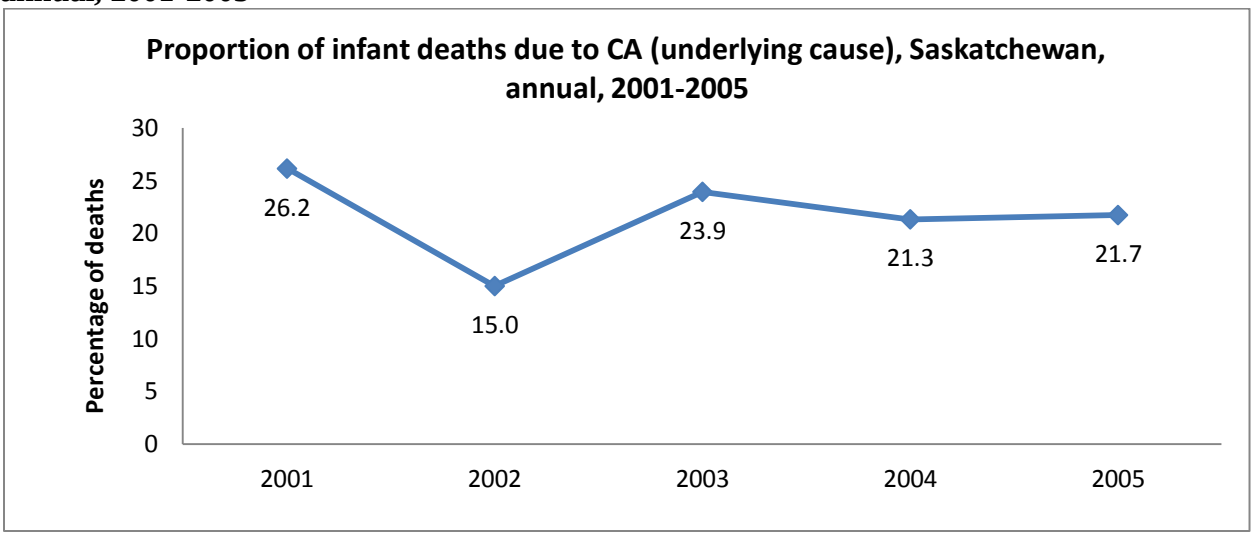
Figure 4.38 Comparison of crude infant mortality rates (crude, congenital anomaly-specific, and excluding deaths due to congenital anomaly), Saskatchewan, annual, 2001-2005



	2001	2002	2003	2004	2005
CA-specific IMR (underlying cause)	1.4	0.8	1.4	1.4	1.7
Crude IMR	5.4	5.2	6.0	6.3	7.8
IMR excluding CA-specific death (underlying cause)	4.0	4.4	4.6	5.0	6.1

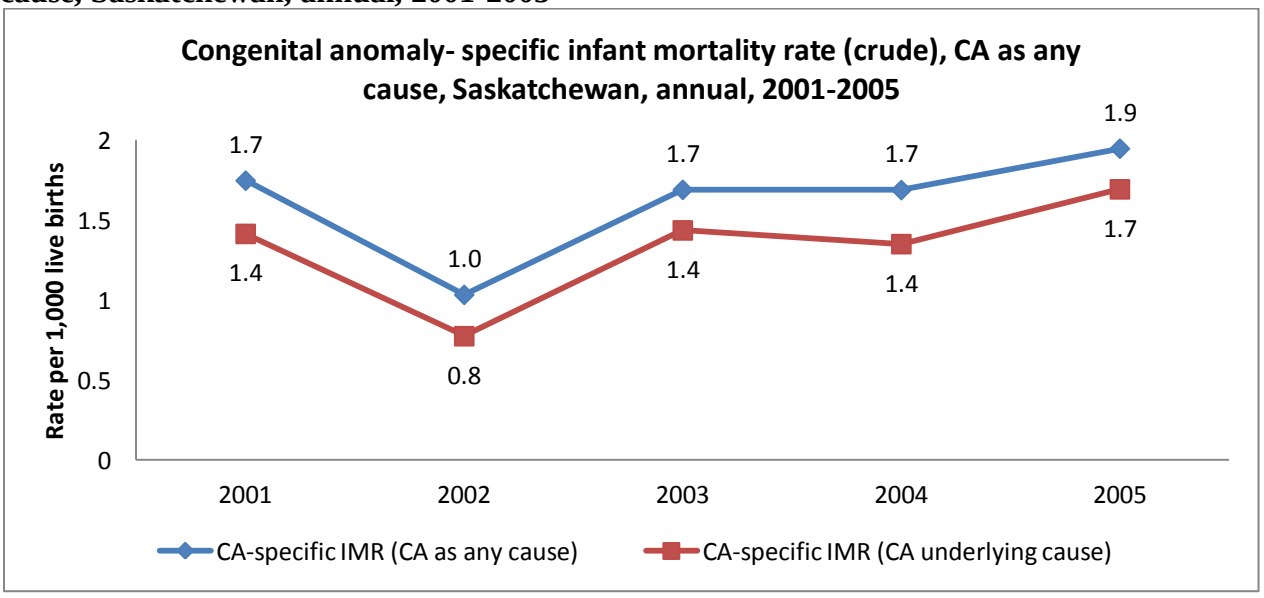
[33] A closer investigation of this finding was not possible, as our working dataset did not contain the 'death year' variable.

Figure 4.39 Proportion of infant deaths due to CA (underlying cause), Saskatchewan, annual, 2001-2005



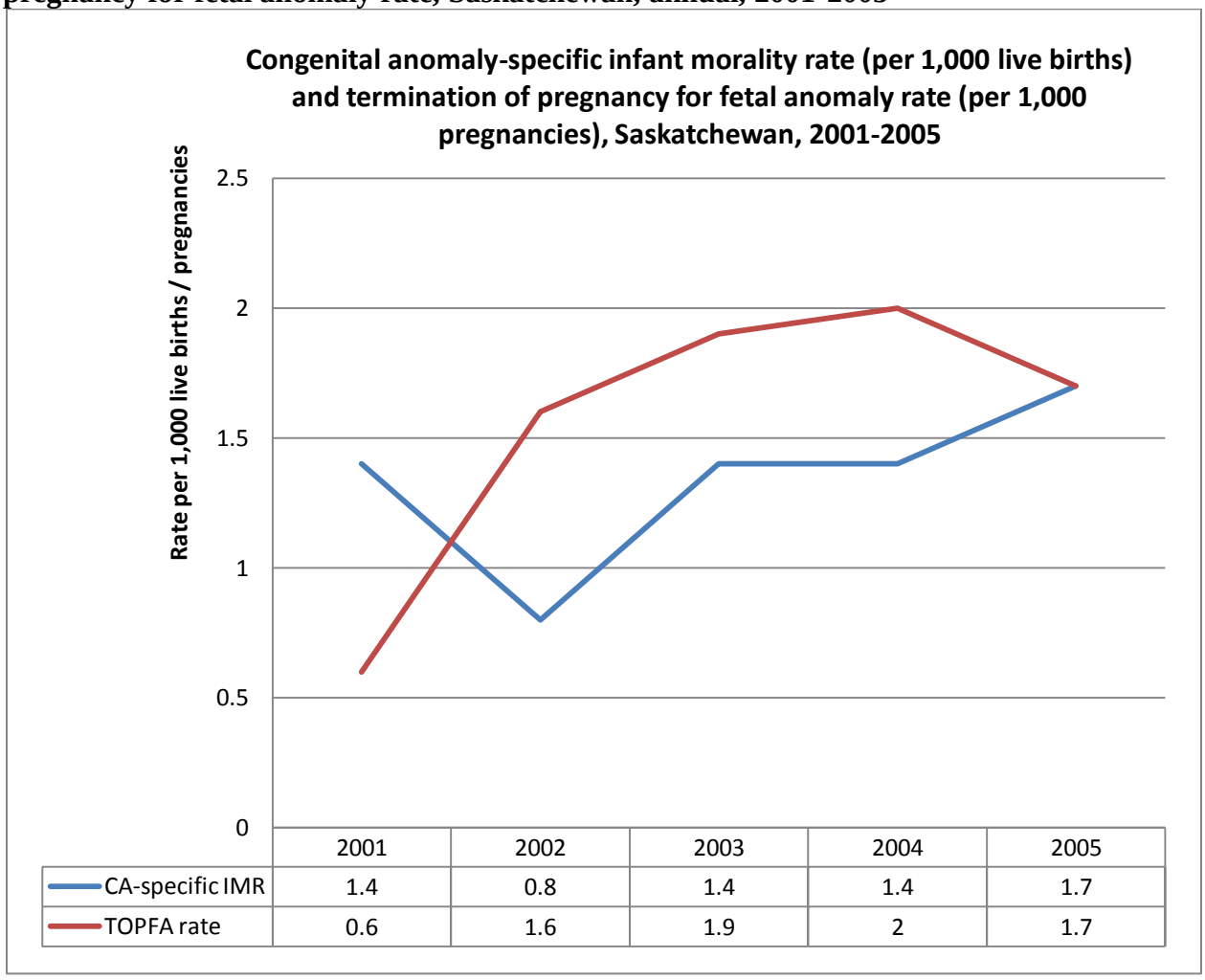
Given that determining the role of each condition in infant deaths can be complex and cause-of-death investigations and documentation may vary, rates of infant death due to CA were calculated two ways (figure 4.40): (1) including only cases where a CA was the underlying/main cause; and (2) including all cases where a CA contributed to an infant's passing. The trend remains similar, but the rate including all CA-related deaths was higher overall (+23.1%) than the rate including only deaths where CAs were the main cause of death .

Figure 4.40 Congenital anomaly-specific infant mortality rate, CA as underlying versus any cause, Saskatchewan, annual, 2001-2005



When the congenital anomaly-specific IMR is plotted alongside the TOPFA rate (figure 4.41), some interesting patterns can be seen. For instance, in 2001, a lower TOPFA rate (0.6 per 1,000 pregnancies) occurred alongside higher rates of CA-related death (1.4 per 1,000 live births). By comparison, in 2002, the TOPFA rate increased by 166.7% and the CA-specific IMR fell by 42.9%. The 2005 results are consistent with this pattern showing an increase in CA-specific mortality at the same time as the annual TOPFA rate declined. Figures for 2003 and 2004 do not illustrate a similar pattern, however the TOPFA rate is a crude indicator in that it does not portray the type of CAs being terminated. Conditions like Down syndrome and spina bifida are less likely to result in death during the first year, therefore the impact on the IMR will be less than if the fetus was affected by a serious and fatal anomaly like anencephaly.

Figure 4.41 Congenital anomaly-specific infant mortality rate and termination of pregnancy for fetal anomaly rate, Saskatchewan, annual, 2001-2005



	2001	2002	2003	2004	2005
CA-specific IMR	1.4	0.8	1.4	1.4	1.7
TOPFA rate	0.6	1.6	1.9	2	1.7

Table 4.27 Congenital anomaly-specific infant mortality rate and termination of pregnancy for fetal anomaly rate, number of deaths and total births and pregnancies, Saskatchewan, annual, 2001-2005

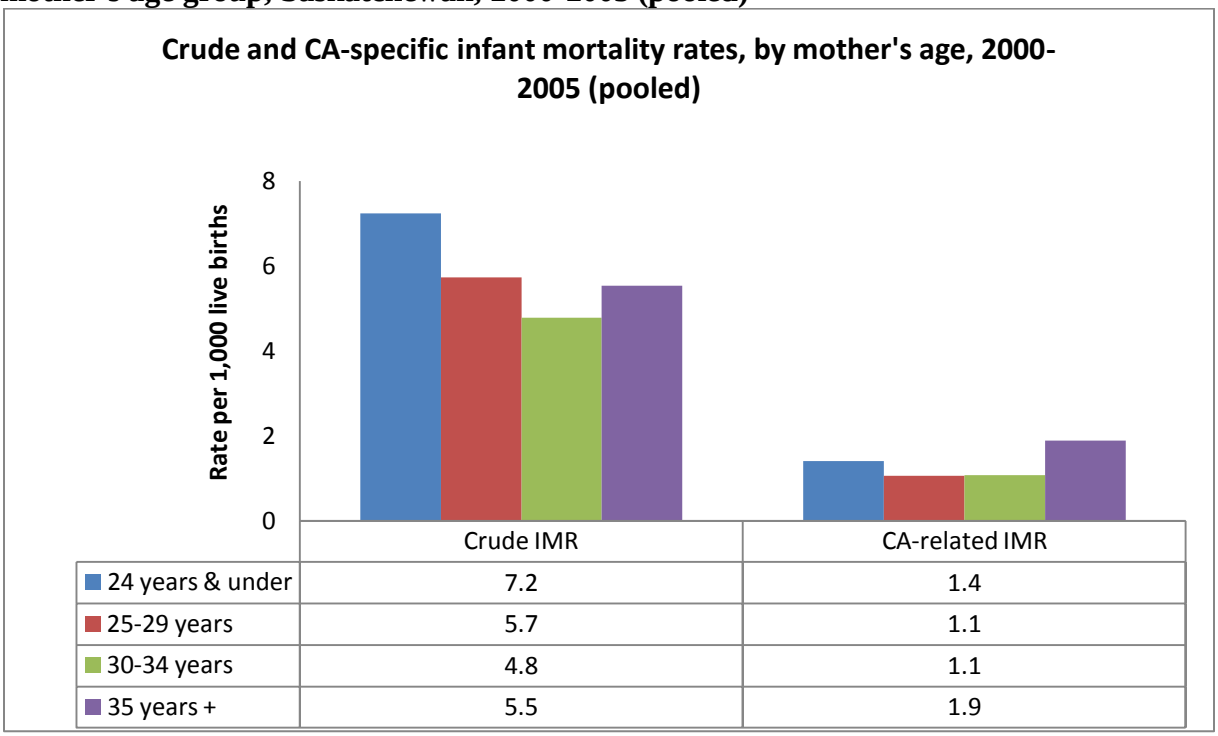
	2001	2002	2003	2004	2005
Number of deaths due to congenital anomaly	17	9	17	16	20
Number of live births	12018	11611	11834	11845	11811
CA-specific infant mortality rate (95% CI)	1.4 (0.9-2.3)	0.8 (0.4-1.5)	1.4 (0.9-2.3)	1.4 (0.8-2.2)	1.7 (1.1-2.6)
Number of TOPFA	7	19	23	24	20
Number of pregnancies	12097	11704	11912	11943	11884
TOPFA rate (95% CI)	0.6 (0.3-1.2)	1.6 (1.0-2.6)	1.9 (1.3-2.9)	2.0 (1.3-3.0)	1.7 (1.1-2.6)

4.6.3 Congenital anomaly-specific and crude infant mortality by mother's characteristics

Crude and CA-specific infant mortality rates were calculated for each age group and by RI status to explore variations in all-cause death and death related to congenital anomalies.[34] Crude rates of infant mortality declined with mother's age up to 34 years of age, then increased in the 35 years and over age group. Infant mortality rates due to CA exhibited a more J-shaped pattern with the highest rates in the oldest (1.9 deaths per 1,000 live births) and youngest age groups (1.4 deaths per 1,000 live births). Women aged 35 years and over had CA-specific infant mortality rates 72.7% higher than women aged 25-34.

[34] Due to suppression of health region of residence information, infant mortality rates could not be analyzed according to urban-rural residence of mother. There were 19 infant deaths where the mother's residence was withheld.

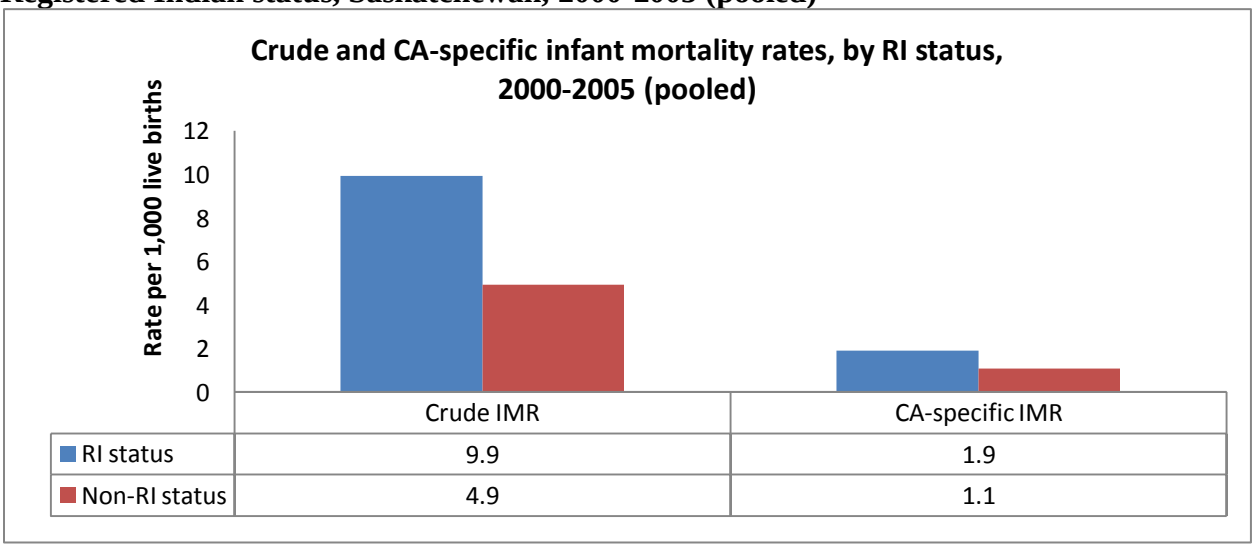
Figure 4.42 Crude and congenital anomaly-specific infant mortality rates, according to mother's age group, Saskatchewan, 2000-2005 (pooled)



	Crude IMR	CA-related IMR
24 years & under	7.2	1.4
25-29 years	5.7	1.1
30-34 years	4.8	1.1
35 years +	5.5	1.9

The difference between infant mortality rates in RI women and non-RI women was substantial for all-cause and CA-specific deaths. The crude IMR was 102.1% higher in RI women compared to non-RI women, and the CA-specific IMR was 72.7% higher.

Figure 4.43 Crude and congenital anomaly-specific infant mortality rates, according to Registered Indian status, Saskatchewan, 2000-2005 (pooled)



	Crude IMR	CA-specific IMR
RI status	9.9	1.9
Non-RI status	4.9	1.1

4.6.4 Congenital anomaly-specific neonatal mortality by mother's characteristics

Congenital anomalies are an important cause of death during the first 27 days of life (or the neonatal period).(5) Rates of CA-specific neonatal mortality were calculated in order to assess any differences between population sub-groups (see table 4.26). Registered Indian women had rates almost twice as high as non-Registered Indian women. Similar to the pattern observed for CA-specific infant death, CA-specific neonatal mortality rates were highest in the 24 years & under and 35 years & over age groups (0.92 and 1.48 per 1,000 live births, respectively), although the difference between the groups was somewhat larger in this case. Rates could not be calculated for women living in rural and urban health regions due to suppression of residence.

Table 4.28 Congenital anomaly-specific neonatal mortality rate (per 1,000 live births), by Registered Indian status, maternal age, and health region of residence, Saskatchewan, 2000-2005 (pooled)

	Congenital anomaly-specific neonatal mortality rate (per 1,000 live births)
Registered Indian Status	
Registered Indian	1.41
Non-Registered Indian	0.76
Maternal age group	
24 years & under	0.92
25-29 years	0.79
30-34 years	0.75
35 years & over	1.48
Urban-Rural health region*	
Urban	
Rural	
Overall	0.90

* Information suppressed.

4.6.5 Pregnancy terminations resulting in a birth

The fact that one pregnancy event may fall into more than one outcome category is important to consider. Equally important is the impact of dual classification on the calculation of rates and to the investigation of the impact of TOPFA on birth outcomes. In the case of fetuses aborted following the identification of a CA, events can be documented (and subsequently analyzed) as both a medical abortion and a birth (still or live). Whether or not a stillbirth or live birth record is created depends on the age and weight of the infant - 20 weeks or more or more than 500 grams for stillbirths - and whether or not the infant breaths or has a heartbeat following

delivery. Between 2001-2005, 5.3% of all stillbirths and 2.9% of all infant deaths were the result of a TOPFA.

Table 4.29 Proportion of stillbirths and infant deaths due to TOPFA, Saskatchewan, 2000-2005

	Stillbirths	Infant deaths
Percent of deaths (95% CI)	5.3 (3.6-7.8)	2.9 (1.6-5.0)
Deaths due to TOPFA	25	12
Total events	469	420

Infant and perinatal mortality and stillbirth rates were calculated with and without TOPFA cases, in order to conduct a crude assessment of the impact of these cases on routinely reported indicators. Differences in annual rates were small for most years, with the largest difference observed in 2005 for both infant mortality (7.8 vs. 7.3 per 1,000 live births) and perinatal mortality (9.4 vs. 8.9 per 1,000 live births). The largest difference in regular compared to spontaneous (2) stillbirth rates was in 2004 (7.5 vs. 6.7 per 1,000 live births, respectively).

Table 4.30 Infant and perinatal deaths, with and without termination of pregnancy for fetal anomaly, Saskatchewan, 2000-2005

	Missing	2000	2001	2002	2003	2004	2005	5-year
Infant mortality								
Infant deaths (excluding TOPFA resulting in live births)			65	59	70	73	86	353
Infant deaths (including TOPFA resulting in live births)			65	60	71	75	92	363*
Live births			12018	11611	11834	11845	11805	59119
Regular IMR			5.4	5.2	6.0	6.3	7.8	6.0
IMR- no TOPFA			5.4	5.1	5.9	6.2	7.3	6.1
Perinatal mortality								
Perinatal deaths (excluding TOPFA)	1		118	116	106	112	119	572
Perinatal deaths (including TOPFA)	1		118	122	113	123	130	607
Still- and live births	275		12043	11641	11846	11883	11827	59515
Regular PMR†	43.6		9.8	10.5	9.5	10.4	11.0	10.2
PMR- no TOPFA	43.6		9.8	10.0	8.9	9.4	10.1	9.6
Stillbirth								
Spontaneous stillbirths (excluding TOPFA resulting in stillbirths)	1	68	77	83	67	80	68	444
Regular stillbirths (including TOPFA resulting in stillbirths)	1	69	77	87	73	89	73	469
Live and stillbirths	275	12007	12043	11641	11846	11883	11827	71522
Regular stillbirth rate		5.8	6.4	7.5	6.2	7.5	6.2	6.6
Spontaneous stillbirth rate (excluding TOPFA)		5.7	6.4	7.1	5.7	6.7	5.7	6.2

* Based on MOH year of death variable. 8 cases died in 2006 and were therefore removed from calculation.

† Perinatal mortality: the total number of deaths of a fetus or infant between the end of the 20th week gestation and the end of the 6th day of life in a calendar year per 1,000 total births (live births and stillbirths) in the same calendar year.

CHAPTER 5: DISCUSSION

5.1 Uptake and distribution of prenatal screening

5.1.1 Lower uptake in First Nations and rural women

Screening uptake often varies widely by geographic location and correlates to client and physician characteristics and value systems.(28-30, 173-176) Studies elsewhere have shown maternal age, religious background, ethnicity, and geographic location all predict MSS use. It was not known if similar factors influence utilization in Canada. There was some suggestion, however, that women of Aboriginal ethnicity have been less accepting of prenatal serum screening. In Ontario the decision not to implement MSS in specific aboriginal communities was due to both 'resistance to the concept by First Nations people' and 'geographical and logistical difficulties'.(177 p.1770) There was also the perception among Saskatchewan physicians that Aboriginal patients accept MSS less often.(32) This is the first detailed exploration, to my knowledge, of the predictors of MSS uptake in a Canadian population, while controlling for other covariates.

Prenatal screening uptake was much lower in First Nations women (9.6%) compared to non-First Nations (28.4%) and living in a rural health region exacerbated the difference. Even for women who lived in an urban health region, non-RI women were more than twice as likely to have had MSS than RI women (OR=2.56), when maternal age and year of pregnancy were held constant. This finding dispels the notion that uptake may simply be lower in rural and northern locations due to access barriers, where in some instance these populations comprise of higher proportions of First Nations women. However, living in a rural region still mattered when it came to use of prenatal screening, especially for RI women. First Nations women living in urban regions were also twice as likely to screen when compared to their rural counterparts. By far, the group most likely to screen was non-First Nations women age 35 years and over living in an urban region (54.2%).

Lower screening rates in First Nations and rural populations may reflect differences in the way prenatal care is accessed and delivered and/or in personal value systems. Dillon et al (1994) found resistance to the concept of prenatal screening in Aboriginal communities in Ontario, where some felt the medicalization of pregnancy was contrary to their cultural preference for the natural.(177) Nsiah-Jefferson (1989) theorized that women of different

cultures and of lower socioeconomic status are less accepting of prenatal screening for disabilities than women from the dominant culture, viewing them within a context of eugenic discrimination and medical exploitation.(178) Lower rates of TOPFA after prenatal diagnosis have also been observed in cultural minorities.(179) Aside from cultural and personal belief systems, another contributing factor may be that, on average, Aboriginal women are more likely to receive inadequate prenatal care and therefore may present to their care providers at a time when serum screening cannot be done.(180) While no national data exists to study this claim, in Manitoba an estimated 6.9% of women received inadequate prenatal care, with the figure being as high as 20.4% in neighbourhoods where the number of Aboriginal people was high.(180)[35] A deeper investigation into this hypothesis was beyond the scope of the current study.

Risk increases with age for the most common congenital anomalies and younger, First Nations mothers may (rightly) view themselves as being at lower risk for the conditions detectable by serum screening and therefore view screening as unnecessary. The majority of Registered Indian women were under 25 years old (57.7%) and therefore were notably younger than the remaining pregnancy population in Saskatchewan (32.6%). This proposition cannot fully explain differences, as uptake rates were higher for non-First Nation women for all age groups studied. A multivariate analysis also found First Nation status to be an independent predictor of uptake ($p<.000$), even after controlling for maternal age. Follow-up by means of qualitative study or probing questionnaires will be important to elucidate factors responsible for low uptake in both First Nations and rural women.

The role of physicians and midwives with regard to uptake is uncertain, but differences in acceptance have been well-documented.(21, 32, 181-183) Permaul-Woods (1999) found that physicians in northern and rural Ontario were less likely to offer MSS than those in other regions.(173) Concerns about the social and cultural sensitivity of MSS and the availability of follow-up services affected use. In a 2005 survey, 48% of Saskatchewan physicians reported that fewer Aboriginal pregnant patients accepted MSS and likewise reported low access to resources necessary to deliver screening (ie. genetic counselling, abortion services and amniocentesis).(32) Many physicians had concerns generally, including about the performance of screening tests and creating unnecessary anxiety in women at low risk of having an affected pregnancy; findings

[35] Inadequate prenatal care referred to a low frequency of overall visits, as well as late presentation for first time prenatal care check-up.

similar to other Canadian studies (22, 175). Many physicians lacked sufficient knowledge about the test's performance, follow-up, and importantly, about the implications of having and raising a child with any of the conditions detected by screening. Poor provider understanding of complex screening protocols and inadequate follow-up resources has the potential to impact physician's practice, particularly in rural and remote communities.

5.1.2 The meaning of low uptake

Saskatchewan traditionally has had low rates of prenatal diagnosis compared to other provinces, and MSS rates are equally low, lending support to Renaud's (1993) theory of distinct provincial cultures when it comes to use of reproductive technologies.(181) Differential uptake across populations is important to monitor because MSS may lead to terminations of pregnancy; a practice with implications for CA birth incidence and infant/fetal mortality statistics. Like Saskatchewan, Newfoundland and Labrador have had a low rate of uptake (22%) relative to other provinces (eg. 63% in Ontario, 60% in Manitoba, 49% in British Columbia).(80, 133, 134, 184) A study of women in that province found that screening uptake largely reflects values incongruent with the offer of MSS.(80) Uptake did not change appreciably over the study period in Saskatchewan (18.%-26.8%) and was similar in recent reporting (2006-2009).(135)

Prenatal screening rates are not always a straight-forward reflection of the population's preferences and values. Studies have shown that many women that had screening were not informed, engaged participants in these decisions.(185, 186) As such screening rates may be higher when informed consent is not a priority. In light of this fact, Vassy (2006) argues screening rates can give the erroneous impression that women want screening, which precipitates the investment of more resources and creates a cycle of expansion.(187) Seavilleklein (2009) adds that stopping the program, however, can be seen as removing choice even though women's wishes and wants were never established in the first place.(185) The more moderate uptake observed in Saskatchewan is not necessarily a negative finding, *if* utilization reflects women's own choices and values. A qualitative evaluation of women undergoing screening and those who did not would be an important contribution to our understanding of women's experience in the province.

One study in the United Kingdom found no sign of social inequalities in the uptake of prenatal screening (188), but another reported wide discrepancies (146). Unfortunately individual

data on mothers income and education levels are not available through Saskatchewan's administrative health databases; a future study may consider mapping MSS data using mother's postal code according to neighbourhood income level for some additional insights. In Northern Ireland, where access to abortion services are restricted, the reported offer and uptake of screening was found to be lower in women with less education.(83) Similarly, Khoshnood (2004) found uptake in prenatal diagnostic testing was higher in more educated women in the United States, leading to a lower rate of age-related increase in the birth prevalence of DS.(146)

It is useful to consider the reasons that women choose to have screening and the role that women's need for reassurance may play. MSS is designed to predict just three types of conditions and in most cases provides little information about the fetus' overall wellbeing.(189) Women who opt for screening often desire to know more about the health of their baby and are wanting reassurance of the baby's health.(80, 186) On the other hand, the most common reasons women refuse screening are because they would not terminate the pregnancy and the results are not definitive. Some feminist scholars reason that modern medicine has created a cycle of dependency ('medicalization') where women rely on medical experts to allay their fears and anxieties - fears and anxieties that are often created and reproduced by those in the medical profession.(190, 191) Women from certain cultural groups and those with lower levels of education may internalize medical risk to a lesser extent, and perhaps, may feel less compelled to screen.

5.2 Utilization of Prenatal Diagnostic Testing

An estimated one percent of Saskatchewan pregnancies underwent prenatal diagnostic testing during the study. Reasons for testing over the five year period (2001-2005) shifted from 'maternal age-related concerns' to 'abnormal MSS result', with the overall number of tests gradually decreasing (-13.2% overall from 2002 to 2004).[36] This suggests that MSS is accomplishing one of its stated goals, which is to reduce the number of unnecessary invasive diagnostic tests.(157) Some women with screening results below the risk cut-off (or screen-negative) still pursued amniocentesis, but there may have been other markers or risk factors driving those decisions. In 2011, the SOGC updated its clinical practice guidelines to say that

[36] Absolute numbers obtained from the Saskatoon Cytogenetics Lab reporting on all amniocenteses performed between 2006-2012 were only slightly lower than those reported here. Between 2002-2012 the total number of tests declined by 16.2%.

testing based solely on maternal age 'should be abandoned' and that women age 40 and over should not be offered an amniocentesis unless their screening result is above cut-off or they have another significant risk factor (eg. a previous child with a chromosomal anomaly).(157) The current dataset tells the story of prenatal screening and diagnosis in Saskatchewan prior to these new recommendations. In 2004, for example, 145 women aged 35 and over had an amniocentesis. Of those women, only 28.3% had received a positive MSS screening result and another 21.4% did not have MSS, which seems to contradict the SOGC's latest recommendation that testing should not be done solely based on age. Holding all other variables constant, women that were age 35 and over, non-RI status, and living in an urban health region were most likely to undergo diagnostic testing. These are the same groups most likely to utilize MSS.

Uptake of prenatal diagnostic testing may be viewed as a better marker of a population's preferences and values (as far women's views that abortion is an acceptable intervention following CA diagnosis) than MSS uptake, where many are seeking reassurance and do not pursue follow-up testing. Pregnancy termination rates following a prenatal CA diagnosis are high, but they can often be misleading as they are based on women who chose to proceed to prenatal diagnosis. In Saskatchewan, only one-third of women (32.7%) that received an increased- risk MSS result chose to follow-up with an amniocentesis. Compare this figure to France where 95% of women that received an increased-risk MSS result from 1997-1998 underwent amniocentesis.(71) The fact that two-thirds of Saskatchewan women declined diagnostic testing, helps to put into context the finding that forty percent of women who received a prenatal diagnosis of a chromosomal anomaly terminated their pregnancy (74.1% of prenatally diagnosed Down syndrome or trisomy 18 cases and 18.6% cases of 'other' anomalies). Rates in some regions have been even higher (eg. 99.5% in France)(71, 98), although comparable figures are very difficult to locate. Women who accept prenatal diagnostic testing after an elevated MSS (or the identification of markers on the routine ultrasound scan) have been shown to have different views, values and beliefs regarding pregnancy investigation and intervention compared to those who decline MSS or follow-up.(23, 25, 26, 30) Women who would not have an abortion more often refuse screening and follow-up testing.(17, 25, 30, 80) The personal risk-benefit analysis may favour refusal to screen and/or prenatal diagnostic testing. Women who are not willing to consider abortion might ask themselves - why risk pregnancy loss when nothing can be done to alter the outcome and when the likelihood of being truly affected is low? It is

important to note that the majority of women that screened positive and opted for amniocentesis did not have a pregnancy affected by Down syndrome or trisomy 18 (96.1%) or any chromosomal anomaly (93.8%).

Few population-based studies in Canada have reported on the portion of CA cases that are diagnosed prenatally, and of these, the number that are aborted. Limited data on these outcomes precludes local comparisons. One BC study found that 86.1% of all NTD cases (1997-1999) were diagnosed during pregnancy and that 73% were terminated, however, the current study was not designed to investigate outcomes for NTDs. Even surveillance reporting, for example from Alberta, fails to report on the proportion or number of CA-affected births or fetuses that resulted in pregnancy termination.(192) Smith et al (2011) found that 85% of all trisomy 18 and 84% of all trisomy 13 cases in areas of England and Wales were diagnosed during pregnancy (98); a substantially higher rate than found here. However, in that study antenatal detection included the identification of soft markers, which only signify an increased risk of anomaly and do not provide a definitive diagnosis (193). Saskatchewan data has shown that 63.2% of trisomy 18 cases, 13.9% of Down syndrome cases, and 27.4% of other chromosomal anomalies were diagnosed during pregnancy. More cases may have been suspected due to ultrasound markers but not confirmed by amniocentesis. Future research and surveillance would benefit from the electronic capture of diagnostic imaging findings and its linkage to the administrative health databases, as well as a national reporting of the rate of prenatal diagnoses of various conditions and associated termination rates.

The absence of ultrasound data and diagnostic information on stillbirths and fetal losses for non-chromosomal anomalies, such as neural tube defects, precluded our investigation of the prenatal detection rate for all CA types. In British Columbia, 86% of all NTDs occurring between 1997-1999 were detected during pregnancy and 73% of those pregnancies terminated.(11) Knowing the true NTD incidence rate in Saskatchewan would have provided exceptionally valuable information given that NTDs are largely preventable (up to 79%) with folic acid fortification and supplementation during pregnancy.(90) Knowledge of trends in NTD incidence would be an important contribution to public health planning. Live birth rates of spina bifida and anencephalus were reported and varied considerably year-to-year in Saskatchewan; for example the live birth prevalence of spina bifida dropped by 43% between 2000 and 2001, the same year the MSS program was formally introduced in the province. It is known that

amniotic AFP screening (requiring an amniocentesis) renders a very high detection rate for neural tube defects (99% and 0.3% false-positive rate), therefore most positive samples would identify a true case.(169, 170) Ten of the 54 TOPFA cases with an unknown diagnosis had positive amniotic fluid screens preceding a medical abortion. If these cases were presumed to have had an NTD, it would result in an incidence rate of 1.29 per 1,000 total births, which is 15% higher than the known live birth rate of 1.10 per 1,000 live births. This would also suggest that TOPFA were responsible for the 15% reduction. If we presumed all TOPFA with unknown diagnoses were NTD-related (and diagnosed by ultrasound), the effect would be a 42.7% reduction. Van Allen (2006) reported a 60% difference in British Columbia's NTD live birth prevalence and incidence from 1997-1999 where 72% of all prenatally-diagnosed cases were terminated.(11) In Saskatchewan the difference could be as low as 5.4% (between the live birth prevalence and incidence rates) or as high as 43.1%, if all unknown cases were truly NTD-related.

5.3 Predictors of Termination of Pregnancy for Fetal Anomaly

A focal point of the current study was the identification of selective pregnancy terminations performed following the detection of a fetal anomaly. It was important to first explore characteristics of women ending their pregnancy in this manner, to consider differential effects between population subgroups. While we did not have detailed information on pertinent aspects of women's decision making, a few key personal and demographic variables were examined to gain some basic insights. Follow-up by qualitative inquiry on this highly sensitive topic would be valuable, as little is known about women's experience surrounding TOPFA in a largely rural and relatively more conservative province that has a growing First Nations population.

5.3.1 Registered Indian women

Registered Indian women had a considerably lower rate of uptake of prenatal screening and diagnostic testing than other Saskatchewan women, resulting in fewer pregnancy terminations for an anomaly in this population. Registered Indian women that received an increased-risk MSS result had lower rates of diagnostic testing, with only 18.5% having an amniocentesis after receiving an result above cut-off compared to 33.5% of non-RI women. It

may be that more First Nations women declined further testing, but problems accessing services may have also played a role. Apart from the reason, lower testing rates meant that Registered Indian women were less likely to obtain a prenatal diagnosis when the fetus had a chromosomal anomaly compared to other women (8.3% vs. 27.0%). The number of congenital anomalies diagnosed in RI women who screened-positive and then had amniocentesis was very small (but similar to the rate in non-RI women) and no TOPFA were identified. By comparison, the pregnancy termination rate was 66.7% for non-RI women that screened-positive, followed-up with amniocentesis, and received a diagnosis of a chromosomal anomaly. This resulted in TOPFA rates (per 1,000 total pregnancies) in RI women that were half as high as the rest of the population (0.64 vs. 1.34, per 1,000 pregnancies), although there was some sign that this difference was narrowing over the study period. Small numbers make a confident interpretation quite difficult, but this finding is consistent with RI women's tendency to screen less and also to have follow-up testing less often. This is not the first time ethnicity has been shown to predict this outcome. In England and Wales, women of Pakistani ethnicity had much lower rates of TOPFA than white British or Indian women.(98) It will be important that future research spans longer periods of time, given the relatively smaller population in Saskatchewan and the fact that congenital anomalies are rare, and TOPFA rarer still.

In the Smith et al (2011) study, prenatal detection of serious anomalies was higher and did not vary according to deprivation level or ethnicity (98); another study in the same region found no differences in screening uptake across these population sub-groups (194). However, the rate of TOPFA was significantly lower in the most deprived group compared to the least (63% vs. 79%, respectively), despite universal access to abortion services and prenatal diagnosis. This presents an interesting contrast to current findings where large differences between First Nations and non-First Nations women could be seen in both prenatal screening uptake and diagnosis, and ultimately, fewer TOPFAs. One important difference is the fact that the Smith et al (2011) study included anomalies detected by ultrasound (suspected cases), where use is much more universal, less invasive, and accepted by women as a standard component to prenatal care.(98) Another potential explanation is that uptake varies across ethnic groups, with each group applying its own views, values and cultural and religious norms to decision making. First Nation women may view MSS and prenatal diagnosis in a different light than women from other ethnic groups and the effect of ethnicity may be mediated by socioeconomic circumstances. The data released by

the Saskatchewan Ministry of Health did not allow for analysis across other ethnic groupings, which would have made for a very interesting and more refined analysis.

5.3.2 Maternal age

The study in England found no difference in TOPFA according to maternal age (98), but in Saskatchewan some differences were observed. Selective termination rates following a Down syndrome or trisomy 18 diagnosis were slightly lower in women 30 years and under compared to women over age 30 (71.4% vs. 75%), but were much higher when it came to "other" chromosomal anomalies (33.3% vs. 4.5%). At the population level, overall selective termination rates were more than four times as high (per 1,000 pregnancies) in the 35 years and over age group compared to those 24 years and under. This is a finding that reflects the higher rate of screening, prenatal diagnosis, and CA-risk in the highest age category, but not a greater propensity towards pregnancy termination in the case of a confirmed chromosomal anomaly. Women under 30 years of age were much less likely to receive a prenatal diagnosis when a chromosomal anomaly was present (18.4% vs. 31.8%). While risk for a chromosomal anomaly is considerably lower for younger mothers, 53.5% of all pregnancies with chromosomal anomalies and 40.7% of all DS pregnancies belonged to this group. This finding is consistent with what is known on the topic.(5) From 2001-2004, a notable rise in TOPFA rates (per 1,000 total pregnancies) could be seen for women aged 30 and over, but this rate dropped in 2005 and rose in those under 30 years, particularly those less than 25. Around this time the practice of offering to screening to women under age 35 was beginning to emerge. The 2007 prenatal screening guideline will have likely expanded the uptake of screening in younger populations further, as this study was done at a time when younger women were not a primary target of screening. Recent data on amniocentesis testing in Saskatchewan has shown that testing numbers due to 'advanced maternal age' continued to fall up until 2012, while more and more tests are being done in response to abnormal MSS results and ultrasound findings. It also appears that the trend towards low amniocentesis uptake has continued, perhaps suggesting that the rate of TOPFA in Saskatchewan would be similar to the rate observed in the current study. It will be important to continue to monitor trends in TOPFA across maternal age, ethnicity, and geography as these may mirror changes in health service provision and access and in the views and values of different generations regarding pregnancy intervention and disability.

5.3.3 Timing of diagnosis

Timing of prenatal diagnosis has been shown to influence women's decisions to terminate or continue an affected pregnancy.(98, 195) Smith et al (2011) observed fewer pregnancy terminations with increasing gestational age: 75% of fetuses diagnosed (with select CA types) at less than 22 weeks and 19% after 23 weeks were aborted.(98) In the current analysis, the proportion of fetuses terminated following the diagnosis of a chromosomal anomaly was 58.3% at 12-16 weeks, 41.7% at 17-21 weeks, and 11.1% at 22 weeks or later. Many late diagnoses were cases where an abnormal ultrasound scan led to amniocentesis testing. It is possible that TOPFA rates may also be related to the type of anomalies diagnosed during each gestational period and to timing of diagnosis. In England women from higher deprivations areas were slightly less likely to receive an early diagnosis; a finding that attenuated, but did not eliminate, the differences in rates of pregnancy termination across socioeconomic groupings.(98) The number of First Nations women having amniocentesis was small in the current study, therefore it was not possible to investigate the timing of diagnosis in this population or its impact on TOPFA rates.

5.3.4 Type of anomaly

Rates of pregnancy termination vary widely according to the type of anomaly, with published rates at 80% and higher for chromosomal anomalies and neural tube defects.(6, 11, 98) Variations may reflect a clearer clinical picture around some diagnoses, as well as parents' understanding and concerns relating to raising a child with a chromosomal or nervous system anomaly.(98) The high rate of pregnancy termination following a prenatal diagnosis of Down syndrome was somewhat surprising given that survival is high and most children and adults enjoy a good quality of life, with increasing opportunities for participation in society. Largely due to increasing advocacy by individuals with Down syndrome ('self advocates') and their families, most people with Down syndrome will read, write and participate fully in their communities.(196) Advocates reject its medicalization, maintaining that "Down syndrome is a naturally occurring chromosomal arrangement and is not a disease, defect, or negative medical outcome of pregnancy (197 p.7)". Still termination of pregnancy rates following prenatal diagnosis were similar for both Down syndrome and trisomy 18 (73.3% and 75%, respectively), despite the fact that survival of infants with trisomy 18 is on average less than one month and 94% of infants with Down syndrome live past their first year of life and well into their 50s and

60s (89, 196). Many women who received a positive MSS result for Down syndrome or trisomy 18 opted not to pursue prenatal diagnosis (63.2% and 67.3%, respectively), suggesting that some women who would not end a DS-affected pregnancy likely remove themselves from the diagnostic pathway earlier on.

For women choosing to have prenatal diagnosis testing, perception of quality of life may be an important factor in their decision making about pregnancy termination, specifically, whether the child would suffer physically or emotionally.(198) Given the comparatively high pregnancy termination rate following detection of Down syndrome, one wonders if society has done enough to create awareness in general, and in particular, if counselling accurately portrays life with the condition. Lawson & Peters (2002) suggest that the social construction of disability plays a role in such decisions, given that "the inability [of people without a disability] to imagine the disability experience often translates into a collective mythology that a person with a disability lives a tragic life, marked by deprivation and suffering, a circumstances that should be resolutely avoided. This perception conflicts sharply with the view of many persons with disabilities who do not see themselves as different or abnormal and who hold society's attitudes responsible for disability-based discrimination."(59 p.6) Access to high-quality, accurate, and balanced counselling services is therefore imperative. Care must be taken not to oversimplify descriptions, portraying a life to be lived with deficits and illness, without counterbalancing the conversation with the joys and successes. Many Saskatchewan physicians admitted that they were not knowledgeable enough to counsel women on the implications of having a child with Down syndrome or trisomy 18. Given the immense challenge of providing fair, balanced, and value-neutral information to parents following a diagnosis, the CDSS (2007) maintains that increased investment in screening programs must be accompanied by funding to promote public awareness of Down syndrome and information materials to facilitate pre-test counselling about conditions being screened, which would support a more informed decision about screening.(197) Chapter 6 includes a more in-depth discussion on the topic of informed consent, non-directive counselling and the inherent challenges.

5.4 Termination of pregnancy for fetal anomaly and Population Health Outcomes

5.4.1 Congenital anomaly trends

A key objective of this study was to determine if the practice of termination of pregnancy for fetal anomaly led to decreases in the number of live births with a screenable congenital anomaly. Rate differences between live birth prevalence and incidence were observed for three outcomes - anencephalus, Down syndrome, and trisomy 18. In the case of both Down syndrome and trisomy 18, the prevalence and incidence lines both demonstrated an increasing trend over the study period, but the incidence line (accounting for pregnancy terminations) was steeper (10.0% for Down syndrome and 84.6% for trisomy 18, $p>.05$). The prenatal detection rate for trisomy 18 was higher than for Down syndrome (63.2% and 13.9%, respectively), which led to a greater difference in the number of infants born with trisomy 18 compared to the number of fetuses known to be affected. A difference could be seen for anencephalus for some years, but as discussed, the incidence will be an underestimate for this outcome due to lack of diagnostic information (in the study dataset) on fetal losses with non-chromosomal anomalies.

When six-year pooled birth prevalence and incidence rates were stratified by RI status and mother's age, the largest discrepancy was observed in women aged 35 years and over for Down syndrome, with the incidence being 29.6% higher than the live birth prevalence rate. In the case of trisomy 18, the rate differences were much larger and were observed across all age groups (144%-193%, increasing with age). Trisomy 18 is highly detectable during the routine screening ultrasound (199), which means that more cases in younger women would be detected without MSS, making ultrasound a pathway to prenatal diagnosis requiring further study. When examining rates according to RI status, the discrepancy between Down syndrome live birth and incidence rates was greater for non-RI women compared to RI women (13% vs. 5.2%, overall), reflecting both lower risk and lower utilization of screening/diagnosis and pregnancy termination in RI women. Close attention should be paid to CA rates in rural and First Nations mothers in future analyses, specifically watching for differences owing to pregnancy termination. Moreover, evaluation of primary prevention strategies or etiological research should not be undertaken unless TOPFA can be accounted for, as erroneous conclusions may result.

5.4.2 Impact of pregnancy termination for congenital anomaly on fetal and infant mortality

5.4.2.1 Infant mortality

Infant mortality is a powerful and commonly used indicator of the health of populations, largely due to the unique vulnerability of infants in harsh social and economic environments.(34) Less-than-optimal infant mortality rates are seen to reflect poorly on inequalities in societies and the tragic impact these have on the most vulnerable, in essence, "illuminating the machinery of social injustice (34 p.111)". Inequities between First Nations and non-First Nations, in Canada and Saskatchewan, have been well-documented, as have the health consequences.(38, 122, 200) Substantial disparities in infant mortality rates are known to exist and the current study set out to provide additional insights. In particular, I wondered if greater uptake of prenatal screening, diagnosis and pregnancy termination for CAs in non-First Nations women would enhance disparities in infant mortality rates, or at the very least maintain them in the wake of improvements in social and economic conditions over time.

Socioeconomic disparities in infant death are well-established, but there is still much to be learned about the causal pathways. Gortmaker and Wise (1997) mount a strong case for the need to recognize the influence that modern reproductive technologies exert on infant and fetal death in industrialized countries, often maintaining or escalating traditional socioeconomic disparities.(34) While these two sociologists were speaking specifically about breakthroughs in neonatal intensive care, differences in the uptake of prenatal screening, diagnosis, and TOPFA make it highly likely that the more recent generation of reproductive technologies have produced disparities of a distinctly different nature. Disparities potentially masked by difficulties in identifying and quantifying the impact of TOPFA and the extent to which this practice varies across social, economic, cultural and geographic lines. Central to this research was the hypothesis that TOPFA has consequences for infant mortality, shifting a number of deaths to the fetal period.

Limitations in the dataset precluded plans to model a 'TOPFA-adjusted infant mortality rate' and restricted analysis around fetal death in general. Similar to indicators like the well-used hospital standardized mortality ratio (HSMR), an adjusted IMR indicator could be designed to correct for TOPFA by estimating the likelihood that aborted fetuses would have resulted in a live birth, followed by a death within the first year. In the absence of such an indicator, we relied on the CA-specific infant and neonatal mortality rates, as well as the stillbirth rates. During the

study period, 20.8% of infant deaths (overall) were due to a CA; a figure that is lower than the proportion of deaths due to CA nationally, which was 30% in 1998 (1). This difference can likely be explained by Saskatchewan's higher overall rate of infant death (many of which were the result of non-CA related causes), since the overall CA-specific IMR (>=500 grams) in Saskatchewan was 37.8% higher than the national rate from 2000-2005.[37] A clear trend in one direction or the other could not be seen in regards to CA-specific IMR. The 2002 rate was 42.9% lower than 2001 ($p<.05$), potentially pointing to an impact of the newly introduced MSS program, but the rates remained relatively unchanged (or even higher) during subsequent years studied (1.4, 0.8, 1.4, 1.4, and 1.7 CA-related deaths per 1,000 live births, respectively by year). These results span a relatively short time period and represent a significant decline from similar statistics dating back to 1985 (2.92 per 1,000 live births >=500 grams)(130), but they do not suggest a notable, or at least sustained, population impact attributable to the MSS program. One must also consider the (apparent) rise in the incidence rates of specific anomalies, including anencephalus (and similarly severe NTD), trisomy 18, and Down syndrome (average annual percent changes of 29.6%, 83.9%, and 10.0%).[38] If more children are being born with vulnerabilities that cannot be effectively treated, despite improvements in medical and surgical care, the CA-specific IMR will rise.

A key consideration of the current study was how differences emerge along the pathway from prenatal serum screening through the first year of life. Smith et al (2011) found that socioeconomic variations in TOPFA resulted in socioeconomic inequalities in the rate of fetal loss, stillbirth, and live birth associated with an anomaly.(98) The effect was substantial, with the most deprived population experiencing a 20% higher rate of CA-related stillbirth, a 61% higher rate of live birth with a CA, and a 98% higher risk of CA-related neonatal mortality. After adjusting for maternal age, the disparities widened to 57%, 85%, and 123%, respectively. Comparing First Nations and non-First Nations in Saskatchewan, the CA-specific infant and

[37] Based on data from the Public Health Agency of Canada, the 6-year pooled (2000-2005) CA-specific IMR (in births 500 grams or more) was 1.11 per 1,000 live births for Canada (excluding Ontario) and 1.53 per 1,000 live births for Saskatchewan. Figures from the Public Health Agency of Canada were used here to compare Saskatchewan to the rest of the country because Canadian statistics for all deaths (not just those 500 grams or more) were not available at the time of writing, and to ensure better comparability.

[38] A portion of the observed increase in chromosomal anomalies may be due to under ascertainment of cases in 2000 and 2001, thereby making the change over time appear to be greater than it was. Nonetheless increases in the incidence of Down syndrome and Trisomy were detected between 2002-2005 (average annual percent change was 19.0% and 6.4%, respectively).

neonatal mortality rates were 42.1% and 85.5% higher (respectively) in the First Nations population. Higher levels of infant death due to a CA in the children of First Nations women may be somewhat unexpected given the fact that rates of congenital anomalies (combined) were lower in this population (140.5 vs. 101.2 per 10,000 pregnancies, p<.000) and rates of chromosomal anomalies were substantially lower (44.5 vs. 22.8 per 10,000). Increased uptake of prenatal screening, diagnosis and higher rates of TOPFA in non-First Nations women will explain some of this observed difference, but there are other factors that could be studied (eg. differences in the survival of infants born with a congenital anomaly).

Looking at infant mortality risk across maternal age groups, it was found that infants of both the youngest and oldest mothers were at greater risk of dying during the first year of life. The crude IMR generally declined with age of mother and was 30.9% higher in mothers under age 25 compared to those age 35 and over (7.2 vs. 5.5 deaths per 1,000 live births, respectively). However, the higher frequency of deaths due to a CA in children of mothers age 35 and over (34.1% of deaths in this age group were due to a CA compared to 19.3% in those under 25 years) led to a higher crude rate for this age group. When the analysis was restricted to the first 27 days, the CA-specific neonatal mortality rate was 61%-97% higher in infants born to women age 35 and over compared to younger age groups, which may be explained by the much higher incidence of chromosomal anomalies in the older age group (97.2 per 10,000 pregnancies[39] for women aged 35 and over vs. 31.0 per 10,000 pregnancies in women under 25 years). The overall congenital anomaly incidence increased significantly with age as well (11.0% of women under age 25 vs. 12.9% of women aged 35 and over, p<.000). The trend towards delayed childbearing may have a direct impact on provincial and regional infant mortality, depending on older mothers' use of prenatal screening, diagnosis and decisions to terminate or continue affected pregnancies. In the current study, TOPFA was more common with increasing maternal age (2.78 per 1,000 pregnancies in women aged 35 and over vs. 0.61 per 1,000 pregnancies in those under age 25) and future research and surveillance efforts investigating pregnancy outcomes according to maternal characteristics (ie. age group, ethnicity, and geography) should take into consideration these differences.

[39] Here pregnancies refers to those that resulted in a live or stillbirth, or spontaneous abortions or elective abortions that underwent prenatal diagnostic testing.

The interrelationship between pregnancy termination and infant death is not entirely straightforward. In Canada, there is no gestational age limit at which a termination of pregnancy can be legally performed for a serious anomaly.(201) If an abortion is done in the second or third trimester when the fetus is viable, the possibility of a live birth increases. Even if the baby is not born alive, all infants born at 20 weeks or later (or weighing 500 grams or more) must be registered as a stillbirth in Saskatchewan according to the Vital Statistics Act.(202) A central hypothesis to this research was that TOPFA may lower the perinatal and infant mortality rates, however, this oddity in coding and birth registration practices complicates the association given that it may actually increase the number of infant deaths and stillbirths depending on the CA and the timing of the abortion. An unexpected finding was that 5.3% of all stillbirths and 2.9% of all infant deaths were the result of TOPFA, even though the death certificate only identified five cases as being 'termination of fetus or newborn' (the ICD code used to denote a TOPFA). When TOPFA were removed from indicator calculations, the difference between regular and spontaneous rates were small for infant mortality (6.0 vs. 6.1 per 1,000 live births), but somewhat wider for stillbirths (6.6 vs. 6.2 per 1,000 total births). The largest difference in annual rates was 6.4% (in 2005) for infant deaths and 10.7% (in 2004) for stillbirths. In settings where this practice is more prevalent, the impact is likely to be sizeable. In the case of the termination of a Down syndrome fetus, the likelihood of a fetus/infant with DS dying naturally as a stillbirth or live birth in the first year is low, so the practice of TOPFA, depending on its timing, can lead to an increase in the number of infant deaths or stillbirths. In the case of anencephalus and trisomy 18, the impact on mortality rates would be neutral or a decrease, if the termination was performed before 20 weeks and the fetus weighed less than 500 grams and no heartbeat or breath, as most babies born die within the first year. Because there is no simple calculation able to add or subtract such cases, there is need for a more sophisticated TOPFA-adjusted IMR.

Initially the hope was to model an adjusted infant mortality rate and to explore the impact of TOPFA on perinatal mortality. However, the absence of stillbirth diagnostic data and ICD codes that enable the identification of TOPFA less than 20 weeks and less than 500 grams from the hospital data file precluded such analysis. Year of infant death was not included in the dataset for all CAs detectable by the MSS program, therefore making it impossible to investigate the

contribution of these outcomes to the annual IMR.[40] Congenital anomaly research is often limited by the absence of accurate and complete diagnostic data for whole populations. To model an adjusted-IMR, complete, detailed diagnostic information would be required, and even still, a larger dataset necessary in order to estimate survival of affected fetuses into infancy. Once survival-to-infancy rates were calculated, one would need to model the likelihood that each infant would survive beyond the first year of life. There were just 289 cases of screenable anomalies in Saskatchewan over this 6-year period, or an average of 48 cases per year. Even with a much larger population dataset, estimating survival for different CA types may be a challenge. When it comes to survival estimates for CA-affected fetuses and infants, national figures from the Public Health Agency of Canada only contain births and are therefore biased by the exclusion of many TOPFA cases over the period. Earlier data from PHAC or another provincial registry, predating prenatal screening programs, may underestimate survival amongst vulnerable infants due to advances in neonatal intensive care over time. If survival data could be pooled from multiple CA surveillance systems and a system created for categorizing the severity of TOPFA cases, estimates could be applied to local level TOPFA data to estimate adjusted infant and fetal mortality rates.

Some progress has been made in regards to congenital anomaly surveillance in Saskatchewan. A Congenital Anomaly Surveillance System is being piloted in the Saskatoon Health Region (CASS-S), and it is hoped that it will expand to the rest of Saskatchewan. Still the administrative health databases contain a wealth of data not available in such systems. If timeliness and access could be improved, linking of both administrative health data and the CASS-S would be necessary to capture information on non-CA births, CA outcomes, and data on health care utilization patterns for the entire population. In recent years health information coding practices in the Discharge Abstract Database (hospital file) have improved, which should enable better capture of TOPFA and spontaneous loss due to fetal anomaly.(37) Given the concerns described in detail here regarding the IMR and the differential impact of TOPFA, another option might be to report on 'IMR excluding CA-specific deaths' and 'CA-specific IMR' separately for international and interprovincial comparisons. These rates can be easily calculated and allow for consideration of differences in CA and non-CA related death in infancy.

[40] Access to the full dataset was permitted on one occasion at the Ministry of Health's offices in Regina, making some analysis possible.

Pregnancy terminations for fetal anomaly are likely much less common in Saskatchewan compared to provinces where MSS uptake is considerably higher. Adjusted fetal and infant mortality rates would be very valuable for other regions/provinces to apply to their own populations, in particular, when TOPFA is prevalent or rates vary across key sub-populations. Liu et al (15) found that provinces and territories with higher rates of fetal death due to pregnancy termination and/or congenital anomalies at 20-23 weeks gestation had lower CA-specific IMR.(15) Moreover, they reported that the fetal death rate due to pregnancy termination/ congenital anomalies at 20 to 23 weeks' gestation was almost eight times higher in Nova Scotia (16.7 per 100,000 fetuses at risk in Saskatchewan vs. 131.4 per 100,000 fetuses at risk in Nova Scotia). Analysis of the CA-specific stillbirth rate was not possible here, but would have made a valuable contribution to our understanding in this province. Nationally the proportion of stillbirths <500g due to CA/TOPFA constituted 11.6% of all stillbirths <500g in 1985 and it increased to 40.4% in 200. (37) The proportion of neonatal deaths <500g that were due to CA/TOPFA increased from 3.6% in 1985 to 19.7% in 2003. In Saskatchewan, 13.6% of neonatal deaths < 500g were due to CA/TOPFA from 2000-2005; a figure lower than the national rate in 2003.[41] All signs point to a large and increasing impact of TOPFA on population-based birth and mortality statistics nationally, whereas in Saskatchewan, the effect appears to be less pronounced.

5.4.2.2 Fetal mortality

A recent study by Joseph et al (2013)(2) found that increases in stillbirth rates from 2000-2010 were due to increases in pregnancy terminations, resulting in subsequent declines in CA live birth rates. The observed increase was predominantly due to stillbirths weighing less than 500 grams. The authors emphasize the importance of differentiating between spontaneous stillbirths and those resulting from pregnancy terminations. For instance, in British Columbia (BC), the rate of spontaneous stillbirths decreased non-significantly by 16% between 2000-2010 and the same rate declined non-significantly by 5.7% in Saskatchewan between 2000-2005. In comparison, the rate of stillbirths (overall) increased in BC by 31% over the same period,

[41] This number would be 11.3% if only using Vital Statistics death certificate data to identify CA-related cause of death (as the previously reported PHAC figures did). The 3.6%-19.7% figure for Canada likely represents an underestimate as not all provinces submitted stillbirth cause of death data for the entire period and due to the limitations of coding of stillbirths.

whereas a much smaller increase of just 3.3% was observed in Saskatchewan between 2000-2005. Two important differences to note are that the increasing stillbirth trend in BC only emerged in 2006-2010 (the rate was stable during 2000-2005) and that the overall rate was 22.7% higher than Saskatchewan's rate during the study period (2000-2005). The BC study also found that the rate of TOPFA (resulting in a live or stillbirth) increased by 133% (from 2.4 per 1000 total births in 2000-2002 to 5.7 per 1000 total births in 2008-10). While the same rate increased by 67% in Saskatchewan from 2002-2005 (0.51 to 0.93 per 1,000 total births)[42], rates in BC were more than four times higher. This finding makes sense given the higher rate of maternal serum screening in that province (recall that rates were two times higher than for Saskatchewan in 2006) and potentially higher prenatal detection rate (although there is no data available to confirm this). In the context of a provincial evaluation of an increasing stillbirth trend, Joseph et al (2013) recognize the importance of reporting separately on spontaneous stillbirths and those due to pregnancy termination.(2) Similarly it is easy to see how important this distinction will be for comparisons between and within provinces, where variations have been shown to exist in the acceptance and use of prenatal screening and pregnancy termination.

Early spontaneous fetal losses resulting from congenital anomalies are an important outcome, but one that administrative databases are not well-designed to capture. A small number could be seen in the current dataset (n=7), but only those where an amniocentesis was completed prior to loss or where physicians reported a detected anomaly to the provincial MSS program. A number of early fetal losses known to be affected by a CA will have been missed due to absence of O35/655 codes, in addition to those never recognized (eg. spontaneous abortions not investigated). The current investigation focused on the impact of TOPFA on fetal-infant mortality, and not spontaneous loss, due to the fact that the latter should occur at fairly similar rates across populations, while we see here that TOPFA does not. First trimester screening techniques raise the importance of surveillance for early losses, which can only be captured in the hospital data and not through Vital Statistics reporting.

[42] 2000 and 2001 data was omitted from comparison due to the number of TOPFAs that were shown to have been missed, based on comparisons with CIHI data. The rate of TOPFA (resulting in live or stillbirth) was 0.08 per 1,000 total births for these two years combined.

5.5 Amniocentesis-related fetal loss

Amniocentesis is the "gold standard" test used to diagnosis chromosomal anomalies and neural tube defects in Saskatchewan (as CVS is not available), with high levels of accuracy (98-99%) (203). The fetal loss rate following amniocentesis is a contentious question and the answer is vital to informed decision-making. The “First and Second Trimester Evaluation of Risk for Aneuploidy” (FASTER) trial suggested fetal loss was substantially lower than previously reported, prompting the SOGC to review studies dating back to 1986.(171) Their conclusion (2007) was

> "There is *no* single percentage (or odds ratio) that can be quoted as the risk of pregnancy loss following midtrimester amniocentesis in singleton pregnancies. The risk is unique to the individual and is based on multiple variables including ....patient factors (eg. maternal age, reproductive history, pre-existing maternal conditions, pregnancy-related factors such as placental location, multiples, or use of assisted reproductive techniques); procedure factors (eg. needle size, operator experience, ultrasound guided or freehand, and maternal BMI); and post procedure factors (eg. infection) (p. 588-9)." (171)

Even still the SOGC puts forth 0.6-1.0% as the best estimate of increased rate of pregnancy loss attributable to amniocentesis. Studies may estimate the procedure-related pregnancy loss rate separate from the background pregnancy loss rate, in order to quantify the additional risk imposed on the pregnancy by the procedure. Based on amniocentesis data and linked outcomes in Saskatchewan, the stillbirth rate was 2.2% in tested pregnancies and 0.61% in those not having amniocentesis. When restricting the analysis to stillbirths less than 24 weeks, the stillbirth loss rate dropped to 0.95% in the tested group and 0.12% in the control group. This finding is consistent with the SOGC's estimate above. During the process of informed consent, the SOGC recommends sharing the combined overall risk with the patient.(171)

5.6 Consideration of the MSS program in relation to screening principles

5.6.1 Acceptable treatment

What makes a screening program worthwhile? To answer this question I draw upon Wilson & Junger's influential principles for evaluation of screening programs.(204)

The principle that Wilson and Junger (1968) proposed as being most important was the existence of an acceptable treatment for patients with recognized disease.(204) In the case of

prenatal screening, the choice is to either continue or terminate the pregnancy, however, its acceptability is more morally problematic than interventions associated with other screening programs. Whether or not abortion is an acceptable option will depend on a multitude of factors, including the couple's beliefs, values, and understanding of the condition. In countries where abortion is not permitted, prenatal serum screening programs would not meet Junger's criterion. Abortion is permitted in Canada, although abortion services are perhaps not easily accessible throughout. In Saskatchewan, current and past abortion trends clearly show a lower demand for elective medical abortion, presumably revealing less demand or support for abortion generally. The current study found that rates of pregnancy terminations following prenatal diagnosis are close to those in Australia and British Columbia (6, 205), if not slightly lower (73% of prenatally diagnosed cases of Down Syndrome and 75% of trisomy 18 were aborted), but the rate of prenatal diagnosis was considerably lower than in Europe (8). An absence of good, comparable data on prenatal detection rates across provinces and countries makes interpretation of these figures difficult. Women who would not terminate most likely refused amniocentesis, therefore uptake of prenatal diagnostic testing rates tell us more about a population's views and preferences and comparable data across regions would provide additional insights.

Prior to its implementation, opposition was raised to the MSS program on the premise that it discriminated against unborn children with disabilities and due to its link to abortion, raising the question of whether it met the proposed principle that the test should be acceptable to the population. In the most recent release of guidelines on prenatal screening programs, the SOGC echoes this belief stating "the screen must be acceptable to the population being screened (p. 738)."(48) Prenatal screening programs have emerged in several Canadian provinces, but it is unlikely that any of these have made efforts to engage the population to determine its level of acceptability. While certainly ideal, the question is how best this might be accomplished. This line of thinking will be explored further in Chapter 6.

While treatment options are limited, the program allows some women with affected pregnancies to receive a diagnosis prior to delivery, which may help prepare mothers emotionally. This claim has been used to promote screening but there is little evidence supporting this notion, therefore more research is needed to compare any differences in the experience of mothers who learn about their child's condition before delivery and those that are told after. Given that most prenatally diagnosed cases are aborted, the number would be small. In

addition, many women that would not abort, do not proceed to diagnostic testing due to the risk to the fetus. Looking at the results from the current study, only seven out of the 27 confirmed cases of Down syndrome and trisomy 18 detected over a five-year period might have benefited from the information in this way. Ninety-three women did not know that their baby had either Down syndrome or trisomy 18 until after delivery. In the case of Down syndrome, 22.4% of women with an affected pregnancy had MSS and 70.8% received a "screen-positive" result, of those, 41.1% chose to follow-up with an amniocentesis and 85.7% aborted.[43] For the most part, in the case of Down syndrome and trisomy 18, most women who choose amniocentesis also choose to have an abortion.(185) It is not known if women benefit from the awareness that they are at increased risk, even when they do not pursue diagnostic testing to know for certain.

5.6.2 An important health problem

Wilson & Junger contend that the condition being screened for must be an important health problem.(204) Important, by their definition, does not necessarily depend on prevalence only, but also should be considered from the point of view of individuals and communities. Often program materials, the media, and academic articles declare that MSS screens for 'serious' or 'severe' health conditions in the fetus. In the case of anencephalus and trisomy 18, this is certainly true as the majority of infants with such conditions will die within the first year of life, if not shortly after birth.(206) However, this label can be problematic when it comes to children born with Down syndrome or spina bifida; conditions that have increasingly good survival rates and quality of life.(207, 208) The variation from child-to-child, as well as the medical system's inability to predict outcomes using information available during the prenatal period, makes assessing severity difficult and subject to the biases and limited perspectives of providers. Most people have no prior knowledge of individuals with such conditions; therefore will base their understanding on what is shared by their physicians, pamphlets, and the internet. Similarly, pregnant women often rely on friends and the internet to answer their questions about screening.(209) In a 2005 survey of Saskatchewan physicians, just half of physicians who offered MSS to their patients said they had enough knowledge to explain the implications of raising a child affected by spina bifida or Down syndrome to a women with an affected

[43] The termination of rate of 85.7% is higher than the previously reported 73.3%, however, the latter includes cases that did not have MSS initially but went directly to amniocentesis.

pregnancy.(32) Many (85%) agreed that having an affected child presents a considerable burden for parents and fewer (59%) felt that people with Down syndrome or spina bifida have the potential to lead full lives and make important contributions to our communities. Congenital anomalies (both minor and major) affected an estimated 11.8% of pregnancies in Saskatchewan and only a small portion have known primary prevention strategies.(79) The question of what conditions should be screened for is a complex moral question and the debate will only become more complex as other tests are added to the screening arsenal.

5.6.3 Diagnostic follow-up testing

Wilson & Junger emphasized the importance of a test to determine whether the person with a positive screen truly has the condition, and the need for facilities for diagnosis and treatment.(204) Amniocentesis or chorionic villa sampling (CVS) are the two prenatal diagnostic tests used to confirm chromosomal anomalies and neural tube defects, however, only amniocentesis is available in Saskatchewan. While amniocentesis is generally performed between 15-18 weeks gestation, CVS can be performed at 10-12 weeks (although the fetal loss rate is higher). The challenge for Saskatchewan is that the newer generation screens, which can be done earlier in the pregnancy, will require earlier diagnostic testing to detect an anomaly. The benefit, it is argued, is that women can receive an earlier diagnosis and may be more accepting of an abortion. Since CVS is not available, most will still need to wait until 15-18 weeks for a diagnosis.

Such is the case with many specialized techniques, amniocentesis presents a special challenge in a province with a widely dispersed and relatively small population. Few rural health regions have obstetricians willing to perform the test, perhaps due to the fact that the skill of the practitioner is linked to procedure-related fetal loss.(171) Women wanting amniocentesis will usually need to travel to Saskatoon or Regina for testing and all samples are currently processed through the Saskatoon cytogenetics laboratory. While the procedure-related risk to the fetus may seem small (0.5-1.0%), the risk of having a child with a CA is also small for most women. First trimester screening methods are most sensitive when they incorporate a nuchal translucency measurement, which is a specialized ultrasound scan that few practitioners in Saskatchewan are certified to collect. Even in the two largest cities, access is not always timely. As testing continues to evolve, disparities in access should be monitored.

5.6.4 SOGC guidelines

While the Saskatchewan MSS program has taken up the SOGC's recommendation to routinely offer MSS to all pregnant women, there are other key recommendations that have not been adopted. For instance, the SOGC guideline states that "performance of the screen should be substantiated by annual audit (48 p.737)", yet the first audit performed by the MSS program was completed in 2012 and covers the same period as the current study (May 2001- March 2005). The program would certainly receive a failing grade as far as timely audits. It is important to note, however, that this is largely due to poor data access and the difficulty around linking MSS results to population outcomes, which rely on administrative data from the province. Next, the SOGC recommended that the nuchal fold and fetal nasal bone measurements only be taken by sonographers trained and accredited for this service and when there is ongoing quality assurance; it is unclear if this type of evaluation has been built-in to the current system. Ultrasound dating in the first trimester is important to accurate determination of gestational age, and as such, the SOGC recommends that it be available when there is uncertainty or for any abnormal screen calculated on the basis of menstrual dates. Some rural Saskatchewan hospitals have not been able to perform ultrasound dating due to resource challenges and travel distance can significantly hinder access for women, particularly in northern communities. The SOGC recommends that maternal weight, ethnicity, insulin-dependent diabetes mellitus, and use of assisted reproduction technologies (ART) should be incorporated into the screen in order to improve the accuracy of testing. Currently maternal weight is used as part of risk calculation, but ethnicity, diabetes status and ART history are not.(135) Finally, the SOGC makes a general recommendation that sufficient resources be available for genetic counselling services, patient and health care provider education, as well as resources for annual clinical audit and data management. Genetic counselling services are situated in Saskatoon, and are not well-integrated within the current MSS program. While genetic counsellors do some post-test counselling prior to amniocentesis, the majority is done by physicians and midwives. Given the centrality of genetic counselling to most prenatal screening programs, this is an area that merits further exploration.

5.6.5 Practice implications

The provincial MSS program fares poorly on some criteria, and better on others. Based on its performance during the time period from 2002-2005, the MSS program was a moderate

detective when it came to Down syndrome and trisomy 18. Data limitations precluded assessment of its performance for neural tube defects. Even though the detection rate was moderate, performance at the population level is largely dependent on how many women utilize screening. A highly sensitive test that is used by very few may not justify its existence. The current study estimates that 22 cases of congenital anomalies in Saskatchewan were diagnosed after a screen-positive MSS result that was followed by amniocentesis (2001-2005), many of which may not have been in the absence of such screening.[44] Having said this, false-positive tests have been an important point of contention for MSS programs generally. The patient finds themselves in a position where they accept the offer of a test designed to help them know more about the health of their baby, only to often worry unnecessarily. In Saskatchewan, 958 women during the study period received a "screen positive" result, but very few had an affected pregnancy (eg. 2.1% of those who screened positive had a baby with DS). Research has shown a clear increase in maternal anxiety in the face of a false-positive screening result (186, 210, 211) and this rate must be monitored closely.

The question of whether or not the Saskatchewan MSS program, or any similar prenatal screening program, optimizes outcomes for those who chose to have screening is a difficult one to answer. Screening is argued to improve the following outcomes: lowering the live birth rate of infants with DS, trisomy 18, or a neural tube defect; reducing the number of unnecessary amniocentesis tests in pregnant women wanting to (or perceiving themselves to need to) undergo diagnostic testing; giving pregnant women a choice of whether to carry an affected child or terminate when a CA is confirmed; and for women who will deliver an affected child, helping them to prepare emotionally and practically. The current study is the first to provide evidence on prenatal serum screening in Saskatchewan, shedding some light on important measures that may help planners judge if it is indeed a worthwhile program. The extent to which the live birth rate is impacted depends largely on the uptake of MSS in the population and the number of diagnosed cases that are terminated. In Saskatchewan, MSS uptake was low over the course of the study (topping out at 26.8%) and more recent data from the Provincial Laboratory has not shown a

[44] In total, there were 70 CA cases diagnosed by amniocentesis over the study period. Forty-seven of these women had MSS testing prior to undergoing amniocentesis, but only 22 of these women received an increased-risk or "screen-positive" result.

discernible increase since that time.[45](135) There was a 13.2% decrease in the number of amniocenteses performed from 2002-2004. The proportion of testing due to 'advanced maternal age' fell from 74.5% to 39.0% during the study period, while the proportion of tests performed due to 'abnormal MSS result' increased from 7.5% to 38.2%.[46] While the proportion of tests performed in the oldest age group (women aged 35 and over) dropped, it increased in all other younger age groups as a result of increased screening and 'increased risk' results.

Low precision is a well-documented limitation of the triple test. The problem of false-positives should not be downplayed. False-positive results can lead to increased anxiety during a vulnerable time, inconvenience, expensive follow-up, and perhaps most important, increased risk for fetal loss associated with amniocentesis.(186, 212) In Saskatchewan, out of 9909 women screened for DS or trisomy 18 between 2001-2005, 754 experienced a false-positive (7.6%), and 273 of those women (36.2%) underwent amniocentesis and were later found not to have an affected pregnancy, with four fetal losses following the procedure (1.5%). The fact that one out of every 13 women screened for DS or trisomy 18 received a false-positive result is concerning. A subsequent increase in anxiety has been well-documented, and most concerning is research that shows this anxiety often does not abate (ie. residual anxiety), even after confirmation by diagnostic testing.(186, 213, 214) Newer tests including the quadruple screen, NT measurements, and first trimester testing have been incorporated into the province's protocols and have a higher detection rate (~80%) with a slightly lower false-positive rate (5%). While the performance should be somewhat better than the triple test, false-positive results remain a concern.

Research is lacking on other potential negative consequences of screening. Very little is known about the long term impact of abortion in the case of a diagnosed anomaly. For instance, a certain proportion of fetuses affected by a serious anomaly would be lost naturally between diagnosis and term; but I could not locate any research exploring the psychological, emotional, and spiritual costs to families when they chose to intervene/terminate compared to continuing the pregnancy. Are there benefits to allowing nature to 'take its course', even when the prognosis is grim, or do families and mothers fare better when the pregnancy is ended. Another potential source of harm is to individuals living with these conditions. The existence of a population-based

[45] With the addition of integrated screening, aggregate reports on the number of MSS specimens processed no longer enable one to calculate an estimated rate of uptake. This is because some that provide a first trimester sample did not present for a second trimester sample, and vice versa.

[46]More recent data from the Saskatoon Cytogenetics Laboratory shows that 'advanced maternal age' accounted for just 13.1% of all tests in 2012; abnormal ultrasound findings for 25.8%; and abnormal MSS for another 56.6%.

screening program clearly expresses the thinking that it is morally, legally, and socially acceptable to end the lives of fetuses with such conditions through government-sanctioned health programs. Chapter 6 explores this question further.

Absence of concrete guidelines, policies or laws governing screening programs and interventions is glaring. The task of policy-making in the arena of reproductive screening, testing and interventions is a daunting one, which is almost certainly why such decisions remain in the hands of women (and their families) and health care providers to negotiate. While this may seem to be the best available option, resolution of ethical dilemmas within the confines of the clinical encounter can have important limitations that will be discussed.

Finally, the finding that MSS and amniocentesis uptake is low in Saskatchewan is not necessarily a negative one. It may reflect greater acceptance of the possibilities inherent in any pregnancy and a tendency away from medicalization. Many women who opt for screening often do so for reassurance of the baby's health, not necessarily intending to intervene on the pregnancy.(80) The most common reasons women refuse screening is because they would not terminate the pregnancy and the results obtained are not definitive. If progress continues to be made - developing new treatments, refining therapies, adapting environments for those with challenges - living with a disability will not be the same today as it is ten years from now. Just as life for a child with Down syndrome looks very different today than it did a few decades ago. Those advocating for the rights of individuals with disabilities fear that eliminating children with such characteristics from society will lead to diminished resources and research efforts geared towards improving quality of life for those with disabilities. It is typically parents and families of affected individuals that advocate and lobby for greater social inclusion and against discriminatory policies and attitudes. Fewer families raising children with a disability, means a smaller lobby effort. In addition, research has found that women that give birth to affected infants were more often of low socioeconomic status or part of an ethnic minority, meaning that infants requiring greater social and medical support are disproportionately being born into families with the fewest resources.(98, 110) Unique from other screening programs, MSS presents women with an opportunity to learn more about the health of their fetus, with the possibility that pregnancy termination will result. The gravity of such decisions cannot be underestimated and reinforces the importance of the intent, design and delivery of any program including the MSS.

5.7 Surveillance: the missing pieces

A wealth of information is contained in Saskatchewan's administrative health databases, which is naturally exciting to those wishing to undertake research, evaluation, or surveillance. Even so, compiling data for the current study was a gruelling and cumbersome process taking more than five years to complete. Pregnancies and congenital anomalies are two especially challenging outcomes to study in the absence of perinatal and congenital anomaly surveillance systems. Women may experience multiple, consecutive pregnancy outcomes, some of which require hospital care and others physician care. While hospital data has been well-validated for pregnancy events, physician data has not. Physician data does, however, provide an opportunity for greater capture of events. There may have been a slight trade-off as far as sensitivity and specificity go.

While our study was able to identify some interesting trends and patterns, it is only a snapshot in time. On-going, regular evaluation and surveillance are integral to our understanding of risks encountered during the prenatal period, those threatening healthy pregnancies and ultimately healthy infants and children. Key to the production of useful surveillance is timely information. The current system is not timely, nor is it user-friendly for researchers, health regions or governments. A provincial overhaul is warranted in both the mechanism by which researchers access data and in the handling of data. Classification experts, well-versed in the intricacies of coding standards and data systems, would be invaluable. While researchers typically possess important analytical and methodological skills, it is unrealistic to expect they have expert knowledge of how health information is coded and where each variable is contained within a number of disparate databases.

Even when well-designed, sophisticated surveillance systems are in place, variations in registration and coding present challenges as far as the validity and reliability of indicators, and often where rankings are concerned.(36) In the case of infant and perinatal mortality, variations in the registration of extremely small babies and of births affected by lethal congenital anomalies, accurate assignment of cause of death, and differences in the modality of ascertainment of gestational age are known problems. Variations across countries may present more of a challenge than those within, but even in Canada with a definition-based birth registration system, regional variations exist.(37) Registration of TOPFA births vary across health regions, further complicating assessment of the growing, and evolving, impact of prenatal

diagnosis. Internationally there is disagreement about the birth registration of pregnancy terminations even when they constitute a live birth or stillbirth (36), further challenging comparisons across countries. The Better Outcomes Registry & Network (BORN) in Ontario is an innovative perinatal and congenital anomaly surveillance system worthy of modelling.(3) Characterized by its high-quality data, research embrace, and capacity for knowledge translation, BORN Ontario links data on prenatal screening, congenital anomalies, and maternal-newborn outcomes. In contrast, the Saskatchewan Ministry of Health has never released a report on congenital anomalies and limited work has been done to further study the problem of high infant mortality. In 2010 the World Health Assembly adopted a resolution and called all Member States to promote primary prevention and the health of children living with congenital anomalies through the development of strong registration and surveillance systems, building capacity and expertise, and more research on causal factors, diagnosis and prevention.(215) Efforts have been made nationally to meet some of these goals and this will be an important direction for Saskatchewan in the future.

Abortion data has become increasingly politicized in Canada, leading to underreporting of its prevalence, timing and causes. A number of private clinics, though publicly funded, have refused to report even aggregate figures to the national Therapeutic Abortion Database. Starting in 2010 CIHI assumed responsibility from Statistics Canada to manage data collection and publish statistical reports on therapeutic abortions data.(129) Private abortion clinics do not operate in Saskatchewan, therefore provincial estimates should be accurate. Estimates from Manitoba, British Columbia, and New Brunswick are the most affected. Abortion data are integral for the calculation of teen pregnancy rates, understanding the problem of untimely pregnancy and contraceptive use, identifying TOPFA, and studying the shift in provision of abortion services from hospital to clinic (eg. 21.8% of all abortions in Canada were performed in a clinic in 1990 and 45.6% were in 2003). Because of the debate that persists around the ethics of elective medical abortion, some may be hesitant to report on this issue for fear of inciting controversy. For instance, the Association of Public Health Epidemiologist of Ontario (APHEO) goes as far as to say "Given the sensitive nature of therapeutic abortion data, extra care should be given when presenting this information. Consider presenting pregnancy rates only to the public and providing specific therapeutic abortion information internally for public health staff."(216) Whether the result of an untimely pregnancy or in the case of the identification of a CA, the topic

of abortion is morally contentious and socially divisive in Canada. Recognition of this fact is important to research involving pregnancy outcomes, with the expectation that it should be treated equal to other events and not be concealed given its relevance to research, policy, planning, and even moral and ethical debate. Consideration should be given to mandatory reporting by private clinics to their respective provincial governments, or at minimum, government reporting of physician claims for abortion services to CIHI.

5.8 Study strengths

The strengths of the Maternal-Fetal-Infant dataset lie in its population-based and longitudinal design, large sample size, comprehensive ascertainment of pregnancy outcomes, and its ability to link several important datasets. The study sample included 93,171 pregnancies spanning a six-year period (2000-2005). Because the study population included all pregnancies, and not a sample of pregnancies, there were fewer concerns regarding selection bias. While the inability to account for confounding factors can introduce a level of bias to a cohort study design, a number of confounders (eg. maternal age, RI status, and RHA) were available for inclusion in analysis. Follow-up was very high, with a small number of participants lost to follow-up due to moving outside the province (n=1645 or 1.8%). Both Vital Statistics, hospital and physician services data were used to identify pregnancy outcomes and should capture nearly all pregnancy events involving Saskatchewan residents. Confidence is strong in the validity and reliability of Vital Statistics birth and death certificate data (217), which represents a census of events and is a legal requirement in each province and territory. Based on a comparison of hospital births reported in the DAD and Vital Statistics birth registrations (Statistics Canada), CIHI estimated that 98.9% of all births in 2008 were captured in the DAD (218), making Vital Statistics the gold standard for birth data. Physician data was also used in this study to capture congenital anomalies in live born infants. While Saskatchewan data has not been validated for such purposes, a Quebec study found physician data on congenital anomalies to be reasonably reliable.(219) Parents of infants diagnosed with a CA were contacted to assess the accuracy of codes in RAMQ database and there was 60% (or higher) agreement with very high specificity. An important benefit of the cohort design, coupled with the ability to link clinical testing data with administrative databases, was that the time-order of 'exposure' (ie. testing) and pregnancy

outcomes were clear and linked; much of the surveillance and research performed to date has not been able to directly link screening to outcomes in populations.

The current study was designed to detect cases of TOPFA following amniocentesis that were terminated prior to 20 weeks, which is a crucial component missing from the Canadian CA Surveillance System (CCASS) and a limitation in many studies. A study done in South Australia found that 79% of TOPFA (1980-1998) were done before 20 weeks gestation.(131) This figure was estimated to be lower (61.1%) in the current study, but still represents an important share of these events that would otherwise have been missed. Even with greater awareness of coding standards amongst health coders (ie. to apply O35 codes to flag TOPFA), the ICD-10 codes are still too general for an accurate accounting of the types of CAs in fetuses being aborted.

Screening data from the Provincial Laboratory and cytogenetics data from the two tertiary centres was necessary to investigate factors related to MSS and amniocentesis utilization, as well as to assist in the identification of TOPFA. A common methodological limitation of previous studies and the Canadian CA surveillance system has been the inability to link screening and diagnostic practices to pregnancy outcomes. Covariates such as mother's age, health region of residence, and Registered Indian status were available for the entire population, and through use of appropriate statistical modelling strategies and interaction assessment, a detailed analysis was conducted and relationships explored. Most studies on predictors of MSS to date have been descriptive in nature and none have done a thorough exploration of the relationship between First Nations ethnicity and screening.

5.9 Study limitations

Limitations encountered during the course of this study are described below. Consideration of the type and nature of these limitations is important in validating the study's findings.

5.9.1 Exposure measurement

Screening and cytogenetics laboratory data is expected to be of high quality, given its importance in risk estimation and diagnosis of anomalies. While MSS and amniocentesis data was fairly complete, a small number of cases may have been missed where patients sought out testing in a neighbouring province and for those that had double marker serum screening in 2000

and 2001 before a formal screening was launched in the province.[47] By restricting the investigation of MSS predictors to 2002-2004, there is no concern of misclassifying those that had double marker screening as non-screeners. In some cases blood was taken more than once when screening was done outside the 15-20 week period or sometimes if the result was positive. It was also not uncommon for a woman to have submitted a sample, to have received an increased-risk result, then for the Provincial Laboratory to request that the doctor confirm the gestational age and recalculate that woman's risk based on the revised age. Most cases where there was more than one sample, the physician ordered the blood draw too early, requiring a second sample. Given that one patient may have had multiple screens, and the complexity of examining more than one result, the final result was used here. The last result was deemed to be the most accurate risk estimate, but we may be underestimating the occurrence of interim false-positive results and their associated impact. Some 'screen negatives' will have actually screened positive initially, potentially explaining at least some of the follow-up diagnostic tests observed in those at decreased risk.

The timeframe spanned by some components of the dataset was less-than-ideal, but was due to data availability. Data from the screening program and the Cytogenetics laboratories were not available for the entire study period, which meant that analysis was largely restricted to 2002-2004 when investigating predictors of screening and diagnostic testing uptake. For infant mortality outcomes, the study period was 2001-2005 due to the fact that study was designed to only include births occurring in 2000; this meant that some deaths to infants born in 1999 would have been excluded from the 2000 death data. Because the provincial MSS program was implemented in May of 2001, a decision was made to request data back to 2000 and forward to 2005 (the most recent year as of the date of request). Data compilation took more than five years and we requested the study period be extended, but were informed by the Ministry of Health that the inclusion of more recent data would create further delays. Finally, the lack of amniocentesis data for 2000, and from January - September of 2001 for the southern half of the province, complicated interpretation. Cases of chromosomal anomalies that ended through pregnancy termination during this time would have been missed (discussed in more detail in 5.9.2).

Demographic information collected on women and infants for this study came from the

[47] Prior to program implementation, some blood samples were sent out-of-province for double marker screening. Data was not available for the current study.

provincial Person Registry System (PRS). While data from the PRS is of high quality and is updated routinely, information on health region of residence and Registered Indian status will be affected by people who moved and did not report their change of address to the Ministry of Health and by those who chose not to declare themselves to be Registered Indian. Registered Indians are Saskatchewan Health beneficiaries registered under Section 6 of the Indian Act and assigned a ten-digit number in the Indian Registry.(220) Declaration of RI status to the Ministry of Health is voluntary, meaning that not all individuals who have RI status will be identified in the PRS. Based on a comparison of federal government RI population figures and the Saskatchewan Ministry of Health's covered population reports, we estimated that 85% of RI people declared themselves to the Ministry of Health. Non-status Aboriginal people are not identified as such in the PRS.

5.9.2 Outcome ascertainment

Determining the cause of death for infants can be complex, leaving one to question the accuracy of the underlying (or primary) cause on the death record. Exact causes of death are not always clear, resulting in somewhat subjective primary causes of death being listed on death certificate.(37) The reported cause of death may also be influenced by the social or legal conditions surrounding the death and by the level of medical investigation. The ICD-10-CA was used to code causes of death for all infants dying during the study period, which has the benefit of lending consistency. Canadian data quality for ICD-10 coding is high.(221)

As described in the section on 'study strengths', the use of both Vital Statistics birth data and physician claims data enabled better capture of pregnancy events. However, physician claims data have not been validated for this purpose and there appeared to be errors in the use of the 'other abortion' code. Hospital and Vital Statistics data were available in many cases to ensure the most accurate categorization of pregnancy events, but not for all.

A potential source of bias in cohort studies comes from the degree of accuracy with which subjects have been classified with respect to their exposure or disease status.(212) While our confidence was high in the data on exposure (ie. screening and diagnosis), there were unavoidable limitations as far as ascertaining congenital anomaly outcomes. In particular, the absence of CA diagnoses for stillbirths inevitably resulted in an underestimation of cases. Cause of death for stillbirths is coded in both the DAD and on the Vital Statistics birth record.

Regrettably the DAD diagnostic data was omitted from the study request by the Ministry of Health (due to lack of awareness of its existence) and from the Vital Statistics data. Until recently the Ministry of Health did not have Vital Statistics cause-of-death data available for stillbirths in an electronic format (220). Ultimately we were not able to analyze trends in the causes of fetal deaths, which would have been measured through indicators like CA-related stillbirth rate and CA-related perinatal mortality. Pregnancies that underwent amniocentesis, then ended in stillbirth, did have diagnostic information pertaining to chromosomal anomalies. Stillbirths that were not tested would not have been identified as having a CA, even where one was known or suspected. The biggest gap would be for non-chromosomal anomalies. Availability of ultrasound diagnostic information would have been incredibly valuable given that many affected pregnancies will be screened, and some diagnosed, using this screening modality. Fetuses with anencephaly can be identified through high-resolution ultrasound examination (222, 223), therefore many affected cases will have been missed. In the Smith et al (2011) study in England and Wales, 90% or more of all spina bifida and anencephaly cases were detected during pregnancy either by serum screening or ultrasound.(98) It is likely that many known or suspected cases of NTDs resulting in spontaneous abortion or stillbirth have been missed in the current study, which is why NTD outcomes were not explored in detail. Most important to this piece of research are fetuses with an NTD that were terminated following prenatal diagnosis. Because likelihood of pregnancy termination is high for this category of anomaly, in particular for anencephalus and similarly severe conditions, these pregnancies are important to our understanding of prenatal ultrasound and serum screening and the pathway to diagnosis and pregnancy outcome.(109, 110)

Identification of pregnancies that were aborted following a CA diagnosis were not directly coded in the data. Rather we relied on the observation that prenatal screening or diagnosis was followed by a medical abortion, or a live birth or stillbirth (with or without a termination of newborn or fetus code) was preceded by a medical abortion. After applying these broad criteria, all diagnostic and procedural codes relating to the pregnancy were examined to confirm that there was high likelihood of a TOPFA. Pregnancies where a CA was diagnosed solely by use of an ultrasound, then terminated, would have been missed unless it resulted in a live birth. However, we suspect that very few women or physicians would proceed with an abortion without first having ordered MSS or an amniocentesis, but it is still possible that some

cases bypassed serum screening and invasive testing. In an effort to remedy this data gap, a request was submitted to the Canadian Institute for Health Information for aggregate counts of cases in Saskatchewan where an induced abortion code was accompanied by a 655/O35 code, indicating the abortion was the result of a fetal anomaly.[48] While consistency of coding for TOPFA may have been less accurate in the DAD during the early years (1990s), the number of TOPFA identified in the current study were close to the CIHI figures from 2001-2005. For the period from 2000-2005, the aggregate data from CIHI identified 115 pregnant women that had a TOPFA compared to 94 identified in the current dataset. Most of the missing TOPFA cases occurred in 2000; a year that was intentionally omitted from many of the analyses due to the absence of amniocentesis information and the recognition that most TOPFA would be missed, as described earlier. The divergence in live birth prevalence and incidence of Down syndrome and trisomy 18 from 2002 will reflect true differences, while rates in 2000 and 2001 may be the result poor case capture. As such, the emergence of the disparity between CA incidence and prevalence cannot be attributed to the MSS program with confidence. Having said that, the requested CIHI data (for the province of Saskatchewan) also showed a slight increasing trend in TOPFA rates from 2000-2010.

The classification of congenital anomaly covers a broad range of conditions from the relatively minor to those with an exceptionally poor prognosis. While analyses pertaining to MSS-detectable conditions (ie. Down syndrome, NTD, and trisomy 18) were highly specific, reporting on the 'other CA' or 'congenital heart defect' categories included the grouping of a range of conditions with varying severities, especially given the use of physician claims data where less severe anomalies are more likely to be captured. These categories of outcomes, while included in the dataset, were not a focus of this study.

Some key sources of information were unavailable for inclusion in the study dataset. Stillbirth diagnoses, ICD codes (O35/655) detailing the reason for pregnancy terminations when a CA is known or suspected, and variables from the reproductive abstract in the DAD (eg. gestational age) would have all supplied valuable information better-enabling the dataset to meet the needs of this piece of research. Nonetheless the current study is the first comprehensive investigation examining the use of prenatal screening, diagnosis, and their combined impact on

[48] Before making this request, we asked the Ministry of Health to provide these codes, however our request was denied.

several important pregnancy outcomes in Saskatchewan, even if only for a six-year period. It is unique in that it incorporates data from multiple sources, with a wide-range of information collected for each pregnancy.

5.9.3 Assumption of independence

Because pregnancies were not linked in the dataset, it was impossible to account for repeat observations (or multiple pregnancies involving individual women over the study period). Logistic regression models assume that all observations are independent from one another, which was not the case for the MSS uptake and amniocentesis testing models. When such a scenario cannot be avoided, it is ideal that a small percent of data is affected. The lack of independence will primarily impact the statistical significance of the parameter estimates in the model, but may affect the strength of the association. To further investigate the number of women appearing more than once in the MSS model, the Ministry of Health ran a report on their copy of the dataset and found that 31,628 out of 35,537 (89%) cases represented discrete individuals. In total, 3899 pregnancies were second and third pregnancies. The effect of pregnancy-specific factors such as age are less of a concern, as these change from pregnancy-to-pregnancy and will be less correlated. Parameter estimates around person-specific factors that do not vary with time have greater potential for error. For instance, First Nations ethnicity is constant and this sub-group has a higher fertility rate, which may have slightly elevated the effect of Registered Indian status in the models. To test the robustness of the MSS model, only one year of data was used to fit the model, which eliminated repeat pregnancies. Using the midpoint year (2003), the final model was nearly identical to the three-year model, with the exception of the Registered Indian status and mother's age interaction term, which became borderline non-significant (p=.061). This may have been due to the diminished power of the model given its smaller sample size. Given the very similar models produced using the two time periods, confidence in the final model is restored.

5.10 Summary

This study was carried out to produce an epidemiological profile of birth outcomes in Saskatchewan, including the termination of pregnancies for congenital anomaly. Ninety-four women terminated their pregnancy following detection of a fetal anomaly, which led to a lower live birth prevalence of infants with Down syndrome, trisomy 18, and anencephalus. When

pregnancy terminations were included in the analysis, a steeper increase in the incidence of those anomalies could be seen in Saskatchewan. Women that were not Registered Indian, those age 35 and over, and those living in the Saskatoon or Regina Qu'Appelle health regions were more likely to have MSS during their pregnancy. Due to lower MSS uptake and use of amniocentesis, the difference between the live birth prevalence and incidence of Down syndrome and trisomy 18 was smaller for Registered Indian women than for the rest of the population. Chromosomal anomalies were also less common in Registered Indian infants and fetuses. At the population level, selective termination rates were more than four times as high (per 1,000 pregnancies) in the 35 years and over age group compared to those 24 years and under. This finding reflects the higher rate of screening, prenatal diagnosis, and risk in the highest age category.

Since the implementation of the provincial MSS program, amniocentesis testing numbers declined slightly, but more women in the younger age groups are now testing due to abnormal MSS results and fewer women are testing due to age-related concerns alone. The majority of women that opted to have an amniocentesis and received confirmation of a CA diagnosis chose to terminate the pregnancy. The rate of pregnancy termination was similar for Down syndrome (73.3%) and trisomy 18 (75%), but was much lower for 'other chromosomal anomalies' (18.3%). Women under 30 years of age were much less likely to receive a prenatal diagnosis when a chromosomal anomaly was present (18.4% vs. 31.8%). While risk for a chromosomal anomaly is considerably lower amongst younger mothers, 53.5% of all pregnancies with a chromosomal anomaly belonged to this group. In total, 37 cases of pregnancy termination resulted in live or stillborn infants, which had consequences for mortality statistics.

Strong surveillance systems and reasonable access to research datasets will be an on-going challenge for the province of Saskatchewan and should be looked at as a priority. Trends in infant and fetal mortality are important to our understanding of the health of our populations. As per the SOGC's guidelines, performance of the MSS program must be monitored on an on-going basis, which will require data linkage and dedicated resources. Beyond surveillance and research, the field of prenatal screening and diagnosis is advancing at a rapid pace and the provincial government would be wise to engage citizens and experts on the profound ethical dilemmas raised by the termination of select pregnancies. Following along with protocols developed by other centres and organizations will not ensure that programming reflects local values, as these pertain to prenatal screening and intervention.

Chapter 6: ETHICAL, SOCIAL, AND POLICY INQUIRY

6.1 Introduction to the Dilemma

This chapter is dedicated to describing some of the ethical and moral challenges provoked by prenatal screening, both in its current and prospective forms. Much has been written in the ethics literature on this topic, with the occasional controversy popping up in abbreviated form in the news media. Academic papers in non-ethics' journals typically focus on the technical or programmatic aspects of screening and do not effectively alert the reader to the complex, profound, and intensely debated moral dilemmas raised by the practice. The current dissertation explored some of the more technical aspects of screening, but also investigated factors influencing individual uptake and the impact of pregnancy terminations on population outcomes. A discussion of ethics was felt necessary to ensure a well-rounded portrayal of the issue, putting findings into context and helping to ensure their moral relevance did not remain hidden behind the scientific complexities. Here I lay out the themes of the major arguments in a descriptive manner, recognizing that volumes have been written on the ethics of both screening and abortion. My goal is not to highlight all the particulars of the debate as they are numerous and complex, but instead to think about prenatal screening from a broader sociopolitical framework and consider what this approach might offer. A major ethical tension arising within the context of population based prenatal screening is the tension between community morality and the principle of respect for personal autonomy. Western medicine has framed prenatal screening and selective termination as a personal moral dilemma, thereby deemphasizing the social context in which the practice has materialized and the importance of community values. I will consider how a broader sociological perspective, one that takes into account the relevance of community values and limitations of the clinical encounter, could inform key practice and policy issues involving prenatal screening. It is my position that the community's voice must be invited to the conversation and public engagement processes should occur prior to any additional expansion in programming. I end with a look at how the community's voice might be better heard on key issues, even those issues that at first glance seem to be the problems of individuals.

Since the introduction of a formal prenatal screening program in Saskatchewan in 2001, it has remained a self-regulating program, with the Provincial Laboratory and a small group of Obstetricians making decisions about its design, test offerings, and physician education. Locally there has been no move to address ethical issues in an organized, comprehensive way, nor is

there a clear description of the specifics of these concerns. In November 1993, the Royal Commission on New Reproductive Technologies released its final report, consisting of several volumes, which included the topic of prenatal genetic diagnosis and the now out-dated maternal serum alpha-fetoprotein screen.(102) The report helped guide the creation of the Assisted Reproduction Act, passed many years later in 2004, but the Act fell short of legislating any parameters around prenatal screening.(224) The Act did not ban or control any activities relating to prenatal screening, diagnosis, or the use of termination of pregnancy for identified conditions, despite several recommendations by the Commission to ban sex selection abortions and prenatal genetic testing for multifactorial disorders and to restrict presymptomatic testing (eg. for conditions like Huntington disease) to genetic centres. The Act did, however, prohibit sex selection as part of assisted reproduction activities (eg. the selection of embryo based on gender). Much has changed in the field of reproductive screening and medicine since its writing, yet it is unclear what policy mechanisms exist for updating this legislation and how future policy decisions will be made. It must also be noted that much of the Act has been struck down, although the initial prohibitions remain in effect. The legislation was successfully challenged through the judicial process based on the fact that health falls within the jurisdiction of each province and territory, further challenging policy creation and standardization across Canada. At the same time, it presents an opportunity for legislation to be better-tailored to local norms and values.

In comparison, the United States has made a more concerted effort to engage the public (including experts) and has introduced legislation around screening. The National Human Genome Research Institute supports a scholarly program on the ethical, legal and social implications (ELSI) of genetics research. The ELSI inquiry examines the values underlying the use of new genetic technology, ideally before being implemented.(155). In 1999, the ELSI program was expanded to specifically address issues arising when genetics is used to advance the public's health, resulting in PHELSI. While Canadian scholars have contributed to the work being done as part of the ELSI research program, there does not appear to be a formal mechanism by which this work is connected to Canadian policymaking processes for consideration of implications for citizens in this country. In the United States, the 'Prenatally and Postnatally Diagnosed Conditions Awareness Act' was enacted into federal law in 2008 in response to growth in this field.(225) This piece of legislation mandates the creation and

expansion of services to better educate women who receive a diagnosis confirming the existence of a congenital anomaly, using the best current evidence relating to Down syndrome and other diagnosed conditions. In addition, it requires formal programs that link women having testing to groups that specialize in children living with disabilities; enhanced awareness and education programs for health providers providing pre- or post-test counselling; and has even mandated the establishment of a national registry of families willing to adopt newborns with Down syndrome. I will argue that the absence of a well-defined mechanism for community and expert engagement, linked to policy creation, leaves Canadians poorly equipped to discuss and debate the sociopolitical and moral implications that accompany scientific and technological adaptations in the field of reproductive medicine and genetics.

In the past five years, several new developments have together reshaped the landscape of prenatal screening in Canada, lending urgency to the need for dialogue on the salient ethical questions. The four most notable developments include: a 2007 recommendation from the Society of Obstetricians and Gynaecologists of Canada (SOGC) to expand the offer of screening to routinely include all pregnant women (48); testing techniques enabling earlier and better detection (eg. first trimester screening and non-invasive prenatal diagnosis) (45, 47, 226); recent evidence suggesting that sex selection abortions have skewed the male-female birth ratio in Canada (56); and the latest technologies (ie. preimplantation genetic diagnosis) that bypass the fetus all together and select against congenital anomalies or particular traits before the embryo meets the womb. In the past two decades, the pace of change in the fields of genomics and prenatal screening has accelerated, exceeding society's capacity to integrate this science into coherent public policy.

Two important ethical dilemmas lie at the heart of the moral debate regarding prenatal screening. First, is the use of abortion to avoid the birth of children (with disabilities) morally permissible? This dilemma has roots in the abortion debate, but also brings to light special concerns about discrimination and eugenic practices. Second, if we think this practice is acceptable (at least in some instances) should all decisions about when abortions can be performed remain with the individual or should the broader society be part of the conversation about parameters of screening and terminations of pregnancy when fetal anomalies are detected (TOPFA)? While the current approach to screening in Canada is described as non-discriminatory while prioritizing personal autonomy, there has been no coherent, organized debate on this moral

stance. Within these two broad questions, the ethical arguments made are multi-faceted and numerous. The role that science and technology and social and cultural systems play in the evolution of prenatal screening and diagnosis also warrants our attention, and will be interwoven into the current analysis.

6.2 Re-examining the Autonomy-only Perspective

In Western societies, respect for personal autonomy is the operative ethical paradigm governing the use of prenatal screening.(227) Autonomy is the idea that we must protect an individual's ability to act independently and to make his or her own moral decisions.(228) When one hears it said, "it's her choice", or "she'll do what is right for her", the principle of autonomy is being employed. Some ethicists view autonomy as being a key element in making morality possible, therefore underlying all other ethical decision-making theories. Others have critiqued the absolute focus on autonomy as excessive and limiting.(156) A focus on autonomy has presented a seemingly straightforward way to resolve ethical dilemmas around prenatal screening.

Both prenatal screening and abortion are often framed as measures that support women's reproductive choices. In the case of prenatal screening, autonomy provides a powerful argument for women's rights to make decisions about screening and subsequent termination of the pregnancy. Autonomy is also a strong argument used in the abortion debate generally. However, as Callahan argues, it is limited both in its ability to provide a good rationale for why we should accept prenatal screening and in its power to ensure ethically sound decision-making.(156) Most arguments based on this line of thinking propose that a woman, as an independent moral agent, has the right to additional information about her pregnancy based on available technology and the right to make autonomous choices about termination based on her own values and life situation. Interestingly many feminist scholars have challenged the common claims put forth in support of prenatal screening programs - that women want screening and that screening supports women's autonomy.(185, 191, 229) An exclusive focus on autonomy is limiting in so far as it blinds us to the broader social forces at play, and precludes consideration of why screening is widely available and endorsed by particular groups within the medical profession.

When it comes to the delivery of prenatal screening the ethical focus has been primarily on informed consent and non-directive counseling.(227) Both factors are seen as integral in

allowing women to guide their own autonomous decisions. The most recent clinical practice guideline released by the Society of Obstetricians and Gynaecologists of Canada (2007) states that counselling must be non-directive, respecting a woman's right to accept or decline any and all testing.(157) Non-directive counselling is commonly viewed as the proper way to delivery an offer to screen, providing women with necessary information in an unbiased manner to help them make decisions about prenatal screening and follow-up. In theory, following these guidelines is crucial to helping the patient make the right decision, which means her own decision. However, evidence has shown that many factors external to the patient, and specific to the clinical encounter, can impact the choice she will make. Factors such as how information is provided; who provides the information; and the provider's expectation that the patient will act (i.e. abort); all play a role in women's decisions whether or not to screen and to pursue diagnostic testing.(21, 32, 138, 230, 231) Non-directive counselling requires the provider to remove their own personal values from the counselling episode, even when their own views and values are incongruent with the offer of screening. In practice, non-directive counselling is difficult to deliver. Studies of midwives have found many experience personal and professional conflicts when they offer screening, in particular for those who had experience of Down's syndrome.(232-234) In a random survey of physicians providing counselling to women following a prenatal diagnosis of Down syndrome, Wertz (2000) found that 63% of doctors tried to remain neutral in their advice, while 23% admitted urging parents to terminate or emphasizing the negative aspects of DS to favour pregnancy termination and 14% emphasized the positive aspects of DS to favour continuation of pregnancy or actively urged parents to continue the pregnancy.(231) Marteau et al (1994) also found that obstetricians tend to be more directive in their advice and more likely to advocate pregnancy termination compared to geneticists and genetic counsellors.(235) By maintaining that the counseling process is value-neutral, there is risk of misleading the patient by denying and hiding the existence of such biases. As a result, the evidence suggests that 'non-directive counseling' is a misnomer and fraught with hidden biases. Its moral superiority to overtly paternalistic approaches remains questionable.(185, 227) Arthur Caplan (1993) explains that the adoption of non-directive counseling was an attempt to adhere to an ethic of value neutrality, which has enabled the field of clinical genetics to distance itself from historical abuses.(236) However, he argues that with the expanding possibilities and availability of testing

that the time has come to start a new debate about what ethos should replace this approach, as the endeavor for value neutrality is “no longer healthy” for clinical practice or public policy.

Seavilleklein (2009) makes a strong case for why we should be concerned that women's autonomy is not being protected or promoted by the routine offer of screening.(185) Among her concerns is the finding that the information necessary to achieve informed consent is often disclosed incorrectly, not at all, or a discussion does not take place. All of these violate the assumption that all pregnant women receive and adequately understand the pertinent information being provided. Marteau and Dormandy (2001) critique the counseling process as flawed by inadequate information, being directive, and too complex.(237, 238) In a small study in England, they found that 57% of women screened were not sufficiently informed to make decisions about screening.(238) Seavilleklein cites a body of research showing that most women do not fully understand the basics of testing; a failing that does not appear to differ among those who opt for testing or those who decline, and is common even among women with high educational levels.(185) The current confines of the prenatal visit may be partly responsible, given the limited amount of time available to adequately discuss all the information that would be necessary to achieve informed consent.

Some have raised concerns that the offer of MSS is disproportionately focused on the process of screening, rather than on actual details about the conditions being screened for and the potential results.(232, 239) Grant & Flint (2007) echoed these concerns, questioning physicians’ knowledge regarding people who live with a disability.(197) They call for greater awareness of these conditions when speaking to prospective parents, which includes the sharing of appropriate resources with women and their families (eg. parent support groups, genetic counselling, early intervention and developmental clinics, and relevant specialists). They go as far to say that "if front line health care providers lack this information, telling a pregnant woman about a fetal Down syndrome karyotype is prejudicial and contrary to the SOGC's recommendation that 'screening programs should show respect for the needs and quality of life of persons with disabilities.' "(197 p.581)[49] Many health care providers have never had experience with individuals with the conditions being screened and there is a high-level of variation in provider's capabilities when it comes to counselling.(239) Several studies in Canada and beyond have

[49] The line referenced by the Canadian Down Syndrome Society in a commentary on the SOGC's revised screening guidelines was later removed from the guideline.

documented insufficiencies in physician knowledge about prenatal screening, and importantly, the conditions being screened for.(22, 32, 240) In a 2005 survey, Saskatchewan physicians acknowledged limitations in their knowledge of prenatal screening and the conditions being screened for, and about one-quarter of respondents expressed concerns about future developments and additions to testing protocols.(32)

One wonders if it is realistic to think that physicians can continue to be responsible for counselling as screening possibilities expand along with the knowledge base needed to support informed consent. Physicians and midwives in Saskatchewan and elsewhere are currently handed the responsibility for much of the pre- and post-test counseling; many of whom see small numbers of pregnant patients each year, and even fewer screening test results that show an increased-risk. According to 2002-2004 statistics from the Provincial Laboratory, 81.1% of physicians ordering a MSS test ordered fewer than seven tests on average each year.(135) Out of the 635 physicians that ordered a MSS test during this three-year period, fewer than 50 physicians ordered 50% of all MSS tests and six physicians ordered 20% of all tests in the province. Together, the complexities of testing and infrequent experiences with MSS for most physicians raise questions about the appropriateness of physicians being made responsible for the majority of counselling. This concern is likely to grow as the number, types, and complexity of genetic tests increases. If patients are not fully aware of the implications and risks associated with screening and follow-up diagnosis, any hope for autonomous decision-making is greatly jeopardized.

It is commonly accepted that population-based programs offering prenatal serum screening must be optional or voluntary to preserve woman's autonomy, as opposed to being routinely ordered by the physician. This is a necessary caveat to avoid the implementation of potentially eugenic policies. Studies have shown that many women tested are not aware screening is voluntary, as it may at times be presented as being routine.(213, 241). The offer of prenatal screening may also occur at the same time as other routine tests, giving the impression that screening is routine and therefore should be accepted. While the thinking is that women make their own decisions, a reoccurring theme in qualitative research on this topic has been that they often look to the health care provider for guidance. How testing is offered by health care providers is an important factor in the acceptance or refusal of testing.(230) In a qualitative study by McNeil (2009), women who screened and those who did not both reported that health

professional's attitudes and opinions affected their decision.(242), compounding concerns that informed consent and the counselling process is not sufficient to resolve inherent ethical dilemmas. It makes sense that the opinion of one's physician or midwife holds significant weight, but it should be noted that no studies could be found directly linking provider's approach to counselling to women's decision-making process or pregnancy outcomes. Given the obstacles to truly informed consent, Seavilleklein recommended that the expansion of screening to include all women (as per the SOGC's guideline), regardless of risk, be reconsidered.(185) It is debatable whether or not individual decisions can truly be autonomous, but clear that the current situation faces real challenges that should be addressed.

Some fear that the decision to have screening may become an expectation more than a choice.(243) Women who test may be viewed by others as doing the responsible thing for herself, her family and her baby, and this may create a sense of obligation for them to accept. Women who do not accept testing or those who continue a pregnancy known or likely to be affected by a disability may be viewed by others as irresponsible and selfish.(243) The fact that such births can be prevented may increase the expectation that they are. Screening and TOPFA have the potential to become normalized, and therefore expected, in which case women who do not make 'proper' use of screening may be blamed for their decisions.(103) One survey found that 75% of pregnant women found it too difficult to refuse diagnostic testing when a physician recommends it.(244) Moreover, 78% believed they would not receive sympathy or support if they knowingly gave birth to an affected infant or after refusing diagnostic testing. These concerns may be reasonable given studies that have found community members and physicians assign greater levels of blame to women who give a birth to a baby with a disability after refusing screening compared to those who were not offered testing.(245, 246) Lawson (2003) found the general public and physicians judged women who continued a pregnancy despite a CA diagnosis as less deserving of financial aid and sympathy. Findings such as these force us to ask whether new technologies will serve to further marginalize those living with congenital anomalies and other genetic conditions, conditions that may increasingly be viewed as "preventable".[50]

[50] Screening and prenatal testing is one means whereby the fetus may be assessed for anomalies or genetic risk. However, preimplantation genetic diagnosis (PGD) has a much greater capacity for evaluating and removing embryos with unwanted markers. Mykitiuk and Nisker (2010) argue that the biomedical determinations of embryo 'health' through PGD have important consequences for our (changing) definition of health, and put forth the concept

While there is great concern that MSS be voluntary, some worry that the distinction between routine and optional testing may be no more than a shift from public to private eugenics. Duster (1990) raises the possibility that the application of new genetic technologies could lead to a return of eugenics through the 'back door'.(248) Some disability rights groups agree and have argued the current individualistic approach to selective termination allows discriminatory and covertly eugenic attitudes to flourish.(227) Shakespeare (1998) views current prenatal screening practices as 'weakly eugenic' because they operate at a level of individual choice rather than state population policy, but cautions that screening could become 'strongly eugenic' if applied to entire populations and if framed in terms of cost savings to society.(227) One solution, I argue throughout this chapter, is to open up the debate to wider scrutiny and invite the values of more stakeholders, in particular those most affected (ie. people with disabilities and women).

In the absence of published data regarding general awareness about prenatal screening and TOPFA, it is difficult to know how many people are aware of its existence and the nuances to the debate. Outside of women who were offered screening during pregnancy and those directly affected, basic awareness might be quite low and more in-depth knowledge of this technical field lower yet. This may be due to the fact that discussions about the morality of screening and TOPFA have been largely restricted to the individual and the clinical encounter, at the point where women are often hearing about prenatal screening for the first time. As such the invitation to have screening can come at an unanticipated moment, one where the pregnant mother is looking for reassurance of her growing fetuses' health, but instead is sensitized to the possibility of a health dilemma. Accordingly, reassurance of the baby's health is one of the most common reasons given by women who accept testing.(80)

Screening uptake and the impact of TOPFA on population rates were explored in earlier chapters, giving the impression that some populations of women are less interested in testing of this nature. Burgess and William-Jones caution that the aggregate social impact of the actions of many individuals may be significant, but do not necessarily reflect the intentions of those making the individual decisions.(249) For instance, women opting for termination of a fetus with a

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of social determinants of health of embryos as a means of identifying the social factors (eg. poverty, poor nutrition) that impact the embryos health, and distinguish these factors from the social context through which health is constructed (eg. parent's perceptions as to the meaning of genetic markers for their lives and their potential child's life).247. Mykitiuk R, Nisker J. Social determinants of 'health' of embryos. In: Nisker J, Baylis F, Karpin I, McLeod C, Mykitiuk R, editors. The 'Healthy' Embryo: social, biomedical, legal and philosophical perspectives. New York: Cambridge University Press; 2010. p. 116-35.

disability may be seen as rejecting the condition itself, and not the social circumstances (eg. financial cost, prejudice), which may encourage others to act in the same way.(250) Individual women's decisions about prenatal selection might affect the way society views pregnancy and fetuses and children with disabilities, by suggesting criteria with which we judge humans to be worthy of respect and consideration. Fewer people being born with these conditions may diminish our comfort and awareness of such conditions. The increasing number of participants in prenatal screening and prenatal selection might also reduce the pressure on governments and institutions to affect change, because change would increasingly involve challenging the norm.

Some scholars, writing on the topic of medicalization of pregnancy and women's health, critique the social construction of pregnancy in modern times as a high-risk event, requiring a high degree of medical and technological intervention.(251, 252) Even normal, non-complicated pregnancies have become medically problematic as opposed to being viewed as normal, natural processes and events. While increased medical intervention and monitoring have undeniably had benefits for the health of pregnant women and their infants, the medical gaze in combination with new prenatal genetic testing technologies have important consequences for women and children's health and their definitions (247). Abby Lippman (1999) argues that the genetics model frames the individual as the agent of prevention, thereby eliminating society's obligation to remove adverse social circumstances damaging to health - transforming illness into a private event.(253) With mother and fetus as the focal point of prevention and personal responsibility, it inherently downplays the broader influences on women's and children's health. It also may act as an impetus for a particular standard of health.(253) In the case of prenatal screening, where there are no medical cures for screenable conditions, the only way to eliminate the condition, is to eliminate the fetus through a medical abortion. With abortion as the principle solution to genetic test result 'problems', it has the power to devalue certain kinds of human life and trivialize the use abortion as a powerful method of prevention.(226)

Mykitiuk and Nisker (2010) consider the ways in which disability and health are medicalized through the application of reproductive technologies, heavily shaping future conceptions of health and sharpening the focus on the embryo and fetus as a determinant.(247) As the science advances, it is likely that both will come under greater scrutiny and that our conception of health and disease will stem from what can be known or forecasted based on the embryo. Lippman (1998) cautions that technologies are problematic when advanced under the

pretence that they are trying to improve lives by creating more options and freedom, if at the same time they are actually preserving gender, class, and racial disparities.(253) Furthermore, she asserts "the extent to which geneticization will lead to further devaluation of specific groups of people is vast; it would be naive to think that developing genetic analyses in a society that is already hierarchically gendered, racist, and classist and that systematically discriminates against those with disabilities can do other than reflect and reinforce these attitudes."(253 p.65) Moreover, as expectations shift, choosing may not be a straightforward concept when it comes to deciding whether or not to intervene.

The new fields of Public Health and Community Genetics (PHG and CHG) have called for the reframing of current genetic practices and controversies as population health or community health issues.(254) On the one hand, the emergence of these fields represents a movement away from the traditional clinical perspective in genetics, which may increase the potential for consideration of broader research, policy and practice issues. On the other hand, it might result in an expansion from individual test offering to population-based initiatives targeting whole groups, which raises concerns about the growing support for genomics at the population level, in spite of major deficiencies in our ability to grapple with these issues.

6.3 Birth defects: A Personal Trouble or Public Issue

The prevailing view that prenatal screening and selective termination are the decisions of individuals is evident. The way screening is provided in the health care system and the type of ethical inquiry that occurs in the literature both reflect a strong predilection towards seeing abnormal pregnancies as problems for individual women. This is comparable to how most medical conditions have traditionally been viewed.[51] At the same time, a shift is occurring where people are recognizing the wisdom of looking at the broader context of health, well-being and illness. The ushering in of the population health paradigm has challenged researchers, health care professionals and lay people to go beyond the individual risk factors to consider the social, environmental, and political determinants of health.[52] While there remains a strong inclination

[51] This line of thinking, concerned with the framing of health as a personal issue and potentially diminishing the role of the social context, applies to current conversations on personalized medicine as well.

[52] Population health is an approach that aims to improve the health of the whole population and reduce health inequities among population groups. It focuses on health outcomes, patterns of health determinants, and policies and interventions that link these two. 85. Kindig D, Stoddart G. What is population health? American journal of public health. 2003 Mar;93(3):380-3. PubMed PMID: 12604476. Pubmed Central PMCID: 1447747.

towards individualized approaches, a call for a broader way of thinking about prenatal screening and its ethical basis will bring about a richer exploration of the many nuances to this debate.

Partly owing to medicine's paternalistic roots, health care issues typically focus exclusively on individuals (i.e. the doctor as expert and the individual patient as health care recipient). Health care ethics by extension is guilty of the same way of framing problems.(156) Callahan (2003) critiques the dominant focus on individual-as-moral decision-maker as the "complete triumph of liberal individualism in bioethics."(156 p.498) He views liberal individualism as a Western ideology, as opposed to a moral theory, which powerfully determines what ideas and ways of framing issues are acceptable. Issues arising in health care ethics today, by default, are often framed as individual issues, which then require individual responses. This is not unexpected seeing that health care providers work at the 'micro-level' on a day-to-day basis and require practical tools for resolving sensitive dilemmas. An added pressure is physicians' liability if they do not offer prenatal screening. For example, in Canada, there have been an increasing number of 'wrongful birth' lawsuits filed against physicians who did not offer screening or who may have misinterpreted the woman's risk for an affected pregnancy.(255, 256) Therefore the only prudent option for the physician is to offer the test and guide the patient through an individualized process of ethical decision-making within their own constraints of time, knowledge and individual values. A logical consequence is that physicians, midwives, and genetic counsellors may then see their roles as limited to assisting the patient to make the best decision based on the patient's values, priorities and life circumstances, without either the physician or the patient giving full consideration to the social context in which these options have come about. The provider may also bring his or her own biases and assumptions into the encounter, yet may not fully be aware of them and their impact. Callahan states, "…it is [not] easy for any of us to see how our tacit political and social ideologies, lurking just below the surface, are pulling the strings of our 'rational' thought."(156 p.501) Health care providers cannot be held responsible for the fact that ethical discussions are limited to the clinical encounter, but it is the accepted, and generally uncontested, way in which ethical dilemmas are resolved today. It is also a practice with inherent and strong limitations.

It is useful to consider that health care ethics occur at the micro (individual), meso (organizational) and macro (societal) levels (257); all interconnected, but requiring different types of questions and decision-making strategies. Many issues like prenatal screening cut across

all three planes, but because health care ethics is tailored to guiding clinical decisions for medical professionals, it has emerged largely as a way of thinking about individual ethical dilemmas. The clinical encounter is wrought with challenges - time constraints, less than optimal clinician understanding, information bias, personal value differences - which call into question who is the most appropriate and best-equipped person to assist in this ethical decision-making process. The intent of this analysis is not to find fault in well-intentioned health professionals who must act and react within the current system, but to question the wisdom of leaving patients and providers to navigate through these ethical minefields, when issues could, and perhaps should, first be openly discussed in the public realm to create greater awareness of the complexities. Such an approach would also enable the inclusion of the 'disabled voice' in screening policy (227) - a group that has not been consulted in regards to prenatal screening practices in Canada. There is a recognizable appeal in using more easily applied ethical principles at the individual level rather than engaging in major public controversies, which may partly explain why ethical dilemmas are often deferred to individuals and practitioners. This way of resolving issues has become the norm in medical practice despite its limitations. Drawing from the social sciences may help place individual experiences in the broader, sociopolitical context and to consider the importance of community dialogue.

Much can be learned about the roots of individual and social morality from Sociology's prominent theorists. In *The Sociological Imagination* (1959), C Wright Mills points to the value of thinking about personal troubles as public issues and supports a critical examination of how such issues are framed.(258) Most interesting and relevant to the current discussion is Mill's notion that any issue must be considered simultaneously at the level of the individual and society, since they are interrelated and indivisible. Mills thoughtfully writes,

> "Know that many personal troubles cannot be solved merely as troubles, but must be understood in terms of public issues - and in terms of the problems of history making. Know that the human meaning of public issues must be revealed by relating them to personal troubles - and to the problems of the individual life. Know that the problems of social science, when adequately formulated, must include both troubles and issues, both biography and history, and the range of their intricate relations. Within that range the life of the individual and the making of societies occur; and within that range the sociological imagination has its chance to make a difference in the quality of human life in our time."(258 p.226)

Drawing from Mill's work, a fuller understanding of the intricate connections between the individual and public spheres is needed to appreciate how individual choices around prenatal screening are inextricably linked to the social, political and shared moral values of the larger society. Recall the eugenic philosophies that flourished throughout North America in early 1900's culminated in the atrocities of Nazi Germany, where millions of Jewish people, the disabled and the mentally ill were exterminated.(259) Most academics and researchers, although initially active participants, quickly disassociated themselves from this way of thinking. It has often been misunderstood that this dangerous ideology originated with the Nazi regime, when medicine and science built the foundation.(259) Following the war, many concentration camp victims were scorned by other citizens and the crimes against them were often not acknowledged, demonstrating the same prevailing attitudes that led up to the murder of millions. Canada was not exempt from the eugenic mindset. Sterilization laws were implemented in British Columbia and Alberta where official government policy allowed sterilization of people who were mentally ill and those with disabilities – the former requiring 'consent' from the individual.(259) Once legal, involuntary sterilization is now considered battery under Canadian law; a tremendous shift in definition over a relatively short period of time (this practice occurred in Alberta all the way up to the early 1970s). This is but one recent and local example of how social conceptions of worth and respect shape the values and actions of individuals. In the same way, public eugenic policies did not emerge in a vacuum, but rather came about through the actions of individuals over time, leading to their normalization (even if temporarily). Applying a critical analysis to current screening practices will be important if we are to avoid serious consequences and violations similar to tragedies throughout history.

6.4 The Contribution of a Communitarian Perspective

While individualism has become a popular ideology in Western societies, ethicists from the communitarian tradition critique the notion of the individual as the focal point of moral concern.(228) Callahan (2003) argues that an absolute focus on the individual blocks what he calls 'serious ethical inquiry'.(156) Due to the relentless focus on autonomy, deeper ethical inquiry must yield to individuals' notions of right and wrong. In this way of thinking, individual rights take precedence over the interests of the larger society, and the society must not impose any notions about good and value. Communitarianism counters this perspective, responding that

history, tradition and moral communities are the true sources of moral thought and action.(228) Communitarians also believe public controversies cannot be resolved by focusing on the well-being of one person at a time, but rather discussion needs to happen around community values and what a 'good society' would look like. From a communitarian perspective, the first question then that needs to be asked should focus on the social and cultural impact of a decision. Communitarians object to the preoccupation with the individual and its lack of recognition of the individual as a social being. Both the choices afforded to individuals and the thinking used to make decisions about these choices are a result of the larger society we live within.(156) Prenatal screening and selective termination is only an option for individuals to the extent that society permits this option and social institutions have created the means to make it optional at all.

6.5 A Technoethical Inquiry Perspective

The biotechnology revolution is a powerful social force that has quietly yet dramatically changed the way we think, value, live and relate to one another. Science and the market appeal of its new technologies are social forces that have an incalculable impact on our way of thinking.(156) As Callahan points out, due to our view of biotechnology, if something is available and some individuals want it, then it is thought it should be released and only prohibited when scientifically proven to be harmful.(156) This is often referred to as the 'technological imperative (260)'. The mere availability of prenatal screening has become a justification for its provision. Because technologies must be used in order to gauge whether they are harmful or not, by the time it is found to be harmful, its use is often normalized and expected. To remove prenatal screening services from the slate of tests currently offered to pregnant women, screening would need to proven to be harmful, ineffective, and costly (or a combination of these). However, society's working definition of harm is narrow and often does not include social, moral and political consequences.(156) Furthermore, science is often framed as a value-free activity, a view that seems to support the unrestrained development of new prenatal screening tools. Shakespeare (1998) disagrees, arguing that science is a social activity and scientists must take responsibility for its application.(227)

Prenatal screening is a good example of a cluster of reproductive technologies that are reshaping the way society views childbirth, disability, and genetics. Similar to most technologies, prenatal screening was created and implemented with virtually no input from the broader

community, including women or people living with disabilities. Because prenatal screening leads to fewer children born with these conditions, these groups, and society generally, have major stakes in how this technology plays out. Its unilateral release is evidence that it is not the public that guides policy around the introduction of new technology; for the most part, technology leads us.

Technoethical inquiry is an interdisciplinary framework with an explicit focus on the role of technology in society and the interplay between technology and other social systems (261), and it has much to offer to the current conversation. Using this perspective, the transformative power of technology is recognized as one that plays an intermediary role in all human activity, and to some extent, has replaced nature. Luppicini (2009) maintains that

> "The rise of the technological society is accompanied by a social and ethical crisis that society is now struggling to deal with. Because of the tremendous power and impact of such technological intertwinements, social and ethical considerations are now at the forefront of public concern and academic interest. However, due to the complexity and multiplicity of human-technological intertwinements that arise, it is an ongoing challenge for social scientists to keep up with changes that occur in so many areas. What further complicates the situation is that many of these changes are not directly observable and require sophisticated strategies to discern. ...Reflecting on the complex character of our contemporary world defined by technology is perhaps the most challenging problem of the 21st century. What makes this challenging is not due to technology (in itself), but rather, the elusive character of technology within society. As some new technologies become accepted and integrated in society (i.e., cell phones, Internet), they tend to become invisible to individuals and disappear into the background of everyday life (Volti, 2009). The main consequence of this is that the powerful intermediating role of technology is poorly understood because it is not noticed. This blocks any efforts to provide responsible decision making about which technologies to nurture, which to suppress, and in what contexts."(261 p.6-7)

As new reproductive technologies like prenatal screening become increasingly integrated into our societies, they too will become less noticed, less contested. Perhaps the greatest value of the current dissertation is that it begins to describe the social impact of a new individually applied technology - prenatal screening in Saskatchewan - a practice that cannot be understood without rigorous, in-depth study and data access.

Prenatal screening today is not what it will be tomorrow, and it is almost certain that as our ability to screen changes, so too will our sensibilities about what is acceptable. With this in mind then, we (as a society) must recognize that each new wave of technology is gradually redefining the maternal-child relationship (as conditional on the child's health and/or parental

preferences[53]); the nature of human reproduction; and our definitions of health.(247, 262) We must also question how future decisions will be made given the current direction (or lack thereof) in Canada, and evaluate if this is consistent with how they *ought* to be made. Currently there is no legal regulation of prenatal screening or selective abortions, which means that each individual is asked to decide for herself, with all the biases and limitations of the current clinical process and all the outside pressures and expectations weighing down on her. It is unclear what a more regulated screening practice might look like. At one end of the spectrum could be a situation where the government regulates which tests are offered and who provides and receives the offer, with heavy restrictions on when and for which reasons a fetus can be aborted or even prohibiting abortions for this reason. Given prevailing political and social ideologies, a more moderate approach might better appeal to the general population. This could include elements where public and expert engagement help to create some legislative controls (eg. which screening tests are offered in Canada; how to handle new tests as they become available), while still allowing women the decision to terminate a pregnancy affected by fatal anomalies.

New reproductive technologies can place governments, providers and women in difficult positions when forced to reject or turn away "progress", or when they take a "wait and see" approach. Saskatchewan took this very approach to the implementation of the MSS program, yet was viewed by some as being behind the times or not current with evidence-based medical practice. Central to this dilemma is the notion of personal responsibility on the part of the inventor of the technology who creates new possibilities in the first place. Mario Bunge (1977), the first to coin the term technoethics, argued that technologists and engineers must be held both technically and morally responsible for what they design and implement.(263) Moreover, the invention should not be harmful, but beneficial, in both the short and long term. Harm, according to Callahan (2003), should be conceived of in the broadest sense of what truly harms people (eg. threats to their values, social relationships).(156)

The current way of thinking conveys that what the inventors of prenatal screening technologies have created are essentially value-neutral until a woman applies them to her own circumstance. Still Seavilleklein (2009) reminds us that women's choices are determined by

[53] In her book, Rothman (1986) describes how modern medicine, with its new capacity for prenatal screening/ diagnosis, preimplantation genetic diagnosis, surrogacy, has promoted a situation where pregnancy is viewed as tentative.262. Rothman BK. The tenative pregnancy: prenatal diagnosis and the future of motherhood. New York: Viking; 1986.

whichever options are available and that these options are the result of broader contextual factors such as political and economic interests, historical circumstance, and research agendas.(185) Vassy (2006), for instance, argued that prenatal screening in the United Kingdom did not come about in response to women's demands, but as a result of particular interests (eg. medical supply industry, sectors of the medical profession, and government organizations).(187) Tests are brought to market by private companies, who are intrinsically profit-driven and therefore have a vested interest in expanding testing technologies. In the case of prenatal screening, testing reduces costs associated with caring for affected individuals throughout their life course; a fact that has been highlighted and studied in many cost-benefit analyses.(264-267) As more women are tested (whether they have provided informed consent or not), those involved in screening interpret this as women wanting more testing and use it as evidence to support expanded testing services.(187) Callahan (2003) cautions that the power and profit of technology can effectively control and manipulate, but is very difficult to see, much less retaliate against.(156)

A key challenge in a world with a global economy and access to the internet is that tests banned in one country can be easily shipped from another country, and then an abortion performed in the woman's home country or in a country where this type of abortion is permitted. Reproductive tourism, as it has sometimes been called, presents challenges to creating policies and legislation to prevent activities judged to be unethical and undesirable. This has been seen in the case of sex-selection abortions (which are similar in nature to pregnancy terminations for fetal anomaly in that, for some individuals, a particular sex is an undesirable outcome) where Canadian couples have accessed services in the United States.(268) While sex selection abortions are not illegal in Canada, it is almost impossible to find a physician who would perform one or a hospital that would knowingly allow one.(269) A good sign that social and moral consensus can be achieved in Canada on particular controversies. Because abortion is generally permitted for unwanted pregnancies in Canada and sex determination by ultrasound is exceedingly common, sex selection abortions invariably do occur unbeknownst to the physician and are not as rare as one might think.(56) Luppicini (2008) tells us that "one of the overarching guiding principles of Technoethics, referred to as the Law of Technoethics, asserts that ethical rights and responsibilities assigned to technology and its creators increases as technological innovations increase their social impact (p. 16)." (261) In the case of prenatal screening and selective abortions for sex selection, the social impact can be profound. In the case of sex

selection abortions, many regions in countries like India and China are disproportionately male - a situation that has further exacerbated abuse of female children (eg. feticide by families and infanticide when a female child is born) and has obvious repercussions for fertility and women's equality.(57) In societies where underlying biases and prejudices prevail, the use of abortion to remove marginalized groups of individuals may exacerbate the existing problem. It is unclear what the current expectations are for those researching and creating new reproductive testing technologies. If these individuals indeed have responsibilities to the larger society, a challenge will be helping them identify which of their creations will be largely benevolent and which might be too problematic.

Science and medicine are not the only stakeholder groups that should take responsibility for regulating the field of prenatal screening and selective abortion in Canada. Muller-Hill reflects on the holocaust and concludes, “medicine and science should never again be trusted when they promise to deliver their own ethical values; these values have to come from other sources (p.49).” (259 p.49) Citizens, interest groups, religious organizations, and politicians, along with experts from medical and non-medical fields, all can and should play an important role in setting policy directions. Where possible, individuals with disabilities and carriers of genetic disease should be engaged directly, recognizing that even family members will sometimes have different views.(227) At present, obstetricians, medical geneticists and genetic counsellors, and laboratories have almost exclusive influence on practice and policy, which should be recognized as being problematic. And while prenatal screening is almost universally available throughout Canada, it does not mean current practice should not be reevaluated.

The emergence of prenatal ultrasound screening has opened a window to the womb, allowing women to better-bond with their child before birth, lowering maternal anxiety, and reducing risk behaviours.(270) Ultrasound has become particularly ingrained into the prenatal care experience, with most women waiting with anticipation until the time they can 'see their baby', enabling mothers to bond in a way not possible before the introduction of this technology. On the other hand, it has consequences for pre-birth discrimination, value judgements about what constitutes a life worth living, transformation of the pregnancy experience, and potentially repealing the hard-won victories of the disability rights movement. Luppicini (2009) refers to this as the 'paradox of technology', where a technology provides opportunities to improve human life and society, while simultaneously having "anti-human consequences against which

individuals ought to defend and protect themselves."(261 p.15) In the case of prenatal screening, it may for some individuals redefine their relationship with their fetus/baby as conditional based on his or her health, functionality, and normalcy. Even for those who refuse screening there are unavoidable consequences, namely that society is repositioning itself in relation to individuals with disabilities and health risks, in which case having a child with a CA may inadvertently increase the burden for families. Seveilleklein (2009) explains how new choices can soon become the socially expected choice, and can have unexpected consequences that include the disappearance of previous options.(185) In France, a country where screening and diagnosis is remarkably common and pregnancy termination high, it may not be long until the population of people with Down syndrome disappears. From 1983-2002, 71% of all Down syndrome cases in Parisian mothers were detected prenatally and 95% were terminated (31), effectively making the decision to birth and raise a child with Down syndrome socially inconceivable and practically much more difficult without community support groups and programming. Having a child with a disability in a society where fewer and fewer are granted entrance, runs the risk for lower levels of practical support and less positive regard for people living with these conditions. It eliminates others from the population that may have acted together as a community of support and kinship. It also limits the range of human experience and the richness inherent in the diversity of experience. As such, it is important that we further study and remedy such imbalances that favour one option, without enabling the other option to remain a viable alternative (eg. similar to the earlier discussed conditions attached to the Postnatally Diagnosed Awareness Act in the United States).

Part of the challenge in technoethical inquiry is to identify sub-system imbalances, explain why they are so, and consider their impact on the lives and choices of individuals.[54] Social inequalities are produced by sub-system operations and must be analyzed at that level. It could be argued for example that reproductive technologies (falling within the medical sub-

[54] Under the technoethical inquiry approach, sub-systems include law, politics, religion, economy, science, communication, culture, medicine, and education; each with their own core operations and values. Law has as its core operation, the production of social norms and regulation of conflict and justice as its core value. Religion's core operation is the production of spiritual guidance, and faith is its core value. While each system has separate and mutually exclusive operations, they are open to the environment and each other. Luppicini describes that "each subsystem has its own set of perspectives by which it observes the other subsystems. For example, politics can observe the other sub-systems from a political standpoint and interpret society in political terms... economics .... in economic terms (p.9)".261. Luppicini R. Technoethical inquiry: from technological systems to society. Global Media Journal - Canadian Edition. 2009;2(1):5-21.

system) produce social inequalities. The current study and others have provided data suggesting that greater uptake of screening by more educated, wealthy women and certain ethnic communities means CAs might disproportionately affect lower income and First Nation families.(31, 83, 98) This may represent an inequity in a context wherein community resources and social support for women is insufficient to support the decision to continue an affected pregnancy. Within the technoethical systems perspective, social change is achieved when society reacts to changes in its sub-system operations involving human agents (eg. changing medical norms), not by human agency directly.(261) Using this way of thinking any significant change in prenatal screening practice would not only require individuals to act differently, but also require changes in sub-system operations. This may be in the form of professional guidelines, legislation, legal precedent, or increasingly through collective action orchestrated through social media campaigns (also part of the technological sub-system). The focus of the technoethical paradigm is on knowledge acquisition and understanding the system under inquiry.(261) Technoethical inquiry can help us to better evaluate the ethical responsibilities that accompany new inventions, which can help us navigate the system in ways that reduces these tensions. A successful analysis occurs when a shared understanding is achieved in regards to the key ethical dilemmas, but does not require consensus.(261)

6.6 Screening for Any Condition or Only the 'Severe'

The existence of prenatal screening programs, in contexts where abortion is permitted, is associated with the belief that abortion of fetuses with certain traits is socially and morally acceptable. Often it is said that screening detects 'severe conditions', however severe is a relative term and used in this context includes Down syndrome and spina bifida. Alone these conditions are not severe, many would argue, but could be if there were other co-morbidities. The Canadian Down Syndrome Society (CDSS) views "Down syndrome [as] a naturally occurring chromosomal arrangement that has always been part of the human condition, seeing it as neither a disease nor a negative medical outcomes of pregnancy." (197 p.580) The severity of the condition is likely to influence people's beliefs about when abortion should be permitted, therefore is an important component to the debate. If certain parameters were set within which fetuses could be aborted, what might those parameters be? Some working in the field of prenatal diagnosis and fetal medicine have been skeptical that a consensus on what constitutes severe

could be achieved in a general way. The SOGC states "screening for a disorder should be undertaken only when the disorder is considered to be serious enough to warrant intervention (157 p.738)", but does not go as far as to define what constitutes a serious disorder. A challenge will be determining how we (as a society) decide which disorders are serious. For the most severe cases, those that are predictably fatal, it could be argued that the practice simply shifts the timing of death, intervening earlier in a dying process that is inevitable. For a truly terminal condition, like anencephalus, this could very well be true.

Claims are often made that people with disabilities are valued (or should be), similarly to those without but one cannot help notice the apparent inconsistency when we have population-based programs aimed at the prenatal detection of such fetuses with the offer to prevent their birth. The fact that some or all women may choose to intervene not only means that future persons with these conditions may be removed from our society, but it also implies that their value as a human being in this world hinges on that identifiable trait or condition. In essence, it creates entrance requirements for humanity.(4) Seavilleklein (2009) favours the use of a relational autonomy framework to encourage a deeper look at the options made available through prenatal screening and to consider why some options and not others are available.(185) For instance, a woman may screen for Down syndrome and abort, but cannot choose to abort based on fetal sex. Looking to future possibilities, society may find it unsettling if programs expanded the offer of screening to include the identification of fetuses at-risk for less severe or late-onset conditions (eg. BRCA mutations for breast cancer or at-risk APOE alleles for Alzheimer's disease). Heterogeneity is part of the human condition and a large segment of the population will have an increased likelihood of experiencing one condition or another. Some of the problems are that there is subjectivity in the interpretation of 'risk', limited ability to predict degree of impairment, as well as varying abilities to understand and imagine a future child (unknown to you as yet) living with any given condition or risk. Already in Saskatchewan and other jurisdictions women are having their pregnancies prenatally tested for Cystic Fibrosis, which given its frequency in the general population may be the next condition approved for screening.

One might posit that population-based screening for other, less serious conditions, is unlikely, however, the potential integration of new genomic technologies into non-invasive testing techniques is thought to be inevitable.(226) This would mean that a plethora of conditions and risks could be detected in the first trimester, without immediate risk to the fetus, and by way

of a simple blood draw. Such a development would have irrevocable and vast implications for the field of prenatal detection and ultimately the filtering of fetuses affected by such conditions. A chief concern is that children could then be born with a pre-mapped genome, without having given their own consent for testing, which could have repercussions for care and treatment for those with 'at-risk' genomes, as well as infringing on their right to *not* know.(226) Parental consent for testing for conditions viewed by the parents as severe with immediate consequences is one thing, but non-consensual complete genome mapping is far more problematic. Taken alone one condition or another may not dissuade a parent from giving birth, but multiple risks together may have a more powerful impact on their choice. The timing of testing has also been shown to impact the decision to have an abortion or not. de Jong (2010) notes that a majority of people in western countries view the moral significance of the fetus and embryo as something that increases with development.(226) The fact that earlier testing enables earlier abortions might make this option more acceptable to women, as well as altering their views about new testing possibilities.

6.7 Baby or Fetus: Complex Implications for Word Choice

During the writing of this thesis, seemingly simple decisions about word choice often became agonizing selections for someone wanting to give a reasonably balanced perspective on the topics. Describing and discussing the subject matter in a way that was accurate and straightforward was not always an easy task. Often the easier way to phrase an event led to reliance on the common clinical terminologies, which some view as value-neutral or objective language. Others, like the Canadian Down Syndrome Society (CDSS), take exception with much of the language used to describe the process of screening to patients who are potentially carrying a fetus with Down syndrome.(197) The CDSS argues that terminology can send implicit messages about the desirability of having a child with the condition or any other condition. Nondirective language is a fundamental principle of genetic counseling. The decision to use the term 'risk' instead of 'likelihood or chance' or 'diagnosis' instead of 'determination' when speaking about screening results, as the CDSS and others argue, denotes an undesired outcome.(197, 271) Another example is the use of 'normal' when speaking about unaffected children, as opposed to saying 'children without a congenital anomaly or disability'. Skotko (2006) notes that this type of partiality is built into the educational materials of many programs, thereby often biasing parents

early on towards particular choices.(271) Saskatchewan MSS program patient brochures use a mix of word choices, with very little information on the conditions being screened in the regular brochure and no information on conditions screened in the low literacy version.

Aside from the language used to describe screenable conditions, care must also be taken in describing abortion and the developing fetus in an academic paper. Words like 'termination of pregnancy' or 'pregnancy interruption' are recent examples of new word choices, perhaps with the intention of creating distance from the term 'abortion' (ie. medical or therapeutic abortion). The term 'fetus', widely used in academic contexts, may be referred to as an 'unborn child', 'child in utero', or 'baby' depending on the contexts. Feticide is a less common reference to abortion. Another attempt at reframing contentious practices by means of a language change is the recent substitution of 'after-birth abortion' in place of 'infanticide', although the ethicists who chose to use this term also insert "killing of newborn" in brackets.(272) The authors admit their language choice was intentional and meant to emphasize their view that "the moral status of the individual killed is comparable with that of a fetus (on which 'abortions' in the traditional sense are performed) rather than to that of a child."(273 p.2) One term that was used often in this dissertation is "termination of pregnancy for fetal anomaly", which was sometimes abbreviated to TOPFA to make reading easier. The short form was used with hesitation, recognizing that it is inherently reductionist and downplays the significance of a complex, painful, moral and personal dilemma with far-reaching societal implications.

6.8 Abortion and the Moral Status of the Fetus

Today in North America and most developed nations, the general acceptance of abortion has allowed supporters to sidestep the issue of human rights, given that most unborn children have not been conferred formal, legally enforced rights. The usual argument goes that the fetus, although human, alive, and having its own unique DNA, does not meet the legal criteria for personhood. Still the fact that the fetus is not viewed as a person by legal systems in many countries does not preclude the fetus from possessing what ethicists call *moral status*.[55]

[55] Dwyer (2010) defines moral status as "a characteristic that we human moral agents attribute to entities, by virtue of which they matter morally for their own sake, so that we must pay attention to their interests or integrity when we consider actions that might affect them, regardless of whether other beings are concerned about them. When an entity has moral status, I may not act toward it in any way I please, disregarding its well-being, preferences, or continued existence. I owe some moral obligations to that entity itself. As a moral agent, I must care to some degree

Intuitively, and increasingly as a result of our ability to study and view the fetus via new technologies, we recognize the importance of this phase of growth to achieving personhood. Some, like Gillon (1988), view people (from embryo to elder) as existing on different points in the life continuum and being the same human being (biological) that they were as embryos and as fetuses.(275) Some argue that human life, however it exists, is inviolable, while others view the fetuses right to protection as increasing with development. This latter line of thinking supports the concept of the fetus as a patient, in which case, Chervenak & McCullough (1995, 1996) argue that before viability it is up to the pregnant woman to confer moral status, but after viability the fetus becomes a patient to whom doctors have duties.(276, 277) In this case directive counselling for fetal benefits is ethically justified. The physician caring for a pregnant woman has two patients, not one.

Countless arguments have been made in support of abortion, including that human persons may have been human embryos and fetuses, but that human persons, embryos, and fetuses are not the same.(275) The three most ethically significant factors used to determine the fetus' moral standing seem to be: whether the mother wants the fetus to be born; fetal viability outside the womb; and the health of the fetus. Those that accept abortion as morally unproblematic often accept the view that the killing of embryos and fetuses is permissible in the interests of the pregnant mother.(275) Therefore while the fetus may have moral status, this status is secondary to what is deemed to be in the mother's (or family's) best interests. As Shakespeare (1998) observes, peoples' views about abortion in the case of a fetal anomaly are often more complex than being 'pro-choice' or 'pro-life'.(227) For example, some people who oppose social abortions support abortion in the case of fetal anomaly, while some disability rights activists argue for abortion rights except where an anomaly is diagnosed. The threat of an anomaly is also sometimes used to justify abortion rights in general.

Concerning the morality of terminating a pregnancy due to a known or suspected fetal anomaly, the common dilemma is whether we can morally justify limiting abortion for particular reasons, when we do not limit abortion for any reason. That is, in North America women do not need to provide justification for early abortions, which typically are the result of unwanted or untimely pregnancies. In a legal sense, abortions for all reasons are treated equally,

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about what it wants or needs, or simply what it is; this imposes some limitations on how I may act toward it."274.

Dwyer JG. Moral status and human life: Cambridge University Press; 2010.

even if ethically many do differentiate between an abortion due to a rape and one due to the mother's career.(227) The feminist argument is that women have the fundamental right to make their own decisions about their bodies, which is necessary for their full participation in society.(278) Here the fetus is viewed as having no moral status, or a moral status subordinate to its mother's interests. An important difference between abortions for any of these reasons and abortions following a CA diagnosis is that the mother in the latter instance had the intention of carrying the child to term, to bring it into personhood. It was not that the mother did not want to bear a child, but she did not want to bear that particular child.(279) Gillon (1988) makes the case that "any embryo or fetus that is intended to be kept alive and allowed to develop normally and *become* a human person nothing should be done to it that would harm the person it will become which would not be accepted if done to a 'fully fledged' person." (later called "The Actual Future Principle" by Harman 1999) (275 p.4). In essence, the fetus should be treated as having the moral standing of a person, not because it is a person, but because it is intended to be one.(280) This thinking is reflected in public health prenatal programming that aims to optimize outcomes for infants, and to a large extent, holds women responsible for their choices and behaviours once they have made the commitment to carry the child.

Those that oppose the selective termination of fetuses with an anomaly may or may not favour abortion for other reasons. However, writers in the field of disability equality have concerns about the push women may feel towards choosing abortion after a prenatal diagnosis. Because many physicians and genetic counsellors view selective termination as a favourable option (281-283) and biases exist that frame disabled lives as those not worth living (278), women may feel compelled to abort. Disability rights activists object to the notion that these lives are less valuable, distinguishing between 'impairment' (the physical condition) and 'disability' (social consequences of impairments). Sharp and Earle (2002) explain this position further saying "... it may be that in the current social and economic environment, disabled lives are not [viewed by the medical establishment as] worth living; however, that is not a consequence of impairment itself, but instead of prevailing social and economic conditions which militate against impaired individuals leading full and satisfying lives (p.140)".(278 p.140) While Shakespeare accepts the notion that women should have the right to choose, he does not see their choices as currently being truly free due to the broader forces at play in any decision. While Shakespeare views the ethical tensions between the feminist and disability rights

discourses as reconcilable, Sharp & Earle (2002) mount an interesting case as to why they are fundamentally in opposition.(278)

Prenatal selection, the termination of a fetus affected by a condition undesirable to the mother and/or posing serious threats to the quality of life of the child, is allowed in our society because it involves a fetus. That is, the current mindset and value system of most Canadians would likely not permit the euthanizing of children or adults with cystic fibrosis, Down syndrome or spina bifida. This is not to say that this cannot change. Consider the Netherlands, where the Groningen Protocol was designed for the euthanasia of sickly newborns.(284) Two medical ethicists from Oxford University incited controversy following a paper published in the *Journal of Medical Ethics* that argued 'after-birth abortion' is not inherently different than late termination of pregnancy because the moral status of the infant is similar to a fetus, saying "neither is a 'person' in a morally relevant sense."(273 p.2) The concept of postnatal abortion is quite relevant to the current analysis, in that it may be viewed by some as a justifiable extension of pregnancy terminations for congenital anomaly (eg. when a prenatal diagnosis is not made and the parents are given the choice to end the infant's life shortly after birth). In Saskatchewan, the current study identified 12 cases where the pregnancy termination resulted in a live birth. Such cases can be quite traumatic for health care staff and parents, who then must witness the infant die over the course of minutes, hours, or even days.(285) While these early births are the result of an abortion procedure, the question of the healthcare teams' duty to the born-alive infant becomes another difficult ethical dilemma.[56]

Women today are increasingly aware of early risk exposures and most treat themselves, and by extension treat their growing fetuses, with care. A large and growing body of evidence has shown that the quality of life inside the womb (ie. the uterine environment and the interaction between mother-child) has a substantial impact on future health and development, making the prenatal period a critical determinant of the lives most hope to experience. There is, at times, an uncomfortable contradiction inherent in society's treatment of the growing unborn child. There is immense concern for the life within and anticipation of its birth. People will lay hands on

[56] In January of 2013, Canadian Members of Parliament for the Conservative party asked the RCMP to initiate a homicide investigation of an estimated 491 cases of fetuses 'born alive' following an abortion procedure between the years 2000-2009. They note that these cases appear to meet the criminal code definition of a homicide, which is someone causing a child to die after birth by causing an injury during or before birth. 286. Hopper T. Birth of a legal quandry: live-birth abortions a perilous grey zone in Canada's criminal code. National Post. February 1, 2013.

pregnant mothers' stomachs waiting to sense the movement from within; mothers will worry about the chemicals they are exposed to and the vitamins and nutrients they consume; some will plan to preserve the cord blood stem cells, to document the pregnancy in beautiful artwork; day-to-day accounts of the experience may be detailed via social media; and most mothers will visit their care providers routinely to ensure that everything possible is done to increase the chance of having a healthy child. Virtually no mother refers to her growing child as a "fetus", but rather it is a "baby" and the family's longing to meet the child is often palpable.

When it happens, the diagnosis of a fetal anomaly can be devastating for the mother and family and a sudden shift may occur when the fetus is suspected to have health concerns. Barbara Rothman (1986, 1993) powerfully describes women's painful experiences and the shift where they begin to try and conceal their pregnancy (while awaiting a diagnosis), deny fetal movements, and the immense pressure to act swiftly before the fetus grows further, assuming an earlier abortion will be easier.(287) She laments the lack of full consideration of the toll that the prenatal screening and diagnostic process, as well as the decision to continue or terminate, take on the pregnant woman. Emphasizing the inability of genetic testing information to provide a true picture of the condition, its consequences (ie. level of impairment), and future quality of life, Rothman is concerned about the decisions that women are faced with. In line with Shakespeare's argument, she is also skeptical about women's true ability to choose. "When a woman 'chooses' aborting rather than bringing to birth a child with a particular condition or predisposition, she is doing so in a world that sets the parameters of that child's life just as surely as genes do. Abortion can be the right choice, the moral choice, the only choice, but it, like birthing the child, is always a choice in a context."(287 p.267)

The key controversy here may well be the question of when and under which circumstances abortion is ethically permissible, if at all. If we believe it is moral to allow women to terminate pregnancies when they are untimely and therefore likely to impact the quality of a woman's life, then can we argue it is morally wrong to terminate any specific *kind* of pregnancy? Is it unethical to terminate pregnancies based on sex, race, sexual orientation, intelligence, or other aesthetic qualities? There seems to be fairly widespread consensus in the medical community that prenatal sex selection should be prohibited in Canada.[57] Hence we are faced with

[57] Interestingly, the practice is also illegal in India, where it has become widespread, particularly in many rural communities.

a distinction between prenatal screening for the purpose of selecting fetuses based on sex as opposed to selection based on disability and future quality of life. Ethical analyses find similarities between the two and question whether different recommendations (i.e. for the prohibition of prenatal sex selection and the acceptance of prenatal selection due to disability) are more a result of better-developed social pressures against sex discrimination than disability discrimination.(249) The fact that both the public and medical profession reject the notion that abortion is morally permissible in certain circumstances (ie. female gender or aesthetic characteristics), suggests that traditional rationale supporting abortion (as a woman's individual choice) does not extend to all situations. Similarly, feminists have struggled with the concept of sex selection abortion, generally opposing this practice, but have difficulty morally reconciling it against the claim that it is each woman's right to have an abortion for whatever reason she chooses.(288)

Here in Canada, many would argue our society values a woman's ability to decide whether or not she carries her pregnancy to term, but there is no clear social consensus on the question of abortion, when it should be permitted, and under which circumstances.(289) Support for abortion varies across provinces, with individuals polled in British Columbia and Quebec showing greater support than those polled from the prairies. No information is available on Canadians' views of the termination of fetuses with varying conditions or traits. Given that we also know that support can change when dialogue is guided by evidence, it is unclear what abortion policies Canadians would be willing to support. More in-depth investigation in this area would be valuable and may be guided by the Genetic Town Hall model that was successfully utilized in the United States (described in section 6.12).

6.9 The Moral Ideal: Embracing Diversity and Respecting Disability

A more idealized approach to moral controversies such as prenatal selection may move us beyond what some describe as libertarianism's 'selfish ethos' to more fully consider others (156). Emmanuel Kant wrote about the duty of beneficence, which means acting in a way that furthers the happiness or welfare of another.(290) Three interesting studies that looked at parents and siblings of children with Down syndrome found overwhelming life satisfaction and pride in their family member with Down syndrome.(291-293) When surveying those with the

condition, Stoyko (2011) found that almost 99% of people with DS said they were happy with their lives, 97% liked who they are, and 96% liked how they look. For those with direct experience of life with Down syndrome, the diagnosis is not the tragedy that some may perceive. Interestingly, studies using a community sample have found that parenting a child with DS was thought to be less rewarding, more costly, and result in less family continuity, yet the majority of respondents within these studies had no personal experience of persons with DS or any other intellectual disability.(294) Those with negative views of parenting a child with a disability were also more likely to say they would terminate an affected pregnancy. Parents' perceptions are important to screening decisions and may be unrealistic. Given the mostly positive reports from families with someone who has Down syndrome and the fact that most of these pregnancies are wanted pregnancies prior to diagnosis, more must be done to ensure women have a full understanding of the conditions about which they are making vital decisions for their pregnancy. Parens and Asch (2003) remind us that the disability is one aspect of the individual not the sum total.(295) Still Asch (1999) laments that "once a prospective parent knows of the likely disability of a future child, there is nothing else to know or imagine about who the child might become: disability subverts parental dreams."(p.1652)"

The International Convention on Disability Rights is a covenant guaranteeing people living with disabilities equal human rights, fundamental freedoms, and respect for their inherent dignity.(296) The Convention, signed by 155 states in 2006 and put into force in 2008, places a heavy emphasis on the prevention of discrimination and awareness raising to foster greater respect for those living with disabilities, including combating stereotypes and prejudices and promoting awareness of their capacities and contributions. Canada has signed and ratified this agreement, but one cannot help to recognize the incongruence between respect for disability and population-based screening programs that aim to prevent their entry into our society. It seems disingenuous for Canada and other developed national to affirm the rights of those living with disabilities and to speak against discrimination, yet to continue to leverage sophisticated technologies to seek out those fetuses who show signs of potential disability and to utilize various, invasive techniques to remove them from the trajectory of human existence. Even if we concede that this population does not yet meet the moral requirements of personhood and therefore ending their lives cannot be viewed as an infringement of their human rights, the act of measuring, evaluating, and destroying affected fetuses might still be seen as a hostile, uncaring

act that blocks certain types of fetuses from coming to enjoy life within the world community. Several Members of Parliament in the United Kingdom share similar concerns about legislation that allows late pregnancy termination in the case of a CA only, in the face of laws protecting people with disability from being treated less favourably.(297) As such, a parliamentary inquiry was launched (report published July 17th, 2013) to seek out evidence from parents, medical practitioners, academia, support groups, disability groups, lawyers and other interested individuals to help inform possible new legislation.

6.10 Current Regulatory Environment

Not all provinces in Canada currently offer prenatal screening as part of a comprehensive and centrally organized provincial program, but nearly all offer maternal serum and ultrasound screening and prenatal diagnosis through amniocentesis or chorionic villus sampling. Policy creation and implementation of practice guidelines appear to vary across jurisdictions, often occurring in a rather disjointed way. Decisions about prenatal screening are made predominantly by professional medical groups, which then are implemented by provincial health departments, and become mandatory and routine aspects of prenatal care delivery by physicians and midwives. Currently the SOGC, and more recently the Canadian College of Medical Geneticists (CCMG), consisting almost entirely of medical doctors in these specialties, review the scientific literature and make recommendations for the implementation of new testing possibilities. The SOGC has released recommendations on prenatal screening as it pertains to those conditions currently tested through serum screening (i.e. Down syndrome, trisomy 18, and neural tube defects), cystic fibrosis carrier screening and sex selection abortion. No open discussion of ethics is visible in any of these documents, calling into question the adequacy of the analysis and the suitability of the SOGC to make decisions with such far-reaching social consequences. Practicing physicians and midwives are primarily used as agents to deliver testing, which has helped legitimize the practice, but arguably, their authentic voices have not been heard either. A 2005 survey of Saskatchewan physicians found that physicians held diverse views regarding prenatal screening, selective termination, and disability.(32) Many expressed concerns about the increasing capacity for genetic testing of fetuses and the social, ethical and clinical implications. With the forward momentum of screening, it was perhaps surprising when the SOGC stated in August of 2002 that population-based prenatal screening for cystic fibrosis for all pregnant

women could not be recommended at this time. While this could be described as a prudent course of action, there was no mention of ethical uncertainties, but rather practicalities of clinical implementation. The predicament is that the SOGC and other health care policy makers either support or oppose the implementation of new testing regimens based on clinical and scientific evidence, which does not contemplate their ethical significance and societal implications. Webster and Baylis (2000) note that it is not uncommon for ethical issues arising in the clinical setting to be camouflaged and portrayed as ordinary by using familiar nonmoral language.(298) The end result is that the technology is essentially unevaluated in terms of its ethical merit.

6.11 Public Engagement as an Ethical Issue

Prenatal screening has been framed as a purely private or medical matter, where the focus is on procedural solutions when substantive debate is actually what is required (156). Academic publications compare one screening method against another and debate the cost-effectiveness of population-based screening; however less is published in the medical literature about the ethical merits of the practice generally. Debates around the morality of prenatal screening still rage, but typically within the refuge of ethics' journals. The health care community owns the practice of prenatal screening and diagnosis, yet its focus largely rests on the 'how', overlooking its moral underpinnings. The fact that the much-needed ethics debates have been excluded from the mainstream media is also concerning. Public awareness and inquiry may be one means of helping to promote accountability, and ensuring medical practice reflects a spectrum of values and perspectives. It may also invite others from outside the healthcare community to contribute and even lead the much-needed debate.

Prenatal screening today is framed as a legitimate practice exempt from moral scrutiny (largely due to the claim that it is the individual's choice), therefore impeding further dialogue about its parameters, delivery and the social consequences today and in the future. It is my position that the public must be engaged on the topic of prenatal screening and the availability of abortion for affected pregnancies. One might ask if broad public engagement around prenatal screening, or any major moral issue in society, will result in a more ethical outcome than if only a select group of experts had been consulted. In health care, the structure and culture of the clinical setting can be constraining.(298) Inadequate space exists where ethical issues can be openly and fully explored, rather there may be "tremendous pressure to get along by going along

(299 p.298)". Increasingly there is recognition (by policymakers, scholars, scientists, and the public) of the importance of hearing from 'citizens', which may be a means of increasing the public's trust in both policy and scientific technologies.(300)

What is it about public debate and consultation that will help to ensure deeper ethical inquiry? While the health care setting, as a workspace, is also a 'moral community' where ethical dilemmas can be openly discussed; it removes the recipients (mothers being offered testing) of care and those with invested interests (people with disabilities) from the deeper and broader dialogue. It also does not allow input from other citizens and groups with an interest in the outcomes (eg. focuses on 'patients'). For the same reasons moral communities within health care settings are supported, moral communities are necessary in a broader sense. Intentional dialogue that includes the views and knowledge of a variety of persons, from a mix of backgrounds and social circumstances, will bring about a fuller analysis than is possible in a clinical encounter. It may also sensitize women to the nature of the issue before the offer of screening, giving them time to consider their own personal views and values before making a decision. Decisions with wide-ranging social implications that have the ability to change who we are, how we relate to one another and the type of world we live in. Already we may be greatly disadvantaged in our ability to critically evaluate the offering of prenatal screening as the practice has to a large extent become normalized (at least for a handful of conditions).

Consider a hypothetical scenario where a pregnant mother is offered a noninvasive screening test during her 10th week of pregnancy and receives a genetic profile that identifies a genetic risk factor that has important implications for the child's future health and survival -- the BRCA genetic mutation for breast cancer. The mother then requests that her pregnancy be terminated, fearing for her daughter's future wellbeing and her own pain and suffering living with this knowledge. In this hypothetical case, the mother may find it consistent with her personal and family values to carry through with the termination, but as a society we must reflect on the sentiment underlying this decision and the social impact if such decisions were to become common. This dilemma calls into question the limits of personal autonomy. While society has been conditioned to believe it should remain silent about the choices individual women make about their own bodies, that silence has come with a price; the sacrifice of reasoned societal debate and formulation of a coherent social morality with respect to genetic testing. These concerns are beyond the realm of personal ethical dilemmas and are serious society-wide moral

controversies. As Rayna Rapp (2000) poignantly observed, women today are 'moral pioneers' not by choice, but by necessity.(4)

6.12 The Task of Involving the Public

Using a model similar to that employed in the Genetic Town Halls in the United States or the use of theatre in Canada (300, 301), broad public consultation can be conducted that will offer citizens the opportunity to deeply engage on the morality of prenatal screening and its parameters. Cox and Nisker (2010) advocate for novel strategies that can be used for "broad and inclusive public participation in genetic policy development."(300 p.153) With a knowledge translation plan in place, finding from such consultations could effectively be used by decision-makers to shape public policy. At present the public has not been well-engaged in ongoing ethical debate around biotechnology. The introduction of the Canadian Biotechnology Strategy (CBS) has created opportunities for greater public engagement (eg. Consulting with Canadians website) and may prove to have benefits as far as delving into the deeper ethical and social inquiry needed. A renewed sense of public empowerment over decision-making may encourage community members to become engaged about what decisions provide the most good for society. As much as personal empowerment promotes health and well-being, engagement in policy debates may be empowering in a moral and social sense, potentially alleviating the powerlessness people feel when they must submit to social practices contrary to their own morality, which may be thought of as a form of social 'moral residue (290)'.

More attention should be paid to innovative and comprehensive strategies for eliciting public input on issues like prenatal screening and diagnosis. Rosalee Starzomski suggests that first a space must be created for the public to critically evaluate the use of genetic technologies.(290) In order to engage people in a meaningful way, at minimum, there is a need for increased awareness; a mechanism for feedback; accountability of government, industry and science; legitimization of lay knowledge; transparency; and a way to engage all types of people, especially people with disabilities and cultural groups who traditionally have been underrepresented (and less interested) in genetics.(290, 302) The CBS covers some of these components, but it's scope is wide and the link between its research and policy uncertain. No public consultations have been conducted on prenatal genetic screening or testing to date. Starzomski (2004) presents another interesting example of public participation in decision-

making around new technology in Canada.(290) The Canadian Public Health Association (CPHA) used mixed methods to connect with a variety of Canadians on xenotransplantation. Most interesting, the process revealed significantly different opinions depending on how much information respondents were given. If people knew less, there were more likely to support the new technology than if they were well informed. This has important implications for future processes designed to gather public feedback, especially on complex and not well understood issues. It also underscores the limitations of public polling or surveys where many respondents may not have an adequate understanding to provide an informed opinion at that time. Education is a crucial component to developing meaningful engagement processes that are designed to inform policy.(300, 303, 304) A key aspect of the CPHA's process is that lay knowledge was valued and used to formulate a broad policy. Because new technologies, directly or indirectly, impact us all, input from a broad range of stakeholders will be important.

In 2005, Jeffrey Nisker led a novel approach whereby Canadians in Vancouver, Edmonton and Toronto were engaged on the topic of preimplantation genetic diagnosis.(300) Using a theatre presentation of a play called *Orchids* that presents two women in a fertility clinic for in vitro fertilization - one leaving it to chance if her child will inherit the genetic condition she has and the other requesting PGD to ensure her child does not carry that same condition. Participant discussion followed the performance in the form of either a large group discussion or a focus group. Discussions were taped, transcribed, and results were shared with Health Canada for policy development on the topic of PGD. Cox and Nisker (2010) note that "Canadians attach enormous importance to opportunities such as this to engage in dialogue and contribute to health policy development."(300 p.157) Feedback was also positive in regards to using this medium to educate, engage and arouse discussion. While some of the discussion that occurred during the course of this project could be applied to prenatal screening/testing and genetics generally, public engagement specifically on the topic of prenatal screening would be most valuable for policy guidance. In addition, broad-based participation is an important guiding principle for public engagement efforts and must include other citizens outside large metropolitan centres, as the current study highlights variations that likely reflect distinct geographical and cultural values and norms.

In 2004, a unique public engagement model, called *Genetic Town Halls: Making Every Voice Count*, was used in six cities across the United States.(301) Over a focused 3.5 hour

session, participants learned, debated, and voted in a series of polling questions and provided their opinions during facilitated small- and large-group discussions. With the intention of going beyond basic focus groups, the Genetics and Public Policy Center (at the Phoebe R. Berman Bioethics Institute, Johns Hopkins University) prepared and shared videos that provided grounding in the science of reproductive genetic testing, including carrier testing, preimplantation genetic diagnosis, and prenatal testing. Interviews were also videotaped that provided various viewpoints about genetic testing from experts in fields ranging from medicine to theology. On-site experts were available to clarify any issues that came up during discussions. Local community members shared their views during panel discussions, and often included clergy, parents having experience with genetic testing, medical professionals, community activists, elected officials, and those from the biotech industry. The sessions were open to all interested individuals and the participants (n=536) came from various demographics groupings, political and religious affiliations, and varied experiences with testing. However, there was no mention of recruiting individuals with first-hand experience with disability or carriers of particular genetic conditions. The majority of participants rated the experience positively. During the sessions, participants expressed the desire to be better informed, to contribute to the broader discussion, and to have input into the implementation and development of these technologies on an on-going basis.

The Town Hall model was motivated by the recognition that public opinion research through surveys, focus groups and interviews falls short due to individual's limited knowledge on complex technologies.(301) The Genetic Town Hall approach was designed to gather opinions from and facilitate debate amongst a better-informed group of citizens. Three major issues were considered: acceptable uses of testing/ limits; safety and accuracy of testing; and effects of reproductive genetic testing on individuals, families, and societies. The majority (89%) felt there should be limits set on testing, with many supporting the ability to test for fatal childhood diseases (81.9%) and fewer supporting testing for adult-onset disease (56.4%) or hypothetical genes for intelligence or strength (21.3%). A major theme that emerged was the need for diversity in society and the fear of the loss of diversity and discrimination against those with a condition, however, many also agreed that reproductive genetic testing helps parents make informed choices and have healthy babies. At the same time that the Genetic Town Halls were being held, the same issues were being discussed online. Using this format, participants met

three times for one-hour, were sent the videos to watch in advance of the session, and sessions were moderated by a content expert in order that questions were answered immediately. Findings were largely the same using both approaches and were shared with decision-makers in hopes of contributing to public policy. A subsequent session was held in 2008 on the topic of biobanking. The Genetic Town Hall represents an ambitious and novel undertaking capable of successfully educating and engaging citizens on complex and ethically contentious technologies. It is a model worthy of consideration here in Saskatchewan and Canada to better engage citizens on technically complex ethical dilemmas, in order to create policy that is better-aligned with the community's values while simultaneously raising awareness.

6.13 Concluding Thoughts

An extensive body of research spanning many years has explored the challenges to informed consent in the context of prenatal screening and identified hurdles that are difficult to resolve. Less-than-optimal provider knowledge, directive counseling, involuntary screening, time constraints of the clinical visit, the complexity of information, and poor patient understanding all present challenges to autonomous decision making. A better alternative will require changes to ensure more ethical patient-provider encounters and public participation in policymaking and agenda setting. Very little information has been provided to the public to increase awareness about the practice of prenatal screening or its ethical controversies. The same is true when screening is offered to a pregnant woman; there is no mention of moral concern, despite the fact that the practice of TOPFA is highly debated. A pregnant woman may have a nagging sense that the practice is ethically sensitive, but when her physician does not broach these topics it may erroneously leave the impression that there is social and moral consensus around its use. There is also very little, if any, engagement of the local community by governments or screening programs, despite the SOGC and CCMG having recommended that local values be taken into consideration *prior* to implementation of a program.(48) Largely due to its intimate link to abortion, the provincial government and health system appears reticent to engage the public on the topic of prenatal screening. Yet any meaningful social critique must open itself up to the larger society, which extends beyond academic journals and medical texts.

A more open clinical encounter may be just as important as more open public debate. In response to the inherent limitations in the operationalization of informed consent and non-

directive counseling, Wyatt (2001) suggests an approach where the patient-provider relationship is characterized by openness and transparency about the provider's personal values and morals, not manipulated by masking personal biases.(305) Such an approach should be considered whether or not meaningful public debate occurs. Social critiques must occur at all levels (micro-, meso-, and macro-), bringing to light the factors influencing available options.

We must recognize that greater public input does not necessarily mean drastic restrictions would be imposed on current practice, although possible, but instead it might be decided that personal choice is the best approach within certain limits. Creation of ethical boundaries in a society are important, as limits help reaffirm collective beliefs, values, and preferences. Engagement of this nature should occur before the next new prenatal screening test hits the market. Recently, the SOGC reviewed the prenatal screen for cystic fibrosis, eventually recommending that it not be implemented at a population level *yet*, but rather be reserved for high-risk parents. It is useful to have the educated opinions of a group of experts from the field reviewing this technology, however it is not enough. Cystic fibrosis may well be the next condition added to the accepted list for screening and prenatal selection; this will qualitatively change the prenatal screening environment as it would represent a shift from conditions with immediate and notable health ramifications to those that are relatively less severe and associated with much longer life expectancies. It is not hard to imagine how screening practice will expand from severe and immediately terminal conditions like anencephalus; to the less predictable and less serious such as Down syndrome; to the questionably severe, unpredictable and often undiagnosed until later in life, including cystic fibrosis and BRCA mutations. The key question is: will the decision makers be willing to consult the public? If the SOGC had recommended mass screening for cystic fibrosis, the weight of this recommendation likely would have trickled down to the local level, where provincial health departments (lacking the knowledge needed to fully evaluate such a request) would feel compelled to offer the best care possible. Eventually lay people would discover this technology was being used, well-after its implementation, but many would presume that someone evaluated the practice for its moral and social consequences. Opposing voices would have little hope of influencing policy after implementation.

Not only do prevailing social norms shape individual's way of thinking, but individual choices also shape the society we live in. Individuals make decisions for themselves, but they are also making political and social decisions that have the potential to indisputably change the

world we live in.(156) In her review of xenotransplantation, Starzomski explains how one individual seeking out treatment in another country where the technology is legal can lead to catastrophic implications for the home community and even the world, given the potential for new viruses to emerge.(290) The consequences of prenatal screening are less obvious and require more investigation, but are similarly profound. It is difficult to discern if there are fewer individuals living with Down syndrome in our communities without large and sophisticated research able to accurately identify cases of TOPFA and the factors contributing to observed trends. Still the disappearance of such individuals represents an important loss, especially to other families within the Down syndrome community and to those living with other disabilities. If we hope to genuinely optimize reproductive options for women, it will be important that we attend to any systematic imbalances that favour TOPFA over socially supportive environments and a culture that embraces all individuals equally. Further qualitative research should be done in Saskatchewan to deepen our understanding of the reasons that women choose to screen or not, and their experiences along the prenatal screening pathway, including the decision to continue or terminate a pregnancy following prenatal diagnosis.

While screening, in its current form, is limited to a small number of conditions, de Jong et al (2010) warn that the new non-invasive prenatal diagnosis (NIPD) exacerbates the moral challenges presented by traditional prenatal serum screening.(226) Because NIPD is easier, safer, and can occur earlier in the pregnancy, the fear is that informed consent may become harder to achieve and selective abortion normalised. However, there is a real likelihood that this technology will expand to include testing for a much broader range of abnormalities, genetic risks and non-medical traits. In this case, informed consent might be nearly impossible to achieve, given the herculean challenge of explaining to women the implications of numerous conditions and the inability to predict outcomes with any degree of certainty. de Jong et al (2010) put forth an urgent call for proactive analysis of the implications of NIPD in an expanded form, and further ethical dilemmas that will emerge.(226) We cannot foretell what form future testing will take, but we can appreciate the urgent need to be prepared with an engagement process and decision-making framework able to respond to the next controversy.

Individual autonomy is an important principle that supports individual freedom, but it is not enough to justify a practice that will profoundly change the way we live together as a society and our treatment of a most vulnerable sector of our population (the fetus). The social

implications of prenatal screening today, and even more so tomorrow as technology advances, are too immense to force upon individuals who may or may not be aware of their social and historical embeddedness. It is our moral obligation to seek authentic input from individuals and communities within a well-informed context, not only on specific issues but common values. When controversial issues are dealt with strictly on an individual basis, there is greater risk that other voices from the broader society will be ignored and potentially reshaped by those of science and markets. As public health professionals, practitioners, academics, and citizens, it is our responsibility to move forward debates about public involvement and call for a culture of public consultation, where all Canadians are invited to shape policies around prenatal screening and genomics, helping to shape the scientific and medical agenda early on.

References Cited

1. Liu S, Joseph KS, Wen SW. Trends in fetal and infant deaths caused by congenital anomalies. Semin Perinatol. 2002 Aug;26(4):268-76.
2. Joseph KS, Kinniburgh B, Hutcheon JA, Mehrabadi A, Basso M, Davies C, et al. Determinants of increases in stillbirth rates from 2000 to 2010. CMAJ. 2013 May 14;185(8):E345-51.
3. Ontario Ministry of Health and Long Term Care. Born Ontario Ontario, Canada [June 20, 2013]. Available from: www.bornontario.ca.
4. Rapp R. Testing women, testing the fetus: the social impact of amniocentesis in America. London: Routledge; 2000.
5. Health Canada. Congenital anomalies in Canada - A perinatal health report, 2002. Ottawa: Minister of Public Works and Government Services Canada; 2002 [cited May 29, 2013]. Available at: **http://publications.gc.ca/collections/Collection/H39-641-2002E.pdf**
6. Cheffins T, Chan A, Haan EA, Ranieri E, Ryall RG, Keane RJ, et al. The impact of maternal serum screening on the birth prevalence of Down's syndrome and the use of amniocentesis and chorionic villus sampling in South Australia. BJOG. 2000 Dec;107(12): 1453-9.
7. Olsen CL, Cross PK, Gensburg LJ. Down syndrome: interaction between culture, demography, and biology in determining the prevalence of a genetic trait. Hum Biol. 2003 Aug;75(4):503-20.
8. Loane M, Morris JK, Addor MC, Arriola L, Budd J, Doray B, et al. Twenty-year trends in the prevalence of Down syndrome and other trisomies in Europe: impact of maternal age and prenatal screening. Eur J Hum Genet. 2013 Jan;21(1):27-33.
9. Irving C, Richmond S, Wren C, Longster C, Embleton ND. Changes in fetal prevalence and outcome for trisomies 13 and 18: a population-based study over 23 years. J Matern Fetal Neonatal Med. 2011 Jan;24(1):137-41.
10. Khoshnood B, De Vigan C, Vodovar V, Goujard J, Goffinet F. A population-based evaluation of the impact of antenatal screening for Down's syndrome in France, 1981-2000. BJOG. 2004 May;111(5):485-90.
11. Van Allen MI, Boyle E, Thiessen P, McFadden D, Cochrane D, Chambers GK, et al. The impact of prenatal diagnosis on neural tube defect (NTD) pregnancy versus birth incidence in British Columbia. J Appl Genet. 2006;47(2):151-8.
12. Gucciardi E, Pietrusiak MA, Reynolds DL, Rouleau J. Incidence of neural tube defects in Ontario, 1986-1999. CMAJ. 2002 Aug 6;167(3):237-40.
13. Wen SW, Liu S, Joseph KS, Rouleau J, Allen A. Patterns of infant mortality caused by major congenital anomalies. Teratology. 2000 May;61(5):342-6.
14. Wen SW, Liu S, Joseph KS, Trouton K, Allen A. Regional patterns of infant mortality caused by lethal congenital anomalies. Can J Pub Health. 1999 Sep-Oct;90(5):316-9.
15. Liu S, Joseph KS, Kramer MS, Allen AC, Sauve R, Rusen ID, et al. Relationship of prenatal diagnosis and pregnancy termination to overall infant mortality in Canada. JAMA. 2002 Mar 27;287(12):1561-7.
16. Liu S, Joseph KS, Wen SW, Kramer MS, Marcoux S, Ohlsson A, et al. Secular trends in congenital anomaly-related fetal and infant mortality in Canada, 1985-1996. Am J Med Genet. 2001 Nov 15;104(1):7-13.
17. Rapp R. Refusing prenatal diagnosis: the meanings of bioscience in a multicultural world. Sci Technol Human Values. 1998 Winter;23(1):45-70.

18. De-Kun L KK, Soora W, Norern C. Factors influencing women's acceptance of prenatal screening tests. PrenatDiagn. 2008;28:1136-43.
19. Lewis SM, Cullinane FN, Bishop AJ, Chitty LS, Marteau TM, Halliday JL. A comparison of Australian and UK obstetricians' and midwives' preferences for screening tests for Down syndrome. Prenat Diagn. 2006 Jan;26(1):60-6.
20. Lippman-Hand A, Cohen DI. Influence of obstetricians' attitudes on their use of prenatal diagnosis for the detection of Down's syndrome. CMAJ. 1980 Jun 21;122(12):1381-6.
21. Yankowitz J, Howser DM, Ely JW. Differences in practice patterns between obstetricians and family physicians: use of serum screening. Am J Obstet Gynecol. 1996 Apr;174(4):1361-5.
22. Carroll JC, Reid AJ, Woodward CA, Permaul-Woods JA, Domb S, Ryan G, et al. Ontario Maternal Serum Screening Program: practices, knowledge and opinions of health care providers. CMAJ. 1997 Mar 15;156(6):775-84.
23. Carroll JC, Brown JB, Reid AJ, Pugh P. Women's experience of maternal serum screening. Can Fam Physician.
24. Santalahti P, Hemminki E, Aro AR, Helenius H, Ryynanen M. Participation in prenatal screening tests and intentions concerning selective termination in Finnish maternity care. Fetal Diagn Ther. 1999 Mar-Apr;14(2):71-9.
25. Liamputtong P, Halliday JL, Warren R, Watson F, Bell RJ. Why do women decline prenatal screening and diagnosis? Australian women's perspective. Women Health. 2003;37(2):89-108.
26. Santalahti P, Aro AR, Hemminki E, Helenius H, Ryynanen M. On what grounds do women participate in prenatal screening? Prenat Diagn. 1998 Feb;18(2):153-65.
27. Dormandy E, Marteau TM. Uptake of a prenatal screening test: the role of healthcare professionals' attitudes towards the test. Prenat Diagn. 2004 Nov;24(11):864-8.
28. Dormandy E, Michie S, Hooper R, Marteau TM. Low uptake of prenatal screening for Down syndrome in minority ethnic groups and socially deprived groups: a reflection of women's attitudes or a failure to facilitate informed choices? Int J Epidemiol. 2005 Apr;34(2):346-52.
29. Dormandy E, Michie S, Weinman J, Marteau TM. Variation in uptake of serum screening: the role of service delivery. Prenat Diagn. 2002 Jan;22(1):67-9.
30. van den Berg M, Timmermans DR, Kleinveld JH, Garcia E, van Vugt JM, van der Wal G. Accepting or declining the offer of prenatal screening for congenital defects: test uptake and women's reasons. Prenat Diagn. 2005 Jan;25(1):84-90.
31. Khoshnood B, De Vigan C, Vodovar V, Breart G, Goffinet F, Blondel B. Advances in medical technology and creation of disparities: the case of Down syndrome. Am J Pub Health. 2006 Dec;96(12):2139-44.
32. Winquist B, Ogle K, Muhajarine N. Exploring physicians' views and values in relation to maternal serum screening. J Obstet Gynaecol Can. 2008 Jul;30(7):564-72.
33. Joseph KS, Kramer MS. Recent trends in Canadian infant mortality rates: effect of changes in registration of live newborns weighing less than 500 g. CMAJ. 1996 Oct 15;155(8):1047-52.
34. Gortmaker SL, Wise PH. The first injustice: socioeconomic disparities, health services technology, and infant mortality. Annual Rev Sociol. 1997;23:147-70.
35. Gould JB, Chavez G, Marks AR, Liu H. Incomplete birth certificates: a risk marker for infant mortality. Am J Pub Health. 2002 Jan;92(1):79-81.

36. Joseph KS, Liu S, Rouleau J, Lisonkova S, Hutcheon JA, Sauve R, et al. Influence of definition based versus pragmatic birth registration on international comparisons of perinatal and infant mortality: population based retrospective study. BMJ. 2012;344:e746.
37. Public Health Agency of Canada. Canadian Perinatal Health Report - 2008 Edition. Ottawa 2008 [cited Jun 18, 2013]. Available at: **http://www.phac-aspc.gc.ca/publicat/2008/cphr-rspc/index-eng.php**
38. Smylie J, Fell D, Ohlsson A, Joint Working Group on First Nations Indian I, Metis Infant Mortality of the Canadian Perinatal Surveillance S. A review of Aboriginal infant mortality rates in Canada: striking and persistent Aboriginal/non-Aboriginal inequities. Can J Pub Health. 2010 Mar-Apr;101(2):143-8.
39. Reidpath DD, Allotey P. Infant mortality rate as an indicator of population health. J Epidemiol Community Health. 2003 May;57(5):344-6.
40. United Nations Development Programme. Human development report. New York, New York: 2005 [cited Jul 8, 2013]. Available at: **http://hdr.undp.org/en/library**
41. Labonte R, Muhajarine N, Winquist B, Quail J. Healthy populations. A report of the Institute of Wellbeing. 2010.
42. Verp MS. Prenatal diagnosis of genetic disorders. In: N G, editor. Principle and practices of medical therapy in pregnancy. Norwalk, CT.: Appleton and Lange; 1992. p. 159-70.
43. Doran TA, Valentine GH, Wong PY, Wielgosz G, Benzie RJ, Soltan HC, et al. Maternal serum alpha-fetoprotein screening: report of a Canadian pilot project. CMAJ. 1987 Aug 15;137(4):285-93.
44. Wald NJ, Kennard A, Hackshaw A, McGuire A. Antenatal screening for Down's syndrome. J Med Screen. 1997;4(4):181-246.
45. Messerlian GM, Canick JA. Recent advances in maternal serum screening for Down syndrome. Med Health R I. 2002 Dec;85(12):362-5.
46. Coory MD, Roselli T, Carroll HJ. Antenatal care implications of population-based trends in Down syndrome birth rates by rurality and antenatal care provider, Queensland, 1990-2004. Med J Aust. 2007 Mar 5;186(5):230-4.
47. Reddy UM, Mennuti MT. Incorporating first-trimester Down syndrome studies into prenatal screening: executive summary of the National Institute of Child Health and Human Development workshop. Obstet Gynecol. 2006 Jan;107(1):167-73.
48. Summers AM, Langlois S, Wyatt P, Wilson RD, Society of O, Gynaecologists of C. Prenatal screening for fetal aneuploidy. JOGC. 2007 Feb;29(2):146-79.
49. Kaback MM. Population-based genetic screening for reproductive counseling: the Tay-Sachs disease model. Eur J Pediatr. 2000 Dec;159 Suppl 3:S192-5.
50. Weil E. A wrongful birth? The New York times magazine. 2006 Mar 12:48-53.
51. Wieacker P, Steinhard J. The prenatal diagnosis of genetic diseases. Dtsch Arztebl Int. 2010 Dec;107(48):857-62.
52. Wilson RD, Davies G, Desilets V, Reid GJ, Shaw D, Summers A, et al. Cystic fibrosis carrier testing in pregnancy in Canada. JOGC. 2002 Aug;24(8):644-51.
53. Grosse SD, Boyle CA, Botkin JR, Comeau AM, Kharrazi M, Rosenfeld M, et al. Newborn screening for cystic fibrosis: evaluation of benefits and risks and recommendations for state newborn screening programs. MMWR Recommendations and reports, Centers for Disease Control. 2004 Oct 15;53(RR-13):1-36.
54. Gruneir R. SOGC statement on gender selection. JOGC. 2008 Mar;30(3):197.

55. Thiele AT, Leier B. Towards an ethical policy for the prevention of fetal sex selection in Canada. JOGC. 2010 Jan;32(1):54-7.
56. Ray JG, Henry DA, Urquia ML. Sex ratios among Canadian liveborn infants of mothers from different countries. CMAJ. 2012 Jun 12;184(9):E492-6.
57. Sharma BR, Gupta N, Relhan N. Misuse of prenatal diagnostic technology for sex-selected abortions and its consequences in India. Public Health. 2007 Nov;121(11):854-60.
58. Hesketh T, Lu L, Xing ZW. The effect of China's one-child family policy after 25 years. N Engl J Med. 2005 Sep 15;353(11):1171-6.
59. Peters Y LK. The ethical and human rights implications of prenatal technologies: the need for federal leadership and regulation. Prairie Women's Health Centre of Excellence, 2002.
60. Cuckle HS, Nanchahal K, Wald NJ. Maternal serum alpha-fetoprotein and ethnic origin. BJOC. 1987 Nov;94(11):1111-2.
61. Wald NJ, Cuckle HS, Densem JW, Nanchahal K, Royston P, Chard T, et al. Maternal serum screening for Down's syndrome in early pregnancy. BMJ. 1988 Oct 8;297(6653):883-7.
62. Benn PA, Horne D, Craffey A, Collins R, Ramsdell L, Greenstein R. Maternal serum screening for birth defects: results of a Connecticut regional program. Conn Med. 1996 Jun;60(6):323-7.
63. Alberman E, Huttly W, Hennessy E, McIntosh A. The use of record linkage for auditing the uptake and outcome of prenatal serum screening and prenatal diagnostic tests for Down syndrome. Prenat Diagn. 2003 Oct;23(10):801-6.
64. Piggott M, Wilkinson P, Bennett J. Implementation of an antenatal serum screening programme for Down's syndrome in two districts (Brighton and Eastbourne). The Brighton and Eastbourne Down's Syndrome Screening Group. J Med Screen. 1994 Jan;1(1):45-9.
65. Wald NJ, White N, Morris JK, Huttly WJ, Canick JA. Serum markers for Down's syndrome in women who have had in vitro fertilisation: implications for antenatal screening. BJOC. 1999 Dec;106(12):1304-6.
66. Wald NJ, Kennard A, Densem JW, Cuckle HS, Chard T, Butler L. Antenatal maternal serum screening for Down's syndrome: results of a demonstration project. BMJ. 1992 Aug 15;305(6850):391-4.
67. Wald NJ, Kennard A, Hackshaw A, McGuire A. Antenatal screening for Down's syndrome. Health Technol Assess. 1998;2(1):i-iv, 1-112.
68. Graves JC, Miller KE, Sellers AD. Maternal serum triple analyte screening in pregnancy. Am Family Physician. 2002 Mar 1;65(5):915-20.
69. Knight GJ, Palomaki GE. Epidemiologic monitoring of prenatal screening for neural tube defects and Down syndrome. Clinics in laboratory medicine. 2003 Jun;23(2):531-51, xi.
70. Summers AM, Farrell SA, Huang T, Meier C, Wyatt PR. Maternal serum screening in Ontario using the triple marker test. J Med Screen. 2003;10(3):107-11.
71. Muller F, Forestier F, Dingeon B, Group ABAS. Second trimester trisomy 21 maternal serum marker screening. Results of a countrywide study of 854,902 patients. Prenat Diagn. 2002 Oct;22(10):925-9.
72. Kishida T, Hoshi N, Hattori R, Negishi H, Yamada H, Okuyama K, et al. Efficacy of maternal serum screening in the prenatal detection of fetal chromosome abnormalities in Japanese women. Fetal Diagn Ther. 2000 Mar-Apr;15(2):112-7.
73. Palka G, Guanciali Franchi P, Papponetti M, Marcuccitti J, Morizio E, Calabrese G, et al. Prenatal diagnosis using the triple test. Minerva Ginecol. 1998 Oct;50(10):411-5.

74. Suzumori K, Tanemura M, Murakami I, Okada S, Natori M, Tanaka M, et al. A retrospective evaluation of maternal serum screening for the detection of fetal aneuploidy. Prenat Diagn. 1997 Sep;17(9):861-6.
75. Thix J. [Prenatal serum screening of aneuploidy and of neural tube defects in the second trimester of pregnancy among the population of Luxembourg. Evaluation of risk by the triple test (AFP+THCG+UE3)]. Bull Soc Sci Med Grand Duche Luxemb. 1997;134(1):25-9.
76. Kellner LH, Weiss RR, Weiner Z, Neuer M, Martin GM, Schulman H, et al. The advantages of using triple-marker screening for chromosomal abnormalities. Am J Obstet Gynecol. 1995 Mar;172(3):831-6.
77. Rahim RR, Cuckle HS, Sehmi IK, Jones RG. Compromise ultrasound dating policy in maternal serum screening for Down syndrome. Prenat Diagn. 2002 Dec;22(13):1181-4.
78. Benn PA, Borgida A, Horne D, Briganti S, Collins R, Rodis JF. Down syndrome and neural tube defect screening: the value of using gestational age by ultrasonography. Am J Obstet Gynecol. 1997 May;176(5):1056-61.
79. Evans MJ, M. Yaron, Y. Drugan, A. Prenatal diagnosis: McGraw-Hill Medical Publishing Division; 2006.
80. Park AD, Mathews M. Why do women choose or decline maternal serum screening? JOGC. 2009 Feb;31(2):149-55.
81. Muller F, Thibaud D, Poloce F, Gelineau MC, Bernard M, Brochet C, et al. Risk of amniocentesis in women screened positive for Down syndrome with second trimester maternal serum markers. Prenat Diagn. 2002 Nov;22(11):1036-9.
82. Sher C, Romano-Zelekha O, Green MS, Shohat T. Factors affecting performance of prenatal genetic testing by Israeli Jewish women. Am J Med Genet Part A. 2003 Jul 30;120A(3):418-22.
83. Alderdice F, McNeill J, Rowe R, Martin D, Dornan J. Inequalities in the reported offer and uptake of antenatal screening. Public Health. 2008 Jan;122(1):42-52.
84. Health Canada, Population Health Development Division. Taking action on population health: a position paper for health promotions and programs branch staff. 2003.
85. Kindig D, Stoddart G. What is population health? Am J Pub Health. 2003 Mar;93(3):380-3.
86. Moore KP, TV. Before we are born: essentials of embryology and birth defects. 5th ed. Philadelphia: W.B. Saunders; 1998.
87. Stevenson R. The genetic basis of human anomalies. In: Stevenson RH, JG. Goodman, RM., editor. Human malformations and related anomalies. 1. New York.: Oxford University Press; 1993. p. 115.
88. Congress NDS. Facts about Down Syndrome. [Cited December 7, 2010]. Available from: **http://www.ndsccenter.org/**
89. Trisomy 18 Foundation. [Cited June 15, 2013]. Available from: www.trisomy18.org
90. Bonin MM, Bretzlaff JA, Therrien SA, Rowe BH. Knowledge of periconceptional folic acid for the prevention of neural tube defects. The missing links. Northeastern Ontario Primary Care Research Group. Arch Fam Med. 1998 Sep-Oct;7(5):438-42.
91. Persad VL, Van den Hof MC, Dube JM, Zimmer P. Incidence of open neural tube defects in Nova Scotia after folic acid fortification. CMAJ. 2002 Aug 6;167(3):241-5.
92. Ray JG, Meier C, Vermeulen MJ, Boss S, Wyatt PR, Cole DE. Association of neural tube defects and folic acid food fortification in Canada. Lancet. 2002 Dec 21-28;360(9350):2047-8.

93. De Wals P, Tairou F, Van Allen MI, Uh SH, Lowry RB, Sibbald B, et al. Reduction in neural-tube defects after folic acid fortification in Canada. N Engl J Med. 2007 Jul 12;357(2):135-42.
94. Wilson RD, Johnson JA, Wyatt P, Allen V, Gagnon A, Langlois S, et al. Pre-conceptional vitamin/folic acid supplementation 2007: the use of folic acid in combination with a multivitamin supplement for the prevention of neural tube defects and other congenital anomalies. JOGC. 2007 Dec;29(12):1003-26. Available from: **http://www.skprevention.ca/wp-content/uploads/2013/01/2-457_Infant_Mortality_Report.pdf**
95. Winquist B, Osei W, Findlater R. Oral facial clefts in Saskatchewan: birth prevalence trends over a ten-year period (1994-2003). Canadian Congenital Anomalies Surveillance Network: Public Health Agency of Canada; 2004.
96. Forrester MB, Merz RD. Trisomies 13 and 18: prenatal diagnosis and epidemiologic studies in Hawaii, 1986-1997. Genet Test. 1999;3(4):335-40.
97. Rankin J, Pattenden S, Abramsky L, Boyd P, Jordan H, Stone D, et al. Prevalence of congenital anomalies in five British regions, 1991-99. Arch Dis Child Fetal Neonatal Ed. 2005 Sep;90(5):F374-9.
98. Smith LK, Budd JL, Field DJ, Draper ES. Socioeconomic inequalities in outcome of pregnancy and neonatal mortality associated with congenital anomalies: population based study. BMJ. 2011;343:d4306.
99. Zlotogora J, Amitai Y, Kaluski DN, Leventhal A. Surveillance of neural tube defects in Israel. Isr Med Assoc J : IMAJ. 2002 Dec;4(12):1111-4.
100. Forrester MB, Merz RD, Yoon PW. Impact of prenatal diagnosis and elective termination on the prevalence of selected birth defects in Hawaii. Am J Epidemiol. 1998 Dec 15;148(12):1206-11.
101. Siffel C, Correa A, Cragan J, Alverson CJ. Prenatal diagnosis, pregnancy terminations and prevalence of Down syndrome in Atlanta. Birth Defects Res A Clin Mol Teratol. 2004 Sep;70(9):565-71.
102. Government of Canada, Royal Canadian Commission on New Reproductive Technologies. Proceed with care: Final report of the Royal Commission on New Reproductive Technologies. Ottawa: 1993.
103. Lawson KL, Pierson RA. Maternal decisions regarding prenatal diagnosis: rational choices or sensible decisions? JOGC. 2007 Mar;29(3):240-6.
104. Chan A, Robertson EF, Haan EA, Keane RJ, Ranieri E, Carney A. Prevalence of neural tube defects in South Australia, 1966-91: effectiveness and impact of prenatal diagnosis. BMJ. 1993 Sep 18;307(6906):703-6.
105. Cragan JD, Roberts HE, Edmonds LD, Khoury MJ, Kirby RS, Shaw GM, et al. Surveillance for anencephaly and spina bifida and the impact of prenatal diagnosis--United States, 1985-1994. MMWR CDC surveillance summaries : Morbidity and mortality weekly report CDC surveillance summaries / Centers for Disease Control. 1995 Aug 25;44(4):1-13.
106. Roberts HE, Moore CA, Cragan JD, Fernhoff PM, Khoury MJ. Impact of prenatal diagnosis on the birth prevalence of neural tube defects, Atlanta, 1990-1991. Pediatrics. 1995 Nov;96(5 Pt 1):880-3.
107. Crider KS, Olney RS, Cragan JD. Trisomies 13 and 18: population prevalences, characteristics, and prenatal diagnosis, metropolitan Atlanta, 1994-2003. Am J Med Genet Part A. 2008 Apr 1;146(7):820-6.

108. van Gameren-Oosterom HB, Buitendijk SE, Bilardo CM, van der Pal-de Bruin KM, Van Wouwe JP, Mohangoo AD. Unchanged prevalence of Down syndrome in the Netherlands: results from an 11-year nationwide birth cohort. Prenatal diagnosis. 2012 Nov;32(11):1035-40.
109. Boyd PA, Devigan C, Khoshnood B, Loane M, Garne E, Dolk H, et al. Survey of prenatal screening policies in Europe for structural malformations and chromosome anomalies, and their impact on detection and termination rates for neural tube defects and Down's syndrome. BJOG. 2008 May;115(6):689-96.
110. Velie EM, Shaw GM. Impact of prenatal diagnosis and elective termination on prevalence and risk estimates of neural tube defects in California, 1989-1991. Am J Epidemiol. 1996 Sep 1;144(5):473-9.
111. Bray I, Wright DE, Davies C, Hook EB. Joint estimation of Down syndrome risk and ascertainment rates: a meta-analysis of nine published data sets. Prenat Diagn. 1998 Jan;18(1):9-20.
112. Cuckle HS, Wald NJ, Thompson SG. Estimating a woman's risk of having a pregnancy associated with Down's syndrome using her age and serum alpha-fetoprotein level. BJOC. 1987 May;94(5):387-402.
113. Hecht CA, Hook EB. Rates of Down syndrome at livebirth by one-year maternal age intervals in studies with apparent close to complete ascertainment in populations of European origin: a proposed revised rate schedule for use in genetic and prenatal screening. Am J Med Genet. 1996 Apr 24;62(4):376-85.
114. Statistics Canada. Live births, by age of mother, Canada, provinces and territories, annual. CANSIM. Ottawa.
115. Health Canada. Canadian Perinatal Health Report, 2003. Ottawa: Minister of Public Works and Government Services Canada; 2003.
116. Lee KS, Park SC, Khoshnood B, Hsieh HL, Mittendorf R. Human development index as a predictor of infant and maternal mortality rates. J Pediatr. 1997. Sep;131(3):430-3.
117. Milan A. Mortality: Overview, 2007. Statistics Canada. Ottawa. 2011.
118. Conference Board of Canada. How Canada performs 2008: A report card on Canada. 2008 [cited 2013 May 29]. Available from http://www.conferenceboard.ca/.
119. Statistics Canada. Infant mortality rates, by province and territory. CANSIM Table 102-0504.
120. Saskatchewan Prevention Institute. Infant mortality in Saskatchewan: Evidence to inform Public Health practice. 2009 [cited 2013 May 29].
121. Health Canada, First Nations & Inuit Health Branch. The final report of the Royal Commission on Aboriginal Peoples. Ottawa: Canada Communication Group Publishing; 1996.
122. Health Canada, First Nations & Inuit Health Branch. A statistical profile on the health of First Nations in Canada: determinants of health, 1999 to 2003. Ottawa: 2005.
123. Luo ZC, Wilkins R, Platt RW, Kramer MS, Fetal, Infant Health Study Group of the Canadian Perinatal Surveillance S. Risks of adverse pregnancy outcomes among Inuit and North American Indian women in Quebec, 1985-97. Diatr Perinat Epidemiol. 2004 Jan;18(1):40-50.
124. The Canadian Press. Canada has second-highest rate of first-day infant deaths in industrialized world: report May 8, 2013 [cited 2013 July 18]. Available from: **http://www.canada.com/health/Canada+secondhighest+rate+firstday+infant+deaths+industrialized+world/8349883/story.html**

125. Baldwin LM, Grossman DC, Murowchick E, Larson EH, Hollow WB, Sugarman JR, et al. Trends in perinatal and infant health disparities between rural American Indians and Alaska natives and rural Whites. Am J Pub Health. 2009 Apr;99(4):638-46.
126. Wilkins RB, J-M. Ng, E. . Trends in mortality by neighbourhood income in urban Canada from 1971 to 1996. Health reports / Statistics Canada. 2002;13:45-71.
127. Wise PH, Pursley DM. Infant mortality as a social mirror. N Engl J Med. 1992 Jun 4;326(23):1558-60.
128. Canadian Institute for Health Information. Therapeutic Abortion Survey Table 106-9013. Ottawa.
129. Canadian Institute for Health Information. Update to the Privacy Impact Assessment of the Therapeutic Abortions Database, 2003. March, 2011 [cited 2013 May 29]. Available from: **http://www.cihi.ca/cihi-ext-portal/pdf/internet/tad_pia_update_2011_en**
130. Public Health Agency of Canada. Congenital anomaly national prevalence data, 1989-2006. Ottawa: 2012.
131. Bourke J, Bower C, Blair E, Charles A, Knuiman M. The effect of terminations of pregnancy for fetal abnormalities on trends in mortality to one year of age in Western Australia. Diatr Perinat Epidemiol. 2005 Jul;19(4):284-93.
132. Shohat M, Frimer H, Shohat-Levy V, Esmailzadeh H, Appelman Z, Ben-Neriah Z, et al. Prenatal diagnosis of Down syndrome: ten year experience in the Israeli population. Am J Med Genet Part A. 2003 Oct 15;122A(3):215-22.
133. Mattman A. Biochemist, Department of Pathology and Laboratory Medicine. Children's and Women's Centre of British Columbia. Personal communiction (email). Vancouver, Canada.November 10, 2007.
134. Evans J. Professor. Departments of Biochemistry and Medical Genetics, Pediatrics, and Child Health, and Community Health Sciences. Member Manitoba Maternal Serum Screening Committee. Personal communication (email). Winnipeg, Manitoba.November 10, 2007.
135. Thompson G. Section Manager - Chemistry, Maternal Serum Screening Department, Saskatchewan Disease Control Laboratory. Personal Communication (email). Regina, Saskatchewan Saskatchewan Disease Control Laboratory 2011.
136. Huang T. Unpublished serum screening data. Personal Communication (email). Ontario: Ontario Multiple Marker Screening Program; 2007.
137. Dormandy E, Hooper R, Michie S, Marteau TM. Informed choice to undergo prenatal screening: a comparison of two hospitals conducting testing either as part of a routine visit or requiring a separate visit. J Med Screen. 2002;9(3):109-14.
138. Press N, Browner CH. Why women say yes to prenatal diagnosis. Soc Sci Med. 1997 Oct;45(7):979-89.
139. Jorgensen FS. Attitudes to prenatal screening, diagnosis and research among pregnant women who accept or decline an alpha-fetoprotein test. Prenat Diagn. 1995 May;15(5):419-29.
140. Hart JT. The inverse care law. Lancet. 1971 Feb 27;1(7696):405-12.
141. Fiscella K, Franks P, Gold MR, Clancy CM. Inequality in quality: addressing socioeconomic, racial, and ethnic disparities in health care. JAMA. 2000 May 17;283(19): 2579-84.
142. Sokal DC, Byrd JR, Chen AT, Goldberg MF, Oakley GP, Jr. Prenatal chromosomal diagnosis. Racial and geographic variation for older women in Georgia. JAMA. 1980 Sep 19;244(12):1355-7.

143. Kuppermann M, Gates E, Washington AE. Racial-ethnic differences in prenatal diagnostic test use and outcomes: preferences, socioeconomics, or patient knowledge? Obstet Gynecol. 1996 May;87(5 Pt 1):675-82.
144. Halliday J, Lumley J, Watson L. Comparison of women who do and do not have amniocentesis or chorionic villus sampling. Lancet. 1995 Mar 18;345(8951):704-9.
145. Khoshnood B, Pryde P, Wall S, Singh J, Mittendorf R, Lee KS. Ethnic differences in the impact of advanced maternal age on birth prevalence of Down syndrome. Am J Pub Health. 2000 Nov;90(11):1778-81.
146. Khoshnood B, Wall S, Pryde P, Lee KS. Maternal education modifies the age-related increase in the birth prevalence of Down syndrome. Prenatal diagnosis. 2004 Feb;24(2):79-82.
147. Julian-Reynier C, Macquart-Moulin G, Moatti JP, Aurran Y, Chabal F, Ayme S. Reasons for women's non-uptake of amniocentesis. Prenat Diagn. 1994 Sep;14(9):859-64.
148. Meschino WS. Fetal Alert Network: Surveying congenital anomalies. Paediatr Child Health. 2007 May;12(5):365-6.
149. Kline J, Stein Z, Strobino B, Susser M, Warburton D. Surveillance of spontaneous abortions. Power in environmental monitoring. Am J Epidemiol. 1977 Nov;106(5):345-50.
150. Morris JK, Savva GM. The risk of fetal loss following a prenatal diagnosis of trisomy 13 or trisomy 18. Am J Med Genet Part A. 2008 Apr 1;146(7):827-32.
151. Davidson N, Halliday J, Riley M, King J. Influence of prenatal diagnosis and pregnancy termination of fetuses with birth defects on the perinatal mortality rate in Victoria, Australia. Diatr Perinat Epidemiol. 2005 Jan;19(1):50-5.
152. van der Pal-de Bruin KM, Graafmans W, Biermans MC, Richardus JH, Zijlstra AG, Reefhuis J, et al. The influence of prenatal screening and termination of pregnancy on perinatal mortality rates. Prenat Diagn. 2002 Nov;22(11):966-72.
153. Kerr GR, Ying J, Spears W. Searching for preventable causes of infant mortality in Texas. Tex Med. 1997 Jan;93(1):81-8.
154. Sheremeta LH, L. Canadian Institutes of Health Research. Research into genetic testing services and related matters. Prepared for the Canadian Institutes of Health Research. 2002.
155. Centers for Disease Control and Prevention. Genomics and Population Health: United States 2003. Atlanta, Georgia. 2004 [cited 2013 May 29]. Available from: **http://www.cdc.gov/genomics/about/file/print/2003report/2003Full.pdf**
156. Callahan D. Individual good and common good: a communitarian approach to bioethics. Perspect Biol Med. 2003 Fall;46(4):496-507.
157. Chitayat D, Langlois S, Wilson RD. Prenatal screening for fetal aneuploidy in singleton pregnancies. JOGC. 2011 Jul;33(7):736-50.
158. Health Canada. Canadian Biotechnology Strategy: An ongoing renewal process. Ottawa: 1998.
159. Saskatchewan Ministry of Health, Epidemiology Research and Evaluation Unit. Technical description. Regina, SK; 2009.
160. Altman D. Practical statistics for medical research. London: Chapman and Hall; 1991.
161. Hosmer DL, S. Applied logistic regression. Third ed. New York: John Wiley & Sons, Inc; 2000.
162. Kleinbaum D. Logistic regression: a self-learning text. First ed. New York: Springer-Verlag Inc; 1994.
163. Ikeda M IT, Tamauchi K. Relationship between Brier score and area under the binormal ROC curve. Computer Meth Prog Biomedicine. 2002;67:187-94.

164. Harrell FE LK, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med. 1996;15:361-87.
165. Redelmeier DA BD, Hickam DH. Assessing predictive accuracy: how to compare Brier scores. J Clin Epidemiol. 1991;44:1141-6.
166. World Health Organization. Manual of the international statistical classification of diseases, injuries, and causes of death: based on the recommendations of the Ninth Revision Conference, 1975, and adopted by the Twenty-ninth World Healt Assembly. Geneva: World Health Organization; 1977.
167. Buescher P. Problems with rates based on small numbers. 1997 [cited 2013 Sept 10]. Available at: **http://www.schs.state.nc.us/SCHS/pdf/primer12.pdf**
168. Benn PA, Leo MV, Rodis JF, Beazoglou T, Collins R, Horne D. Maternal serum screening for fetal trisomy 18: a comparison of fixed cutoff and patient-specific risk protocols. Obstet Gynecol. 1999 May;93(5 Pt 1):707-11.
169. Wald NJ, Cuckle H, Brock JH, Peto R, Polani PE, Woodford FP. Maternal serum-alpha-fetoprotein measurement in antenatal screening for anencephaly and spina bifida in early pregnancy. Report of U.K. collaborative study on alpha-fetoprotein in relation to neural-tube defects. Lancet. 1977 Jun 25;1(8026):1323-32.
170. Wald N, Cuckle H, Nanchahal K. Amniotic fluid acetylcholinesterase measurement in the prenatal diagnosis of open neural tube defects. Second report of the Collaborative Acetylcholinesterase Study. Prenat Diagn. 1989 Dec;9(12):813-29.
171. Wilson RD, Langlois S, Johnson JA, Society of O, Gynaecologists of C. Mid-trimester amniocentesis fetal loss rate. JOGC. 2007 Jul;29(7):586-95.
172. Eddleman KA, Malone FD, Sullivan L, Dukes K, Berkowitz RL, Kharbutli Y, et al. Pregnancy loss rates after midtrimester amniocentesis. Obstet Gynecol. 2006 Nov;108(5):1067-72.
173. Permaul-Woods JA, Carroll JC, Reid AJ, Woodward CA, Ryan G, Domb S, et al. Going the distance: the influence of practice location on the Ontario Maternal Serum Screening Program. CMAJ. 1999 Aug 24;161(4):381-5.
174. Chandra S, Crane J, Hutchens D, Bennett K, O'Grady T, Duff A, et al. Maternal serum screening: practice patterns of physicians in Newfoundland. JOGC. 2003 Oct;25(10):825-9.
175. Cavanagh J, Mathews M, Crane J. Awareness and use of maternal serum screening among women from the St. John's region of Newfoundland and Labrador. JOGC. 2007 Aug;29(8):630-4.
176. Li DK, Karlberg K, Wi S, Norem C. Factors influencing women's acceptance of prenatal screening tests. Prenat Diagn. 2008 Dec;28(12):1136-43.
177. Dillon M, Lam T, Beardy N, Gordon J, Dooley J, Harris S. Maternal serum screening in the Sioux Lookout Zone. Complicated test for an unspecified need. Can Fam Physician. 1994 Oct;40:1766-71. 178. Nsiah-Jefferson L. Reproductive laws, women of color, and low-income women. Women's Rights Law Report. 1989 Spring;11(1):15-38.
179. Tararbit K, Bui TT, Lelong N, Thieulin AC, Goffinet F, Khoshnood B. Clinical and socioeconomic predictors of pregnancy termination for fetuses with congenital heart defects: a population-based evaluation. Prenat Diagn. 2013 Feb;33(2):179-86.
180. Heaman MI, Gupton AL, Moffatt ME. Prevalence and predictors of inadequate prenatal care: a comparison of aboriginal and non-aboriginal women in Manitoba. JOGC. 2005 Mar;27(3):237-46.

181. Renaud M, Bouchard L, Bisson J, Labadie J, Dallaire L, Kishchuk N. Canadian physicians and prenatal diagnosis: prudence and ambivalence. Ottawa: 1993.
182. Cavanagh J, Mathews M. Maternal serum screening in Newfoundland and Labrador: do attitude and knowledge affect physicians' practice? Canadian Fam Physician. 2006 Oct;52(10):1268-9.
183. Woodward CA, Carroll JC, Ryan G, Reid AJ, Permaul-Woods JA, Arbitman S, et al. Maternity care and maternal serum screening. Do male and female family physicians care for women differently? Canadian Fam Physician. 1997 Jun;43:1078-84.
184. Huang T. Research Scientist, Genetics Program, North York General Hospital. Personal communication (email). Toronto, Canada. March 19, 2007.
185. Seavilleklein V. Challenging the rhetoric of choice in prenatal screening. Bioethics. 2009 Jan;23(1):68-77.
186. Green JM, Hewison J, Bekker HL, Bryant LD, Cuckle HS. Psychosocial aspects of genetic screening of pregnant women and newborns: a systematic review. Health Technol Assess. 2004 Aug;8(33):iii, ix-x, 1-109.
187. Vassy C. From a genetic innovation to mass health programmes: the diffusion of Down's Syndrome prenatal screening and diagnostic techniques in France. Soc Sci Med. 2006 Oct;63(8):2041-51.
188. Rowe RE, Garcia J, Davidson LL. Social and ethnic inequalities in the offer and uptake of prenatal screening and diagnosis in the UK: a systematic review. Public Health. 2004 Apr;118(3):177-89.
189. Hui D, Okun N, Murphy K, Kingdom J, Uleryk E, Shah PS. Combinations of maternal serum markers to predict preeclampsia, small for gestational age, and stillbirth: a systematic review. JOGC. 2012 Feb;34(2):142-53.
190. Lippman A. Prenatal genetic testing and screening: constructing needs and reinforcing inequities. American journal of law & medicine. 1991;17(1-2):15-50. PubMed PMID: 1877608.
191. Sherwin S. Normalizing reproductive technologies and the implications for autonomy. In: Tong RA, G. Santos, A., editor. Globalizing feminist bioethics. Boulder, Colorado: Westview Press; 2001. p. 96-113.
192. Alberta Health and Wellness. Alberta congenital anomalies surveillance system nineth report: 1997-2009. Edmonton, Alberta: 2012.
193. Van den Hof MC, Wilson RD. Fetal soft markers in obstetric ultrasound. JOGC. 2005 Jun;27(6):592-636.
194. Rowe R, Puddicombe D, Hockley C, Redshaw M. Offer and uptake of prenatal screening for Down syndrome in women from different social and ethnic backgrounds. Prenat Diagn. 2008 Dec;28(13):1245-50.
195. Rauch ER, Smulian JC, DePrince K, Ananth CV, Marcella SW, New Jersey Fetal Abnormalities R. Pregnancy interruption after second trimester diagnosis of fetal structural anomalies: the New Jersey Fetal Abnormalities Registry. Am J Obstet Gynecol. 2005 Oct;193(4):1492-7.
196. Canadian Down Syndrome Society. [cited 2013 June 6]. Available from: **http://www.cdss.ca/**
197. Grant R, Flint K. Prenatal screening for fetal aneuploidy: a commentary by the Canadian Down Syndrome Society. JOGC. 2007 Jul;29(7):580-2.
198. Ahmed S, Hewison J, Green JM, Cuckle HS, Hirst J, Thornton JG. Decisions about testing and termination of pregnancy for different fetal conditions: a qualitative study of

European White and Pakistani mothers of affected children. J Genet Couns. 2008 Dec;17(6):560-72.
199. Lai S, Lau WL, Leung WC, Lai FK, Chin R. Is ultrasound alone enough for prenatal screening of trisomy 18? A single centre experience in 69 cases over 10 years. Prenat Diagn. 2010 Nov;30(11):1094-9.
200. Luo ZC, Kierans WJ, Wilkins R, Liston RM, Uh SH, Kramer MS. Infant mortality among First Nations versus non-First Nations in British Columbia: temporal trends in rural versus urban areas, 1981-2000. Int J Epidemiol. 2004 Dec;33(6):1252-9.
201. Rahman A, Katzive L, Henshaw SK. A global review of laws on induced abortion, 1985-1997. Int Fam Plann Persp. 1998 Jun;24(2):56-64.
202. Government of Saskatchewan. The Vital Statistics Act, 2009. Regina, Saskatchewan: The Queen's Printer; 2009.
203. Evans MI. Prenatal diagnosis. Evans MI, editor. New York: McGraw-Hill Medical Publishing Division; 2006.
204. Wilson JMG JG. Principles and practice of screening for disease. Public Health Papers, #34. 1968;22(11).
205. Wilson RD, Johnson JA, Summers A, Wyatt P, Allen V, Gagnon A, et al. Principles of human teratology: drug, chemical, and infectious exposure. JOGC. 2007 Nov;29(11):911-26.
206. Rosa RF, Rosa RC, Zen PR, Graziadio C, Paskulin GA. Trisomy 18: review of the clinical, etiologic, prognostic, and ethical aspects. Rev Paul Pediatr. 2013 Mar;31(1):111-20.
207. Kucik JE, Shin M, Siffel C, Marengo L, Correa A, Congenital Anomaly Multistate P, et al. Trends in survival among children with Down syndrome in 10 regions of the United States. Pediatrics. 2013 Jan;131(1):e27-36.
208. Shin M, Kucik JE, Siffel C, Lu C, Shaw GM, Canfield MA, et al. Improved survival among children with spina bifida in the United States. J Pediatr. 2012 Dec;161(6):1132-7.
209. Park A, Mathews M. Women's decisions about maternal serum screening testing: a qualitative study exploring what they learn and the role prenatal care providers play. Women Birth. 2009 Jun;22(2):73-8.
210. Marteau TM, Cook R, Kidd J, Michie S, Johnston M, Slack J, et al. The psychological effects of false-positive results in prenatal screening for fetal abnormality: a prospective study. Prenat Diagn. 1992 Mar;12(3):205-14.
211. Santalahti P, Latikka AM, Ryynanen M, Hemminki E. Women's experiences of prenatal serum screening. Birth. 1996 Jun;23(2):101-7.
212. Fletcher RHF, S W. Clinical epidemiology: the essentials. Baltimore, MD: Lippincott Williams & Wilkins; 2005.
213. Al-Jader LN, Parry-Langdon N, Smith RJ. Survey of attitudes of pregnant women towards Down syndrome screening. Prenat Diagn. 2000 Jan;20(1):23-9.
214. Lobel M, Dias L, Meyer BA. Distress associated with prenatal screening for fetal abnormality. J Behav Med. 2005 Feb;28(1):65-76.
215. World Health Organization. Birth defects. Report by the Secretariat. 2010 [cited 2013 May 29]. Available at: **http://apps.who.int/gb/ebwha/pdf_files/WHA63/A63_10-en.pdf**
216. Association of Public Health Epidemiologists in Ontario. Therapeutic abortion data [cited 2013 June 20]. Available from: **http://www.apheo.ca/index.php?pid=216**
217. Fair M, Cyr M, Allen A, Wen S, Guyon G, MacDonald R, et al. Validation study for a record linkage of births and infant deaths in Canada. Ottawa: Statistics Canada, 1999.

218. Canadian Institute for Health Information. Discharge Abstract Database data quality re-abstraction study. Ottawa, ON: 2002.
219. Kulaga S, Berard A. Congenital malformations: agreement between diagnostic codes in an administrative database and mothers' reports. JOGC. 2010 Jun;32(6):549-54.
220. Beck P. Technical description: Population outcomes of a provincial prenatal screening program. Regina, SK: Saskatchewan Ministry of Health; 2005.
221. Mathers CD, Fat DM, Inoue M, Rao C, Lopez AD. Counting the dead and what they died from: an assessment of the global status of cause of death data. Bull World Health Organ. 2005 Mar;83(3):171-7.
222. Prevalence of neural tube defects in 20 regions of Europe and the impact of prenatal diagnosis, 1980-1986. EUROCAT Working Group. J Epidemiol Community Health. 1991 Mar;45(1):52-8.
223. Periodic health examination, 1994 update: 3. Primary and secondary prevention of neural tube defects. Canadian Task Force on the Periodic Health Examination. CMAJ. 1994 Jul 15;151(2):159-66.
224. Government of Canada. Assisted Human Reproduction Act. Minister of Justice. 2004.
225. United States of America Congress. Prenatally and postnatally diagnosed conditions awareness act. 2007.
226. de Jong AD, WJ. de Die-Smulders, C. Frints, S. de Wert G. Non-invasive prenatal testing: ethical issues explored. Eur J Hum Genet. 2010;18:272-7.
227. Shakespeare T. Choices and rights: eugenics, genetics and disability equality. Disabil Soc. 1998 Nov;13(5):665-81.
228. Arras JS, B. London, AJ. Moral reasoning in the medical context. In: Arras JS, B. , editor. Ethical issues in modern medicine. Fifth edition. Toronto, Ontario: Mayfield Publishing Company; 1999. p. 1-40.
229. Lippman A. Choice in prenatal testing. Genewatch : a bulletin of the Committee for Responsible Genetics. 1999 Apr;12(2):1, 3-4.
230. Paul DB. The politics of heredity: essays on eugenics, biomedicine, and the nature-nuture debate. Albany, NY: State University of New York Press; 1998.
231. Wertz DC. Drawing lines: notes for policymakers. In: Parens E, Asch A, editors. Prenatal testing and disability rights. Washington, D.C.: Georgetown University Press; 2000.
232. McCourt C. Supporting choice and control? Communication and interaction between midwives and women at the antenatal booking visit. Soc Sci Med. 2006 Mar;62(6):1307-18.
233. Levy V. Protective steering: a grounded theory study of the processes by which midwives facilitate informed choices during pregnancy. J Adv Nurs. 1999 Jan;29(1):104-12.
234. Ryder IH. Prenatal screening for Down syndrome: a dilemma for the unsupported midwife? Midwifery. 1999 Mar;15(1):16-23.
235. Marteau T, Drake H, Bobrow M. Counselling following diagnosis of a fetal abnormality: the differing approaches of obstetricians, clinical geneticists, and genetic nurses. J Med Genet. 1994 Nov;31(11):864-7.
236. Caplan AL. Neutrality is not morality: the ethics of genetic counseling. In: Bartels DM, eRoy BS, Caplan AL, editors. Prescribing our future: ethical challenges in genetic counseling. New York: Aldine De Gruyter; 1993.
237. Marteau TM, Dormandy E. Facilitating informed choice in prenatal testing: how well are we doing? Am J Med Genet . 2001 Fall;106(3):185-90.

238. Marteau TM, Dormandy E, Michie S. A measure of informed choice. Health Expectations. 2001 Jun;4(2):99-108.
239. Williams C, Alderson P, Farsides B. What constitutes 'balanced' information in the practitioners' portrayals of Down's syndrome? Midwifery. 2002 Sep;18(3):230-7.
240. Chodirker BNE, J. A. Maternal serum AFP screening: The Manitoba experience. Current practice of prenatal diagnosis in Canada: Research studies of the Royal Commission on New Reproductive Technologies. 13. Ottawa, Ontario: Canada Communications Group; 1993. p.535-610.
241. Santalahti P, Hemminki E, Latikka AM, Ryynanen M. Women's decision-making in prenatal screening. Soc Sci Med. 1998 Apr;46(8):1067-76.
242. McNeill J, Alderdice F. Exploring the perspective of midwives involved in offering serum screening for Down's syndrome in Northern Ireland. J Clin Nurs. 2009 Oct;18(20): 2888-96.
243. Gregg R. "Choice" as a double-edged sword: information, guilt and mother-blaming in a high-tech age. Women Health. 1993;20(3):53-73.
244. Gates EA. The impact of prenatal genetic testing on quality of life in women. Fetal Diagn Ther. 1993 Apr;8(Suppl. 1):226-43.
245. Lawson K. Perceptions of deservedness of social aid as a function of prenatal diagnosis testing. J Appl Soc Psychol. 2003;33(1):76-90.
246. Marteau TM, Drake H. Attributions for disability: the influence of genetic screening. Soc Sci Med. 1995 Apr;40(8):1127-32.
247. Mykitiuk R, Nisker J. Social determinants of 'health' of embryos. In: Nisker J, Baylis F, Karpin I, McLeod C, Mykitiuk R, editors. The 'Healthy' Embryo: social, biomedical, legal and philosophical perspectives. New York: Cambridge University Press; 2010. p. 116-35.
248. Duster T. Backdoor to eugenics. New York: Routledge; 1990.
249. Burgess M, William-Jones B. Law in tension with evolving ethical perception: prenatal genetic testing for sex and disability. Cardiff University: Cardiff Institute of Society, Health and Ethics, Cardiff School of Social Sciences. ISBN 1 904815 37 5.
250. Lippman A. Prenatal diagnosis: Reproductive choice? Reproductive control? In: Overall C, editor. The Future of Human Reproduction. Toronto: The Women's Press; 1989. p. 182-94.
251. Lippman A. Choice as a risk to women's health. Health, Risk, and Society. 1999;1(3):281-91.
252. Karpin IS, K. Perfecting pregnany: law, disability, and the future of reproduction. Cambridge: Cambridge University Press; 2012.
253. Lippman A. The politics of health: geneticization versus health promotion. In: Sherwin S, editor. The politics of women's health: exploring agency and autonomy. Philadelphia: Temple University Press; 1998.
254. Khoury MB, W. Thomson, E. Genetics and public health: a framework for the integration of human genetics into public health practice. In: Khoury MB, W. Thomson, EJ., editor. Genetics and public health in the 21st century: using genetic information to improve health and prevent disease. New York: Oxford University Press; 2000.
255. Pioro M, Mykitiuk R, Nisker J. Wrongful birth litigation and prenatal screening. CMAJ. 2008 Nov 4;179(10):1027-30.
256. Capen K. New prenatal screening procedures raise spectre of more "wrongful-birth" claims. CMAJ. 1995 Mar 1;152(5):734-7.

257. Gallagher A. Moral distress and moral courage in everyday nursing practice. Online J Issues Nurs. 2011 May;16(2):8.
258. Mills C. The sociological imagination. Oxford: Oxford University Press; 2000.
259. Muller-Hill B. Eugenics: The science and religion of the Nazis. In: Caplan AL, editor. When medicine went mad: Bioethics and the Holocaust. Totowa, New Jersey: Humana Press Inc; 1992. p. 43-52.
260. Fuchs V. The growing demand for medical care. N Engl J Med. 1968;279(4):190-5.
261. Luppicini R. Technoethical inquiry: from technological systems to society. Global Media Journal - Canadian Edition. 2009;2(1):5-21.
262. Rothman BK. The tenative pregnancy: prenatal diagnosis and the future of motherhood. New York: Viking; 1986.
263. Bunge M. Towards a technoethics. Monist. 1977;60(1):96-107.
264. Ohno M, Caughey A. The role of noninvasive prenatal testing as a diagnostic versus a screening tool - a cost-effectiveness analysis. Prenat Diagn. 2013 Jul;33(7):630-5.
265. Odibo AO, Stamilio DM, Nelson DB, Sehdev HM, Macones GA. A cost-effectiveness analysis of prenatal screening strategies for Down syndrome. Obstet Gynecol. 2005 Sep;106(3):562-8.
266. Metcalfe A, Currie G, Johnson JA, Bernier F, Lix LM, Lyon AW, et al. Impact of observed versus hypothesized service utilization on the incremental cost of first trimester screening and prenatal diagnosis for trisomy 21 in a Canadian province. Prenat Diagn. 2013 May;33(5):429-35.
267. Gekas J, Durand A, Bujold E, Vallee M, Forest JC, Rousseau F, et al. Cost-effectiveness and accuracy of prenatal Down syndrome screening strategies: should the combined test continue to be widely used? Am J Obstet Gynecol. 2011 Feb;204(2):175 e1-8.
268. Laucius J. Canadians crossing into the U.S. to select baby's sex. Ottawa Citizen. 2006 Tuesday, July 4.
269. Bowman K. Ethical implications in genetic testing: promise and peril. One Gene, One Origin, One Earth Conference. Calgary, Alberta: Alberta Civil Liberties Research Centre; 2007.
270. Boukydis CF, Treadwell MC, Delaney-Black V, Boyes K, King M, Robinson T, et al. Women's responses to ultrasound examinations during routine screens in an obstetric clinic. J Ultrasound Med. 2006 Jun;25(6):721-8.
271. Skotko B. Words matter: the importance of nondirective language in first-trimester assessments for Down syndrome. Am J Obstet Gynecol. 2006 Aug;195(2):625-6; author reply 6-7.
272. Giubilini A, Minerva F. Defending after-birth abortion: responses to some critics. Monash Bioeth Rev. 2012 Sep;30(2):49-61.
273. Giubilini A, Minerva F. After-birth abortion: why should the baby live? J Med Ethics. 2013 May;39(5):261-3.
274. Dwyer JG. Moral status and human life: Cambridge University Press; 2010.
275. Gillon R. Pregnancy, obstetrics and the moral status of the fetus. J Med Ethics. 1988 Mar;14(1):3-4.
276. Chervenak FA, McCullough LB. The fetus as a patient: an essential ethical concept for maternal-fetal medicine. J Matern Fetal Med. 1996 May-Jun;5(3):115-9.
277. Chervenak FA, McCullough LB, Campbell S. Is third trimester abortion justified? BJOC. 1995 Jun;102(6):434-5.

278. Sharp K, Earle S. Feminism, abortion, and disability: irreconciliable differences? Disability and Society. 2002;17(2):137-45.
279. Botkin JR. Fetal privacy and confidentiality. Hastings Cent Rep. 1995 Sep-Oct;25(5): 32-9.
280. Anderson G, Strong C. The premature breech: caesarean section or trial of labour? J Med Ethics. 1988 Mar;14(1):18-24.
281. Green JM. Obstetricians' views on prenatal diagnosis and termination of pregnancy: 1980 compared with 1993. BJOC. 1995 Mar;102(3):228-32.
282. Wertz DC, Gregg R. Genetics services in a social, ethical and policy context: a collaboration between consumers and providers. J Med Ethics. 2000 Aug;26(4):261-5.
283. Katz-Rothman B. The tentative pregnancy: amniocentesis and the sexual politics of motherhood. London: Pandora; 1994.
284. Verhagen E, Sauer PJ. The Groningen protocol--euthanasia in severely ill newborns. N Engl J Med. 2005 Mar 10;352(10):959-62.
285. Canadian Nurses Forced to Perform Late-Term, Genetic-Based Abortions. Alberta Report. April 12, 1999.
286. Hopper T. Birth of a legal quandry: live-birth abortions a perilous grey zone in Canada's criminal code. National Post. February 1, 2013.
287. Rothman BK. The tentative pregnancy: then and now. Fetal Diagn Ther. 1993 Apr;8(Suppl. 1):60-3.
288. Moazam F. Feminist discourse on sex screening and selective abortion of female foetuses. Bioethics. 2004 Jun;18(3):205-20.
289. Angus Reid. Canadians have mixed feedlings on abortion, but shun a new debate. Vancouver: 2013 January 28. Report No.
290. Storch JR, P. Starzomski, R. Toward a moral horizon: nursing ethics for leadership and practice. First ed. Toronto: Pearson Prentice Hall; 2004.
291. Skotko BG, Levine SP, Goldstein R. Self-perceptions from people with Down syndrome. Am J Med Genet Part A. 2011 Oct;155A(10):2360-9.
292. Skotko BG, Levine SP, Goldstein R. Having a brother or sister with Down syndrome: perspectives from siblings. Am J Med Genet Part A. 2011 Oct;155A(10):2348-59.
293. Skotko BG, Levine SP, Goldstein R. Having a son or daughter with Down syndrome: perspectives from mothers and fathers. Am J Med Genet Part A. 2011 Oct;155A(10):2335-47.
294. Lawson K. Expectations of the parenting experience and willingness to consider selective termination for Down syndrome. J Reprod Infant Psychol. 2006;24:43-59.
295. Parens E, Asch A. Disability rights critique of prenatal genetic testing: reflections and recommendations. Ment Retard Dev Disabil Res Rev. 2003;9(1):40-7.
296. United Nations General Assembly. Convention on the rights of persons with disabilities 2006 [cited 2013 June 27]. Available from:
http://www.un.org/esa/socdev/enable/rights/convtexte.htm#convtext
297. United Kingdom Parliamentary Inquiry. Inquiry into abortion on the grounds of disability 2013 [cited 2013 July 27]. Available from: **http://www.abortionanddisability.org/**
298. Webster GB, F. Moral residue. In: Rubin SZ, L., editor. Margin of error: The ethics of mistakes in the practice of medicine. Hagerstown, MD.: University Publishing Group Inc.; 2000.
299. Freedman B. Where are the heroes of bioethics? J Clin Ethics. 1996 Winter;7(4):297-9.

300. Cox SM, Nisker J. Public understandings of a 'healthy' embryo. In: Nisker J, Baylis F, Karpin I, McLeod C, Mykitiuk R, editors. The 'Healthy' Embryo: Social, biomedical, legal and philosophical perspectives. New York: Cambridge University Press; 2010. p. 151-69.
301. Genetics and Public Policy Center. The Genetic Town Hall: making every voice count. Washington DC: 2004.
302. Brunger F, Cox SM. Ethics and genetics: the need for transparency. The gender of genetic futures: the Canadian Biotechnology Strategy, women and and health. York University, Toronto: National Network on Environments and Women's Health; 2000.
303. Nisker J, Martin DK, Bluhm R, Daar AS. Theatre as a public engagement tool for health-policy development. Health Policy. 2006 Oct;78(2-3):258-71.
304. Einsiedel EF, Eastlick DL. Consensus conferences as deliberative democracy: a communications perspective. Science Communication. 2000;21:323-43.
305. Wyatt J. Medical paternalism and the fetus. J Med Ethics 2001 Oct;27 Suppl 2:ii15-20.

APPENDIX A -

TECHNICAL DESCRIPTION, SASKATCHEWAN MINISTRY OF HEALTH

Examination of Population-Based Outcomes of a
Provincial Prenatal Screening Program (SR 05-011)

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GENERAL FEATURES

1. Time Period: Subject inclusion: January 1, 2000 to December 31, 2005
   History: January 1, 2000 to December 31, 2006
2. Databases: Person registry
   Hospital separation data
   Physician services data
   Vital Statistics (birth registration data)
   Vital Statistics (death registration data)
   Provincial Lab maternal serum screening test data (May 1, 2001 to March 31, 2005 only)
   RHA amniocentesis data (January 1, 2001 to December 31, 2005 for Saskatoon Health Region data; October 1, 2001 to December 31, 2005 for Regina Qu'Appelle Health Region data)
3. Sex: Females
   Babies – both males and females
4. Age: Women – all ages
   Babies – 0 to 365 days old
5. Population: Saskatchewan Health covered population

OBJECTIVES

Maternal serum screening (MSS) is a screening method used to identify women at an increased risk for pregnancies with congenital anomalies and offer these women follow-up diagnostic testing. The Saskatchewan MSS program first became available to all pregnant women throughout the province early in 2001. The first MSS tests recorded were in May 2001.

While Saskatchewan's infant mortality rate has traditionally been higher than the national average, it is hypothesized that at least part of this difference is due to Saskatchewan's lower uptake of prenatal screening technologies. For the same reason, infant mortality rates and rates of congenital anomalies may vary across health regions within Saskatchewan. The primary objective of this Study is to assess whether or not Saskatchewan's prenatal screening program has a measurable impact on population health outcomes. There are four broad research questions being examined:

- What effect, if any, does the MSS program have on the population? Specifically, has the program resulted in measurable decreases in the live birth prevalence of infants with congenital anomalies? Has the program resulted in a change to annual infant mortality rates?

- What are the patterns of utilization of prenatal screening by Saskatchewan women? Might differences in uptake help to explain variations in the live birth prevalence of congenital anomalies or infant mortality rates?
- Are there unique characteristics of the province (e.g., large rural population, challenges in care accessibility) and its people (e.g., aboriginal culture, values) that contribute to or detract from the program utilization?
- What are the social, legal and ethical implications for current and future policy and practice?

STUDY OUTLINE

The population-based cohort for this Study is all female residents, eligible for Saskatchewan Health benefits coverage, who either delivered a baby (live or stillborn) or experienced a pregnancy termination (spontaneous, medical and/or "other or unspecified" abortion) between January 1, 2000 and December 31, 2005, inclusive. Women will be identified using the Vital Statistics (live birth and stillbirth data), person registry, hospital separation, and physician services files as described below.

Identification of women with births and stillbirths during the study period
Saskatchewan Health beneficiaries who delivered a live born or stillborn baby in Saskatchewan between January 1, 2000 and December 31, 2005 will be identified using the Vital Statistics birth registration file. Vital Statistics birth and stillbirth registration data for out-of-province births/stillbirths to Saskatchewan residents will be included where the data are available. Adoptions will be excluded because it is not possible to link the baby with his/her birth mother. (From 1999 to 2003, public adoptions dropped from 66 to approximately 20 per year.) For birth and stillbirth events, the **index date** for the mothers will be defined as the date of baby birth or stillbirth.

Identification of women with abortions during the study period
Saskatchewan Health beneficiaries who had a spontaneous, medical or other/unspecified abortion during the study period of January 1, 2000 and December 31, 2005 will be identified using hospital separation and physician services data as follows.

Spontaneous abortion subjects will be identified as female Saskatchewan Health beneficiaries who had one or more physician service or hospital separation record with any of the following diagnostic and/or procedure codes during the study period:

Spontaneous abortion codes

ICD-9 code	ICD-10-CA code	Fee-for-Service code
632	O02.1	350P
634.x	O03.x	

Medical abortion subjects will be identified as female Saskatchewan Health beneficiaries who had one or more hospital separation record with any of the following ICD-9 or ICD-10-CA diagnostic codes during the study period. In Saskatchewan, medical abortions are performed as day surgery or inpatient procedures. Subjects who had a medical abortion in Saskatchewan will, therefore, be identified only through the hospital separation data using the ICD-9 or ICD-10-CA codes listed below.

Subjects who had a medical abortion outside Saskatchewan will be identified using both hospital separation data (using the ICD-9 and ICD-10-CA codes listed below) and physician services data. Physician services data with the following ICD-9 and/or fee-for-service codes will used only to identify medical abortions performed outside Saskatchewan. Physician services data will not be used to identify medical abortions performed in Saskatchewan.

Medical abortion codes

ICD-9 code	ICD-10-CA code	Fee-for-Service code
635.x	O04.x	50P 250P

Other and unspecified abortion subjects will be identified as female Saskatchewan Health beneficiaries who had one or more physician services or hospital separation records with any of the following diagnostic codes during the study period:

Other and unspecified abortion codes

ICD-9 code	ICD-10-CA code	Fee-for-Service code
636.x 637.x	O05.x	

The three types of abortion events (i.e., spontaneous, medical and other/unspecified) will first be identified separately and will then be combined into a single "abortion event file" as described below.

Spontaneous (SA), medical (MA) and other/unspecified (OA) abortion records from the physician services and hospital separation data will be processed separately using a "90-day rule" to collapse records into MA, SA, and OA episodes. The 90-day rule will be applied as follows: if a woman has two or more physician service and/or hospital separation records for a given type of abortion, the record with the earliest service date is identified as the **index date** and all records for the same type of abortion (MA, SA, or OA) within 90 days following the index date will be considered part of the same episode.

The resulting three abortion episode files (i.e., one file each for SA, MA and OA episodes) will then be combined into a single abortion event file using a 90 day rule to collapse overlapping episodes. The 90-day rule will be applied as follows: if a woman has two or more abortion episodes, the episode with the earliest index date will be considered the "**index abortion event"** and any other episodes occurring within the following 90 days will be considered part of that abortion event. In these cases, flags on the subject file will indicate that one or more abortion episodes were identified in the 90 day period following the **"index abortion event"** (i.e., flags will identify the type of abortion, number of days after the index date and data source (physician service record vs. hospital separation record).

The abortion event file will then be combined with the birth/stillbirth file as follows to create a comprehensive subject file. In instances where an abortion event for a woman occurs within 180 days before or 90 days after the date of birth/stillbirth, the abortion will be considered part of the birth/stillbirth event. In these cases, the abortion event will be included in the abortion subject file, but it will have the same study identification number as the corresponding birth/stillbirth record for that woman.

Preparation of subject files

The comprehensive subject file will then be used to create two subject files for women: one file relating to women who had birth/stillbirth events and one file relating to women who had abortion events during the study period. Note that a woman may be included in the study more than once (e.g. for two or more birth, stillbirth, or abortion events). Women included in the study more than once will have a different study identification number assigned for each event. The exception to this is abortion events that occur up to 180 days before or 90 days after the date of birth/stillbirth. In these cases, the abortion record is considered likely to be part of the birth/stillbirth event and is assigned the same study identification number as the corresponding birth/stillbirth event.

For women, the **study entry date** will be the later of January 1, 2000 or health coverage initiation date up to December 31, 2005. A **study exit date** will be set to the index date of the livebirth, stillbirth, or abortion event. As noted above, women with more than one event during the study period are included once for each qualifying event. In these cases, a **study exit date** corresponding to the index date of each event is assigned and the **study entry date** for the second event will be set to the later of 90 days after the first event or the health coverage initiation date, the **study entry date** for the third event will be set to the later of 90 days after the second event or the health coverage initiation date, and so on.

A baby subject file containing demographic and birth/stillbirth information for the liveborn and stillborn infants will also be created. For babies, a **study exit date** is set to the earliest of the date of death, date of emigration from the province, or one year after birth.

Compilation of service information

For women, hospital separation, physician services, and MSS test data will be compiled from the study entry date to the study exit date. Amniocentesis data from the Cytogenetic Laboratory, Saskatoon Health Region and from the Regina General Hospital, Regina-Qu'Appelle Health Region will also be compiled from January 1, 2001 to December 31, 2005 and from October 1, 2001 to December 31, 2005, respectively. A flag will be included on the mother's subject file to indicate a mother's registered Indian status. MSS test data to be provided are shown in Table 3. Residence information to be compiled for subjects will be based on the Regional Health Authority (RHA) of mother's residence as of December 31 of the year of the subject's study exit date.

For babies, hospital separation, physician services and vital statistics data will be compiled for the period beginning on the date of birth and ending on their study exit date. For babies whose study exit is due to death, cause of death will be determined from the death registration file.

For both women and babies, diagnoses of interest are reported by specific codes or grouped (Table 1). All other codes or records will be suppressed.

For women, specific hospital procedure codes that may affect pregnancy outcome (CCP and CCI), and, for both women and babies, physician fee-for service (FFS) codes of interest are reported by specific codes or grouped (Table 2). All other records are suppressed.

Note:
- Not all services provided by Saskatchewan physicians are captured in the Medical Services Branch data. Some physicians are on contract and/or alternative payment arrangements and either do not submit claims at all or do not consistently submit shadow/dummy claims.

DATA TO BE RELEASED TO THE RESEARCHER

Note:

- *Release of any information for analyses off-site is dependent on cell size issues being addressed to comply with legislation and departmental policies and procedures. Depending on small number issues, aggregation of certain variables (e.g., mother's age group, residence, diagnoses, etc.) will be carefully considered. These issues will be assessed and discussed at the time when data are being compiled.*

Aggregate Data

Aggregate data on congenital anomalies will be compiled in order to provide information on trends in the birth prevalence of congenital anomalies and how rates naturally fluctuate overtime. The aggregate data will be at the RHA and provincial level and will be compiled by year from 1990 to 2005 for live births and from 2000 to 2005 for stillbirths with the following categories of congenital anomalies: Down syndrome, neural tube defects, oral facial clefts, congenital heart defects, and limb reduction defects. Data on live births will be based on hospital separation data during the first year of life. Data on stillbirths will be based on hospital delivered stillbirths identified in hospital separation data. (Stillbirths have only been coded in hospital data since the 1999/00 fiscal year.)

Person-Level Research Datasets

Subject file #1 – women – birth and stillbirth events

Unique Mother Study ID number[58]
Unique Baby Study ID number[1]
Count *(number of times mother in study; may be grouped)*
Age Group *[calculated as of the exit date and grouped (e.g., <20, 20-24, 25-29, 30-34, 35-39, 40+)]*
RHA of residence as of December 31 of the year of the exit date *(may need to be grouped)*
Study days *(This field reports the number of days from the study entry date to the study exit date. The study entry date is defined as the later of January 1, 2000 or actual coverage initiation; for women with more than qualifying event in the study, the **study entry date** for the second event is set to the later of 90 days after the first event or the health coverage initiation date, the **study entry date** for the third event is set to the later of 90 days after the second event or the health coverage initiation date, and so on.)*
Study exit date *(reported as the year of the birth/stillbirth event)*
Registered Indian Flag *(1=yes)*
Event flag *(B=birth,S= stillbirth)*
MSS test flag *(1=yes)*

Subject file #2 – women – abortion events

Unique Mother Study ID number[1]
Count *(number of times mother in study; may be grouped)*
Age Group *[calculated as of the exit date and grouped (e.g., <20, 20-24, 25-29, 30-34, 35-39, 40+)]*
RHA of residence as of December 31 of the year of the exit date *(may need to be grouped)*
Study days *(This field reports the number of days from the study entry date to the study exit date. The study entry date is defined as the later of January 1, 2000 or actual coverage initiation; for women with more than qualifying event in the study, the **study entry date** for the second event is set to the later of 90 days after the first event or the health coverage initiation date, the **study entry date** for the third event is set to the later of 90 days after the second event or the health coverage initiation date, and so on.)*
Study exit date *(reported as the year of the abortion event)*
Registered Indian Flag *(1=yes)*
MSS test flag *(1=yes)*

[58] The study ID numbers are sequential study reference number assigned for this study by the Epidemiology and Research Unit. The study ID numbers bear no resemblance to an individual's HSN. For women with more than one event included in the study, a new Study ID number will be generated for each qualifying event. There will be no baby ID for those pregnant women whose pregnancy ends in an abortion.

Index abortion type (*M=medical; S=spontaneous; O=other/unspecified)*
Source *(D=physician services; H=hospital separation)*
Days1 *(date of first overlapping abortion episode; reported as the number of days after the date of the index abortion event)*
Source1 *(D=physician services; H=hospital separation)*
Abortion type1 (*M=medical; S=spontaneous; O=other/unspecified)*
Days2 *(date of second overlapping abortion episode; reported as the number of days after the date of the index abortion event)*
Source2 *(D=physician services; H=hospital separation)*
Abortion type2 (*M=medical; S=spontaneous; O=other/unspecified)*

Hospital discharge file - women

Unique Mother Study ID number[1]
Admission date *(reported as the number of days before the study exit date)*
Discharge date *(reported as the number of days before the study exit date)*
Diagnostic code *(all available)*
Diagnostic type *(0=optional, 1=pre-admit comorbidity, 2=post-admit comorbidity, 3=secondary, 6=asterisk code, 9=external cause of injury)*
Procedure categories *(all available)*
Diagnosis flag *(ICD-9/ICD-10-CA)*
Day surgery flag

Physician services file - women

Unique Mother Study ID number[1]
Service date *(reported as the number of days before the study exit date)*
Diagnostic code
Fee-for-service code

MSS lab file - **women** – see Table 3.

Amniocentesis file - **women**
Unique Mother Study ID number[1]
Date tested *(reported as the number of days before the study exit date)*
Indication *(Reason for test: Abnormal Ultrasound [AUS], Advanced Maternal Age [AMA], fetal anomaly, positive maternal screen, etc.)*
Gestational age *(at test date; only available on SHR data)*
Fetus sex *(male, female; only for RQHR data, SHR provides this in the Karyotype field)*
Cytogenetic result *(normal or abnormal - only available on RQHR data)*
Amniocentesis diagnosis *(e.g., Trisomy 21, Trisomy 18, etc. Provided only if cytogenetic result was abnormal; only available on RQHR data)*
Karyotype *(Amnio. result; e.g., 46XX-female normal, 46XY-male normal, 47XX+18, 47XY+18, 47XX+21, 47XY+21, etc.; only available on SHR data)*

Subject file - babies **(Vital Statistics birth/stillbirth information included in this file)**

Unique Baby Study ID number[1]
Date of birth/stillbirth *(provided as year; may need to be grouped or not provided)*
Stillbirth flag *(1=Yes)*
Sex *(male or female)*
Study exit date *(reported as the number of days after baby's date of birth; blank for stillbirths)*
Exit flag *(0=study exit, 1=death, 2=coverage termination; blank for stillbirths)*
Birth weight *(grouped as <500, 500-999, 1000-1499, 1500-2499,2500-3999, 4000+ grams)*
Gestational age *(duration of pregnancy in weeks; grouped)*
Mother's parity *(number of previous births (live & stillbirths) including current birth; grouped)*
Plurality *(single or multiple births)*

Hospital discharge file - babies **(age 0-365 days)**

Unique Baby Study ID number[1]
Admission date *(reported as the number of days after baby's date of birth)*
Discharge date *(reported as the number of days after baby's date of birth)*
Diagnostic code *(all available)*
Diagnostic type *(0=optional, 1=pre-admit comorbidity, 2=post-admit comorbidity, 3=secondary, 6=asterisk code, 9=external cause of injury)*
Diagnosis flag *(ICD-9/ICD-10-CA)*
Day surgery flag

Physician services file - babies

Unique Baby Study ID number[1]
Service date *(reported as the number of days after baby's date of birth)*
Diagnostic code
Fee-for-service code

Death registration file - **babies**
Unique Baby Study ID number[1]
Age at death *(grouped as 0 days, 1-6 days, 7-27 days, 28-364 days, 365 days)*
Underlying cause of death
Multiple causes of death *(all available)*
Autopsy flag
Autopsy used *(identifies whether or not autopsy finding was used in determining the cause of death)*
RHA of mother's residence

APPENDIX B –

TABLE OF DIAGNOSTIC AND PROCEDURAL CODES

Table 1: Diagnostic reporting: The following ICD-9 and ICD-10 codes will be reported for specific codes of interest or grouped as specified; all others will be suppressed.

Category	MSP Assigned Codes*	ICD-9**	ICD-10-CA	Description
Infants:				
DG01		740.x, 742.0	Q00-Q01.x	Anencephalus & encephalocele
DG02		741.x	Q05.x	Spina bifida
DG03		758.0	Q90.0-Q90.2; Q90.9	Down's syndrome - Trisomy 21
DG04		758.2	Q91.0-Q91.3	Edwards' syndrome - Trisomy 18
DG05		745-747.x	Q20-Q28.x	Congenital malformations of circulatory system
DG06		752.x	Q50-Q56.x	Congenital malformations of genital organs
DG07		742.1-742.9	Q02-Q04.x, Q06.x, Q07.x	All other congenital anomalies of nervous system
DG08		758.1, 758.3-758.9	Q91.4-Q99.x	All other chromosomal anomalies
DG09		743-744.x, 748-751.x, 753-757.x, 759.x	Q10-Q19.x, Q30-Q45.x, Q60-Q89.x	All other congenital anomalies
DG10		779.6	P96.4	Other conditions originating in the perinatal period - termination of pregnancy, fetus and newborn
DG11		761.8	P01.8	Fetus and newborn affected by other maternal complications of pregnancy - spontaneous abortion, fetus
DG12			P95	Stillbirth
DG13		760-761.7, 761.9-779.5, 779.8, 779.9	P00-P01.7, P01.9-P94.9, P96-P96.3, P96.5-P96.9	Other fetus or newborn conditions originating in the perinatal period (i.e., the time period around birth up to 7-10 days after birth)

*Medical Services assigns codes for the identification of specific conditions that are grouped within general categories within the International Classification of Diseases. Available on the physician services file only.

**Four digit ICD-9 codes are only available on the hospital file; physician file has only three digit diagnoses. Therefore, on the physician file, four digit codes will have to be grouped (e.g., ICD-9 742.0 will be grouped in DG07; ICD-9 758.0 and 758.2 will be grouped into DG08; ICD-9 761.8 and 779.6 will be grouped in DG13; 656.4 will be grouped in DG22; DG21 will include all of V28 on the physician file). Note also that V27 is not a valid code in the Medical Services data. V26 will not be provided on the physician file because the three-digit code is too broad to fit into either DG21 or DG23.

***DG19 Antenatal screening: ICD-9 codes - flag that screening was done; ICD-10-CA codes - flag for abnormal findings on antenatal screening of mother.

Category	MSP Assigned Codes*	ICD-9**	ICD-10-CA	Description
Women:				
DG14	Z62	656.4, V27.1, V27.3, V27.4, V27.6, V27.7	O36.42, O36.43, O36.49, Z37.1, Z37.3-Z37.4, Z37.6-Z37.7x	Stillbirth
				Pregnancy with Abortive Outcome (pregnancy termination):
DG15		630, 631, 633	O00.x, O01.x, O02.0, O02.8 - O02.9	Non-viable pregnancy
DG16		632, 634.x	O02.1, O03.x	Spontaneous abortion/miscarriage
DG17		635.x	O04.x	Medical/Therapeutic or other abortion
DG18		636.x, 637.x	O05.x	Other or unspecified abortion
DG19		638	O07.x	Failed attempted abortion
DG20			O31.1, O31.2	Continuing pregnancy after abortion or intrauterine death of one fetus or more
DG21		V26.3, V28.0-V28.2, V28.8-V28.9, V83-V84.x	O28.x, Z36.x, Z31.5	Antenatal screening & abnormal findings***
DG22		639-656.3, 656.5-676.x, 678-679.x, V23.x	O08-O27.x, O29-O31.0, O31.8-O36.41, O36.5-O99.x, Z35.x	All other pregnancy/childbirth related complications
DG23		V26.1, V26.8	Z31.1, Z31.2, Z31.3	Assisted reproductive therapy
DG24	Z22			Pregnancy exam

Table 2: Hospital procedures and physician fee-for-service codes of interest to be grouped and reported; all others will be suppressed.				
Category	**CCP**	**CCI**	**FSC***	**Description**
Women only:				
PG01			241P	Stillbirth
PG02			350P	Spontaneous abortion
PG03	81.21, 86.3	5.CA.93.^^	48P, 248P	Ectopic gestation removal
PG04	86.4x, 87-87.2x	5.CA.88.^^, 5.CA.89.^^, 5.CA.90.^^	50P, 250P	Therapeutic/medical abortion
PG05	87.56	5.FG-5.FM.^^	n/a	Surgical repair of Fetus
PG06	87.3	5.AB.02.^^	57P, 58P, 59P, 44W	Amniocentesis
PG07	84-86.2x, 86.8-86.9x, 87.4-87.55, 87.57-87.99	5.AB-5.AB.01.^^, 5.AB.03.x--5.AD.14.^^, 5.FB-5.FD.^^, 5.FT-5.MD.^^	3B, 9B, 5P, 8B, 8P, 13P, 40P-47P, 49P, 51P-55P, 118P, 200P-218P, 246P, 258P, 269P, 279P, 580P	Other obstetric-related procedures
PG08			149W	Nuchal translucency screen
PG09	n/a	n/a	40W, 47W, 48W, 41W, 45W, 46W, 446W, 50W	Other diagnostic procedures related to pregnancy
PG10	81.92	1.RM.83.^^, 1.RB.57.^^	108P	Assisted reproductive therapy
Women and infants:				
PG11	n/a	n/a	5G, 7G, 9G, 11G, 13G, 38G, 39G, 40G, 50G	Genetic assessment**

*Data from physician FFS's has now been added to provide some information on numbers of tests performed for subjects included. Only counts of tests performed, NOT results, can be provided from the above databases. Some of the amniocentesis test results available in Saskatchewan will, instead, be obtained directly from the Saskatoon Health Region. In addition, since pregnancy outcomes are of interest, it was thought that FFS codes related to terminations and complications related to pregnancy could be added. Information would be beneficial.

**Data on whether genetic assessments were ordered for infants for up to 1 year after birth could be compiled if desired, so this has also been included in the FFS codes (as for the amniocentesis information based on physician claim data, these data will NOT include results).

[Website for FFS codes: http://www.health.gov.sk.ca/ic_pub_2005oct1_pps.html]

Table 3. Maternal serum screening test data for release (May 2001 to March 2005): Two files - Patient and Results			
MSS Test Field/Variable Description	**MSS Evaluation**	**PRA DB V29Jul05 Loc.**	
	Variable Name	**Table Name**	**Field #**
MSS PATIENT TABLE			
Unique mother study ID number	STUDYID	n/a	n/a
Was the fetus affected with anencephaly? (0,1) ****	ANENCEPH_RESULT	FETUS	32
Was the fetus affected with Cleft Lip? (0,1) **	CLEFT_LIP_RESULT	FETUS	37
Was the fetus affected with Closed Spina Bifida? (0,1) **	CSB_RESULT	FETUS	34
Was the newborn infant affected with Down Syndrome? (0,1) **	DS_RESULT	FETUS	14
Was the fetus affected with encephalocele? (0,1) **	ENCEPHALOCELE_RESULT	FETUS	40
Gravida (number of times patient has been pregnant)	GRAVIDA	PREGNANCY	4
Last menstrual period (reported as the number of days prior to study exit date)	LMP_DATE	PREGNANCY	5
How many fetuses are there? (Multiple pregnancy: -1 to 5)	MULTIPLE (-1 TO 5)	PREGNANCY	12
Was the newborn infant affected with Neural Tube Defect? (0,1) **	NT_RESULT	FETUS	15
Delivery type code (0-13) **	OUT_DELIVERY	FETUS	23
Karyotype of the fetus (1-8)	OUT_KARYOTYPE	FETUS	28
Gestational age in weeks at date of delivery **	OUT_WEEKS	FETUS	25
Para (number of live children the patient has)	PARA	PREGNANCY	3
Gestational age as of the date of physical exam (reported in days)	PE_GA	PREGNANCY	8
Pregnancy outcome (result of pregnancy) **	PREG_OUTCOME	PREGNANCY	20
Race Flag (for racial origin; Aboriginal 1 = Yes; all others suppressed)	RACE_FLG	RACE	4 (PK)

Was the fetus affected with Trisomy 13? (0,1) **	T13_RESULT	FETUS	36
Was the newborn infant affected with Trisomy 18? (0,1) **	TRI18_RESULT	FETUS	16
Ultrasound gestational age (reported in days)	US_GA	FETUS	4
**** Data are not complete for these fields.**			
MSS RESULTS TABLE			
Unique mother study ID number	STUDYID	n/a	NEW
Patient age at expected date delivery (grouped)	AGE_EDC	INTERPRETATION	16
Age equivalent risk - the maternal age that is equivalent to the calculated risk after screening	AGEEQUIV	INTERPRET_CONDITION	9
Is this an amended result?	AMENDED		
The risk before screening: for DS, and T18, this is the age-based risk; for OSB, this is the population prevalence.	BACKGROUND_RISK	INTERPRET_CONDITION	11
Condition ID # (1 = Down Syndrome (DS); 2 = Open spina bifida (OSB) or neural tube (NT) defect; 3 = Trisomy 18 (T18))	COND_ID	INTERPRET_CONDITION	4 (K)
Screening results for current interpretation version	CURRENT_RESULT	INTERPRETATION	~~49~~
Gestational age as of the specimen date (reported in days)	GA	INTERPRETATION	~~10~~
Gestational age determination date (reported as the number of days prior to the study exit date)	GA_DET_DATE	INTERPRETATION	~~42~~
Method of estimation of gestational age (0-9)	GA_EST_METHOD	INTERPRETATION	~~5~~
Initial screening status (First screen result) (0-19)	INIT_SCRNSTAT	INTERPRETATION	33

The interpretative message number related to the test result(s) for physician - OSB, T18, DS (look up codes in Message Table to be included in the file layout document)	MSGID	INTERPRET_CONDITION	14
Version of the interpretive message	MSGVER		
Reference MOM (i.e., user defined MoM cut-off for OSB)	REFMOM	INTERPRET_CONDITION	16
Reference risk (i.e., user defined cut-off for OSB, DS & T18; Results above will be positive)	REFRISK	INTERPRET_CONDITION	13
Requisition identifier number	REQ_ID		
Calculated risk after screening	RISK	INTERPRET_CONDITION	10
Risk qualifier printed on the report (OSB 0-4; DS 0-6; T18 0-4)	RISKFLAG	INTERPRET_CONDITION	7
Risk qualifier printed on the report for age-based risk of DS (0-5)	RISKFLAG4	INTERPRET_CONDITION	8
Screen Result for OSB, DS, T18 (0-4)	SCREEN	INTERPRET_CONDITION	12
Current screening status (Initial sample, repeat…etc.; 0-19)	SCRNSTAT	INTERPRETATION	32
Date of MSS specimen collection (reported as the number of days prior to study exit date)	SPEC_DATE	SPECIMEN	5
Specimen flag for number of specimens taken per requisition per patient	SPEC_FLG	[created]	NEW
Specimen type (1= serum; 2 = amniotic fluid)	SPEC_TYPE	SPECIMEN	4
Date of ultrasound (reported as the number of days prior to study exit date)	US_DATE	INTERPRETATION	53
Ultrasound gestational age in days (reported if available)		n/a	n/a

APPENDIX C-

SPECIFICATIONS SHEET, CANADIAN INSTITUTE FOR HEALTH INFORMATION

Canadian Institute for Health Information
Data Request Specifications Form Date: April 19, 2012
Aggregate Data Prepared By: Decision Support Services

Specifications Status: FINAL

Requestor's Organization: University of Saskatchewan
Requestor's Name (GSDAP student): Brandace Winquist
Requestor's Supervisor: Dr. Nazeem Muhajarine
Project Title: Population-based outcomes of a provincial prenatal screening program: examining impact, uptake and ethics.

Database(s):
- Discharge Abstract Database (DAD)
- Hospital Morbidity Database (HMDB)
- National Ambulatory Care Reporting System (NACRS)

Level(s) of Care (facility type):
- DAD/HMDB
  - Acute Care (All submitting provinces/territories)
  - Day Surgery (All submitting provinces/territories)
- NACRS (All submitting provinces/territories)

Calendar Year(s):
- DAD/HMDB: 2000 to 2010
- NACRS: 2003 to 2010

Scope:
- All acute inpatient and day surgery Therapeutic Abortions (TA) records associated with Saskatchewan residents submitted to the DAD/HMDB during the study period.
- All Therapeutic Abortions (TA) records associated with Saskatchewan residents submitted to NACRS during the study period.

Output Format:
- Excel format.

Details of Data Request:

Inclusions:

- All acute inpatient and day surgery Therapeutic Abortions records (including Deaths) associated with Saskatchewan residents regardless of the submitting province/territory.

  - **DAD/HMDB Records**

- Acute Inpatient / Day Surgery – ICD-10-/CA/CCI
  - Diagnosis Code = O04.^^ **AND**
  - Diagnosis Type = M, 1, 2, W, X, Y, or C
    CODED IN CONJUNCTION WITH
  - Intervention Code = 5.CA.88.^^, 5.CA.89.^^, 5.CA.20.^^, or 5.CA.24^^
    Additional diagnoses codes to identify those records where Congenital Anomaly was recorded.
  - Diagnosis Code = O35.^^ **AND**
  - Diagnosis Type = Any
  - Analytical Institution Type = Acute Inpatient / Day Surgery
  - Submitting Province/Territory = All
  - Calendar Year = 2001 to 2010

- Acute Inpatient / Day Surgery – ICD-9/CCP
  - Diagnosis Code = 635.^^ **AND**
  - Diagnosis Type = M, 1, 2, W, X, or Y
    CODED IN CONJUNCTION WITH
  - Intervention Code = 10.56, 87.0, 81.93, 87.1, 87.21, 85.5, 87.29, 86.41, 86.42, or 81.7
    Additional diagnoses codes to identify those records where Congenital Anomaly was recorded.
  - Diagnosis Code = 655.^^ **AND**
  - Diagnosis Type = Any
  - Analytical Institution Type = Acute Inpatient / Day Surgery
  - Submitting Province/Territory = All
  - Calendar Year = 2000 to 2006

- Saskatchewan Residents
  - Province/Territory Issuing Health Care/Card Number = Saskatchewan
    OR
  - Province/Territory Issuing Health Care/Card Number = CA or 99 **AND**
  - Postal Code = Saskatchewan postal code or Mini-Code (SK)

- **NACRS Records**
  - Therapeutic Abortions (TA) – ICD-10-CA/CCI
    - Diagnosis Code = O04.^^ **AND**
      CODED IN CONJUNCTION WITH
    - Intervention Code = 5.CA.88.^^, 5.CA.89.^^, 5.CA.20.^^, or 5.CA.24^^
      Additional diagnoses codes to identify those records where Congenital Anomaly was recorded.
    - Diagnosis Code = O35. ^^
    - MIS Functional Centre = All
    - Submitting Province/Territory = All
    - Calendar Year = 2003 to 2010
  - Saskatchewan Residents
    - Province/Territory Issuing Health Care/Card Number = Saskatchewan
      OR
    - Province/Territory Issuing Health Care/Card Number = CA or 99 **AND**
    - Postal Code = Saskatchewan postal code or Mini-Code (SK)

Exclusions:

- Exclude stillbirths and cadaveric donations.
- Exclude records where the specified intervention was cancelled, abandoned, previous or performed out of hospital (OOH).

Groupings:

- Gestational Age: <=11 weeks, 12-14 weeks, 15-19 weeks, and 20+ weeks (provided by B. Winquist)
- Congenital Anomalies (CA): ICD-10-CA: O35.^^, ICD-9: 655.^^

Format of Output:

- The two reports will be presented in excel worksheets and formatted as shown below:
    - Report 1 – TAs performed in Saskatchewan (Saskatchewan residents only)
    - Report 2 – TAs performed in Canada (Saskatchewan residents only)
- Each Classifications System (ICD-9/CCP, ICD-10-CA/CCI) will have its own report(s).

Number of SK Residents that had a TA performed and had a CA diagnosis recorded

Gestational Age	CA Diagnosis Code	Calendar Year		
		2000	…	2010
<=11 wks.	O35.00			
	…			
	Other			
12-14 wks.	O35.00			
	…			
	Other			
15-19 wks.	O35.00			
	…			
	Other			
20+ wks.	O35.00			
	…			
	Other			

METHODOLOGICAL NOTES AND DATA LIMITATIONS

- If several abstracts for one patient meet the selection criteria and occurred within 28 days, only the first one is retained. This avoids counting the same termination of pregnancy multiple times.
- The findings are limited by the availability of the input data.

NOTES:

To comply with CIHI's Privacy and Confidentiality Policies, in instances in which there are fewer than 5 cases to report in a cell, Decision Support Services will review the output and determine whether or not the number of cases will be suppressed.

Description of Diagnosis Types

Diagnosis Types: Diagnosis type is a one-digit code used to indicate the relationship of the diagnosis to the patient's stay in hospital.

- **M – Most Responsible Diagnosis:** The one diagnosis or condition that can be described as being the most responsible for the patient's stay in hospital. In the event that multiple diagnoses are listed, the most responsible diagnosis from the condition associated with the longest length of stay or most resource intensity will be designated as the Most Responsible.
- **1 – Pre-admit Comorbidity:** A diagnosis or condition that existed prior to the patient's admission to hospital, and which satisfies the requirements for determining comorbidity (see note below on comorbidities).
- **2 – Post-admit Comorbidity:** A diagnosis or condition that arises post-admission and satisfies the requirements for determining comorbidity (see note below on comorbidities). If a post-admit comorbidity also becomes Most Responsible Diagnosis, it will be recorded twice: once as the MRDx and once a diagnosis type 2.
- **3 – Secondary Diagnosis:** A diagnosis or condition for which a patient may or may not have received treatment and does not satisfy the requirements for determining comorbidity.
- **4 – Morphology code:** Diagnosis type (4), morphology codes describe the type and behaviour of neoplasm.
- **6 – Asterisk Code (as of 2005-2006):** Assigned to an asterisk code on the second line of the diagnosis field of the abstract whenever the manifestation rather than the underlying cause is responsible for the greatest length of stay and or resources used during hospitalization.
- **9 - External cause of injury code:** A diagnosis type (9) is an external cause of injury code.
- **0 – Optional diagnoses (newborns):** restricted to Newborn codes only.
- **5, 6 (prior to 2005-06), 7, 8 - Optional diagnoses:** Optional diagnosis data
- **W** – Diagnosis Associated with First Service Transfer
- **X** - Diagnosis Associated with Second Service Transfer
- **Y** - Diagnosis Associated with Third Service Transfer

Co-morbidities

Co-morbidities are all conditions that co-exist at the time of admission or develop subsequently and demonstrate at least one of the following:

- significantly affects the treatment received
- requires treatment beyond maintenance of the pre-existing condition
- increases the length of stay by at least 24 hours.

DEFINITION OF A THERAPEUTIC ABORTION

1. Diagnosis code **635 – Legally induced abortion** in ICD-9/ICD-9-CM at the 3rd level digit **or**
   Diagnosis code **O04 – Medical abortion** at the 3rd digit level
   AND
2. Diagnosis type of **M, 1, 2, W, X, Y, or C**
   AND
3. At least one of the following CCP, ICD-9-CM or CCI Intervention codes in any position, not just the principal intervention. Any intervention with a status attribute of 'A' (procedure abandoned after onset) should not be included.

INTERVENTION CODES

CCP	ICD-9-CM	CCI* (at the 5th digit level)
10.56 – Other genitourinary instillation	96.49 – Other genitourinary instillation	5CA88^^ – Pharmacological termination of pregnancy
87.0 – Intra-amniotic injection for termination of pregnancy	75.0 – Intra-amniotic injection for abortion	5CA89^^ – Surgical termination of pregnancy
81.93 – Insertion of laminaria	69.93 – Insertion of laminaria	5CA20^^ – Pharmacotherapy (in preparation for), termination of pregnancy
87.1- Vacuum aspiration for termination of pregnancy	69.01 – Dilation and curettage for termination of pregnancy	5CA24^^ – Preparation by dilating cervix (for), termination of pregnancy
87.21 – Dilation and curettage for termination of pregnancy	69.51 – Aspiration curettage of uterus	
85.5 – Medical induction of labour	73.4 – Medical induction of labour	
87.29 – Other termination of pregnancy NEC	74.91- Hysterotomy to terminate pregnancy	
86.41 – Hysterotomy to terminate pregnancy	69.6 – Menstrual extraction or regulation	
86.42 - Hysterectomy to terminate pregnancy	68.3 – Subtotal abdominal hysterectomy	
81.7 – Menstrual extraction or regulation	68.4 – Total abdominal hysterectomy	
	68.51- Laparoscopically assisted vaginal hysterectomy (LAVH)	
	68.59 – Other abdominal hysterectomy	
	68.6 – Radical abdominal hysterectomy	
	68.7 – Radical vaginal hysterectomy	
	68.9 – Other and unspecified hysterectomy	

CONGENITAL ANOMALIES CODES

ICD-9/ICD-9-CM	ICD-10-CA
655.0^ - Central nervous system malformation in fetus. Includes: fetal or suspected fetal: anencephaly hydrocephalus spina bifida (with myelomeningocele)	O35.00^ - Maternal care for (suspected) fetal anencephaly
655.0^ - Central nervous system malformation in fetus.	O35.01^ - Maternal care for (suspected) fetal spina bifida
655.0^ - Central nervous system malformation in fetus.	O35.02^ - Maternal care for (suspected) fetal hydrocephalus
655.0^ - Central nervous system malformation in fetus.	O35.03^ - Maternal care for (suspected) fetal spina bifida with hydrocephalus
655.0^ - Central nervous system malformation in fetus.	O35.08^ - Maternal care for (suspected) other neural tube defects in fetus
655.0^ - Central nervous system malformation in fetus.	O35.09^ - Maternal care for (suspected) central nervous system malformation in fetus, unspecified
655.1^ - Chromosomal abnormality in fetus	O35.1^ - Maternal care for (suspected) chromosomal abnormality in fetus
655.2^ - Hereditary disease in family possibly affecting fetus	O35.2^ - Maternal care for (suspected) hereditary disease in fetus
655.3^ - Suspected damage to fetus from viral disease in the mother Includes: suspected damage to fetus from maternal rubella	O35.3^ - Maternal care for (suspected) damage to fetus from viral disease in mother (maternal cytomegalovirus infection, maternal rubella, etc)
655.4^ - Suspected damage to fetus from other disease in the mother Includes: suspected damage to fetus from maternal: alcohol addiction, listeriosis, toxoplasmosis	O35.4^ - Maternal care for (suspected) damage to fetus from alcohol
655.5^ - Suspected damage to fetus from drugs	O35.5^ - Maternal care for (suspected) damage to fetus by drugs (damage to fetus from drug addiction)
655.6^ - Suspected damage to fetus from radiation	O35.6^ - Maternal care for (suspected) damage to fetus by radiation
655.8^ - Other known or suspected fetal abnormality, not elsewhere classified Includes: suspected damage to fetus from: environmental toxins, intrauterine contraceptive device	O35.7^ - Maternal care for (suspected) damage to fetus by other medical procedures (damage to fetus by amniocentesis, biopsy procedures, haematological investigation, intrauterine contraceptive device, intrauterine surgery)
655.8^ - Other known or suspected fetal abnormality, not elsewhere classified Includes: suspected damage to fetus from: environmental toxins, intrauterine contraceptive device	O35.8^ - Maternal care for other (suspected) fetal abnormality and damage (damage to fetus from maternal listeriosis, from maternal toxoplasmosis)
655.9^ - Unspecified	O35.9^ - Maternal care for (suspected) fetal abnormality and damage, unspecified