PATTERNS OF REFERRAL AND INVASIVE PRENATAL DIAGNOSIS IN WOMEN OF ADVANCED MATERNAL AGE: MANITOBA 1990-1995

BY

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Patterns of Referral and Invasive Prenatal Diagnosis in Women of Advanced Maternal Age: Manitoba 1990-1995

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ABSTRACT

Pregnant women 35 years or older at delivery represent the largest users of prenatal genetic services in Canada: in 1990, 78% of referrals for prenatal testing were because of advanced maternal age (AMA), yet this represented only 52% of eligible women. The degree to which aspects of the organisation and delivery of care and maternal characteristics were involved in the process of obtaining genetic prenatal diagnosis in Manitoba was assessed using a linked dataset.

The study sample included all AMA Manitoba women in whom pregnancy had been diagnosed between November 25, 1989 and March 31, 1995 (n=12,116 determined from hospital discharge abstracts). Pregnancies ending in a social termination (n=1,693) or a miscarriage (n=1,981) were excluded from the analyses. AMA women who were referred for genetic prenatal diagnosis (n=3,422) were compared to those who were not referred (n=5,020)

Highly significant predictors of referral included (1) seeing an obstetrician before 16 weeks gestation (odds ratio 4.7, 95% CI 4.1-5.5), (2) a Down syndrome risk determined by serum screening to be increased over the age-related risk (odds ratio: 2.7, 95% CI: 2.4-3.1), (3) maternal age of 36+ years at term (36-39 years: odds ratio 2.3, 95% CI 2.1-2.5; 40+ years OR 2.2, 95% CI 1.8-2.6), (4) urban residence (odds ratio: 1.9, 95%CI: 1.7-2.2), (5) previous poor obstetric history (odds ratio: 1.9, 95% CI: 1.5-2.5), (6) being in the top

income quintile (odds ratio: 1.6, 95% CI: 1.3-1.8) and (7) seeing a general practitioner by 16 weeks (odds ratio: 1.4, 95% CI: 1.2-1.6).

Over the study period, approximately 41% (3,422/8,442) of the eligible AMA population was referred for prenatal diagnosis counselling and 74% (2,527/3,422) went on to have invasive genetic prenatal testing. The strongest predictor of uptake of invasive testing was seeing an obstetrician before 16 weeks gestation (odds ratio 2.3, 95% CI: 2.0-2.7). Belonging to eitner of the top two income quintiles was a stronger predictor of invasive testing than was having a Down syndrome risk increased over the age-related risk (odds ratio Quintile 4: 1.7, 95% CI: 1.3-2.1; odds ratio Quintile 5: 2.0, 95% CI: 1.6-2.5 vs. odds ratio 1.4, 95% CI: 1.2-1.7). A woman was also more likely to have invasive testing if she was between 36-39 years of age, rather than 40+ years at term (odds ratio 1.5, 95% CI: 1.2-1.7, p= 0.0001 vs. odds ratio 1.4, 95% CI: 1.1-1.8, p= 0.0194). Seeing a general practitioner before 16 weeks of pregnancy, urban residence and poor obstetric history were not found to be significant predictors of invasive testing. Early complications of pregnancy had a significant negative association with uptake of invasive testing (odds ratio: 0.6, 95% CI: 0.5-0.8, p=0.0001).

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and thanks for their support and encouragement.

"Not everything that can be counted counts,
and not everything that counts can be counted."
Albert Einstein

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GLOSSARY

A priori	Relating to, or derived by reasoning from, self-evident propositions (modified from WWWebster Dictionary, 1999)
Administrative data	*See administrative health care data*
Administrative health care data	Information that is routinely gathered and stored in an electronic form as part of the process of the delivery of health care
Advanced maternal age	Maternal age of 35 years or more at term
AFP Screening	*See also maternal serum AFP*
AFP	*See alpha-fetoprotein*
Alpha-fetoprotein	A protein produced by the fetus which crosses the transplacental barrier into the maternal bloodstream. Maternal serum AFP levels have been used to screen for pregnancies at increased risk of neural tube defects or Down syndrome
AMA	*See advanced maternal age*
Amniocentesis	Transabdominal penetration of the amniotic sac to aspirate amniotic fluid
Anencephaly	Congenital absence of all, or a major part of, the brain (Merriam Webster WWWebster Dictionary, 1999)
Anonymized database	A database with individual identifiers such as name, address, phone numbers etc. removed. In Manitoba, health care number is altered in a consistent fashion by Manitoba Health. This protects confidentiality while still permitting linkage across different datasets for research purposes
Birth Events Database	An "in-house" MCHPE database developed from hospital claim files. It contains all birth admission records linked to the corresponding admission record for the mother
Candidate record pair	Those records, each from different databases, which, among all possible pairwise combinations, are most likely to refer to the same individual
Census division	A geographic area intermediate in size between the municipality and the province (modified from Statistics Canada, 1996)
Chorion villus sampling	Transabdominal or transcervical aspiration of chorionic villi for genetic analysis
Cordocentesis	Transabdominal penetration of the amniotic sac to sample fetal blood from the umbilical cord for genetic analysis. Also known as perumbilical blood sampling (PUBS)

CVS	*See chorion villus sampling*
Cytogenetics	That branch of genetics devoted to the cellular constituents i.e. the chromosomes (modified from Dorland's Pocket Medical Dictionary, 1982)
Day surgery	*See outpatient surgery*
De novo	Arising spontaneously. From the Latin: *de*—down or from, *novo*—new (modified from WWWebster Dictionary, 1999)
Deterministic matching	Generation of candidate records pairs based on a categorical approach which quantifies the relative ability of each linkage variable to identify potential matches and the number of linkage variables that must agree for a pair to be considered a match (modified from Newcombe, 1967)
Deterministic linkage	Record linkage performed using deterministic matching
Dictyotene	A prolonged diplotene stage of meiosis in oocytes. The chromosomes may remain in this stage for years (modified from King & Stansfield, 1997)
Discriminating power	A measure used in record linkage to indicate the utility of a specific variable in distinguishing between records that represent different individuals (modified from Newcombe, 1967)
Down syndrome	A type of mental retardation due to trisomy of the Down syndrome region on autosome 21. In women of advanced maternal age, Down syndrome in the fetus is usually due to an extra copy of the entire chromosome
EDC	Expected date of confinement, the estimated calendar date when the baby will be born (The On-line Medical Dictionary, 1999)
Elevated AFP	An AFP result that is determined to be greater than or equal to 2.3 MOM (the actual AFP level that this corresponds to is gestation specific)
Enumeration area	The smallest geographic area for which census data are reported (modified from Statistics Canada, 1996)
Genotype	The genetic constitution of an organism (modified from King & Stansfield, 1997)
Genetic termination	*See termination due to fetal anomalies*
Health region	Manitoba is divided into regions for the purposes of health care administration. These same Health regions are used as the unit for analysis of Manitoba health care data
Hospital claims	*See hospital discharge abstract*

Hospital abstracts database	A database of all inpatient and day surgery admissions in Manitoba, based on information obtained from the hospital discharge abstract (modified from MCHPE Concept Dictionary – index, 1999)
Hospital discharge abstract	Information coded on the discharge sheet describing the patient's stay. Includes admission and discharge dates, diagnosis and procedure codes for the episode of care (modified from MCHPE Concept Dictionary - Glossary and Related Terms, 1999)
ICD-9-CM	International Classification of Disease, Version 9 with clinical modifications
Income Quintile	An ordinal measure used to divide the population into 5 equal groups, each containing 20% of the population, based on level of household income, with Q1 being poorest and Q5 the wealthiest (modified from MCHPE Concept Dictionary - Glossary and Related Terms, 1999)
Increased Down syndrome risk	The situation whereby the risk of Down syndrome exceeds an arbitrary threshold of 1/384; the risk attributed to women 35 years of age at term. Younger women may also experience an increased Down syndrome risk when factors other than age are included in the risk calculation i.e. serum marker levels
Inpatient	(a) an individual who is admitted to hospital for treatment (b) performed in hospital i.e. an inpatient procedure
Invasive Prenatal Genetic Testing	Invasive prenatal tests, such as amniocentesis, CVS or cordocentesis, that permit a sample to be obtained that can provide information about the fetal karyotype, or the likelihood of birth defects
IPGT	*See invasive prenatal genetic testing*
Karyotype	The chromosomal complement of a cell, individual or species (modified from King & Stansfield, 1997)
Kindred number	A five digit numeric sequence assigned by the Section of Genetics & Metabolism that uniquely identifies members of the same extended family (kindred). When more than one person in a kindred has been seen they are identified using a 3 digit numeric sequence following the original file number, separated from it by a decimal point
Last menstrual period	Date of the start of the last menses before conception
Linkage	*See record linkage*
Linkage key	*See linkage variable*

Linkage variable	A variable which, due to its ability to uniquely and reliably identify an individual, is used in record linkage (modified from Newcombe, 1967)
LMP	*See last menstrual period*
Low AFP	An AFP result that is determined to be less than or equal to 0.4 MOM
Manitoba Health	The agency responsible for overseeing health care services covered under the provincial health care plan
Matching	One of the steps in the linkage process in which rules are applied to decide whether or not a pair of records likely refer to the same individual (modified from Newcombe, 1967)
Maternal serum AFP	A prenatal screening test where AFP levels ascertained from a maternal blood sample are used to determine the risk of neural tube defects or certain chromosome anomalies i.e. Down syndrome, in the fetus
MCHPE	Manitoba Centre for Health Policy and Evaluation
Medical Claims database	A database of all physician claims for the reimbursement of medical care in Manitoba. This includes services rendered in offices and hospitals as well as those performed in hospitals on an outpatient basis (modified from MCHPE Concept Dictionary – index, 1999)
Meiosis	A specialised form of cell division in which there two successive nuclear divisions (meiosis I and II) without any chromosome replication between them. Each division can be divided into 4 phases similar to those of mitosis (prophase, metaphase, anaphase and telophase). Meiosis reduces the number of chromosomes in the parent cell (2n) by half. Each cell receives only one copy of each homolog. During prophase of meiosis I (classically divided into stages: Leptotene, Zygotene, Pachytene, Diplotene and Diakinesis), homologous chromosomes pair to form bivalents, thus allowing crossing over, the physical exchange of chromatid segments. This results in the recombination of genes. Meiosis occurs during the formation of gametes in animals (modified from The On-line Medical Dictionary, 1999)
MHSIP	Manitoba Health Services Insurance Plan
Miscarriage	An unplanned and spontaneous expulsion of the fetus from the womb before 20 weeks
MOM	Multiples of the median value

Monosomy	The condition in which one chromosome of a pair is missing (King & Stansfield, 1997)
Mosaicism	The occurrence in an individual of two or more cell populations of different chromosomal constitutions, derived from a single zygote (The On-line Medical Dictionary, 1999)
MS-AFP	*See maternal serum AFP*
Neural tube defect	Abnormal development of the neural tube resulting in anencephaly or spina bifida (modified from The On-line Medical Dictionary, 1999)
Neural tube	That structure which gives rise to the central nervous system, the brain and the spinal cord (modified from The On-line Medical Dictionary, 1999)
Non-disjunction	Failure of two members of a chromosome pair to separate during meiosis resulting in missing or extra genetic information in the gamete (modified from King & Stansfield, 1997)
Odds ratio	A comparison of the presence of a risk factor in a sample of exposed subjects and non exposed controls (modified from The On-line Medical Dictionary, 1999)
OR	*See odds ratio*
Outpatient surgery	Surgery that does not involve a hospital admission
Personal identifier	*See unique identifier*
PHIN	Personal Health Identification Number. A 9 digit numeric sequence assigned by Manitoba Health that uniquely identifies an individual covered under the MHSIP
Physician claims	"Claims" or requests for reimbursement for services rendered. These are submitted by physicians to Manitoba Health. Such claims describe the type of service provided, who received the service and when it was performed (modified from MCHPE Concept Dictionary - Glossary and Related Terms, 1999)
Physician Master file	An anonymized database of all physicians registered with Manitoba Health. It contains scrambled physician code numbers, training and specialty information and the billing postal code (modified from MCHPE Concept Dictionary-index, 1999)
Probabilistic matching	Generation of candidate records pairs based on a probabilistic approach that utilizes the information in the linkage variables to estimate the likelihood

	that the records represent a match (modified from Gill & Baldwin, 1987)
Probabilistic linkage	Record linkage performed using probabilistic matching
Record Linkage	The merging of two or more files to distinguish records referring to the same individual (modified from Gill & Baldwin, 1987)
Referral	A woman was considered to have been referred for AMA genetic counselling if her physician's office contacted the Prenatal Diagnosis Co-ordinator and requested a counselling appointment or, in the case of women who had previously been counselled for this reason, an IGPT appointment. Not all referrals necessarily had counselling; they may have miscarried or decided against counselling.
Registration number	A 6 digit numeric sequence assigned by Manitoba Health that uniquely identifies nuclear families covered under the MHSIP
Regno	*See Registration number*
Rural residence	Residence in an area having a population density less than or equal to 400 persons per square km (modified from Statistics Canada, 1988)
Sibship	Relationship, especially between individuals born of the same parents (Dorland's Pocket Medical Dictionary, 1982)
Spina bifida	A congenital defect of the spinal column characterised by the absence of the vertebral arches through which the spinal membranes and spinal cord may protrude (modified from Merriam Webster WWWebster Dictionary, 1999)
Spontaneous abortion	*See Miscarriage*
Spontaneous loss	*See Miscarriage*
Stillbirth	The birth of a fetus which shows no signs of life and which has a gestational age of $\geq$ 20 weeks and weighs 500g or more
Termination	Intentional ending of a pregnancy through the removal of a fetus from the uterus usually before 20 weeks gestation
Termination due to fetal anomalies	Termination of pregnancy performed due to an abnormal fetal karyotype or fetal anomalies
Tetrasomy	The condition in which a diploid organism contains 2 extra chromosomes, both of which are homologous with one of the existing pairs, so that 4 copies of one chromosome are present (modified from King & Stansfield, 1997)

Therapeutic abortion	Termination of pregnancy performed either to save the life or health of a pregnant woman, or because of fetal anomalies that are not compatible with life or will lead to significant hardship
Translocation	A chromosome aberration that results in a change in position of a chromosomal segment within the genome but does not change the total number of genes present (modified from King & Stansfield, 1997)
Treaty First Nations	People of aboriginal ancestry who hold treaty status under the Federal Indian Act (modified from MCHPE Concept Dictionary - Glossary and Related Terms, 1999)
Triple test	A prenatal screening test that determines an individual's risk of having a fetus with Down syndrome based on the values of three markers (AFP, estriol and human chorionic gonadotrophin), determined from a maternal blood sample in combination with the maternal age. Also known as the triple screen.
Trisomy	A condition in which a diploid organism contains an extra chromosome which is homologous with one of the existing pairs, so that one kind of chromosome is present in triplicate (modified from King & Stansfield, 1997)
Trisomy 21	*See Down syndrome*
Unique identifier	An assigned sequence of characters and/or numeric values that identify a particular individual
Urban residence	Residence in an area having a population density greater than 400 persons per square km (modified from Statistics Canada, 1988)

CHAPTER 1. INTRODUCTION

Assessment of the physical and genetic status of the fetus during pregnancy, using a variety of diagnostic and screening procedures, has become increasingly prevalent. Diagnostic techniques that can determine the genetic status of the fetus include invasive tests such as amniocentesis, chorion villus sampling (CVS) and cordocentesis. Non, or minimally, invasive screens include maternal serum alpha-fetoprotein (AFP) testing or triple testing (utilizing maternal serum AFP, β-hCG and unconjugated estriol), in combination with maternal age, to provide risk figures for adverse outcomes such as the birth of a baby with a neural tube defect or chromosome abnormality. Though ultrasound examination is commonly performed in pregnancy and may also be used to detect physical defects in the fetus, it is generally used to ensure that the fetus' growth is appropriate or to determine the gestation of the pregnancy, rather than to screen for anomalies. When necessary for the latter purpose, the expertise of the operator, the type of equipment used, the gestation of the fetus, and the nature of the anomaly suspected are key to obtaining useful information.

Pregnant women aged 35 years or more at term represent the largest users of invasive prenatal genetic services in Canada. In 1990, 78% of referrals for prenatal testing were for this reason; however, this represented only 52% of eligible women (Stranc et al., 1994). Determining factors which may impede access to prenatal genetic services for this group is complex. Participation in prenatal testing is voluntary and, when the indication for testing is advanced maternal age (AMA), the risk of finding a problem in the fetus is relatively low; prenatal genetic diagnosis may not be sought although it is known to be

available. In addition to personal choice, the opportunity to have testing may also be influenced by the organization and delivery of care. Utilization rates can only crudely approximate the proportion of the eligible population that actually has access to these services. Referral rates provide a more accurate indicator of the number of women accessing these services; they reflect the number of women who were potentially interested in testing and were successful in obtaining the appropriate referral, and not just those who decided to have IPGT.

The opportunity to examine issues access to prenatal diagnosis is limited. A national survey of Canadian centres performing genetic prenatal diagnosis found that it was not a trivial task to obtain accurate information on the numbers of women being referred for, or having, invasive prenatal genetic testing (Stranc et al., 1994). Obtaining this information through other avenues, such as administrative health care data, is limited since both invasive tests, such as genetic amniocentesis and CVS, and non-invasive ultrasounds are performed as outpatient procedures; as such they are poorly captured by hospital claims data. Fortunately, in Manitoba, the Section of Genetics and Metabolism performs all genetic prenatal diagnosis counselling and processes all prenatal genetic specimens, providing a single repository of information regarding referrals for prenatal diagnosis and invasive prenatal genetic testing. This permits complete ascertainment of individuals referred for prenatal testing, as well as an accurate determination of those that went on to have prenatal diagnosis.

This study examines women referred for genetic counselling regarding invasive prenatal genetic testing because of their age; this group is compared to women who were not referred to determine if specific characteristics are more likely to result in referral. Secondly, the extent to which individual or obstetric characteristics influence the decision regarding prenatal diagnosis is explored.

A cohort of women who would have been over 35 years of age at expected date of confinement (EDC) or term, was constructed from birth, termination and miscarriage records in the administrative data. These records were linked to their counterparts in the prenatal database of the Section of Genetics and Metabolism and in the Maternal Serum Screening database. Individual-based measures from the linked data were used to describe variation in referrals and uptake of prenatal diagnosis. An analysis of the relative contribution of each measure to this variation was performed. It is hoped that this will permit improving education regarding genetic testing, for both providers and patients, so that all AMA women eligible for prenatal genetic counselling have the opportunity to make an informed decision regarding genetic testing.

CHAPTER 2. LITERATURE REVIEW

2.1 PRENATAL DIAGNOSIS

2.1.1 Prenatal diagnosis for Advanced Maternal Age (AMA)

The majority of genetic prenatal diagnosis performed in Canada is done for advanced maternal age (AMA). It is offered to older mothers because of an increased incidence of chromosome number abnormalities in the fetus, particularly Trisomy 21 or Down syndrome, with increasing maternal age. In Canada, any woman who will be 35 years or older on her expected date of delivery, or who has a Down syndrome risk equivalent to that of a 35 year old woman is eligible, at her discretion, for counselling and prenatal diagnosis to determine the fetal karyotype (Canadian College of Medical Geneticists & Society of Obstetricians and Gynaecologists of Canada 1993). Prenatal diagnosis has been widely available in North America since the early 1970s (MacKay & Fraser, 1993).

2.1.2 Down syndrome

Shortly after the human chromosome number was confirmed in 1956 (Ford & Hamerton, 1956; Tjio & Levan, 1956), it was realised that certain disorders, such as Down syndrome, had a chromosomal basis (Lejeune et al., 1959). Down syndrome, first reported in 1866 by Langdon Down (Langdon Down, 1866), is one of the most common and widely recognised genetic conditions, occurring in approximately 1/650-1/1,000 live births (Hook, 1982; Antonarakis, 1998). It is characterised by moderate mental retardation, a characteristic appearance (Øster, 1953) and a constellation of physical findings. As with most other genetic syndromes, there is considerable variability in the type and severity of the defects.

Many Down syndrome babies survive the neonatal period. However, approximately 40-50% will have significant congenital heart disease (Berg et al., 1960; Rowe & Uchida, 1961; Buckley, 1983) and about 5% will have serious gastrointestinal anomalies, such as duodenal or anorectal atresia (Kallen et al., 1996). Other health problems common in individuals with Down syndrome include obstructive airway disease, hearing loss, hypothyroidism, cataracts or other eye disorders, atlantoaxial instability and seizures (Pueschel, 1990; Hayes & Batshaw, 1993; van Schrojenstein Lantman de Valk et al., 1996). Children with Down syndrome have a 10-15 fold increased risk of developing leukaemia (Avet-Loiseau et al., 1995) and, after the third decade of life, almost all individuals with Down syndrome develop an Alzheimer-like dementia (Burger & Vogel, 1973; Wisniewski et al., 1998).

Historically, many theories have been proposed to explain the pathology of Down syndrome, these included familial tuberculosis (Shuttleworth, 1906), syphilis (Sutherland 1899; Stevens 1915), parental alcoholism (Cafferata, 1909) and radiation exposure (Uchida et al., 1968). Eventually, given that Down syndrome was present at birth, it was suspected that it might have a genetic basis. The association of Down syndrome and birth order, where Down syndrome infants were often the last-born in a sibship, had long been known (Fraser & Mitchell, 1876; Shuttleworth, 1909), and was ultimately determined to be due to advanced maternal age at the time of conception (Penrose, 1933).

As a woman ages, her risk of conceiving a fetus with Down syndrome increases (Table 1). Approximately 95% of Down syndrome cases are due to a non-disjunctional event, where paired chromosomes that should normally separate during meiosis fail to do so (Magenis et al., 1977). In about 80% of such cases, this occurs in meiosis I of oogenesis, resulting in a fetus with three copies of chromosome 21 (Langenbeck et al., 1976; Magenis et al., 1977). Unlike males, who go through a regular cycle of sperm production, females are born with their complete complement of gametes (Mintz, 1959).

Table 1. Rates of Down syndrome at live birth and at amniocentesis

Maternal age (years)	Risk of Down syndrome (rate/1,000)	
	At the time of amniocentesis•	At livebirth#
35	1/286 (3.5)	1/336 (3.0)
36	1/175 (5.7)	1/268 (3.7)
37	1/147 (6.8)	1/211 (4.7)
38	1/123 (8.1)	1/164 (6.1)
39	1/92 (10.9)	1/127 (7.8)
40	1/81 (12.3)	1/97 (10.1)
41	1/68 (14.7)	1/75 (13.2)
42	1/46 (21.9)	1/57 (17.3)
43	1/31 (32.4)	1/43 (22.7)
44	1/34 (29.6)	1/33 (29.7)
45$	1/22 (45.3)	1/25 (38.9)

$ At maternal ages over 45 there are considerably less data available with which to generate accurate risk figures

\# After Bray et al., 1998 (Estimated livebirth prevalence as determined excluding Trimble & Baird's data is quoted)

• From Table 6, Ferguson-Smith & Yates, 1984.

Each month a primary oocyte matures, completing meiosis I. The chromosome complement is reduced to 23,X and the oocyte is released from the ovary. In older mothers, each "egg" that undergoes this process will be as old as the mother herself, and will have potentially spent several decades in dictyotene of meiosis I.

Non-disjunction was first put forward as a cause for Down syndrome in 1932 by Waardenburg (Waardenburg, 1932), however, the precise mechanism that results in increased non-disjunction of chromosome 21 with increasing maternal age remains unknown. It has been hypothesised that this is due to the ageing of the ova (Jenkins 1933, Rosanoff & Handy 1934, Bleyer, 1934); a theory that is premised on the degeneration of the spindle mechanism over time. A woman who will be 35 years of age when she delivers has a risk of 1 in 336 of having a liveborn infant with Down syndrome (Table 1, Bray et al., 1998). However, the probability of finding a fetus with Down syndrome during the second trimester is 1 in 286 (Table 1, Ferguson-Smith & Yates, 1984). The disparity in these two figures is due to spontaneous losses or miscarriages, since a significant proportion of Down syndrome pregnancies are lost between the second trimester and term (Hook et al., 1995).

Though there is a strong association between Down syndrome and increasing maternal age, this is also seen in other non-disjunction syndromes, such as Trisomy 13 or 18. However, their incidence is lower, thus the age-specific risk of having a liveborn child with one of these syndromes is decreased over that seen with Trisomy 21 (Ferguson-Smith & Yates, 1984). We rarely see, either at livebirth or at the time of prenatal diagnosis, fetuses that have an extra copy of the larger chromosomes i.e. those from groups A [chromosomes 1,2 & 3], B [4,5], C [6,7,8,9,10,11,12,X] or trisomy for the F group chromosomes [19,20] (Boué & Boué, 1966), with the exception of the X chromosome. This may indicate that having three copies of all the genes on any one

chromosome, or even of specific genes, may cause too great a disruption in the regulation of genes during embryonic development for fetal development to continue.

The majority of individuals with Down syndrome have an extra copy of chromosome 21; however, in about 5% of cases the chromosome number is normal and the Down syndrome phenotype is due to a translocation involving chromosome 21 (Antonarakis, 1998). Individuals with "translocation" Down syndrome are indistinguishable from those who have "standard" Trisomy 21. Though commonly involving an entire extra chromosome, only a specific portion of chromosome 21—the Down syndrome critical region at 21q22.2-q22.3—is required to effect the phenotype (Hagemeijer & Smit, 1977).

Approximately one third of cases of translocation Down syndrome are due to a translocation segregating in the family, while the others represent de novo events that occurred during gametogenesis in a parent, usually the mother (Mikkelsen, 1971; Antonarakis, 1998). When the translocation is familial, there are serious implications for "carriers"—who will have a balanced genome and be phenotypically normal—with regard to their risk of having a child with Down syndrome. Such individuals can produce any of six possible types of gametes, of which only three will be potentially viable. These include gametes with a normal chromosome complement, or those where the translocated chromosome is present but no essential genetic material is duplicated or deficient. Alternatively, the gametes may contain an unbalanced translocation with additional or missing genetic material for either, or both, of the two chromosomes involved in the translocation. When the latter is the case, either trisomy or monosomy for

the two chromosomes involved may be present. The empirically derived recurrence risk for a couple who have had a child with "standard" Trisomy 21 is 1% (Carter & Evans, 1961). When a parent carries the balanced translocation, the risk of having a child with Down syndrome depends on the gender of the parent who has the translocation: 10-15% if it is the mother and approximately 5% if it is carried by the father (Brissenden et al., 1977).

Prior to the advent of prenatal diagnosis, Down syndrome was one of the most prevalent genetic diseases—even before the trend of deferring child bearing until later in life. Currently, with screening and selective termination, the proportion of Down syndrome conceptuses surviving to livebirth has declined (Williamson et al., 1996; Caruso et al., 1998). In Canada in 1990, Hamerton et al., reported that 88% of couples decided to terminate the pregnancy upon receiving a diagnosis of Down syndrome in the fetus, and that only 8% of such fetuses were carried to term (Hamerton et al., 1993). In those pregnancies where a fetus with Down syndrome was detected, the most common indication for genetic testing was that the mother was of advanced maternal age (85%), a further 5% had an adjusted Down syndrome risk equivalent to that of a 35+ year old woman based on their AFP screening test.

2.1.3 Methods of Prenatal Diagnosis

Prenatal diagnosis of genetic disorders, was first explored in 1966 when Steele and Breg reported having performed chromosome analysis of human amniotic fluid cells (Steele & Breg, 1966). Currently in Canada, the option of prenatal fetal karyotyping is available to women who will be 35 years of age or older on their expected delivery date solely on the

basis of their age-related risk of having a trisomic child. This cut-off was adopted in North America based primarily on the findings of a large study on the safety of amniocentesis which found that the risk of an amniocentesis-related miscarriage was approximately equivalent to the risk of having a liveborn child with Down syndrome at a maternal age of 35 years (NICHHD, 1976).

There are several approaches to obtaining fetal cell samples. The most commonly used is amniocentesis although, during the period covered by this study, chorion villus sampling (CVS) was also offered for this indication. Cordocentesis is an option for women requesting prenatal testing at late gestations when a rapid result is required since, at late gestations, options become limited. Although in most cases a single diagnostic procedure is sufficient, upon occasion—either to clarify an ambiguous result or if the original sampling failed—more than one procedure may be necessary.

All of the above noted methods of prenatal diagnosis provide information about the fetal karyotype, by looking directly at cultured fetally derived cells. All are invasive and have an associated procedure-related risk of miscarriage above and beyond the background loss rate for the particular stage of pregnancy at which they are performed. The major difference between the techniques is the window of gestational ages within which they can be performed, their associated risk of miscarriage and the turn-around time necessary to obtain a result. Indications for prenatal testing fall into four categories: increased risk of cytogenetic, molecular or biochemical abnormalities in the fetus, or of structural defects. The choice of technique depends on three factors: the availability of the

procedure, the gestation at which the need for prenatal diagnosis is recognised, the a priori risk of an abnormality in the fetus and the suitability of the technique for the diagnosis being attempted e.g. CVS would not be appropriate if the indication for prenatal diagnosis was to rule out a neural tube defect.

Amniocentesis Amniocentesis first became available as a tool for prenatal diagnosis in 1966, when it was demonstrated that the fetal genotype could be examined using cells obtained by this technique (Steele & Breg, 1966). It has been routinely offered for genetic testing since the mid-1970s and is considered the gold standard of invasive genetic prenatal diagnosis. Genetic amniocentesis can be used to provide cytogenetic, molecular or biochemical diagnoses in the fetus, as well as to suggest the presence of a neural tube defect. Amniocentesis involves the withdrawal of amniotic fluid from the amniotic sac surrounding the fetus. The timing of the procedure, which is usually performed at 15-16 weeks gestation, is determined by the following factors: the accessibility of the uterus, the presence of a sufficient quantity of amniotic fluid to permit the safe withdrawal of the sample, and the quantity of viable fetal cells in the amniotic fluid. The procedure is optimally performed as soon as these requirements are met to allow sufficient time to complete diagnostic studies and still permit any necessary and desired interventions.

Amniocentesis is either performed under direct ultrasound guidance or an ultrasound is performed immediately before sampling to determine the best site for needle entry. The procedure-related fetal loss rate for amniocentesis is approximately 0.5-1.0% (NICHHD,

1976; Tabor et al., 1986; Canadian Collaborative CVS-Amniocentesis Clinical Trial Group, 1989). Other potential maternal complications include spotting, amniotic fluid leakage, cramping post procedure, and amnionitis. Amnionitis occurs in fewer than 1 in 1,000 cases (MRC, 1991). Other potential complications include needle puncture of the fetus, placental abruption and pre-term labour; however, these risks are considered remote. The time from sampling to a result being available is generally 10-21 days. The diagnostic accuracy of amniocentesis may be compromised by maternal cell contamination, which occurs in approximately 1% of all samples. However, this problem is difficult to identify unless the infant is male.

Chorion villus sampling Chorion villus sampling, usually first trimester method of prenatal diagnosis, first became available in Canada in 1984 for those women participating in the Canadian CVS-Amniocentesis randomised trial (Canadian Collaborative CVS-Amniocentesis Clinical Trial Group, 1989). Although attempts to biopsy fetal tissue had been made in the late 1960s (Mohr, 1968), this technique did not attain widespread interest until the early 1980s. At that time, the fetal loss rate accompanying the procedure declined markedly due to improvements in instrumentation, ultrasound and sampling technique, and a concomitant improvement in cytogenetic expertise in dealing with this cell type that permitted karyotypes to be reliably obtained (Simoni et al., 1983).

Chorion villus sampling involves passing a sampling instrument into the developing placenta and sampling a tissue—the chorionic villus—that is fetal in origin. This test is

performed under continuous ultrasound guidance between 11 and 13 weeks gestation and can be attempted either transcervically or transabdominally. In addition to the earlier time of sampling, CVS offers a faster turnaround time than amniocentesis with results generally available within 7-10 days. Although both CVS and amniocentesis are highly accurate tests, confined mosaicism within the placenta may occasionally result in a discrepancy between the chromosome results obtained from the villi on CVS and the actual fetal karyotype. Mosaicism has been noted to occur in 0.8-1.6% of samples (MRC, 1991; Ledbetter et al., 1992).

As with amniocentesis, CVS entails a risk of miscarriage and of maternal complications. The fetal loss rate following CVS is generally quoted as 0.6-0.8% above that of amniocentesis (Rhoads et al., 1989; Lippman et al., 1992). However, it has been shown to be significantly affected both by the approach used to obtain the sample (Smidt-Jensen et al., 1992) and by the learning curve evident for CVS. In view of the latter, the Canadian College of Medical Genetics and the Society of Obstetricians and Gynaecologists of Canada recommend that an obstetrician perform at least 50 CVS procedures per year before being recognised as competent to provide this service (Canadian College of Medical Geneticists & Society of Obstetricians and Gynaecologists of Canada, 1993). Other potential complications of CVS include amniotic fluid leakage, which occurs in less than 1% of cases (Rhoads et al., 1989; Lippman et al., 1992), spotting which occurs in about 7% of cases (Rhoads et al., 1989; MRC, 1991) and, rarely, sepsis.

Cordocentesis Cordocentesis is generally performed after 18 weeks of gestation and involves directly sampling fetal blood, usually from the placental origin of the umbilical vein, while under ultrasound guidance. Of all the methods of prenatal diagnosis described, successful sampling using this procedure requires a particularly skilled team. The miscarriage rate associated with this procedure is difficult to determine with quoted rates varying from 1-6% (Bernaschek et al., 1995; Daffos et al., 1985). The higher risk is associated with pregnancies where the fetus is known to be compromised. Accordingly, cordocentesis is generally reserved for those occasions where a timely result is not possible using amniocentesis either due to a late referral, or following the discovery of mosaicism or a failed culture.

2.1.4 Prenatal serum screening

2.1.4a *Maternal serum alpha-fetoprotein screening*

On occasion, the decision to have prenatal testing is predicated on receiving an increased risk of having a fetus with Down syndrome based on results obtained from the serum AFP or triple screen blood test. Alternatively, women who may have already decided to have prenatal testing may change their minds if they do not receive an increased risk of Down syndrome from this minimally invasive screening test.

The maternal serum alpha-fetoprotein screening test was originally developed to identify pregnancies where the fetus was at increased risk of having a neural tube defect such as spina bifida and anencephaly (Brock & Sutcliffe, 1972). It is particularly valuable since approximately 90% of such conceptuses occur in pregnancies where there is no previously affected child or positive family history (Wald et al., 1977). Alpha-

fetoprotein is secreted by the fetal liver and, because of transplacental passage, can be detected in the mother's blood. The level of AFP in maternal serum varies according to the gestation of the pregnancy, rising above pre-pregnant levels at about 13 weeks gestation, peaking around 32 weeks and then gradually declining (Brock and Sutcliffe, 1972). Pregnancies where the fetus had a neural tube defect were found to experience an elevation in the expected level of AFP. In addition to neural tube defects, higher than expected concentrations of AFP levels may also be associated with multiple pregnancies (Wald et al., 1975), placental complications that may lead to intrauterine growth retardation (Brock et al., 1977; Katz et al., 1990) or recent fetal demise (Cusick et al., 1996).

2.1.4b *The association of low MS-AFP values with Down syndrome*

In 1984, it was first suggested that there was an association between low values of AFP and trisomies such as Down syndrome and Trisomy 18 (Merkatz et al., 1984). Subsequent investigation confirmed this association for Down syndrome (Cuckle et al., 1984), though the physiological mechanism underlying this phenomenon is unknown. The risk of Down syndrome is determined based on maternal age, the gestation of the pregnancy and the concentration of the AFP in the maternal serum. The MOM value that is considered low will vary according to maternal age (Table 2), consequently the result is usually reported as an "age-adjusted" Down syndrome risk and placed in the context of the maternal age to which this risk corresponds. For example, a woman who would be 33 years of age on her expected delivery date with an AFP value at 0.4 MOM would have a Down syndrome risk equivalent to that of a 38-39 year old woman (1/180). When the

adjusted risk is equivalent, or greater than, that of a 35 year old woman's, counselling and an amniocentesis is offered (Chodirker & Evans, 1993).

Table 2. Age-specific AFP MOM cutoffs at which the risk of Down syndrome is equivalent to that of a 35 year-old

Age (years)	Risk of Down syndrome equivalent to a 35 year old if AFP MOM less than or equal to:
27-29	0.40
30	0.45
31	0.50
32	0.55
33	0.60
34	0.70

2.1.4c *The Triple Screen*

In the late 1980s it was observed that the levels of two hormones, estriol and human chorionic gonadotrophin were also altered in pregnancies in which the fetus has Down syndrome. Reduced levels of the former were found, while levels of the latter were elevated above that considered normal in pregnancy (Bogart et al., 1987; Wald et al., 1988). Due to the increased detection rate of fetuses with Down syndrome most North American centres offering maternal serum screening now use the "triple screen" for Down syndrome and the individual's risk is calculated based on the values of all three of these markers in combination with the maternal age (Palomaki et al., 1997). In Manitoba at the time of this study, only AFP testing was available to indicate a potentially elevated risk of Down syndrome in the fetus. Triple screening was introduced in May 1999.

2.1.5 Factors influencing utilization of prenatal diagnosis

The last three decades have seen major changes, not only in the development of prenatal diagnosis, but also in the social context of pregnancy. In Canada, a decline in unexplained pregnancy losses and stillbirths (Wadhera & Millar, 1996) and infant and perinatal mortality rates (Nault, 1997) has been accompanied by a concomitant reduction in family size (Ford & Nault, 1996) and an increase in maternal age over the last two decades (Wadhera & Millar, 1996; Nault, 1997). There has also been an increasing "medicalization" of pregnancy, with the status of both the mother and the fetus being continually monitored during the course of gestation (Riessman, 1983; Hubbard, 1995). Many are reassured by the information that can now be provided about the pregnancy and the fetus, while others are concerned by the intrusion of technology into this domain (Grant, 1993; Tudiver, 1993; Hubbard, 1995). Even for those women who are eligible for prenatal diagnosis on the basis of their age, the risk of finding Down syndrome in the fetus is still low. For a woman 35 years of age, with no positive family history, the a priori probability of having a liveborn child with Down syndrome is approximately 0.3% (or 1 in 336, Bray et al., 1998). Though this risk is still low, it is still approximately four times higher than that of a woman in her 20s, where the corresponding livebirth prevalence is approximately 0.07%, or 1 in 1,493 (Bray et al., 1998). This information, when viewed in conjunction with the status of genetic prenatal diagnosis as a "halfway" technology—one which identifies a problem for which no cure exists (Thomas, 1979)—might understandably make couples anxious about prenatal diagnosis.

In theory, health services utilization is a function both of individual and societal determinants that effect health behaviour and outcomes (Figure 1). Within the constraints of the organization and resources of the health care system, use of health care services can be seen as a type of individual behaviour that is influenced by a variety of factors. These have been modelled by Andersen as predisposing characteristics and enabling resources which interact to produce "need" for health care services based on perceived health status (Andersen & Newman, 1973; Andersen, 1995).

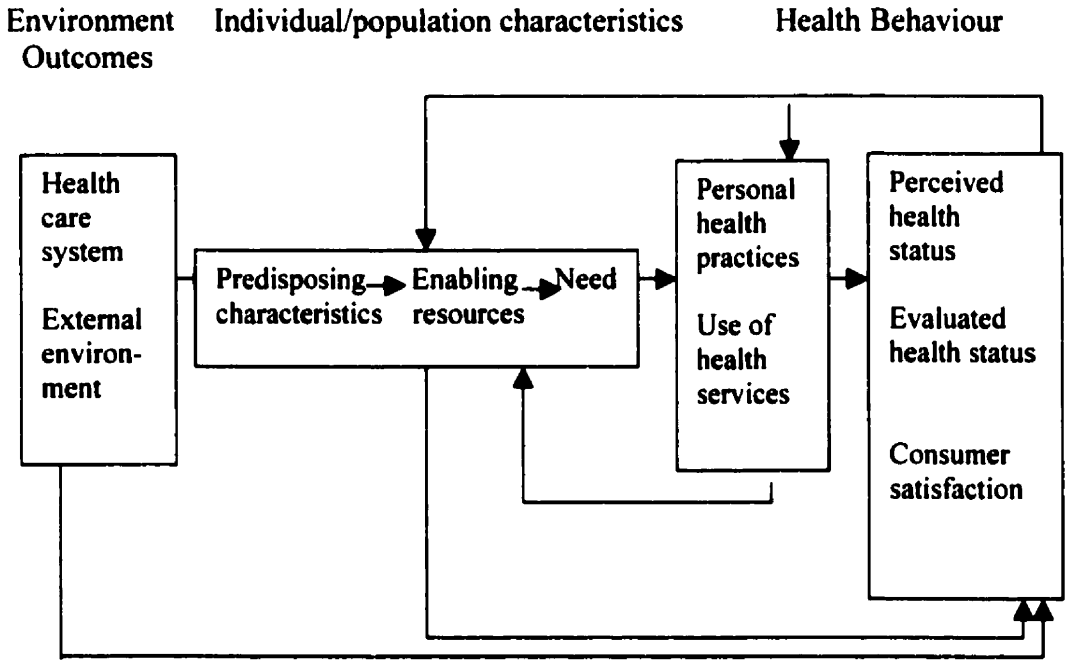

Figure 1. Health services use model
(after Andersen, 1995).

Predisposing characteristics include biologic risk factors such as age or gender that directly relate to the likelihood that people will require health services; a social or cultural component, estimated through education or occupation and ethnicity; and individual

health beliefs such as knowledge of, and attitudes towards, health (Andersen & Newman, 1973).

Enabling resources are those necessary in order for individuals to avail themselves of healthcare. At the community level, this requires that the services be available and, at the personal/family level, that the existence of such services be known, and accessible, to individuals. This is not a simple linear system as indicated by the feedback loops in Figure 1 that demonstrate interdependence between the various categories. For example, societal determinants affect utilization both at the level of individual characteristics (in the provision of enabling resources) and at the level of the health care system/external environment.

This same complexity can be seen in the context of genetic prenatal diagnosis. Though universal coverage, accessibility, portability, comprehensiveness and public administration are the cornerstones upon which the Canadian health care system is based (Canada Health Act, 1985), it has long been recognised, both in Canada and elsewhere, that the uptake of invasive prenatal genetic diagnosis is skewed toward women of higher socio-economic status (Coffman et al., 1993; Grant, 1993). It is not known whether this is reflective of increased educational attainment leading to heightened concerns about having a baby with an abnormality, or rather reflects practical obstacles to obtaining counselling and invasive testing faced by women from lower socio-economic groups. Few studies exist that specifically address this question. In their description of barriers to reproductive services in rural Oklahoma, Coffman et al. identified four major areas which

contributed to this phenomenon (Table 3): Cost to payees, limited system capacity, organization of services and, finally, cultural barriers (Coffman et al., 1993). Similar problems have been reported both in other states (Nsiah-Jefferson, 1993; Undermann Boggs et al., 1995) and internationally (Corchia et al., 1995).

Table 3. Barriers to accessing genetic reproductive care

1. *Financial*
   - Medicaid[@]
   - Un/under insured[@]
2. *System capacity barriers*
   - Lack of prenatal clinics[#]
   - Lack of clinical genetic professionals
3. *Organisation, practices and atmosphere of services*
   - Geography (transport, lack of affordable child care)
   - Accessing the system
   - Genetic education of health care professionals
4. *Cultural, personal and other system barriers*
   - Client's knowledge, personal concerns and support
   - Cultural barriers between providers and clients
   - Attitudes towards abortion*

After Coffman et al., 1993

[@] Limited coverage or reimbursement for prenatal genetic testing i.e. MS-AFP screening or triple testing

[#] Decreases the likelihood of referral for genetic testing

* Includes both individual attitudes and those of government/ policymakers

Not surprisingly, the literature on barriers to prenatal care in general echoes these concerns. The Institute of Medicine's Committee to Reduce Low Birthweight found five major categories of non-financial barriers to general prenatal care in the United States (Institute of Medicine, 1985): (1) a less than optimal number of providers, (2) insufficient prenatal services in areas with a large at-risk population, (3) experiences, attitudes and beliefs that prevent women from coming for care (4) inadequate or absent transportation

or child care, and (5) insufficient targeting of education or information to encourage women to come for care. Since prenatal diagnosis is a sub-specialty within obstetrics, barriers to prenatal care must interact both directly and indirectly to influence access to genetic prenatal care. A large body of literature exists that corroborates the findings of the Committee to Reduce Low Birthweight (Burks, 1992; Aved et al., 1993; Harvey & Faber, 1993; Melnikow and Alemagno, 1993; York et al., 1993; Johnson et al., 1994; LaVeist et al., 1995; Larson et al., 1997; Liu, 1998).

Ford, Nault, Wadhera and Millar have examined trends in pregnancy outcomes, changing fertility patterns, infant mortality and low birthweight in Canada from the mid 1970s to the mid 1990s using data provided by the provincial and territorial Vital Statistics Registries (Ford & Nault, 1996; Wadhera & Millar, 1996; Nault, 1997). Although, over this period, there had been a slight decline in unexplained pregnancy losses and stillbirths (Wadhera & Millar, 1996) and infant and perinatal mortality rates (Nault, 1997), the rate of the decline in infant and perinatal mortality was seen to have slowed in recent years (Nault, 1997). This was attributed, in part, to an increase in the incidence of babies of low birthweight, a circumstance felt to have been influenced by the rising proportion of births to women of advanced maternal age, as well as births to unmarried women (Nault, 1997).

In the Manitoban obstetric population, Mustard and Roos (1994) found the relationship between prenatal care and birthweight to be complex. Infants born to women in the poorest income quintile tended to have lower birthweights than those born to wealthier

women, but the difference was associated with a higher prevalence of complications, smoking, unmarried status, as well as to inadequate prenatal care (Mustard & Roos, 1994). This study also demonstrated that, in this population, universal health insurance did not prevent barriers to access to prenatal care: Poorer women initiated care later in pregnancy and had consistently and substantially reduced utilization of prenatal care compared to other income groups.

In Canada, we assume there is no direct financial barrier to genetic prenatal diagnosis since out-of-pocket payment for such services is not required. However, indirect barriers such as difficulty taking time off work, the availability of child care for existing children, the distance that must be traversed to get to the centre offering testing and the cost of travel must still be considered. These are difficult problems to quantify and address. Though genetic centres in Canada can describe the population that they serve (Stranc et al., 1994), information about those individuals who do not make contact is less easily available. We are fortunate to have a wealth of relatively recent information about the culture of genetic prenatal diagnosis as a result of the studies of the Royal Commission on New Reproductive Technologies. This commission was established in 1989 and reported to the Federal government in 1993. The findings of the interdisciplinary research program it mandated, and the results of its consultations, represent a body of knowledge that is exceptionally detailed and comprehensive, spanning 15 volumes. Of particular interest are papers by Hamerton et al. "Prenatal Diagnosis in Canada—1990: A Review of Genetic Centres"; Chodirker and Evans "Maternal Serum AFP Screening Programs: the Manitoba Experience"; Renaud et al. "Canadian Physicians and Prenatal

Diagnosis: Prudence and Ambivalence" and MacLeod et al. "A Demographic and Geographic Analysis of the Users of Prenatal Diagnostic Services in Canada".

Potential obstacles to obtaining prenatal diagnosis that have been researched include physician knowledge and attitudes, geographic and ethnic variation in utilization and the knowledge of eligible women about prenatal diagnosis. Physicians play a fundamental role as "gatekeepers" to prenatal diagnosis. It is assumed that all physicians will be aware of the guidelines as to when to refer women for genetic testing for advanced maternal age. This assumption of a common body of knowledge about, or attitude towards, medical technology may be facile. Rather, whether or not a woman is referred appears to depend on a complex mix of level of knowledge about prenatal diagnosis and genetic conditions, attitudes towards abortion, and concern regarding potential medico-legal repercussions (Renaud et al., 1993).

In 1990, Renaud et al. conducted a survey of Canadian physicians who were likely to see pregnant patients (Renaud et al., 1993). This included obstetricians, paediatricians, radiologists and a "representative" sample of general practitioners with an obstetric component to their practice. Slightly over half of the physicians contacted (52%, n=3,072) responded. Province and medical specialty were the only indicators that significantly influenced both attitude toward, and opinion of, genetic prenatal diagnosis. Physicians who were older, and those who had more direct contact with prenatal diagnosis, tended to favour the use of this technology, as did physicians from Quebec. Approximately half (51%) of the respondents felt that prenatal testing should not be

offered to women who would not terminate the pregnancy were an anomaly to be found. Approximately the same proportion agreed with selective termination for certain anomalies (Trisomy 21, Duchenne muscular dystrophy, and Huntington disease). Generally, an increased tolerance of selective termination was seen with increasing familiarity of the physician with the condition or anomaly and/or its perceived severity. Nationally, 56% of respondents indicated that, when doubt existed, their decision to refer patients for prenatal diagnosis was influenced by the possibility of lawsuits. Again, the strong influence of province was demonstrated, with this proportion being lowest in Quebec (40%) and highest in Saskatchewan (65%).

Such findings should not be taken as minimising the importance of other factors, such as religious affiliation and practice, to decisions made about prenatal diagnosis. In other studies, both have been seen to be important determinants of the attitudes of both women and their physicians towards genetic prenatal diagnosis (Bernhardt et al., 1982; Blustein & Fleischman, 1995; Seals et al., 1985). This is perhaps not surprising because of the role religion plays in providing a specific frame of reference with which to view the world.

The survey of Manitoba physicians performed by Chodirker and Evans provides information about the relationship between the physician attitudes towards AFP testing and their knowledge of the same (Chodirker & Evans, 1993). This work is particularly germane to the current study as it was performed in 1992, in the middle of the current

study period, and documented the attitudes of Manitoban physicians who provided primary obstetric care, and may provide insights into the referral patterns seen.

A clear need for further education of physicians, particularly general practitioners and non-Winnipeg doctors was demonstrated: Almost 16% of respondents were unaware that the threshold for prenatal diagnosis for advanced maternal age was 35 years of age. Furthermore, 61% of respondents were unaware that this criterion was determined by the maternal age at term. A lack of knowledge on the part of health care providers is not novel having been commented upon by numerous other authors (Holtzman, 1992; Smith et al., 1994) and will certainly act to hinder the speedy adoption of new tests and technology. The reported rates of referral (defined as either a referral or an offer of referral) for prenatal diagnosis were less than optimal, with 4.5% of respondents stating that they never refer eligible patients for prenatal diagnosis and a further 16% only referring some women (Chodirker & Evans, 1993). Perhaps not surprisingly, physicians who tended to refer their patients for prenatal diagnosis also tended to approve of AFP screening. In Manitoba at that time, it appeared that the larger the obstetric component of the practice the more informed the medical professional was about both prenatal diagnosis and AFP screening.

Many factors have been shown to influence the attitudes of women or couples towards prenatal diagnosis. These include weighing of potential risks and benefits of the procedure (Seals et al., 1985); how the risk figures presented are interpreted (Marteau et

al., 1991; Press & Browner, 1993) and the resolution of potential conflicts between prenatal testing and religious beliefs (Seals et al., 1985). Finally, women or couples may feel pressure from their peers (Marteau et al., 1995) or health care providers to undergo genetic testing (Grant, 1993; Press & Browner, 1993).

A more easily quantifiable barrier to prenatal diagnosis is that of geography, or the distance that must be travelled in order to obtain counselling and testing. The work by MacLeod et al. (1993) for the Royal Commission on New Reproductive Technologies, found high rates of prenatal diagnosis for advanced maternal age (a high utilization rate was defined as one greater than 60%) for those census divisions that included Winnipeg and southern Manitoba, with low rates in rural census divisions and northern Manitoba (MacLeod et al., 1993). However, the majority of analyses reported in this study group the prairie provinces as a single unit and so are of limited value. The study by Hamerton et al. which describes the same population of women (over the same time period), demonstrates that the three prairie provinces are indeed quite different in their provision of prenatal diagnostic services (Hamerton et al., 1993).

2.2 Linkage Methodology

2.2.1 Linking data in Health Research

Record linkage provides an attractive opportunity to improve the power or depth of unlinked data sources with minimal fiscal outlay as well as reducing the likelihood of recall or other biases that may be present in retrospective studies. Although secondary

data sources can provide relatively inexpensive access to large amounts of relatively accurate and complete data, the methods by which they were collected are not under the control of the researcher. This may compromise the utility of the data for research and the validity of the results obtained. Prior to embarking on a linkage project, the following factors must be evaluated: the extent to which the database captures information on the desired cohort, the accuracy and completeness of the variables, the size of the population covered and the period covered (Table 4). Finally, the ease with which access to the data can be obtained and likely success at producing linked databases should be considered.

Table 4. Factors affecting the value of secondary data in epidemiological research

1. Comprehensiveness of registration of individuals/coverage of desired cohort
   a. Comparing the data source with one or more independent reference sources
   b. Comprehensive record review
   c. Aggregated methods
2. The accuracy and completeness of variables
   a. Precision
   b. Validity
3. Size of data sources
4. Registration period/period covered
5. Data accessibility, availability and cost
6. Data format
7. Ease, extent and reliability of record linkage

After Sorensen et al., 1996

The concept of linking data from multiple sources, and the term "record linkage," were first put forward by Halbert Dunn, in 1946, when he proposed creating a "book of life (which)... starts with birth and ends with death" to provide an accurate accounting of "vital" records for each individual (Dunn, 1946). Little came from this early suggestion: yet, as computer technology developed in the 1960s and databases became increasingly

electronic in nature, the possibilities provided by linkage became more enticing. The next major proponent of linkage was a Canadian geneticist, Harold Newcombe, who was particularly interested in linking individuals from the same family and developed the concept of "probability matching" to link records despite discrepant and incomplete data (Newcombe et al., 1959).

Newcombe advocated using computers as "filing clerks" to compile same-person records from various source files, or to build family histories of births, marriages, deaths and ill health (Newcombe et al., 1959). Though this did not require that the computers should perform complex mathematical operations, it did request a much more unconventional functionality: that the computer produce valid linkages using information—of which any one piece might be fallible but that collectively possessed considerable discriminating power (Newcombe, 1967).

The objective of linkage is to estimate the probability that two records refer to the same individual (Howe, 1998); ultimately, the success of the venture will depend on the ability of the computer to mimic the actions of a human filing clerk, and the completeness and accuracy of the data in the files that are to be linked. Two databases or "files" with some level of commonality, or overlapping information, are required for linkage. The information for each individual is arranged in individual-specific rows ("records") and variable-specific columns. The process of linkage requires that records from each file are brought together and that pre-specified "linkage variables" (which contain information common to both files) are compared across records.

Generally, more than one linkage variable is used even when unique identifiers, such as health care number, are available since errors can occur even in unique identifiers. To that extent, linkage is inevitably probabilistic (Howe, 1998). Agreement on one or more linkage variables is necessary for linkage to be considered, but is not adequate to establish linkage. If a sufficient number of linkage variables in two records, one from each file agree, that record pair is preliminarily assigned to a set of "matched" or "linked" records. If there is no such agreement, the records are returned to the original source files and are available for other potential pairings. This process continues until no further matches can be determined using the specified criteria.

Although it is simplest to explain record linkage as a linear sequence, it tends to be an iterative process with multiple passes and refinements necessary to train our "clerk" to file correctly. The outcome of each phase of linkage leads to a re-examination of earlier results and assumptions to see if appropriate matches were made and to develop linkage keys for the next iteration of linkage that might improve the linkage rate (Roos et al., 1987).

Generally, when a variable is crucial for a particular purpose or used in a regular basis to retrieve information, it will have a high degree of reliability and validity (Roos et al., 1989). The quality of other variables that are less important to the purpose driving the data collection (i.e. management, billing claims, administration and planning, surveillance or research) may be poorer (Roos et al., 1989).

Linkage may reveal inconsistencies and errors between records that would not have been apparent had the records not been linked. There should therefore be a cycle(s) of validation and error checking incorporated into the linkage process (Gill et al., 1993; Shevchenko et al., 1995). As a result, even in highly automated environments, record linkage requires extensive "hands on" input to determine what effect different combinations of linkage variables will have on the linkage rate, to examine candidate record pairs, and to dictate the format of the next linkage iteration (Turner et al. unpublished, 1999).

2.2.2 Types of linkage

The comparison process can be implemented using either a deterministic (all-or-none) or probabilistic approach, or a combination of these strategies may be employed sequentially adjusting the matching strategy to the specific characteristics of the databases (Roos et al., 1986). Deterministic linkage generates matched record pairs based on explicit instructions as to the number and nature of the agreements between linkage variables that will permit a candidate record pair to be considered linked (Gill & Baldwin, 1987; Roos & Wajda, 1991). This approach provides a simple, but subjective, categorical assessment of the likelihood that any candidate record pair represents a match. Deterministic linkage is relatively simple and is used primarily when data contain a variable that uniquely identifies individuals and that data are known to be complete and to have low levels of coding errors (Roos & Wajda, 1991; Muse et al., 1995).

Probabilistic record linkage uses the information in the data to provide a more precise, numeric estimate of the likelihood that the records represent a match. Probabilistic

linkage is more robust when few linkage variables are available, the data are incomplete or coding errors are common, or when deterministic linkage results in many ties (Roos & Wajda, 1991). Each method has advantages; probabilistic linkage is more complex to implement than deterministic linkage and in linkage accuracy versus simplicity often becomes an important trade-off (Newcombe et al., 1989a; Newcombe et al., 1989b; Wajda et al., 1991).

The last phase of record linkage involves determining which of the candidate record pairs are appropriate matches and which are not. In deterministic linkage, acceptable matches are separated from the set of candidate record pairs on the basis of the number of variables in agreement and as an implicit part of the linkage process (Roos & Wajda, 1991). In probabilistic linkage, probability calculations are used to determine "thresholds" beyond which candidate record pairs are accepted as matches. These thresholds are generally calculated using a linear sum assignment approach to matching, which is an extension of the estimation of maximum likelihood model, and estimates the probability that the values for a specific variable will agree given that the record pair is indeed appropriately matched (Jaro, 1989). This is based on earlier work that was done by Newcombe, Kennedy, Fellegi and Sunter (Newcombe & Kennedy, 1962; Fellegi & Sunter, 1969). Although thresholds can be altered to improve linkage rates, this may potentially result in the generation of false positive matches in addition to identifying more genuine links (Wajda & Roos, 1987).

The likelihood that a candidate pair represents a true link is represented by a weight or probability determined by the calculation of a frequency ratio for each variable of interest. This quantifies outcomes among linked pairs of records against unlinked records that have been brought together at random :

$$\textit{Frequency Ratio} = \frac{\textit{frequency of outcome (x, y) among linked pairs}}{\textit{frequency of outcome (x, y) among unlinked pairs}}$$

Where x is the value of the linkage variable for a record from file A, and y is the value of the linkage variable for a record from file B (Newcombe, 1967).

The weights estimate the likelihood that two records indeed refer to the same individual (Roos & Wajda, 1991). This approach can be further refined using outcome-specific weights where each outcome is assigned a weight, allowing partial agreements in variables to be taken into account i.e. discrepancy in the year or month of birth (Roos & Wajda, 1991). Candidate pairs with weights greater than an arbitrarily set threshold are considered to be matched, while those below are rejected. A "grey zone" will often exist where records require verification. This will include tied records, where two or more records from one file match equally well with a record from the other file and duplicates. Such situations are commonly resolved through manual inspection, unless this approach is impractical due to the number of records involved.

2.2.3 Types of error encountered in linkage

Obtaining an accurate estimate of the amount of error in any given data set is difficult. Roos and Wajda suggest that any dataset with a large numbers of duplicate records, or where key variables have a large proportion of missing values, will be difficult to link (Roos & Wajda, 1991). Both random and systematic errors in the data files must be

considered in the context of the linkage process. Random errors arise as a result of incorrect data entry or lack of entry of available information, while systematic errors may occur if the original source of the information does not reflect the true experience of the subject.

Numbers are prone to several common random errors: transcription or substitution errors, where digits are incorrectly recorded because of mishearing, misreading or miskeying; transposition errors, in which correct digits are entered in the wrong order; and shift errors, which occur as a result of addition or omission of zeros (Baldwin & Gill, 1987). While random error affects reliability, systematic error (bias) is considered more serious because it affects validity. Systematic errors may not be as easily anticipated and require thorough understanding of the data collection system. Tactics for improving linkage have been documented by Wajda and Roos and are shown in Table 5 (Wajda & Roos, 1987).

Table 5. Tactics for improving linkage

Tactic	Pro	Con
Check possibilities for recoding, finding other usable variables etc.	Payoff can be high as knowledge of file increases	Will not be able to generate improvements after a certain point
Alter weights	Reflects knowledge of file	Improvements may be few
Alter cutting points	Can lead to more linked cases	Improvements may be few; have trade off between false negatives and false positives
Generate extra records when particular problems are known	Permits linkage of records which otherwise may not be linked	May increase false positives
Look at cases which linked and did not link	May greatly increase understanding of the data set. Easy to do technically	
Add one or more new variables from an intermediate file	Another file may incorporate information with different biases and be less intercorrelated with available variables	Access to a new file may present problems
Manual checks	May generate new ideas as one tries to resolve difficult pairs. May provide useful data on false positives	Expensive on a case by case basis

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2.2.4 Methodologic considerations in obstetric linkage

Although the use of linked records to obtain a cohort of mothers and their offspring is not uncommon in the published literature, papers which discuss methodologic issues raised by this type of linkage are considerably less numerous. Interestingly, one of the seminal papers on record linkage was, in part, inspired by the need to link family records while preserving information on the relationships within the family group (Newcombe, 1967). Despite the paucity of papers dealing with linkage of this type of data, potential problem areas have been detailed and methods of dealing with them suggested. The former include handling of multiple births (potential one to many linkages), the periodicity of pregnancy (linking a pregnancy to the correct outcome), synchronising databases to ensure that the appropriate cohorts are generated for matching and problems raised by pre-term births and miscarriages/abortions.

The potential for "one to many" or "many to one" pairings in linkage projects involving mothers and babies must always be considered. Such situations arise when a woman has more than one pregnancy during the study period, or if the pregnancy outcome is a multiple birth. Although the problem is a disruption of the usual one to one linkage, the solution will differ depending on the nature of the problem being examined. Matching to the correct pregnancy requires that the linkage variables used include those with information specific to a particular pregnancy, such as date of baby's birth or date of last menstrual period (Stanley et al., 1994; Holian, 1996; Olsen et al., 1996). Stanley et al. suggest frequency checks on key fields to detect biologically implausible situations i.e. gestations of more than 42 weeks, an approach which may aid in ensuring that records are

linked to the correct pregnancy (Stanley et al., 1994). Dealing with multiple births from a single pregnancy is more complex: how this situation is addressed will depend on the nature of the study and whether the maternal or offspring outcome is of interest. If infant outcomes are the focus of the investigation, it will be necessary to link each infant's record to the appropriate maternal record (Stanley et al., 1994). If maternal outcomes are the focus of the study, it may be sufficient to indicate that the pregnancy ended in a multiple birth to avoid duplicating maternal records.

Potential biases noted to have influenced the number and type of records linked include detection bias, occasioned by a differential knowledge or effort that results in disparate proportions of linked records among different categories of records (Holian, 1996; Adams et al., 1997a), and information bias. An example of the former is evidenced by improved linkage rates for records for infants known to have been born with a birth defect due to more assiduous manual verification (Holian, 1996). Bias of the latter type, information bias, may be introduced if more data are present for some cases than for others (Holian, 1996; Adams et al., 1997a). If situations such as these go unrecognised, conclusions based on the results of the linkage may be biased. Records that do not link are often distinctly different from ones that do, as they tend to occur in a non-random fashion i.e. differential or incomplete reporting of pre-term births compared to term deliveries (Stanley et al., 1994; Griffin et al., 1995; Holian, 1996; Adams et al., 1997a; Adams et al., 1997b). One suggestion for dealing with this is to exclude groups of records that tend to have insufficient or unreliable identifying information, i.e. pre-term pregnancies, from the study (Adams et al., 1997a).

Many authors emphasise the need for multiple rounds of linkage, often using differing linkage keys, to improve the proportion of records linked (Haas et al., 1994; Stanley et al., 1994; Adams et al., 1997a). Similarly, manual inspection of the data to ensure appropriate and extensive linkage was also stressed (Haas et al., 1994; Stanley et al., 1994; Olsen et al., 1996; Adams et al., 1997a). The majority of the papers cited used a deterministic linkage strategy combined with manual inspection to verify links and generate new linked pairs from records that had not been linked during the linkage process (Haas et al., 1994; Stanley et al., 1994; Holian, 1996; Olsen et al., 1996). Deterministic linkage appears to have been chosen for obstetric linkages primarily because of the limited number of identifiers present on the datasets and the availability of individuals to manually check the results of linkage.

CHAPTER 3. METHODS

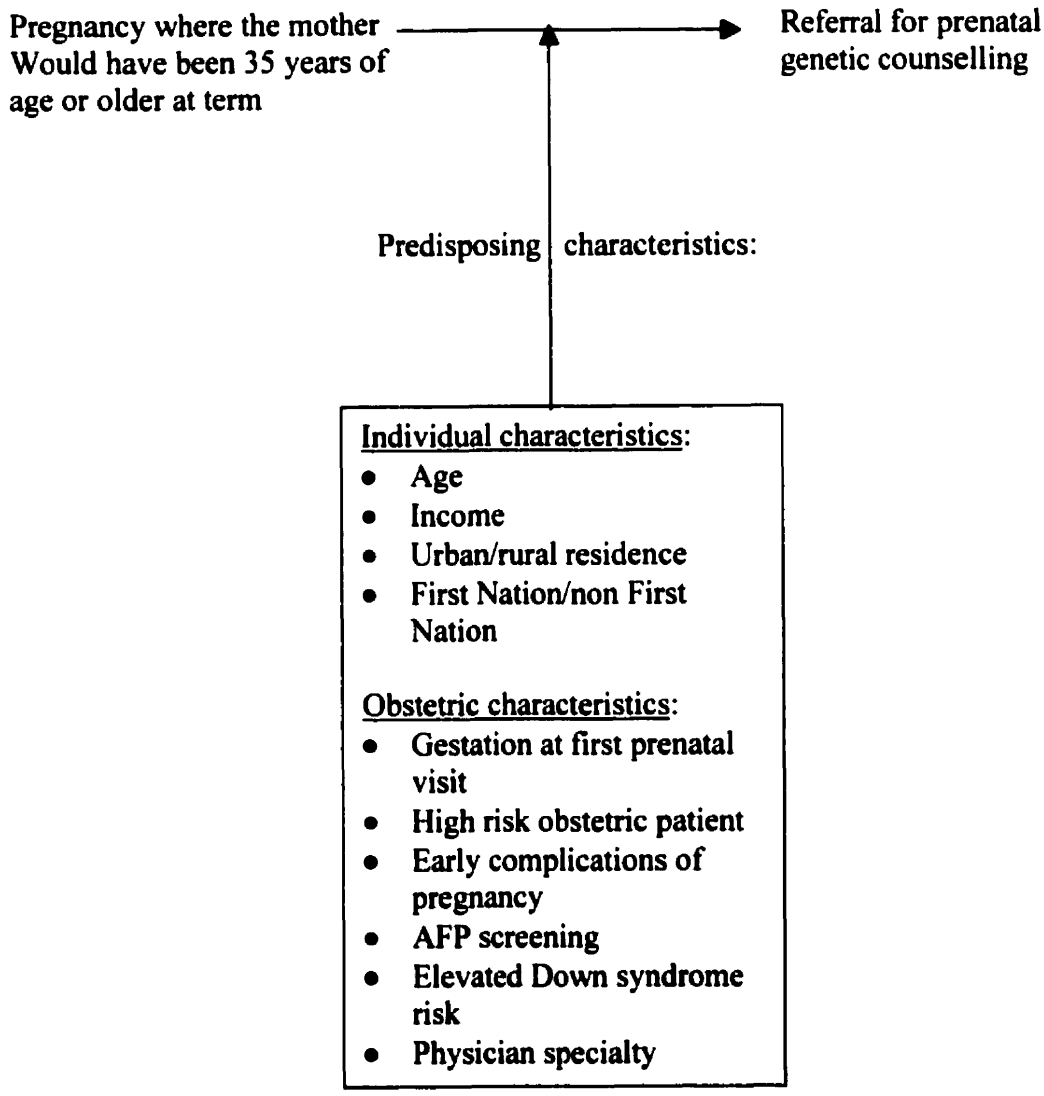
3.1 RESEARCH FRAMEWORK AND OBJECTIVES

The specific objectives of this study were to:

1. Determine the feasibility of linking records from the patient database from the Section of Genetics and Metabolism and the Manitoba Maternal Serum AFP Programme to routinely collected administrative health care data.
2. Compare AMA Manitoba women referred for prenatal diagnosis to AMA women who were not referred with respect to maternal socio-demographic and obstetric factors.
3. Compare AMA Manitoba women having prenatal diagnosis to AMA women who were referred but decided against testing with respect to maternal socio-demographic and obstetric factors.
4. Make recommendations regarding the delivery of prenatal genetic services in Manitoba.

The conceptual framework used to generate the hypotheses (Figure 2) was premised on the health services use model suggested by Andersen (see Figure 1) and hypothesized that both individual and obstetric characteristics would have a direct effect on the outcomes of interest: referral for genetic counselling and uptake of invasive prenatal diagnosis. This model is undeniably simplistic and does not include many other important influences.

Figure 2. Research Framework



The model and the variables chosen to operationalize this framework were selected on the basis of previous work in this area and the availability of the data within the research databases. For example, characteristics such as maternal age, region of residence, AFP screening and gestation at first prenatal visit would be expected to influence the likelihood of referral for prenatal genetic counselling and were present and accessible in one or more of the study databases. We were unable to include undeniably important factors such as a woman's, or her provider's, opinion of prenatal diagnosis, since such information was not available to us.

3.1.1 Research Objectives

Part I: *Comparison of AMA Manitoba women referred for genetic prenatal diagnosis to AMA women who were not referred with regard to*

(a) Maternal age
(b) Income
(c) First Nations/non-First Nations status
(d) Urban/rural residence
(e) Early obstetric complications
(f) High risk obstetric patient status
(g) AFP screening
(h) Gestation at which prenatal care was initiated
(i) Medical speciality of prenatal caregiver prior to 16 weeks gestation

Part II: Comparison of AMA Manitoba women having genetic prenatal diagnosis to AMA women who were referred but did not choose testing with regard to

(a) Maternal age

(b) Income

(c) First Nation/non-First-Nation status

(d) Urban/rural residence

(e) Early obstetric complications

(f) High risk obstetric patient status

(g) AFP screening

(h) Gestation at which prenatal care was initiated

(i) Medical speciality of prenatal caregiver prior to 16 weeks gestation

3.2 ASSUMPTIONS

1. *To be included in the study, a gestation of at least 5 weeks must have been reached*

   This will set a minimum gestation prior to which a woman would not be expected to have been referred for counselling.

2. *Women were not referred for counselling prior to 5 weeks of gestation.*

   Since most pregnancies are not diagnosed as such before 5 weeks of gestation, this would seem to be reasonable.

3. *A normal gestation is 40 weeks, with an upper limit of 42 weeks.*

   The range is 38-42 weeks. Since a gestation of 42 weeks is still considered normal, this figure was used in the interval calculation to ensure that cases were not missed.

4. *There may be more than one pregnancy per woman in the study period.*

5. *Not all referrals necessarily had invasive testing or genetic counselling*

   (see Glossary for definition of referral)

6. *Individuals should have been referred for prenatal testing by 20 weeks gestation.*

   Routine amniocentesis is performed between 15-18 weeks gestation. By 20 weeks, the referral would not be considered routine since the ability to obtain a result and offer a termination if necessary would be compromised.

7. *MS-AFP is usually performed in the 16th week of gestation*

   A 16-week draw date represents the modal value. Blood samples are accepted for testing between 15 and 24 weeks. Later samples are interpreted and entered in the AFP database, but officially no standard measurements exist for these gestations. According to Chodirker and Evans (1993), in calendar 1990-1991, 87.3% of samples were received by the 20th week of gestation and 93.4% by 24 weeks gestation.

8. *CVS is performed between 11-13 weeks of gestation*

9. *Routine amniocenteses are usually performed between 15-18 weeks gestation.*

   Amniocentesis may be performed up to 20 weeks. However, a cordocentesis would generally be done after 20 weeks gestation since chromosome results would be obtained more quickly.

10. *Cordocenteses are usually performed between 20-24 weeks.*

    Cordocenteses may be performed up to term for infants with anomalies for purposes of pregnancy management. However, the option of termination at later stages of gestation may not be available.

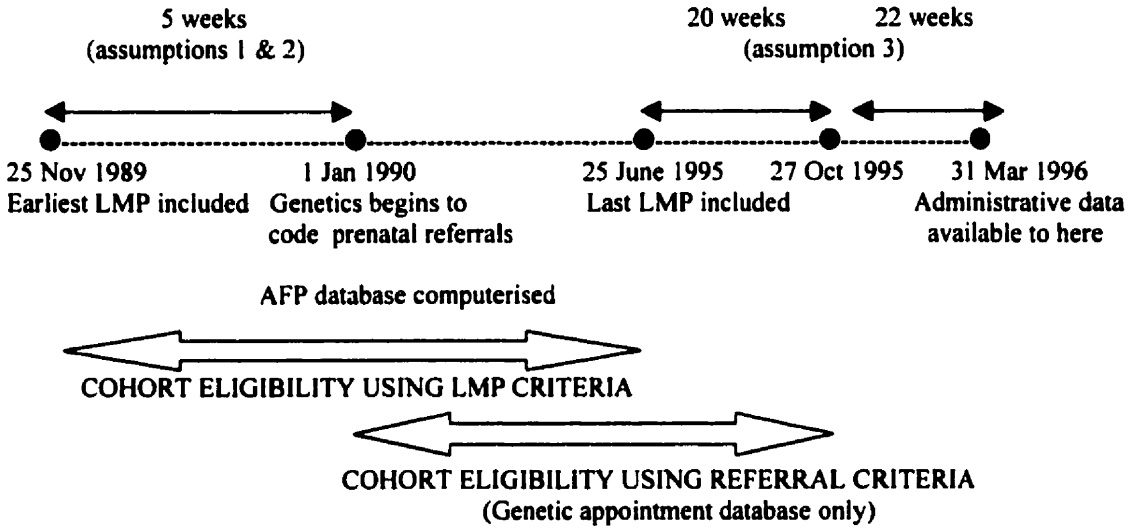
11. *The outcome of pregnancy is not necessarily a singleton live birth.*

    Potential outcomes of pregnancy also include multiple births, miscarriages, terminations (both genetic and social) and stillbirths.

3.3 DATA CONSTRAINTS AND EXCLUSIONS

1. Referrals for genetic prenatal diagnosis counselling where the woman did not go on to have prenatal diagnosis were not coded prior to January 1st, 1990.
2. The AFP database was not computerised before January 1st, 1990

Figure 3. Timeline for cohort eligibility



Exclusions:

Pregnancies meeting one or more of the following criteria were excluded from the study:

1. The mother was not of advanced maternal age. However, if she was in a subsequent pregnancy, that pregnancy would have been included.
2. The mother was not a resident of Manitoba.
3. The pregnancy did not fall within the specified timeframe.
4. Pregnancies that ended in a social termination.

3.4 DATA SOURCES

3.4.1 MCHPE Data Repository

The Manitoba Health Research Data Repository at the Manitoba Centre for Health Policy and Evaluation (MCHPE) contains anonymized (see Glossary) encounter-based records of individual Manitobans' interactions with the provincial health care system. This information is derived from the Manitoba Health Insurance Registry and health insurance claims routinely filed with Manitoba Health by physicians and health care facilities. Since the 1970s, Manitoba Health has provided the MCHPE with anonymized copies of the hospital abstract database, which contains hospital admission/discharge abstracts (also known as hospital claims); physician requests for reimbursement of medical care ("medical claims"), a physician master file and the Manitoba Health Master Registration database (Roos et al., 1993). The use of a consistent set of identifiers (with identification numbers for both patients and physicians scrambled to ensure confidentiality) enables medical "histories" to be compiled for individuals across databases. For instance, records for an individual who was discharged from hospital can be linked to the medical claims database to determine if they subsequently saw a physician for whatever reason. Not captured are the few services that are funded through a global budget and those individuals whose health care is funded under separate federal programs i.e. members of the military or the Royal Canadian Mounted Police and prisoners in Federal penitentiaries, however, this is considered to be an insignificant proportion of the population (Roos et al., 1986).

a) ***Hospital Abstracts database***

This database covers all inpatient and day surgery admissions and is based on information from the hospital discharge summary. Captured information includes the encrypted MHSIP number, dates of hospital admission and separation, up to 16 ICD-CM diagnosis codes and 12 ICD-9-CM procedure codes and encrypted identification numbers for attending physicians (Roos et al., 1979). Maternal hospital discharge abstracts provide information on age, postal code, treaty Indian status, gravidity, parity, ICD-9-CM diagnosis codes for morbidity associated with pregnancy (when appropriate), labour and delivery, and ICD-9-CM procedure codes describing the delivery and other perinatal obstetric interventions. Additionally, newborn hospital discharge abstracts provide information about the newborn i.e. date of birth, birthweight, ICD-9-CM codes describing the delivery and any problems noted at birth and a cross reference to the mother's hospital chart number.

b) ***Medical Claims database***

All physician claims for the reimbursement of medical care in Manitoba are submitted to the MHSIP. This database encompasses services rendered in offices and hospitals as well as those performed in hospitals on an outpatient basis. Billing for prenatal care is generally performed as a fixed-fee global tariff covering all routine care provided in the prenatal and postpartum periods although specific, non-routine, services may be provided on a fee for service basis submitting a claim for each encounter. Captured information includes the date the service was rendered, the physician's encrypted identification number, patient information such as encrypted personal identifier, postal code and diagnosis and the tariff code (Roos et al., 1979).

c) ***The Birth Events database***

The birth events database, which is maintained by the MCHPE, contains records that link the hospital abstracts of newborns (both births and stillbirths) to those of their mother. There is a single record per child (thus a mother giving birth to twins will have two records); records contain information on date of admission for the mother and the date of birth for the child, the encrypted PHINs of both mother and newborn, MHSIP registration number, other personal identifiers and information pertinent to the birth.

d) ***Public use census files***

In the absence of individual-level measures of socio-economic status, income data from the 1991 Canadian census, aggregated to the geographic unit of enumeration area, was used to rank neighbourhoods into population quintiles by average household income. The full six-digit postal code was used to link women to their enumeration area of residence. This approach has been used previously in research using administrative data (Krieger, 1992; Anderson et al., 1993; Wilkins, 1993).

3.4.2 The Section of Genetics and Metabolism

The Section of Genetics and Metabolism at the Health Sciences Centre serves the province of Manitoba, the Keewatin district of the North West Territories, and the western half of Northwestern Ontario: a population of approximately 1.3 million. In 1997, this catchment area drew approximately 3,000 patients, of which 40% were prenatal referrals (Personal communication, Cheryl MacLean). Weekly prenatal genetics clinics are held, though, due to time constraints, patients may also be seen at other times.

Patients who decide to have invasive prenatal genetic testing most commonly have amniocentesis. However, during the study period, cordocentesis and CVS were also available. From 1985 to 1990, CVS was only available in Manitoba on a restricted basis, as part of the Canadian amniocentesis-CVS trial. Barring exceptional circumstances, such as the need for specialised diagnostic techniques or if the laboratory's capacity is exceeded, samples are analysed at the cytogenetic laboratory associated with the Section.

Genetics Prenatal database

The patient database of the Section of Genetics and Metabolism has been active since 1990 (Personal communication, B. Chodirker). It is a relational database and data from more than one of the subsidiary databases can be viewed and updated simultaneously using a series of "views" that have been designed to facilitate the booking and tracking functions that this system provides. Minimally, each record will contain the following information about each client: Name, address, registration number, Genetic Clinic chart number (Kindred number), Health Sciences Centre hospital chart number, date of birth, diagnosis and referring physician. For prenatal patients, information is potentially available on LMP (last menstrual period), referral indication, type of invasive test (if performed), gestation at time of testing, karyotype and the results of biochemical or metabolic testing. Additionally, the AFP file number is often included for prenatal patients, the majority of whom have maternal serum-AFP serum screening. First names, surnames and addresses of both women and their doctors were excluded to ensure confidentiality.

3.4.3 The Manitoba Maternal Serum Alpha-Fetoprotein Screening Programme

Introduced in 1985, the Maternal Serum AFP Programme annually screens approximately 65% (~10,000) of Manitoban pregnancies (See Table 6 for Manitoba livebirths). In May 1999, when triple testing was introduced, it became the Manitoba Serum Screening Program.

Table 6. Livebirths by maternal age in Manitoba

Year	Maternal age less than 35 years	Maternal age 35 years or older (% of total births)	Maternal age not stated	Total
1990	15,985	1,361 (7.8%)	6	17,352
1991	15,907	1,373 (7.9%)	2	17,282
1992	15,116	1,474 (8.9%)	0	16,590
1993	15,233	1,475 (8.8%)	1	16,709
1994	14,942	1,535 (9.3%)	3	16,480
1995	14,461	1,649 (10.2%)	3	16,113

Source: Statistics Canada Catalogue No. 84-210-XPB, Table 2.3

Since November 1994, the College of Physicians and Surgeons of Manitoba has recommended that AFP screening be offered to all pregnant women (College of Physicians and Surgeons of Manitoba Guideline No. 610, 1994). Maternal Serum Screening is a provincially funded, interdisciplinary program run jointly by The Section of Genetics and Metabolism, Department of Paediatrics & Child Health; the Fetal Assessment Unit, Department of Obstetrics, Gynaecology & Reproductive Sciences; the Department of Biochemistry and Medical Genetics and the Cadham Provincial Laboratory. The Manitoba Maternal Serum Programme is the largest centralised provincial serum screening database: laboratory facilities, counselling and follow-up are all co-ordinated as a single unit. Approximately 84,000 pregnancies were screened between 1990-1997 (Personal communication, B. Chodirker).

In Manitoba, it is recommended that AFP screening be performed between 15 and 18 weeks gestation. Individual AFP results are reported as multiples of the median (MOM) value, determined from a standard reference population, for the appropriate half-week of gestation i.e. a value twice the median is reported as 2 MOM. These reference values were determined in-house (Personal communication, B. Chodirker). Under the Manitoba AFP protocol, all pregnancies with abnormal screening results are offered follow-up, usually with counselling and an ultrasound, fetal assessment or invasive testing offered as appropriate (See Figure 4). Although initially designed to provide information regarding risk of neural tube defects, the AFP report also indicates if the woman will be 35 years of age or over at term and, since 1986, includes an adjusted Down syndrome risk. This information is available for all pregnant women, irrespective of their age.

Manitoba Maternal Serum AFP Screening database

The Manitoba Maternal Serum Screening database was created in January 1990 and captures data on each woman screened using the AFP blood test. A separate AFP file number is assigned to each pregnancy, but there may be more than one AFP sample submitted in a pregnancy. Items captured include patient name (only first and last initial were available on the subset of information used for this project), address (not included in the current study to maintain confidentiality), MHSIP registration number, date of birth, LMP and AFP level. Also recorded are the gestation at which the blood was drawn, the physician of record, the report message that was generated (See Figure 5), whether ultrasound or prenatal testing have been performed, early complications of pregnancy if experienced and diabetic status.

Figure 4. Flow chart for Maternal Serum AFP Screening

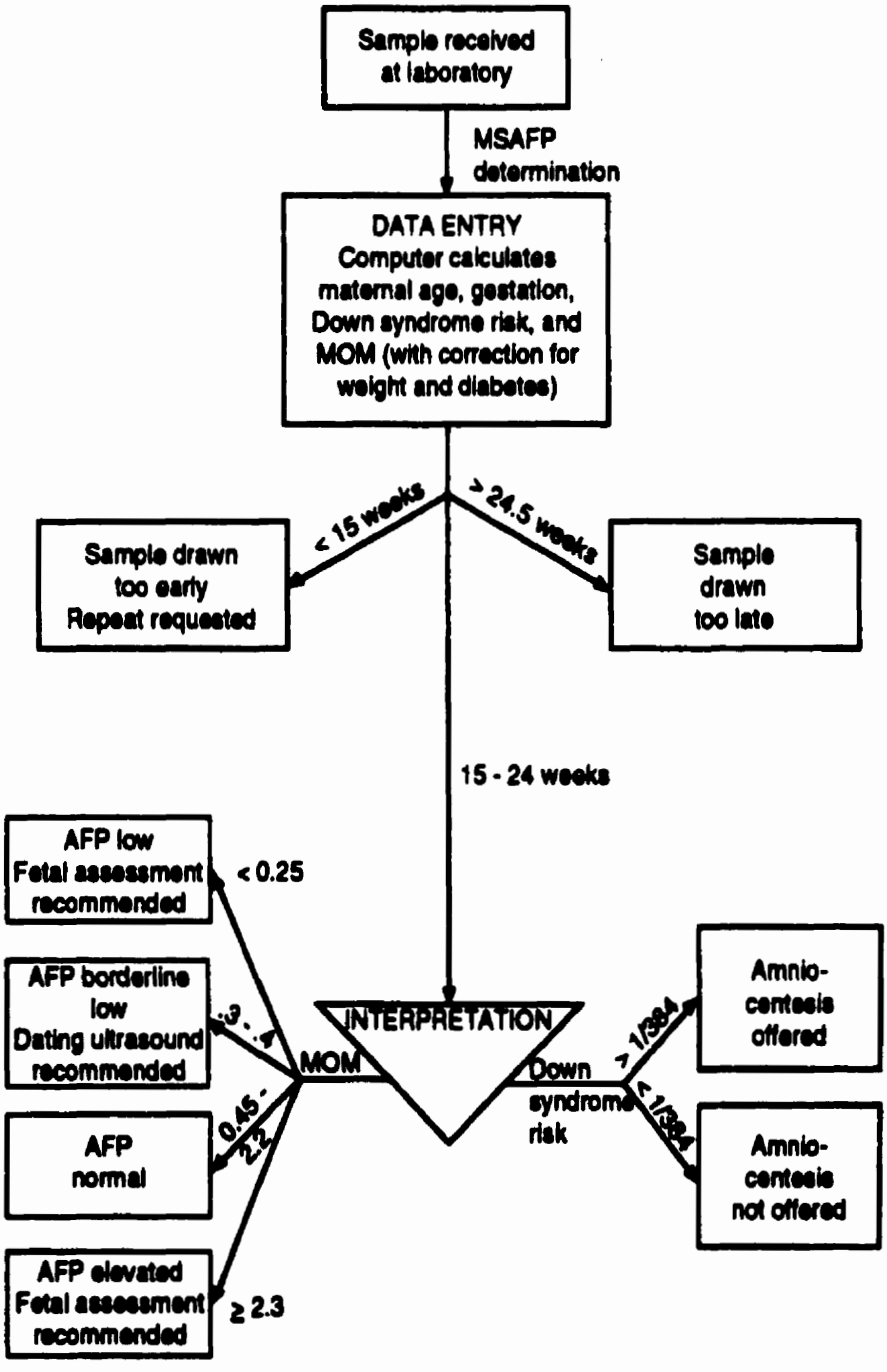


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Figure 5. Potential AFP report messages

1 THE AFP IS BORDERLINE LOW. As the dates are confirmed and the risk of Down syndrome is below the cut-off at which amniocentesis is offered, no further follow-up is recommended.

2 THE AFP IS LOW. We recommend a fetal assessment. Please call ***-**** to arrange.

3 THE AFP IS BORDERLINE LOW. Please confirm dates with an ultrasound (at >14 weeks' gestation) and send us a report. If the dates are accurate no further follow-up is necessary.

4 THE AFP IS LOW. We recommend a fetal assessment be done. If the gestation is accurate an amniocentesis will be offered at that time.

5 THE AFP IS NORMAL. If the gestation is considered accurate, no further screening is necessary.

6 THE AFP IS LESS THAN THE MEDIAN. The risks for Down syndrome are therefore increased. If an amniocentesis is desired, call ***-**** to arrange.

7 THE AFP IS ELEVATED. We recommend a detailed fetal assessment as soon as possible. Call ***-**** to arrange.

8 (Blank, appropriate message to be hand-written)

9 THIS SAMPLE WAS DRAWN TOO EARLY. Please send another sample between 16 and 18 weeks' gestation or if this is not possible send sample at next visit.

10 THIS SAMPLE WAS DRAWN TOO EARLY. Please send another sample between 16 and 18 weeks' gestation. On the basis of the patient's age on the due date, an amniocentesis could be offered. Please call ***-**** to arrange if the patient wishes.

11 THIS SAMPLE WAS DRAWN TOO LATE (i.e., > 24 weeks) and therefore cannot be reliably interpreted. If you have concerns regarding fetal growth or anomalies, you may wish to arrange a detailed ultrasound or a fetal assessment.

12 Considering the diabetic correction, THE SAMPLE WAS DRAWN TOO EARLY. Please repeat between 18 and 20 weeks' gestation.

13 Considering the diabetic correction, THE SAMPLE WAS DRAWN TOO EARLY. Please repeat between 18 and 20 weeks' gestation. On the basis of the patient's age on the due date, an amniocentesis could be offered. If desired, please call ***-**** to arrange.

14 (There is no message 14)

15 THE MATERNAL SERUM AFP IS LESS THAN THE MEDIAN. The risk for Down syndrome is therefore increased over the age-related risk. However, given the gestation, no accurate Down syndrome risk can be quoted. If genetic counselling and amniocentesis are desired, call ***-****.

16 THE AFP IS CONSIDERED ELEVATED even though this is a multiple gestation pregnancy. A fetal assessment is recommended. Please call ***-**** to arrange.

17 THE AFP IS NORMAL. However, as the patient will be over age 35 by the due date an amniocentesis may be offered. Please call ***-**** to arrange if the patient wishes.

3.5 COHORT DEVELOPMENT

3.5.1 Administrative databases

3.5.1a *Hospital abstract cohort*

To create a subset of the hospital abstracts database, records for fiscal years 1989/90 to 1995/96 that represented an endpoint to pregnancy were extracted and the event summarised as one record per pregnancy. Pregnancy endpoint was defined either as birth (including multiple births), stillbirth, miscarriage or termination of pregnancy (social or genetic). See Appendix 1 for ICD-9-CM codes used. Only those records where the mother would have been 35 years of age or older at term were kept (See Appendix 2 for details).

Potentially, pregnancies may be missed using this approach; those where birth or termination records are absent from hospital files. This circumstance could be due to:

a) an early miscarriage (without concurrent hospitalisation)

b) the claim for birth/loss/miscarriage/termination not being made until after March 31, 1996 (the end of the study period)

c) the mother leaving the country or registering for health care in another province before the birth of the child. However, if the mother moved within Canada she would continue to be covered by Manitoba health care insurance for a period of 3 months after leaving or until Manitoba Health was notified that she had registered for health care in another province.

In total, 12,259 AMA pregnancies were determined (Figure 6). Missing gestational ages were updated, where possible, from the AFP and Birth Events databases and duplicate records removed (For details see Appendix 2). 8,364 (68.2%) of the pregnancies ended in births (120 or 1.4% of births did not have a gestational age), 81 (0.7%) in stillbirths (1 case or 1.2% of these did not have a gestational age), 1,739 (14.2%) in terminations and 2,075 (16.9%) in miscarriages. A subset of the birth events database was created using the same criteria for age and LMP that generated the hospital abstracts, retaining only one record per pregnancy (n=8,382 pregnancies). This was used to verify the hospital abstract cohort.

Identifying terminations of pregnancy performed for fetal anomalies

The 12,116 AMA pregnancies included 24 pregnancy terminations performed for fetal anomalies or an abnormal karyotype. Since the ICD-9-CM does not have a specific code for this circumstance, these cases were identified by reviewing abnormal outcomes in the genetic laboratory data. Only 15 of the 24 (63%) terminations for fetal anomalies were identified as terminations in the hospital records. Eight were classified as stillbirths and one as a miscarriage (Figure 6).

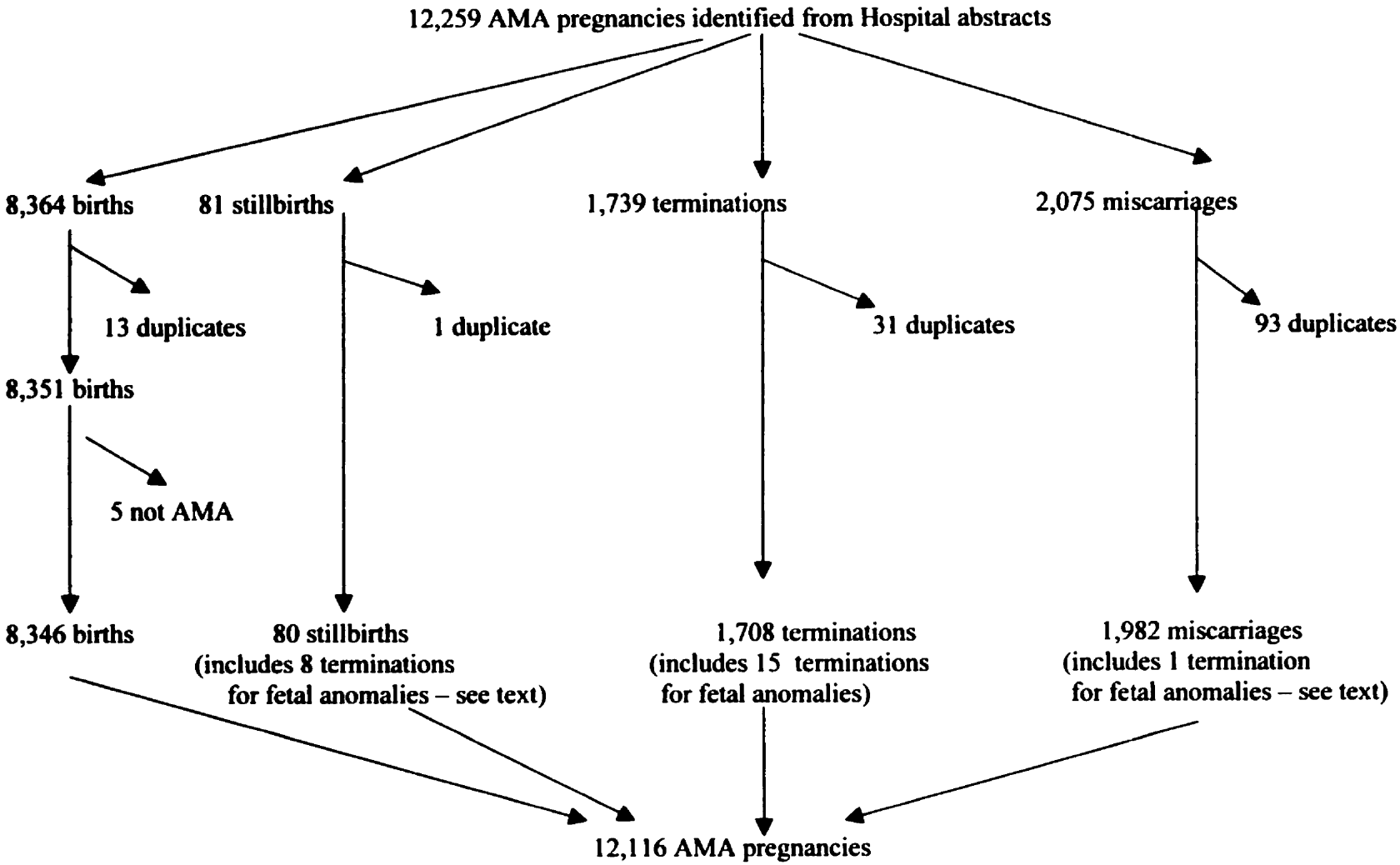

Figure 6. Generation of hospital abstract cohort

3.5.1b *Identification of pregnant women from Physician claims*

Although most pregnant women will have some contact with a hospital during pregnancy (usually for a delivery or, in the case of a miscarriage, for a D&C), some will not. This situation could arise, for example, when a pregnancy is spontaneously lost early in gestation, or if the woman moved out of province early in her pregnancy and no delivery record was returned to Manitoba Health. Acknowledging this, physician claims for 1990-95 were searched for women aged 34 years or older who visited a physician and where the associated diagnosis or tariff code was likely to have been associated with pregnancy (see Appendix 3). A 34 year cut-off was used since, without a way to estimate LMP, it would have been very difficult to determine which of the 34 year old women would have been 35 at term. This generated 311,682 records (note: this figure does not represent either the number of pregnant women or pregnancies, merely records with codes potentially related to pregnancy).

333.5.2 Creation of the Genetic Prenatal database

Appointment and laboratory data representing Manitoban prenatal referrals from January 1, 1990 (when data entry for this database started) to the end of calendar 1995 were obtained from the Section of Genetics and Metabolism. Since it was felt that data entry might have been incomplete during the start-up period, entries in the appointment database were checked against hard copy appointment books. Missing records were added to the database and flagged (n=296, of which only 52 matched our criteria). The search strategy employed is detailed in Appendix 4.

Generally, most prenatal referrals were represented in the database; even those for women who did not go on to have invasive testing. However, data quality for early records was poor. Since this was the case, key fields (see Appendix 4) were checked against the hard copy appointment books and updated when appropriate and possible. These fields included MHSIP registration number, Kindred number, date of birth, name, LMP, EDC, reason for referral, counsel date, and referring doctor[1].

Also represented in the genetic database were AMA women who had had an abnormal result from maternal serum screening and who had gone on to have invasive testing. This represented a distinct subgroup since they had not necessarily requested routine referral for genetic counselling, rather they had come to be counselled because of their screen result. Due to the interdisciplinary nature of the serum screening program and the difficulty in distinguishing the primary indication for genetic testing such women were included in both referral and testing data, while recognising that this would result in a slight overestimation of the number of routine AMA women referred for counselling to the Section of Genetics & Metabolism. An estimate of the number of AMA women having invasive testing due to an abnormal AFP screening result is given in Table 7.

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[1] For approximately the first three years of data, referring doctor was inaccurately coded in the appointment database. This is felt to have represented a discrete event which occurred during the data transfer process when the Section of Genetics and Metabolism moved to a different application for their patient database and does not appear to be an ongoing problem. The physician appears to be correctly listed in the laboratory database, but this information would only be available for those women who went on to have invasive testing.

Table 7. AMA women having invasive testing due to an abnormal serum screen

Year of screening	Number of women having testing
1990	14
1991	17
1992	26
1993	14
1994	17
1995	21
Total	109

(Data from the Manitoba Maternal Serum AFP Programme)

For any woman, the genetic database potentially contained multiple records. These might represent more than one pregnancy or multiple records for a particular pregnancy. Records were condensed to one per pregnancy with only AMA records that fell within the study time frame kept (see Appendix 4). MHSIP registration numbers were checked against the registry and updated where necessary. MHSIP registration number was incorrect in 162 cases (3.9%), the majority of which were due to missing or transposed digits.

Encrypted PHINs were added to the database by linking to the registry. Tied records (4) were examined: in each case, the records were identical except for the spelling of the first name. There were no unlinked records. Those records that matched on fewer than 3 of the 5 linkage keys (n=4), and those that only matched on 3 keys, not including birth year (n=14), were inspected but the links generated appeared to have been genuine. The raw genetics appointment dataset had contained 11,219 records. This dropped to 4,155 when one record per pregnancy was required.

Merging laboratory data to appointment data

Merging the Genetics laboratory data to the appointment dataset proved challenging since it required a "many to many" merge: More than one record was potentially present for any individual in either dataset. Multiple records could represent successive pregnancies or multiple records for a particular pregnancy (where more than one test was performed). Individual pregnancies were defined and the records grouped by pregnancy. However, only one record per pregnancy could be kept, so retaining the appropriate record was crucial to link to the correct pregnancy in the appointment database. Only records pertaining to amniocentesis, CVS or cordocentesis were retained from the laboratory database (n=5,208). Since the laboratory database had multiple, occasionally discrepant, test-related fields i.e. sample type and test type, a new test variable was created for the data analysis (see Appendix 4).

Determining which of the prenatal laboratory records belonged to AMA women proved awkward: it was not possible to extract AMA records using the "indication" or "reason for testing" fields either separately or in combination due to missing data. Both fields were missing in approximately 50% of cases. Similarly, data on LMP was necessary both to ascertain the number of pregnancies represented in the laboratory dataset and whether or not these belonged to AMA women. LMP data was missing in 66.1% (n=3,441/5,208) of laboratory records. It was updated so that only 10.7% (n=555/5,208) of records lacked this information using a combination of AFP file number, gestation and date sample received and manual checking of the original records (see Appendix 4 for

details). Only that record which represented the first invasive genetic test in a pregnancy was retained.

Laboratory records were merged against the Genetics AMA appointment dataset using Kindred number. Those records that matched on Kindred number were kept with the exception of 95 that were removed because they represented pregnancies where the mother was not yet of advanced maternal age, although she would be in a subsequent pregnancy. This reduced the number of records to 2,630 AMA tests/pregnancies. Across the study period, the maximum number of referrals for an AMA pregnancy was four (n=1), with the majority (91.9%) of women referred for only one pregnancy (n= 2,417). Ninety seven percent (n=2,562/2,630) of the records from the laboratory database were linked to an appointment. From these data, it would appear that only 62.0% of the AMA women referred to the Section of Genetics & Metabolism for prenatal counselling went on to have an invasive genetic prenatal test (2,562/4,155). However, it must be remembered that this minimally includes 225 women known to have miscarried post referral, 18 who had social terminations and 10 who had twins or triplets.

Table 8. Summary table for the genetic prenatal cohort

Genetics appointment database	
Initial number of records	11,219
Number of AMA pregnancies after age/LMP exclusions	4,155
Genetics laboratory database	
Initial number of records	14,757
Final number of AMA pregnancies after age/LMP exclusions	2,630
Complete AMA records	
Records with both appointment and laboratory data	2,562
Records with no laboratory data (i.e. did not have invasive testing)	1,593
Unlinked laboratory records	68

3.5.3 Creation of the Maternal Serum AFP Screening cohort

All records for AFP samples received from 1990 to 1995 were downloaded (n=63,684) and the data examined. Not all AFP file numbers were consecutive; however, this did not represent missing data, rather it reflected the manual assignation of AFP file numbers as opposed to an automatic generation of AFP file number when new data was entered. A subset of this database was generated, containing only those records with Manitoba noted as the province of residence in their address, an LMP falling within the appropriate limits and AMA women (n=6,277). Maternal age at term was calculated using date of birth and LMP. Records that did not have a 6 digit numeric MHSIP registration number were not included (n=2,599). Such records appeared to be for out of province women or for those with private health insurance or in military service.

Records were condensed to one record per woman, per pregnancy. Although each pregnancy had a unique AFP file number, more than one record could exist for a given AFP file number since multiple samples could be submitted in a single pregnancy. This might have occurred when the patient changed doctors, with both sending in an AFP sample, or where there was a problem interpreting the initial sample and a repeat blood sample was requested, or the AFP was abnormal and the pregnancy was followed. Records were sorted by AFP file number and sample number and the database was reduced to one record per file number selecting the first interpretable sample drawn after 15 weeks. If all samples received a message 8 "override," i.e. the program was unable to provide an interpretation for the sample and a hand-written response was required (see Figure 5. Potential AFP report messages), then the first sample was retained. In 12

cases, the same pregnancy was recorded under two different file numbers. These records were matched by comparing LMP on requisition, initials, and MHSIP registration number. The more complete record was retained.

Determining if a woman was of advanced maternal age was relatively straightforward since date of birth and LMP are mandatory fields on the AFP requisition. If these data were not initially present when the sample was sent in, the office of the physician who requested the test would have been contacted to determine these values. Furthermore, since the correct interpretation of the AFP blood test is dependent on having an accurate gestational age, the last menstrual period is usually correctly reported. For those women who had unsure dates, and where a clinical assessment was unreliable, a dating ultrasound was usually recommended and the updated information entered. Ten records did not have a recorded date of birth for the mother. Birth dates for nine of these were obtained from the registry database, using MHSIP registration number and first initial.

For purposes of analysis, categorising the AFP result was based on the MOM or the Down syndrome risk values rather than the messages generated by the interpretative program. This was due to the large number of reports that required a hand-written message rather than being automatically interpreted (see "message 8" column in Table 29 and Figure 5), and so the interpretation of the screen was unavailable to us. Consequently, the AFP level was considered "high" if the MOM was ≥ 2.3 and low if the MOM was ≤ 0.4 (see Figure 4). Greater than age-related risk of Down syndrome was

determined using the age-specific risk figures published by Hershey et al. (1986). After May 31, 1991, the risk-figures produced by Cuckle et al. were used (1987).

3.6 Data Linkages

3.6.1. Linking the Birth Events database to hospital discharge abstracts

The purpose of this linkage was to verify the quality of the administrative data retrieved from the hospital files. Although both databases were generated using the same parameters, the hospital abstract database included 3,698 pregnancies that had ended in a termination or a miscarriage and, as such, would not have had a match in the Birth Events database. 8,377 records were linked using REGNO and date of admission for pregnancy endpoint. This represented 99.9% (8,377/8,382) of records in the Birth Events dataset and 99.4% (8,377/8,426) of records from the hospital abstracts database. Five records remained unlinked from Birth Events dataset and 50 from the hospital abstracts dataset. The five unlinked records from the Birth Events dataset were investigated further; four were found not to have belonged to women of advanced maternal age.

3.6.2 Linking the AFP database to the hospital abstract database

Since AMA women having AFP testing are a subset of all pregnant women and AFP testing is done at a stage in pregnancy where pregnancy loss is less common, it was felt that most of the AFP records should link to the hospital abstracts data. The AFP database was linked to the hospital abstracts based on agreement on 5 out of 8 linkage keys: MHSIP registration number, birth year, birth month, first initial, month of LMP, year of LMP, month of EDC and year of EDC). Linkage was not forced on any one variable; however, all records in the linkage ultimately had to link to a correct registration number.

This was not necessarily the identical registration number to that on the hospital abstract record. Previous registration numbers assigned to an individual were checked and if the registration number used on the AFP requisition was an old number, but both numbers corresponded to the same individual, the link was kept.

Additionally, for a record to be considered linked, at least one of EDC year or LMP year was required to match between the AFP and administrative record (to ensure linkage to the correct pregnancy) and, similarly, the date of admission for birth/stillbirth/termination had to be after the date of AFP testing. Non-links and poor-quality links (those that disagreed on MHSIP registration number) were reviewed manually.

In total, 6,176 AFP records were initially linked to the administrative data (Figure 7). One hundred and forty five of these links were discarded: 137 linked records disagreed on MHSIP registration number and when the encrypted PHIN associated with the MHSIP registration number from the AFP database was checked against the hospital abstracts, a matching individual could not be found. A further eight records, which agreed on MHSIP registration number were timed inappropriately i.e. did not match to the correct pregnancy. After these exclusions, 6,031 of the linked pairs were kept. The 246 unlinked records were checked manually: 90 more links were made, 19 unlinked records were found to belong to women who were too young (due to birth date errors in the AFP database), 95 records could be linked to a woman, but not a pregnancy, 42 records could not be linked to any individual covered under Manitoba Health. The 19 non-AMA records were removed from the analysis. Ultimately, 6,121 of the 6,277 AFP records (97.5%) were linked to the hospital abstract file.

Link on 5 of 8 criteria (no link forced on Regno)

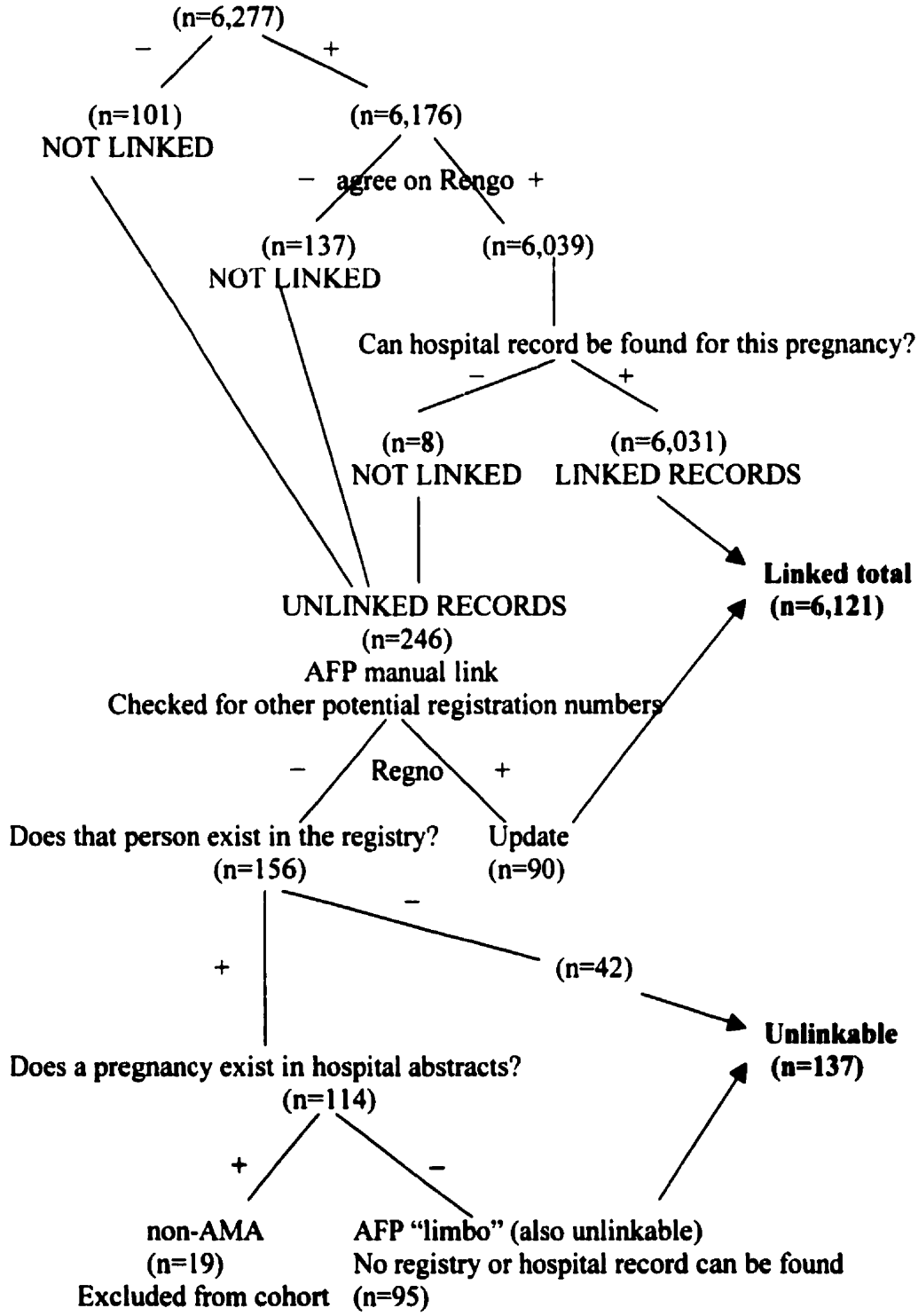


Figure 7. Schematic for linkage of AFP and administrative data

3.6.3 Linking the Genetics data to hospital abstracts

92.7% (n=3,850) of the records from the genetics appointment database (n=4,155) linked to the abstracted hospital abstracts database. Linkage keys used were encrypted PHIN, year of LMP, month of LMP, year of EDC and month of EDC. There were 23 tied records (0.6%) and 305 records from the Genetics database (7.3%) that did not link to the hospital abstracts file. These were searched for in the physician claims database, since they might potentially represent early pregnancy losses that did not generate a hospital record.

3.6.4 Unlinked Genetics/Physician Claims linkage

Linkage of the genetics prenatal database to the hospital discharge abstracts showed that 327 of the women referred to Genetics for counselling did not have a match in the latter database. An inspection of the result field in the genetics prenatal dataset showed that in 49 out of 157 (31% of the 157) cases where this field was not blank the woman had miscarried. We attempted, using encrypted PHIN, to find records in the physician claim dataset that corresponded to the unlinked individuals from the genetic prenatal dataset. Records were found for 142 (43.4%) of these women and an examination of the tariff codes revealed that 66% (n=93) had had a pregnancy test (tariff code: 9521) within 9 months of their calculated LMP. Diagnosis codes for the same period indicated that 30 (21%) of these had a diagnosis of normal pregnancy (V22), and 27 (19%) had a diagnosis indicating a disorder of menstruation (626). A further 12 (8%) individuals had a diagnosis consistent with pregnancy loss. For the 185 women who did not link, we know from the result field in the Genetics prenatal dataset that at least 4 of these miscarried and

one had a pregnancy termination. Of the 327 prenatal records that did not link to a hospital record, only 142 (43.4%) were linked to a medical claim.

3.7 ANALYTIC METHODS

The proposed analysis cohort was comprised of livebirths, stillbirths and genetic terminations, pregnancies where the potential existed for referral for genetic counselling. Please note: the term "genetic termination," though not technically accurate, will be used as a shorthand notation to describe those pregnancies terminated because of fetal anomalies or an abnormal karyotype.

The three main analysis groups were (1) not referred for genetic counselling; (2) referred for counselling and (3) had invasive genetic prenatal testing. Pregnancies that ended in a miscarriage presented a problem. On the whole, the data quality tended to be poorer for this group. It would have been ideal to include pregnancies that ended in a miscarriage in the analysis cohort, since such women might have had the opportunity to be referred for genetic counselling. Gestation at miscarriage could have been used to interpret observed utilization patterns in the light of the opportunity to be referred or have testing; however, gestation at miscarriage is not recorded. Consequently, a decision was made to exclude miscarriages from the analysis group, but to first assess potential consequences of excluding them.

To determine the impact of removing pregnancies that ended in a miscarriage, sensitivity testing was undertaken. Chi-square tests of association were used to compare the

distribution of key variables (age, residence and income quintile) for those pregnancies known to have ended in miscarriage and the proposed analysis cohort (livebirths, stillbirths and genetic terminations) across three analysis groups.

Univariate analyses of demographic and obstetric factors in the analysis cohort and their relationship to referral for genetic counselling and uptake of invasive prenatal genetic testing were examined using a chi-square, ANOVA or t-test as appropriate. Significance for trend was assessed using the Cohran-Armitage Trend test. Additionally, the multivariate relationship between referral for AMA genetic counselling and the obstetric and demographic variables (listed in Table 9) were examined using logistic regression. The latter analysis models the relationship between a binary dependant variable and one or more explanatory variables and permits an evaluation of the individual contribution of each predictor to the outcome response, having adjusted for all other variables in the model. Final models reported were based on stepwise regressions. Operational definitions for the variables are given in Table 10.

Similar analyses were undertaken using the uptake of invasive prenatal diagnosis as the dependant variable. The first modelled predictors of invasive testing for the entire AMA cohort and the second investigated the relationship between referral and invasive testing. All data analysis and statistical testing was performed using SAS Version 6.12 (SAS Institute Inc., 1996).

Table 9. Logistic regression variable definitions

INDIVIDUAL CHARACTERISTICS

Variable name	Description
AGE	Age in years at term
SES2	Income quintile 2 (yes=1)
SES3	Income quintile 3 (yes=1)
SES4	Income quintile 4 (yes=1)
SES5	Income quintile 5 (yes=1) Reference: Income quintile 1
RES	Urban/rural residence (urban=1) Reference: rural
TREATY	Treaty status: First Nations or non-First Nations (First Nations=1). Reference: non-First Nations

OBSTETRIC CHARACTERISTICS

Variable name	Description
POOROB	Poor obstetric history (yes=1) Reference: obstetric history not noted to be "poor"
PHYS2	Early prenatal care (15 weeks of gestation or less) given by general practitioner (yes=1)
PHYS3	No prenatal care in the first 15 weeks of pregnancy (yes=1) Reference: Early prenatal care given by an obstetrician
COMP	Early complications of pregnancy (yes=1) Reference: no early complications noted
AFP	AFP screening (yes=1) Reference: Did not have AFP screening
ABN	Abnormal AFP result (yes=1) Reference: AFP result normal or Down syndrome risk=age risk

Table 10. Operational definitions of independent variables

INDIVIDUAL CHARACTERISTICS

VARIABLE	DESCRIPTION	VALUES	PROPERTIES	DATA SOURCE	INFORMATION USED
AGE	Age in years at term	35 - 48	Discrete, interval	Hospital Claims	Age in years at term. Calculated from gestation at delivery and mother's date of birth (see Appendix 2)
SES	Income quintile	Q1 – Q5	Nominal	Hospital Claims	Income quintile. Q1=poorest; Q5=wealthiest. (For description see Glossary)
RES	Residence	Urban/rural	Dichotomous	Hospital claims	Urban/rural residence. Based on postal code. (See glossary definition of urban/rural residence)
TREATY	Treaty status First Nation Membership	Yes/No	Dichotomous	Hospital claims	Treaty status assigned based on municipal code. (See glossary definition of Treaty First Nations)

OBSTETRIC CHARACTERISTICS

VARIABLE	DESCRIPTION	VALUES	PROPERTIES	DATA SOURCE	INFORMATION USED
POOROB	Poor obstetric history	Yes/No	Dichotomous	Hospital claims	Diagnosis codes indicative of a poor obstetric history (see Appendix 1)
COMP	Early complications of Pregnancy	Yes/No	Dichotomous	Hospital claims	Diagnosis codes indicative of early pregnancy complications (see Appendix 1)
AFP	Did the woman have AFP screening in this pregnancy?	Yes/No	Dichotomous	AFP database	Evidence of an AFP screening test in the current pregnancy
ABN	Down syndrome risk as determined from AFP screen increased over age-related risk	Yes/No	Dichotomous	AFP database	Pregnancies with a risk of Down syndrome greater than the age-related risk
OBGYN	Did the woman see an obstetrician before 16 weeks gestation?	Yes/No	Dichotomous	Medical claims, hospital claims	Searched medical claims for the first 16 weeks post LMP for an obstetric claim (see Appendix 1)
GP	Did the woman see a general practitioner before 16 weeks gestation?	Yes/No	Dichotomous	Medical claims, hospital claims	Searched medical claims for 16 weeks post LMP for a prenatal claim (see Appendix 1)

CHAPTER 4. RESULTS

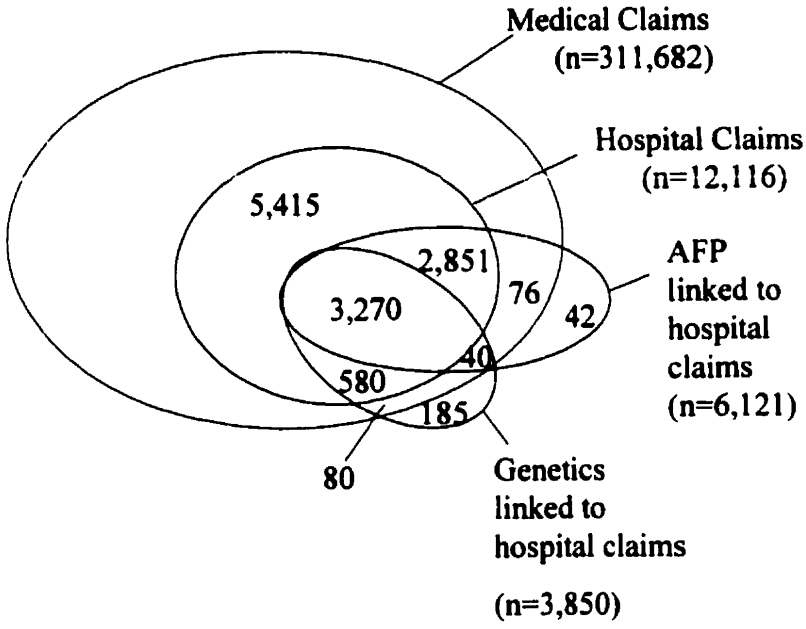
4.1 SUMMARY OF DATABASE LINKAGE

Almost 98% of the AFP screening records and 93% of the genetic records were linked to a hospital record (Table 11). The linked databases describe pregnancy outcomes, AFP screening, referral for genetic counselling and the uptake of invasive genetic testing for a group of 12,116 AMA pregnancies. Overall, 68.9% of the pregnancies ended in a livebirth, 16.4% in a miscarriage and 0.6% in stillbirth. A further 14.1% of pregnancies ended in terminations, of which 1,693 were performed for social reasons and 24 because of a genetic/congenital anomaly in the fetus. A summary of the database linkages is given in Figure 8.

Table 11. Analysis databases

Database	Original record Number	AMA pregnancies in final database	Pregnancies linked to administrative data (% linked)	Excluding miscarriages and social terminations
AFP	63,684	6,277	6,121 (97.5%)	6,025
Genetics Appointment	11,219	4,155	3,850 (92.7%)	3,422
Genetics Laboratory	14,757	2,562	2,562	2,527
Hospital discharge abstracts	12,654	12,116 8,346 livebirths 72 stillbirths 3,698 losses & terminations		8,442
Physician claims	311,682	311,682 claims		

Figure 8. Summary of data linkage



Ns	Interpretation:
76	AMA pregnancies with no hospital record or referral to Genetics, but that did have AFP testing.
40	AMA pregnancies with no hospital record, but that did have AFP testing and a referral to Genetics.
3,270	AMA pregnancies with a hospital record that were referred to Genetics and had AFP testing. Will have had either a live/stillbirth, late loss or termination for fetal anomalies
580	AMA pregnancies with a hospital record that were referred to Genetics, but did not have AFP testing.
2,851	AMA pregnancies with a hospital record that had AFP screening, but which were not referred to Genetics for counselling
80	AMA pregnancies that did not have a hospital record, were referred to Genetics, but did not have AFP screening
185	AMA pregnancies that did not have AFP screening, or a hospital record, but did have a referral to Genetics
42	AMA pregnancies that had AFP screening that did not have a hospital record/medical claim or a referral to Genetics for counselling
5,415	AMA pregnancies which were neither referred for AFP screening nor genetic counselling. Note: the majority of these ended in a miscarriage or a social termination

4.1.1 Unlinked records

Of the 305 records from the Genetic database that remained unlinked, 20% were noted in a comment field in the genetic database to have lost the pregnancy (n=59) to have had a social termination (n=5), or to have moved out of province (n=1). At the time of the study, CVS testing was available, and interest in this test would have resulted in early referrals for counselling. However, not all doctors offices would inform the Prenatal Co-ordinator for the Section of Genetics and Metabolism if the patient miscarried, and such an early loss may not have been captured appropriately in the administrative data. Biologically plausible reasons explaining the unlinked AFP screening records (n=157) are less obvious, particularly since this test is performed later in pregnancy.

4.2 VALIDATION OF HOSPITAL COHORT DATA

4.2.1 Births

The figure determined from our hospital cohort of 8,418 AMA pregnancies resulting in a birth compares favourably with that of 8,867 reported by Statistics Canada (see Table 6) and the 8,382 determined from the Birth Events database maintained by the MCHPE (See Appendix 2). Discrepancies are likely explained by the different time frames that these data represent: the figures reported by Statistics Canada included births in calendar years 1990 to 1995, however, this study included only pregnancies with an LMP between November 25, 1989 and June 5, 1995. Assuming term deliveries, these would end between September 1990 and mid-March 1996.

4.2.2 Terminations of pregnancy

Pregnancy terminations identified (Table 12) from the hospital abstracts cohort compared favourably to those reported by Statistics Canada (Table 13). That our figures were higher, reflected that these data were generated using ICD-9-CM codes in addition to the one for "legally induced abortion" (ICD-9-CM code 635). When this code alone was used (see Table 14), excellent agreement was obtained.

Table 12. Therapeutic abortions# by year and age of mother from hospital claims

	1990	1991	1992	1993	1994	1995	Total
35-39	202	171	165	169	205	198	1,110
40-44	50	49	59	44	53	49	304
45-49	6	2	5	4	1	5	23
>49	1	--	--	--	--	--	1
Total	259	222	229	217	259	252	1,438

Therapeutic abortions identified using ICD-9-CM codes 635, 636, 637 & 779.6 (see Appendix 1 for associated diagnoses)
Note: Some terminations were also performed in 34 year old women (n=213) and 1996 (n=70). These were not included since they do not represent full data for that age group or period.

Table 13. Manitoba therapeutic abortions by year and age of mother reported by Statistics Canada

	1990	1991	1992	1993	1994	1995
< 15 years	NA	6	13	19	24	19
15-19	NA	582	580	636	669	702
20-24	NA	873	937	915	992	1020
25-29	NA	549	536	545	588	519
30-34	NA	315	283	327	336	341
35-39	NA	153	154	148	200	182
40-44	NA	44	56	42	48	45
45-49	NA	2	4	3	1	5
>49	NA	--	--	--	--	--
Total	2,529	2,524	2,564	2,635	2,858	2,833
35+ total	NA	199	214	193	249	232

NA = Not available. Source: "Therapeutic Abortions" Statistics Canada publication 82-219-XMB.

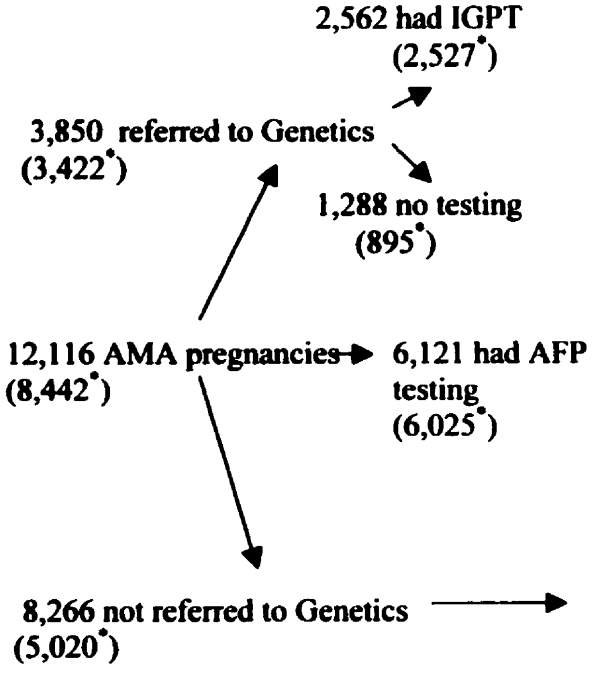
Table 14. Therapeutic abortions in Manitoba by year and age of mother identified in the hospital claims using only the 635 ICD-9-CM code for "legally induced abortion"

	1990	1991	1992	1993	1994	1995	Total
35-39	180	153	155	146	196	183	1,013
40-44	44	44	55	41	49	45	278
45-49	4	2	4	4	1	5	20
>49	--	--	--	--	--	--	0
Total	228	199	214	191	246	233	1,311

Note: Some terminations were also performed in 34 year old women (n=193) and in 1996 (n=67). These were not included since they do no represent full data for that age group or period.

4.3 SUMMARY OF AMA PREGNANCY ENDPOINTS

Figure 9 summarises AFP screening and genetic referral in the cohort, and the pregnancy outcomes in each group. Note that the relative proportions of livebirths, stillbirths, miscarriages, and social terminations reflect the chronology of the processes: miscarriages and social terminations were most common in the group that was not referred for genetic testing or AFP screening. Of the women referred for genetic counselling but who did not have invasive testing, approximately 27% miscarried, reflecting the tendency for referrals to be made relatively early in gestation. Amongst the 2,562 AMA women who had invasive testing, a lower percentage 1.1% (n=28) went on to miscarry and an even smaller number (n=7) had social terminations of pregnancy. Comparing these outcomes to those seen amongst women having AFP screening, the pattern seen is more similar to those of women having invasive testing, with a low miscarriage and social termination rate and a high proportion of livebirths.



Miscarriage	Social Termination	Termination for fetal anomalies	Stillbirth	Livebirth
1.1% (28)	0.3% (7)	0.9% (24)	0.8% (20)	96.9% (2,483)
27.2% (350)	3.3% (43)	--	0.6% (8)	68.9% (887)

Miscarriage	Social Termination	Termination for fetal anomalies	Stillbirth	Livebirth
19.4% (1,603)	19.92 (1,643)	--	0.5% (44)	60.2% (4,976)

Figure 9. Referrals for genetic counselling, uptake of AFP Screening and outcomes of pregnancy for AMA pregnancies
(* Numbers used in group comparisons with social terminations and miscarriages removed)

4.4 MISCARRIAGE SENSITIVITY TESTING

Although pregnancies ending in a social termination or a miscarriage were included in the overall description of the AMA cohort generated, they were excluded from the analyses that described patterns of referral and invasive testing. The rationale for excluding pregnancies that ended in a social termination was that such women were not likely to have been interested in referral for prenatal genetic counselling.

Pregnancies ending in miscarriage presented a dilemma since these represented potentially wanted pregnancies where counselling might have been desired and feasible (to be considered a miscarriage the pregnancy must end spontaneously before 20 weeks). Indeed, women who went on to have a miscarriage accounted for almost 10% (378/3,850, see Figure 9) of referrals for AMA genetic counselling. However, the inclusion of such pregnancies might introduce a significant bias since the data quality was noted to be inferior for this group compared to that of pregnancies that ended in a livebirth. In particular, gestational age was not recorded for pregnancies ending in either a social termination or a miscarriage so it would be difficult to determine if the miscarriage occurred late enough in pregnancy for a referral to have been possible. Recognising that pregnancies that ended in a miscarriage might be distinctly different from those that ended in a livebirth, sensitivity testing was performed to describe differences between these groups.

The proportion of pregnancies referred, having AFP screening or invasive testing by pregnancy outcome is given in Table 15.

Table 15. Proportion referred for counselling, having AFP Screening and/or IGPT by pregnancy outcome
(% = percent of total in group)

	Livebirth	Stillbirth	Social termination	Miscarriage	Genetic termination
Total in group	8,346	72	1,693	1,981	24
Referred	40.4% 3,370	38.9% 28	3.0% 50	19.1% 378	100% 24
Had AFP Screening	71.4% 5,961	56.9% 41	1.0% 17	4.0% 80	91.7% 22
Had IGPT	29.8% 2,483	27.8% 20	0.4% 7	1.4% 28	100% 24

Compared to the analysis group (livebirths, stillbirths and genetic terminations), women who went on to miscarry were less likely to be referred for counselling or to have had AFP screening.

4.4.1 Region of residence

Figure 10 shows the distribution of urban or rural residence for the analysis group (livebirths, stillbirths and genetic terminations), miscarriages and social terminations. It appears that more urban pregnancies end in a social termination (15.5% vs. 9.0% for rural AMA pregnancies, p=0.001, Table 16). The miscarriage rate was comparable between urban (16.6%) and rural (15.4%) AMA pregnancies (p=0.120) but the proportion of continuing pregnancies was lower in the urban group (67.9% vs. 75.7%, p=0.001) reflecting the higher rate of social terminations seen in that group.

Figure 10. Urban/rural residence by pregnancy outcome

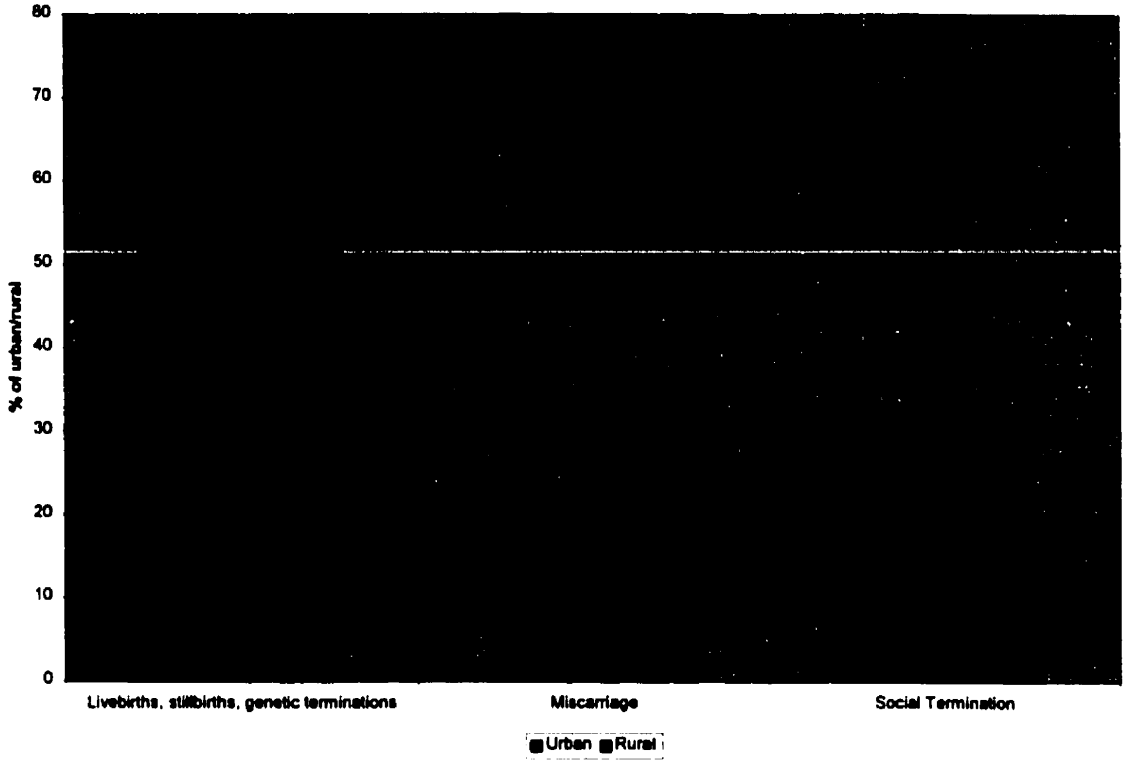


Table 16. Urban/Rural distribution for AMA miscarriages, social terminations and the analysis group
(% = % of column total)

	Analysis group[#]	Miscarriage	Social Termination	Overall
Urban	67.9% (6,329)	16.6% (1,551)	15.5% (1,440)	76.9% (9,320)
Rural	75.7% (1,998)	15.4% (406)	9.0% (237)	21.8% (2,641)
Missing	115	24	16	155
Total	8,442	1,981	1,693	12,116

[#] Livebirths, stillbirths and genetic terminations

Comparing the miscarriage and analysis groups (Table 17) in terms of the proportion of each that was referred, no significant difference was found. However, the distribution of

the "not referred' group did differ (p=0.001), with a larger proportion of urban AMA pregnancies ending in miscarriage.

Table 17. Sensitivity testing for region of residence
(% = % of column total)

Region	Not referred		Referred		Had IGPT	
	Analysis group[#]	Miscarriage	Analysis group[#]	Miscarriage	Analysis group[#]	Miscarriage
Urban	3472 69.2%	1220 76.1%	2857 83.5%	331 87.6%	2100 83.1%	28 100%
Rural	1488 29.6%	364 22.7%	510 14.9%	42 11.1%	377 14.9%	--
Missing	60 1.2%	19 1.2%	55 1.6%	5 1.3%	50 2.0%	--
Total	5,020	1,603	3,422	378	2,527	28
x^2	0.001		0.121		Not available	

[#] Livebirths, stillbirths and genetic terminations

4.4.2 Maternal age

Figure 11 shows the age distributions among continuing pregnancies and those that ended in a miscarriage or a social termination. Miscarriage and analysis groups differed significantly for both "not referred" and "referred" groups (Table 19). In both as maternal age increased, so did the proportion of pregnancies ending in miscarriage.

Figure 11. Age distribution in the analysis group and among women having miscarriages and social terminations

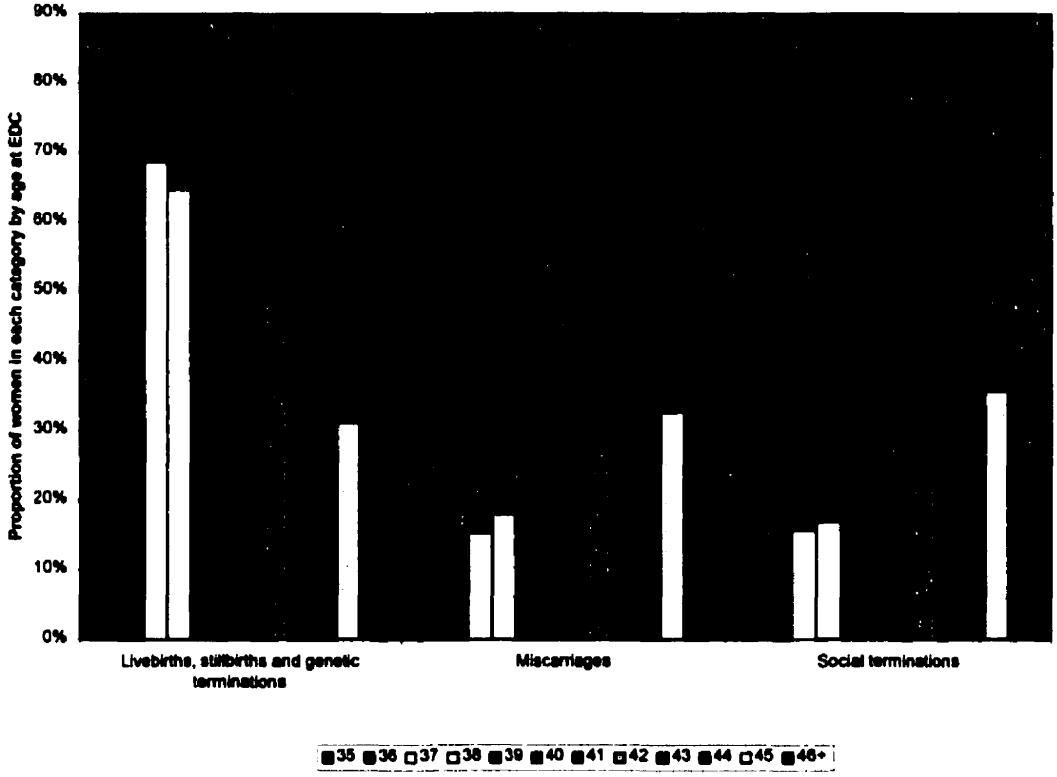


Table 18. Age distribution in the analysis group and among women having miscarriages and social terminations
(% = % of women aged *x* years at term)

Age at EDC	Analysis group#	Miscarriage	Social termination	Total
35	81.3% (3,080)	10.4% (394)	8.3% (313)	3,787
36	74.2% (1,799)	14.2% (343)	11.6% (281)	2,423
37	68.7% (1,215)	15.4% (273)	15.8% (280)	1,768
38	64.8% (867)	18.1% (242)	17.1% (229)	1,338
39	61.2% (608)	21.7% (215)	17.1% (170)	993
40	56.9% (347)	24.6% (150)	18.5% (113)	610
41	49.3% (241)	28.2% (138)	22.5% (110)	489
42	48.9% (138)	28.4% (80)	22.7% (64)	282
43	40.0% (76)	30.5% (58)	29.5% (56)	190
44	34.0% (35)	32.0% (33)	34.0% (35)	103
45	31.3% (21)	32.8% (22)	35.8% (24)	67
46+	22.7% (15)	50.0% (33)	27.3% (18)	66
Total	8,442	1,981	1,693	12,116

Livebirths, stillbirths and genetic terminations

Table 19. Sensitivity testing for maternal age at EDC
(% = % of group total)

Maternal age at EDC	Not referred		Referred		Had IGPT	
	Analysis group#	Miscarriage	Analysis group#	Miscarriage	Analysis group#	Miscarriage
35	42.3% (2,125)	24.3% (389)	27.9% (955)	1.3% (5)	26.0% (658)	3.6% (1)
36	19.5% (979)	17.0% (273)	24.0% (820)	18.5% (70)	24.4% (616)	17.9% (5)
37	13.3% (666)	13.8% (222)	16.0% (549)	13.5% (51)	16.9% (428)	17.9% (5)
38	9.3% (465)	11.4% (183)	11.7% (402)	15.6% (59)	11.8% (298)	7.1% (2)
39	6.1% (308)	9.5% (153)	8.8% (300)	16.4% (62)	9.1% (231)	14.3% (4)
40	3.5% (177)	6.9% (110)	5.0% (170)	10.6% (40)	5.2% (131)	7.1% (2)
41+	5.9% (300)	17.0% (273)	6.5 (226)	24.1% (91)	6.5% (165)	32.1% (9)
Total	5,020	1,603	3,422	378	2,527	28
x^2	0.001		0.001		0.001	

Age categories were pooled to permit testing
Livebirths, stillbirths and genetic termination

4.4.3 Income quintile

Figure 12 shows the distribution of individuals across income quintiles for each of the groups. The analysis and social termination groups displayed opposite trends, with the majority of the analysis group belonging to the wealthiest income quintile (Q5: 25%, Table 20) and the minority to the poorest quintile (Q1, 17%). The converse relationship was seen for social terminations, where the majority of women belonged to the lowest income quintile (24%) and progressively fewer to higher income groups (Q5, 18%). The pattern in the miscarriage group was similar to that of the analysis group.

Figure 12. Income quintile distribution in the analysis group, miscarriages and social terminations

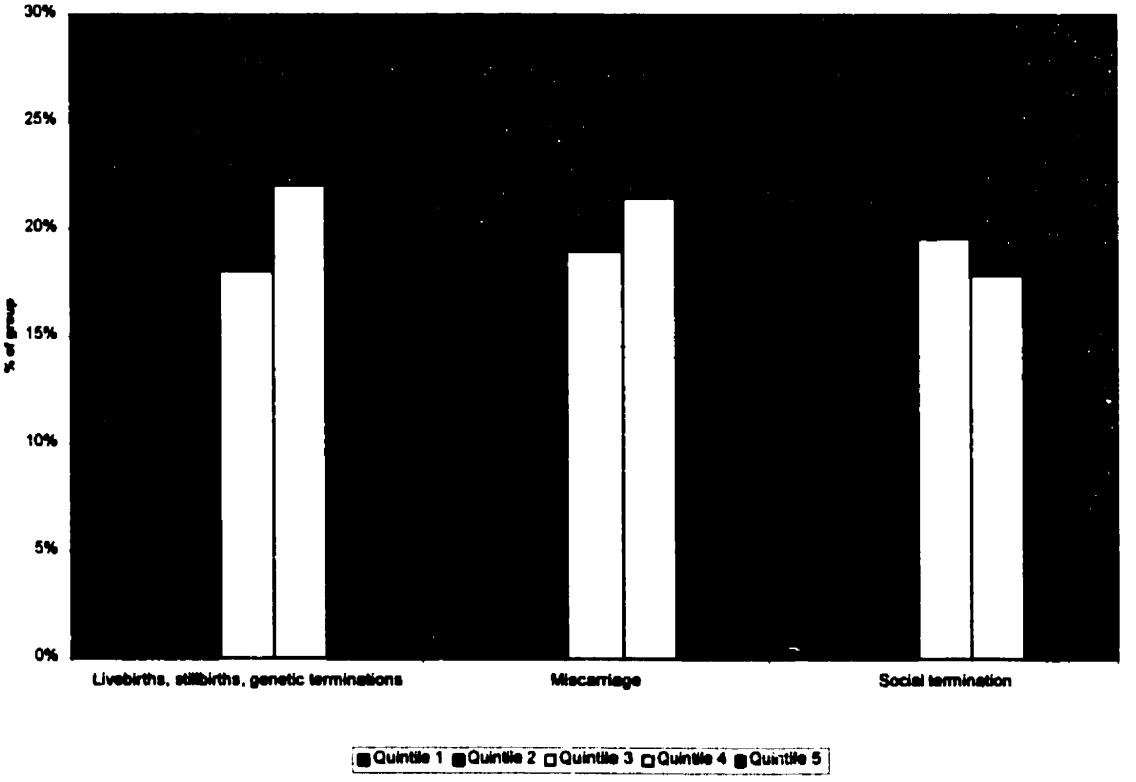


Table 20. Income quintile distribution in the analysis group and among miscarriages and social terminations
(% =% of group total)

Income quintile	Analysis group*	Miscarriage	Social termination	Total
1	17.1% (1,444)	18.6% (368)	24.1% (408)	2,220
2	16.2% (1,364)	15.6% (310)	19.8% (336)	2,010
3	18.1% (1,529)	19.0% (376)	19.6% (332)	2,237
4	22.1% (1,864)	21.5% (426)	17.9% (303)	2,593
5	25.2% (2,126)	24.1% (477)	17.6% (298)	2,901
Missing	1.4% (115)	1.2% (24)	0.9% (16)	155
Total	8,442	1,981	1,693	12,116

No significant difference was seen in the distribution across income quintiles between the analysis group and the miscarriage group for either the "referred" or "not referred" groups (Table 21).

Table 21. Sensitivity testing for socio-economic status
(%=% of column total)

	Not referred		Referred		Had IGPT	
Income quintile	Analysis group*	Miscarriage	Analysis group*	Miscarriage	Analysis group*	Miscarriage
Q1	19.3% (970)	19.3% (310)	13.9% (474)	15.3% (58)	11.7% (295)	21.4% (6)
Q2	17.7% (888)	16.0% (256)	13.9% (476)	14.3% (54)	13.7% (345)	17.9% (5)
Q3	19.1% (961)	19.5% (313)	16.6% (568)	16.7% (63)	15.9% (401)	17.9% (5)
Q4	21.1% (1,059)	21.7% (348)	23.5% (805)	20.6% (78)	24.2% (611)	14.3% (4)
Q5	21.6% (1,082)	22.3% (357)	30.5% (1,044)	31.7% (120)	32.6% (825)	28.6% (8)
Missing	1.2% (60)	1.2% (19)	1.6% (55)	1.3% (5)	2.0% (50)	--
Total	5,020	1,603	3,422	378	2,527	28
x^2	0.750		0.829		Not available	

* Livebirths, stillbirths and genetic terminations

4.4.4. Sensitivity testing summary

The group of women who miscarried were comparable to the study group with respect to income quintile (Table 21) and urban/rural miscarriage rates (urban: 16.6%, rural: 15.4%, p=0.12). The age distributions demonstrated that women who miscarried tended to be older than AMA women who carried the pregnancy to term. Finally, not surprisingly, women who miscarried were less likely to be referred for Genetic counselling or to have had invasive prenatal testing than were AMA women with continuing pregnancies.

By excluding AMA pregnancies that went on to miscarry, we were unlikely to be introducing significant bias with respect to any conclusions made regarding income or region of residence. Since the miscarriage rate increased with increasing maternal age (11.3% at 35 years at term; 30.2% at 40 years at term, see data in Table 19), excluding pregnancies that ended in a miscarriage would potentially reduce the magnitude of any age-related effects seen in the older age groups.

4.5 DESCRIBING PREGNANCIES REFERRED FOR GENETIC COUNSELING

Table 22 describes the distribution of first invasive prenatal genetic test over the study period as compiled by the Section of Genetics and Metabolism. This data includes both non-AMA and non-Manitoban individuals.

Table 22. Distribution of invasive prenatal genetic tests (AMA and non-AMA, Manitoban and "other") by first IGPT per person.
(% = % of total tests for the year)

	Amniocentesis patients	CVS Patients	Cordocentesis Patients	Total
1990	84.9% (639)	13.4% (101)	1.7% (13)	753
1991	79.8% (621)	17.2% (134)	3.0% (23)	778
1992	82.6% (735)	13.4% (119)	4.0% (36)	890
1993	84.9% (648)	10.9% (83)	4.2% (32)	763
1994	89.1% (724)	6.8% (55)	4.2% (34)	813
1995	93.1% (864)	2.9% (27)	4.0% (37)	928
Total	4,231	519	175	4,925

Table 23 presents the data from the genetic cohort assembled for this study. The lower numbers reflect the exclusion of non-AMA and non-Manitoban women and pregnancies that ended in a miscarriage (43) or social termination (7). Due to constraints of cohort eligibility, neither 1990 nor 1995 represent complete calendar years.

Table 23. Distribution of first invasive prenatal genetic test for AMA
(Year = year sample received, % = % of year total)

	Amniocentesis Patients	CVS Patients	Cordocentesis patients	Total
1990*	83.7% (293)	16.3% (57)	--	350
1991	78.3% (360)	21.3% (98)	0.4% (2)	460
1992	78.7% (384)	21.1% (103)	0.2% (1)	488
1993	80.0% (347)	19.8% (86)	0.2% (1)	434
1994	73.5% (350)	26.3% (125)	0.2% (1)	476
1995*	79.7% (282)	19.8% (70)	0.6% (2)	354
Total	2,016	539	7	2,562

* Note: Data for 1990 & 1995 do not represent complete years due to study cut-offs

When the proportionate difference between the annual totals for Table 22 and Table 23 are compared across those years with full data (1991-1994), they are consistent across the two groups (p=0.789).

Referrals of AMA women to the Section of Genetics and Metabolism for counselling in each of the study years are given in Table 24. Sixteen records had neither a counselling date nor an LMP and were excluded. None of these women went on to have IGPT. Since this table presents the proportion of referrals that had invasive testing and the type of testing that they had, the number of procedures reflects the year of the referral and not necessarily the year of testing.

Using year of LMP to estimate year of referral in the non-referred population, the proportion of referred AMA pregnancies ranged between 24-36% (Table 24). When miscarriages and social terminations were removed from the denominator, this rose to 35-55% of continuing AMA pregnancies. The proportion of women having IGPT remained relatively constant over the study period, ranging from 72-79%. The number of miscarriages among referred women perhaps reflected the need to refer early for pre-CVS counselling and the higher loss rate experienced at earlier gestations.

Table 24. Number of AMA pregnancies referred for genetic counselling and the proportion having IGPT
(Year = year of referral. If not referred, year = year of LMP)

	1990	1991	1992	1993	1994	1995*	Missing year	Total
Proportion AMA pregnancies referred (including miscarriages and social terminations)	24.1% (493/2042)	33.4% (661/1977)	36.2% (749/2070)	31.0% (652/2100)	32.6% (743/2276)	31.5%* (506/1605)	46	3,850
Proportion of AMA pregnancies referred (excluding miscarriages and social terminations)	32.2% (450/1398)	41.7% (595/1427)	43.6% (668/1531)	38.0% (581/1527)	40.8% (664/1627)	48.9%* (448/916)	16	3,422
Number of counselling referrals (Excluding miscarriages and social terminations)	450	595	668	581	664	448*	16	3,406
Referrals that miscarried or had a social termination	43	66	81	71	79	58*	30	428
Proportion having IGPT (n) (Excludes miscarriages and social terminations)	79.6% (358)	75.3% (448)	72.3% (483)	73.0% (424)	72.7% (483)	73.9%* (331)	--	2,527
CVS	59	93	101	87	121	62*	--	523
Amniocentesis	299	353	381	336	361	267*	--	1,997
Cordocentesis	--	2	1	1	1	2*	--	7
	358	448	483	424	483	331	--	2,527

Note: only includes the first test performed in a pregnancy
Note: includes all referrals irrespective of pregnancy outcome
* Not a complete year of data

4.5.1 Urban/rural residence and referral

Across the study period, approximately 75% of referrals were urban AMA women and 25% rural residents (Table 25). Neither urban or rural referral rates for AMA genetic counselling increased significantly over 1990-1994, the period for which we have complete years of data (p=0.229 urban; p=0.387 rural, Figure 13). The proportion of urban and rural AMA women referred also remained constant over the study period with approximately 45% of eligible women referred in urban areas and 25% of their rural counterparts being referred.

Figure 13. AMA referrals by year and residence

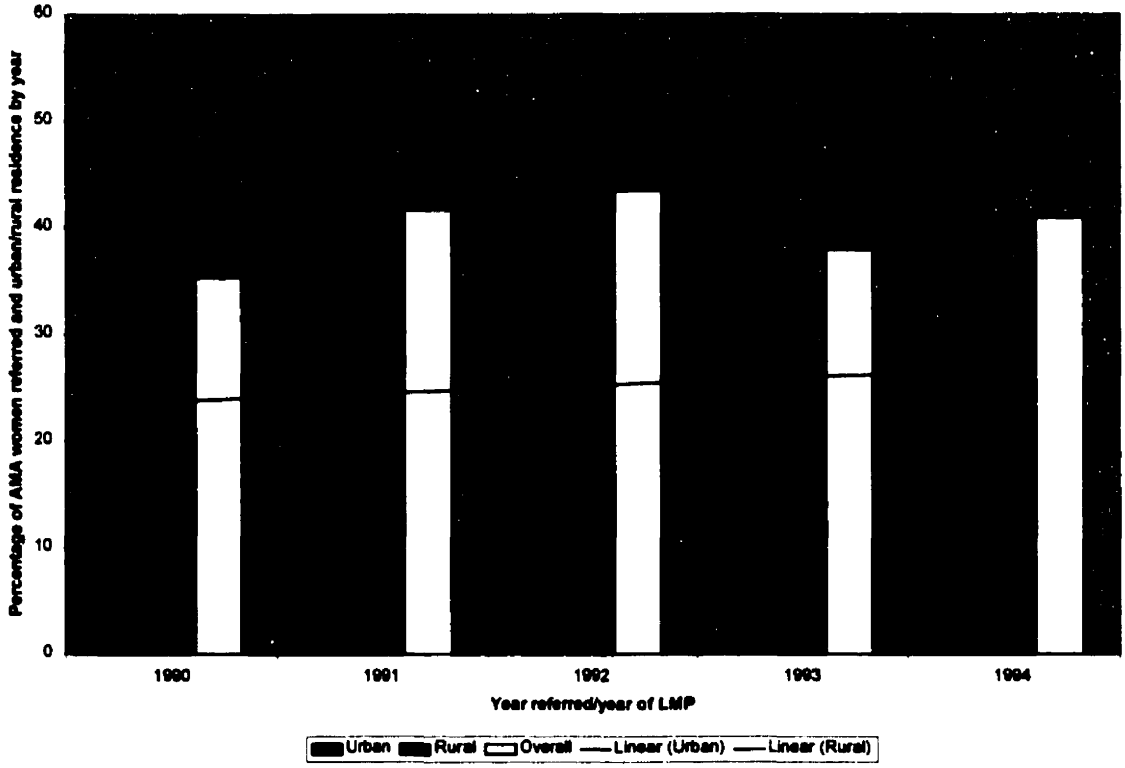


Table 25. Referral over time by urban/rural residence

Year	AMA referrals			Total referrals	Urban/rural distribution of pregnancies (% = % of year total)	
	Urban	Rural	Region missing		Urban	Rural
1990	40.0% (380/949)	21.2% (66/312)	4	450	75.6% (949)	24.4% (312)
1991	46.7%% (505/1,082)	25.8% (87/337)	3	595	72.7% (1,082)	27.3% (337)
1992	47.7% (550/1,153)	30.4% (112/369)	6	668	75.8% (1,153)	24.2% (369)
1993	43.1% (485/1,124)	22.6% (86/381)	10	581	74.7% (1,124)	25.3% (381)
1994	45.2% (553/1,223)	26.4% (96/363)	15	664	77.1% (1,223)	22.9% (363)
1995*	54.0% (369/683)	29.8% (62/208)	17	448	76.6% (683)	23.3% (208)
Total	2842	509	55	3,406	6,214	1,970
Year missing	16			16	131	

* 1995 referrals do not represent a full year of data

Note: does not include pregnancies ending in a miscarriage or social termination

4.5.2 Income quintile and referral

When referral was examined by income quintile as well as urban/rural residence (Figure 14), the trend across quintiles was significant for both urban and rural groups and across all years (p=0.001), with increasing referrals as income increased. This was seen less convincingly in the rural group, where referral rates were relatively static at approximately 20% (Table 26), except for the highest income group (Q5), where approximately 40% of women were referred. Even so, the referral rate in the wealthiest rural income quintile is comparable to those seen in urban quintiles 2 or 3. These findings were supported by the Q1/Q5 ratios which were 0.73 for the urban group and 0.47 in the rural group (Table 26). The Q1/Q5 ratio quantifies the proportional difference

between the highest and lowest income quintiles. Values close to "1" indicate that the proportions in both quintiles are comparable. As the proportion in Q5 increases relative to Q1, the ratio approaches zero. Despite the more obviously linear rise in referral rates with increasing income for urban AMA pregnancies, the difference in referral rates between women in the wealthiest and poorest income groups was smaller than that observed for rural AMA women (13.9% urban vs. 21.6% rural).

Figure 14. AMA referrals by income quintile and residence

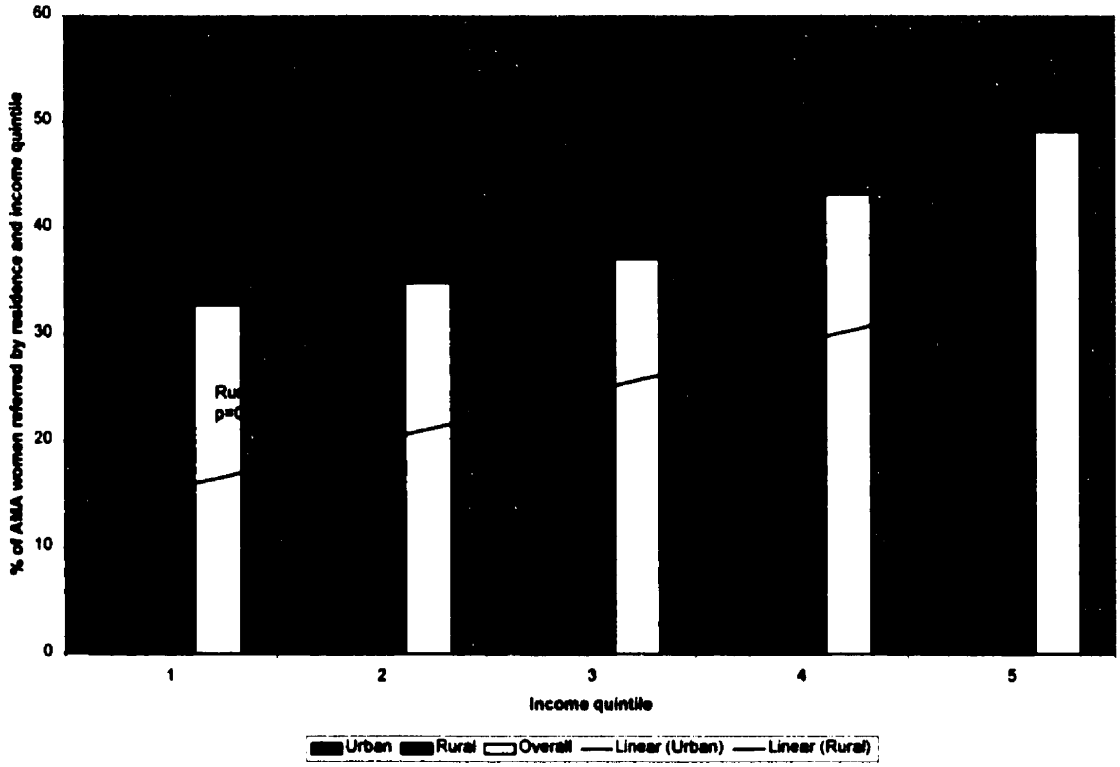


Table 26. Proportion of AMA women referred by income quintile and residence (% = # referred in quintile *x*/total pregnancies in quintile *x* x 100)

Income quintile	AMA referrals		
	Urban	Rural	Overall
1	37.6% (402/1,069)	19.2% (72/375)	32.8% (474/1,444)
2	39.2% (404/1,031)	21.6% (72/333)	34.9% (476/1,364)
3	44.1% (498/1,130)	17.5% (70/399)	38.3% (586/1,529)
4	48.5% (704/1,451)	24.5% (101/413)	43.2% (805/1,864)
5	51.5% (849/1,648)	40.8% (195/478)	49.1% (1,044/2,126)
Q1/Q5 ratio*	0.73	0.47	
Missing	55		115
Total	2,857	510	3,422

* The percentage of referred AMA women in Q1 divided by that in Q5

4.6 AFP SCREENING IN THE AMA COHORT

Figure 15 and Figure 16 describe AFP screening in the AMA population and across the individual analysis groups. Overall, 50.5% (6121/12,116) of AMA women had AFP screening. Of these, 80 (1.3%) miscarried and 16 (0.3%) had social terminations (Figure 9). These individuals are not included in Figure 16 or subsequent tables. The 6,025 women that had AFP screening represented 8,394 discrete samples (Table 27), with the majority of women (72%) having only one sample submitted in a pregnancy. It is recommended that AFP screening samples are obtained between 15-18 weeks of gestation. In our population, 84.9% of AMA pregnancies had at least one sample submitted during those gestations (Table 28). Where multiple samples were submitted over the course of a single pregnancy the one drawn closest to 15-18 weeks was kept, thus the figure of 85% would not necessarily be representative of the distribution of gestational ages for the first AFP sample received in a pregnancy.

8,442 AMA pregnancies

↓

6,025 had AFP testing

↓

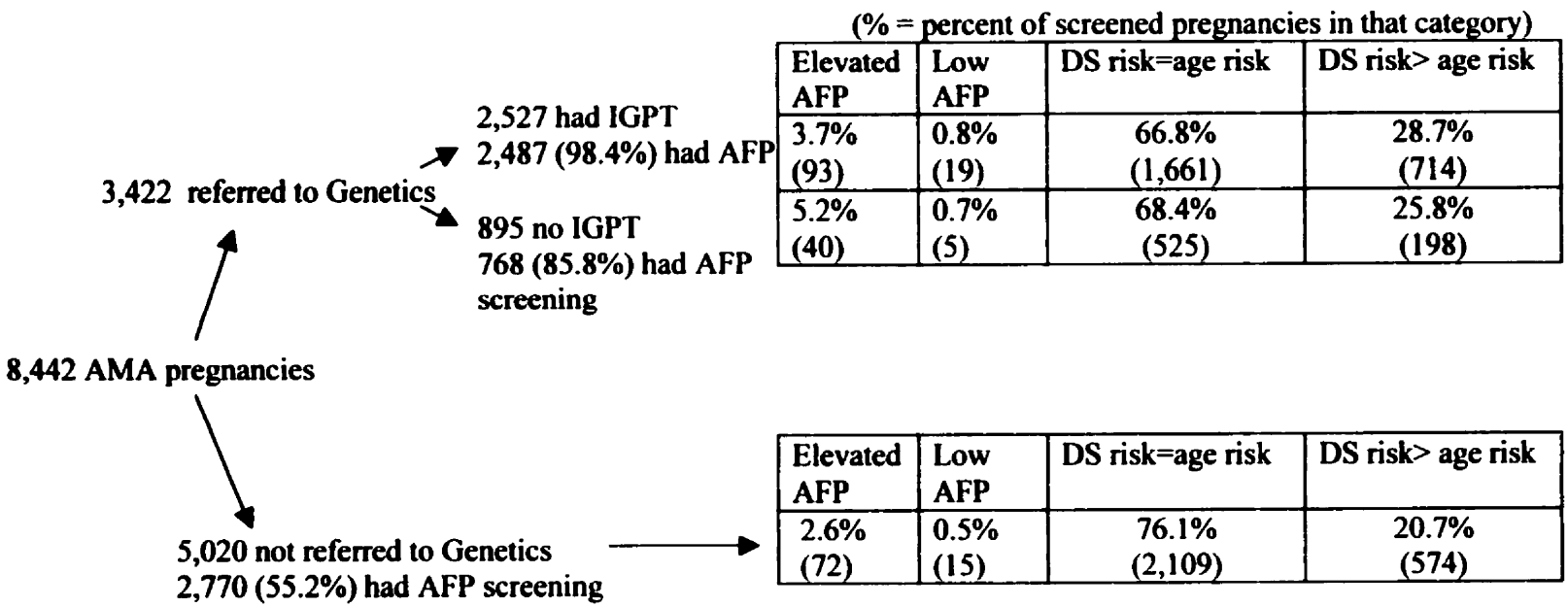
Screening results

Elevated AFP	Low AFP	DS risk=age risk	DS risk> age risk	Not screened
3.4% (205)	0.6% (39)	71.3% (4,295)	24.7% (1,486)	2,417

Outcomes of pregnancy

Miscarriage	Social Termiation	Termination for fetal anomalies	Stillbirth	Livebirth
1.3% (80)	0.3% (16)	0.4% (23)	0.7% (41)	97.4% (5,961)

Figure 15. Results of AFP Screening and pregnancy outcomes for the AMA women who had AFP Screening



Elevated AFP	Low AFP	DS risk=age risk	DS risk> age risk
3.7% (93)	0.8% (19)	66.8% (1,661)	28.7% (714)
5.2% (40)	0.7% (5)	68.4% (525)	25.8% (198)

Elevated AFP	Low AFP	DS risk=age risk	DS risk> age risk
2.6% (72)	0.5% (15)	76.1% (2,109)	20.7% (574)

Figure 16. Results of AMA AFP Screening by analysis group (excluding miscarriages and social terminations)

Table 27. Distribution of samples per AFP file number linked to hospital data (excluding miscarriages and social terminations)

Number of samples received	% (n)
1	71.9% (4,329)
2	23.0% (1,387)
3	2.6% (155)
4	0.7% (44)
5	0.8% (48)
>5	1.0% (62)
Total	6,025 women, 8,394 AFP samples

Table 28. Distribution of gestational ages on AMA AFP samples

Gestation (weeks)	Number	%
< 12	15	0.2%
12-14.9	89	1.5%
15-15.9	1,735	28.8%
16-16.9	1,806	30.0%
17-17.9	1,007	16.7%
18-18.9	561	9.3%
19-19.9	273	4.5%
20-24	293	4.9%
25+	21	0.3%
Not determined	225	3.7%
Total	6,025	100.0

Note: The sample retained was not necessarily the first sample (see Section 3.3.2), rather the first sample that could be interpreted. If all samples required a hand written message ("message 8"), the first sample submitted was kept.

Table 29 describes the distribution of AFP report messages by year. Note the large proportion of samples (23.7%), where a manual interpretation was required ("message 8").

Table 29. Proportion of abnormal AFPs by report message and year
(Year = year sample drawn; % = % of year total)

	1990	1991	1992	1993	1994	1995	Total
AFP drawn too early or too late	2.2% (16)	2.0% (20)	1.2% (13)	1.6% (18)	1.7% (20)	1.8% (17)	104
Normal*	44.9% (332)	52.3% (515)	51.9% (578)	55.1% (623)	49.6% (592)	67.7% (651)	3,291
Low**	--	--	0% (1)	--	--	0.1% (1)	2
High***	1.6% (12)	3.7% (36)	2.8% (31)	2.7% (30)	1.8% (22)	2.8% (27)	158
↑ Down syndrome risk# (over age-related risk)	18.4% (136)	14.2% (140)	14.6% (163)	10.6% (120)	11.6% (138)	13.6% (131)	828
Message 8	31.5% (233)	25.5% (252)	28.2% (314)	28.1% (318)	33.6% (401)	12.9% (124)	1,642
Total	739	985	1113	1131	1193	961	6025

Increased Down syndrome risk: AFP program messages 6,15
* Normal AFP: AFP program messages 5 & 17
** Low AFPs: AFP program messages 1,2,3 & 4
*** Elevated AFPs: AFP program messages 7,16
Note: 1990 and 1995 do not represent a complete year of data

To avoid eliminating those records where a manual interpretation had been performed and no internal record of the status of the screen was available, categories of response were determined based on the available AFP multiples of the mean (MOM) and Down syndrome risk grouped, according to the AFP protocol, into high, low and increased Down syndrome (above age-related) risk (Table 30).

Table 30. Proportion of normal, low and elevated AFPs by year in the linked sample using MOM and Down syndrome risk.
(year = year sample drawn; % = % of year total)

	1990*	1991	1992	1993	1994	1995*	Total
AFP level:							
Normal	56.2% (410)	63.0% (607)	70.6% (777)	75.0% (832)	74.8% (877)	72.5% (689)	69.6% (4,192)
Low (≤ 0.4 MOM)	1.4% (10)	0.8% (8)	0.8% (9)	0.4% (4)	0.4% (5)	0.3% (3)	0.6% (39)
High (≥2.3 MOM	2.9% (21)	4.3% (41)	3.7% (41)	3.7% (41)	2.6% (30)	3.2% (31)	3.4% (205)
Down syndrome risk:							
> age related risk	37.3% (272)	29.9% (288)	23.6% (260)	19.3% (214)	20.6% (241)	22.2% (211)	24.7% (1,486)
Sample drawn too early/late to interpret	2.2% (16)	2.0% (19)	1.1% (13)	1.6% (18)	1.7% (20)	1.8% (17)	1.7% (103)
Year total	729	963	1100	1109	1173	951	6,025

*Does not represent a full year of screening

Overall, only 1.7% (103/6,025) of samples were drawn too early or too late for interpretation. A "normal" screening result was obtained in 69.6% (4,192/6,025) of pregnancies i.e. the calculated risk of Down syndrome was appropriate for the woman's age and the AFP value was within the normal range. Elevated AFP levels were found in 3.4% of pregnancies, and low AFP levels in 0.6%. The number of women who had a risk of Down syndrome that was greater than their age-related risk varied over the study period from 19-30% (based on completed years, see Table 30), but over the entire study period, approximately 25% of the screened cohort had a Down syndrome risk that was greater than their age risk.

Differential rates of AFP screening were seen depending on whether a woman was referred for genetic counselling or not and also on whether she had invasive genetic testing. Fifty five percent (2,770/5,020) of AMA women who were not referred for

genetic counselling had AFP screening. This compared to 95% (3,255/3,422) of referred women and 98.4% (2,487/2,527) of women who had invasive testing (Table 31).

Table 31. AFP screening in the analysis groups
(% = % of screened total for column)

	Not referred	Referred	Had IGPT	Total
Normal AFP	74.0% (2,050)	65.8% (2,142)	65.7% (1,635)	69.6% (4,192)
Elevated AFP	2.6% (72)	4.1% (133)	3.7% (93)	3.4% (205)
Low AFP	0.5% (15)	0.7% (24)	0.8% (19)	0.6% (39)
DS risk >age risk	20.7% (574)	28.0% (912)	28.7% (714)	24.6% (1,486)
Too early/late	2.1% (59)	1.4% (44)	1.0% (26)	1.7% (103)
Screened total:	2,770	3,255	2,487	6,025
Not screened	45.0% (2,250)	4.9% (167)	1.6% (40)	28.6% (2,417)
Group total:	5,020	3,422	2,527	8,442
X^2	Referred: not referred: p=0.001 Referred (no IGPT):had IGPT p=0.001			

Sixty-one percent (912/1486) of women with a Down syndrome risk greater than their age-related risk were referred for genetic counselling and 78.3% (714/912) had invasive genetic testing. There were more normal AFP screens (i.e. an age-appropriate Down syndrome risk) in the "not referred" group than in the referred group (74.0% vs. 65.8%; p=0.001) and, where the screen indicated an abnormal result, these women were more likely to be referred for counselling regarding IGPT (p=0.001).

Figure 17 shows the age distribution for AMA AFP samples by year.

Figure 17. Age distribution for AMA AFP samples

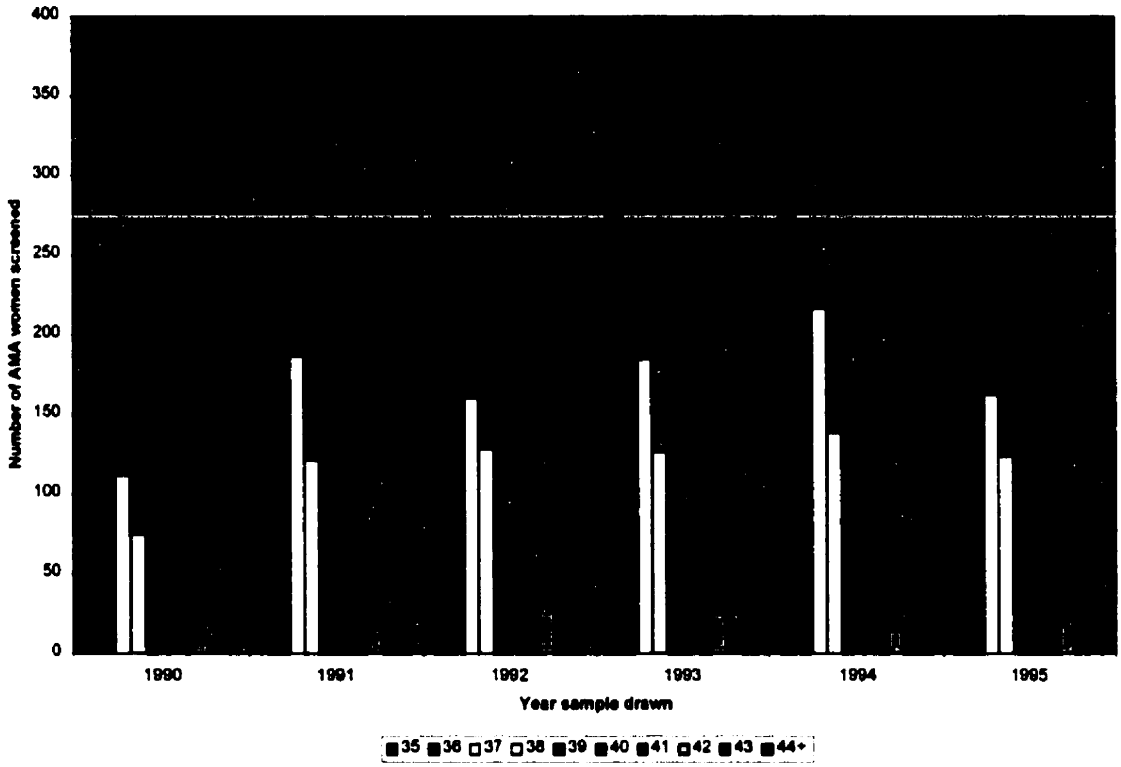


Table 32. Age at EDC on AMA AFP records
(Year = year sample drawn)

Age at EDC	1990	1991	1992	1993	1994	1995	Total	Proportion of age group screened
35	228	255	335	313	306	259	1,696	55.1%
36	167	206	230	268	270	192	1,333	74.1%
37	112	187	161	185	217	163	1,025	84.4%
38	75	122	129	127	139	124	716	82.6%
39	53	70	92	80	101	100	496	81.6%
40	45	51	61	55	71	47	330	95.1%
41	20	37	42	30	37	19	185	76.8%
42	7	16	30	25	15	22	115	83.3%
43	9	10	14	14	10	11	68	89.5%
44+	13	9	6	12	7	14	61	85.9%
Total:	729	963	1100	1109	1173	951	6,025	

Figure 18 shows the proportion of AMA women having AFP screening by income quintile and residence. Significant differences (Cochran-Armitage trend test. Urban: p=0.001; Rural: p=0.001) were seen between quintiles, with women in higher income groups being more likely to have AFP screening irrespective of urban or rural residence. Women living in urban areas had AFP screening more often than did rural AMA women (p=0.001) and the proportion of women screened across quintiles was greater for urban AMA women than for rural AMA women (Q1: 69.1% vs. 39.7% Q5: 83.6% vs. 72.4%; p=0.001) (Table 33).

Figure 18. AMA AFP Screening by income quintile and residence

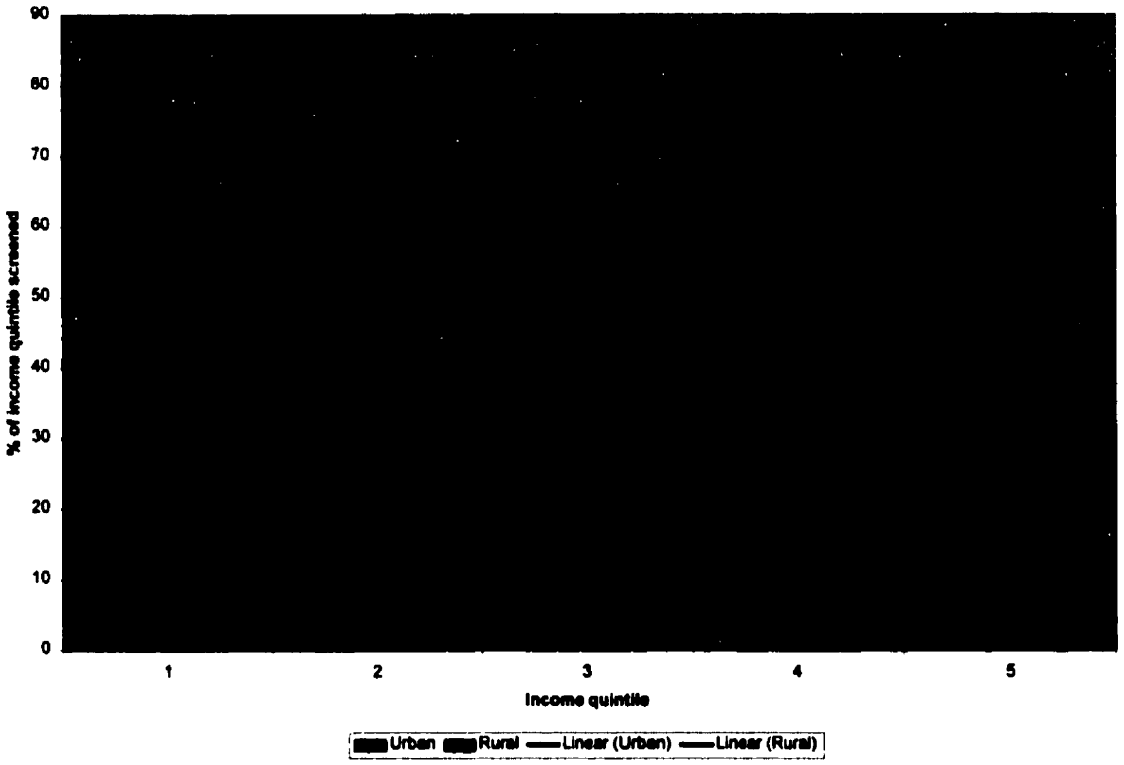


Table 33. AMA AFP screening by income quintile and urban/rural residence (% = % of income quintile having AFP screening)

Income quintile	AFP screening		
	Urban	Rural	Overall
Q1	69.13% (739/1069)	39.73% (149/375)	61.5% (888)
Q2	68.96% (711/1031)	46.25% (154/333)	63.4% (865)
Q3	76.99% (870/1130)	45.36% (181/399)	68.7% (1,051)
Q4	81.81% (1187/1451)	53.51% (221/413)	75.5% (1,408)
Q5	83.56% (1377/1648)	72.38% (346/478)	81.0% (1,723)
Q1/Q5	0.83	0.54	0.71
Total	4884	1051	5935
Missing	90		
Total	6,025		

Figure 19 shows the proportion of AMA women having AFP screening by year and residence. Overall, a higher proportion of urban pregnancies were screened, a trend which continued over time (Cochran-Armitage trend test p=0.035). However, larger gains in screening coverage were seen in rural areas (p=0.011).

Figure 19. AMA AFP Screening by year and residence

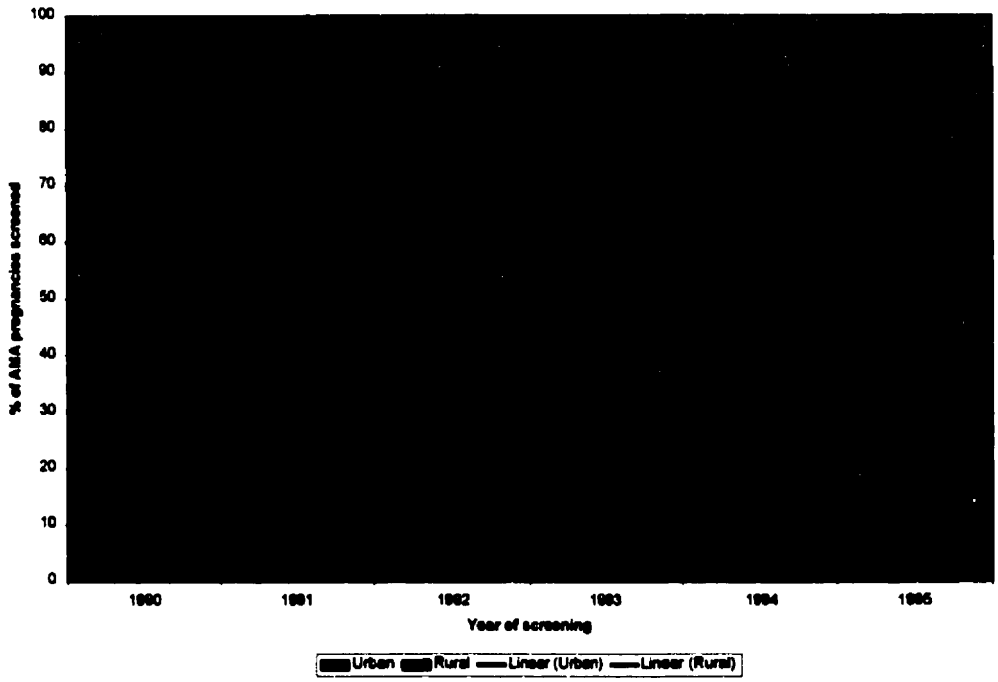


Table 34. AMA AFP screening over time by urban/rural residence
(% = % of urban/rural AMA women having AFP screening)
Year = year sample obtained

Year	AFP screening		
	Urban	Rural	Overall
1990*	71.68% (605/844)	41.46% (119/287)	64.0% (724)
1991	76.34% (797/1044)	49.24% (163/331)	69.8% (960)
1992	80.18% (898/1120)	54.32% (195/359)	73.9% (1,093)
1993	81.52% (909/1115)	50.96% (186/365)	74.0% (1,095)
1994	79.86% (924/1157)	60.50% (219/362)	75.2% (1,143)
1995*	87.33% (751/860)	66.27% (169/255)	82.5% (920)
Total	4,884	1,051	
Missing	90		
Total	6,025		

* Not a full year of AFP screening

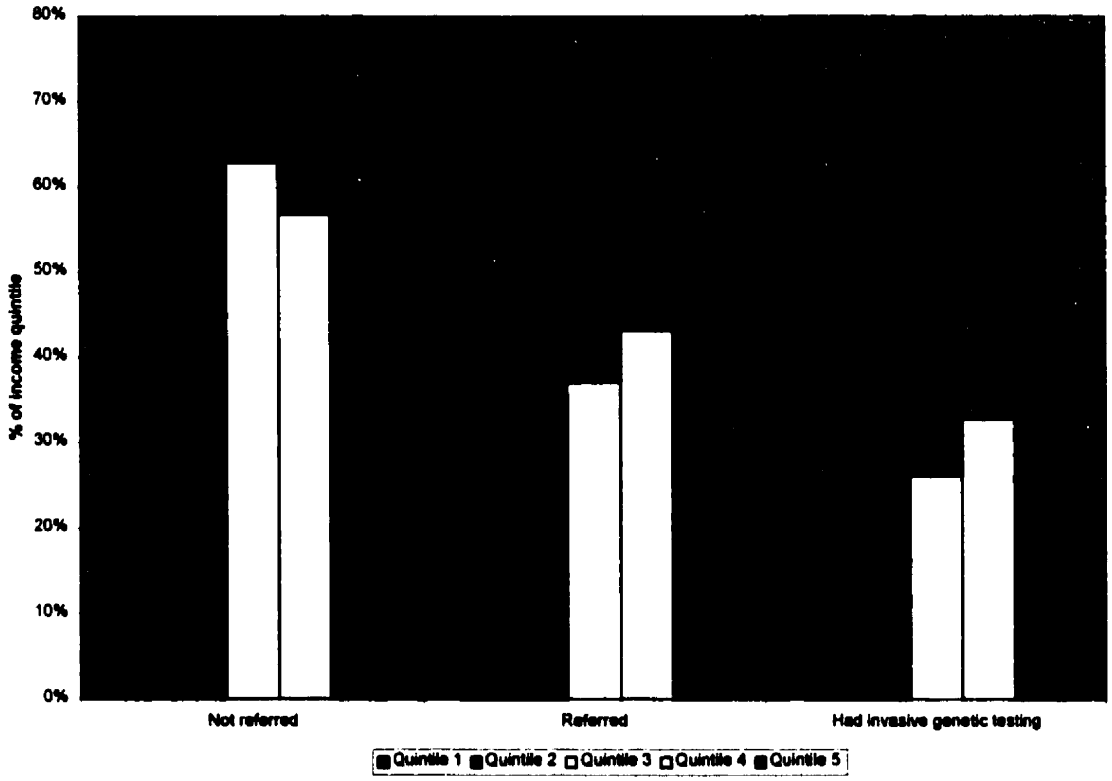
4.7 DESCRIBING THE GROUPS

Pregnancies ending in social terminations and miscarriages were excluded and removed from the following analyses. The remaining pregnancies were subdivided into groups for analysis as follows: (1) AMA women not referred for genetic counselling and (2) those that were referred. For analyses where the outcome of interest was uptake of prenatal diagnosis the latter group was further partitioned into (3) pregnancies which had invasive testing and (4) those that did not. Not all women in the referred group necessarily had counselling: referral denoted that a request for prenatal counselling had been received (see Glossary). This was consistent with the intent of the study that was to look at access to, and not receipt of, genetic counselling for advanced maternal age. These four groups were compared with regard to demographic and obstetric characteristics.

4.7.1 Income quintile

As Figure 20 demonstrates, women in the higher income quintiles were more likely than those in the lower income quintiles to be referred for AMA counselling or to have invasive testing (Q1 represents the poorest group and Q5 the wealthiest). Interestingly, not only was a larger proportion of women from higher income quintiles referred, but they were also correspondingly more likely to have invasive testing.

Figure 20. Relationship between income quintile and referral



Note: Summing across the "not referred" and "referred" group totals 100% within a given income quintile. The group that had invasive testing is a subset of the "referred" group. The graph shows the proportion of quintile *x* that had invasive testing i.e. 20.4% of women in income quintile 1 had invasive testing.

For example, almost 40% of women from the wealthiest quintile had invasive testing and this represented 79% of referrals from that quintile (Table 35). By contrast, only 20% of women from the poorest income quintile had invasive testing but this represented 62% of referrals for genetic prenatal counselling.

Table 35. Relationship between income quintile and referral/invasive testing (% = proportion of Q* women/total for that income quintile)

Income quintile	Not referred	Referred	Had IGPT	
			% of Quintile	% of referred in that quintile
Q1	67.2% (970)	32.8% (474)	20.4% (295)	62.2%
Q2	65.1% (888)	34.9% (476)	25.3% (345)	72.5%
Q3	62.9% (961)	37.1% (568)	26.2% (401)	70.6%
Q4	56.8% (1,059)	43.2% (805)	32.8% (611)	75.9%
Q5	50.9% (1,082)	49.1% (1,044)	38.8% (825)	79.0%
Ratio Q1/Q5*	1.32	0.67	0.55	0.79
Missing	60	55	50	50
Total	5,020	3,422	2,527	2,527
x^2	Referred: not referred: p=0.001 Referred (no IGPT): had IGPT : p=0.001			

* The ratio is the percentage of AMA women in Q1 divided by the percentage for Q5

4.7.2 Regional distribution

Women from urban areas were almost twice (1.8 times: 45.1/25.5) as likely to be referred for genetic counselling (Table 36). However, once referred, these women were no more likely to have invasive testing than were women from rural regions. Probability of IGPT once referred: 73.5% urban (2,100/ 2,857) and 73.9% (377/510) rural.

Figure 21. Region of residence, referral and invasive prenatal diagnosis

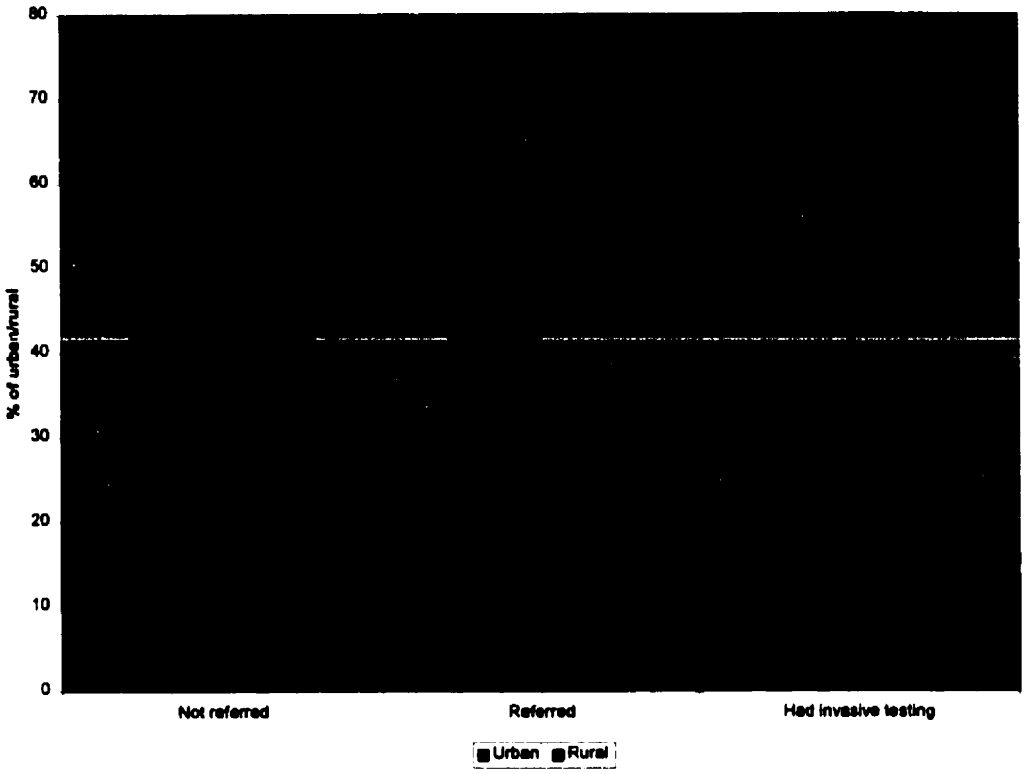


Table 36. Relationship between urban/rural residence and referral/invasive testing (% = % of urban/rural pregnancies that were referred etc)

	Not referred	Referred	Had IGPT	
			% of total urban/rural	% of referred urban/rural
Urban	54.9% (3,472)	45.1% (2,857)	33.2% (2,100)	73.5%
Rural	74.5% (1488)	25.5% (510)	18.9% (377)	73.9%
Missing	60	55	50	
Total	5,020	3,422	2,527	
x^2	Referred: Not referred		p=0.001	
	Referred (no IGPT):Had IGPT		p=0.001	

Mean age at term was comparable across urban and rural groups (urban 36.7 years, rural 36.8 years, p=0.138). Women who were referred tended to be about five months older than those who were not referred (37.0 vs. 36.6, p=0.0001).

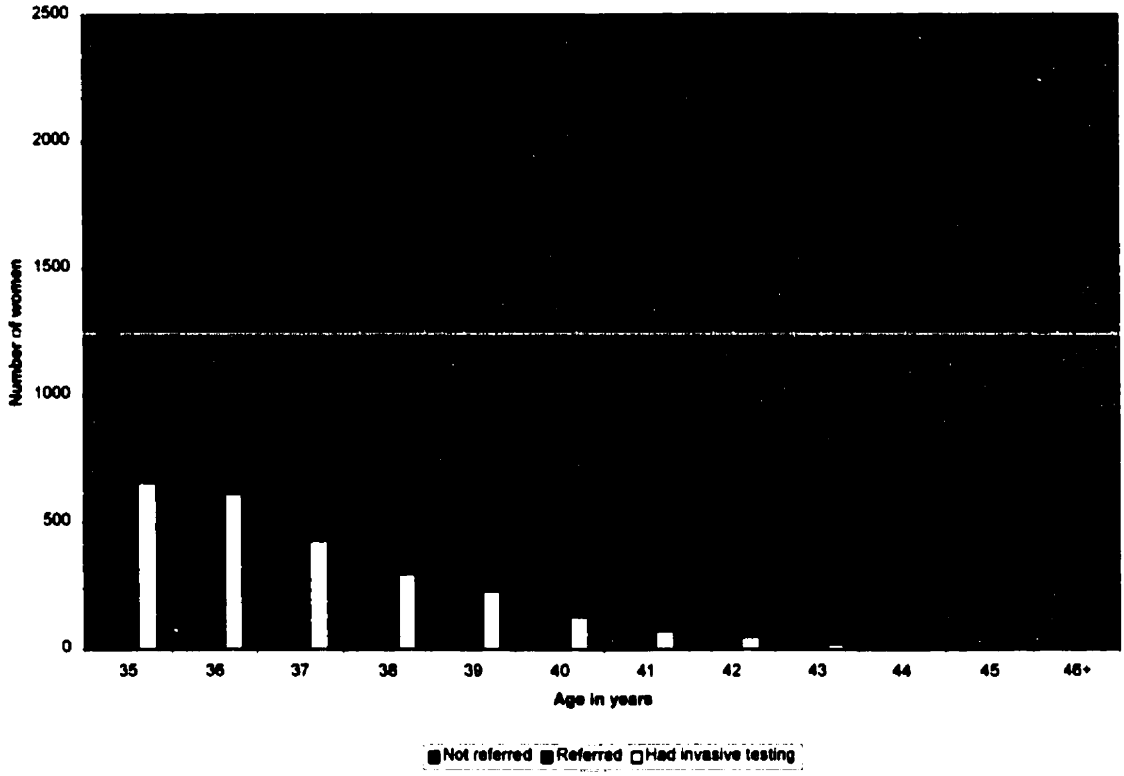
4.7.3 Maternal age

Figure 22 shows the distribution of maternal ages across the three analysis groups. Age distributions for both the referred/not referred groups and the "had invasive testing"/"referred but no invasive testing" groups differed significantly (Table 37). Far fewer of the women who would be 35 at term were referred for counselling than was the case for older women. Referral rates within each age group appeared to increase as maternal age increased up to 40 years of age and then declined. This apparent reduction was, however, complicated by a concomitant decrease in the number of pregnant women making interpretation of this data difficult. Approximately 70% of the women who were referred had invasive testing. Though this varied somewhat, evidence of a trend was not convincing because of the small number of women in the higher age groups

Table 37. Maternal age at EDC for the three analysis groups
% = % of age group

Maternal age at EDC	Not referred	Referred	Had IGPT	Total
35	69.0% (2,125)	31.0% (955)	21.4% (658)	3,080
36	54.5% (979)	45.5% (820)	34.2% (616)	1,799
37	54.8% (666)	45.2% (549)	35.2% (428)	1,215
38	53.6% (465)	46.4% (402)	34.4% (298)	867
39	50.7% (308)	49.3% (300)	38.0% (231)	608
40	51.0% (177)	49.0% (170)	37.8% (131)	347
41	58.5% (141)	41.5% (100)	30.7% (74)	241
42	55.8% (77)	44.2% (61)	36.2% (50)	138
43	53.9% (41)	46.1% (35)	28.9% (22)	76
44	60.0% (21)	40.0% (14)	25.7% (9)	35
45	61.9% (13)	38.1% (8)	33.3% (7)	21
46+	46.7% (7)	53.3% (8)	20.0% (3)	15
Total	5020	3422	2527	
x^2		Referred: not referred: p=0.001 Referred (no IGPT): had IGPT: p=0.001		

Figure 22. Patterns of referral and invasive genetic testing by maternal age at EDC



The population was examined to determine the likelihood of referral for women who were 35 and 36 years of age at term, since it is somewhat counterintuitive that eligibility for prenatal testing for advanced maternal age would be based on maternal age at term rather than, perhaps, maternal age at LMP. A large proportion of women who are 35 years of age at term are 34 during much of their pregnancy. Referral rates were examined to see if they were lower in women who were not yet 35 during much of their pregnancy.

Figure 23 shows that the likelihood of referral increases with the length of time that the woman was 35 years of age during the pregnancy (Table 38). Only 25% of women who would have just turned 35 years of age at term were referred i.e. those who were 35 $^{1}/_{12}$

years of age at term, compared to 42% of those who were 36 $^{1}/_{12}$ years at term. The former would have been 34 years of age when referred for counselling.

When the data on referrals were examined for women who were 36 years at term (i.e. who had already have crossed the "35" year threshold), the rate was relatively static between 40-50% (Figure 23), unlike that seen for the 35 year olds. It would appear that once a woman was obviously of "advanced maternal age" based on her age at the time of referral, referral rates did not vary substantially within that one year period. This was examined for women aged 38 at term and a similar pattern was seen (Table 38).

Figure 23. Referral rates by maternal age at EDC around the "threshold" for invasive prenatal diagnosis

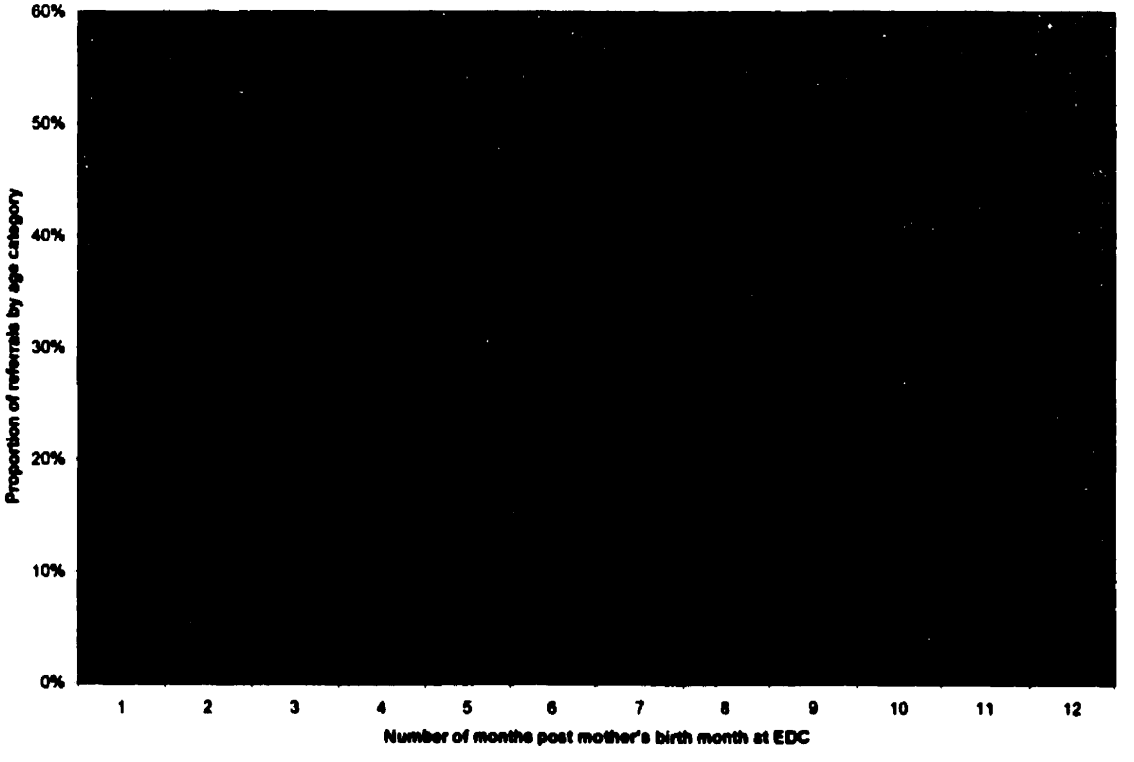


Table 38. Proportion of women aged 35 and 36 years at EDC referred for genetic counselling by the number of months post maternal birth month

At EDC, number of months beyond birth month	Referred			Had invasive testing		Overall	
	35 years	36 years	38 years	35 years	36 years	35 years	36 years
1	24.6% (79)	42.2% (73)	44.8% (39)	17.4% (56)	30.1% (52)	10.4% (321)	9.6% (173)
2	32.7% (91)	50.0% (83)	47.9% (34)	23.0% (64)	38.0% (63)	9.0% (278)	9.2% (166)
3	29.9% (92)	42.0% (71)	46.6% (41)	20.5% (63)	25.4% (43)	10.0% (308)	9.4% (169)
4	34.2% (91)	48.5% (80)	46.3% (31)	23.7% (63)	38.2% (63)	8.6% (266)	9.2% (165)
5	28.6% (79)	42.8% (74)	45.9% (39)	18.8% (52)	36.4% (63)	9.0% (276)	9.6% (173)
6	25.3% (67)	48.4% (74)	38.6% (32)	17.4% (46)	34.6% (53)	8.6% (265)	8.5% (153)
7	30.6% (79)	48.6% (71)	45.9% (34)	20.2% (52)	34.2% (50)	8.4% (258)	8.1% (146)
8	28.6% (69)	40.3% (58)	48.6% (35)	15.4% (37)	32.6% (47)	7.8% (241)	8.0% (144)
9	31.2% (92)	47.5% (66)	49.3% (35)	22.0% (65)	35.3% (49)	9.6% (295)	7.7% (139)
10	33.6% (75)	45.7% (53)	40.4% (21)	25.1% (56)	38.8% (45)	7.2% (223)	6.4% (116)
11	37.0% (70)	43.6% (58)	48.5% (33)	28.0% (53)	31.6% (42)	6.1% (189)	7.4% (133)
12	44.4% (71)	48.4% (59)	57.1% (28)	31.9% (51)	37.7% (46)	5.2% (160)	6.8% (122)

Referred % = Referred/not referred + referred

Had invasive testing % = Had IGPT/not referred + referred

When referrals were examined by maternal age and region of residence, referral rates from urban areas for the "35 years at term" group were comparable to those seen for rural women aged 36 or 38 years at EDC (85.1% vs. 83.2% and 83.6% respectively). Examined by income quintile, the proportion of women from the highest income quintile (Q5) decreased as the maternal age increased (32.4% vs. 31.0% and 27.7% respectively).

4.7.4 Gestation at first prenatal visit

By 15 completed weeks' gestation, 73.2% of the women who were not referred for genetic counselling had had a prenatal visit compared to 86.7% in the referred group overall and 88.0% in the invasive testing group (Table 39). The latter two groups had a similar distribution for gestation at first prenatal visit, distinct from that of the "not referred" group (Figure 24). Mean gestation at first prenatal visit was 13.2 weeks in the "not referred" group and 10.9 weeks in the referred group ($p<0.001$). Within the referred group, mean gestation at first visit for women who had IGPT was 10.8 weeks and 12.9 weeks for those who decided not to have IGPT ($p<0.001$)

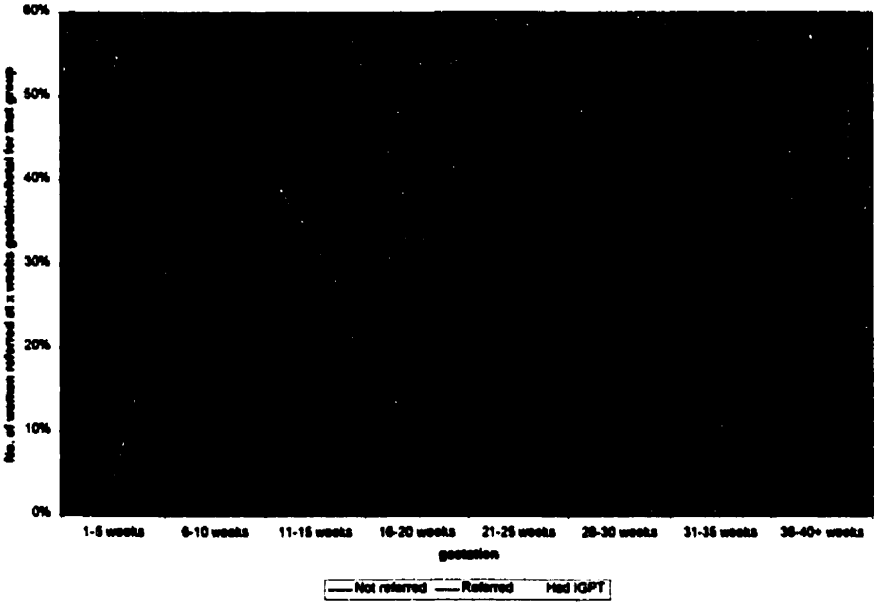
When examined by region of residence, mean gestation at first prenatal visit was 15.0 weeks for the rural "not referred" group and 12.4 weeks for the urban group ($p=0.0001$). Similarly, women who were referred tended to have their first visit earlier: 11.4 weeks for the rural group and 10.8 weeks for the urban group ($p=0.014$).

Table 39. Gestation at first prenatal visit: relationship between referral and testing
% = # referred at x weeks gestation/total in group

Weeks gestation	Not referred	Referred	Had IGPT
1-5 weeks	2.9% (144)	4.4% (150)	4.4% (112)
6-10 weeks	40.0% (2008)	50.6% (1733)	51.0% (1288)
11-15 weeks	30.3% (1521)	31.7% (1085)	32.6% (825)
16-20 weeks	12.7% (636)	9.0% (308)	8.8% (222)
21-25 weeks	5.4% (269)	1.7% (57)	1.3% (32)
26-30 weeks	3.2% (160)	0.7% (24)	0.6% (14)
31-35 weeks	2.3% (114)	0.4% (15)	0.4% (11)
36-40 weeks	1.6% (80)	0.4% (12)	0.3% (8)
Missing	1.7% (88)	1.1% (38)	0.6% (15)
Total	5020	3422	2527
x^2	Referred: Not-referred p=0.001 Referred (no IGPT): had IGPT p=0.001		

Women whose first prenatal visit was between 6-10 weeks gestation were 1.4 times more likely to be referred than those whose first prenatal visit was between 16-20 weeks (95% CI: 1.3,1.6) and 2.6 times more likely to be referred than those whose first prenatal visit was between 21-25 weeks (95% CI: 2.1,3.4).

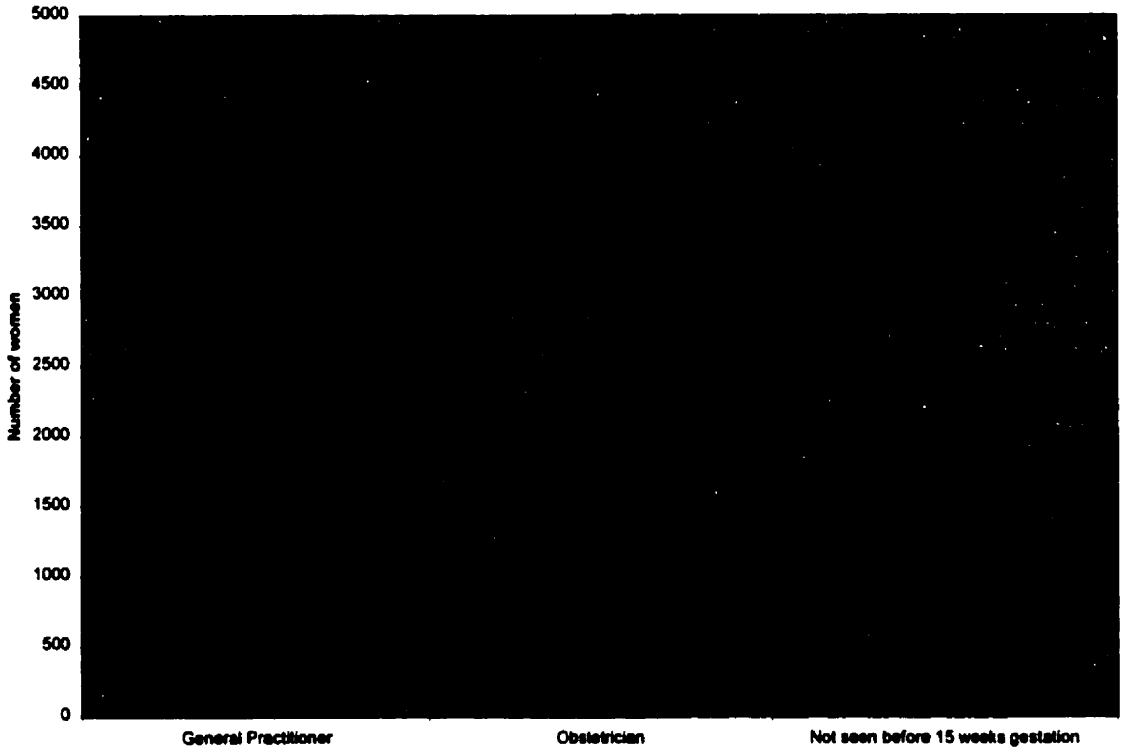
Figure 24. Gestation at first prenatal visit by referral/IGPT status



4.7.5 Physician contact in early pregnancy

For the purposes of this study, early pregnancy was defined as the first 15 weeks of gestation. This was done to capture events that might influence the decision to be referred for genetic counselling or to have invasive prenatal testing. Overall, approximately 20% of AMA women had not seen a general practitioner or an obstetrician by 16 weeks gestation, 53% had seen a general practitioner and 27% had at least one visit with an obstetrician (Figure 25).

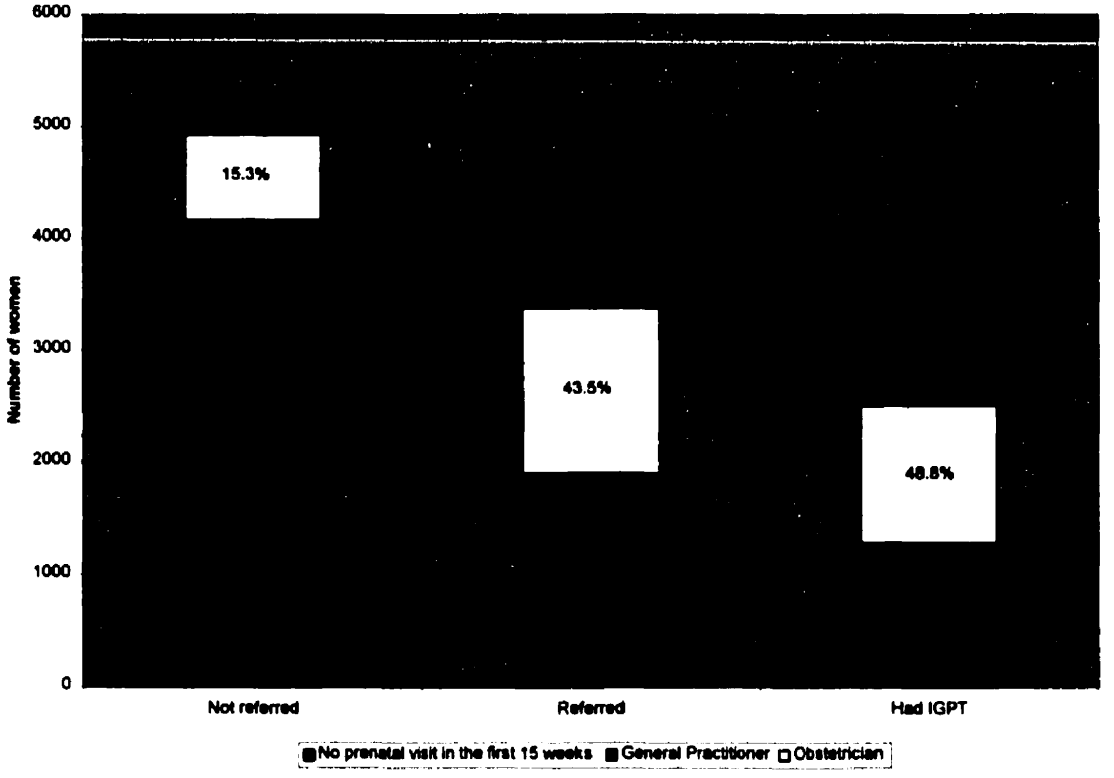
Figure 25. Proportion of women seeing a general practitioner or an obstetrician by 16 weeks gestation



Approximately 25% of the "not referred" group had no prenatal visit recorded by 16 weeks gestation (Figure 26, Table 40). This compared to 12.2% in the "referred" group and 11.4% in the group that went on to have invasive testing. Women who saw an

obstetrician were almost twice as likely to be referred as those who saw a general practitioner (33.8% [1,480/4,383] referred by general practitioners vs. 65.9% [1,488/2,258] for obstetricians, p=0.001).

Figure 26. Physician contact in the first 16 weeks of pregnancy



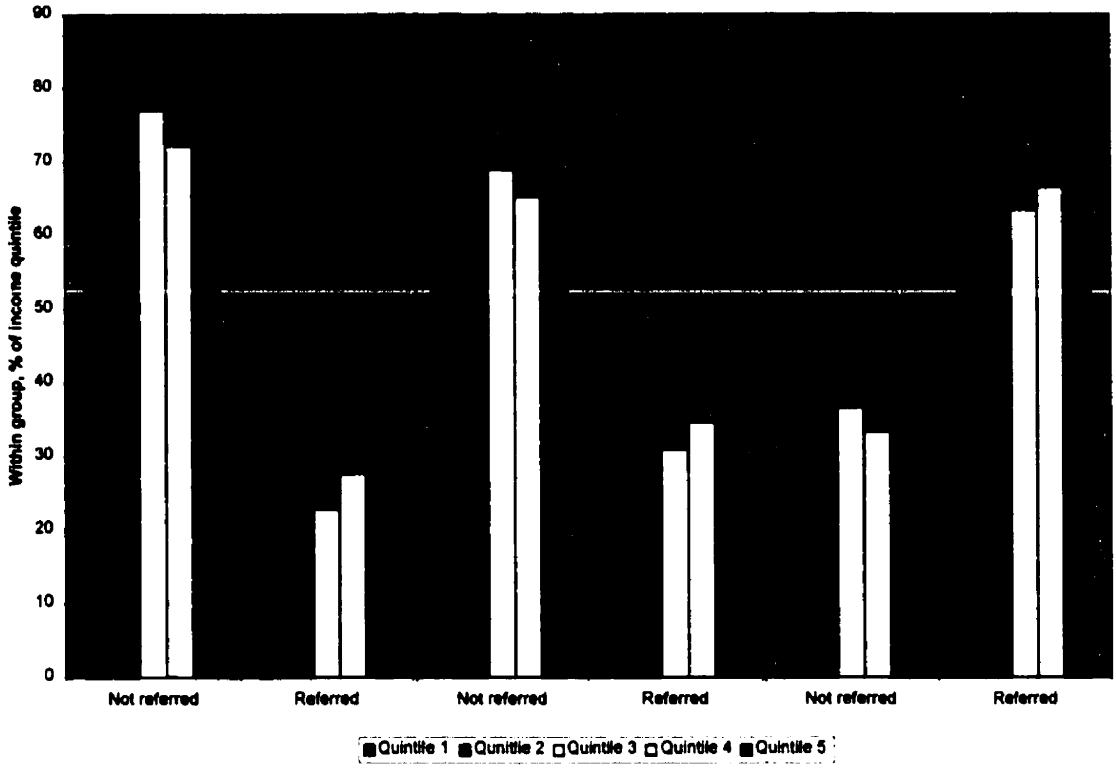
Similarly, a higher proportion of the women who were referred and went on to have invasive testing had seen an obstetrician before 16 weeks gestation (82.9% [1,233/1,488] versus 67.0% [992/1,480] for women who were referred for counselling by general practitioners; p=0.001).

Table 40. Physician contact in the first 15 weeks of pregnancy
(% = % of column total)

	Not referred	Referred	Had IGPT	Total
No prenatal visit in the first 15 weeks	25.1% (1259)	12.2% (416)	11.4% (287)	19.8% (1675)
Saw a general practitioner	57.8% (2903)	43.2% (1480)	39.3% (992)	51.% (4383)
Saw an obstetrician	15.3% (770)	43.5% (1488)	48.8% (1233)	26.7% (2258)
Missing	1.8% (88)	1.1% (38)	0.6% (15)	1.5% (126)
Total	5020	3422	2527	8442
x^2	Referred: not referred Referred (no IGPT): had IGPT		p=0.001 p=0.001	

Figure 27 describes the referred and not-referred groups by income quintile and physician contact in the first 15 weeks of pregnancy. The women who had not had a prenatal visit in the first 15 weeks of gestation were predominantly from the lowest income quintile (p=0.001). This group comprised 24.7% (408/1,655) of the no prenatal visit group, and women from the highest income quintile represented 18.7% (310/1,655). Women who had seen either a general practitioner or an obstetrician and were from the highest income quintile were more likely to be referred than those from the lowest quintile (p=0.001). However, the difference in referral rates between the lowest and highest income quintiles was larger for AMA women who had seen an obstetrician before 16 weeks of pregnancy, with 69.7% of women in the highest income quintile who saw an obstetrician being referred, but only 56.7% of those in the lowest income quintile (p=0.001). This represented 24.6% (516/2,098) of women in the highest income quintile being referred but only 11.1% (157/1,414) of women in the lowest quintile (Table 41).

Figure 27. Prenatal visits before 16 weeks gestation by income quintile and referred/not referred



(Note: Income quintiles add to 100% within each category)

Table 41. Prenatal visits before 16 weeks gestation by income quintile and referral status (% = % of row total within each category)

	No prenatal visit		Saw a general practitioner		Saw an obstetrician	
	Not referred	Referred	Not referred	Referred	Not referred	Referred
Quintile 1	80.4% (328)	19.6% (80)	68.6% (500)	31.4% (229)	43.3% (120)	56.7% (157)
Quintile 2	80.3% (256)	19.7% (63)	69.8% (510)	30.2% (221)	34.1% (98)	65.9% (189)
Quintile 3	77.1% (243)	22.9% (72)	69.0% (569)	31.0% (256)	36.6% (135)	63.4% (234)
Quintile 4	72.3% (219)	27.7% (84)	65.3% (643)	34.7% (341)	33.4% (187)	66.6% (373)
Quintile 5	64.8% (201)	35.2% (109)	61.4% (643)	38.6% (405)	30.3% (224)	69.7% (516)

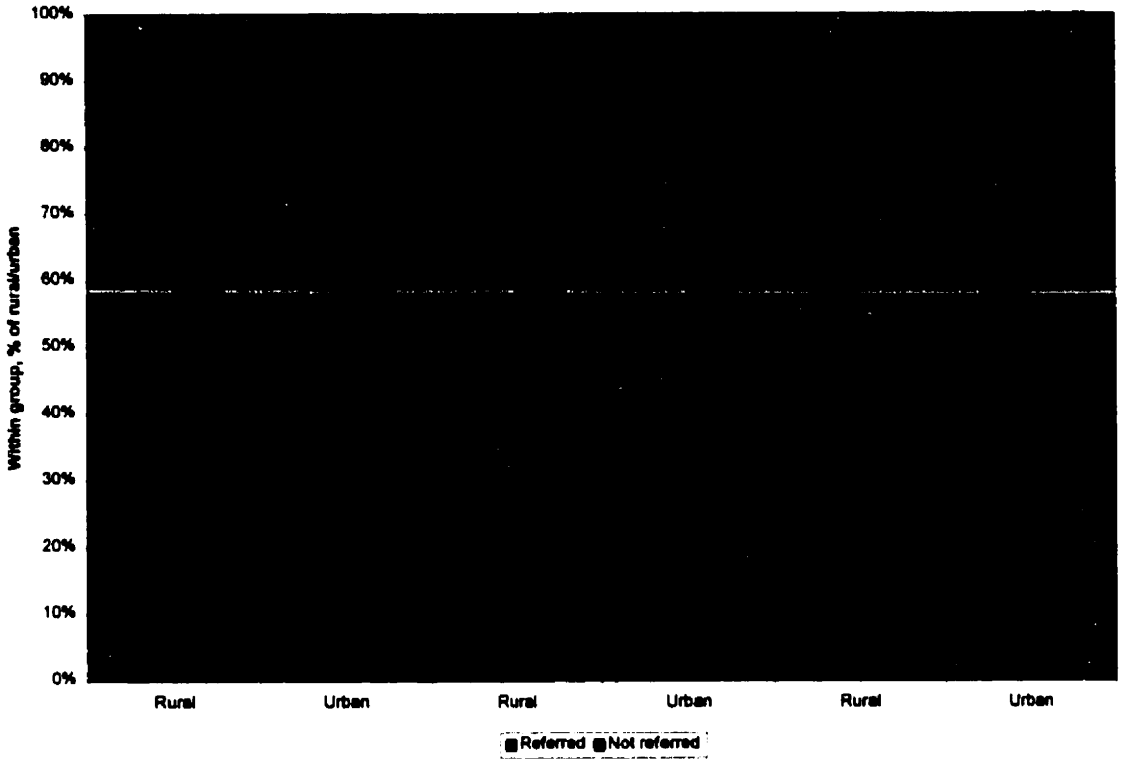
Average age at term across the income groups was examined to see if the women in higher income groups were older and so might be more likely to pursue referral (Table 42). This did not appear to be so, indeed, the average age of women in the highest income quintile was slightly lower than that seen in the lowest income quintile. As expected, across all income quintiles the average age of women who were referred was higher than that of those who were not referred.

Table 42. Age at EDC by income quintile and referred/not referred

		Average age at EDC (years)		
Quintile	Overall	Not referred	Referred	Had IGPT
1	37.0	36.9	37.3	37.2
2	36.8	36.7	37.1	37.0
3	36.7	36.6	36.9	36.9
4	36.6	36.4	37.0	37.0
5	36.6	36.4	36.9	37.0

When this relationship was examined by region of residence, there were notable differences in the referral patterns both across specialties and region (Figure 28). General practitioners appeared to be more likely to refer urban AMA women for genetic counselling than rural women (23.9% of rural women who saw a general practitioner were referred vs. 36.9% of urban women; p=0.001; Table 43). However, this distinction was less so for obstetricians, who were approximately as likely to refer urban as rural AMA women (61.7% of rural women who saw an obstetrician were referred vs. 66.4% of urban women p=0.129).

Figure 28. Prenatal visits before 16 weeks gestation by physician type, residence and referral status



(Note: Regions add to 100% within each category)

Table 43. Prenatal visits before 16 weeks gestation by physician type, residence and referral status
(% = % of row total within each category)

	No prenatal visit		Saw a general practitioner		Saw an obstetrician	
	Not referred	Referred	Not referred	Referred	Not referred	Referred
Rural	87.8% (540)	12.2% (75)	76.1% (814)	23.9% (255)	38.3% (106)	61.7% (171)
Urban	68.0% (707)	32.0% (333)	63.1% (2051)	36.9% (1197)	33.6% (658)	66.4% (1298)

These trends across region of residence and income quintile can be summarised as follows (Table 44): (1) Rural women from the lowest income quintile were most likely not to have had a prenatal visit before 16 weeks gestation and urban women from the

highest quintile the least likely. (2) Rural AMA women in the lowest income quintile who saw a general practitioner in the first 15 weeks of pregnancy were less likely to be referred for genetic counselling than poor urban women or their wealthier counterparts irrespective of region of residence. (3) Urban AMA women in the highest income quintile were much more likely to be referred for genetic counselling, particularly if they saw an obstetrician before the 16th week of pregnancy. (4) General practitioners referred approximately the same proportion of women irrespective of income or residence, with the exception of poor rural women who were substantially underrepresented.

Table 44. Prenatal visits before 16 weeks gestation by referred/not referred for the highest and lowest income quintiles
(% = % of row total)

	No prenatal visit before 16 weeks		Saw a general practitioner		Saw an obstetrician	
	Not referred	Referred	Not referred	Referred	Not referred	Referred
Quintile 1						
Urban	18.3% (196)	5.6% (60)	32.9% (352)	18.1% (193)	9.6% (103)	13.5% (144)
Rural	35.2% (132)	TSTR	39.5% (148)	TSTR	TSTR	TSTR
Quintile 5						
Urban	7.4% (122)	5.6% (93)	29.8% (491)	19.1% (314)	10.8% (178)	26.1% (340)
Rural	16.5% (79)	TSTR	31.8% (152)	19.0% (91)	TSTR	18.0% (86)

Note:TSTR: numbers are not reported for this cell for reasons of confidentiality, as they are too small to report. Also, those women with no prenatal visit before 16 weeks that were referred for counselling will have been referred after 15 weeks gestation.

4.7.6 Complications of pregnancy and prenatal patients with a poor obstetric history.

It appeared that women who had early complications of pregnancy were not preferentially referred for counselling (11.8% had early complications in the "not referred" group vs. 12.2% in the "referred" group, p=0.520), but they were significantly less likely to have invasive genetic testing (16.0% had early complications in the referred group that did not have invasive genetic testing vs. 10.9% in the had IGPT group, p=0.001) (Table 45).

Table 45. Complications of pregnancy: relationship between referral and testing (% = % of group with complications)

		Not referred	Referred	Referred-no IGPT	Had IGPT
Early pregnancy complications	Yes	11.8% (590)	12.2% (418)	16.0% (143)	10.9% (275)
	No	88.2% (4,430)	87.8% (3,004)	84.0% (752)	89.1% (2252)
x^2		Referred: not referred: p=0.520 Referred (no IGPT): had IGPT p=0.001			

Since the AFP data included information on bleeding early in pregnancy, this was compared to the numbers obtained from the hospital and medical claims (See Appendix 1 for coding details). The AFP data was likely to be relatively accurate since active or recent bleeding can affect the AFP value, altering the interpretation of the test. There were 518 instances where bleeding had been noted on the AFP requisition and only 96 of these could be found in the claims data. Conversely, eighty-eight women had a claim indicating an early bleed that had no counterpart on the AFP record. It would appear from these data that early complications of pregnancy are potentially underestimated in the claims data.

The relationship between poor obstetric history in hospital or medical claims and referral indicated that such women were more likely to be referred, (p=0.001, Table 46) but less likely to have prenatal testing (p=0.003). Again, the number of cases was low and this circumstance may be under-reported in the claims.

Table 46. Poor obstetric history: relationship between referral and testing (% = % of group with complications)

		Not referred	Referred	Referred-no testing	Had IGPT
Poor obstetric history	Yes	2.4% (122)	6.4% (220)	4.4% (39)	7.2% (181)
	No	97.6% (4,898)	93.6% (3,202)	95.6% (856)	92.8% (2,346)
x^2		Referred: not referred p=0.001 Referred (no IGPT): had IGPT p=0.003			

4.7.7 First Nation comparison

Women who did not have Treaty First Nation status were more than twice as likely (95% CI: 1.8, 2.6, p=0.001) to be referred for genetic counselling than those who did, with only 19.2% of AMA women with First Nations status being referred compared to 41.8% of non-First Nations women (Table 47). Similarly, women who were not identified as having Treaty First Nation status were almost three times as likely (95% CI: 2.1,3.5) to have invasive prenatal testing than those who had First Nation status (Proportion having IGPT First Nations: 11.5%; Non-FN: 31.0%, p=0.001). Once referred for counselling, First Nations women were still less likely to choose to have invasive testing: 60% vs. 74% (p=0.002).

Table 47. First Nations/non-First Nations: relationship between referral and testing

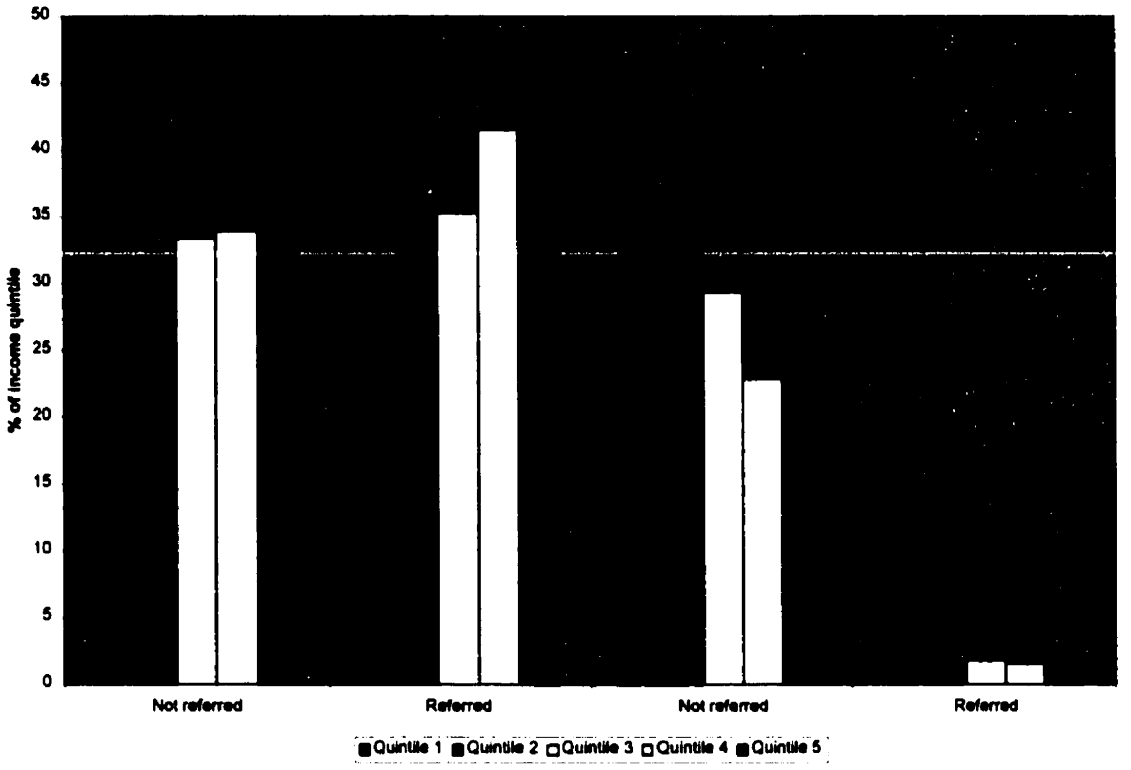
	Not referred	Referred	Had IGPT
First Nation	7.7% (387)	2.7% (92)	2.2% (55)
Non-First Nation	92.3% (4633)	97.3% (3330)	97.8% (2472)
Total	5020	3422	2527
x^2	Referred: Not referred		p=0.001
	Referred (no IGPT): Had IGPT		p=0.002

It must be remembered that it is difficult to identify aboriginal peoples in the administrative data: only approximately two thirds of those individuals who have Treaty status can currently be identified: There is a documented bias towards an older male population and a severe undercounting of women under 50 years of age (Pat Martens, personal communication). Additionally, Treaty Status (as defined under the terms of the 1876 "Indian Act") does not include Métis or Inuit people, consequently, such individuals cannot be identified in the administrative data.

4.7.8 AFP Screening

Figure 29 describes the distribution of the income quintiles across women who had/did not have AFP screening and by whether the woman was referred for genetic counselling or not. For those women who had AFP screening and were referred for genetic counselling (Table 48), the income distribution closely follows that seen in referrals for genetic counselling (Table 35). This is not surprising since most of the women who have genetic counselling will also have AFP screening. In the group that had AFP screening but who were not referred for AMA counselling, the proportion of individuals from each income quintile was approximately equivalent (around 32%).

Figure 29. AMA AFP Screening by income and referral status



In the referred group that did not have AFP screening (n=167, Table 48), the numbers were small, but the income distribution appears similar across quintiles. These cases probably represented women referred for genetic counselling late in pregnancy, or where a problem was found in the fetus and where AFP screening would not be appropriate. The group that did not have screening and was not referred (n=2,225), was of particular interest since it represented 26% of the total study population. A significant difference was seen across income quintiles (p=0.001). It appears that not only were you less likely to be referred for AMA genetic counselling if you were in a lower income group, but that you were also less likely to have AFP screening.

Table 48. AMA AFP screening by income quintile and referral status

	Had AFP screening		Not screened		Total
Income quintile	Not referred	Referred	Not referred	Referred	
1	31.5% (455)	30.0% (433)	35.7% (515)	2.8% (41)	1,444
2	30.2% (412)	33.2% (453)	34.9% (476)	1.7% (23)	1,364
3	33.4% (511)	35.3% (540)	29.4% (450)	1.8% (28)	1,529
4	34.0% (633)	41.6% (775)	22.9% (426)	1.6% (30)	1,864
5	34.1% (724)	47.0% (999)	16.8% (358)	2.1% (45)	2,126
	2,735	3,200	2,225	167	8,327

From Table 49, it appears that the group that did not have screening and was not referred was predominantly urban (58.6%), reflecting the different proportion of AMA pregnancies in urban and rural constituencies. When these data were examined from the perspective of referral rates following AFP screening, it appeared that urban and rural women were equally likely to be referred following AFP screening (55.6% urban, 46.1% rural). However, only 2.6% (25/947) of rural women who did not have AFP screening were referred for genetic counselling, compared to 9.8% of urban women (p=0.001).

Table 49. AMA AFP screening by residence and referral for counselling
% = Number of referred/non referred rural/urban AMA women/total for that group

	Had AFP screening		
	Urban	Rural	Total
Referred for genetic counselling	55.6% (2,715)	46.1% (485)	3,200
Not referred	44.4% (2,169)	53.9% (566)	2,735
Total	4,884	1,051	5,935
	Not screened		
Referred for genetic counselling	9.8% (142)	2.6% (25)	167
Not referred	90.2% (1,303)	97.4% (922)	2,225
Total	1,445	947	2,392

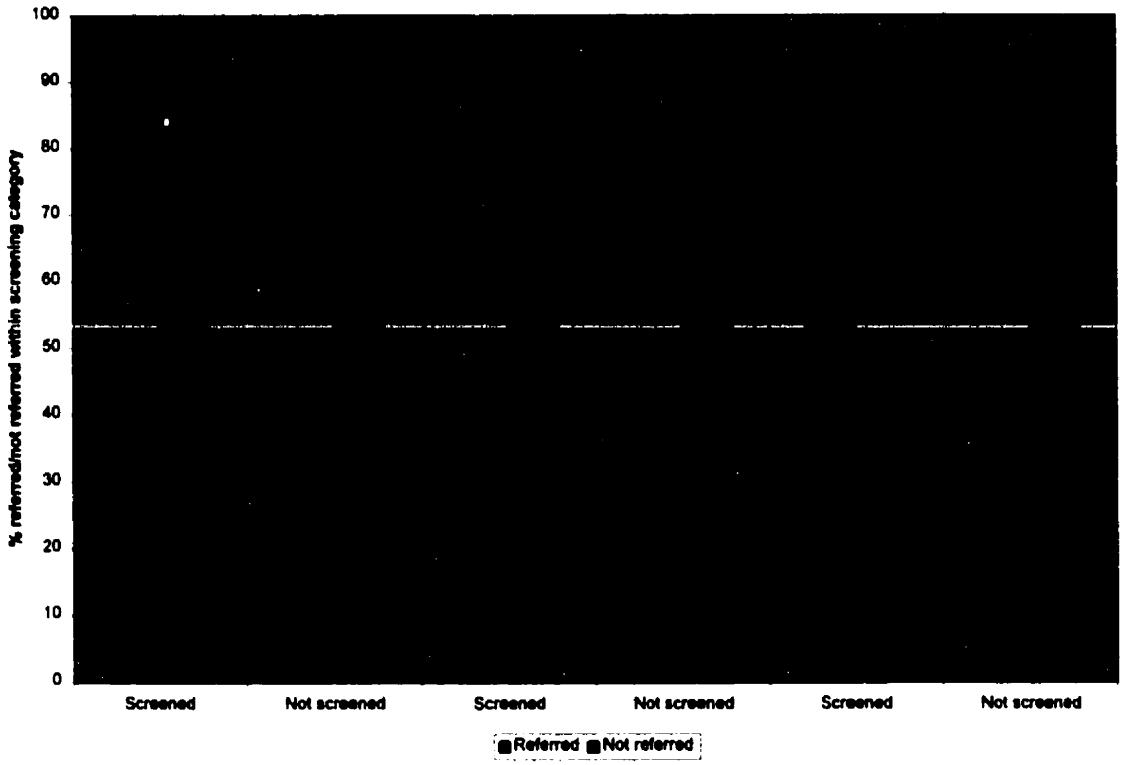
The proportion of women with a higher than age-related risk of Down syndrome from AFP screening was examined by region of residence, and it was found that only 53.3% (167/313) of rural women at increased risk were referred for counselling compared to 62.0% (893/1441) of urban women (p=0.005).

When AFP screening was examined by provider, 20% (838/8,316) of women had not yet had a prenatal visit by 16 weeks gestation, 27% (2121/8316) had seen an obstetrician on at least one occasion and the remainder, 53% (3031/8316) had seen a general practitioner regarding pregnancy. As Table 50 shows, AFP screening was highest for those women who had seen an obstetrician, with 93.9% (2121/2258) of women who saw an obstetrician having AFP screening. This compared to 69% (3031/4383) of women who saw a general practitioner and 50% (838/1675) of those women who had not yet had a prenatal visit by 16 weeks gestation.

Table 50. AMA AFP screening by provider (up to 15 weeks gestation) and referral status
(% = % of column total)

	No prenatal visit		general practitioner		obstetrician	
	Screened	Not screened	Screened	Not screened	Screened	Not screened
Referred	46.5% (390)	3.1% (26)	45.2% (1,371)	8.1% (109)	69.6% (1,476)	8.8% (12)
Not referred	53.5% (448)	96.9% (811)	54.8% (1,660)	91.9% (1,243)	30.4% (645)	91.2% (125)
Total	838	837	3,031	1,352	2,121	137
Total	1,675		4,383		2,258	
% screened	50.0%		69.2%		93.9%	

Figure 30. AMA AFP Screening by provider and referral status



4.8 PREDICTING REFERRAL FOR COUNSELING AND UPTAKE OF INVASIVE GENETIC PRENATAL TESTING

Multivariate modelling of the relationship between referral and the explanatory variables described in Table 10 was performed using multiple logistic regression. The same procedure was used to model predictors of invasive genetic testing both for the population as a whole, and for the group that was referred for counselling.

Prior to performing the regression, the variable distributions were examined. Three age groups were considered in the regressions: age 35 at term, ages 36-39 and ages 40 and over. As demonstrated in Figure 31, women 35 years of age at term clearly differed from

the rest of the population, however, dramatic differences were not seen across other age groups (with the exception of the 46+ year-old category, however this was a composite due to small numbers in each individual age group), thus the division of the rest of the population into two subgroups was arbitrary.

Figure 31. Relationship between age at term and referral or invasive genetic prenatal testing

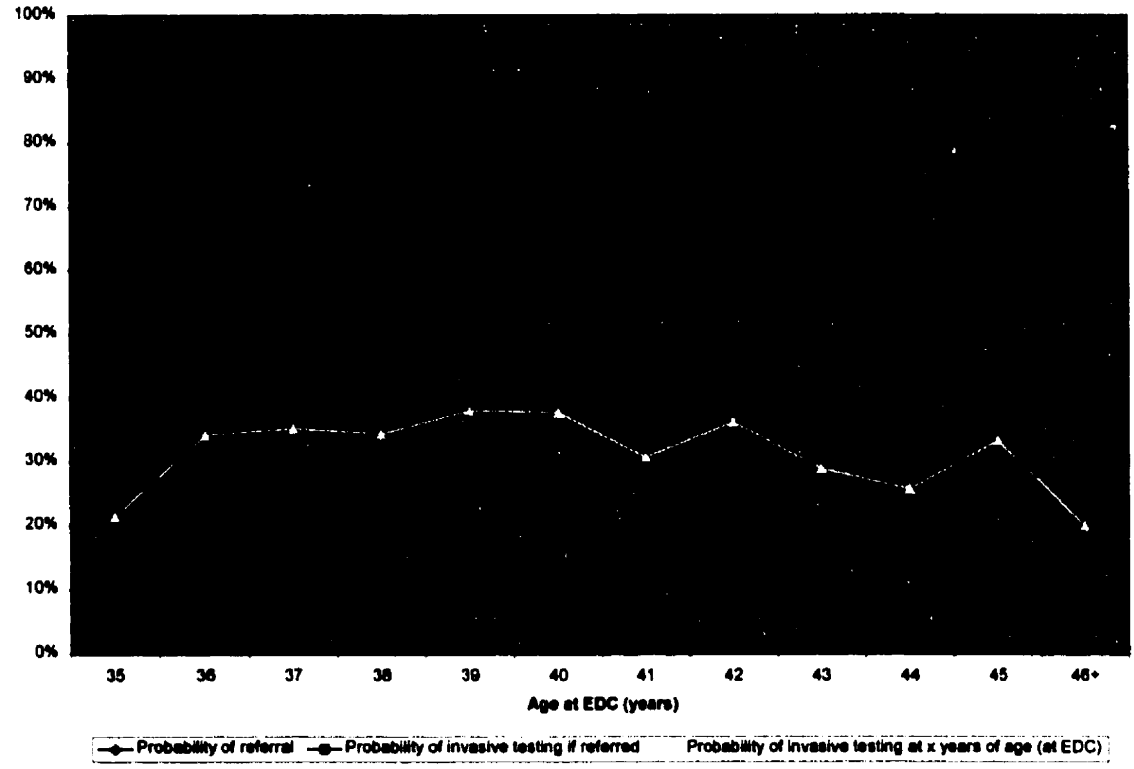


Table 51. Probability of referral or IGPT based on age at EDC

Age in years	Probability of referral at *x* years at EDC	Probability of IGPT at *x* years at EDC	Probability of IGPT if referred
35	31.0% (955/3080)	21.4% (658/3080)	68.9% (658/955)
36	45.6% (820/1799)	34.2% (616/1799)	77.1% (616/820)
37	45.2% (549/1215)	35.2% (428/1215)	78.0% (428/549)
38	46.4% (402/867)	34.4% (298/867)	74.1% (298/402)
39	49.3% (300/608)	38.0% (231/608)	77.0% (231/300)
40	49.0% (170/347)	37.7% (131/347)	77.0% (131/170)
41	41.5% (100/241)	30.7% (74/241)	74.0% (74/100)
42	44.2% (61/138)	36.2% (50/138)	82.0% (50/61)
43	46.1% (35/76)	28.9% (22/76)	62.9% (22/35)
44	40.0% (14/35)	25.7% (9/35)	64.3% (9/14)
45	38.1% (8/21)	33.3% (7/21)	87.5% (7/8)
46+	53.3% (8/15)	20.0% (3/15)	37.5% (3/8)

The logistic regressions for referral and genetic testing in the AMA cohort were based on 8,205 observations, excluding (censoring) 237 records with missing values. The latter represented 115 records without a postal code and 126 whose prenatal visit status by 16 weeks was unknown. The regression modelling predictors of invasive testing following referral for genetic counselling was based on 3,329 observations, excluding 93 censored values.

4.8.1 The AFP problem

The effect of the AFP screening variable dominated all analyses and was consistently the most important predictor both of referral or uptake of invasive testing (see Tables 52, 53 and 54). However, since 98.4% (Figure 17) of women referred for genetic counselling also had AFP screening, the screening variable was highly correlated with referral and must be considered biased. This variable might have been "salvageable" had it been possible to elucidate the temporal sequence of referral and screening, unfortunately, this

was not feasible since the data did not permit distinguishing woman who had actually had genetic counselling from those who had been referred but had not been counselled. Consequently, the logistic regressions were repeated excluding this variable. The exclusion of the screening variable did not precipitate a dramatic change in most of the significant terms, odds ratios or p values.

A derived variable, which indicated an increased Down syndrome risk following AFP screening, was retained since (although almost all women who were referred had the AFP screen) 54% of women who had not been referred had had AFP screening. The proportion of screened individuals receiving an increased Down syndrome risk following AFP screening was roughly equally distributed between women who were referred and those who were not, with 28% of women who were referred having an increased Down syndrome risk and 21% of those who were not referred (Figure 17). Complete results from the referral and uptake of invasive testing logistic regressions are presented in Appendix 5.

Table 52. Predictors of referral for genetic counselling

	Including AFP screening variable			Not including AFP screening variable		
	OR	(95% C.I.)	p value	OR	(95% C.I.)	p value
Individual characteristics						
36-39	2.4	(2.1-2.7)	0.0001	2.3	(2.1-2.5)	0.0001
40+	2.3	(2.0-2.8)	0.0001	2.2	(1.8-2.6)	0.0001
Residence	1.6	(1.4-1.8)	0.0001	1.9	(1.7-2.2)	0.0001
Quintile 4	--			1.2	(1.1-1.5)	0.008
Highest income quintile	1.4	(1.2-1.6)	0.0001	1.6	(1.3-1.8)	0.0001
Obstetric characteristics						
Saw obstetrician before 16 weeks	2.5	(2.2-2.8)	0.0001	4.7	(4.1-5.5)	0.0001
Saw a general practitioner before 16 weeks	--			1.4	(1.2-1.6)	0.0001
Poor obstetric history	1.6	(1.3-2.1)	0.0002	1.9	(1.5-2.5)	0.0001
AFP screening	11.5	(9.6-13.8)	0.0001	--		
↑ DS risk from screening	1.6	(1.4-1.8)	0.0001	2.7	(2.4-3.1)	0.0001
Early complications of pregnancy	--			--		

Table 53. Predictors for the uptake of genetic testing in the AMA cohort

	Including AFP screening variable			Not including AFP screening variable		
	OR	(95% C.I.)	p value	OR	(95% C.I.)	p value
Individual characteristics						
36-39	2.4	(2.1-2.7)	0.0001	2.4	(2.1-2.7)	0.0001
40+	2.4	(1.9-2.9)	0.0001	2.3	(1.9-2.7)	0.0001
Residence	1.3	(1.1-1.5)	0.0004	1.7	(1.4-1.9)	0.0001
Quintile 4	1.5	(1.2-1.8)	0.0001	1.5	(1.3-1.8)	0.0001
Highest income quintile	1.8	(1.5-2.1)	0.0001	1.9	(1.6-2.3)	0.0001
Obstetric characteristics						
Saw an obstetrician before 16 weeks	2.8	(2.5-3.2)	0.0001	4.9	(4.1-5.7)	0.0001
Saw a general practitioner before 16 weeks	--			1.3	(1.1-1.5)	0.0006
Poor obstetric history	1.6	(1.3-2.1)	0.0001	1.9	(1.5-2.4)	0.0001
AFP screening	25.3	(18.3-34.9)	0.0001	--		
↑ DS risk from screening	1.6	(1.4-1.8)	0.0001	2.5	(2.2-2.8)	0.0001
Early complications of pregnancy	0.7	(0.6-0.9)	0.0002	0.7	(0.6-0.9)	0.0002

Table 54. Predictors of uptake of invasive testing for referred AMA women

	Including AFP screening variable OR (95% C.I.) p value	Not including AFP screening variable OR (95% C.I.) p value
Individual characteristics		
36-39	1.5 (1.2-1.8) 0.0001	1.5 (1.2-1.7) 0.0001
40+	1.5 (1.1-2.0) 0.009	1.4 (1.1-1.8) 0.0194
Residence	--	--
Quintile 4	1.6 (1.2-2.1) 0.0005	1.7 (1.3-2.1) 0.0001
Highest income quintile	1.9 (1.5-2.5) 0.0001	2.0 (1.6-2.5) 0.0001
Obstetric characteristics		
Saw an obstetrician before 16 weeks	2.0 (1.7-2.4) 0.0001	2.3 (2.0-2.7) 0.0001
Saw a general practitioner before 16 weeks	--	--
Poor obstetric history	--	--
AFP screening	6.5 (4.4-9.5) 0.0001	--
↑ DS risk from screening	1.3 (1.0-1.5) 0.02	1.4 (1.2-1.7) 0.0001
Early complications of pregnancy	0.6 (0.5-0.8) 0.0001	0.6 (0.5-0.8) 0.0001

In the referral portion of the analysis, terms that were affected by the removal of the AFP screening variable were "seeing an obstetrician before 16 weeks gestation" and "Down syndrome risk increased over age-related risk". The odds ratio for both of these increased: from 2.5 to 4.7 for seeing an obstetrician and from 1.6 to 2.7 for an increased Down syndrome risk over the age-related risk. A similar change in odds ratio for these variables was seen in the logistic regression that evaluated the uptake of genetic testing in the AMA population. When factors influencing the uptake of invasive testing in the referred population were examined, the only major differences seen were that age 40+ became a less significant predictor of invasive testing; p=0.02 with an odds ratio of 1.4 as compared to an odds ratio of 2.2 (p=0.0001) for referral and one of 2.3 (p=0.0001) for invasive testing in the AMA population. Similarly, the odds ratio for "elevated Down

syndrome risk over age-related risk" was lower for the regression modelling invasive testing following referral, at 1.4 (p=0.0001) versus 2.5 (p=0.0001) for both referral and predictors of invasive testing in the entire AMA group. In the following, the results of the logistic regressions that excluded the AFP screening variable will be discussed.

The logistic regression for referral for genetic counselling determined 8 of the 14 terms to be significant at the 0.0001 level (see Table 52): in order of importance these included seeing an obstetrician before 16 weeks gestation (OR 4.7, 95% CI: 4.1-5.5), a Down syndrome risk (from AFP testing) that was increased over the age-related risk (OR 2.7, 95% CI: 2.4-3.1), maternal age at term of 36-39 or 40+ years (OR 2.3, 95% CI: 2.1-2.5 and OR 2.2, 95% CI 1.8-2.6 respectively), urban residence (OR 1.9, 95% CI: 1.7-2.2), poor obstetric history (OR 1.9, 1.5-2.5), being in the highest income quintile (OR 1.6, 95% CI: 1.3-1.8) and seeing a general practitioner in the first 15 weeks of pregnancy (OR 1.4, 95% CI: 1.2-1.6). Belonging to the fourth (second wealthiest) income quintile was significant at p=0.008 (OR 1.2), but women in the second and third income quintiles did not differ significantly from those in the lowest (reference) group. However, when the income quintiles were added jointly, the overall statistic was significant at p=0.0001.

The logistic regression for the uptake of invasive genetic testing among AMA women generally showed very similar effects as in the referral regression. Major differences included that income quintile 4 was also a significant predictor of invasive testing (OR 1.5, 95% CI: 1.3-1.8), and a significant negative association between early complications in the current pregnancy and invasive testing (this was also seen in the analysis of

invasive testing following referral for genetic counselling), with an odds ratio of 0.7 (p=0.0002) for the former and 0.6 (p=0.0001) for the latter.

There were fewer predictors of invasive testing following referral for genetic counselling, the most important of which was seeing an obstetrician before 16 weeks gestation (OR 2.3 95% CI: 2.0-2.7). Interestingly, seeing a general practitioner before 16 weeks gestation was no longer significant at the 0.0001 level, nor was urban residence or poor obstetric history. Belonging to income quintiles 4 or 5 was still highly significant (OR 1.7 and 2.0 respectively). Being 40+ years of age showed a weaker relationship to invasive testing than it did to referral. Finally, having a Down syndrome risk that was increased over the age-related risk was still significant, but the odds ratio was lower for invasive testing once referred (odds ratio 1.4, 95% CI: 1.2-1.7) than for referral (odds ratio 2.7, 95% CI: 2.4-3.1) or as a predictor of invasive testing in the entire AMA population (odds ratio 2.5, 95% CI: 2.2-2.8).

CHAPTER 5: DISCUSSION

THE FINDINGS IN PERSPECTIVE

This chapter summarises the study findings, framing them with respect to existing knowledge. The validity of the study is discussed, commenting on strengths and weaknesses of the study design. Finally, suggestions for program changes and directions for future research in this area are considered.

5.1 RECORD LINKAGE ISSUES

In order to be useful for analysis purposes, databases must be accurate and complete, serve a well-defined population, and contain comprehensive data on all persons in the study population. In the current study, record linkage has been successfully accomplished across the three datasets despite the technical complexity of identifying and linking to the correct pregnancy. External reports (such as those from Statistics Canada and summary statistics from the Section of Genetics & Metabolism) provided an opportunity to independently verify the appropriateness of the linkages as did the ability to cross check identifiers across datasets (i.e. using the AFP file number as a cross reference to the Genetics dataset).

Each dataset presented specific challenges: the primary obstacle to generating the administrative AMA cohort was determining maternal age at term, given that the date of last menstrual period was not available on that dataset. This was of particular concern for that group of women who would have been 35 years of age at term, but who were 34

years of age for a portion of their pregnancy. A simple solution; including all pregnant women who were 34 years of age in the AMA cohort, would have ensured complete ascertainment of women 35 years at term. However, this would also have resulted in an underestimation of both referral and testing rates since some of the 34 year old women would still be 34 years at term and thus not eligible for prenatal diagnosis. This potential problem was circumvented by determining maternal age at term using the maternal date of birth in concert with the date of delivery and gestation at delivery.

In addition to the possibility that the cohort might overestimate the number of pregnant women of advanced maternal age, there was also the possibility that a small number of pregnancies, those where birth or termination records were absent from hospital files, could be missed from the cohort. This circumstance could be due to:

(a) an early miscarriage (without concurrent hospitalisation for a dilatation & curettage)

(b) the mother leaving the country or registering for health care in another province before the birth of the child. However, if the mother moved within Canada she would continue to be covered by Manitoba health care insurance for a period of 3 months after leaving or until Manitoba Health was notified that she had registered for health care in another province.

Comparisons with Statistics Canada reports of AMA livebirths and social terminations—within the limitations of somewhat asynchronous time frames—verified that an appropriate cohort had indeed been accurately generated, although early losses were found to have been underreported. As a consequence of the early referrals required for

CVS counselling, information was available for a number of women whose pregnancy could not be found in the administrative data. Forty-nine out of the 327 women, or 31% of the 157 unlinked records for which there was additional information available, were noted to have miscarried. Since it was not possible to determine at what point in gestation miscarriages took place, and as such records had less information than continuing pregnancies, both miscarriages and social terminations were excluded from the main analyses. Few of the administrative datasets used in obstetric linkages capture information on miscarriages or terminations. In a study which linked 1.4 million fetal death and birth certificates to construct pregnancy histories, Adams et al. also found that the small subset of records that were the most difficult to link tended to over-represent groups with the greatest risk of adverse pregnancy outcomes (Adams et al., 1997b).

The maternal serum screening cohort was perhaps the easiest to generate and link to the administrative healthcare data both because of the quality of the data, in particular of the health care number, and the ease with which AMA women could be distinguished. Also, since each pregnancy was assigned a unique AFP file number, distinguishing individual pregnancies was not problematic. Two attributes of the data did complicate the analysis somewhat: (1) when more than one sample was received in a pregnancy, determining which record should be retained could be difficult. Devising an algorithm to pick a record with sufficient information that had been drawn at the appropriate gestation was challenging. (2) A large number of samples received a hand-written interpretation ("message 8"), the content of which was not captured in the database. Since this was the case, the risk figures calculated by the interpretative program for Down syndrome and

neural tube risks were used and the presumed interpretation determined according to the Manitoba Maternal Serum Screening protocol (Figure 4).

The genetic appointment and laboratory databases proved the most challenging with which to work. Both were keyed on kindred number and encounter-based—often with multiple records per pregnancy. Since data resided in separate datasets (laboratory or appointment) with little or no overlap, attempting to link the appropriate laboratory record(s) to appointment record(s) was not a trivial task since a single identifier unique to a particular pregnancy (such as date of last menstrual period) was rarely present on both datasets. Similarly, distinguishing individual pregnancies was not necessarily straightforward. Though relatively easy to distinguish between pregnancies manually, it was difficult to design an algorithm that would be robust in all circumstances. This was particularly problematic where a relatively short period elapsed between pregnancies, such as occurred when a miscarriage followed the referral for CVS counselling and the woman became pregnant again relatively quickly.

Difficulties linking databases that describe pregnancies or their outcomes have been previously described (Stanley et al., 1994; Holian, 1996; Olsen et al., 1996; Adams et al., 1997a; Halliday et al., 1997) and the necessity of having an adequate understanding of the data to avoid biologically implausible situations stressed (Stanley et al., 1994). Where multiple records existed, deciding which record to retain was not always straightforward. Since there were no field checks in the genetics database, incorrect and/or contradictory data could exist in the same record. Similarly, determining which

test was performed on a given occasion, or the indication for the test, was complicated by having multiple fields where this information could be entered, free-text entry and no internal data consistency checks. These features either have been, or could be easily be, corrected improving data quality and the ease with which future projects could be performed.

The number of referrals to the Section of Genetics & Metabolism ultimately determined represents a slight overestimate as it includes at least 109 women (3.2% of the 3,422 AMA women referred for genetic counselling) who were of advanced maternal age but had invasive testing due to an abnormal serum screening result. These women were not referred for routine genetic counselling, having been counselled as part of the serum screening program. However, as they chose to have an amniocentesis, both a laboratory record and an appointment record were generated.

To a limited extent, the datasets used in this study provided opportunities to verify that the appropriate linkage had been made. For example, kindred number, when known, was entered onto the AFP record permitting verification that the AFP/Genetic database linkage had identified the right woman. Similarly, AFP file number was sometimes present both on the maternal serum screening record and in a comment field on the laboratory dataset.

Although reasonable rates of linkage were achieved between and across the various datasets, the data quality occasionally limited potential data manipulations and analyses.

Specifically, it was not possible to obtain an independent estimate of the number of invasive prenatal tests performed from the hospital claims: due to block funding within the department where these tests were performed, the claims data do not capture such tests reliably. Additionally, data quality was not always optimal, as evidenced in the under-representation of claims for bleeding early in pregnancy. Such imperfect concordance has been previously described for common medical conditions such as diabetes and hypertension in a linkage of the Manitoba administrative data to a large health study (Robinson et al., 1997). Bleeding early in pregnancy, though significant for the interpretation of the maternal serum screening test and therefore accurately noted, may otherwise represent a relatively benign clinical situation so the motivation to capture such information is limited. Similarly, Treaty First Nation status is known to be imperfectly captured in the claims data. Irrespective, the decision was made to include variables such as these to obtain at least preliminary data on their impact on referral and testing.

Overall, a satisfactory linkage rate was obtained across all databases despite difficulties identifying individual pregnancies or selecting an appropriate record where more than one was present (See Section 4.1). Performing this type of record linkage permitted us to examine a complete cohort of AMA women including their pregnancy outcomes and to describe the choices made about prenatal diagnosis counselling and testing. More importantly, it permitted a better understanding of the demographic and obstetric characteristics of those AMA women who were not referred for genetic counselling.

5.2 STUDY DESIGN

This study is unique in permitting an insight into those AMA Manitoban women who do not come for genetic prenatal counselling. Such research is difficult since it requires knowledge of the entire cohort of pregnant AMA women and such information is rarely available. Manitoba is one of a very few jurisdictions where high-quality, complete and comprehensive genetic and administrative healthcare data exist jointly. Without linking to population-based data, socio-demographic profiles can only be generated for those AMA women who receive genetic counselling.

Linked data, can provide a better idea of factors predictive of referral, as well as obtaining information about that group of women not referred for counselling. This will be an invaluable tool to permit planning of educational sessions, or the targeting of specific areas or barriers identified. Population-based studies such as the one described in this thesis cannot provide the solution to the problems or circumstances they describe; rather they serve as a "jumping off" point and may indicate areas where further exploration might be useful. One such promising opportunity is the potentially beneficial relationship that already exists between the Maternal Serum Screening Program and the Section of Genetics & Metabolism. The former's established and extensive links into the physician community might be further co-opted to facilitate educating health care providers about the provision of AMA genetic services. Having demonstrated that linkages are feasible between the administrative healthcare data and the genetic and screening databases, this study has also laid the groundwork necessary to monitor and evaluate changes in AMA referral rates and patterns of maternal serum screening.

These findings are potentially generalizable to other constituencies but would be difficult to replicate because of the need for complete and accurate administrative healthcare and genetic data. Though the nature of the health system, and specifically of genetic prenatal services, in Manitoba permit a study such as this, the small number of pregnant AMA women constrain the power of the study. Other limitations of the current study are obvious, such as the lack of data describing whether an offer was made regarding referral for genetic counselling. An ideal study would combine information on the process of care with primary data from maternal interviews. However, this was not possible both due to the retrospective nature of this study and, since the AMA cohort generated was anonymous, it precluded the identification of these women.

There has been some investigation in this area locally, notably a study by Grant concerning the perceptions, attitudes and experiences of Manitoban AMA women towards prenatal diagnosis (Grant, 1993) and a project by McLaren of the factors affecting a women's decision to have prenatal diagnosis (McLaren unpublished, 1999). However, both studies were of women who had already made the decision to be referred for genetic counselling and so are of limited value in understanding the factors that might contribute to the decision to be referred for counselling.

5.3 CONCLUSIONS REGARDING PREGNANCY OUTCOMES

As indicated earlier, the outcomes of pregnancy across the groups were appropriate according to the chronology with which these events occurred. Overall, 69% of women had a livebirth, 0.6% (72) had stillbirths, 16% had social terminations and 24 (0.2%) had terminations of pregnancy for genetic or congenital reasons. These numbers compared favourably to those reported by Adams et al. (1997a). Their study population of 1.4 million births had no data on pregnancies ending in terminations and they estimated that approximately 50% of fetal deaths were not reported. In that population 86% of pregnancies resulted in a livebirth and, once the under-reporting of fetal deaths was corrected, 14% in a fetal loss. Adjusting our population to exclude social terminations, 81% of pregnancies in our cohort ended in a livebirth. Given that this population was comprised exclusively of women of advanced maternal age, we would expect a lower livebirth rate and a higher spontaneous loss rate than that seen in a population survey that encompassed pregnant women irrespective of age.

The number of pregnancies dropped substantially with increasing maternal age. Pregnancies carried to term showed a distinct income gradient with fewest AMA pregnancies in the lowest income quintile and most in the wealthiest quintile. The miscarriage rate increased with increasing maternal age, but was comparable across region of residence (17 urban vs. 15% rural) and income strata (Q1 19.9% vs. Q5 18.3%).

The proportion of social terminations also increased with increasing maternal age but was higher for urban AMA women (15% urban vs. 9% rural) and poor AMA women (Q1:

18.4% vs. Q5: 10.3%). This was not due to a disproportionate representation of poor urban women in the cohort; each income quintile contained equal proportions of urban and rural women (Table 55).

Table 55: Regional distribution within income quintiles

Quintile	Rural	Urban
1	19.4% (513)	18.3% (1,707)
2	16.8% (443)	16.8% (1,567)
3	20.1% (532)	18.3% (1,705)
4	20.5% (541)	22.0% (2,052)
5	23.2% (612)	24.6% (2,289)
Total	2,641	9,320
Missing	155	

In this study, income had been considered as a proxy for socio-economic status—a practice that is not unequivocal. The two main areas of concern are the appropriateness of inferring a woman's socio-economic status using neighbourhood income and whether this methodology is equally appropriate in both urban and rural populations. The former was specifically addressed in a study which compared individual, household and census measures in a sample of Californian women and found to be a satisfactory method of approximating individual-level socio-economic position (Krieger, 1991). The validity of using income groupings based on neighbourhood income for both urban and rural settings was examined across thirteen measures of health status in the Manitoba population and found to be acceptable (Mustard et al., 1999). Another potential problem with the use of a group-level statistic, such as income, is that it cannot be inferred when the residence is unknown (Krieger, 1992). In our population, only 1.4% (115) of records had neither residence nor income quintile assigned.

5.4 PREGNANCIES REFERRED FOR AMA GENETIC COUNSELING

Over the study period, AMA counselling referrals to the Section of Genetics & Metabolism rose only marginally. Approximately one third (3,850/12,116) of all AMA pregnancies and 41% of continuing pregnancies were referred for counselling. Sixty-seven percent (2,562/3,850) of referred pregnancies had invasive genetic prenatal testing, a figure which rose to 74% (2,562/3,457) if miscarriages and social terminations were excluded. Only the first prenatal test performed in an AMA pregnancy was counted. Most commonly this test was amniocentesis (78%). These tests represented approximately 58% (2,562/4,411) of all invasive prenatal tests performed annually (See Table 60, Appendix 4).

The majority of AMA referrals were of urban women, partially reflecting the regional distribution of AMA pregnancies in the province. Though Winnipeg is the main urban centre, accounting for approximately 60% (650,000) of Manitoba's population, about 74% of AMA women resided in urban areas. About 45% of urban AMA women were referred for genetic counselling, but only 25% of rural AMA women. These referral figures do not include the 378 AMA women who were referred but went on to miscarry, or the 50 referred women who had a social termination. Of these, 88% (331) were urban residents, suggesting that the referral rate for urban women may even be slightly higher.

Despite the absence of any direct out-of-pocket costs for medical care, a strong correspondence was seen between income and referral overall. This relationship was primarily seen for urban AMA women where the referral rate rose with increasing

household income. The same relationship was not seen for rural AMA women, where referral rates ranged between 18-25% for all but the wealthiest income quintile whose referral rate was 41%. The significance of these findings is unclear. Examining the income distribution across the complete cohort, as well as for those pregnancies remaining once miscarriages and social terminations were excluded, demonstrated that the cohorts were skewed towards the higher income quintiles (Table 56).

Table 56. Income quintile distribution within the AMA cohorts

Income quintile	% of cohort in income quintile	% in income quintile excluding miscarriages and social terminations
1	18.6% (2,220)	17.3% (1,444)
2	16.8% (2,010)	16.4% (1,364)
3	18.7% (2,237)	18.4% (1,529)
4	21.7% (2,593)	22.4% (1,864)
5	24.3% (2,901)	25.5% (2,126)
Missing	155	115
Total	12,116	8,442

When physician visits before 16 weeks gestation were examined by income, it became apparent that, though poor women were underrepresented in the cohort, they were twice as likely as wealthy AMA women to have had no prenatal visit by 16 weeks gestation (Q1: 28.9% vs. Q5: 14.8%) and also considerably less likely to have seen an obstetrician (Q1: 19.6% Q5: 35.3%).

5.5 PREGNANCIES REFERRED FOR MATERNAL SERUM SCREENING

The effect of maternal serum screening in this study was difficult to gauge since most AMA women referred for counselling to the Section of Genetics & Metabolism had this screening test and it was not possible to accurately determine if the screen had occasioned the referral or vice versa. Due to coding limitations, it was not possible to accurately determine how many of the AMA women who would not otherwise have done so, had invasive testing because of their AFP screening result. Since this was the case, the logistic regressions were repeated without including the AFP screening variable. The variable that described an increased Down syndrome risk over the age-related risk following serum screening was retained. Of the 1,486 women whose Down syndrome risk was increased following serum screening, approximately 60% were referred and 48.0% (714/1486) had invasive testing.

Though screened AMA women were equally likely to be referred irrespective of region of residence, rural AMA women were less likely to have the screening test. This agreed with previous findings. In their review of the 1990 statistics for the Manitoba Maternal Screening program and accompanying physician survey, Chodirker and Evans noted that the serum screening program clearly screened a higher proportion of urban women, and that the (rural) area with the lowest observed screening rate in the province was the same one from which some of the most critical comments about screening were received (Chodirker & Evans, 1993). Examining the AMA population that did not have serum screening, it would appear that most of the women who did not have AFP screening were also not referred for genetic counselling. Of those women who were not screened, there

was a definite income gradient, with the poorest women being less likely to have screening.

5.6 PREDICTORS OF REFERRAL FOR GENETIC COUNSELING

When included in the logistic regressions, having had an AFP screen consistently emerged as the most important predictor for both referral and uptake of invasive testing. However, due to our inability to separate out the temporal sequence of testing and referral, i.e. whether AFP screening caused a referral or resulted from one, this variable was excluded from the final models. Interestingly, significant predictors and their odds ratios changed little when the AFP screening variable was removed from the model. The final model had a respectable "goodness of fit" or ROC (receiver operator curve) statistic of 0.74. A minimum acceptable value for this statistic is 0.6, that is the predictive ability of the model is about 60%.

The strongest predictor of referral was seeing an obstetrician before 16 weeks gestation (odds ratio 4.7, 95% CI 4.1-5.5). Seeing a general practitioner by 16 weeks had a much weaker relationship with referral (odds ratio: 1.4, 95% CI: 1.2-1.6). Approximately half of the AMA women (52.7%) saw a general practitioner by 16 weeks and 33.8% were referred. Though only 27.2% of the AMA women saw an obstetrician by 16 weeks, 65.9% were referred for genetic counselling. This differential rate of referral for counselling between general practitioners and specialists raises questions as to the underlying cause. Do obstetricians have a different manner with patients making them more likely to accept the offer of genetic prenatal counselling or, does seeing a

"specialist" regarding pregnancy cause it to be perceived by the woman as at higher risk, making her more likely to accept counselling? Alternatively, are obstetricians more conversant with genetic testing guidelines? Contemporaneous qualitative data gathered for the Royal Commission on New Reproductive Technologies provides anecdotal evidence that the locus of control regarding decisions about necessary prenatal tests was often seen as the prerogative of the doctor because of his or her expertise (Tudiver, 1993).

In their examination of Canadian physicians attitudes towards prenatal diagnosis, Renaud et al., found that general practitioners were less likely to be in favour of prenatal diagnosis than were specialists (Renaud et al., 1993). Results of a physician survey performed in Manitoba in 1990 indicated a clear need for more education of general practitioners, both about prenatal diagnosis and about maternal serum screening (Chodirker & Evans, 1993). Seventy–three percent of respondents indicated that they offered referral for genetic counselling to all "eligible" women, with 4.2% stating that they never referred women and 7.3% declining to respond. However, with regard to "eligibility," over 16% of surveyed physicians did not know that a woman was a candidate for prenatal diagnosis if she was over 35 years of age, and 65% were unaware that the maternal age was calculated according to a woman's age at term. Given the disproportionately low number of women aged 35 years at term referred for counselling it would appear that this situation had not improved significantly by 1995.

Although this situation may have improved by 1999 and, given advances in serum screening that now permit a more accurate determination of Down syndrome risk, it would perhaps be prudent to examine the desirability of this somewhat arbitrary eligibility cut-off. Both referrals for counselling and AFP screening demonstrate lower than expected rates for women 35 years at term (see Tables 32 and 37). Once women are perceived to be at increased risk, they appear to be more likely both to be referred and to have AFP screening. To identify women at increased risk of Down syndrome, improving the population coverage of the serum screening program may be more prudent than attempting to educate physicians regarding the finer points of applying an unintuitive cut-off.

Other important predictors of AMA referral for genetic counselling were a Down syndrome risk determined by serum screening to be increased over the age-related risk (odds ratio: 2.7, 95% CI: 2.4-3.1), and a maternal age of 36+ years at term (36-39 years: odds ratio 2.3, 95% CI 2.1-2.5; 40+ years OR 2.2, 95% CI 1.8-2.6). The final variables that independently contributed to referral were urban residence (odds ratio: 1.9, 95%CI: 1.7-2.2), previous poor obstetric history (odds ratio: 1.9, 95% CI: 1.5-2.5) and being in the top income quintile (odds ratio: 1.6, 95% CI: 1.3-1.8).

The distinction between urban and rural residence for referral rates is hardly surprising. About 76% of all AMA women came from urban areas and most obstetricians, who comprised the group most likely to refer AMA women for counselling, also had urban practices. There may also be differences in attitude towards prenatal diagnosis between

rural and urban women, perhaps reflective of cultural differences, and in proximity to the centre where counselling or testing is offered that may explain some of the differential referral patterns. However, for those women who had a considerable distance to travel, accommodations were often made to permit counselling and testing over the course of a single visit.

A study by Kuppermann et al., in California, found that racial-ethnic background significantly influenced the likelihood of prenatal testing with Caucasians and Asians being more likely to have invasive testing (Kuppermann et al., 1996). However, this effect was not independent of socio-economic status, since the observed trends persisted, but at diminished magnitude, when socio-economic status was controlled for. In Manitoba, religion seems to play a role in the rate of prenatal referrals, particularly in rural areas: Mennonite women, who tend to reside in rural Manitoba, are reported to be more likely to decline prenatal diagnosis presumably because of religious convictions (McLaren unpublished, 1999). The Manitoba prenatal diagnosis physician survey found that 12.5% of physicians reported that patients decline counselling for religious or moral reasoning, though no data was given regarding the location of the physician's practice or their specialty (Chodirker & Evans, 1993).

That women with previous poor obstetric experiences were more commonly referred for genetic counselling was not surprising. Though a poor obstetric history is not a common reason for referral for genetic counselling, it does identify women at increased risk of miscarriage or stillbirth, or those who might who view themselves as being at increased

risk. Such women appear to desire additional information or reassurance regarding the current pregnancy and accept referral for genetic counselling.

The association of income and referral for prenatal diagnosis was not unexpected. It has long been recognised that uptake of invasive prenatal genetic diagnosis is skewed toward women of higher income. Whether this was because of increased concern regarding the likelihood of having a fetus with an abnormality, or reflected higher levels of education or the ability of the woman to surmount the practical obstacles to invasive testing, is not clear. However, even in health care systems where out-of-pocket payment for medical services is not required, income has been shown to influence both health status and use of health services (Mustard et al., 1991; Wilkins et al., 1991; Mustard et al., 1997).

5.7 PREDICTORS OF INVASIVE TESTING AMONG REFERRED WOMEN:

In the logistic regression for uptake of invasive testing among referred women, seeing a general practitioner before 16 weeks of pregnancy no longer reached significance ($p<0.05$), but the influence of a referral to an obstetrician remained the strongest predictor of invasive testing (odds ratio 2.3, 95% CI: 2.0-2.7). Belonging to either of the top two income quintiles appeared to be a stronger predictor of invasive testing than did having a Down syndrome risk increased over the age-related risk (odds ratio Quintile 4: 1.7, 95% CI: 1.3-2.1; odds ratio Quintile 5: 2.0, 95% CI: 1.6-2.5 vs. odds ratio 1.4, 95% CI: 1.2-1.7). In fact, having an increased Down syndrome risk from serum screening appeared to be less important to the decision to have invasive testing following referral than was maternal age at term for women aged 36-39 years (odds ratio 1.5, 95% CI: 1.2-1.7).

Unlike the referral analyses, residence and poor obstetric history no longer played significant roles in the decision to have invasive testing. It was interesting that residence was not a significant factor following referral for counselling, since this would seem to place less emphasis on geographic barriers to prenatal diagnosis. Not surprisingly, early complications of pregnancy had a significant negative association with testing (odds ratio: 0.6, 95% CI: 0.5-0.8, p=0.0001). Being over 40 years of age, though it had an odds ratio of 1.5 (95% CI: 1.1-1.8), had a much lower p value: 0.02 versus 0.0001 for referral.

McLaren's study of 357 AMA Manitoban women who were counselled regarding prenatal diagnosis, half of whom had testing, found that the three most important predictors of prenatal testing were previous prenatal diagnosis, counselling by a male counsellor and maternal ethnicity. These variables alone correctly identified the prenatal diagnosis decision of 64% of the women in the population (McLaren, unpublished 1999). It must, however, be noted that most of the AMA counselling at the Winnipeg centre is performed by male counsellors. Other data collected included maternal age, distance from the genetic centre and pregnancy complications prior to counselling. Women who declined testing were more likely to be unmarried (common-law or single), referred for counselling at 18+ weeks gestation, or to have a partner of Filipino, First Nations or "other" ethnic background, and less likely to have previously had invasive prenatal testing. No data was obtained on physician specialty, socio-economic status, AFP screening or result. In our study, First Nation Treaty status was also inversely associated

both with referral (odds ratio 0.7, 95% CI: 0.5-0.9, at p=0.005) and testing with an odds ratio of 0.7 (95% CI: 0.5-0.9, at p=0.02).

The ROC statistic for the final model was only 0.65; a minimum acceptable value for this statistic is 0.60. This is perhaps not surprising due to the complex nature of the decision to undergo invasive testing. The decision to have (or not have) genetic counselling can be seen as one that is made either based on strongly held personal beliefs, or as an exploratory "next step" that does not commit a woman or couple, to a course of action. The decision to have invasive testing requires a greater acknowledgement of potential consequences to the fetus and, is likely influenced by a variety of factors not captured in our model such as desire to carry the pregnancy to term, likelihood of subsequent pregnancies and family size.

5.8 AREAS FOR FUTURE RESEARCH

Several areas for future research are suggested as a result of this study. The first is to attempt to untangle the effect serum screening has on referral for AMA genetic counselling. A serum screen result returned to the doctor's office is accompanied by a reminder, when appropriate, that the woman is eligible for prenatal diagnosis based on her age. It would be interesting to see what proportion of AMA referrals are generated through this route and the outcomes in this group compared to "regular" referrals or those determined to be at an increased risk (i.e. increased risk of Down syndrome etc).

The methodology developed for the current study could also be used to look at additional years of data to see if AMA referral patterns continued to change over time with the phasing out of CVS testing and a greater community awareness of prenatal diagnosis. A larger sample size might permit additional factors, such as the effect of family size on referral, or having had a prenatal diagnosis in a previous pregnancy, to be assessed. Similarly, the population that had serum screening, irrespective of age, could be examined to see if similar utilization patterns are seen in the non-AMA population to the AMA population with respect to income and geography. Again, a larger population size will enable looking at regional distributions, rather than performing comparisons based on urban or rural residence. Finally, were the findings of this study regarding income and region of residence and their effect on referral and serum screening to be confirmed, it would be important to explore further why this might be so, and attempt to design interventions that could reduce the magnitude of these effects.

5.9 SUGGESTIONS FOR FUTURE PROGRAM DEVELOPMENT

The following section lists problem areas identified in the current study and suggests potential mechanisms for improvement. These are divided into "database" and "program" issues, the former dealing with idiosyncrasies and limitations of the screening and genetic databases used in this study, and the latter with issues regarding the delivery of the AMA prenatal diagnosis program.

5.9.1 Database management/data collection

Genetic database

1. Checks on data fields to avoid erroneous values i.e. incorrect or conflicting dates
2. Standard nomenclature for fields i.e. indication for referral and/or testing. This would reduce the need for costly and tedious data pre-processing
3. Incorporate a field in the datasets to facilitate retrieving records belonging to the same pregnancy as well as linking across the different genetics databases and to other databases.
4. Continue and encourage the practice of including other identifiers i.e. AFP file number, to facilitate linkage and cross checking between data across databases.

Maternal Serum Screening database

1. Is there a way to circumvent the use of "message 8" or to capture the information that was returned to the physician regarding the sample?
2. Continue to enter the genetics file number, when known, in the comment field to permit cross checking.
3. Consideration should be given to incorporating into the database a field which identifies those AMA women who had invasive testing as a result of an abnormal serum screen.

5.9.2 AMA prenatal diagnosis program issues

1. Patient and physician educational strategies should be targeted to rural regions in an attempt to improve serum screening and referral rates.
2. Since obstetricians appear to refer more eligible women for counselling than do general practitioners, consideration should be given to improving knowledge of AMA prenatal diagnosis testing guidelines in the latter group.
3. Patient education should be targeted toward women in lower income groups in an attempt to improve serum screening and referral rates. However, this may require a change in the overall prenatal care-seeking behaviour of this group.
4. The 35 years at term cut-off for "advanced maternal age" should be reviewed and reconsidered with respect to its importance to other risk factors for Down syndrome. This will have implications for the content of educational strategies and how they present risk factors for Down syndrome. It may prove more effective to promote serum screening of all pregnant women (combined with appropriate notification of AMA status) than to focus on increasing awareness of the appropriate cut-off for advanced maternal age.

5.10 SUMMARY OF MAJOR FINDINGS

1. Approximately one third of all AMA pregnancies and 41% of continuing pregnancies were referred for counselling. Sixty-seven percent of referred pregnancies had invasive genetic prenatal testing, a figure which rose to 74% if miscarriages and social terminations were excluded.

2. Excluding pregnancies that went on to end in a social termination or miscarriage, 45% of urban AMA women were referred for genetic counselling, but only 25% of rural AMA women.

3. Despite the absence of any direct out-of-pocket costs for medical care, a strong correspondence was seen between income and referral. This was primarily so for urban AMA women where the referral rate rose with increasing household income. The same relationship was not seen with rural AMA women. There, referral rates were relatively similar across all but the wealthiest income quintile, which had a considerably higher referral rate (though this was lower than the comparable rate for urban AMA women).

4. When physician visits before 16 weeks gestation were examined by income, it became apparent that poor women were twice as likely as wealthy AMA women to have had no prenatal visit by 16 weeks gestation (Q1: 28.9% vs. Q5: 14.8%) and also considerably less likely to have seen an obstetrician (Q1: 19.6% Q5: 35.3%).

5. Predictors of referral for AMA genetic counselling were determined to be:
   (a) Seeing an obstetrician before 16 weeks gestation (OR 4.7)
   (b) A Down syndrome risk determined by serum screening to be increased over the age-related risk (OR 2.7)
   (c) Maternal age of 36+ years at term (36-39 years: OR 2.3; 40+ years OR 2.2)
   (d) Urban residence (OR 1.9)

(e) Previous poor obstetric history (OR 1.9)

(f) Being in the top income quintile (OR 1.6, 95% CI: 1.3-1.8) and

(g) Seeing a general practitioner by 16 weeks (OR 1.4, 95% CI: 1.2-1.6).

6. Predictors of invasive prenatal testing following referral were determined to be:

(a) Seeing an obstetrician before 16 weeks gestation (OR 2.3)

(b) Belonging to one of the top two income quintiles (Quintile 4 OR: 1.7; Quintile 5 OR: 2.0)

(c) Having a Down syndrome risk increased over the age-related risk (OR 1.4)

(d) A maternal age of between 36-39 years of age at term (OR 1.5)

(e) Early complications of pregnancy had a significant *negative* association with testing (OR 0.6, p=0.0001).

BIBLIOGRAPHY

Dorland's Pocket Medical Dictionary. 23rd Ed. W.B. Saunders, 1982. Philadelphia.

Canada Health Act. R.S.C.1985, c.C-6:1985.

MCHPE Concept Dictionary - Glossary and Related Terms. Cited 20/10/1999. Available from:URL:http://www.umanitoba.ca/centres/mchpe/concept/thesaurus/thesaurus.glossary.html

MCHPE Concept Dictionary - index. Cited 20/10/1999. Available from: URL: http://www.umanitoba.ca/centres/mchpe/concept/concept.frames.html

Merriam Webster WWWebster Dictionary. Cited 20/10/1999. Available from: URL: http://www.m-w.comdictionary.htm

The On-line Medical Dictionary. Cited 20/10/99. Available from URL: http://www.graylab.ac.uk/omd/index.html

Adams MM, Wilson HG, Casto DL, Berg CJ, McDermott JM, Gaudino JA, McCarthy BJ. Constructing reproductive histories by linking vital records. *Am. J. Epidemiol.* 1997a; 145:339-348.

Adams MM, Berg CJ, McDermott JM, Gaudino JA, Casto DL, Wilson HG, McCarthy BJ. Evaluation of reproductive histories constructed by linking vital records. *Pediatr. Perinat. Epidemiol.* 1997b; 11:78-92.

Andersen R, Newman JF. Societal and individual determinants of medical care utilization in the United States. *Millbank Memorial Quarterly* 1973; 51:95-124.

Andersen RM. Revisiting the Behavioural Model and access to medical care: does it matter? *J. Health Soc. Behav.* 1995; 36:1-10.

Anderson G, Grumbach K, Luft H, Roos LL, Mustard C. Use of coronary artery bypass surgery in the United States and Canada: influence of age and income. *JAMA* 1993; 269:1661-1666.

Antonarakis SE. 10 Years of Genomics, Chromosome 21, and Down Syndrome. *Genomics* 1998; 51:1-16.

Aved BM, Irwin MM, Cummings LS, Findeisen N. Barriers to prenatal care for low-income women. *West. J. Med.* 1993; 158:493-498.

Avet-Loiseau H, Mechinaud F, Harousseau J-L. Clonal hematologic disorders in Down syndrome. A review. *J. Pediatr. Hematol. Oncol.* 1995; 17:19-24.

Berg JM, Crome L, France NE. Congenital cardiac malformations in monoglism. *Bri. Heart J.* 1960; 22:331.

Bernaschek G, Yildiz A, Kolankaya A, Stuempflen I, Deutinger J. Complications of cordocentesis in high-risk pregnancies: effects on fetal loss or preterm delivery. *Prenat. Diagn.* 1995; 15:995-1000.

Bernhardt BA, Bannerman RM. The influence of obstetricians on the utilization of amniocentesis. *Prenat. Diagn.* 1982; 2:115-121.

Bleyer A. Indications that mongoloid imbecility is a gametic mutation of degenerative type. *Am. J. Dis. Child.* 1934; 47:342.

Blustein J, Fleischman AR. The pro-life maternal-fetal medicine physician: a problem of integrity. *Hast. Center Report* 1995; 25:22-26.

Bogart MH, Pandian MR, Jones OW. Abnormal maternal serum chorionic gonadotropin levels in pregnancies with fetal chromosome abnormalities. *Prenat. Diagn.* 1987; 7:623-630.

Boue JG, Boue A. Chromosomal aberrations in spontaneous human abortions. *Comptes Rendus Hebdomadaires des Seances de l'Academie des Sciences de Science Naturelles* 1966; 263:2054-2058.

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; 18:9-20.

Brissenden JE, Costa MT, Roberts MH. Report of large kinship with familial translocation between chromosomes 21 and 22. *Can. Med. Assoc. J.* 1977; 17;117(12):1411-1413.

Brock DJ, Barron L, Jelen P, Watt M, Scrimgeour JB. Maternal serum-alpha-fetoprotein measurements as an early indicator of low birth-weight. *Lancet* 1977; 2(8032):267-268.

Brock DJ, Sutcliffe RG. Alpha-fetoprotein in the antenatal diagnosis of anencephaly and spina bifida. *Lancet* 1972; 2(7770):197-199.

Buckley LP. Congenital heart disease in infants with Down syndrome. In: Pueschel SM, Editor. *A study of the young child with Down syndrome.* New York: Human Sciences Press, 1993:351-364.

Burger PC, Vogel FS. The development of the pathologic changes of Alzheimer's disease and senile dementia in patients with Down's syndrome. *Am. J. Pathol.* 1973; 73:457-476.

Burks JA. Factors in the utilization of prenatal services by low-income black women. *Nurse Pract.* 1992; 17:34, 46-49.

Cafferata JF. Contribution a la litterature du mongolisme. *Arch. Med. Enf.* 1909; 12:929.

Canadian Collaborative CVS-Amniocentesis Clinical Trial Group. Multicenter randomised clinical trial of chorion villus sampling and amniocentesis. First report. *Lancet* 1989; 1(8628):1-6.

Canadian College of Medical Geneticists, Society of Obstetricians and Gynecologists of Canada. Canadian Guidelines for Prenatal Diagnosis of Genetic Disorders: An Update. *J. Soc. Ob. Gyn. Can.* 1993; 15 (Supp):16-39.

Carter CO, Evans KA. Risks of parents who had one child with Down's syndrome (mongolism) having another child similarly affected. *Lancet* 1961; 2:1042.

Caruso TM, Westgate M, Holmes LB. Impact of prenatal screening on the birth status of fetuses with Down syndrome at an urban hospital, 1972-1994. *Genet. Med.* 1998; 1:22-28.

Chodirker BN, Evans JA. Maternal serum AFP screening programs: the Manitoba experience. In: Volume 13 Research studies of the Royal Commission on New Reproductive Technologies. *Current Practice of Prenatal Diagnosis in Canada.* Minister of Supply and Services Canada, 1993. p. 535-610.

Coffman MA, Kinney SK, Shissler JN, Leuthard JL, DePersio SR. Reproductive services in rural Oklahoma. *Fetal Diagn. Ther.* 1993; 8(Supp 1):128-141.

Corchia C, Mastroiacovo P, Lanni R, Grimaldi V, Scarano G, Baronciani D. Social and geographic inequalities in prenatal care in Italy. *Prenat. Diagn.* 1995; 15:535-540.

Cuckle-HS, Wald-NJ, and Thompson-SG. Estimating a woman's risk of having a pregnancy associated with Down's syndrome using her age and serum alpha-fetoprotein level. *Br. J. Obstet. Gynaecol.* 1987; 94(5):387-402.

Cuckle HS, Wald NJ, Lindenbaum RH. Maternal serum alpha-fetoprotein measurement: a screening test for Down syndrome. *Lancet* 1984; 1(8383):926-929.

Cusick W, Rodis JF, Vintzileos AM, Albini SM, McMahon M, Campbell WA. Predicting pregnancy outcome from the degree of maternal serum alpha-fetoprotein elevation. *J Reprod. Med.* 1996; 41:327-332.

Daffos F, Capella-Pavlovsky M, Forestier F. Fetal blood sampling during pregnancy with use of a needle guided by ultrasound: a study of 606 consecutive cases. *Am. J. Obstet. Gynecol.* 1985; 153:655-660.

Dunn H. Record Linkage. *Am. J. Pub. Health* 1946; 36:1412-1416.

Fellegi IP, Sunter AB. A theory of record linkage. *J. Am. Stat. Assoc.* 1969; 64:1183-1210.

Ferguson-Smith MA, Yates JR. Maternal age specific rates for chromosome aberrations and factors influencing them: report of a collaborative European study on 52,965 amniocenteses. *Prenat. Diagn.* 1984; 4 Spec No:5-44.

Ford CE, Hamerton JL. The chromosomes of man. *Nature.* 1956; 1020-1023.

Ford D, Nault F. Changing fertility patterns, 1974 to 1994. *Health Report.* 1996; 8:39-46.

Fraser J, Mitchell A. Kalmuk idiocy: Report of a case with autopsy with notes on sixty-two cases. *J. Mental. Sci.* 1876; 22:169-179.

Gill L, Goldacre M, Simmons H, Bettley G, Griffith M. Computerised linking of medical records: methodological guidelines. *J. Epi. Comm. Health* 1993; 47:316-319.

Gill LE, Baldwin JA. Methods and technology of record linkage: some practical considerations. In: Baldwin JA, Acheson ED, Graham WJ, Editors. *Textbook of medical record linkage*. Oxford, New York, Tokyo: Oxford University Press, 1987. p.39-54.

Grant KA. Perceptions, attitudes and experiences of prenatal diagnosis: a Winnipeg study of women over 35. In: Volume 12 Research studies of the Royal Commission on New Reproductive Technologies. *Background and Impact on Individuals*. Minister of Supply and Services Canada, 1993. p.185-346.

Griffin GW, Gaudino JA, Rochat R. Two techniques for evaluating the accuracy of record linkages. *Am. J. Pub. Health* 1995; 85:1294-1295.

Haas JS, Brandenburg JA, Udvarhelyi IS, Epstein AM. Creating a comprehensive database to evaluate health coverage for pregnant women: the completeness and validity of a computerized linkage algorithm. *Med. Care* 1994; 32:1053-1057.

Hagemeijer A, Smit EME. Partial Trisomy 21. Further evidence that trisomy of band 21q22 is essential for Down's phenotype. *Hum. Genet.* 1977; 38:15-23.

Halliday J, Griffin O, Bankier A, Rose C, Riley M. Use of record linkage between a statewide genetics service and a birth defects/congenital malformations register to determine use of genetic counselling services. *Am. J. Med. Genet.* 1997; 72:3-10.

Hamerton JL, Evans JA, Stranc L. Prenatal diagnosis in Canada-1990: a review of genetic centres. In: Volume 13 Research Studies of the Royal Commission on New Reproductive Technologies. *Current Practice of Prenatal Diagnosis in Canada.* Minister of Supply and Services Canada, 1993. p.1-184.

Harvey SM, Faber KS. Obstacles to prenatal care following implementation of a community-based program to reduce financial barriers. *Fam. Plann. Perspect.* 1993; 25:32-36.

Hayes A, Batshaw ML. Down syndrome. *Pediatr. Clin. North Am.* 1993; 40:523-535.

Hershey DW, Crandall BF, Perdue S. Combining maternal age and serum alpha-fetoprotein to predict the risk of Down syndrome. *Obstet. Gynecol.* 1986; 68:177-180.

Holian J. Client and birth record linkage: a method, biases and lessons. *Eval. Pract.* 1996; 17:227-235.

Holtzman NA. The diffusion of new genetic tests for predicting disease. *FASEB J* 1992; 6:2806-2812.

Hook EB. Epidemiology of Down Syndrome. In: Pueschel SM, Rynders JE, Editors. *Down Syndrome. Advances in Biomedicine and the Behavioral Sciences.* Cambridge: Ware Press, 1982.

Hook EB, Mutton DE, Ide R, Alberman E, Bobrow M. The natural history of Down syndrome conceptuses diagnosed prenatally that are not electively terminated. *Am. J. Hum.Genet.* 1995; 57:875-881.

Howe GR. Use of computerised record linkage in cohort studies. *Epi. Reviews* 1998; 20:112-121.

Hubbard R. Transparent women, visible genes, and new concepts of disease. *Cam. Q. Healthcare Ethics* 1995; 4:291-295.

Institute of Medicine. *Preventing low birthweight.* Washington, D.C.: National Academy Press, 1985.

Jaro MA. Advances in record-linkage methodology as applied to matching the 1985 census of Tampa, Florida. *J. Am. Stat. Assoc.* 1989;84:414-420.

Jenkins RL. Etiology of mongolism. *Am. J. Dis. Child.* 1933; 45:506.

Johnson JL, Primas PJ, Coe MK. Factors that prevent women of low socioeconomic status from seeking prenatal care. *J. Am. Acad. Nurse Pract.* 1994; 6:105-111.

Kallen B, Mastroiacovo P, Robert E. Major congenital malformations in Down syndrome. *Am. J. Med. Genet.* 1996; 65:160-165.

Katz VL, Chescheir NC, Cefalo RC. Unexplained elevations of maternal serum alpha-fetoprotein. *Obstet. Gynecol. Surv.* 1990; 45:719-726.

King RC, Stansfield WD. *A Dictionary of Genetics.* 5 ed. New York, Oxford: Oxford University Press, 1997.

Krieger N. Women and social class: a methodological study comparing individual, household, and census measures as predictors of black/white differences in reproductive history. *J. Epi.Comm. Health* 1991; 45:35-42.

Krieger N. Overcoming the absence of socioeconomic data in medical records: validation and application of a census-based methodology. *Am. J. Pub. Health* 1992; 82:703-710.

Kuppermann M, Gates E, Washington AE. Racial-ethnic differences in prenatal diagnostic test use and outcomes: preferences, socioeconomics, or patient knowledge? *Obstet. Gynecol.* 1996; 87:675-682.

Langdon Down J. Observations on an ethnic classification of idiots. *London Hosp. Clin. Lect. Rept.* 1866; 3:259-262.

Langenbeck U, Hansmann I, Hinney B, Honig V. On the origin of the supernumary chromosome in autosomal trisomies-with special reference to Down's syndrome. *Hum. Genet.* 1976; 33:89-102.

Larson EH, Hart LG, Rosenblatt RA. Is non-metropolitan residence a risk factor for poor birth outcome in the U.S.? *Soc. Sci. Med.* 1997; 45:171-188.

LaVeist TA, Keith VM, Gutierrez ML. Black/white differences in prenatal care utilization: an assessment of predisposing and enabling factors. *Health Serv. Res.* 1995; 30:43-58.

Ledbetter DH, Zachary JM, Simpson JL, Golbus MS, Pergament E, Jackson L, Mahoney MJ, Desnick RJ, Schulman J, Copeland KL. Cytogenetic results from the U.S. Collaborative Study on CVS. *Prenat. Diagn.* 1992; 12:317-345.

Lejeune J, Gautier M, Turpin MR. Etudes des chromosomes somatiques de neuf enfants mongoliens. *CR Acad. Sci.(Paris)* 1959; 248:1721-1722.

Lippman A, Tomkins DJ, Shime J, Hamerton JL. Canadian multicentre randomized clinical trial of chorion villus sampling and amniocentesis. Final report. *Prenat. Diagn.* 1992; 12:385-408.

Lui G. Birth outcomes and the effectiveness of prenatal care. *Health Serv. Res.* 1998; 32:805-823.

MacKay IF, Fraser FC. The history and evolution of prenatal diagnosis. In: Volume 12 Research studies of the Royal Commission on New Reproductive Technologies. *Background and Impact on Individuals.* Minister of Supply and Services Canada, 1993. p.1-60.

MacLeod PM, Rosenberg MW, Butler MH, Koval SJ. A demographic and geographic analysis of the users of prenatal diagnostic services in Canada. In: Volume 12 of the Royal Commission on New Reproductive Technologies. *Current Practice of Prenatal Diagnosis in Canada.* Minister of Supply and Services Canada, 1993. p.105-184.

Magenis RE, Overton KM, Chamberlin J, Brady T, Lovrien E. Parental origin of the extra chromosome in Down's syndrome. *Hum. Genet.* 1977; 37:7-16.

Marteau T, Michie S, Drake H, Bobrow M. Public attitudes towards the selection of desirable characteristics in children. *J. Med. Genet.* 1995; 32:796-798.

Marteau TM, Kidd J, Cook R, Michie S, Johnston M, Slack J, Shaw RW. Perceived risk not actual risk predicts uptake of amniocentesis. *Br. J. Obstet. Gynaecol.* 1991; 98:282-286.

McLaren P. Parameters affecting a woman's decision to undergo amniocentesis. 1999. Unpublished. University of Manitoba.

Melnikow J, Alemagno S. Adequacy of prenatal care among inner-city women. *J. Fam. Pract.* 1993; 37:575-582.

Merkatz IR, Nitowsky HM, Macri JN, Johnson WE. An association between low maternal serum alpha-fetoprotein and fetal chromosomal abnormalities. *Am. J. Obstet. Gynecol.* 1984; 148:886-894.

Mikkelsen M. Down's syndrome. Current stage of cytogenetic research. *Humangenetik* 1971; 12:1-28.

Mintz B. Continuity of the female germ cell line from embryo to adult. *Arch. Anat. Microscop. Morphol. Exptl.* 1959; 48:155-172.

Mohr J. Foetal genetic diagnosis: development of techniques for early sampling of foetal cells. *Acta Pathol. Microbiol. Scand.* 1968; 73:73-77.

MRC working party on the evaluation of chorion villus sampling. Medical Research Council European trial of chorion villus sampling. *Lancet* 1991; 337(8756):1491-1499.

Muse AG, Mikl J, Smith PF. Evaluating the quality of anonymous record linkage using deterministic procedures with the New York State AIDS registry and a hospital discharge file. *Stat. Med.* 1995; 14:499-509.

Mustard C. *Maternal demographic risk factors and the incidence of low birthweight, Manitoba 1979-1989.* 1991; Manitoba Centre for Health Policy and Evaluation. Report 91-11-04.

Mustard C. *The utilization of prenatal care and relationship to birthweight outcome in Winnipeg, 1987-88.* 1993; Manitoba Centre of Health Policy and Evaluation. Report 93-01.

Mustard C, Derksen S, Berthelot JM, Wolfson M. Assessing ecologic proxies for household income: a comparison of household and neighbourhood level income measures in the study of population health status. *Health & Place* 1999; 5:157-171.

Mustard C, Derksen S, Berthelot JM, Wolfson M, Roos LL. Age-specific education and income gradients in morbidity and mortality in a Canadian province. *Soc. Sci. Med.* 1997; 45:383-397.

Mustard C, Roos NP. The relationship between prenatal care and pregnancy complications to birthweight in Winnipeg, Canada. *Am. J. Public Health* 1994; 84:1450-1457.

Nault F. Infant mortality and low birthweight, 1975 to 1995. *Health Reports* 1997; 9:39-46.

Newcombe HB. Record linking: the design of efficient systems for linking records into individual and family histories. *Am. J. Hum. Genet.* 1967; 19:335-359.

Newcombe HB, Fair ME, Lalonde P. Discriminating powers of partial agreements of names for linking records. Part I: The logical basis. *Methods Inf. Med.* 1989a; 28:86-91.

Newcombe HB, Fair ME, Lalonde P. Discriminating powers of partial agreements of names for linking personal records. Part II: The empirical test. *Methods Inf. Med.* 1989b; 28:92-96.

Newcombe HB, Kennedy JM. Record linkage. *Communications of the Association for Computing Machinery* 1962; 5:563-566.

Newcombe HB, Kennedy JM, Axford SJ, James AP. Automatic linkage of vital and health records. *Science* 1959; 130:954-959.

NICHHD National Registry for Amniocentesis Study Group. Midtrimester amniocentesis for prenatal diagnosis. Safety and accuracy. *JAMA.* 1976; 236:1471-1476.

Nsiah-Jefferson L. Access to reproductive genetic services for low-income women of color. *Fetal Diagn. Ther.* 1993; 8(Supp 1):107-127.

Olsen CL, Polan AK, Cross PK. Case ascertainment for state-based birth defects registries: characteristics of unreported infants ascertained through birth certificates and their impact of registry statistics in New York State. *Ped. Perinat. Epi.* 1996; 10:161-174.

Oster J. Mongolism: a clinical and genealogical investigation comprising 526 Mongols living on Seeland and neighbouring islands in Denmark. Danish Scientific Press, Copenhagen, 1953.

Palomaki GE, Knight GJ, McCarthy JE, Haddow JE, Donhowe JM. Maternal serum screening for Down syndrome in the United States: a 1995 survey. *Am. J. Obstet. Gynecol.* 1997; 176:1046-1051.

Penrose LS. The relative effects of paternal and maternal age in mongolism. *J. Genetics* 1933; 27:219-224.

Pueschel SM. Clinical aspects of Down syndrome from infancy to adulthood. *Am. J. Med. Genet.* 1990; 7(Supp):52-56.

Renaud M, Bouchard L, Bisson J, Labadie J-F, Dallaire L, Kishchuk N. Canadian physicians and prenatal diagnosis: prudence and ambivalence. In: Volume 13 Research Studies of the Royal Commission on New Reproductive Technologies. *Current Practice of Prenatal Diagnosis in Canada.* Minister of Supply and Services Canada, 1993:235-508.

Rhoads GG, Jackson LG, Schlesselman SE, de la Cruz FF, Desnick RJ, Golbus MS, Ledbetter DH, Lubs HA, Mahoney MJ, Pergament E. The safety and efficacy of chorionic villus sampling for early prenatal diagnosis of cytogenetic abnormalities. *N. Engl. J. Med.* 1989; 320:609-617.

Riessman CK. Women and medicalization: a new perspective. *Soc. Policy* 1983; 14:3-18.

Robinson JR, Young TK, Roos LL, Gelskey DE. Estimating the burden of disease. Comparing administrative data and self-reports. *Med. Care* 1997; 35:932-947.

Roos-LL J, Nicol JP, Cageorge SM. Using administrative data for longitudinal research: comparisons with primary data collection. *J. Chronic. Dis.* 1987; 40:41-49.

Roos-LL J, Wajda A, Nicol JP. The art and science of record linkage: methods that work with few identifiers. *Comput. Biol. Med.* 1986; 16:45-57.

Roos LL, Mustard CA, Nicol JP, McLerran DF, Malenka DJ, Young TK, Cohen MM.. Registries and administrative data: organization and accuracy. *Med. Care* 1993; 31:201-212.

Roos LL, Nicol JP, Johnson C, Roos NP. Using administrative databanks for research and evaluation: a case study. *Eval. Quart.* 1979; 3:236-255.

Roos LL, Sharp SM, Wajda A. Assessing data quality: a computerized approach. *Soc. Sci. Med.* 1989; 28:175-182.

Roos LL, Wajda A. Record linkage strategies. Part I: Estimating information and evaluating approaches. *Methods Inf. Med.* 1991; 30:117-123.

Rosanoff AJ, Handy LM. Etiology of mongolism with special reference to its occurrence in twins. *Am. J. Dis. Child.* 1934; 48:764

Rowe RD, Uchida IA. Cardiac malformations in mongolism: a prospective study of 184 mongoloid children. *Am. J. Med.* 1961; 31:726

SAS/STAT Software. SAS Institute. 1996; (Release 6.12)

Seals BF, Ekwo EE, Williamson RA, Hanson JW. Moral and religious influences on the amniocentesis decision. *Soc. Biol.* 1985; 32:13-30.

Shevchenko IP, Lynch JT, Mattie AS, Reed-Fourquet L.L. Verification of information in a large medical database using linkages with external databases. *Stat. Med.* 1995; 14:511-530.

Shuttleworth GE. Comment's on R. Langdon Down's paper. *J. Ment. Sci.* 1906; 52:189

Shuttleworth GE. Mongolian imbecility. *Brit. Med. J.* 1909; 2:661

Simoni G, Brambati B, Danesino C, Rossella F, Terzoli GL, Ferrari M, Fraccaro M. Efficient direct chromosome analyses and enzyme determinations from chorionic villi samples in the first trimester of pregnancy. *Hum.Genet.* 1983; 63:349-357.

Smidt-Jensen S, Permin M, Philip J, Lundsteen C, Zachary JM, Fowler SE, Gruning K. Randomised comparison of amniocentesis and transabdominal and transcervical chorionic villus sampling. *Lancet* 1992; 340(8830):1237-1244.

Smith DK, Slack J, Shaw RW, Marteau TM. Lack of knowledge in health professionals: a barrier to providing information to patients? *Qual. Health Care* 1994; 3:75-78.

Sorensen HT, Sabroe S, Olsen J. A framework for evaluation of secondary data sources for epidemiological research. *Int. J. Epi.* 1996; 25:435-442.

Stanley FJ, Croft ML, Gibbins J, Read AW. A population database for maternal and child health research in Western Australia using record linkage. *Paed. Perinatal Epi.* 1994; 8:433-447.

Statistics Canada. *Postal Code Conversion File: Detailed User Guide.* 1988. Statistics Canada. Ottawa, Ontario.

Statistics Canada. *Census Dictionary.* 1996 Statistics Canada. Ottawa, Ontario. Catalogue number 92-351-XPE

Steele MW, Breg WRJ. Chromosome analysis of human amniotic-fluid cells. *Lancet* 1966; 1(7434):383-385.

Stevens HC. Mongolian idiocy and syphilis. *JAMA* 1915; 64:1936.

Stranc LC, Evans JA, Hamerton JL. Prenatal diagnosis in Canada-1990: a review. *Prenat. Diagn.* 1994; 14:1253-1265.

Sutherland GA. Mongolian imbecility in infants. *Practitioner* 1899; 63:632.

Tabor A, Madsen M, Obel EB, Philip J, Bang J. Randomised controlled trial of genetic amniocentesis in 4606 low-risk women. *Lancet* 1986; 1(8493):1287-1292.

Thomas L. On the science and technology of medicine. In: Albrecht GL, Higgins PC, editors. *Health, Illness and Medicine: a reader in medical sociology.* Chicago: Rand McNally, 1979.

Tjio HJ, Levan A. The chromosome numbers of man. *Hereditas* 1956; 42:1-6.

Tudiver S. Manitoba voices: a qualitative study of women's experiences with technology in pregnancy. In: Volume 12 Research Studies of the Royal Commission on New Reproductive Technologies. *Background and Impact on Individuals.* Minister of Supply and Services Canada, 1993 p.347-460.

Turner, D., Stranc, L., Roos, L. L., Fields, A. L. A., and Bryant, H. Record Linkage: from theory to practice. Unpublished, 1999.

Uchida IA, Holunga R, Lawler C. Maternal radiation and chromosomal aberrations. *Lancet* 1968; 2(7577):1045-1049.

Undermann Boggs K, McLeod J, Stubbs TM. Barriers to prenatal care in Mecklenburg county: a study of 500 women. *Nth. Carolina Med. J.* 1995; 56:159-163.

van Schrojenstein Lantman de Valk HM, Haveman MJCHF. Comorbidity on people with Down's syndrome: a criteria-based analysis. *J. Intellect. Disabl.* 1996; 40:385-399.

Waardenburg PJ. *Das menschliche auge und seine erbanlagen.* Haag: Martinus Nijhoff 1932;

Wadhera S, Millar WJ. Pregnancy outcomes. *Health Reports* 1996; 8:7-15.

Wajda A, Roos LL. Simplifying record linkage: software and strategy. *Comput. Biol. Med.* 1987; 17:239-248.

Wald N, Barker S, Peto R, Brock DJ, Bonnar J. Maternal serum alpha-fetoprotein levels in multiple pregnancy. *Br. Med. J.* 1975; 1:651-652.

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; 1(8026):1323-1332.

Wald NJ, Cuckle HS, Densem JW, Nanchahal K, Royston P, Chard T, Haddow JE, Knight GJ, Palomaki GE, Canick JA. Maternal serum screening for Down's syndrome in early pregnancy. *Br. Med. J.* 1988; 297:883-887.

Wilkins R. Use of postal codes and addresses in the analysis of health data. *Health Reports.* 1993; 5:157-177.

Wilkins R, Adams O, Brancker A. Changes in mortality by income in urban Canada from 1971 to 1986. *Health Reports.* 1991; 1:137.

Williamson P, Harris R, Church S, Fiddler M, Rhind J. Prenatal genetic services for Down's syndrome: access and provision in 1990-1991. Steering Committee of the National Confidential Enquiry into Counselling for Genetic Disorders. *Br. J. Obstet. Gynaecol.* 1996; 103:676-683.

Wisniewski KE, Wisniewski HM, Wen GY. Occurrence of neuropathological changes and dementia of Alzheimer's disease in Down syndrome. *Ann. Neurol.* 1998; 17:278-282.

York R, Williams P, Munro BH. Maternal factors that influence inadequate prenatal care. *Public Health Nurs.* 1993; 10(4):241-4.

Appendix 1: ICD-9-CM definitions by topic

A. ICD-9-CM CODES POTENTIALLY INDICATING A DIAGNOSIS OF PREGNANCY

626.0x	Absence of menstruation
626.1x	Scanty or infrequent menstruation
626.4x	Irregular menstrual cycle
626.8x	Other (Includes suppression of menstruation)
626.9x	Unspecified
V22.x	Normal pregnancy (all codes)
V23.x	Supervision of high-risk pregnancy (all codes)
V72.4	Pregnancy examination or test, pregnancy unconfirmed

B. ICD-9-CM DIAGNOSES FOR PREGNANCY ENDPOINTS

Diagnoses for birth

V27.0/V30.x	Single liveborn
V27.2/V31.x	Twins, both liveborn
V27.3/V32.x	Twins, one liveborn and one stillborn
V27.5/V34.x	Other multiple birth, all liveborn
V27.6/V36.x	Other multiple birth, some liveborn
V27.9	Unspecified outcome of delivery
V33.x	Twins, unspecified
V37.x	Other multiple, unspecified
650.xx	Normal delivery
651.xx-651.9x	Multiple gestation

Diagnoses for stillbirth

V27.1	Single stillborn
V27.4	Twins, both stillborn
V27.7/V35.x	Other multiple birth, all stillborn
656.41	Intrauterine death, fetus delivered

Diagnoses for termination

779.6x	Termination of pregnancy
635.xx	Legally induced abortion
636.xx	Illegally induced abortion
637.xx	Unspecified abortion

Procedures for termination

69.01	Dilation and curettage for termination of pregnancy
69.51	Aspiration curettage for termination of pregnancy
74.91	Hysterotomy to terminate pregnancy
75.0x	Intra-amniotic injection for abortion

Diagnoses for miscarriage

761.4x	Ectopic pregnancy
656.4x	Interuterine death
632.xx	Missed abortion
634.xx	Spontaneous abortion

C. POOR OBSTETRIC HISTORY/HIGH RISK

646.3	Habitual aborter
V23.0	Pregnancy with history of infertility
V23.4	Poor obstetric history

D. EARLY COMPLICATIONS OF PREGNANCY

640.xx-640.9x	Hemorrhage in early pregnancy	
	Includes:	
	640.0x	Threatened abortion
	640.8x	Other specified hemorrhage in early pregnancy
	640.9x	Unspecified hemorrhage in early pregnancy
643.1x	Hyperemesis gravidum with metabolic disturbance	
761.0x	Incompetent cervix	
648.xx	Other current conditions in the mother classifiable elsewhere, but complicating pregnancy, childbirth or the puerperium	
	Codes used:	
	648.0x	Diabetes mellitus
	648.5x	Congenital cardiovascular disorders
	648.8x	Abnormal glucose tolerance

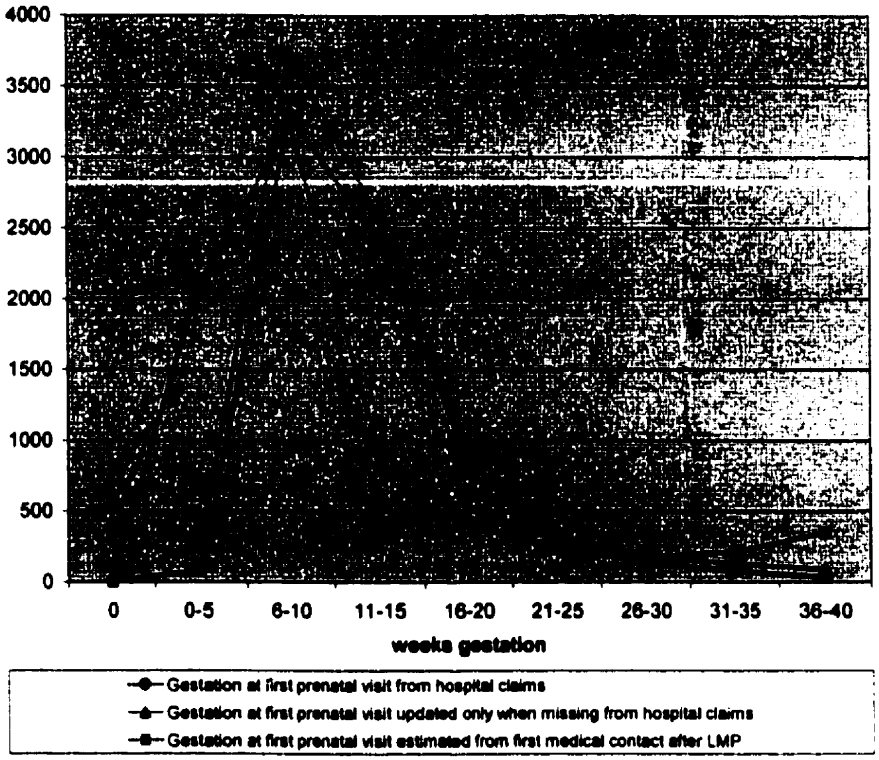
E. CONSTRUCTING THE OBGYN AND GP VARIABLES

Determining whether a woman saw a general practitioner or an obstetrician prior to 16 weeks gestation was accomplished using a combination of the following: LMP, a variable on the hospital database that indicated the gestation at first prenatal visit, and by searching medical claims for the first 15 weeks of pregnancy. Records that reported a gestation at first prenatal visit later than 15 weeks were removed. For the remaining records medical claims for the 15 weeks following LMP were examined. Where the medical claim was from an obstetrician, it was imputed that the woman had been referred to an obstetrician. Where no such claim existed, pregnancy management was inferred to have been by a general practitioner.

Where gestation at first visit were missing, as it was in 15% of records (n=1,256), this value was estimated. The first pregnancy-related physician claim after the date of LMP was determined from medical claims using a combination of tariff and diagnosis codes, following the approach of Dr Mustard (Mustard, 1993). When the variable distributions were compared, the generated variable appeared to be weighted towards an earlier initiation of prenatal care (see Figure 32 below). Consequently, the generated variable

was only used when necessary. 1,138 records were updated. The mean gestation at first prenatal visit for the updated variable was 11.3 weeks.

Figure 32. Distribution of the "gestation at first prenatal visit" variable



3.1 DETERMINING WHICH RECORDS BELONGED TO AMA WOMEN:

Since only those records where the mother was 35 years of age or older at term were to be included in our hospital abstracts cohort, it was necessary to determine the maternal age at term. This data set contained neither information on last menstrual period nor on EDC. However, most birth or stillbirth records document the baby's date of birth, gestational age at delivery and the mother's date of birth, making it possible to estimate EDC and LMP. Only records for mothers 35 years old or over at term were kept (see Table 57).

Table 57. Description of AMA pregnancy endpoints for the study period identified through hospital discharge abstracts

	# of records
AMA births with gestation	8,244
AMA births w/o Gestation	120
Total AMA births	8,364
AMA stillbirths with gestation	80
AMA stillbirths w/o Gestation	1
Total AMA stillbirths	81
AMA terminations & miscarriages	3,814
Total AMA pregnancies	12,259

3.2 RECORDS MISSING A GESTATIONAL AGE

For those birth or stillbirth records where gestational age was not present (n=121; Table 57), deciding if the record should be included in the cohort was determined using the following rationale: at least 20 weeks gestation were assumed to have been completed since, had the loss occurred prior to 20 completed weeks of gestation, this would have been considered a spontaneous loss rather than a birth or stillbirth. Thus, in order to be included in the cohort, the date of admission for the pregnancy endpoint had to be at least 20 weeks after 25/11/89 (the earliest accepted LMP in our range). No upper limit was enforced. Records for women who would have been under 35 years of age at term were removed.

Records where the pregnancy ended in a termination, whether spontaneous or surgically performed, do not include a gestational age. A minimum of five weeks gestation at the date of termination was assumed since most pregnancies are not diagnosed as such prior to this time. Thus, for inclusion in the cohort, the date of admission had to fall at least five weeks beyond 25/11/89. To exclude women who were not AMA it was required that the mother's age had to be 35 or over at term.

3.3 Obtaining Missing Gestational Ages

Hospital abstracts for deliveries missing the gestational age at delivery were merged against the AFP database in an attempt to attempt to obtain an LMP. Consequently, 57 of the 121 records with missing gestational ages were updated: 56 birth records were given a gestational age, as was one stillbirth record. Five records originally missing a gestational age were removed from the study since the gestational age determined resulted in a maternal age or LMP that fell outside the study parameters.

3.4 Duplicate Entries in the Hospital Abstract Database

A number of pairs of entries were found that appeared to refer to the same pregnancy (n=138). The record that was retained was identified using the following criteria:

If the endpoint was a birth:

a) that record where the date of admission that was confirmed against the newborn record
b) if the dates were the same, the record that contained more information/diagnoses
c) if both entries contained identical information, one was picked arbitrarily

If the endpoint was a termination:

a) that record that indicated a "complete" termination (fifth-digit code of '2')
b) if both records were identical except for service date, the later date
c) if both entries contained identical information, one was picked arbitrarily

These records, which represented 13 births, 1 stillbirth, and 124 terminations, were eliminated.

Appendix 3: Physician tariff codes[1]

A. PREGNANCY OUTCOME

4811 Extrauterine pregnancy, ectopic, removal by laparotomy
4850 Abortion, spontaneous (under 20 weeks) no surgery
4855 Abortion, spontaneous, requiring dilatation and curettage (D&C)
4860 Abortion, therapeutic, by D&C and/or suction method
4861 Abortion, therapeutic, by amnio infusion with or without D&C
4871 Vaginal delivery following previous C-section
4800 C-section (with or without sterilization)
4801 C-section, including pre and post-visits (with or without sterilization)
4821 Confinement, including antepartum and post partum visits
4822 Confinement excluding antepartum and post partum visits

B. OBSTETRIC CARE

9521 Pregnancy test
4806 Amniocentesis, initial or subsequent
4809 Incompetent cervix in pregnancy, suture
4812 Fetal transfusion
4813 Surgical induction of labour
4814 Medical induction of labour
4816 Diagnostic or therapeutic cordocentesis or fetal transfusion
4818 CVS
4819 Initial fetal assessment
4820 Subsequent fetal assessment
4823 Complete pre and post-partum visits, excluding confinement
4832 Multiple pregnancy
4833 Forceps and/or vacuum extraction
4834 Augmentation of labour
4840 PET/eclampsia
4842 Severe associated maternal condition or risk during pregnancy

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[1] A tariff code and fee is specified for every service for which a physician may bill Manitoba Health.

Appendix 4: Combining the Genetic Prenatal databases

The Genetics Appointment and Laboratory databases were read in as delimited text files and then formatted into SAS databases i.e. dates were converted to SAS dates. MHSIP registration numbers were checked for extraneous or missing characters. Remaining records with a MHSIP registration number that exceeded 6 digits in length or which contained non-numeric characters were presumed to represent an out of province patient, or an individual not represented in the administrative data, i.e. a member of the armed forces.

4.1 Fields captured from the Appointment database

The following fields were extracted from the Appointment database:

MHSIP registration	Manitoba health care number number
Kindred number	Note: There was occasionally more than one kindred number per person (a situation which was encountered in both the hardcopy and the database), or discrepancies between the two sources were occasionally encountered.
Date of birth	
Name	
Counsel date	
Referring doctor	Note: For approximately the first three years of data, referring doctor was inaccurately coded in the appointment database. This is felt to have represented a discrete event, which occurred during the data transfer process when the Section of Genetics and Metabolism moved to a different application for their patient database and does not appear to be an ongoing problem. The physician appears to be correctly listed in the laboratory database, but this information would only be available for those women who go on to have invasive testing.
LMP	Note: Last menstrual period was rarely coded in the early data.
EDC	Note: Expected date of confinement was not often coded.
Reason for referral	Note: A woman may have multiple reasons for referral in a given pregnancy i.e. AMA and abnormal AFP findings.

4.1.1 Condensing records to one per pregnancy for the Appointment database

For any individual, the appointment database potentially contained multiple records. These records could represent more than one pregnancy or multiple records for a particular pregnancy. These records were condensed to one per pregnancy as follows:

1) At least one record per MHSIP registration number was retained
2) If there was more than one record per MHSIP registration number:

Records with an appointment date within 6 weeks (either side) of the earliest "date booked" were dropped, keeping that record which contained the most information. Records thought to represent instances of multiple pregnancies during the study period were visually inspected to confirm that this was a reasonable assumption. Records with an LMP beyond October 25, 1995 or prior to November 25, 1989 were removed to ensure the cohort spanned the appropriate time frame. Similarly, records belonging to women who were not of advanced maternal age (as calculated using DOB and LMP or EDC) were also removed from the database.

4.2 Fields captured from the Laboratory database

Fields in the laboratory database included information specific to the pregnancy such as LMP, indication for testing, test type, date sample obtained and when received by the laboratory, gestation at time of testing, chromosome result, AFP file number and Genetic chart number.

4.2.1 Identifying the type of invasive genetic prenatal test

Although the laboratory database had multiple test-related fields i.e. sample type and test type, it was sometimes difficult to identify what test a woman actually had. The laboratory report number was reported to identify the type of testing performed more accurately than either sample or test type. This variable consists of an initial character which indicates the type of test performed character (A=amniocentesis, C=CVS, B=cordocentesis) followed by the last two digits of the year of testing and an accession number indicating the chronological order of all types of samples received by the laboratory. Upon inspection, it did not reliably identify the type of test performed, particularly with the early data (see Table 58) To remedy this, a new test variable was created as indicated in the "analysis designation" column of Table 58.

Table 58. Combinations of sample type, test and lab number variables in the Laboratory dataset

First character of lab number	Sample	Test	Number	Analysis designation
A	Amniotic fluid	CVS	345	CVS
A	Amniotic fluid	Pre-Termination	1	Amniocentesis
A	Amniotic fluid	Routine	4,241	Amniocentesis
A	Amniotic fluid	Routine + FISH	6	Amniocentesis
B	CVS	Routine	1	Cordocentesis
B	Cordocentesis	CVS	6	Cordocentesis
B	Cordocentesis	Routine	104	Cordocentesis
B	Cordocentesis	Routine + FISH	1	Cordocentesis
C	Amniotic fluid	Routine	2	CVS
C	CVS	CVS	35	CVS
C	CVS	Routine	471	CVS

Assigned based on gestation at which sample was taken

4.2.2 Determining the number of AMA pregnancies represented in the Laboratory data

The original laboratory file included some women who were not of advanced maternal age and more than one record per pregnancy. To determine the number of pregnancies represented in the database it was essential that LMP be determined (see Table 59). LMP was missing in 66.5% (n=3,441) of records. LMP was updated so that only 3% of AMA records lacked this information by obtaining LMP from the AFP or Appointment datasets.

Table 59. Determining LMP in the Laboratory dataset

Action	LMP present	# of LMPs updated
Prenatal samples only (n=5,174)	1,733 (33.5%)	--
Merging to Appointment database	3,976 (76.8%)	2,243
Merge to AFP database	4,465 (86.3%)	489
Update LMP with gestation	4,599 (88.9%)	134
Update LMP from text file	4,619 (89.3%)	20

The exclusions and the order in which they were executed to retain only one AMA record per pregnancy is given in Table 60. To determine which records belonged to what pregnancy sampling date was compared between records. If the difference was more than 10 weeks, the records were said to represent different pregnancies. Ten weeks was chosen since the earliest test, CVS, was usually performed at 12 weeks and the latest, cordocentesis, after 20 weeks. Thus, even had a woman come in for a CVS procedure, miscarried immediately afterward, immediately become pregnant again and come in for a CVS, more than 10 weeks would likely have elapsed. Since only one record was kept per pregnancy, the records were arranged in order of descending sampling date and the earliest record kept for each pregnancy (n=3,583). Non-AMA records were removed (n=953).

Table 60. Selecting one record per AMA pregnancy in the Laboratory dataset

Action	Number of records
Number of prenatal samples	5,174
Remove records with no LMP:	n=554
Outside time frame	n=763
Non-AMA records	n=274
Keep only one record per pregnancy	n=953
Final number of AMA records	2,630
Link to Appointment records	2,562 (97.4%)

4.3 Merging Laboratory and Appointment databases

The remaining pregnancies (n=2,630) were linked to their counterpart in the Appointment database. 97.4% (n=2,565) of the AMA pregnancies in the Laboratory database were linked to a record in the Appointment database.

Appendix 5. Logistic regressions for referral and testing

Table 61: Stepwise logistic regression model for referral, excluding AFP screening variable (8,205 observations)

VARIABLE	DESCRIPTION	BETA	S.E.	P	OR	C.I.
INTERCEPT		-2.4374	0.1099	0.0001	.	.
INDIVIDUAL CHARACTERISTICS:						
AGE3639	Age 36-39	0.8249	0.0550	0.0001	2.282	2.049 2.541
AGE40P	Age 40+	0.7833	0.0877	0.0001	2.189	1.843 2.599
SES2	Income quintile 2	0.0286	0.0890	0.7478	1.029	0.864 1.225
SES3	Income quintile 3	0.0593	0.0878	0.4996	1.061	0.893 1.260
SES4	Income quintile 4	0.2220	0.0835	0.0078	1.249	1.060 1.470
SES5	Income quintile 5	0.4388	0.0816	0.0001	1.551	1.322 1.820
			(SES test: 46.4318, 4 df, p=0.0001)			
RES	Residence	0.6667	0.0642	0.0001	1.948	1.717 2.209
TREATY	Treaty First Nation status	-0.3842	0.1381	0.0054	0.681	0.519 0.893
OBSTETRIC CHARACTERISTICS:						
POOROB	Poor obstetric hist/high risk	0.6675	0.1276	0.0001	1.949	1.518 2.503
AGERISK	DS risk > age risk	0.9892	0.0648	0.0001	2.689	2.368 3.053
OBGYN	Did the woman see an obstetrician before 16 weeks?	1.5550	0.0771	0.0001	4.735	4.071 5.507
GP	Did the woman see a GP before 16 weeks?	0.3578	0.0689	0.0001	1.430	1.249 1.637

Table 62: Stepwise logistic regression model for invasive testing excluding AFP screening variable (8,205 observations)

VARIABLE	DESCRIPTION	BETA	S.E.	P	OR	C.I.
INTERCEPT		-2.9598	0.1240	0.0001	.	.
INDIVIDUAL CHARACTERISTICS:						
AGE3639	Age 36-39	0.8583	0.0600	0.0001	2.359	2.097 2.653
AGE40P	Age 40+	0.8120	0.0937	0.0001	2.252	1.875 2.706
SES2	Income quintile 2	0.2160	0.0992	0.0295	1.241	1.022 1.508
SES3	Income quintile 3	0.1912	0.0977	0.0503	1.211	1.000 1.466
SES4	Income quintile 4	0.4197	0.0919	0.0001	1.522	1.271 1.822
SES5	Income quintile 5	0.6562	0.0895	0.0001	1.927	1.617 2.297
		(SES test: 71.1508, 4 df, p=0.0001)				
RES	Residence	0.5028	0.0704	0.0001	1.653	1.440 1.898
TREATY	Treaty First Nation	-0.3925	0.1659	0.0180	0.675	0.488 0.935
OBSTETRIC CHARACTERISTICS:						
POOROB	Poor obstetric hist/high risk	0.6476	0.1243	0.0001	1.911	1.498 2.438
COMP	Early complications of pregnancy	-0.3158	0.0851	0.0002	0.729	0.617 0.862
AGERISK	DS risk > age risk	0.9084	0.0653	0.0001	2.480	2.182 2.819
OBGYN	Did the woman see an obstetrician before 16 weeks?	1.5824	0.0832	0.0001	4.867	4.134 5.729
GP	Did the woman see a GP before 16 weeks?	0.2671	0.0782	0.0006	1.306	1.121 1.523

Table 63. Stepwise logistic regression model for invasive testing given referral, excluding AFP screening variable (3329 observations)

VARIABLE	DESCRIPTION	BETA	S.E.	P	OR	C.I.
INTERCEPT		0.00445	0.1243	0.9714	.	.
INDIVIDUAL CHARACTERISTICS:						
AGE3639	Age 36-39	0.3729	0.0907	0.0001	1.452	1.215 1.734
AGE40P	Age 40+	0.3323	0.1425	0.0194	1.395	1.055 1.845
SES2	Income quintile 2	0.3918	0.1440	0.0065	1.479	1.116 1.962
SES3	Income quintile 3	0.2996	0.1375	0.0294	1.349	1.031 1.767
SES4	Income quintile 4	0.5055	0.1303	0.0001	1.658	1.284 2.140
SES5	Income quintile 5	0.6873	0.1268	0.0001	1.988	1.551 2.549
			SES test: 32.0248, 4 df, p=0.0001			
OBSTETRIC CHARACTERISTICS:						
COMP	Early complications of pregnancy	-0.4764	0.1174	0.0001	0.621	0.493 0.782
AGERISK	DS risk > age risk	0.3696	0.0961	0.0001	1.447	1.199, 1.747
OBGYN	Did the woman see an obstetrician before 16 weeks?	0.8401	0.0866	0.0001	2.317	1.955 2.745