University of Alberta

Effectiveness of Prenatal Screening for Congenital Heart Disease in the Province of Alberta

by

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Abstract

Ultrasound technology has been available for several decades with it's origins in science, industry and military innovations. Ultrasound imaging is a non invasive procedure used for many diagnostic purposes, and is a standard of care for pregnant women. Fetal growth can be followed and congenital anomalies, including congenital heart disease (CHD), can be identified. Screening for CHD is performed as part of routine prenatal care, usually between 18 to 24 weeks gestation. The effectiveness of screening for CHD in Alberta or Canada is not known but is low in other jurisdictions. This thesis: describes the impact of CHD on the patient, family and health care system; defines the capabilities of fetal echocardiography; determines the proportion of fetuses with CHD detected prenatally in Alberta; reports risk factors for missed disease; and describes clinical outcomes for those with and without a prenatal diagnosis.

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1.1 Introduction

Congenital Heart Disease

"A congenital anomaly is an abnormality of structure, function or body metabolism that is present at birth (even if not diagnosed until later in life) and results in physical or mental disability, or is fatal"(1).

The incidence of moderate to severe congenital heart disease (CHD) is about 6/1000 live births (2) and when this is extrapolated to Alberta's population (52,000 births for 2009-2010)(3) there are approximately 156 children born, every year with CHD, who will require the care of a pediatric cardiologist. Newborns with unrecognized CHD may be discharged home and are at increased risk of dying before they can receive any intervention (4, 5).

The detection of most forms of CHD during fetal life is possible with current technology. A prenatal diagnosis allows for parental counseling, option for termination of pregnancy or preparation for the delivery of a critically ill newborn, and may prevent mortality and reduce morbidity in the neonatal period. The majority of CHD occurs in fetuses having no known risk factor for CHD (6), with the most common reason for prenatal referral to a pediatric cardiologist being a suspicion of CHD during routine obstetrical ultrasound. However, referral rates to cardiologists for suspected CHD are low, and consequently, detection for CHD in many jurisdictions is below 50% (7, 8). The percent detected or risk factors for a missed prenatal diagnosis in Alberta are not known. Research in

this area may lead to improved detection in the prenatal period for severe CHD, better outcomes for the newborn and/or children in the longer term living with CHD.

1.2 Thesis Organization

My thesis is on the effectiveness of screening for severe CHD during routine obstetrical ultrasound assessment in Alberta. It is organized as follows:

Chapter 1: Congenital Heart Disease and its Detection

Chapter one provides the reader with background information. The historical origin of ultrasound and why ultrasound has become an important component of prenatal care is reviewed. A background of the surgical advances is given and this provides insight into the currently available treatments for children with CHD. In the section on the heart, a short explanation is given of cardiac structures and the congenital cardiac lesions that affect the heart.

Chapter 2: The Impact of CHD

Chapter two explains the implications for the patient, the family and the health care system. The currently available screening processes in Alberta are outlined and explained and then the impact that a prenatal diagnosis can have on the fetus and the neonate, the prevalence of CHD and the outcomes after birth are addressed.

Chapter 3: The Research Study

Chapter three includes the study “Effectiveness of Prenatal Screening for Congenital Heart Disease in the Province of Alberta”. The objectives for the study are: to determine the percent detected, overall and by individual lesion; define risk factors for the absence of a prenatal diagnosis; and describe clinical outcomes with and without a prenatal diagnosis.

Chapter 4: Discussion and Conclusion

Chapter four explains and interprets the results of the study in detail, defines the limitations of prenatal ultrasound and then concludes with a discussion on recommendations and directions for future research.

1.3 Background

1.3.1 History of Ultrasound

The wide use of ultrasound to image fetal structures has its origins in science, the military and industry that date back two centuries. Lazzaro Spallanzani, in 1794, demonstrated how bats navigate using high frequency reflected sound waves. A century later the Curie brothers described the piezo-electric effect, making it possible to generate and receive high frequency sound waves that were eventually used in echo sounding devices. The sinking of the Titanic in 1912 prompted the first attempts at locating submerged objects leading to the use of sound navigation and ranging (SONAR) for military and civilian purposes.

During the same time, industry developed methods using sound technology to detect stress flaws in metal, often used on ships, during war time (9, 10). The transition to the use of sound for medical purposes sprang from these innovations and developed over several decades. Initially, such practices for medical purposes were met with much skepticism. It was not until Ian Donald's pinnacle publication in 1958, where he reported the use of ultrasound to diagnose a non cancerous cyst in a young woman, that the concept of using ultrasound for diagnostic purposes seemed valid (11).

The development of real time ultrasound scanners in the 1960s, and the first documented use in obstetrics by Hoffman and Hollander in 1968 opened the door to the current use of ultrasound for prenatal diagnosis (9). Eventually the technology became practical for imaging the heart and during the late 70's and early 80's, the pediatric cardiologist's growing interest in this diagnostic tool drove the need for better resolution and more powerful processors (6).

The development of this technology made it possible to diagnose most forms of congenital heart disease in the fetus. This has had a profound impact on the medical field by increasing the understanding of CHD and improving the care and outcomes for affected fetuses (12). Improvements in the management of patients with CHD including surgical techniques have provided the means for children with CHD to survive beyond childhood.

1.3.2 Surgical advances

Children with CHD today are living longer and the majority of babies born with CHD will live into adulthood (13). These improvements in survival can be attributed to advances in open heart surgery which was rarely attempted before

the 1950s. Development of “heart lung” machines during this time showed promise but the majority of patients did not survive.

Walton Lillehei successfully operated on young patients using his innovative “cross circulation” approach where a parent was used as the pump while the child’s heart was being repaired (14). This provided the evidence that surgical correction on the heart could successfully be done but it also placed the parent at risk for surgical complications. What was needed was a mechanical way to provide circulation and oxygen to the brain and the body during the surgery. Cardio pulmonary bypass developed and techniques improved between the 1950s-1970s (14). It was then possible for simple lesions such as atrial septal defects, ventricular septal detects and patent ductus arteriosus, to be closed, preventing eventual cardiac failure.

Treatment of more complex lesions followed. Fontan’s concept that the “right ventricle” could be bypassed and still provide circulation to the lungs, opened the door for palliation of children with a variety of single ventricle type defects (15).

Such advances were not without consequences. Correction of the heart defect or palliation did not guarantee a “normal” life span or quality of life. The presence of the cardiac anomaly during fetal life, and the consequences of delivery and suboptimal circulation after birth may have a profound and long lasting impact. Newborns with CHD may be affected in multiple organ systems compounding the physiological impact of the altered circulation to the body.

1.4 The Heart

The human heart is a complex organ that is composed of two collecting chambers, the atria, and two pumping chambers, the ventricles. Each ventricle is connected to an outlet vessel, the pulmonary artery from the right ventricle and the aorta from the left ventricle. There are systemic and pulmonary venous vessels that connect to the right and left atria respectively. The heart and its connecting structures are defined in a segmental way and this terminology has developed over the course of many decades.

When the heart does not form correctly during the early stages of development, the resulting outcomes are varied and in many cases very complex. It is not possible to define in this thesis, all the lesions that exist however a brief summary of the types of lesions identified in this study is given below.

1. Defects of Septation

    a. Atrial Septal Defect (ASD)- an abnormal communication between the left and right atria.

    b. Atrio-ventricular Septal Defect (AVSD) - a defect involving the atria, ventricles and inflow valves of the heart. This type of lesion is commonly associated with Trisomy 21.

    c. Ventricular Septal Defect (VSD)- an abnormal communication between the left and right ventricle

2. Defects of connection

    a. Transposition of the Great arteries (TGA) –the pulmonary artery and the aorta arise from the incorrect ventricle. In come cases the ventricles

may also be connected to the improper atria and this is called “corrected” transposition

b. Double Outlet Right Ventricle (DORV) – both the pulmonary artery and the aorta arise from the right ventricle.

c. Truncus Arteriosus (Truncus) – there is only one outlet from the heart providing circulation to the body and to the lungs. There is also a large ventricular septal defect (VSD) between the ventricles which allows the blood to flow from both ventricles to the single outlet.

d. Double Inlet Left Ventricle (DILV) - both the atria are connected to the left ventricle.

3. Defects of development.

a. Single ventricle hearts - such as Hypoplastic Left Heart Syndrome (the left ventricle has failed to grow properly) and hypoplastic right heart (the right ventricle has not developed to full size)

b. Tricuspid Atresia - the tricuspid valve (the valve between the right atria and ventricle) has not developed.

c. Ebstein’s Anomaly - the tricuspid valve is abnormally formed and positioned.

4. Obstructive Lesions

a. Aortic Stenosis - the aortic valve is abnormal obstructing the blood flow from the left ventricle to the body

b. Pulmonary Stenosis - the pulmonary valve is abnormal obstructing the blood flow from the right ventricle to the lungs.

c. Coarctation - the distal part of the aortic arch obstructs blood flow to the lower body. In extreme cases the aortic arch may be completely interrupted.

d. Shone's Complex - the left sided structures such as the mitral valve, aortic valve and the aortic arch are all abnormal, affecting the blood supply to the body.

e. Tetralogy of Fallot (TOF) - the outflow tract from the right ventricle to the pulmonary artery is hypoplastic and a large VSD exists beneath the aortic valve.

Some lesions are "duct dependent", which means that once the baby is born, the fetal circulation (the ductus arteriosus and the foramen ovale) must remain open for sufficient blood flow to reach all parts of the body. These duct dependent lesions include hypoplastic left heart syndrome, pulmonary atresia, severe coarctation, interruption of the aortic arch and complete transposition of the great arteries.

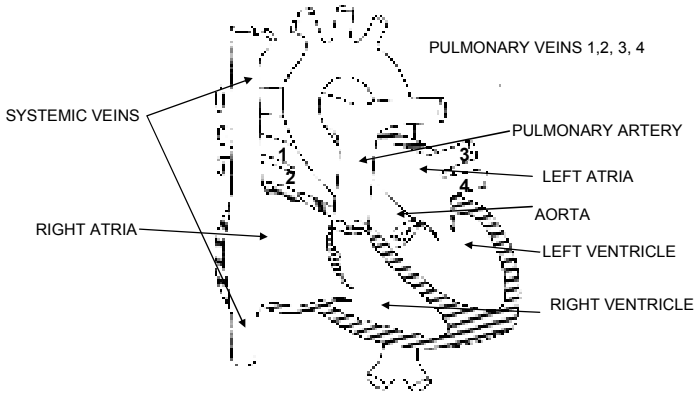

Figure 1: Normal Cardiac structures

Other lesions provide adequate blood circulation to all parts of the body but allow mixing of the oxygen rich blood with the “blue” venous blood. The lungs may receive too much blood flow causing congestion and heart failure. Each cardiac lesion also has a spectrum of severity that impacts the survival for the babies affected.

1.5 Summary

Ultrasound has become a widely used diagnostic tool for detection of congenital anomalies in the fetus. The child who is born with CHD may need immediate attention in the newborn period. Many forms of CHD may now be surgically corrected or palliated and advances in these areas have improved survival for children born with CHD. Efforts are now focused on limiting the negative impact in the long term for these children, adolescents and adults living with CHD.

Chapter 2: The Impact of CHD

2.1 Introduction

CHD is responsible for 3% of neonatal deaths in the U.S. (13). In the UK, approximately 20% of affected babies will die before one year of age with 95% of those surviving infancy living to 16 years of age (16). As outlined in the previous chapter, surgical palliation and correction for CHD has developed over the past several decades. Long term outcomes for these patients are just now becoming evident.

This chapter will address and review: the concerns for the patient, family and medical system; the available and commonly used screening protocols; the utility of fetal echocardiography; and the impact of prenatal diagnosis.

2.2 Impact of CHD

Three areas of concern will be addressed in the following sections. The implications related to:

1. the central nervous system of the patient:
2. the impact on the family unit: and
3. the changes that are taking place in medical systems as they adjust to the growing numbers of patents with CHD.

2.2.1 Impact on the Central Nervous system

Outcomes in the pre and post operative period have improved but survivors still live with long term disabilities. The central nervous system is vulnerable and up to 2/3 of children who have undergone cardiac repair will have some form of neurological deficit (13, 17). School aged children with CHD have higher incidences of learning disabilities, hyperactivity, attention deficit disorders and behavioral problems (18). These deficits may be a result of injury in the pre, peri and post operative periods due to metabolic acidosis, prolonged hypothermia and bypass, long post operative ventilation requirements and repeated surgeries.

Brain injury may occur after birth but children born with CHD may already be predisposed to neurological abnormalities. Some neonates with CHD show abnormal brain development at birth suggesting that the fetal brain is negatively affected during pregnancy (19). Cardiovascular and neurological development occurs during the same embryological time frames and brain development is dependent on nutrient-rich blood flow (20). The fetus affected by some forms of CHD experiences decreased oxygen levels to the brain and other vital organs. Consequently, decreases in cerebrovascular resistance in these areas occur in efforts to compensate for the lack of oxygen (21). Certain parts of the brain are more reactive to this “brain sparing” effect than others but the cerebral arteries will eventually lose this ability over long periods of compromise (17). The severity of the heart lesion most likely impacts the degree of compromise exerted on brain development; particularly those lesions that alter the direct delivery of oxygen rich blood supplied by the right ventricle. Such altered physiology, for

example is evident in transposition of the great arteries and hearts with a single pumping chamber (19).

As infants transition into childhood, the longer term neurological effects have become evident. Griffin's review on the academic outcomes for school aged children living with CHD showed significant differences in academic achievement between those children with CHD and normal controls (22).

The contributions of the pre natal and post natal environments to the neurological deficits are unclear. Research in this area has become increasingly important to document the long term impact of CHD for the patient, the family and the public health sector.

2.2.2 Impact on Family

The impact on the patient may be obvious, but the families of these patients may be affected negatively. The family burden may continue well into adulthood as it has been shown that patients are more likely than healthy peers to remain dependent on the family unit (23). The increased financial burden alone is insurmountable for many families. The family has to cope with costs related to travel, hospitalizations and medications and becomes anxiety ridden while attempting to keep both parents employed during this stressful time. Making the necessary lifestyle changes to care for a sick child creates emotional and chronic physiological stresses that continue throughout the life of the child. Many families express the anxiety of dealing with the uncertainty of what the future holds (24). Children, adolescents and adults with CHD have a significant risk of dying prematurely. In one cohort of patients with complex CHD who were

18 to 32 years of age, identified retrospectively in 1999, 49% (123 of 251) had died (25).

As patients and families cope with the challenges associated with the physical and neuro -developmental deficits, health related quality of life (QOL) becomes an important factor. QOL scores in most dimensions, for children who undergo surgery, were significantly lower than for the general population (25, 26). Body image, social and emotional functioning and family and peer relationships were adversely affected (23). Parents of children with CHD suffer an appreciable reduced QOL which is directly related to the clinical status of their child (27). Such long term problems require continued follow up. This follow up involves medical interventions for some as well as social and financial support and family counseling.

As the numbers of children and adult survivors with CHD continue to increase, the growing impact on the health care system deserves consideration.

2.2.3 Medical System Requirements.

The prevalence of CHD in any population is a changing parameter that is difficult to estimate at any given time. A population based study from Quebec in 2010 reported a prevalence of 4/1000 adults and 12/1000 children with CHD. Extrapolated to the Canadian population of 24 million, is it estimated that there are 96,000 adults living with CHD in our country (28). These numbers have increased greatly over the past few decades and will continue to increase as the majority of babies born with CHD now reach adolescence (13, 29). The treatment and management of adults with CHD has become an area of sub

specialization in the field of adult cardiology, with its own mandates and guidelines (28).

The transition of the pediatric patient to the adult medical system requires a planned process involving the pediatric and adult centers to prevent patients being lost to follow-up (30). Adult centers are developing the strategies to optimize the care of the adult patient with CHD which requires an extensive medical team. This team includes the services of cardiologists, surgical and interventional specialists, genetic counselors and specialists in the area of pregnancy and contraception, for management of women with CHD who are of child bearing age (31).

Having a newborn with CHD is a life changing event. The impact of this should be considered for each woman who becomes pregnant. Providing women and families with counseling and choices in the prenatal period is not only possible, but necessary. Improved prenatal screening is required if women and families are to be provided with this type of service.

2.3 Fetal screening: a short outline

The majority of pregnant women will have prenatal testing that will include ultrasound assessment of the fetus at various stages throughout the pregnancy. The following section outlines the screening processes available in Alberta at various periods during the pregnancy and the impact a prenatal diagnosis may have on the pregnancy and on neonatal outcomes.

2.3.1 Early pregnancy screening

In the first trimester, ultrasound and blood serum markers are used to screen for chromosomal abnormalities, particularly Trisomy 21 and neural tube defects (32). Ultrasound assessment in the first and early second trimester, between 11 to 14 weeks gestation may image the fold at the back of the fetal neck (nuchal fold). An increased measurement of this fold is associated with increased risk of Trisomy 21 and other chromosomal abnormalities (figure 2). The results of these tests and other factors, such as the mother's age and ethnicity, are combined and a risk factor may be calculated. If the risk factor is increased, chorionic villus sampling or amniocenthesis (DNA testing) may be offered to confirm the presence of anuploidy. When markers are abnormal, further testing at tertiary care centers is commonly recommended.

The nuchal fold may also be increased in the presence of normal chromosomes (33). In such cases, the risk for CHD is increased and mothers should be referred for a fetal echocardiogram, to rule out CHD. This type of ultrasound examination is supervised and interpreted by a pediatric cardiologist and involves a more comprehensive assessment of the fetal heart than one done during routine obstetrical screening.

Early ultrasound assessment of structural defects in the fetus is now more common, with the superior resolution of current ultrasound equipment (34). If the mother is sent for a dedicated fetal echocardiography study in the early stages of pregnancy, a high frequency trans vaginal probe may be used to image the fetal heart (35). In cases where a diagnosis of severe CHD is made, along with positive findings from the "first trimester combined screening test", the parents can be counseled accordingly at an early stage in the pregnancy.

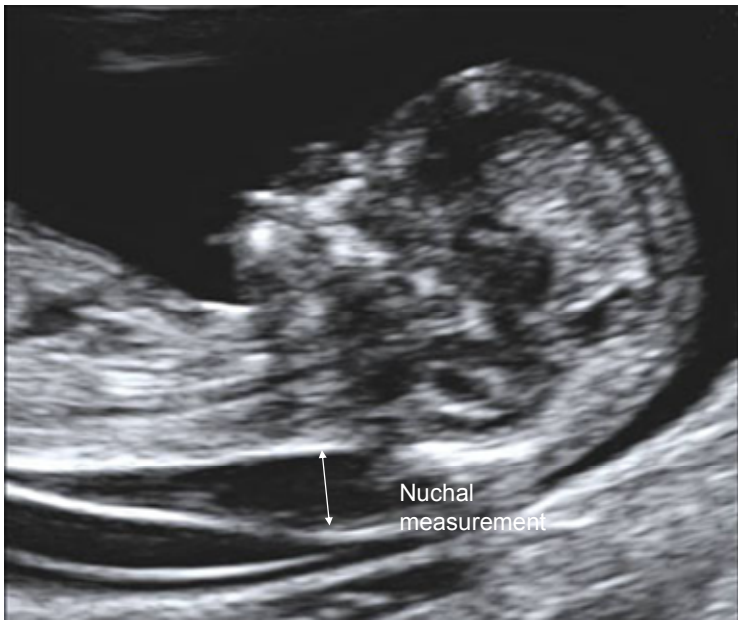

Figure 2: Ultrasound picture of increased nuchal fold.

2.3.2 Second trimester assessment

An ultrasound that is performed early in the first trimester is used to determine the gestational age of the fetus. Once 18 to 24 weeks gestation is reached, a more comprehensive ultrasound assessment is performed. The timing of this second assessment is more conducive to quality images due to the increased size of the fetus and the progression of the uterus out of the pelvis. The fetal heart is also imaged at this time, however the images obtained and the degree to which the heart is assessed varies widely (36, 37).

The AIUM (American Institute of Ultrasound in Medicine) is the governing professional body for the practice of medical ultrasound. The “Practice Guideline for the Performance of Obstetric Ultrasound Examinations” states, "The basic

cardiac examination includes a 4-chamber view of the fetal heart. If technically feasible, views of the outflow tracts should be attempted as part of the cardiac screening examination."

It is commonly felt by those who perform fetal echocardiography that images of the outflow tracts must be part of all routine anatomy fetal assessments if the majority of cardiac pathology is to be diagnosed before birth (8, 34, 38). Some cardiac lesions, such as complete transposition of the great arteries and tetralogy of Fallot, cannot be recognized prenatally if only the 4 chamber view is visualized, because in many of these cases, this view appears normal. Many centers that do fetal screening provide a more thorough cardiac assessment, regardless of the minimum recommendations of the AIUM. Still, such structural abnormalities may not be easily recognized by groups doing routine screening.

Pediatric cardiac programs that take the initiative to educate personnel involved in screening can improve the proportions of severe CHD detected prenatally (4, 8, 38, 39). Collaboration between specialties, i.e. those who do fetal echocardiography and obstetrics and radiology groups involved in fetal screening at the local and tertiary care centers, provide the opportunity for communication and feedback. Programs with such initiatives can optimize triaging for mothers with an affected fetus and provide continuity of care during pregnancy and after.

Despite the almost universal use of ultrasound as part of prenatal care, in the western world, the detection for CHD has remained in most cases well below 50% (7, 40, 41). If prenatal detection of severe CHD is to have a positive impact on the management and outcomes for babies born with CHD, the percentages detected must increase substantially.

2.3.3 Utility of Fetal Echocardiography

Fetal echocardiography (Fetal Echo) has proven to be a valuable tool for the detection of all forms of cardiac problems (12, 34, 42, 43). It has been shown to be highly accurate in the diagnosis of CHD with strong correlation to the postnatal diagnosis (34, 44). The management of women with affected fetuses has changed with the involvement of multidisciplinary teams focused on providing optimal care during the pregnancy. This collaboration often results in delivery of the fetus in a tertiary care center. Women who are known to be at higher risk than the general population for having a child with CHD, may be referred directly to a pediatric cardiologist. A family history of CHD, a previous child with a chromosomal abnormality, maternal disease such as diabetes and exposure to some environmental factors (e.g. maternal alcohol use) increase the risk for the fetus. A Fetal Echo may be done as early as 12 weeks but more commonly the study is successfully completed between 18 and 24 weeks gestation.

The majority of babies born, however, are born to mothers who are at low risk of having a child with CHD. Mothers may never be referred for Fetal Echo if the CHD is not discovered at the routine 18 to 24 week scan (section 2.3.2) and the CHD will remain undetected until after birth.

2.4 Impact of a Prenatal Diagnosis.

CHD is a rare occurrence but it still has a profound impact on affected children, their families and the health care system. In Alberta approximately 350

babies are born each year with some form of CHD. Half of those will have moderate to severe lesions (5). The rarity of the disease, the heterogeneity of lesions and the spectrum of severity has made it difficult to study the impact of a prenatal diagnosis on outcomes.

A large population based study in Paris showed a reduction in neonatal deaths as prenatal detection of CHD increased over time (45). The majority of babies with CHD, even without a prenatal diagnosis, survive beyond childhood but morbidity, especially for some lesions, is reduced for those with a prenatal diagnosis (12, 44, 46-49). Prevention of physiological compromise in the preoperative period, earlier intervention and shorter hospital admissions has the potential for improved outcomes for babies and for children and adults in the longer term.

Elective pregnancy terminations increase with earlier detection of severe CHD and this has the potential for changing the spectrum of lesions seen in the neonatal period (44, 50, 51). Estimates of a reduction of 21% in the prevalence of CHD are possible with better and earlier diagnosis (42). The potential impact on pediatric cardiology, cardiac surgery and the follow through to adult groups can only be speculated.

The management of the fetus and mother is optimized with the knowledge provided by a prenatal diagnosis (5, 12, 37). The fetus may be followed throughout the pregnancy to screen for progression of disease (52). Early intervention and treatment is possible for some cases, particularly when the fetus is affected by abnormal cardiac function or rhythm (53-55). For example, the administration of an anti arrhythmic drug in sufficient amounts to the mother may normalize the rhythm of the fetal heart. Controlling abnormal rhythms maintains good cardiac output and prevents fetal compromise. Interventions for

structural obstructive lesions, such as aortic and pulmonary stenosis, have been attempted prenatally and are offered in extreme cases in only a few centers. This involves insertion of a catheter with a balloon tip, through the mothers' abdomen and into the fetal heart, to dilate the affected heart valve. Such interventions are based on the concept that improving and maintaining blood flow to the affected cardiac chamber will allow continued growth and prevent hypoplasia of that chamber. Ultimately, such techniques may prevent the need for surgical palliation in the neonate. Currently, this kind of fetal intervention, although promising, has had limited success. (56, 57)

2.5 Summary

CHD has a profound impact on the patient, the family and the health care system. Improved screening modalities have increased the detection for CHD in the prenatal period. A prenatal diagnosis of CHD has important implications for the mother, fetus and newborn. Some lesions may be managed and treated in the fetus. Increased detection may reduce neonatal mortality and morbidity, change the spectrum of disease seen in the post natal period and allow for better care and management of the mother and fetus.

Chapter 3: The Research Study: *Effectiveness of Prenatal Screening for Congenital Heart Disease in the Province of Alberta*

3.1 Abstract

Objectives: To determine the frequency of prenatal detection of severe congenital heart disease (CHD), its influence on outcomes and risk factors for the absence of a prenatal diagnosis in Alberta.

Study Design and Methods: We enrolled children less than one year of age undergoing catheter or surgical intervention for CHD in the province of Alberta between January 1st 2007 and December 31st, 2010. We also identified pregnancy terminations and sudden infant deaths having a diagnosis of severe CHD. Data was obtained by review of patient charts and databases. Student t-test, Chi-square test, Fisher's exact test and logistic regression were used for analysis.

Results: One hundred and eighty eight of 374 fetuses with severe CHD were detected prenatally (50%). Approximately half (49%) of those detected before 24 weeks led to terminations. Fetuses having a lesion associated with an abnormal 4 chamber view were more frequently diagnosed before birth than after birth (RR=**1.86, 95% CI (1.48, 2.35), *P* <0.001**). The proportion diagnosed prenatally was significantly lower in the Central Region of Alberta in comparison to the Calgary/South region (p=0.04). Infants with a prenatal detection had fewer days to admission (P<0.001) and to operation (P=0.003), and higher PaO_2 levels

(P=0.008) and use of prostaglandins (P=0.001) than infants detected after birth. Sub-group analysis for infants who underwent surgery within 15 days of age, with a prenatal detection compared to those with a postnatal diagnosis, revealed higher preductal O_2 saturations (P=0.04), fewer days to admission (P= 0.03) and less requirement for intubation (P=0.004), atrioseptostomy (p=0.04) and inotropes (P=0.001) . Those infants diagnosed prenatally with duct dependent lesions revealed significantly higher preductal O_2 saturations (P=0.02) and significantly shorter cross clamp times (P=0.01).

Conclusion: Only 50% of fetuses with severe CHD were detected in the prenatal period. Prenatal detection may improve postnatal clinical outcomes for children born with severe CHD. The type of cardiac lesion and the place of residence were factors related to prenatal detection.

3.2 Introduction

CHD is a common form of congenital anomaly. Health Canada reported the incidence, for all forms, of CHD in 1999 as 10 per 1000 live births (58). The incidence of moderate to severe forms of CHD has been reported in other countries as ranging from 3 to 6 per 1000 live births (2). There is significant mortality and morbidity associated with this diagnosis; however, a prenatal diagnosis may lead to improved management and outcomes for children born with CHD (59-61). Since most cases of CHD occur in low-risk groups, the diagnosis of CHD in the fetus must be determined at the time of routine obstetric ultrasound examinations. In spite of the nearly universal use of routine ultrasound screening, proportions of fetuses having CHD detected in the prenatal period remain low in most centers (60, 62). The percent detected prenatally in Alberta is not known. Therefore, our objectives were to estimate the proportion of fetuses with severe CHD detected prenatally in Alberta, define the reasons for missed diagnoses in the prenatal period and evaluate the impact of a prenatal diagnosis on postnatal outcomes.

The Stollery Children's Hospital is the center of pediatric cardiac surgery and catheter intervention in Alberta. All children who require this type of intervention, including all infants with severe CHD lesions, are referred to this center.

3.3 Research Methods

3.3.1 Inclusion Criteria

The subjects included in our study are: (1) all patients who were residents of Alberta, referred to the Stollery Children's Hospital with a diagnosis of "severe" CHD and had surgery and/or intervention before turning one year of age; (2) children under one year of age who may have died outside of the hospital as a result of CHD; and (3) pregnancy terminations resulting from a diagnosis of CHD. Severe CHD was defined as having a requirement for surgery or intervention before one year of age. This definition has been used previously (63).

3.3.2 Exclusion Criteria

Simple lesions such as atrial septal defect, single ventricular septal defect, and patent ductus arteriosus were excluded even if intervention or surgery occurred in the first year of life. These lesions may cause excessive blood flow to the lungs and may require closure early on, however, they are not considered life threatening or in the realm of severe lesions. Atrial septal defects are difficult to assess in fetal life due to the presence of the normal foramen ovale, which is an opening between the two atria and shunts blood away from the lungs. The ductus arteriosus is a normal communication in the fetus, between the pulmonary artery and the aorta, and also shunts blood away form the lungs. It may persist after birth and require surgical closure but it is not possible to predict this outcome in the fetus. Single ventricular septal defects, if small to moderate in size, commonly close without intervention and if found in the prenatal period are usually of little concern but would warrant post natal follow up.

Fetuses and children with severe CHD who were found to have other multiple congenital anomalies were also excluded from the study as this would have prompted further investigation and possible fetal echocardiography studies which would preclude them to having a prenatal diagnosis (Appendix 1). Children were also excluded from the study if the timing of diagnosis (prenatal vs. postnatal) could not be determined.

3.3.3 Chart and database review

Data collection forms (Appendix 2) were developed and used to record patient data from medical charts all of which were retrospectively accessed in the medical record departments at the University of Alberta, Stollery Children's Hospital and the Royal Alexandra Hospital in Edmonton, and the Alberta Children's Hospital and The Foothills Hospital in Calgary. Online databases were also accessed in most cases as needed, but particularly when the information in the chart was not evident or clarification was needed. The Office of the Chief Medical Examiner provided information related to sudden infant deaths. Charts and termination records were reviewed for evidence of severe CHD and inclusion and exclusion criteria.

3.3.4 Parental Survey

Parents were approached and asked to complete a survey related to the prenatal care they received. The purpose of the survey was to evaluate the type and frequency of prenatal screening available and utilized by pregnant women in

Alberta. If parents refused to participate in the study, the child's information was not used as part of the data.

3.3.5 Classifications

Geographical Regions

The place of residence of each patient at the time of the chart review was recorded and grouped into 5 geographical regions across Alberta. These regions are the 5 provincial administrative zones as determined by Alberta Health Services (64).

Classification of lesion type

Each patient was categorized to one of 23 lesions (Appendix 3). It is common for more than one cardiac lesion to occur in the same patient and it was necessary to group some of the lesions similar in nature into one of three categories. These categories included, single right ventricle, single left ventricle and heterotaxies/complex. For single right and left ventricle, any lesion type where the main ventricle was morphologically either a right or left ventricle was given this designation. Other complex lesions with situs ambiguous and complex intra cardiac pathology were given the designation of heterotaxy/complex. Each specific cardiac lesion was also coded as having either a normal or abnormal 4 chamber view.

3.3.6 Data Management

The patient information collected from charts and digital databases was recorded onto the data collection forms and then transcribed into the REDCap™ online database. Upon completion of the data collection, the data was then exported to Stata (College Station, Tx) for statistical analysis.

3.3.7 Statistical Analysis

Exploratory data analysis was conducted to identify any appreciable outliers in distribution patterns. Gestational age at diagnosis and at birth, type of prenatal screening received and numbers for each lesion were examined for their distributions. Detection percentages were calculated for the entire cohort, for individual lesions and by region. Days to admission, operation and/or intervention were calculated from the date of birth. Days to extubation, transfer to the ward and to discharge were calculated from the day of admission.

Variables that measure the patient clinical status before, during and after surgery were analyzed to assess differences between those infants who had a prenatal diagnosis and those who were diagnosed only after birth. These variables include blood results (gases, lactate, creatinine, urea, etc.); requirement for intubation, CPR, or atrioseptostomy; cardiopulmonary bypass time; and post-operative clinical events such as stroke, seizures or renal failure (Appendix 2).

Student t-test, Chi squared and Fisher's exact tests were used to determine differences in outcomes for the prenatal and postnatally detected groups. Multiple logistic regression was used to determine detection percentages across regions adjusting for differences in detection percentages in

each region by lesion type. *P* values were two sided and considered significant at the 0.05 level.

3.3.8 Sub-group Analysis

A sub-group analysis was completed for:

1. those who had surgery or intervention before 15 days of age; and
2. those with duct dependent lesions: (4 lesions - single right ventricle, pulmonary atresia with and without VSD and transposition of the great arteries)

Of the wide variety of lesions we included, some are more severe than others, and each individual lesion also has a spectrum of severity. Children, who required surgery within 15 days of life and those with duct dependent lesions, would be those with the more severe disease and/or lesion. The purpose for these sub-group analyses was to have groups that are more homogeneous and to account for the tendency for the prenatally detected group to have the more severe types of CHD.

All statistical analyses were conducted in Stata, version 10 (Statacorp, 4905 Lakeway Drive, College Station, Texas 77845, USA).

3.3.9 Ethical Considerations

Approval for this study was obtained through the Health Research Ethics Board at the University of Alberta in Edmonton and the Conjoint Health Research Ethics Board in Calgary.

Patient confidentiality

Each patient in the study was given a unique identifier that is known only to the study investigators. All documents were kept in a secure and locked location. Once the study is completed the files will be stored for 5 years at an offsite facility and then the information will be destroyed.

Parental involvement

Parents were approached and invited to complete a survey. This stressful period can be overwhelming and often they are approached by multiple individuals who are involved in research. It was helpful to involve the nurses at the bedside, in cases where the child's condition was tenuous, to determine the parents' anxiety level. At times this contact was delayed until the child's condition changed for the better. Every effort was made to convey to the parents that their participation was completely voluntary and that refusal to participate would not affect the care that they and their child received.

3.4 Results

There were a total of 374 subjects meeting eligibility criteria; 327 infants requiring catheter or surgical intervention between January 1st 2007- December 31st 2010, and 47 pregnancy terminations for severe CHD. No out-of-hospital sudden infant deaths were attributed to unrecognized CHD. The demographic characteristics of the infants are shown in Table 1. The prenatally detected group tended to have a younger gestational age at birth (P=0.06). Infants with a prenatal detection tended to be admitted to hospital sooner, but remained in hospital longer than those diagnosed in the postnatal period. The majority of

patients resided in the Calgary and Edmonton areas, 66% combined, with the smallest number 8%, coming from the south region of the province where the percentage detected prenatally was highest.

Table 1: Demographic and Clinical Characteristics of Infants

	Mean (SD) N=327	
	Postnatally detected	Prenatally detected
Gestational age at birth (weeks)	38.8 (2.2) n=158	38.39(2.2) n=133
Gestational age at diagnosis (weeks)	NA	25.9 (5.6) n=103
Days to Admission	79.1 (93.2) n=186	43.1 (80.6) n=140
Days to Discharge	32.70(64.4) n=169	36.98(48.6) n=128

Family Residence at admission of Infant

	Postnatally detected	Prenatally detected (%)
Calgary area	58	68(55)
Edmonton area	60	60 (50)
Central	30	17 (36)
North	25	24 (49)
South	13	19 (59)

Figure 3 outlines the results of the survey summarizing the prenatal screening received during the course of the pregnancy. A total of 103 mothers were approached to complete the survey of which 97 agreed to participate. Of the 97, one mother admitted to having no prenatal screening done. The majority of mothers (91%) reported having an anatomy scan during the 18 to 24 week gestation period. Half of the mothers (52% or 50 of 97) reported having a fetal echocardiography scan. The fetal echocardiography reports were consistent with the post-natal diagnosis in all cases expect one. In one case that was reported

normal, the newborn was discovered to have complete transposition of the great arteries at birth. A family history of CHD was reported for 25%.

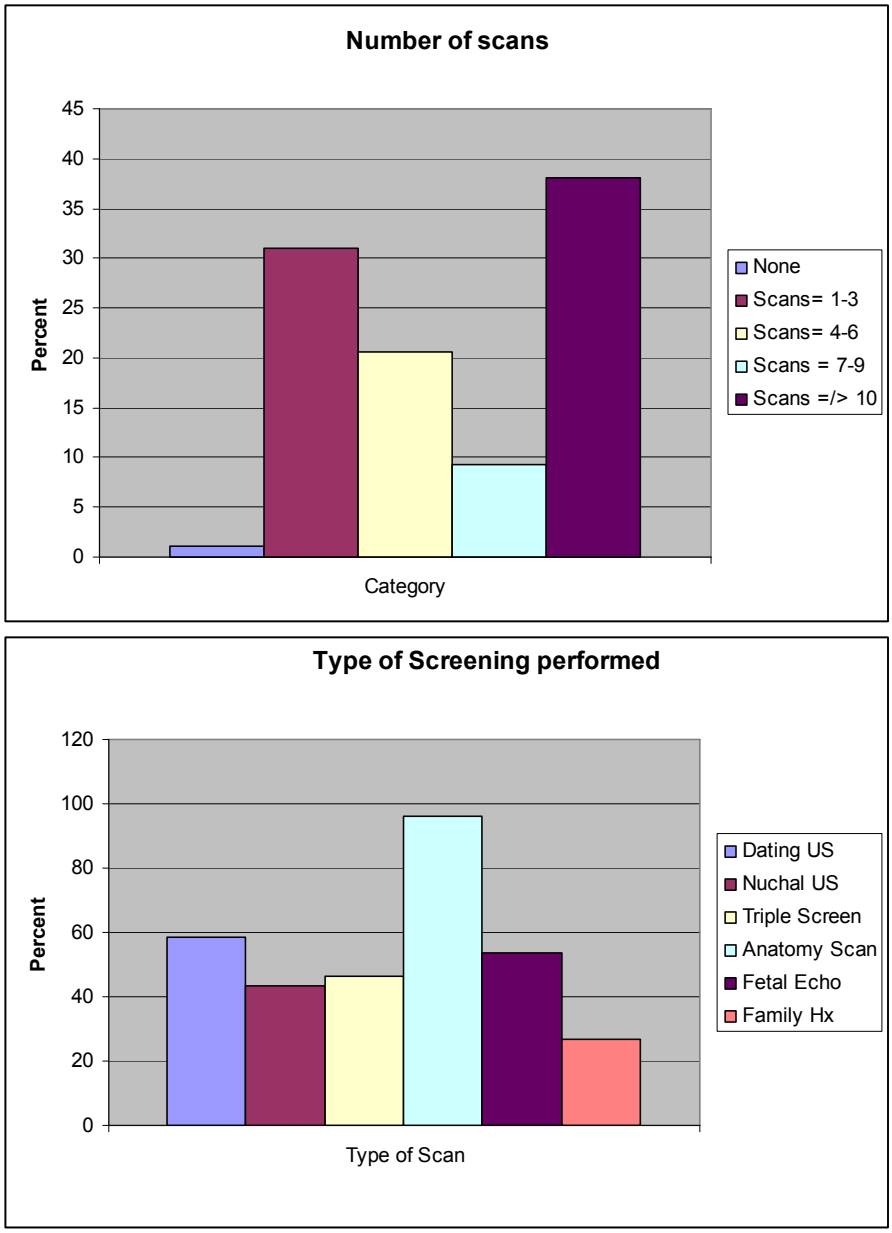

Figure 3: Results of the parental survey related to prenatal screening received (n=97)
(number of scans>/=number of ultrasounds performed during the pregnancy, US=ultrasound, datUS=dating ultrasound, Nuchal=ultrasound at 12-14 weeks to measure nuchal thickness, TripSc= blood serum markers, AnatSc= full anatomy ultrasound between 18-24 weeks, FetSc= fetal echo, FamHx=family history of CHD.)

Table 2: Detection by lesion type & Relative Risk for detection according to 4 chamber status

Cardiac lesion	Pre	Post	Term	(%) Det	95% (CI)	4 Ch status	RR	95% CI	P
Interruption of Aortic Arch	1	0	1	100		no	1.0	0.9, 1.0	1.0
Corrected Transposition	2	0	1	100		yes	1.0	0.9, 1.0	1.0
Heterotaxies, complex	23	3	7	86	70, 96	yes	1.0	0.6, 1.5	1.0
Single Right Ventricle	46	7	19	85	73, 93	yes	1.0	(ref)	(ref)
Double Outlet Right Ventricle	10	2	4	83	51, 98	no	1.0	0.3, 1.4	1.0
Ebstein's Anomaly	3	1	1	75	19, 99	yes	1.0	0.8, 1.3	0.5
Truncus Arteriosus	5	2	2	71	29, 96	no	1.1	0.9, 1.6	0.3
Single Left Ventricle	13	5	3	72	46, 90	yes	1.3	0.8, 2.0	0.3
Pulmonary Atresia/ Intact Septum	9	6	2	60	32, 84	yes	1.5	0.9, 2.3	0.1
Tetralogy of Fallot/ absent valve	1	1	0	50	1, 99	yes	1.0	0.9, 1.4	0.3
Coarctation/ VSD	8	9	0	47	23, 72	yes	1.8	1.1, 3.1	0.002
Atrioventricular Septal Defect	15	22	1	41	24, 57	yes	2.9	1.5, 5.2	<0.001
Pulmonary Stenosis	4	6	0	40	12, 74	no	1.6	1.0, 2.6	0.005
Shone's complex	2	5	1	29	3, 71	yes	1.5	1.0, 2.4	0.008
Pulmonary Atresia/VSD	5	10	0	33	11, 62	no	2.0	1.2, 3.4	<.001
Tetralogy of Fallot	18	34	3	35	22, 48	no	3.8	1.9, 7.2	<.001
Complete Transposition	10	24	0	29	15, 47	no	3.3	1.8, 6.0	<.001
Simple Coarctation	10	28	0	26	13, 42	no	3.7	2.0, 6.9	<.001
Aortic Stenosis	1	6	0	14	0, 37	no	1.7	1.0, 2.7	<.001
Total Anomalous Pulmonary Venous Drainage	1	10	2	11	0, 41	no	2.3	1.3, 4.0	<.001
Hemi Truncus	0	1	0	0		no	1.1	0.9, 1.1	0.2
VSD with outflow tract obstruction	0	1	0	0		no	1.3	0.9, 1.7	0.03
Multiple VSDs	0	2	0	0		yes	1.3	0.9, 1.7	0.03

(*Pre=prenatal, post=postnatal, Term=terminations, %Det=percent detected, 4 Ch status- yes=abnormal, no=normal)*

Table 2 summarizes each lesion sorted according to prenatal detection percentages. Including the terminations, there were 188 prenatally diagnosed lesions. The overall percentage of prenatal detection was **50.0%.** The percent terminated among the prenatally detected cases was 25% (47 of 188). Of those detected before 24 weeks, the percent terminated was 49% (47 of 96). The greatest numbers terminated were for single right ventricle (41% or 19 of 46). The relative risk for not having a prenatal diagnosis for lesions with a normal 4 chamber view was 1.86 (95% CI (1.48, 2.35), P <0.001), when compared to lesions with an abnormal 4 chamber view. Approximately half of the lesions, 52% (195 of 374), had an abnormal 4 chamber view. Single right ventricle which has an abnormal 4 chamber view is 85% detected. The most common cardiac lesion was tetralogy of Fallot, (n=54 or 14%). Lesions seen less frequently and comprising less than 1% for the total cohort include interruption of the aortic arch, corrected transposition of the great arteries, Ebsteins anomaly, tetrology of Fallot with absent valve, hemi truncus, VSD with outflow tract obstruction and multiple VSDs.

Table3: Adjusted OR of pre natal diagnosis by Regions

Region (# prenatally detected / Total)	Odds Ratio	P value	95% CI
Calgary/South (87/158)	1.00	(ref)	(ref)
Edmonton (60/120)	0.74	0.28	0.43, 1.28
Central (17/47)	0.43	0.04	0.19, 0.96
North (24/49)	0.46	0.06	0.21, 1.04

Table 3 shows the results for the prenatal detection of CHD by regions adjusted for the probability of prenatal detection by lesion type. Calgary and the South regions were combined, as the termination data for these regions were aggregate. Calgary/South is taken to be the reference region. The Central region had a significantly reduced percent detected in comparison to the Calgary/South area (P=0.04). The percent detected in the North region was also lower in comparison to the Calgary/South region with a similar OR to the Central region of the province even though this was not statistically significant (P=0.06). For lesion distribution across regions, see Appendix 4.

Table 4: Clinical Outcomes of pre and postnatally detected subjects

	Mean (SD)		Difference between pre-vs. post-natal detection	
Variable (n=prenatally-/ postnatally-detected)	**Prenatal**	**Postnatal**	**Difference (95% CI)**	**P value**
Preductal O_2 Sats* (%) n=79/67	81.3(14)	79.3(15)	-2.0 (-7.0, 2.9)	0.42
Preductal O_2 Sats** (%) n=20/37	94.0 (5.7)	92.4 (10)	-1.6 (-6.6, 3.4)	0.53
pH n=98/151	7.3(1)	7.7(5.2)	.4 (-4.6, 3.5)	0.33
PaO2 (mm Hg) n=98/148	58.1(39)	73.7(48)	15.6 (4.0, 27.1)	0.006
HCO3 (mmol/L) n=92/142	22.6(8.6)	21.8(3.9)	-0.8 (-2.5, .8)	0.38
Lactate (mmol/L) n=93/142	3.1(3)	3.1(4)	0.01 (-1.0, 1.0)	0.99
Urea (µmol/L) n=94/131	5.8(5)	5.3(6)	-0.5 (-2.7, 1.7)	0.65
Creatinine (µmol/L) n=100/143	63.2(25)	50.0(21)	-13.1 (-19.0, 7.2)	<0.001
Days to Admission n=140/186	43.1(80)	79.1(93)	36.1 (16.7, 55.5)	<0.001
Days to Operation n=125/167	58.2(80)	88.8(91)	30.6(10.4, 50.7)	0.003
Duration of Bypass (minutes) n=84/115	103.4(48)	102.4(47)	-1.0 (-14.5, 12.5)	0.89
Duration of Cardiac arrest (minutes) n=44/38	20.5(13)	22.5(31)	2.1 (-8.1, 12.3)	0.69
Duration of cross clamp time (minutes) n=138/91	48.8(29)	50.7(27)	-1.9 (-1.0, 5.6)	0.61
Days to extubation n=110/156	20.1(27)	11.2(16)	-8.8 (-14.1, -3.5)	0.003
Day to extubation gestational age >35 n=102/146	20.2(28)	10.8(15)	-9.5 (-15.0, -4.0)	0.008
Days to transfer from ICU n=83/116	22.7(29)	22.5(48)	-.2 (-11.9, 11.4)	0.97
Days to discharge n=122/164	35.9(48)	32.8(65)	-3.1 (-16.9, 10.7)	0.66

Categorical Variables (n=total/yes)	**Prenatally detected yes/no**	**Postnatally detected yes/no**	**Odds Ratio**	**95% CI**	**P value**
Intubation required n=273/122	47/61	75/90	.92	0.6, 1.5	0.73
CPR required n=252/9	3/95	6/148	.77	0.2, 3.2	0.73
Atrioseptostomy performed n=246/20	5/89	15/137	.51	0.2, 1.5	0.21
Cath preformed n=226/50	19/70	31/106	0.9	0.5, 1.8	0.80
PGEs required n=278/156	79/38	77/84	2.23	1.4,3.7	0.001
Inotropes required n=246/67	21/75	46/104	.63	0.4, 1.1	0.13
Bicarbonates required n=188/9	1/74	8/105	.18	1.0,1.4	0.11
Pre Operative mortality n=307/4	3/127	1/176	4.15	0.4,40.4	0.22

(*yes/no=numbers requiring procedure/numbers not requiring procedure; CPR=cardiopulmonary resuscitation, Cath=catheterization, PGEs=prostaglandin), * cyanotic lesions only, ** non cyanotic lesions only*

Table 4 shows the differences in clinical status in the pre, peri and post operative periods. Preductal O_2 saturations were compared between groups separately for cyanotic and acyanotic lesions. Cyanotic lesions included complete transposition of the great arteries, tetralogy of Fallot, tetrology of Fallot with absent pulmonary valve, total anomalous pulmonary venous drainage, double outlet right ventricle, single right and left ventricles, pulmonary atresia, Ebstein's anomaly, and heterotaxies. The acyanotic lesions included all others (Table 2). The prenatally detected group had lower $PaO_{2,}$ higher creatinine, fewer days from date of birth to admission and operation, greater number of days from operation to extubation and significantly higher use of prostaglandinds prior to surgery. Pre operative mortality was not different between groups. There were 37 patients who underwent catheterization rather than surgery as the index intervention, and among these subjects there was no difference in days to intervention for those pre- vs. post-natally detected.

In the post operative period, 6 patients died, 2 patients developed renal failure, 1 had a stroke and 5 developed seizures. None of these parameters were significantly different between the prenatally and postnatally detected groups.

Table 5: List of lesions for those requiring surgery at < 15 days of age, sorted by lesion and frequency of occurrence.

Lesion	Total	Prenatally detected	Postnatally detected	% Prenatally Detected
Complete Transposition of the Great Arteries	28	8	20	29
Single Right Ventricle	22	20	2	91
Coarctation	16	5	11	31
Coarctation/VSD	11	6	5	55
Heterotaxy/ complex	8	7	1	88
Single Left Ventricle	6	5	1	83
Truncus Arteriosus	5	3	2	60
Pulmonary Atresia/Intact Septum	5	5	0	100
Pulmonary Atresia/VSD	5	2	3	40
Total Anomalous Pulmonary Venous Drainage	5	0	5	0
Shone's Complex	5	2	3	40
Double Outlet Right Ventricle	2	1	1	50
Tetralogy of Fallot	1	1	0	100

Table 5 outlines the lesions that required surgery before 15 days of age. There are 13 lesions included in this subgroup. The percent detected prenatally for this subgroup was 56%. This varied from 100% for pulmonary atresia/intact septum to 0% for total anomalous pulmonary venous drainage.

Table 6: Clinical outcomes for those receiving surgery at less than 15 days of age

	Means (SD)		Difference between pre-vs. post-natal detection	
Variables (n=prenatal / postnatally detected)	**Prenatal**	**Postnatal**	**Difference (95 % CI)**	**P value**
Preductal O2 Sats (%) n=47/38	83.7(13)	77.1(16)	-6.6 (-12.9,-0.2)	0.04
Preductal O2 Sats* (%) n=37/28	80.5(13)	71.4(15)	-9.1 (16.0,-2.2)	0.01
pH n=50/47	7.3(0.1)	7.3(0.2)	-0.03 (-0.1,0.01)	0.16
Po2 (mm Hg) n=50/46	50.5(33)	47.8(25)	-2.7 (-14.8,9.4)	0.66
HCo3 (mmol/L) 46/40	22.1(6)	21.4(3)	-0.7 (-2.7,1.2)	0.46
Lactate (mmol/L) n=48/46	3.0(2)	3.7(4)	0.7 (-0.7,2.1)	0.53
Urea (µmol/L) n=43/40	5.9(10)	4.5(2)	-1.4 (-4.9,2.1)	0.97
Creatinine (µmol/L) n=47/43	69.5(23)	62.0(20)	-7.5(-16.6,1.6)	0.12
Days to Admission n=65/54	0.1(0.4)	3.3(4)	3.2(2.2,4.1)	0.03
Days to Operation n=65/54	7.5(3.8)	8.7(3.2)	1.2 (-0.1,2.5)	0.07
Duration of Bypass(minutes) n=37/35	104.5(9.2)	103.8(6.6)	-0.7 (-23.5,22.0)	0.95
Duration of Cardiac arrest (minutes) n=32/25	21.0(2.5)	16.9(2.5)	-4.2 (-11.4,3.1)	0.25
Duration of cross clamp time (minutes) n=44/45	50.0(4.2)	48.0(4.2)	1.0 (-10.9,12.9)	0.89
Days to extubation n=54/52	13.8(10)	11.0(14)	-2.76 (-7.4,1.8)	0.24
Days to transfer from ICU n=40/33	19.1(1.6)	28.8(9.7)	9.7 (-8.2,27.6)	0.28
Days to discharge n=61/51	31.1(23)	35.5(62)	4.4 (-12.7,21.5)	0.61

Categorical Variables (total/yes)	**Prenatally detected (yes/no)**	**Postnatal detected (yes/no)**	**Odds Ratio**	**95% CI**	**P value**
Intubation required (n=99/65)	24/23	41/11	0.28	0.12, 0.67	0.004
CPR required (n=85/3)	0/40	3/45	0		
Atrioseptostomy preformed (n=69/17)	4/36	13/33	0.28	0.08, 0.95	0.04
Cath preformed (n=67/15)	5/10	10/31	0.4	0.13, 1.39	0.50
PGEs required (n=106/100)	50/3	50/3	1.0	0.19, 5.19	1.00
Inotropes required (n=87/34)	8/33	26/20	0.19	0.71, 0.49	0.001
Bicarbonates required (n=58/6)	1/22	5/30	0.15	0.02, 1.34	0.39
Pre-Operative mortality (n=113/0)	0/??	0/??	NA		

*sats= saturations, (yes=procedure performed/no=procedure not performed), * includes cyanotic lesions only*

Table 6 shows the results for the subgroup of patients who had surgery before 15 days of age. There were 119 patients in this category of which 65 had a prenatal detection (54.6%). Those with a prenatal detection had significantly higher preductal O_2 saturations, shorter time to hospital admission, and fewer

requirements for intubation, atrioseptosotomy and inotropes. Half of the lesions in this group were comprised of those lesions considered to be cyanotic lesions. However, when the cyanotic lesions were analyzed separately for preductal O_2 saturations, the results were similar to the total results for those receiving surgery before 15 days of age (P=0.01 vs. 0.04).

Table 7: Clinical outcomes for those with a duct dependent lesion

	Mean (SD)		Difference between pre vs. postnatally detected	
Variable (n=prenatal / postnally detected	**Prenatal**	**Postnatal**	**Difference (95% CI)**	**P value**
Preductal O_2 Sats (%) n=38/41	81.7 (12)	74.6(14)	-7.1 (-13, -1.14)	0.02
Cross clamp time (minutes) n=37/32	48.54 (20)	60.0 (17)	4.5 (2.5, 20)	0.01

Categorical Variables (n=total/yes)	**Prenatally detected yes/no**	**Postnatal detected yes/no**	**Odds Ratio**	**P value**	**95% CI**
Cath preformed n=64/38	8/22	18/16	0.32	0.03	1, .9

(Sats=saturations, cath=catheterization, yes=procedure preformed/ no=procedure not preformed)

Table 7 shows the results for the subgroup of patients with a duct dependent lesion and summarizes only the outcomes that are significant since all of the lesions in this group are also included, although not exclusively, in the analysis for those requiring surgery at less than 15 days of age. There were four lesions included in this analysis; single right ventricle (n=53), pulmonary atresia/intact septum (n=15), pulmonary atresia/VSD (n=15) and complete transposition of the great arteries (34) for a total of 117. The overall percent detected prenatally for his cohort was 51% and this varied from 85% for single right ventricle to 29% for transposition of the great arteries. Infants in this group

with a prenatal diagnosis had significantly higher preductal O_2 saturations (P=0.02) shorter cross clamp time (P=0.01) and fewer catheterizations performed prior to surgery (P=0.03).

3.5 Discussion

Prenatal Detection

This is the first study in Canada that documents the effectiveness of prenatal screening for CHD and its impact on clinical outcomes. The results from the mother's survey show that a variety of screening processes are available in Alberta. The nuchal translucency ultrasound measurements along with the blood serum markers (triple screen) serve to identify a proportion of those at higher risk for anuploidy and CHD. This may help in recognizing some mothers with affected fetuses, however, the anatomy ultrasound screen that takes place at the 18 to 24 week period of gestation is important, to the prenatal detection of severe CHD, since it has been reported in other studies that the majority of women who deliver babies with CHD have no known risk factor associated with CHD (6). The results show that even though the majority of women receive prenatal screening, 50% of severe CHD remains undetected until after birth. This result may be similar to other jurisdictions, outside of Canada, where percentages detected vary widely from a low of 21% to 71% in the best situations (4, 65-68).

The place of residence and the type of lesion influence the probability of prenatal detection. In assessing differences in percentages detected prenatally across 4 regions with Calgary/South as the reference region, we adjusted for percentages detected according to type of lesion. This was important since the percent detected varied widely by the type of lesion and the mix of lesions was not consistent across regions. The two major urban centers, Edmonton and Calgary, had similar results for percentages detected prenatally. The Central (P= .04) and North (P=.06) regions of the province has appreciably lower

percentages detected prenatally. Other studies have shown that the probability of prenatal detection is higher in university practices and in urban versus rural locations (41, 69). Medical personnel working in urban centers and in centers associated with university teaching programs may have better and more consistent support from experts in the field and exposure and experience with congenital anomalies. This disparity between regions may be changed if collaborations between centers across the province were to improve. Telemedicine could potentially provide the means for such collaborations and consultations. The rural medical communities would benefit from the exposure to the educational initiatives and knowledge of the pediatric cardiologists and others in the urban, university and tertiary care facilities. The patients in the remote regions of the province would then have access to expert medical consultation, without unnecessary travel and expense.

The mean gestational age at diagnosis of 26 weeks is beyond the gestational age where a termination may be offered. The overall percent terminated was 25% but this increases substantially to 49 % when only those detected before 24 weeks are considered. Early detection may influence parental decision to terminate the pregnancy (6) and the spectrum of CHD seen in the neonatal period may change with improved detection of CHD and earlier referral to a pediatric cardiologist (44, 50, 51).

The risk for missed prenatal diagnosis is increased when the 4 chamber view is normal and the outlets are abnormal (RR= 1.86, 95% CI (1.48, 2.35), P <0.001,). Imaging of the outflow tracts during routine fetal screening is not strongly recommended by the American Institute of Ultrasound in Medicine (AIUM) and may not be seen by many in the field as important. Changing this concept and educating sonographers, obstetricians, and radiologists involved in

prenatal imaging to follow a more comprehensive screening protocol that includes assessing the outflow tracts may improve the detection for severe CHD in Alberta (4, 70, 71).

Some lesions, even those associated with an abnormal 4 chamber view, such as atrioventricular septal defect, can be subtle findings on an ultrasound examination during the routine fetal screen at 18 to 24 weeks gestation. Even so, a percentage of single ventricle type lesions, where the 4 chamber view is grossly abnormal are missed as well (15 to 40%). Some of these missed diagnoses may be the result of poor image quality either due to fetal position and/or the mother's body mass. In such cases, where the screen is incomplete, the mother should be referred for a fetal echocardiogram where the expertise of the pediatric cardiologist may prove beneficial.

Other forms of CHD such as aortic and pulmonary stenosis may not be evident at the 18 to 24 week period when anatomy screening is performed since most forms of CHD progress throughout the pregnancy (52). A careful interrogation of the 4 chamber view for any discrepancy in symmetry between left and right sides of the heart, use of high frequency transducers for optimal resolution, zoomed or expanded images to define the smaller cardiac structures and observing the structures in real time as opposed to static images may help in some cases.

Clinical Outcomes

There was no difference in pre operative mortality between pre- and post-natally detected groups; however, the numbers of infants who died before surgery was very small (n=4). Other clinical outcome results for the total cohort were in favor of the post natally detected group (higher PaO_2 levels and lower

creatinine levels) reflecting the tendency for the more severe lesions to be detected more frequently before birth. To limit the impact of the differences in severity of lesion type between the pre and post-natally detected groups, two sub analyses for those requiring surgery before 15 days of age and only those with duct dependent lesions was performed. The outcome variables, significantly in favor of the post-natally detected group, ($P0_2$ and creatinine levels, days to extubation and requirement for PGEs) became non significant in the sub analysis. In the sub analysis, the prenatally detected group had less requirement for intubation, atrioseptostomy and inotrope support, had shorter cross clamp times and higher preductal O_2 saturation levels. This confirms a more homogenous sub set in comparison to the total cohort, but also is due to the prompt clinical support (shorter time to admission) given to those with the prenatal diagnoses. The mothers, who had been identified as having a fetus with a duct dependent lesion, requiring the immediate use of PGEs at birth, would have been delivered at the Royal Alexandra Hospital and the baby then would be promptly transported to the Stollery Children's hospital. The medical team would be more prepared for this neonate due to the prior knowledge gained by the prenatal diagnosis.

It may also be that a prenatal diagnosis has no impact on morbidity in the early stages of life for some types of CHD, particularly where the circulation is not restricted to either the lungs or the body.

Biases and Confounding

Only a minority of the mother's of the infants affected by CHD completed the survey. Approximately half of the patients were identified retrospectively using surgical and catheterization lists and the other half were identified at the

time of admission through the daily patient census. The mothers, of those identified retrospectively, were not contacted to participate in the survey as it was felt the results would have been too greatly impacted by recall bias. Even though every effort was made to contact each mother in person, for those infants identified with CHD on admission, this proved difficult over the course of the 2 year period. Therefore, the results of the survey may not truly represent the total cohort and may be influenced by selection bias. The majority of women who completed the survey did so close to the date of birth of the affected child; however, recall bias may also have an influence on the results.

The prenatal group may inherently have worse pathology which could minimize the impact of a prenatal diagnosis. To control for this discrepancy, the sub analysis compared groups that would have had more similar pathology and/or severity of disease. Two groups were identified for this study, one requiring surgery before 15 days of age and the other having CHD that would likely be duct dependent circulation. The results for these groups were different from the total cohort, for some of the outcome variables, suggesting these groups are more homogeneous. Even so, the mix of lesions between groups varies. This is particularly evident in the cohort who required surgery before 15 days of age where, pulmonary atresia/intact septum (n=5) had 100% and total anomalous pulmonary venous drainage (TAPVD) (n=5) had 0% prenatal detection. These lesions are very different and require different management and treatment strategies. This provides the opportunity for confounding. To explain this further, pulmonary atresia/intact septum is a duct dependent lesion that requires staged palliation. Initially the child may have a simple shunt type procedure only and have further surgery later in life. On the other hand, the child with TAPVD would most likely have a complete repair at this first admission. The

surgical procedure differs for each infant, even though the lesions are all considered severe, and this may influence the results for length of stay, length of intubation etc. The rarity of lesion types and the small numbers for each type of lesion limits the use of further sub analysis in this study. Finding similar groups of patients to compare, is a challenge, however, others have shown the benefit of a prenatal diagnosis for complete transposition of the great arteries and for hypoplastic left heart syndrome (47, 59).

Those mothers who were found to have a fetus with a suspected or confirmed chromosomal abnormality may have been referred to a pediatric cardiologist who would have diagnosed the CHD regardless of the cardiac findings at the routine obstetrical ultrasound assessment. However, there was no difference in prenatal detection when considering the presence of anuploidy.

Those fetuses diagnosed with CHD would be followed closely throughout the pregnancy and there may be the tendency for earlier delivery thereby impacting some of the outcomes for this group (44). In this cohort, the prenatal group had a younger mean gestation at birth, 38.39 versus 38.87 weeks, but this was not statistically significant (P=0.06) and there was no difference in length of hospital stay between the pre and post-natally detected groups.

3.6 Conclusion

The percent of severe CHD detected prenatally in Alberta is in keeping with other centers, however, still needs improvement. Educational initiatives aimed at the individuals responsible for routine prenatal screening across the province may improve the detection of CHD. Prenatal diagnosis of CHD has been shown to impact the management and outcomes in the neonatal period. The prevalence and spectrum of CHD may change in the population with improved detection and timelier referral. The tendency for the prenatally detected babies to have better clinical status in the pre, peri and post operative periods motivates the need for a better understanding of how this can impact the longer term outcomes for neurological and quality of life status.

Chapter 4: Discussion and Conclusion

4.1 Introduction

The purpose for this thesis and the research study was to:

1. Determine the effectiveness of the prenatal screening process in detecting severe CHD in the province of Alberta and
2. To investigate whether a prenatal diagnosis impacts post natal management and outcomes.

Additionally, the objectives within this study are:

1. To define strategies for improved prenatal detection of severe CHD in Alberta and
2. Potentially optimize the medical management in the pre and post natal periods for those affected by severe CHD.

To accomplish this, I have attempted to define the process for prenatal screening in this province, determine the reasons for missed diagnosis and determine termination percentages related to CHD.

Considering the above outline, this chapter will discuss the results of the study in the following way:

1. The prenatal screening options available and utilized in Alberta
2. The detection of severe CHD in Alberta (taking into account the limitations of prenatal ultrasound assessments),

3. The potential impact a prenatal diagnosis may have on management and outcomes,

3. Evaluate the potential problems related to the research, in terms of biases and confounding factors,

4. And considers the validity of the research study.

Finally, the conclusion will give the reader a concise overview of the thesis and research study.

4.2. Discussion of Results

4.2.1 Prenatal screening in Alberta

In Alberta, the health care system offers women options for prenatal care and the majority of women (99%) who were surveyed admitted to having at least one ultrasound assessment during the pregnancy. There were 97 women who agreed to complete the survey and 1 of the 97 reported having no prenatal ultrasound done. The majority of women reported having 3 or more scans during the course of their pregnancy. It is unclear if more access to screening would improve the percent detected since those who are recognized to have a fetus with CHD would naturally be scanned more frequently. The majority of women surveyed (91%) reported having had the routine anatomy scan at 18 to 24 weeks gestation, which is optimal for structural congenital anomaly screening. It is reasonable, therefore, to assume that the type of prenatal screening is adequate for detection of CHD, in Alberta. The timing of referral to a pediatric cardiologist, (26 weeks gestation) however, is beyond the accepted gestational period of 23

weeks for termination. The overall percent terminated was 25% but this increased substantially to 49 % when only those detected before 24 weeks were considered. This limits the options for some women who had a prenatal diagnosis. If the percentages detected were to improve and women were referred for detailed assessment earlier, the terminations for CHD may increase. It has been shown that the spectrum of disease seen in the postnatal period changes with increased detection and terminations (50). Women and families can be counseled appropriately only if referrals to high risk centers are earlier.

Additional screening, including an ultrasound in the early second trimester at 12 -14 weeks, to measure the nuchal fold, potentially identifies those at higher risk (32, 33). Women who fall into this category as well as those who have abnormal blood biomarkers (triple screen assessment) may be referred directly to a pediatric cardiologist to rule out the presence of CHD in the fetus. As this type of screening becomes more common place, the detection for some lesions may increase.

4.2.2 Prenatal Detection of Severe CHD

In Alberta, the majority of pregnant women receive prenatal screening. Overall detection for severe CHD in Alberta is 50%. This result, while not a perfect situation is better than the majority of centers. Detection of CHD varies widely from a low of 21% to 71% in the best situations. (4, 65-68). The Central and North regions of the province did have a lower percent detected prenatally, in comparison to Calgary/South region (P=.04 and .06 respectively). Others have shown that prenatal detection of structural anomalies varies by geography and by institution (69, 72). Initiatives aimed at improving the detection of CHD

prenatally, must therefore consider the entire province. Stronger collaborations between medical specialists in the university, urban and tertiary care centers with those working in the local, rural and private facilities will foster support and knowledge translation. Outreach educational initiatives have been shown to improve the prenatal detection of CHD(4).

The screening for CHD outside of tertiary care centers varies from a standard 4 chamber view with documentation of the heart rate to more comprehensive images that include the outflow tracts. The 4 chamber view is a well recognized image on ultrasound and it is not surprising that the majority of lesions identified before birth are those where the 4 chamber view is abnormal. Imaging the outlets requires additional views of the heart and the normal appearance of these cardiac structures may not be as easily recognized. These views of the cardiac outlets are not strongly recommended by the AIUM and may be viewed by sonographers as less important than achieving the standard 4 chamber view. Abnormalities of the outlets such as transposition of the great arteries and pulmonary atresia, are duct dependent lesions, requiring immediate intervention at birth, to prevent profound cyanosis. The majority of these lesions (70%) were undetected in the prenatal period. The relative risk for not detecting these lesions prenatally is increased, **(RR=1.86, 95% CI (1.48, 2.35), P <0.001)** when compared to the detection of lesions such as single right ventricle where the 4 chamber view is abnormal. Still, a proportion, 15 to 30%, of lesions where the 4 chamber view is profoundly abnormal, was not recognized during fetal screening.

The reasons why such severe forms of CHD are not recognized during routine fetal screening are multiple. Most forms of CHD progress throughout the pregnancy, and in some cases may not be obvious at the 18-24 week anatomy

scan. Obstructive lesions such as aortic and pulmonary stenosis, are uncommonly diagnosed before birth unless the lesion impacts the function of the ventricle and causes the heart to dilate or in the most severe cases, fetal hydrops develops. Other lesions, such as total anomalous pulmonary venous drainage (TAPVD) and coarctation of the aorta, require a careful interrogation of the 4 chamber view for any discrepancy in symmetry between the left and right ventricles. Although these findings are subtle, sonographers can recognized these discrepancies with attention to the details of the 4 chamber view. In some cases of TAPVD, a collecting chamber may be visible at the back of the left atrium.

Another consideration is the size of the heart which is approximately the size of a dime at 18 weeks. Visibility of such small structures requires equipment with high resolution, the fetus to be in a good scanning position and the maternal habitus to be of reasonable size.

The expectations for detection of CHD during routine ultrasound assessment are high. To achieve total perfection may not be possible simply due to circumstances surrounding each patient. Some lesions such as coarctation of the aorta are difficult to ascertain prenatally and even the most experienced pediatric cardiologist will have difficulty being completely confident making this call. We must accept these well known limitations and continue work to improve the overall detection for CHD in the fetus

4.2.3 Impact of a prenatal diagnosis on post natal management

In the total cohort, babies who are diagnosed prenatally were admitted (P=<0.001) and had surgery (P=0.003) sooner than those with a post natal diagnosis. The lower PaO_2 levels and higher creatinine levels in the prenatal

group may reflect the tendency for more severe lesions to be detected more frequently (40). This is plausible since the severe lesions tend to look more abnormal on ultrasound. Lesions in this group include, single right ventricle, pulmonary atresia and complex lesions involving abnormalities of situs (heterotaxy syndrome). Newborns with these types of lesions would tend to require immediate attention to survive and prevent profound morbidity. Those who were diagnosed prenatally would be delivered at the Royal Alexandra Hospital, receive prompt intervention and transfer to the Stollery Children's Hospital. The use of prostaglandin (PGEs) to maintain the patency of the ductus arteriosus, prompt use of catheterization interventions to open the atrial septum or obstructed valves, use of ventilation and immediate correction of acidosis would limit physiological compromise.

This was more obvious in the sub analysis groups where we would expect to see the most severe forms of CHD. For the patients who had surgery before 15 days of age, the impact of the prenatal diagnosis was significant with fewer requirements for intubation, atrioseptostomy and inotrope support. It is interesting to note that the use of PGEs is the same for both groups in the sub analysis cohort but significantly increased for the prenatal group in the whole cohort. It was observed in the chart reviews that PGEs were sometimes initiated even when it was determined by the pediatric cardiologist prenatally that such support would not be required. Medical personnel outside of the Stollery Children's Hospital may initiate the use of PGEs, simply as precautionary measures regardless of the diagnoses. Preductal O_2 saturations were better for those detected prenatally in both sub analysis groups even though the requirements for PGEs in these groups were not different. This may be the result of the shorter time to admission observed for the prenatally detected group.

Children with some forms of CHD already have neurological deficits that are present in the pre operative period as a result of compromised cerebral blood flow during fetal life (17, 18). Miller explained that there were widespread brain abnormalities in his cohort of 41 newborns with transposition of the great arteries and single ventricle physiology. In his cohort only 17% had the benefit of a prenatal diagnosis (19). In this study the prenatal detection for these two lesions was better (29% for transposition of the great arteries and 85% for single right ventricle), however, babies born with duct dependent lesions such as single right ventricle (n=34), pulmonary atresia with and without VSD (n=28) and transposition of the great arteries (n=34) are those most at risk for death and severe morbidity unless they receive prompt intervention. This study showed that cross clamp time was significantly shorter, preductal O_2 saturations were significantly higher and the use of pre operative catheterization was less, in the prenatally detected group. If we are to limit the continued neurological damage that may occur after birth we must increase the percentages detected so that effective intervention may occur, thereby optimizing the circulation to the brain. Strategies to protect the central nervous system during cardiac surgery is an area of continuing research, some of which have proven beneficial for the short term outcomes(18), however, continued research investigating long term outcomes is required to fully understand these implications.

4.2.4 Biases and Confounding

The complexity and lesion type are not consistent in each group. There is the tendency by nature, for the more severe lesions to be identified before birth. For example Ebstein's anomaly and heterotaxy type lesions have 75 and 85% detection. The outcomes for the prenatal group may inherently be worse minimizing the impact of a prenatal diagnosis.

The numbers in this cohort would not support individual lesion analysis and for this reason, we have provided data analysis on two separate groups that would tend to have the more severely affected patients. The hope was to provide more homogenous groups and still have sufficient numbers to compare. However, with in one of these categories, two lesions, pulmonary atresia/VSD and TAPVD are very different and require different management and treatment strategies. The first had a 100% and the latter had a 0% detection in the cohort requiring surgery before 15 days of age. This provides the opportunity for confounding since each lesion would have much different requirements clinically thereby affecting the results for the outcome variables, masking or enhancing the impact of the prenatal diagnosis. This situation may also exist for the other lesions in the sub analysis perhaps to a lesser degree. To avoid this situation and test the outcomes for each lesion type, the study would need larger numbers. Within each lesion type there is also a spectrum of disease, and this was difficult to identify through chart reviews.

Women who received 1st and early 2nd trimester screening may have been referred to a pediatric cardiologist for fetal echocardiography for suspected fetal anuploidy, and this may have precluded some to a prenatal diagnosis of

CHD. The impact of this was limited by the exclusion of those with the most severe and obvious multiple anomalies.

There may be the tendency for those with a prenatal diagnosis to be delivered early thereby impacting the outcomes for this group (44). In this cohort, the prenatal group had a younger mean gestation at birth, 38.39 versus 38.87 weeks, but this was not significant (P=0.06).

Infants in this study are from across the province and may have been first admitted to the institution closest to their residence. This would be particularly true for those infants without a prenatal diagnosis. However, it was possible to only collect admission data from those institutions in the two major urban centers, Edmonton and Calgary. Infants and newborns first delivered or admitted to other institutions, may have had different management and treatment strategies before admission to the Alberta Children's Hospital in Calgary and or the Alexandra Hospital and The Stollery Children's Hospital in Edmonton. It is not possible to know if this has impacted the differences between the groups.

4.2.5 Validity

The incidence of CHD in the general population is less than 1%. The rarity of the cases in Alberta, therefore, makes this retrospective research appropriate, however the retrospective nature of the study does have some limitations. The patient charts and databases at times did not have all the information on every parameter for each patient. In a small number of cases, there was discordant information recorded in the charts and in the databases such as the gestational age at birth. In such cases this type of data was not collected for that patient. However, one of the strengths of this study is that The Stollery Children's Hospital is the only center in Alberta which performs pediatric

cardiac surgery. Therefore, all children with severe CHD would be admitted to this center. Also, the hospital is part of Alberta Health Services (AHS) which administers all hospitals across the province, making access to databases and patient information efficient when access to information is needed from other institutions within the AHS administration. This also allowed for cross reference between databases, particularly in cases where it was unclear if a prenatal diagnosis occurred.

Diagnostic ultrasound and in particular obstetrical and fetal cardiac ultrasound have become commonly used tools for diagnostic purposes (6). We assume that the majority of pregnant women seek prenatal care and screening during the course of the pregnancy. To determine current screening practices and utilization for these services in Alberta, a mother's survey was used in this study. This survey asked questions related to the care received during the pregnancy. The results showed that there are a variety of screening processes available and utilized by the mothers who completed the survey. Only 30% of mothers completed the survey and therefore these results may not fully represent the population in Alberta. The survey was filled out at the time of the child's admission to hospital and in some cases was several months after their child's birth and/or the care received. The potential for selection, volunteer and recall bias may affect the results of the survey.

Not all the variables measured showed significance even where there was a trend in favor of a prenatal diagnosis. The reason being, this study is under powered for some of the comparisons. For example, in the cohort who required surgery at less than 15 days of age, the mean lactate was lower in the prenatally detected group, however the numbers in each group would have had to more than triple for this to show significance. In the case of pre operative

mortality, there were 4 patients (3 prenatally diagnosed) who died before any surgery or intervention. The sample size would need to be over 1000 for this to be a significant outcome at these proportions.

Generalizability

Extrapolation of the results of this study to other provinces and territories may not be valid. The prenatal detection of CHD, prenatally, will vary within programs, between geographical regions, with the expertise of the medical personnel, and by the demographics of the population and their willingness to seek and receive prenatal care. However, other provinces and territories may benefit from the results of this study by being made more aware of the importance of a prenatal diagnosis and the issues and pitfalls surrounding the prenatal screening processes for CHD.

4.3 Conclusion

Prenatal screening is available to the majority of pregnant women in the developed world. Prenatal ultrasound is commonly used to identify congenital anomalies, including CHD, as a component of prenatal screening. CHD is a common form of congenital anomaly but many newborns with CHD are diagnosed only after birth regardless of the almost universal use of prenatal ultrasound. The results of my study show that in Alberta, only half of those babies born with severe CHD are detected in the prenatal period, even though the majority of women have had prenatal ultrasound assessments. Those infants born with duct dependent lesions are the most at risk for serious compromise. Some infants without a prenatal diagnosis may be discharged home and become

severely ill once the fetal circulation changes and are then brought to the emergency departments acutely ill. Others with less severe disease will not receive care until the problem is discovered, usually due to poor feeding or other clinical symptoms noticed by the parents or a physician at follow up. Some infants with severe CHD may benefit from having a prenatal diagnosis by limiting mortality and reducing morbidity in the pre and post operative periods. However, short term outcomes are a challenge to measure for this population due to the rarity of disease, the diversity of patients and the spectrum of disease severity existing between and within lesion types. The results favored the prenatally detected group for the pre operative and peri operative outcomes; preductal 0_2 saturations, the need for intubation, atrioseptostomy, inotropes and cross clamp times.

If the detection of CHD is to improve in Alberta, imaging of the heart and particularly the outflow tracts needs to be more comprehensive. Additional ultrasound images of the outflow tracts may help to identify those that are abnormal (73). Personnel involved in the screening process most likely need to improve their knowledge of cardiac screening and cardiac anatomy. The resources and individuals capable of providing didactic and clinical education for personnel who do fetal screening are available in Alberta. The screening process is provided by Alberta Health Services (AHS) which administers the urban and rural hospitals in the provinces and also by numerous facilities outside of this administration, such as private and corporate clinics. It is important that all those professionals involved with prenatal assessment are given the opportunity to become more proficient with fetal cardiac screening. Even simple educational initiatives have proven to have an impact on improving detection rates (4, 6, 8, 38). As the major provincial health care provider, AHS needs to lead and support

these initiatives more completely for the education to be delivered to all the regions of the province.

Continued research is needed to determine if newborns with a prenatal diagnosis have better long term outcomes in comparison to those without a prenatal diagnosis. Studies that better define the impact of CHD, on neurological deficits evident in school aged children, and on QOL parameters for children, adults and families living with CHD, may help to direct the management for some patients. A better understanding of this area may lead to better social and financial support for those affected.

This study did not look at changes in detection over time, however it is plausible that some of the improvements in prenatal detection for CHD in other jurisdictions have in part been the result of improvements in technology and the improved screening processes for all congenital anomalies. Current technologies such as 3D and 4D imaging are now clinically available for the pediatric cardiac patient. As these technologies are better developed for fetal cardiac imaging, we may see a continued improvement in prenatal detection of CHD. These advances, along with continued and better collaboration between radiologists, obstetricians, pediatric cardiologists, sonographers, perinatologists and neonatologists at all levels will promote a continuity of care for the fetuses, babies, mothers and families affected by CHD.

Appendices

Appendix 1: Multiple anomalies

1. Renal pelviectasis / agensis / poly cystic kidneys
2. Cleft lip and palate
3. Gastroshisis
4. Thoracic wall defects
5. Omphalocele, spina bifida, lemon shaped skull

6. Brain/ head anomalies
   Dandy Walker malformation, holoprosencephaly, brachycephaly, probiscus

7. Skeletal anomlies
   clubbing of lower extremeties, deformed hands, shortened femurs and or limbs, (micromelia) , dwarfism

8. GI abnormalities
   duodenal atresia, anal atresia
   double bubble sign

9. Caudal regression syndrome
10. Conjoined twins
11. Ascities

12. Chromosomal Abnormalities
    Trisomy 13 (can have multiple organ defects, and holoprosencephaly)
    Trisomy 18 (small receding jaw, prominent back part of the head, clenched fists, low set malformed ears, club feet, cleft lip and palate, spina bifida)

Appendix 2: Post natal variables: Data form 1

Patient Information:

Initials _____ History number_____unique identifier_____
Date of birth (DD/MM/YY)_____time of birth _____
Referral institution_____
Parental decision regarding treatment 0=No treatment 1=Tx 2=Stage one

Pre operative variables:

Date of admission (DD/MM/YY) _____
Time of admission _____
Cardiac diagnosis- _____
Prenatal diagnosis 0=no 1=yes
Prenatal diagnosis_____

Chromosomes 0=not done 1=trisomy 21 2=Q22/11 3=other 4=normal
Gestation at diagnosis_____
Gestational age at birth_____
History number of mother if prenatal diagnosis_____
Preductal O2 saturation at time of admission: _____
Preductal blood gases
- Ph- lowest _____
- Po2 _____
- HCO3 (lowest) _____
- Lactate (highest)_____

Urea (highest)_____
Creatinine (highest)_____
Intubation 0=no 1=yes
CPR 0=no 1=yes
Atrioseptostomy0=no 1=yes
PGEs 0=no 1=yes
Inotropes 0=no 1=yes
Bicarbonates 0=no 1=yes

within 48 hours of admission

Degree of systemic ventricular dysfunction:
0= none or mild 1= moderate 2= severe

Presence of TR/MR 0=none or mild 1=moderate to severe
pre op mortality 0=no 1=yes

Operative variables:

Year of surgery_____
Surgeon 1=DR 2=IR
Date of operation (DD/MM/YY)_____
Diameter of ascending aorta (mm)_____
Duration of bypass (minutes)_____
Duration of circulatory arrest (minutes)_____
Duration of cross clamp (minutes) _____

Post operative variables:

Date of first extubation (DD/MM/YY) _____
Date of transfer from ICU (DD/MM/YY)_____
Date of discharge from hospital (DD/MM/YY)_____

Post op seizure 0=no 1= yes
Post op stroke 0=no 1= yes
Post op renal failure 0=no 1=yes

Post op mortality_____

1- 14 days

Catheterization Variables

Preoperative catheterization performed 0=no 1=yes

if Yes: Cath was 1= diagnostic 2= interventional

Date of Cath _____(dd/mm/yy)

If interventional, indicate intervention preformed

1= balloon atrial septostomy
2= balloon aortic valvotomy
3= balloon pulmonary valvotomy
4= radiofrequency pulmonary valve perforation
5= other _____(Indicate)

Appendix 3: List of lesions comprising "Severe Congenital Heart Disease"

1. Complete Transposition of the Great Arteries (TGA)
2. Corrected Transposition of the Great Arteries (L-TGA)
3. Truncus Arteriosus
4. Pulmonary atresia/ intact ventricular septum
5. Pulmonary Atresia/Ventricular Septal Defect
6. Pulmonary Stenosis
7. Single Right Ventricle,
    - Hypoplastic left heart syndrome
    - Double outlet right ventricle with hypoplastic left ventricle,
    - Atrioventricular septal defect with hypoplastic left ventricle
8. Coarctation of the aorta with ventricular septal defect (Coarctation/VSD)
9. Aortic Stenosis
10. Interruption of the aortic arch (interruption)
11. Multiple ventricular septal defects (multiple VSDs)
12. Atrioventricular Septal Defect (AVSD)
13. Total Anomalous Pulmonary Venous Drainage (TAPVD)
14. Heterotaxies/complex anatomy
    - Single ventricles not included in 7 and 17
    - Right and left atrial isomerisms
15. Double Outlet Right Ventricle (DORV)
16. Tetralogy of Fallot (TOF)
17. Single Left Ventricle
    - Tricuspid Atresia
    - Univentricular connection such as DILV
18. Ebsteins Anomaly (Ebsteins) : includes those with dysplastic tricuspid valves with regurgitation and or stenosis
19. Shone's Complex : includes all complex left ventricular outflow tract obstruction
20. Hemi Truncus
21. Tetralogy of Fallot with absent valve
22. Simple Coarctation
23. VSD with outflow tract obstruction

Appendix 4 : Distribution of lesions and detections rates, across regions

Cardiac lesion	Calgary total/%	Edmonton total/%	Central total/%	North total/%	South total/%
Complete Transposition	14/36	12/50	6/0	2/0	1/0
Corrected Transposition	1/100	0	0	0	0
Truncus Arteriosus	2/0	2/100	1/100	0	0
Pulmonary Atresia/ intact septum	5/80	6/50	1/0	1/0	0
Pulmonary Atresia/ VSD	4/0	8/50	1/0	1/100	2/0
Pulmonary Stenosis	6/33	2/50	1/100	1/0	0
Single Right Ventricle	12/92	15/67	2/100	3/67	2/100
Coarctation/VSD	4/50	7/29	2/50	2/100	1/0
Aortic Stenosis	3/33	2/0	0	1/0	0
Interruption of Aortic Arch	0/0	0	0	0	0
Multiple VSDs	0	1/0	0	1	0
Atrioventricular Septal Defect	17/41	14/36	1/100	1/0	5/20
Total Anomalous Pulmonary Venous Drainage	1/0	2/0	3/0	3/0	2/0
Heterotaxies, complex	5/100	3/67	4/50	9/89	0
Double Outlet Right Ventricle	1/100	2/50	1/100	1/0	3/100
Tetralogy of Fallot	15/27	15/27	11/28	7/14	4/75
Single Left Ventricle	3/33	7/86	1/0	3/33	1/100
Ebsteins Anomaly	1/0	0	0	2/100	0
Shone's Complex,	5/40	1/0	0	0	2/0
Hemitruncus	1/0	0	0	0	0
Tetralogy of Fallot/absent valve	1/100	0	0	1/0	0
Simple Coarctation	13/23	12/33	9/0	3/33	2/100
VSD with outflow tract obstruction	0	1/0	1/0	0	0

(Total =numbers of lesions/ %= percentage detected. This table does not include terminations)

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