TRENDS IN AND BARRIERS TO THE PRENATAL DETECTION OF MAJOR CONGENITAL HEART DISEASE IN ALBERTA

by

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Abstract

Introduction

Congenital heart disease (CHD) affects approximately 8-13 per 1000 live births globally, and it is the leading cause of mortality and morbidity among neonates with birth defects. Most CHD can be diagnosed prenatally, which, particularly for more severe disease, is associated with improved outcomes. Despite the ability to diagnose almost all major CHD prenatally, current rates of detection, even in high-income countries, range between 30% to 60%. Whether recent modifications of obstetrical ultrasound (OB US) guidelines have led to improvements in the prenatal detection of certain forms of CHD in North America and internationally is unclear. As well, while the ease of detection of CHD subtypes at OB US is likely a significant predictor of prenatal diagnosis, other factors, including socioeconomic status (SES) and remoteness of residence (RoR) from tertiary care OB US screening and fetal echocardiography services, may also play a relevant role.

Objectives

1) To examine trends in prenatal diagnosis of major CHD in Alberta from 2008 through 2018
2) To examine the impact of SES and geographic RoR on prenatal detection rates and timing in Alberta from 2008 to 2018

Methods

Using provincial databases, we retrospectively identified all fetuses and infants diagnosed between January 2008 to December 2018 with major CHD requiring surgical intervention within the first postnatal year.

Objective 1: We evaluated individual lesions and categorized CHD subtypes based on the OB US fetal cardiac views required for detection: Group 1 - 4 chamber view (e.g. hypoplastic left heart syndrome, Ebstein's anomaly, single ventricle), Group 2 - outflow tract view (e.g. tetralogy of Fallot, double-outlet right ventricle, truncus arteriosus), Group 3 - 3 vessel view/3 vessel tracheal view (3VV-3VT) or other non-standard cardiac views (e.g. coarctation, anomalous pulmonary veins), and 4 - isolated ventricular septal defects (VSDs) using any view.

Objective 2: Using maternal residence postal code and geocoding, SES quintiles and geographic distance from fetal tertiary care, both continuous and categorical, were calculated. Outcome measures included the presence of a prenatal diagnosis and the gestational age at prenatal diagnosis when it occurred.

Results

From 2008-2018, 1405 patients (fetuses and infants) with major CHD were encountered pre and/or postnatally in Alberta, of whom 814 (58%) were diagnosed prenatally. Live births occurred in 1202 (84%), intrauterine fetal death (IUFD) in 47 (3.2%), elective termination of pregnancy (TOP) in 118 (8.3%) and missing data of 38 patient (4.5%).

Objective 1: Over the study period, the proportion of prenatal diagnosis of major CHD significantly improved overall from 277/560 [49% 95% CI (confidence interval) 45, 54] in 2008-2012, 255/417 [61%, 95% CI 56, 65] in 2013-2015, to 282/428, [66%, 95% CI 61, 70] in 2016-2018 (p-value <0.001). Linear regression of the proportion of fetal diagnoses by year predicted an increase of 2.3% per year ($r^2 = 0.73$, p=0.0008). By US OB view, Groups 1 and 2 demonstrated a significant increase in prenatal detection, from 75% to 88% (p=0.008) and from 56% to 79% (p=0.0002), respectively. While rates of prenatal detection increased for Group 3 and 4, from 27%

to 43% (p=0.007) and 13% to 30% (p=0.04), even in the more recent era, rates remain low compared to Groups 1 and 2, with less than half being detected.

Objective 2: Prenatal detection rates of CHD were not associated with SES quintiles; however, the lowest quintile was associated with an estimated 24-28% higher risk of a late diagnosis of CHD. For RoR, maternal residence of >100 km from the tertiary care center was associated with 16% greater risk of a postnatal diagnosis and 47% higher chance of a prenatal diagnosis after 22 weeks of gestation.

Conclusions

Prenatal detection rates of major CHD have significantly increased in Alberta from 2008-2018. With respect to OB US fetal cardiac views, prenatal detection of CHDs associated with four-chamber and outflow tract view abnormalities have increased. Although CHD associated with abnormalities of the 3VV-3VT and nonstandard views and isolated VSDs have also observed improved prenatal detection, rates for these subgroups remain suboptimal. While SES does not appear to impact rates of prenatal detection in our province, lower SES is associated with later gestational age when a prenatal diagnosis is made. In contrast, greater RoR from tertiary OB US and fetal echocardiography services in Alberta is significantly associated with both reduced rates of prenatal diagnosis and later prenatal diagnosis. Further work is needed to enhance prenatal screening through optimized OB US assessments, and to determine factors responsible for inequity in prenatal detection of CHD particularly for remote pregnancies in Alberta.

Preface

This thesis is an original work of Amanpreet Kaur completed with the support and guidance of her supervisors Dr Lisa Hornberger and Dr Luke Eckersley, graduate committee members including Dr Sujata Chandra and Dr Matthew Hicks and coinvestigators, Dr Deborah Fruitman and Dr Deliwe Ngwezi. The reported research studies which form this thesis received ethics approval from the University of Alberta Health Research Ethics Board under the proposal title: "Trends in and Barriers to Prenatal Detection of Congenital Heart Disease in Alberta from 2008-2018" (Pro00078830), initially approved on May 2, 2019. Chapter 3, **"Trends in the prenatal detection of major congenital heart disease in Alberta from 2008 to 2018"** (authors: Amanpreet Kaur, Lisa K Hornberger, Deborah Fruitman, Deliwe P Ngwezi, Sujata Chandra, and Luke G Eckersley), and Chapter 4, **"Location of residence but not socioeconomic status impacts fetal detection of congenital heart disease despite universal health coverage"** (authors: Amanpreet Kaur, Lisa K Hornberger, Deborah Fruitman, Deliwe Ngwezi, and Luke G Eckersley), represent original manuscripts submitted for peer review publication.

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Figure 4.1 Proportion fetal diagnosis in <22 weeks of gestation of major CHD by year or birth/encounter. Error bars are 95% confidence intervals.

Abbreviations

CHD - congenital heart disease

AVSD - atrioventricular septal defect

DILV - double inlet left ventricle

DORV - double outlet right ventricle

HLHS - hypoplastic left heart syndrome

PA/PS IVS - pulmonary atresia/stenosis with intact ventricular septum

d-TGA - dextro-transposition of the great arteries

CoA - coarctation of the aorta

OB US - obstetric ultrasound

SES - Socio-economic status

RoR – remoteness of residence

CCHD - critical congenital heart disease

CHAPTER 1

PRENATAL DETECTION OF CONGENITAL HEART DISEASE

1.1 Prevalence, Burden & Clinical Outcomes of Congenital Heart Disease

Congenital heart disease (CHD) is a term used to describe structural defects of the heart that are present at birth. CHDs are the most common major birth defects, occurring in 8-13% of live births internationally and accounting for 28% of all major congenital anomalies[1]. In 2015, CHD was present in 48.9 million people globally, and its prevalence has dramatically increased from 1970 to 2017 as a consequence of improvements in the medical and surgical care of affected infants, children, adolescents and adults[2]. Relative to that of live-births, the prevalence of CHD among conceptions and reported in fetal autopsies is even higher[3]. In Canada, the birth prevalence of CHD is 12.1 per 1000 total births[4] and, in Alberta, 5.6 per 1000 total births[5].

CHDs can range from very minor anatomical differences, which are not hemodynamically important, cause no symptoms, and may resolve spontaneously, to serious conditions that, without surgical intervention, result in the death of an affected infant or child. Annually, more than 300,000 infant deaths world-wide are attributed to more serious CHD[6], and it is recognized as a major cause of mortality and morbidity in the first year of life[7]. Provincial data from the Alberta Congenital Anomalies Surveillance System (ACASS) found CHD to account for the highest morbidity and mortality associated with birth defects[8]. Approximately 70% of infant deaths attributable to CHD occur in the neonatal period (age <28 days)[9]. Among prenatally diagnosed CHD, the associated mortality and morbidity remains significant, at least in part due to a higher proportion of more severe cardiac pathology, related to detection bias, and pregnancy terminations. In Europe, rates of perinatal mortality and pregnancy terminations due to CHD from 2000-2005 were reported to

be as high as 0.7 per 1000 births[1]. Others have shown of fetuses diagnosed prenatally with CHD, 4.5% die in utero and 21.1% die after birth[10].

The types of CHD most associated with death in infancy are those which require persistence of the fetal vessel, the ductus arteriosus, to support the pulmonary or systemic circulation. Three of the most common forms of neonatal CHDs which typically present as critical lesions are transposition of the great arteries (d-TGA), hypoplastic left heart syndrome (HLHS) and the so-called "neonatal" form of coarctation of the aorta (CoA). If not identified sufficiently early with initiation of prostaglandin E1 to maintain ductal patency, an affected newborn may become profoundly hypoxic and/or present with cardiovascular collapse due to insufficient cardiac output to the body and heart failure. According to Centers for Disease Control, in the United States approximately 7,200 babies born every year have such life-threatening CHDs. A delay in their diagnoses is associated with excess mortality, and contributes to substantial short- and long-term morbidity for survivors[11,12].

Critical CHD (CCHD) as defined above can be a difficult category to extract from datasets due to the complex nature of CHD, leading to variability in ductal dependency even among seemingly similar heart defects, such as CoA. In the United States the National Centers for Disease Control and Prevention define "CCHD" as CHD requiring intervention in the first year after birth[13]. However, for cardiologists and neonatologists, CCHD is often defined as the lesion requiring intervention in the neonatal period, and usually refers to those lesions that are ductus arteriosus dependent. Congenital heart disease (CHD) requiring intervention in the first year is then defined as major CHD. Knowles et al[14] provided a practical classification of CHD that includes 3 main categories that relate to clinical relevance as outlined in Table 1. Still others have also defined CHD as mild, moderate and severe complexity, however, that CCHD may be found

in severe and moderate categories makes analyses a challenge. As a consequence, this classification has been largely used in adolescent and adult CHD, where CHD that is life-threatening in the newborn period is no longer relevant[15].

Table 1.1. Classification of Congenital Heart Disease Based on Clinical Impact

Types of CHD	Definition	Examples
Life threatening CHD	CHD that represents structural cardiac defects in which collapse in the newborn period is likely, most due to dependency and closure of the ductus arteriosus.	d-TGA, CoA, severe aortic stenosis, pulmonary atresia and HLHS
Clinically Significant CHD	CHDs that represent structural cardiac defects that impact heart function but where collapse in early infancy is unlikely	ventricular septal defect, complete atrioventricular septal defect, atrial septal defect and tetralogy of Fallot.
Clinically non-significant CHD	CHDs that represent structural cardiac defects that have no functional, and therefore clinical significance.	small VSDs and ASDs, minor valve abnormalities

Table modified from Knowles et al[14].
Legend: CHD-congenital heart disease, d-TGA- dextro-transposition of arteries, HLHS-hypoplastic left heart syndrome, VSD- ventricular septal disorder, ASD- atrial septal defect

CHD is also associated with genetic syndromes and extracardiac structural defects which may contribute importantly to the morbidity and mortality of an affected infant, even beyond the risks of the CHD. Genetic syndromes are common in CHD encountered postnatally, reported in 5-17%[16, 17] and affecting up to 25% in the current era of microarray and whole exome and genome sequencing[18]. Structural extracardiac pathologies in the absence of a genetic syndrome have been reported to occur in 5-24% of postnatal CHD[16,18,19]. It has long been recognized that such associations are more frequently observed in fetal CHD which likely contribute to higher rates of intrauterine and perinatal loss. In a previous large cohort reported by Song et al, of 382 fetuses with complete prenatal, postnatal and autopsy data, 28% had a genetic diagnosis among those tested, 19% of the total cohort[19]. Furthermore, 37% of fetuses had 289 major extracardiac

abnormalities at autopsy or postnatal exam, of which one-third had a genetic abnormality. It is of note, however, that the high incidence of associated genetic and extracardiac pathologies among fetal CHDs at least in part reflects referral bias, with identification of genetic markers or other structural anomalies leading to referral for fetal echocardiography.

1.2 Prenatal Detection of CHD

Fetal echocardiography, performed by individuals with expertise in echocardiography, fetal ultrasound and CHD pathology/pathophysiology, permits the prenatal diagnosis of CHD. Fetal echocardiography has substantially evolved over the past 4 decades. In the early 1980s, with no ultrasound screening guidelines and poor image resolution, fetal CHD diagnoses only represented major lesions, typically the worst end of the spectrum relative to those encountered after birth[20]. Over the ensuing decades, with experience and evolving ultrasound technology, including the advent of high frequency, high resolution transducers, the prenatal diagnosis of most major and minor forms of CHD became possible[21]. Over the past decade, the goal of fetal cardiology has turned from a basic diagnosis to fine-tuning of anatomical and functional diagnoses, enhancing prenatal counseling and facilitating the accurate prediction of clinical outcomes prenatally, perinatally and postnatally.

1.2.a. Benefits of Prenatal Detection of CHD

An accurate prenatal diagnosis of CHD by fetal echocardiography has many important benefits. Appropriate prenatal counseling of the affected pregnant mother/couple is central, covering associated cardiac and noncardiac pathologies, the implications for the remainder of pregnancy, the birth and postnatal period, the potential for medical and surgical management and the short and long term prognosis. The severity of the CHD, risk of associated non-cardiac defects

or syndromes and potential methods of testing for these associations are discussed. Counseling provides the necessary information for families to make decisions regarding continuation or termination of the pregnancy when the timing of diagnosis is sufficiently early. It allows the family to prepare for the birth of an affected baby. Prenatal diagnosis also prompts investigations for other fetal pathology including structural anomalies and genetic syndromes. Prenatal diagnosis of CHD provides an opportunity to treat certain fetal cardiac conditions before birth that may improve fetal survival, such as fetal arrhythmias and heart failure[12]. Finally, prenatal diagnosis of CHD provides an opportunity to plan perinatal and neonatal care that includes delivery for most within a tertiary or quaternary care program, where the best, most appropriate care can be provided to the infant. For some lesions associated with acute cardiovascular compromise after birth necessitating immediate intervention, prenatal diagnosis allows for planning the right time, place and mode of delivery with the appropriate care team, facilitating the best acute care of the affected newborn [22].

Several studies have demonstrated that accurate prenatal diagnoses lead to enhanced outcomes of newborns with severe neonatal CHD[23]. Prenatal detection of d-TGA has been shown to improve pre-operative outcomes through planned delivery at a tertiary care center, and availability of a care team that can offer urgent balloon atrial septostomy when necessary[24,25,26,27,28]. Prenatal detection of d-TGA is also associated with improved neurodevelopmental outcomes[29], including improvements in postnatal brain maturation and decreased risk of postnatal brain injury associated with inadequate care in the newborn period[30]. Prenatal diagnosis for another common critical CHD, HLHS, responsible for the majority of deaths within the first month associated with CHD[31], has been shown to importantly improve the clinical condition and outcomes[32]. Prenatal diagnosis of HLHS confers both optimized preoperative hemodynamics[33] as well as postoperative survival[34]. Prenatal detection similarly benefits

newborns with critical CoA with improved preoperative haemodynamic stability and reduction in early neonatal death[35].

The prenatal diagnosis of CHD allows optimized delivery planning, tailored for a given CHD case, ranging from local, non-tertiary care center to delivery in a tertiary care center for the initiation of prostaglandins, to delivery in a cardiac operating room and even prenatal cardiac transplant listing as outlined in the 2014 American Heart Association Fetal Cardiology Guidelines[36], and more recently modified by University of Alberta Fetal & Neonatal Cardiology Program (Table 2). This planning is beneficial to both the family / patient and the health care system, as it provides clarity with respect to the safest site for birthing, discourages unnecessary escalation of care for infants with noncompromising CHD, and even provides modest guidelines for the delivery of those predicted to be unstable at birth with CCHD, who may be delivered in quaternary care operating rooms ensuring the presence of highly trained personnel and specialized equipment.

Given the myriad benefits of prenatal detection of CHD, and evolution of optimized perinatal and neonatal management strategies that promise improved outcomes, the development of systems to maximize the rate of detection and ensuring their availability to all pregnant women and their babies in our society are of utmost importance. Knowledge of how a prenatal diagnosis of CHD is made that leads to optimized delivery planning requires an understanding of the indications for fetal echocardiography. These indications been reviewed in detail in the American Heart 2014 Fetal Cardiology guidelines[36].

Table 1.2: University of Alberta Delivery Planning Categories for Fetal CHD

Level of Care	Definition	Example CHD	Delivery Recommendations
1	**1a.** CHD without predicted risk of hemodynamic instability in the DR or first days of life	ASD, VSD, AVSD, minor valve abnormalities	Delivery in local institution with plans for post-discharge cardiology evaluation or care
	1b. more complex defects without predicted risk of instability or need for early (<1 day) intervention	Non PDA-dependent lesions: TOF, TOF/DORV, DORV with normally related great arteries and no/minimal outflow obstruction, single ventricles with mild-mod PS or no outflow obstruction, unbalanced AVSD without left heart obstruction	Delivery in tertiary care center with NICU and early cardiology assessment, most with care on NICU
2	**2a.** CHD with minimal risk of instability in DR but requiring neonatal catheterization/specialized imaging/surgery or monitoring while the PDA closes	Non PDA-dependent lesions: truncus arteriosus (not with IAA), TOF/MAPCAs, coarctation where severity has as yet not been declared	Delivery in tertiary care center with NICU and early cardiology/echo assessment, remain on NICU for 1-2 days then transfer (provides time for mother-baby bonding)
	2b. CHD with minimal risk of instability in DR but requiring PGEs to maintain PDA patency for pulmonary or systemic circulation or require more highly specialized care including daily cardiology involvement	CHDs –Critical left and right heart obstructive lesions, other more complex pathologies that require ventilation, do not behave in the DR as we expect or have clinically compromising extracardiac pathology	Initiate PGEs and transfer to surgical NICU/PICU
3	CHD with risk of instability in the delivery room requiring specialty care for stabilization	d-TGA with concerning atrial septum primum (note: it is reasonable to consider all d-TGA fetuses without an ASD at risk)Uncontrolled arrhythmias, cardiomyopathies without hydops	Planned induction at 38–39 wk; consider C/S if necessary to coordinate services. Delivery at hospital that can execute rapid care, including necessary stabilizing/lifesaving procedures
4	CHD with expected hemodynamic instability with placental separation requiring immediate intervention	HLHS with IAS, DTGA with restrictive atrial septum +/- abnormal ductal flow, obstructed TAPVC, CHB with low rate, decreased function +/- hydrops, severe Ebsteins	C/s at 38-39 weeks, earlier if risk for fetal demise
			Fully planned immediate neonatal care with all necessary personnel, equipment etc
			Initiate PGEs (if appropriate) and transfer to surgical NICU/PICU
5	CHD with expected instability with placental separation requiring immediate intervention and with prenatal transplant listing	Cardiomyopathy, HLHS with IAS, severe Ebsteins and other CHD expected not to have options after birth or to have instability at delivery	Delivery after 34-35 weeks when a heart is available otherwise approach as in Category 4 (potential need for urgent intervention including ECMO)
			Plan your algorithm of care and determine roles of individual specialists!

Legend: DR- delivery room, ASD- atrial septal defects, VSD- ventricular septal defects, AVSD- atrioventricular septal defect, PDA-patent ductus arteriosus, TOF-tetralogy of Fallot, DORV-double outlet right ventricle, d-TGA- Dextro-Transposition of the Great Arteries, HLHS- Hypoplastic left heart syndrome, TAPVC- Total anomalous pulmonary venous connection, IAA Interrupted aortic arch, MAPCAs Major aortopulmonary collateral arteries

1.2.b. Current State of Prenatal Detection of CHD

Although the benefits of a prenatal diagnosis of CHD have been recognized for decades, and the indications for fetal echo have minimally changed over the years, prenatal detection rates have only recently increased. In many jurisdictions in North America and Europe, more than 50% of CCHD is identified before birth. However, worldwide, this has not been as yet observed[37]. For some lesions, particularly more severe forms of CHD, prenatal detection rates have improved. For HLHS, for instance, prenatal detection reported to occur in just over one-third of affected pregnancies in the late 1990s, reached 75%-77% by 2005-2008[38]. In Alberta, prenatal detection of d-TGA has also witnessed an increase from 14% in 2013 to 77% in 2014-2015[39].

Fetal echocardiography itself has a high yield of CHD diagnoses[40,41]; however, fetal echocardiography cannot be provided to all pregnancies. It is labor intensive, there are fewer personnel trained in the technique and with the necessary expertise, and it is not appropriate for most low-risk pregnancies. Over the past few decades, recognition that the majority of significant fetal CHD is found among low-risk pregnancies with suspected fetal heart disease at obstetrical ultrasound (OB US) has led to enhanced and expanded OB US guidelines and educational initiatives to improve prenatal screening of the fetal heart. The finding of extracardiac abnormalities, either structural or chromosomal, with referral for fetal echocardiography has also been shown to lead to the detection of 10-15% of fetal CHD[42], further stressing the importance of routine OB US screening.

1.2.c. Indications for Fetal Echocardiography

Fetal echocardiography in experienced hands has a very low rate of false negative diagnoses. Therefore, referral to a tertiary fetal cardiology centre is the main factor affecting rate

of prenatal detection of CHD. There are many indications for referral of pregnancies for fetal echocardiography. These indications represent risk factors for having a fetus with CHD and can be subdivided into maternal, familial, and fetal/pregnancy categories as outlined in Table 3. Maternal factors include maternal pregestational diabetes, exposure to teratogenic medications, infection, maternal cardiac history, maternal systemic lupus erythematosus and increased body mass index[43,44,45]. Family risk factors include a history of CHD in a first-degree relative, (one of the parents or previously affected child/fetus) or multiple affected relatives. Fetal indications include the finding of a structural abnormality on OB US, fetal arrhythmia, suspected or known fetal chromosomal anomalies, extracardiac structural defects and the presence of polyhydramnios or oligohydramnios. Additional factors include multiple gestation pregnancies, particularly monochorionic twins, which carry a 2-10% risk of fetal heart disease, and assisted reproductive technologies which carry a risk of fetal heart disease of 2% with greater risks among multiple gestations[46,47]. Recent reports indicate up to a 3-fold increase in the prevalence population in infants conceived via intracytoplasmic sperm injection and in-vitro fertilization[48]. Increased fetal nuchal translucency ($\geq$3.5mm internationally and $\geq$3 mm Alberta) present at 10 to 13 weeks gestation is also associated with an increased risk of CHD, even in the absence of chromosomal anomaly, and this risk exponentially increases with the thickness of nuchal translucency[49]. Several studies published over the past 30 years have reported diagnostic yields for fetal echocardiography indications. A recent published study by Boehme et al[46] in Alberta has shown that although referrals for suspected fetal heart disease, extracardiac pathology/markers, twins/multiples and suspected/confirmed genetic disorders represented roughly half (10,099/19,310) of all unique referrals, these referrals accounted for 91.4% (1743/1907) of moderate/severe fetal heart disease identified. Conversely, family history and maternal diabetes made up nearly 1/3 of all referrals but

<5% of affected pregnancies. As the indication with the highest yield of fetal CHD is the finding of suspected fetal CHD on routine OB US screening of low-risk pregnancies, efforts focused on improving rates of prenatal detection must start with optimizing OB US screening of the fetal heart.

Table 1.3: Indications for Fetal Echo Referral Modified from Donofrio et al[36]

Maternal Factors	Fetal Factors	Family Factors
Diabetes mellitus diagnosed in the first trimester	Fetal cardiac abnormality suspected on obstetrical ultrasound	CHD in first degree relative of fetus (maternal, paternal or sibling with CHD)
Maternal phenylketonuria (uncontrolled)	Fetal extracardiac abnormality suspected on obstetrical ultrasound	First or second degree relative with disorder with Mendelian inheritance with CHD association
Maternal autoantibodies (SSA/SSB+)	Fetal suspected/confirmed karyotype abnormality	
Maternal Medications	Fetal tachycardia or bradycardia, or frequent or persistent irregular heart rhythm	
Maternal infection	Fetal increased NT >95% (≥3 mm)	
Assisted reproduction technology	Monochorionic twinning	
Maternal substance like Alcohol	Fetal hydrops or effusions	

1.2.d. Obstetrical Ultrasound in Screening of the Low-risk Pregnancy Population

Since the 1980s, growing experience in prenatal detection of fetal CHD and recognition that the majority of fetal CHD is identified among low-risk pregnancies have led to the development and refinement of fetal cardiac screening guidelines to enhance prenatal detection at routine OB US. The first fetal cardiac screening view to be incorporated into screening guidelines was the four-chamber view, obtained through cross-sectional imaging of the fetal chest directly superior to the diaphragm and obtained in more than 95% of fetuses at 18 weeks[50]. Although this view was implemented internationally, it was eventually recognized that, when used alone, it had

insufficient sensitivity in the detection of all major and specifically CCHD, detecting 30%-60% of fetal CHD[51].

With recognition of the limitations of the four-chamber view in detecting fetal CHD, in 2001, the Society of Obstetrics & Gynecology of Canada included the use of cardiac outflow sweeps, 3VV and other views in their guidelines. However, it was not until the Canadian Association of Radiologists (CAR), who perform the vast majority of OB US in low-risk pregnancies across Canada, incorporated outlet screening in 2010, that prenatal detection rates of such lesions as d-TGA significantly increased, from <15% prior to 2010 to >65% in 2017[39,52]. Other institutions and societies followed suit in 2013 including the American Institute of Ultrasound in Medicine (AIUM) and the International Society of Ultrasound in Obstetrics & Gynecology (ISUOG)[39,52,53], which has led to a substantial improvement in prenatal detection of outlet pathology internationally in more recent years [54,55,56].

Examples of CHD that are associated with an abnormal four-chamber view include atrioventricular septal defect (AVSD), HLHS and tricuspid atresia. Lesions associated with an abnormal cardiac outflow or an arch anomaly which requires sweeping towards the fetal head, include d-TGA, conotruncal lesions (e.g. tetralogy of Fallot, truncus arteriosus, double outlet right ventricle), semilunar valve obstruction and CoA. Such lesions are not uniformly associated with an abnormal four-chamber view. Among conotruncal lesions, for instance, only 30% have been shown to be associated with an abnormal four-chamber view[57]. In further support, prenatal detection rates of d-TGA were very low in diagnostic eras where fetal four-chamber imaging was recommended as the sole screening view[39,58].

1.2.e. Overall Detection & Risk Factors for Missed Prenatal Detection

While refinement of OB US guidelines has importantly improved prenatal detection of CHD, 20-50% of CHD still remains undetected. Factors that may contribute to imperfect rates of prenatal detection can be divided into technical, health system and population level factors. Technical factors include the expertise required to detect a particular form of CHD, the quality of the ultrasound machine, suboptimal fetal position, the mother's body habitus and general acoustic windows, which all may make it difficult to do high quality scanning of the heart of the fetus[59]. Health system factors include access to OB US screening, which is nearly universal in Canada[60], the training and hire of sonographers with experience and expertise in CHD screening, the availability of OB ultrasound appointments at the optimal timing in gestation, with mid gestation representing the optimal time for fetal screening, and in some countries, the cost to the family. Population level factors contributing to imperfect prenatal detection of CHD include socioeconomic, cultural and language barriers, and the geographic distribution of the population. In Canada, the climate and timing of pregnancy may also play a role. Technical, health system and population level factors may all interact. For example, obesity is associated with difficult imaging, and also with lower socioeconomic status (SES), and potentially with particular locations of residence. Later in gestation, suboptimal fetal position, greater calcification of osseous structures and relative oligohydramnios coupled with worse maternal habitus can substantially limit image resolution.

1.3 Impact of Socio-Economic Status on Prenatal Care and CHD Detection

Socio-economic Status (SES) is one of the most important factors associated with health outcomes[61]. People of lower SES are more likely to have worse self-reported health, lower life

expectancy and suffer from more chronic conditions when compared with those of higher SES[62]. They receive fewer diagnostic tests and medications for health care due to cost and coverage[63].

Social deprivation has been shown to importantly impact prenatal care and pregnancy outcomes. Women of lower SES have been shown to receive less prenatal care and have higher rates of pregnancy complications including miscarriage, preterm delivery, preeclampsia, still birth and gestational diabetes[64]. In a large population study in the Umbria region of Italy, which included 37,000 pregnancies encountered from 2005-2010, Chiavarini et al found striking differences in healthcare use during pregnancy, with substantially lower use for women from less advantaged social classes[65]. Such differences have also been observed among aboriginal versus non-aboriginal women in Manitoba, with less prenatal care observed among women in poverty, particularly with co-existent aboriginal ethnicity[66.] Other studies have demonstrated reduced prenatal screening in women of lower SES which has included fetal anatomical ultrasounds[65,67], and in a study from the Netherlands, lower income was associated as a consequence with lower rates of prenatal detection of birth defects in general[68].

Lower SES has also been shown to be associated with higher prevalence of CHD and to impact health outcomes related to CHD encountered after birth[32,69]. A meta-analysis of 33 studies reported in 2014 provided evidence of an association between low SES including maternal educational attainment, family income and maternal occupational prestige and an increased prevalence of CHD[70]. In the United States, CHD has been found to occur more commonly among live-births in black and hispanic as compared to white and Asian populations[71]. In one population study in the Canadian province of Ontario, children born in lower SES neighbourhoods (23% of all births) had a 15 - 24% higher risk of CHD[72].

SES has also been shown to importantly impact mortality associated with CHD managed after birth. Best and colleagues[73] found a higher degree of poverty, lower level of prenatal education, and public as opposed to private health insurance in the United States to be associated with an increased risk of CHD-related mortality among infants. Lower SES has been associated with worse clinical outcomes for other vulnerable pediatric heart disease populations in the United States including those following heart transplantation[74]. Among adolescents and adults with CHD, lower SES is associated with higher rates of hospital admission and emergency department visits, greater likelihood of need for cardiac surgery, and higher odds for major adverse cardiac events[75].

Although CHD is more common among those of lower SES, limited data exists that specifically explores the effect of social determinants of health on prenatal detection of CHD[76]. In a multicenter North American initiative, lower SES was found to be associated with lower rates of prenatal diagnosis among affected newborns in jurisdictions within the United States but not in 2 Canadian provinces, suggesting the Canadian healthcare system may perform better with respect to prenatal care and screening than in the US[31]. However, the latter study only focused on prenatal detection of HLHS and d-TGA. Further studies done across a larger spectrum of fetal CHD are required to better understanding the influence of technical, health system and population level factors on prenatal detection of CHD. Understanding the existing barriers to prenatal detection of CHD is critical for identifying interventions effective in improvement of outcomes for patient with CHD.

1.4 Impact of Geographic Location of Residence on Prenatal Care and CHD detection

Distance to health care is one of the most important geographic challenges that may affect health status and health outcomes and may importantly contribute to disparities in healthcare. The effects of distance on access to health care services have been a subject of research for some time[77].

Several studies have examined the impact of greater remoteness of residence (RoR) from health care facilities specifically on pregnancy outcome[78,79,80,81,82]. Marian Tanou et al[78] in Burkina Faso used a demographic and health survey 2010 dataset, with its sample of 10,364 mothers aged 15-49 years. They found that improving geographical access to health facilities increased the use of appropriate healthcare services during pregnancy and childbirth. In another study, Nesbitt et al[81] found that mothers who lived further away from the delivery facilities were less likely to deliver their baby at those facilities.

Few studies have explored the association between RoR and prenatal detection of CHD, and most have examined both SES and RoR from prenatal centers together given the potential for interaction between these variables in some jurisdictions. Pinto et al 2012 reviewed the experience with 1474 cases of major CHD encountered over a 10-year period (1997-2007) in Utah. They found 39% to be prenatally detected, no improvement in overall prenatal detection over the study period, and that neither SES nor RoR from health care centre were associated with a prenatal diagnosis[83]. However, the latter study was flawed in that up to 25% of fetal cardiac diagnoses in Utah were made by outside maternal fetal medicine specialists with termination of pregnancy occurring prior to confirmation in a cardiac center. As a consequence, these cases were not included among the total numbers and numbers with a prenatal diagnosis[83]. In another study performed in the greater Paris area, Khoshnood and colleagues demonstrated an overall prenatal detection rate of CHD of only 29%, and they too could not demonstrate a relationship between SES or maternal RoR and prenatal diagnosis rate [84]. This latter study included only patients in the immediate area around Paris, which did not allow them to examine the impact of rural or remote residence, and they did not include pregnancies from other parts of the country. In another US study, Peiris et al examined all infants encountered at the Boston Children's Hospital to determine

the impact of SES on prenatal detection rates. While they did find lower SES to be associated with less prenatal detection, the exclusion of prenatally detected cases with pregnancy termination likely biased their results. In addition, this work did not represent a population study as only infants managed in their institution, a quaternary care/referral centre, were included[85]. To date, no population data exists examining the impact of SES and RoR on the prenatal detection of CHD, and little data exists that examines these factors in a jurisdiction with universal healthcare.

1.5 Summary of Knowledge Gaps in Prenatal Detection of CHD to be Explored

The fetal four-chamber view obtained during routine OB US has long been recognized as useful in detecting 30-60% of major congenital heart disease[86]. This has been a part of international OB US guidelines now for decades. More recently, the added benefit of screening the fetal cardiac outflows and 3VV has been recognized with some outflow pathologies achieving 75-80% prenatal detection in jurisdictions, including Alberta, where outlet screening has been integrated into guidelines[39,58]. More than 80% of pregnancies with fetal CHD are referred to fetal cardiology due to a finding on OB US of a suspected CHD or an extracardiac defect[87]. Despite these improvements, there continue to be many affected pregnancies not recognized prenatally. Thus, ***there is a need to explore other barriers to prenatal diagnosis in an effort to continue to enhance detection rates. Furthermore, there is lack of recent population data exploring prenatal detection rates particularly in a jurisdiction of universal health care in the more recent diagnostic era***, which would, as a start, provide insight into whether guideline refinement has contributed to a substantial improvement in prenatal detection. It would also provide insight into where further work is required to optimize routine OB US screening.

In order to improve prenatal detection of CHD, estimation of the impact of existing barriers, including the importance of population factors such as SES and RoR, is required. Recent

studies have suggested that SES is a major risk factor for poor obstetrical outcomes including preterm delivery, preeclampsia and gestational diabetes. In certain jurisdictions, pregnant women of lower SES receive less prenatal care due to accessibility and cost. As a part of inadequate prenatal care, women of lower SES have been shown to have reduced prenatal detection of fetal anomalies. Reduced prenatal detection of major, particularly CCHD, could significantly worsen outcomes of affected fetuses and newborns. ***To date, most of the research that has explored the impact of SES on prenatal detection of CHD has been reported from the United States which may not be translatable to jurisdictions such as Canada where universal healthcare available to the population.***

Greater RoR from health care facilities has also been shown to impact prenatal detection in the United States. Preliminary experience of the Fetal Heart Society would suggest this may also be true in Canada. However, further research in this area is needed to confirm these findings in a larger spectrum of CHD and through population studies. Canada is a country whose population is widely dispersed geographically. ***While in theory Canada has universal prenatal care and this should include OB US screening, whether the services provided to its more remote populations is comparable to those provided in cities where centralized obstetrical and fetal echocardiography facilities exist, is not clear.*** Knowledge of whether SES and RoR impact rates of prenatal detection of CHD, particularly in a jurisdiction of universal healthcare such as Canada, is key to ensuring there is equity in prenatal care, including OB US screening for fetal CHD.

With these knowledge gaps in mind, this thesis has 2 primary objectives:

Objective 1: To examine trends in prenatal detection of major CHD in Alberta from 2008 through 2018

We hypothesized that while most major CHD associated with four-chamber and outlet anomalies will have demonstrated a substantial increase in prenatal detection, lesions such as aortic arch and pulmonary venous anomalies remain a challenge

Objective 2: To examine the impact of SES and geographic RoR on prenatal detection rates and timing of prenatal detection in Alberta from 2008 to 2018. *We hypothesized lower maternal SES and more remote geographic RoR from tertiary care OB US and fetal cardiac programs are associated with lower rates and later prenatal detection of CHD*

The work presented represents a population study that takes advantage of the centralized fetal and pediatric cardiac care in the province of Alberta. Through collaborations with our colleagues from Southern Alberta at the University of Calgary, we examine provincial prenatal detection rates of cardiac lesions as they relate to OB US cardiac screening views and how rates have changed temporally with changing screening guidelines. We further examine the impact of SES and remoteness of residence on prenatal detection rates of CHD using maternal residence postal codes to generate SES quintiles at neighborhood level using the Chan index[88] and measuring distances from the two regional maternal and pediatric cardiac centers.

This data will help us understand where deficiencies lie with respect to OB US screening providing an opportunity for targeted educational and health services initiatives that will enhance prenatal screening for CHD across the province. It will further determine whether there are care gaps in prenatal screening for CHD that relate to lower SES and greater RoR that can be used to

develop strategies to reduce such gaps in care, if they exist in our jurisdiction of universal healthcare.

CHAPTER 2:

REVIEW OF METHODOLOGICAL STRENGTHS & WEAKNESSES

Research methodology provides the blueprint of the specific procedures or techniques used to identify, select, process and analyze information about the research topic. It is crucial to understand the underlying strengths and limitations of the methodology that has been used to answer a research question in order to correctly interpret the results and their potential to be influenced by various forms of bias. Inappropriate methodology may undermine the value of analysis of the findings, reduce the ability to make accurate estimates of effects, and lead to erroneous conclusions.

This section explains the approach to data collection for the thesis and how it was analyzed critically reviewing strengths and limitations of the approaches. There were two objectives for the research. A spectrum of methodologies was employed to analyze the data and are reviewed in this chapter.

2.1 Examining Trends in Prenatal Detection of CHD in Alberta

2.1.a. Development of the Population Dataset

This research represented a retrospective population-based study. It included the development and validation of a database of all fetuses and infants encountered with major CHD, lesions requiring intervention within the first year after delivery, in the province of Alberta from 2008-2018. We first identified all Albertan residents undergoing pediatric cardiac surgical intervention through review of the surgical databases (a list of cases maintained by the surgical team for billing purposes), and the Western Canadian Children's Heart Network (WCCHN)

database (the platform for all referrals for pediatric cardiac surgery in Alberta). This dataset was limited to patients with major CHD according to our definition, (undergoing surgery in the first year of life). To identify cases with a fetal diagnosis, we cross-referenced the list of cases of major CHD based on unique provincial healthcare identifiers (ULI) with the fetal cardiology databases used in the two centralized pediatric cardiology sites within the province, the Stollery Children's Hospital, University of Alberta, in the north, and the Alberta Children's Hospital, University of Calgary in the south. Both represent the only sites within the province offering fetal cardiology services (imaging and counseling) and both have prospectively maintained databases of all fetal cardiac diagnoses encountered since 2008. Both sites are also the primary pediatric cardiac centers in the province where all infants and children are referred for specialized cardiac diagnostic and management services, and surgical intervention is only offered in the Edmonton site. From the fetal databases, we also identified all cases resulting in termination of pregnancy, intrauterine fetal demise, or parental / medical decision for non-surgical comfort care after birth. If these cases had a definitive prenatal diagnosis of major CHD, they were added to the dataset of major CHD. All fetal and infant cases of major CHD encountered and/or born within the study period were therefore included.

Unlike most previous studies, our provincial approach allowed us to capture pregnancies with a fetal CHD diagnosis that ended in elective termination or fetal demise in addition to live births. This is important as such cases need to be included within both the numerator and denominator when calculating accurate prenatal detection rates. Our data would otherwise be biased with respect to major CHD associated with, for instance, a four-chamber abnormality, which may have been more readily detected before birth, and more likely to result in a decision to terminate the pregnancy. We would also not otherwise capture more severe fetal CHD associated

with fetal demise or others with choice of pregnancy termination, such as those with aneuploidy, underestimating prenatal detection rates for such pathologies. These limitations have been observed in many past studies examining prenatal detection rates due to lack of access to clinical outcomes among affected pregnancies. The vast majority of past investigations examining rates of prenatal detection have been limited to newborns or to the experience of a tertiary care program.

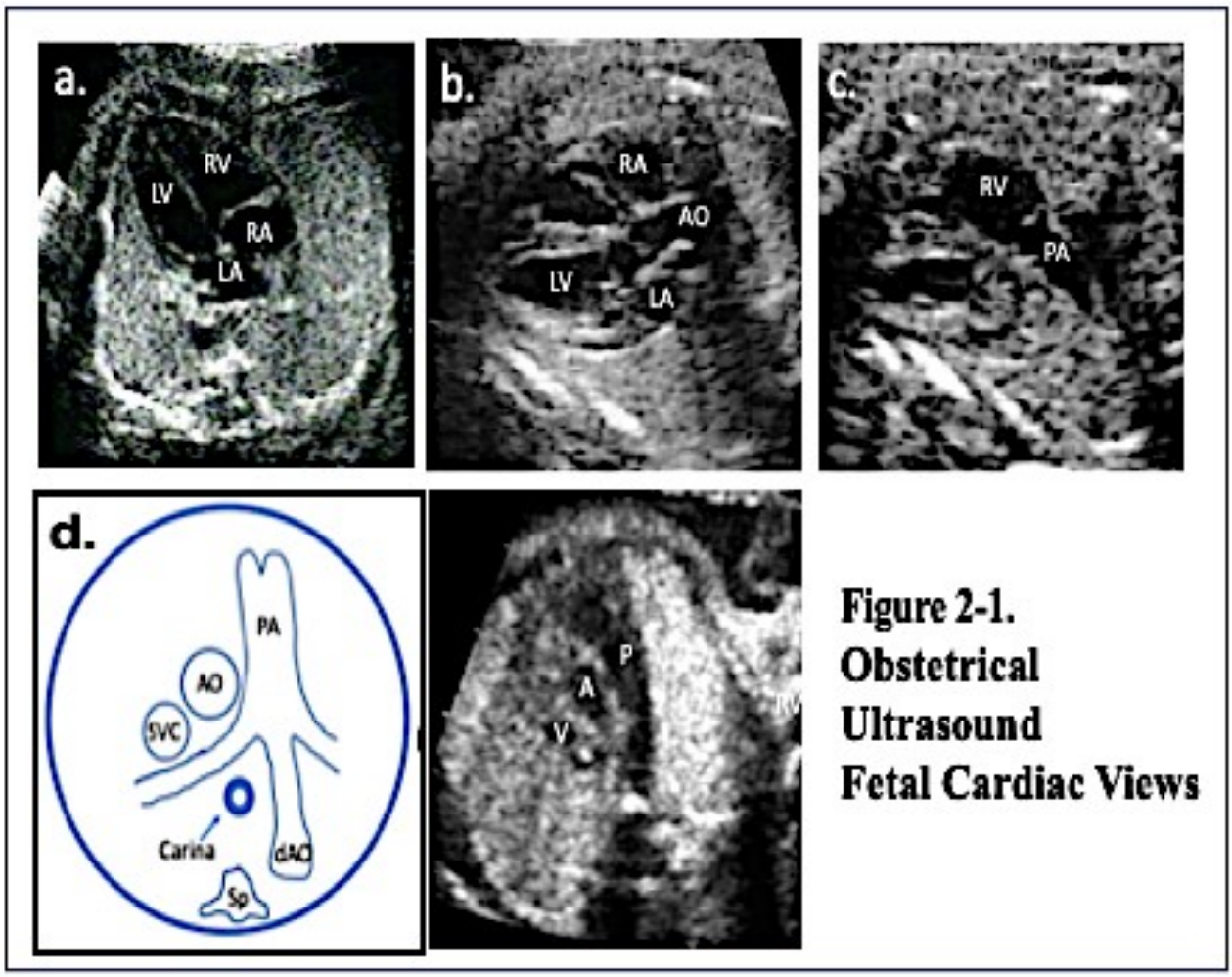
Our approach did have some limitations, however. Although we captured all affected pregnancies and infants encountered at the two centralized referral sites, we could have missed CHD cases with pregnancy termination or fetal demise with lethal aneuploidy, prior to an evaluation within our programs. Furthermore, we cannot be certain all neonates with critical CHD who demised prior to referral to our programs were identified; however, the proportion of such patients relative to the cases identified would have likely been miniscule and thus not have impacted our findings significantly. To confirm we have captured the vast majority of affected pregnancies and infants, we have compared lesion specific birth rates to those reported in Alberta through Alberta Congenital Anomalies Surveillance System (ACASS) as well as those reported across the country. We have identified a total of 1405 patients who were prenatally and postnatally diagnosed during the study period in Alberta. Our study did not include major CHD requiring intervention at cardiac catheterization within the first year due to lack of a reliable provincial database. Some lesions warranting this type of intervention (e.g. semilunar valve obstruction) are not always identifiable in the mid and third trimester. Moreover, we have not included the extra-cardiac anomalies and/or genetic/chromosomal results of our cohort despite the fact that for some affected pregnancies they may have prompted further fetal cardiac assessment. Irrespective of the presence of associated noncardiac pathology, all of the major CHD we have included should be detectable by OB US. Thus, our focus was on the CHD diagnosed pre or postnatally only. Finally,

the gestational age at CHD diagnosis was considered when the patient had a diagnosis made or confirmed at fetal echocardiography. For many affected pregnancies, the first diagnosis is made or suspected at OB US.

2.1.b. Examining CHD Detection by OB US Views and for Lesion Subtypes

With respect to the approach to examining rates of prenatal detection of CHD, we chose to focus not only on lesion specific rates, but on the OB US views most likely necessary to detect such lesions in fetal cardiac screening at routine OB US. In this way we could temporally examine the impact of OB US guideline changes on rate of prenatal detection. We examined and compared 3-year ranges within the study period that reflected timing of publication in Canada, the United States and Europe of guidelines with mandated or recommended ultrasound-based fetal cardiac screening changes. The period of 2008-20012 occurred within SOGC (2009) and CAR (2010 guideline publications, 2013-2015 within AIUM and ISUOG guideline publications (2013) and 2016-2018 would reflect post guideline publication and a more recent era of screening. Without documentation of the training of those performing routine screening OB US exams through the study period for individual fetal cardiac cases, it was difficult to be certain of the direct impact of guideline changes, however, we felt demonstrating a temporal relationship as has been done by our team in one previous report published for d-transposition of the great arteries (d-TGA) in Ultrasound in Obstetrics and Gynecology[89] would provide some sense of the impact of these changes.

Understanding the different fetal cardiac screening views provides insight into the lesions most likely detected in these views. The specific views that were included in our research were the four-chamber view, the cardiac outflow tracts, the 3 vessel/3 vessel-tracheal and other nonstandard views, and assessment of ventricular septal defects using any view (Figure 2-1).



Legend: a. 4 chamber view; b & c. Cardiac outflow views demonstrating the left ventricular (LV)/aortic (AO)(b) and right ventricular (RV)/pulmonary outflows that cross; d & e. Diagram and ultrasound image demonstrating the 3 vessel view. LA-left atrium, RA-right atrium, and in figures d and e: SVC-superior vena cava, Ao-ascending aorta, PA-pulmonary artery, dAo-descending aorta, Sp-spine..

The four-chamber view was the first described fetal cardiac screening view and has been the most widely accepted in OB US[90,91]. It is technically very easy to obtain. It is taken in the transverse section of the fetal thorax. The cardiac size, position, axis, and symmetry can be quickly evaluated in this view. Using this view, the 4 cardiac chambers, the atrial and ventricular septum, the atrioventricular valves, the pulmonary veins, and the ventricular contraction can be assessed. From

this view such major CHD as hypoplastic left heart syndrome (HLHS), other single ventricle lesions, atrioventricular septal defects (AVSD) and isomerisms can almost always be identified. Sweeping from the four-chambers towards the fetal head, the cardiac outlets can be identified beginning with the aortic outflow which courses from the left ventricle towards the fetal right. Sweeping further cephalad, the pulmonary outflow tract arises from the right ventricle wrapping around the aorta and coursing to the left of the fetal midline. Documenting 2 symmetric outflows that cross, such lesions as d-transposition of the great arteries (d-TGA), conotruncal pathology and semilunar valve obstruction, which often have a relatively normal four-chamber view, can be identified. Sweeping further towards the head of the fetus, the 3-vessel view (3VV) and then the 3-vessel tracheal (3VT) views are encountered. The 3VV is obtained in a cross-sectional image through the fetal superior mediastinum where the 3 great arteries, the superior vena cava, which is most rightward and posterior, the ascending aorta, which is just to the right of the midline, and to the left and anterior of the superior vena cava, and the pulmonary artery, which is most leftward and anterior, are transected. The relationship of the 3 great arteries to each other in position, alignment and size are constant in the fetus without structural CHD and thus any abnormality heralds the presence of CHD. The 3-vessel tracheal sweep represents a sweep towards the fetal head from the 3-vessel view and demonstrates the aortic and ductal arches including their course, which is usually to the left of the trachea, also seen in this view, and their symmetry.

Most CHD with abnormalities recognizable on four-chamber or outflow tract views, such as d-TGA, conotruncal lesions or semilunar valve pathologies, are also identifiable on the 3VV/3VT views, therefore providing a second and third chance to detect these forms of CHD if missed in the preceding view. In addition, CHD causing the affected great artery to be too small or too large relative to the unaffected great artery, such as aortic coarctation, can often be suspected

on these views. Coarctation of the aorta includes a more diminutive or, at times, nonvisible aortic relative to ductal arch. CHD which involves an abnormal course of the aortic arch, such as vascular rings, are readily apparent on the 3VT view. Other views which are non-standard for OB US screening of the cardiac structures form a routine element of fetal echocardiography, and include assessment of pulmonary venous connections and sagittal imaging of the heart, including the long-axis of the aortic arch and assessment of the mitral valve and IVC continuity.

While use of groupings of lesions according to the OB US view most likely to facilitate their diagnosis is informative with regards to influence on prenatal detection of screening protocols, there are limitations in this approach. Specific lesions within these OB US view groups are not equivalent in their ease of detection. For example, HLHS will always have abnormal four-chamber, outflow, 3VV and 3VT views, in contrast to AVSDs, which can have normal outflow tract, 3VV and 3VT views. As well, without examining individual cases included in this study, we could have incorrectly categorized a given CHD case. When examining CHD cases, we used a hierarchical approach. If a CHD was associated with an abnormal four-chamber view, outflow tract and 3VV such as HLHS, we included it within the four-chamber category. For conotruncal lesions, although they can be associated with both an outlet and 3VV-3VT abnormality, we categorized them into cardiac outflow abnormalities. Coarctation of the aorta is occasionally associated with asymmetry of the four's chambers and great arteries with smaller left sided structures; however, the finding of a hypoplastic arch and especially posterior shelf best seen in 3VT and sagittal views of the arch are most constant features[92,93]. We further examined specific anatomical CHD subtypes which allowed us to consider al pathologies and to compare our findings to previously published data.

2.2 Measures of Socioeconomic Status

From maternal and infant/family residence postal codes for the individual CHD cases encountered over the study period, we generated Chan Index neighbourhood-level socioeconomic status (SES) percentiles based on the 2006 census data (Chan BMC Public Health 2015)[4]. These scores were then converted to quintiles. These data represent aggregated data from dissemination areas (400-700 people) and thus have inherent limitations.

2.2.a. The Chan Index in Defining Socioeconomic Status

The Chan Index was evolved at the University of Alberta to incorporate measures of Socioeconomic status (SES) as well as environmental exposures and was based on 2006 census data available through Stats Canada[88]. The index used principal component analysis (PCA) which incorporated 22 SES variables including those associated with cultural identities, housing characteristics (Census Canada 2006), variables identified in Canadian environmental injustice studies and variables included in an existing Canadian deprivation index[94] (Pampalon et al), such as household income, highest educational level attained and family structure. The PCA analysis was performed for all the dissemination areas (DA) in Canada (n=52,974) of which there are 5,517 in Alberta. A DA is defined as small neighboring regions consisting of 400 to 700 people. For the current work, we used a postal code conversion file (PCCF) to identify the postal codes belonging to each DA, and assigned the SES index value of the DA to each of the postal codes aggregated to the individual DAs, assuming a homogenous distribution within the DA. The lowest category of SES index (quintile 1) was designated as the reference in the analysis.

2.2.a.1. Strengths and Limitations of the Chan Index for SES

The Chan et al index has important strengths. In addition to being developed here in Alberta and validated in a Canadian population, it explores the impact of SES on a neighborhood level and thus maintains confidentiality as individual cases are not identifiable. It includes more variables that relate to SES and health outcomes than previously published indices including the CanMarg index[95] and incorporates all of the variables assessed within the Pampalon Index[94].

There are also limitations to the use of the Chan index in defining SES. It is not an individual based index, and thus the index does not represent the actual SES of the patient as it assumes all individuals within a given DA are of the same SES. In this index, there is the lack of separation of material and social deprivation. Material deprivation involves deprivation of the goods and conveniences that are part of modern life, including housing, possession of a car, access to high-speed internet, or a neighbourhood with recreational areas, some of which are likely to impact a pregnant mother's ability to navigate the health system and attend an appointment in a timely fashion, for instance. This deprivation may be associated with lack of material resources associated with low education, insecure job situation and an insufficient income. Social deprivation refers to the person having a fragile social network, starting with the family and ultimately including the community. It is characterized by individuals living alone, being a single parent and being separated, divorced or widowed[96].

Another limitation of the Chan index is that it is also based on census data from 2006, but neighborhoods within DAs may have evolved to representing those of higher or lower SES and new neighborhoods may have been developed resulting in lack of data for some cases. The Chan index is undergoing revisions currently to incorporate 2016 census data which may be more relevant for more recent years within the study. It was not available at the completion of the current

work, but future directions include reanalysis with the new index in order to examine the impact of use of 2006 versus 2016 census data.

2.2.b. Other SES Indices

There were at least 2 other SES indices we considered using, the CAN-Marg index and the Pampalon index**.** The Canadian Marginalization Index (CAN-Marg) was developed to link neighbourhood marginalization with poor health. Developed by a Toronto-based research team in 2006, the CAN-Marg is a census-based, geographically derived index for use in research that seeks to understand inequalities in health and other social problems related to health among either population groups or geographic areas. The focus was based on a model that emphasizes economic inequality as being of greatest importance. The four dimensions included in the index are residential instability, material deprivation, ethnic concentration and dependency. The dimensions were defined and inequalities in 18 health and behavioural problems from the Canadian Community Health Survey (CCHS) were reported in its original publication.

The Pampalon index can also be used to track social and health equalities over time and space. There are provincial, regional, and local versions of the originally Québec-derived index. The deprivation index consists of six economic indicators, all derived from Canadian censuses, at the enumeration area (EA) or dissemination area (DA) levels. The shift from larger EA area (1991 and 1996) to smaller DA area (2001,2006 and 2011) resulted in a small increase in the amount of variation predicted over time because smaller DAs are more heterogeneous than the larger EAs[96]. These indicators are the proportion of people aged 15 years and older with no high school diploma (SCOLAR), the population/employment ratio of people aged 15 years and older (EMPLOI), the average income of people aged 15 years and older (REVENU), the proportion of individuals aged 15 years and older living alone (SEULES), the proportion of individuals aged 15 years and older

whose marital status is either separated, divorced, or widowed (S_D_V), and the proportion of single-parent families (F_MONO), while the Canadian Census form from which the index was developed contains over 200 variables. While frequently used in Canadian studies, the Pampalon index does not constitute an explanatory framework for social inequalities in health (e.g., there is no information on ethnicity or Indigeneity). Like the Chan et al index and CAN-Marg, it is also not an individual, but a small-area measure of socio-economic conditions. This means inequalities are systematically underestimated, especially outside of urban areas. Finally, the Chan Index incorporates many of the elements included in the Pampalon index.

2.3 Examining Remoteness of Residence from Tertiary Care Centre

The remoteness of residence (RoR) in geographical kilometers from the tertiary fetal cardiac program in the north (Edmonton) and south (Calgary) of Alberta was calculated using geocoding which involved an "as the bird flies" approach to defining distance based on latitude and longitude data of postal codes. We calculated RoR to the direct distance to each of the tertiary pediatric cardiology centres (the Royal Alexandra Hospital in Edmonton, and the Alberta Children's Hospital in Calgary). The minimum of the two distances was then defined as "minimum distance to tertiary care".

Measuring distance using "as a bird flies" approach involves calculating the distance as a Euclidean distance (straight line) from the mother's/patient's postal code of residence to one of two centralized care centers. This is the simplest way of measuring distance from health care facilities. However, it does not measure the real-world experience of a patient traveling to a health facility, which would rarely represent a straight line, and thus, this methodology has inherent limitations. It does not assess true driving / travel distance or the time necessary to take public transportation which may be how many patients travel. There are other ways of measuring distance

from health care centers such as road network calculation using geographic information systems. By incorporating real world connectivity provided by the road infrastructure, travel distance offers a more accurate characterization of the distance among locations compared to Euclidean distance[97]. Even then, travel distance does not recognize the variations in travel impedance like speed limits or travel speeds. Additionally, not all patients travel by car: some require flights, others multiple means of public transportation and would not necessarily provide an accurate measure of distance or time for travel. We chose the "as the bird flies" approach for all patients which should have resulted in the same limitations being present for all patients included, hopefully reducing the impact of the errors in its use.

Distance and remoteness might not represent exactly the same measure. For instance, some places, even if representing a shorter distance, may cost more from which to travel and others may have greater seasonal limitations. Finally, some studies compare the experience of urban and rural regions which we chose not to do. Given that Alberta has a referral system where any pregnancy with suspected fetal heart disease or other anomalies are referred to centralized programs, and that population numbers in more rural areas are small, we chose only to examine distance from our central sites to define RoR.

2.4 Statistical Methodology

The outcome variables of interest in this study were fetal diagnosis as a binary variable, and timing of fetal diagnosis in gestational weeks / days of pregnancy (a continuous variable). Gestational age at diagnosis was also analyzed as a binary variable with a cut-point at the gestation before which ultrasound diagnosis would be reasonably required (22 weeks) so that termination of pregnancy can be legally performed in Alberta without ethics board review (23^{+6} weeks).

For Aim 1, the proportion of cases that had a fetal diagnosis of major CHD was divided into a) intervals of time within the study period (2008-2012, 2013-2015, 2016-2018), b) OB US cardiac views (four-chamber, outflow tract, three vessel / atypical views, and septal views), and c) individual CHD diagnoses. Each of these categorizations have some limitations. Categorization of the study period was done to explore the hypothesis that altered OB US screening guidelines had an impact on CHD fetal diagnosis rate. Nevertheless, introduction of semi-arbitrary discontinuities in a continuous variable such as time involves assumptions which are unlikely to hold true, including a flat distribution of the outcome variable within the categorized period, and often reduces the power to detect differences due to loss of degrees of freedom[98]. We therefore also performed linear regression of proportion of fetal diagnosis by year and estimated the change per year. OB US view assignment for individual cases was performed based on the view most commonly required for diagnosis; however, review of the individual cases may have resulted in assignment to a different OB US view group due to variation in anatomy within individual lesion class. Similarly, individual CHD diagnoses can differ significantly with regards to ease of fetal diagnosis, introducing heterogeneity within these groups. The proportion of fetal diagnosis in each category was summarized with 95% confidence intervals using the Wilson technique. The time intervals were compared for obstetric ultrasound view or individual CHD lesions using the Chi^2 test, with a null hypothesis of no difference between views or time intervals

For Aim 2, two models were constructed: Model 1 aimed to estimate the association of explanatory variables Chan index quintile and distance of residence from the closest tertiary pediatric cardiology unit with postnatal diagnosis, adjusting for year of diagnosis and OB US group. Model 2 aimed to estimate the association of the same explanatory and adjusting variables with timing of prenatal diagnosis <22 weeks or ≥22 weeks gestational age. Relative risks were

estimated as they are in general more intuitive than Odds Ratios. This can be achieved using log-binomial regression, or, equivalently, Poisson regression with robust standard error estimates where lack of convergence occurs, using the generalized linear model (glm) function in Stata. To explore the impact of an arbitrary cut-point for gestational age at diagnosis, we also fit a multivariable linear regression model of the cases with a fetal diagnosis to estimate the association of explanatory variables Chan index quintile and distance of residence from the closest tertiary pediatric cardiology unit adjusting for year of diagnosis and OB US group, with gestation at diagnosis as a continuous outcome variable.

CHAPTER 3:

TRENDS IN THE PRENATAL DETECTION OF MAJOR CONGENITAL HEART DISEASE IN ALBERTA FROM 2008-2018

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Disclosures: None

3.1 Abstract

Background: The prenatal diagnosis of congenital heart disease (CHD) has been possible for many decades, despite which, many affected newborns are still not identified before birth. The impact of expanded obstetrical ultrasound (OB US) cardiac views on fetal CHD diagnosis has not been fully examined at a population level. We hypothesized there has been a significant increase in the prenatal detection of CHD, particularly for CHD associated with cardiac outflow tract and possibly three-vessel view abnormalities, in Alberta.

Methods: Using provincial databases, we retrospectively identified all fetuses and infants diagnosed between 2008-2018 with major CHD requiring surgical intervention within the first postnatal year. We evaluated individual lesions and categorized CHD subtypes based on the US cardiac views required for detection: 1: four-chamber view (hypoplastic left heart syndrome, Ebstein's anomaly, single ventricle), 2: outflow tract view (tetralogy of Fallot, double-outlet right ventricle, truncus arteriosus), 3: three vessel or other non-standard cardiac views (e.g. coarctation, anomalous pulmonary veins), and 4: isolated ventricular septal defects (VSDs) using any view.

Results: Of 1405 cases with major CHD encountered in Alberta, 814 (58%) were prenatally diagnosed overall. Over the study period, prenatal detection increased in all groups with the greatest increase observed for Group 1 (from 75 % to 88%, p=0.008) and for Group 2 (from 56% to 79%, p=0.0002). While rates of prenatal detection increased for Group 3 (from 27% to 43%, p=0.007) and Group 4 (13% to 30%, p=0.04), for both, less than half of the cases were detected even in more recent years.

Conclusions: While rates of prenatal detection of CHD have significantly improved during the past decade, detection rates of CHD associated with an abnormal 3VV and non-standard views as well as isolated VSDs remain substantially lower.

Key words: congenital heart disease, prenatal diagnosis, obstetric ultrasound, fetal echocardiography.

Abbreviations:

CHD – congenital heart disease

OB US – obstetric ultrasound

3VV – three vessel views

TOP – termination of pregnancy

IUFD – intrauterine fetal demise

AVSD - atrioventricular septal defect

HLHS - hypoplastic left heart syndrome

TOF - tetralogy of Fallot

d-TGA - d-transposition of the great arteries

CoA - coarctation of the aorta

TAPVD - total anomalous pulmonary venous connections

VSD - ventricular septal defects

3.2 Introduction

Congenital heart disease (CHD) affects approximately 10 - 13 per 1000 live births[2,99] and is the leading cause of mortality and morbidity associated with a birth defect[100,101]. Most CHD can be diagnosed before birth [102,36], and prenatal detection is associated with improved outcomes particularly for newborns with critical, ductus arteriosus-dependent lesions[103,104]. The prenatal diagnosis of major CHD provides an opportunity for optimized delivery and newborn management planning[45]. It also provides an opportunity to intervene before birth for certain CHD[38] potentially leading to enhanced neonatal and longer-term postnatal outcomes[19]. Finally, earlier diagnosis before birth provides an opportunity for families to consider discontinuation of pregnancy[105].

Although some pregnancies have risk factors for fetal CHD, the majority of prenatally diagnosed CHD are identified among low-risk pregnancies[44]. Implementation of routine OB US screening of low-risk pregnancies has been shown to substantially improve prenatal detection of major CHD[106]. This knowledge has led to efforts to optimize routine US screening of the fetal heart. The first recognized cardiac screening view was the four-chamber view, implemented in the late 1980s and 1990s in US screening guidelines[20]. With recognition that the four-chamber view was insufficient to detect all major CHD[107,108], imaging of the cardiac outflow tracts was integrated into North American (Society of Obstetrics and Gynecology of Canada 2001 and 2009, Canadian Association of Radiologists 2010, American Institute of Ultrasound in Medicine 2013) and European guidelines (International Society of Ultrasound in Obstetrics and Gynecology 2013)[109,53]. Imaging of the three-vessel view and three vessel-trachea sweep (3VV-3VT) has also been strongly encouraged.

Despite the recognized benefits of a prenatal diagnosis and nearly universal availability of OB US, recent single-center studies and focused regional efforts suggest that prenatal detection

rates for CHD remain between 30% to 60%[110]. Our experience has suggested there has been an improvement in prenatal detection for certain CHD associated with abnormal cardiac outflows[111]; however, whether the evolution of guidelines has impacted the detection of other CHD and whether lesions associated with non-standard OB US cardiac screening views have received improved prenatal detection is unclear. Therefore, the aim of this study was to evaluate, at a population level, trends in prenatal detection of major CHD from Jan 2008 to Dec 2018 in the province of Alberta. We sought to define the rates of CHD diagnosis by year of birth, fetal US screening cardiac views needed to detect the CHD and individual CHD subtype. We hypothesized that there has been an increase in the prenatal detection of CHD, particularly in CHD associated with cardiac outflow tract and possibly three-vessel view abnormalities.

3.3 Methods

This was a retrospective population-based study of all fetal and pediatric patients with major CHD resident during pregnancy and at birth in Alberta encountered or born, respectively, from January 01, 2008, to December 31, 2018. The province of Alberta has two centralized pediatric cardiac centers, one in the north (University of Alberta) and one in the south (University of Calgary) that provide the only fetal echocardiography and pediatric cardiac services (for major CHD) in the province. The Stollery Children's Hospital in Edmonton is the sole pediatric cardiac surgical center for the province.

All patients with major CHD were identified through pediatric and fetal echocardiography and surgical databases. Major CHD was defined as CHD requiring surgical intervention within the first postnatal year. We excluded patients born outside of the province in order to more accurately examine the trends of prenatal detection of CHD in a well-defined Alberta population.

Fetal and pediatric echocardiography reports and medical records were reviewed to define whether or not a diagnosis was made prenatally, the indication for fetal echocardiography, CHD subtype, the pregnancy outcome (termination of pregnancy (TOP), intrauterine fetal demise (IUFD), or live birth).

We divided CHD subtypes into groups based on the cardiac views at screening US likely required for their detection: Group 1 included CHD associated with an abnormal four-chamber view (e.g. atrioventricular septal defect (AVSD), hypoplastic left heart syndrome (HLHS), Group 2 included those with an abnormal outflow tract but normal or near normal four-chamber view (e.g. tetralogy of Fallot (TOF), d-transposition of the great arteries (d-TGA), Group 3 included those with an abnormality often detectable most easily on the 3VV-3VT or other non-standard cardiac views (e.g. coarctation of the aorta, CoA, and total anomalous pulmonary venous connections, TAPVD) and Group 4 included isolated ventricular septal defects (VSDs) irrespective of fetal cardiac view needed. Table 3.1 details CHD subtypes included within each group. We also examined prenatal detection rates among individual lesion subtypes.

3.4 Statistical Analysis

Prenatal detection rates were calculated for the entire cohort, for lesion-specific US views and for individual lesions and compared between the groups by year. Detection percentages by years were assessed for significant trends. To assess the effectiveness of OB US screening in relation to guidelines implementation, data from the period 2008-2012 was compared with data from 2013-2015 and 2016-2018. Chi^2 test was used to determine the prenatal detection rate by year category (2008-2012, 2013-2015, 2016-2018), by US views and by type of CHD. A p-value was considered significant at the 0.05 level. All statistical analyses were conducted by using Stata software (SE 17, College station, Texas).

3.5 Results

From 2008 to 2018, 1405 patients (fetuses and infants) with major CHD were encountered pre and postnatally in Alberta, of whom, 814 (58%) were diagnosed before birth. Among the 1405 cases, 1213 (86%) pregnancies resulted in the birth of a living child, 51 (3.6%) suffered an IUFD and 130 (9.3%) cases resulted in TOP. For 10 patients (0.7%), the outcome of pregnancy could not be determined. Over the study period, the proportion of prenatal detection of major CHD significantly improved overall from 277/560, 49% [95% CI 45, 54] in 2008-2012, 255/417, 61%, [95% CI 56, 65] in 2013-2015, to 282/428, 66%, [95% CI 61, 70] in 2016-2018 (p-value <0.001). Linear regression of the proportion fetal diagnosis by year predicted an increase of 2.3% per year ($r^2 = 0.73$, p=0.0008) (Figure 3.1). In comparison with the proceeding period, an increase in fetal diagnosis was observed in 2013- 2015 compared to 2008-2012 (p<0.0001), but not in 2016-2018 compared to 2013-2015 (p=0.15).

CHD Detection by US Cardiac View: With respect to fetal cardiac views, the prenatal detection rate overall for CHD associated with an abnormality of the four-chamber view was 356/434 (82%), the outflow tract view 314/479 (66%), the 3VV/3VT and other nonstandard views 102/279 (37%) and VSD irrespective of cardiac view 42/213 (20%). Over the study period there were improvements in detection rates for CHD associated with all views: four-chamber (p=0.011), outflow tract view (p<0.0001), 3VV-3VT view (p=0.0007) and VSD views (0.042) (Figure 3.2).

Although there was an increase in prenatal detection concomitantly for CHD associated with an abnormal 3VV-3VT view and other non-standard views, the proportion with prenatal detection, even in the most recent period, remained lower than four-chamber and outflow tract views, with less than half detected prenatally in the most recent period. Prenatal detection of VSDs

requiring surgical intervention in the first year after birth also demonstrated an increase in detection, but likewise, even in more recent years, only 30% were detected prenatally.

In comparison with the proceeding period, an increase in fetal diagnosis was observed in 2013-2015 compared to 2008-2012 for four-chamber and three vessel view lesions, but between 2013-15 and 2016-18 an increase was only observed for outflow tract view lesions.

Prenatal Diagnosis by CHD Subtype: Prenatal detection rates for each CHD lesion subtype are presented in Table 3.2. Prenatal detection of AVSD, HLHS, TOF and d-TGA significantly increased over the study period ($p<0.05$). There was also a significant increase in prenatal detection of CoA ($p=0.04$).

Timing of prenatal Diagnosis: The average gestational age at prenatal diagnosis for all CHD cases was 23$\pm$4.8 weeks. A total of 509 (61%) of CHD cases diagnosed in the prenatal period were detected at <22 weeks of gestation. The proportion of CHD cases detected at <22 weeks of gestation varied by groups, with a detection rate of 64% in Group 1/four chamber lesions (234/366) and Group 2 /outflow tract lesions (202/316), 53% (57/109) in Group 3/3VV-3VT and other nonstandard views and only 36% (16/44) in Group 4/VSDs.

3.6 Discussion

The present population study suggests there has been an overall improvement in the rate of prenatal detection of major CHD over time based on both ultrasound screening views as well as CHD subtypes in the province of Alberta. Although rates of prenatal diagnosis have increased for all OB US screening groups, the majority of CHD associated with 3VV-3VT and other

nonstandard views, and of isolated VSDs requiring surgical intervention in the first postnatal year remain undetected until after birth, even in more recent years.

OB US has become almost universally available, and advances in imaging technology and the approach to routine fetal anatomical assessments have led to improvements in the prenatal detection of CHD and other congenital abnormalities[112]. Following the first description of the prenatal diagnosis of CHD nearly three decades ago in 1985, the four-chamber view was recognized as a critical component for screening of the fetal heart[113,114]. Its routine application led to the detection of many forms of CHD, and early incorporation into US practice guidelines [52,115,116], with initially promising results encouraging its wide-spread application [117]. In the last few decades, as supported by our experience in Alberta, the prenatal detection of four-chamber view pathology, including HLHS and other single ventricle pathophysiology, has achieved rates of >85% [118,119,120].

Although up to 60% of major CHD defects can be detected using the 4-chamber view alone, several major CHDs are typically missed unless views of the outflow tracts are included[121,122,114]. Previous studies have suggested four-chamber view and outflow tract screening together may identify up to 80% of major structural cardiac abnormalities[123], a finding supported by the current study. Overall, abnormalities of the four-chamber and outflow tract views comprised 66% (925/1405) of major CHD cases. We found the prenatal detection of abnormalities of the four-chamber and outflow tract views to have substantially increased from 2008 – 2012 to 2016 – 2018: 75% to 87% and from 55% to 79%, respectively, or from 2008-2012 to 2016-2018: 65% to 83% for Groups 1 and 2 combined. The greatest increase in prenatal detection were observed for AVSD, HLHS, d-TGA and TOF diagnoses, with two-thirds or more now detected.

We found improvement in the detection of CHD associated with abnormalities of the 3VV-3VT and other nonstandard views. Despite this, however, detection rates in more recent years remain suboptimal. In our population, just less than half of CoA cases were detected before birth over the study period, a higher rate than of other studies[38,40], but still suboptimal relative to that observed for four chamber and outlet lesions. Although CoA can at times be associated with discrepancy in the four-chamber and outlet views with smaller left heart structures, this is not a consistent feature[41]. One of the most definitive features of CoA can be demonstrated in the 3VT view, that of discrepancy in the size of the arches with a more diminutive aortic relative to ductal arch[42]. Use of the 3VV-3VT view as recommended in the guidelines[18] should facilitate its diagnosis. A posterior shelf, another key sign of CoA[42], is only demonstrated in the sagittal view and may not be easily recognized at OB US screening. As most routine US screening is performed in the mid trimester, the relatively low detection rates for CoA could also be in keeping with lack of findings or more subtle pathology being present in the mid-trimester. CoA is a progressive lesion that may become more obvious in the 3rd trimester, or only following ductal closure after birth[40,42]. Implementation of late trimester screening at the very least in higher risk pregnancies (e.g. with Turner syndrome or family history of left heart obstruction) and routine evaluation of the 3VV-3VT view and the long-axis of the aortic arch may contribute to improvements in detection.

The fetal diagnosis of TAPVD has also remained challenging to detect, and our findings of an 8% prenatal diagnosis rate mirror those of others, even those jurisdictions recognized as leaders in prenatal detection of CHD[43]. This may be due to inconsistent and more subtle features particularly in the mid-trimester. In the normal heart the descending aorta which lies posteriorly "kisses" the back wall of the left atrium. The finding of a gap between the descending aorta and

the left atrium, which is occupied by the confluence of the pulmonary veins, is an important clue to the diagnosis of total anomalous pulmonary veins [44]. Recognizing this aspect of the anatomy in four-chamber screening and use of color or power Doppler in imaging these structures could improve detection rates for TAPVC[45].

Finally, our findings confirm that VSDs warranting intervention in the first year remain somewhat difficult to identify before birth. When isolated, clinical outcomes are excellent and most manifest symptoms gradually weeks after birth. However, their association with genetic diagnoses renders their prenatal detection of importance[46,47].

Limitations

Although this study covered a relatively large population, interpretation of the results may be difficult for more rare lesions with limited cases, including TAPVC. We included all fetal cases encountered pre and postnatally in Edmonton and Calgary, the two central tertiary care OB US screening and fetal echocardiography sites, and we made every effort to identify any cases with demise prior to arrival to one of the 2 central centers; however, we could not fully exclude the possibility of a neonatal demise in a remote site not reported to provincial registries or a fetal loss prior to referral such as might occur for lethal aneuploidy. With respect to categorization of lesions according to OB US view, we recognize that specific cases of some lesions may have fit best into more than one group. CoA, for instance, may be in some affected fetuses associated with left-right heart discrepancy observed in the four-chamber and great artery views[92,124]. A more definitive feature, however, is arch discrepancy[125], the reason we placed this pathology within the 3VV-3VT view. As we were comparing postnatally to prenatally diagnosed cases and did not have access to

the OB US in the postnatally diagnosed cases, an approach where each case was individually assigned to a group was not possible. Ideally, review of the prenatal imaging in every case included would have allowed us to accurately categorize each case.

3.7 Conclusions

A substantial improvement in the prenatal detection of CHDs has occurred in Alberta since 2008, temporally related to optimized cardiac screening views at routine obstetric ultrasound. While the majority of CHD associated with abnormal four-chamber and outflow views are currently detected, detection rates of CHD associated with an abnormal 3VV-VT as well non-standard views and VSDs remain significantly lower and warrant further strategies to enhance their detection.

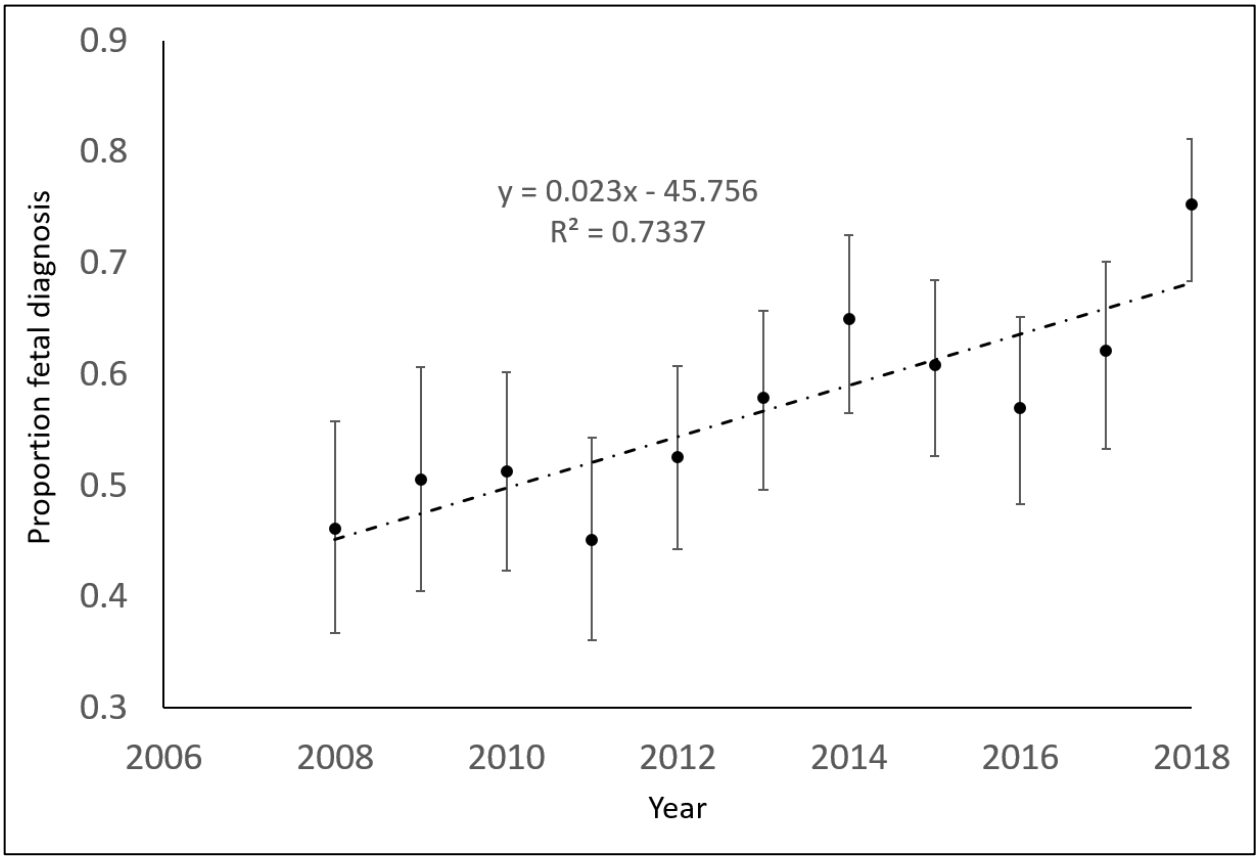

Figure 3.1 - Proportion fetal diagnosis of major CHD by year of birth / encounter. Error bars are 95% confidence intervals (Wilson). Linear regression formula is displayed.

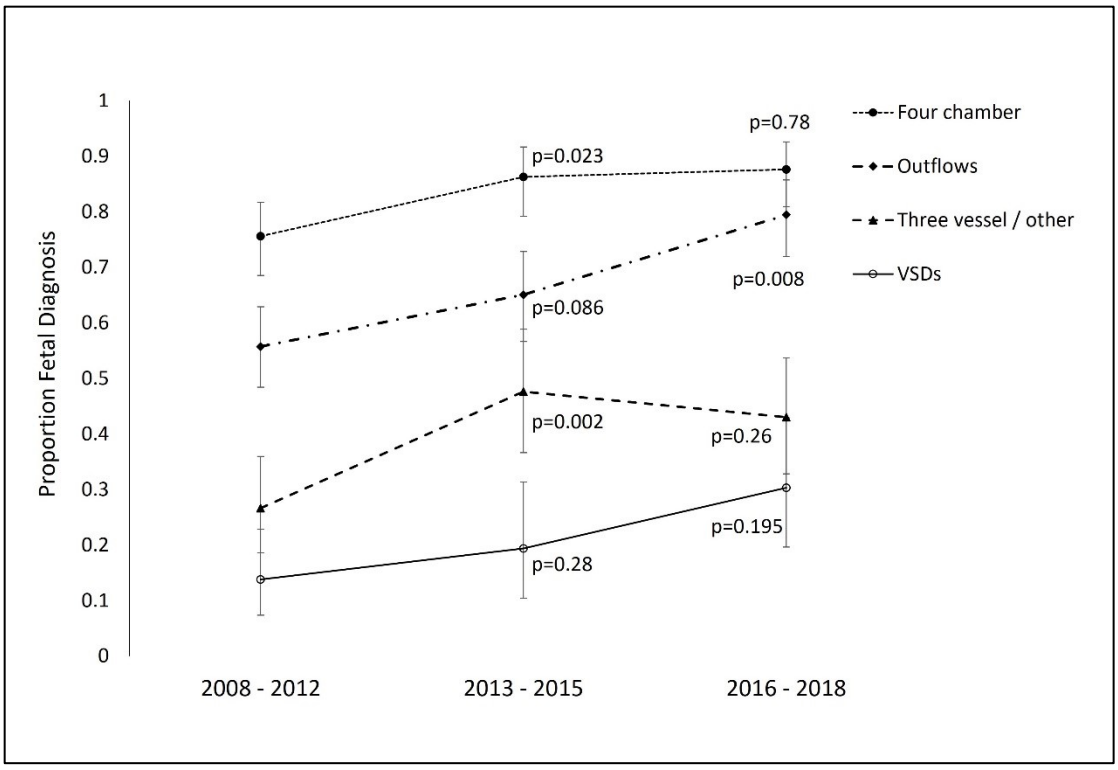

Figure 3.2 - Prenatal detection rates of congenital heart disease based on obstetrical ultrasound fetal cardiac screening views over the study period. Proportion of cases detected, and 95% confidence intervals are presented for each time period. VSDs ventricular septal defects. P-values compare time interval with the prior interval by ultrasound view.

Table 3.1: Cardiac views in obstetrical ultrasound screening required for detection

Group 1 Four Chamber view	Group 2 Outflow View	Group 3 3VV/Other view	Group 4 VSDs
AVSD	Aortic valve disease	AP window	VSDs
HLHS	Conotruncal	COA	
Tricuspid atresia	DORV	TAPVD	
Isomerisms	d-TGA	Vascular ring	
PA/IVS	LVOTO		
DILV	PA/VSD		
TVD/Ebsteins	Pulmonary stenosis		
	TOF		
	Truncus		

Legend: AVSD-atrioventicular septal defect, HLHS-hypoplastic left heart syndrome, PA/IVS-pulmonary atresia with intact ventricular septum, DILV-double inlet left ventricle, DORV-double outlet right ventricle, d-TGA- dextro-transposition of the great arteries, LVOTO - left ventricular outflow tract obstruction, PA/VSD- pulmonary atresia with ventricular septal defect, TOF-tetralogy of Fallot, COA- coarctation of the aorta, TAPVD- total anomalous pulmonary venous return, VSD – ventricular septal defect.

Table 3.2: Lesion Specific CHD Detection Rates Over the Study Period

CHD Subtypes	2008 -2012		2013- 2015		2016 - 2018		*p-value*
Four-chamber view							
Tricuspid atresia	9/10	(90, 59.6-98.2)	10/11	(90.9, 62.3-98.4)	6/6	(100, 61-100)	0.73
AVSD	31/63	(49.2, 37.3-61.2)	36/47	(76.6, 62.8-86.4)	34/45	(75.6, 61.3-85.8)	0.003
Isomerism	11/13	(84.6, 57.8-95.7)	8/8	(100, 67.6-100)	7/7	(100, 64.6-100)	0.29
Ebstein's / TVD	4/4	(100, 51-100)	9/9	(100, 70.1-100)	3/ 4	(75, 30.1-95.4)	0.18
HLHS	54/64	(84, 73-92)	31/36	(86, 70-95)	39/40	(97, 86-99)	0.003
Outflow tract view							
DORV	19/21	(90.5, 71.1-97.3)	17/20	(85, 64-94.8)	28/30	(93.3, 78.7-98.2)	0.63
PAIVS	12/12	(100, 75.8-100)	8/9	(88.9, 56.5-98)	12/14	(85.7, 60.1-96)	0.41
PAVSD	11/21	(52.4, 32.4-71.7)	10/14	(71.4, 45.4-88.3)	18/19	(94.7, 75.4-99.1)	0.012
TOF	33/69	(47.8, 36.5-59.4)	21/35	(60, 43.6-74.4)	31/40	(77.5, 62.5-87.7)	0.01
dTGA	22/47	(46.8, 33.3-60.8)	26/46	(56.5, 42.2-69.8)	25/36	(69.4, 53.1-82)	0.12
Truncus	4/7	(57.1, 25-84.2)	8/8	(100, 67.6-100)	7/10	(70, 39.7-89.2)	0.13
Three-vessel / three-vessel and trachea view / other non-standard views							
CoA	24/81	(29.6, 20.8-40.3)	35/64	(54.7, 42.6-66.3)	32/69	(46.4, 35.1-58)	0.007
TAPVD	0/9	(0, 0-29.9)	0/9	(0, 0-29.9)	1/13	(7.7, 1.4-33.3)	0.49
Vascular ring	2/7	(28, 03-70)	3/5	(60, 14-94)	1/5	(20, 05 – 71)	0.71
Septal views							
VSD	12/89	(13.5, 7.9-22.1)	13/64	(20.3, 12.3-31.7)	20/66	(30.3, 20.6-42.2)	0.037

Legend: CHD- Congenital heart disease, AVSD- atrioventicular septal defect, HLHS-hypoplastic left heart syndrome, PA/IVS-pulmonary atresia with intact ventricular septum, DILV-double inlet left ventricle, DORV-double outlet right ventricle, d-TGA- dextro-transposition of the great arteries, LVOTO - left ventricular outflow tract obstruction, PA/VSD- pulmonary atresia with ventricular septal defect, 3VV/3VT- three vessel and trachea view, TOF-tetralogy of Fallot, COA- coarctation of the aorta, TAPVD- total anomalous pulmonary venous return, VSD – ventricular septal defect.

CHAPTER 4:

LOCATION OF RESIDENCE BUT NOT SOCIOECONOMIC STATUS IMPACTS PRENATAL DETECTION OF CONGENITAL HEART DISEASE IN A JURISDICTION OF UNIVERSAL HEALTH COVERAGE

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Disclosures: None

4.1 Abstract

Background: Socioeconomic status (SES) and residence remote from tertiary care may impact fetal detection of congenital heart disease (CHD), in part through reduced access to and utilization of obstetric screening ultrasound. These risk factors may affect outcomes and inform health system design. There is a paucity of data exploring the effect of SES and remoteness of residence (RoR) on fetal detection of CHD, particularly in a jurisdiction of universal health coverage. In the current study, we examined the impact of SES and RoR on the rate and timing of prenatal detection of major CHD.

Methods: We retrospectively identified all fetal and infant cases of major CHD in Alberta from 2008-2018 who underwent cardiac surgical intervention at < 1 year, died pre-operatively or were stillborn. Using maternal residence postal code and geocoding, SES quintiles and geographic distance from fetal tertiary care were calculated. Outcome measures included presence of prenatal diagnosis (PreDx) and gestation at diagnosis. Risk Ratios (RR) were calculated using log-binomial regression adjusting for year of birth and obstetric ultrasound screening views (Group 1 Four chambers, Group 2 Outflow tracts, Group 3 Three vessel and non-standard views).

Results: Overall, fetal diagnosis of major CHD occurred in 835/1405 (58%). SES did not have an impact on PreDx; however, lower SES was associated with high risk of PreDx after 22 weeks gestation (quintile 1 RR 1.35 [95% CI 1.06-1.72], quintile 2, RR 1.34 [1.04-1.72], quintile 3 RR 1.04 [0.78-1.37], quintile 4 RR 1.21 [0.94-1.56]). Greater RoR was associated with lack of and late PreDx of CHD. Residence >100 km from tertiary care was associated with a RR of 0.88 [95% CI, 0.79-0.98] of a PreDx, and RR of 0.63 [95% CI, 0.51-0.77] of diagnosis of CHD at less than 22 weeks.

Conclusion: Despite universal health care, greater RoR from tertiary fetal cardiac centres in Alberta is associated with reduced PreDx of major CHD and later PreDx, when it occurred. In contrast, SES may have less of an impact in this healthcare system.

4.2 Introduction

Prenatal diagnosis (PreDx) has been shown to improve morbidity and mortality associated with congenital heart disease (CHD) [111,126] due to surveillance for in utero progression, intrauterine management, and referral to a tertiary care facility capable of providing appropriate perinatal and neonatal care. Earlier prenatal detection is preferable, as it allows for parental guidance on prognosis and allows for the option of pregnancy termination in most North American jurisdictions[85]. PreDx of fetal CHD later in pregnancy results in limited options for families, reduced accuracy of diagnosis[127] and potential for fetal demise with progressive disease[111].

Despite the ability to diagnose almost all major CHD in utero with a false negative rate of less than 5% in tertiary fetal cardiology practice[128], the current rate of detection, even in developed countries, ranges between 30% to 60%[129,130]. Although the ease of detection of CHD subtypes at obstetrical anatomic screening ultrasounds is likely a significant predictor of PreDx[131], other factors including socioeconomic status (SES) and remoteness of residence to tertiary care obstetrical ultrasound screening programs (RoR) may also play a role. Lower SES, in particular, has recently been linked to reduced rates of PreDx, at least in the United States[32]. The relative importance of SES and RoR in a jurisdiction such as Canada, with universal care but a wide geographic distribution of its population, is unclear. To further optimize the timing of diagnosis of major CHD, a better understanding of the relative impact of sociodemographic factors on PreDx is required.

In the present study we sought to provide population-level estimates of the impact of SES and RoR on PreDx rates of CHD and gestational age at PreDx within the province of Alberta. We hypothesized that lower maternal SES and greater RoR from centralized tertiary obstetric care and fetal cardiology practices negatively impact PreDx rates and timing of PreDx of CHD.

4.3 Methods

This was a retrospective, population-based study of all fetuses and infants with major CHD in Alberta, Canada born/encountered between Jan 1, 2008 – Dec 31, 2018. Major CHD was defined as CHD requiring surgical intervention within the first postnatal year or associated with termination of pregnancy or intrauterine fetal demise[132]. All patients with major CHD were identified through pediatric and fetal echocardiography databases and the Western Canadian Children's Heart Network surgical database. The province of Alberta has two centralized pediatric cardiac centres, in the north (Edmonton) and the south (Calgary) that provide the only fetal echocardiography and pediatric cardiac services. All surgical care for CHD is provided in Edmonton. We excluded patients born outside of the province to more accurately examine prenatal detection of CHD in a well-defined Alberta population.

Fetal and pediatric echocardiography reports and medical records were reviewed to define the cardiac diagnosis, whether or not a diagnosis was made prenatally, the pregnancy outcome (termination of pregnancy (ToP), intrauterine fetal demise (IUFD), or live birth) and gestational age at diagnosis. The CHD subtype was categorized as whether it would be most likely detected at OB US in the four chamber (Group 1), outflow tract (Group 2), 3 vessel/3 vessel tracheal and nonstandard views (Group 3) and septal views (Group 4). The Alberta Perinatal Health Program (APHP) Registry, which collects data on all registered births in Alberta, was used as a secondary source for maternal and infant demographic and medical history data including maternal age.

Six-digit resident postal codes were derived from medical records where available and matched for validation with five-digit postal codes from APHP. From postal codes aggregated in dissemination areas (400-700 people), we generated Chan Index neighbourhood-level SES quintiles based on the 2006 census data[88]. Finally, the distance of residence in geographical

kilometers from the closest tertiary fetal cardiac program, using an "as the bird flies" approach, was calculated using geocoding[133]. Remoteness was also attributed using the 2016 Index of Remoteness[134] a computational modelling derived measure incorporating travel costs as a surrogate for proximity to population centres, and population size of the centres as a proxy for service availability. The Index assigns remoteness at a census subdivision level (municipality), the most commonly used unit for policy or program delivery analysis in Canada. It has been shown to have strong correlation with measures of access to ambulatory health care facilities.

4.4 Statistical Analysis: The primary outcome variable was PreDx rate as a binary count. The secondary outcome variable was timing of fetal diagnosis as a continuous variable measured in decimalized weeks of gestational age. Descriptive analysis was performed for overall PreDx rates and gestational age at prenatal diagnosis of CHD during the study period. Independent variables included year of diagnosis, maternal age, CHD diagnosis (categorized by fetal ultrasound view most likely required to establish diagnosis), Chan index quintile (with the lowest SES in quintile 1 and highest SES in quintile 5). In exploratory analysis, remoteness was measured firstly using distance (RoR) and using the Index of Remoteness (IoR). For RoR, estimates for outcomes at greater than and less than 100km were calculated post-hoc to approximately capture metropolitan obstetric referral vs referral to rural and remote centers. Preliminary analysis of the distribution of RoR was performed and deciles of the study population also created.

We fit a log-binomial regression model to estimate the risk ratio and 95% confidence intervals for variables hypothesized to influence the probability of PreDx. Timing of PreDx was also fit as a binomial outcome variable with <22 weeks as the cut-point. This was done due to the importance of this gestation clinically, as ToP can be performed at less than 23^{+6} weeks without ethics board review in our province. The generalized linear modelling function in STATA was

used to fit both models. All statistical analyses were conducted using Stata software (SE 17, StataCorp, College Station, Tx).

4.5 Results

Study Cohort: This study included 1405 patients (fetuses and infants) with major CHD encountered pre and postnatally, of whom, 814 (58%) were diagnosed before birth. There was an increase in PreDx rate over the study period. Prenatal diagnosis at <22 weeks of gestation age also increased during the study period (2008, 22% to 2018, 86%, p=0.006). Table 4.1 shows the distribution of SES indicator quintiles, RoR, maternal age and obstetric ultrasound (OB US) views by PreDx and postnatal detection rate of CHD. Table 4.2 shows the distribution of SES indicators quintiles, RoR, and OB US views related to the timing of PreDx of CHD. In those residents less than 100km from a tertiary centre (a distance representing 70% of the study population), PreDx occurred more commonly overall (PreDx <100km 60%, >100km 53%, p=0.032), and at <22 weeks gestation (<100km 55%, >100km 34%, p<0.001). Overall, PreDx occurred in 53% of SES quintile 1 and 59% SES quintile 5. PreDx at <22wks occurred in 45% SES quintile 1 and 58% in SES quintile 5. Classification of lesions by ultrasound view was an important predictor of PreDx, but less so of gestation at diagnosis of <22wks. Termination of pregnancy occurred in 94/410 (23%) of those with a PreDx<22wks compared to 36/404 (9%) of those PreDx≥22wks. (p<0.001). IoR and RoR were strongly correlated (Pearson r = 0.91), whereas there was no correlation between IoR and Chan index quintile (r=-0.039). Preliminary analysis demonstrated a logarithmic distribution of the RoR in study population (ln ROR vs population decile, $r^2 = 0.93$), therefore a natural log transformation of RoR was used for the predictive modelling.

Impact of SES and RoR on prenatal detection rate of CHD: In the evaluation of the entire cohort, adjusted and unadjusted analysis showed no association between Chan Index SES quintile

and PreDx. When adjusting for ultrasound view required for PreDx, Chan Index quintile and year of birth, RoR (per 100km from tertiary care) was associated with an increased risk of missed PreDx (Model 1: RR 1.05 95% CI 1.001-1.10). Similarly, IoR was associated with increased risk of missed PreDx when adjusted for the same covariates (Model 2: RR 1.82 95% CI 1.05 – 3.16). Maternal residence >100 km from the tertiary care centre was associated with a 18% greater chance of having a postnatal diagnosis (RR 1.18, 95% CI 1.04-1.33). In unadjusted and adjusted analysis of OB US view required for detection of CHD, risk of postnatal diagnosis for outflow tract view was 1.9 times, three vessel view was 3.3 times and septal view was 4.2 times higher than four chamber views (Table 4.3).

Association of SES and RoR on timing of PreDx: In unadjusted and adjusted analysis of the PreDx group for associations with gestational age at diagnosis, the lower two Chan index quintiles were associated with an estimated 34-37% higher risk of a diagnosis of CHD after 22 weeks. Greater RoR from a tertiary care center or IoR were also associated with later PreDx of CHD. Maternal residence >100 km from a tertiary care center was associated with an estimated 46% greater chance of PreDx >22 weeks gestation (RR 1.46 [95% CI 1.27-1.69]). Only septal OB ultrasound views (diagnosis of ventricular septal defects) were associated with diagnosis after 22 weeks (Table 4.4). Comparison of distance of residence in the 10th decile (>230km) to those in the 1st decile (<7km) from tertiary care, Model 1 (RoR) predicted a mean absolute reduction in PreDx of 7%, and in PreDx<22wks of 19%. Table 5 demonstrates the adjusted prediction for percentage of missed prenatal diagnosis and diagnosis after 22 weeks.

Figure 4.1 is a chloropleth map of the median Chan index quintile by Census subdivision, with the Risk Ratio for missed PreDx and PreDx>22wks. Visually, the relationship with remote locations

of residence can be easily seen, with, in general, higher median Chan index quintiles in the larger population centres.

4.6 Discussion

This study evaluated a large population of fetuses and infants to determine the association of SES and remoteness on rate and timing of PreDx of CHD. Despite universal health care in Alberta, 30-40% of patients with major CHD were not prenatally diagnosed during the 11-year study period. In Alberta, we found greater linear distance (RoR) from the closest tertiary fetal/maternal care centre to be associated with a lower rate of PreDx of major CHD, and later gestation at PreDx among those with PreDx. This was confirmed using a recent computationally derived Canadian Index of Remoteness (IoR). Although SES did not have a significant impact on rate of PreDx, lower SES was associated with later gestational age at PreDx. These findings are relevant to the development of effective strategies to optimize rates of PreDx and ensuring equity in care across our province.

In many health systems, SES is a major determinant of individual health outcomes and access to health care [135]. People of lower SES are more likely to have worse self-reported health, lower life expectancy and late prenatal care [61]. There is evidence that those of lower SES receive fewer diagnostic tests and medications[136] [63], less frequent prenatal care and have a higher risk of obstetric complications [61,64]. Previous studies have demonstrated lower SES to be associated with lower rates of PreDx of fetal anomalies, including CHD[32,22]. Our study did not demonstrate an association between SES and PreDx of CHD, which could suggest some benefit of a universal health care for such vulnerable populations. This finding is consistent with a recent study from the North American Fetal Heart Society examining the association between prenatal detection of transposition of the great arteries and HLHS, in which lower SES was only found to have an impact

on PreDx in pregnancies from 18 US centers but not 2 Canadian provinces (Ontario and Alberta). While our study provides further evidence for this across a larger spectrum of CHD, we did find differences in timing of PreDx of CHD early in pregnancy across SES quintiles, with 53% diagnosed at <22 weeks of gestation in quintile 1 compared to 74% in quintile 5. This gestational categorization is of importance. A woman can terminate any pregnancy in Alberta prior to 22^{+6} weeks, and only more recently 23^{+6} weeks, whereas thereafter, termination is only offered for very severe lesions and requires vetting through an ethics board, a potential deterrent for some families who might otherwise opt for termination. Diagnoses made on after 22 week leaves less time for full assessments of additional pathology, including genetic syndromes, and time for family consideration regarding the best options for the pregnancy. In addition, PreDx later in pregnancy can lead to more difficult acoustic windows and reduced accuracy[127], and, in some cases, higher risk of fetal complications or demise [137,138].

The factors responsible for later PreDx are likely to include health system limitations as well as logistical and financial challenges for our more vulnerable, lower SES patients resulting in missed or delayed appointments. It is somewhat reassuring that no difference in PreDx rates according to SES quintile were found, suggesting OB US screening as part of routine prenatal care is available; however, there may be challenges for those of lower SES to navigate the healthcare system or logistical issues of finding childcare, lost wages and lack of transportation.

Few past investigations have examined the impact of RoR from a tertiary fetal or pediatric cardiac center with variable findings. In Utah, Pinto et. al [139] found missed PreDx of CHD to be associated with travel time to the tertiary care center, and others have shown rural residence to be associated with missed PreDx of critical CHD[118], and longer time to hospital with neonatal mortality and adverse outcomes at term[140,141]. In Alberta, despite universal healthcare, and that

99% of women undergo OB US screening[58], greater RoR from a fetal cardiology center/IoR was associated with reduced PreDx rates of CHD and even more strongly associated with later PreDx. One of the key mechanisms by which prenatal diagnosis of CHD importantly improves perioperative outcomes of newborns, particularly with critical CHD, is due to relocation of birth to a tertiary center. Missed PreDx in combination with greater RoR / IoR is particularly concerning, as these infants are more likely to be born in smaller local or regional centers and may require lengthy transport prior to reaching the center with expertise in diagnosing and managing CHD, resulting in worse preoperative conditions and contributing to poor survival for some.

Ours is the first study to demonstrate an impact of RoR on timing of PreDx, with greater RoR from a tertiary fetal center being associated with later diagnosis. We found maternal residence >100 km from tertiary care to be associated with a 66% likelihood of a diagnosis at >22 weeks. This risk persisted when adjusting for CHD based on OB US view and year of PreDx, two factors previously shown to have an association with PreDx. RoR / IoR are likely indicator variables in this setting, with several potential latent causes of this finding. Insufficient OB US personnel with reduced scheduling capacity, inadequate training, and lack of sufficient and high-quality equipment may all contribute both to lack of PreDx as well as late screening and late referral, as a consequence. Interventions aimed at improving the skills of those performing and reviewing prenatal screening examinations could increase the PreDx of serious CHD and ensure these diagnoses are made sufficiently early. Furthermore, enhanced access to central expertise for remote review and the integration of artificial intelligence could optimize further rates and timing of PreDx in our province.

Strengths & Limitations This is the first population-based study based in Canada, and one of the first in a jurisdiction of "universal healthcare", to evaluate the association of SES and RoR with the rate and timing of prenatal diagnosis of major CHD. The impact of remoteness on health outcomes is likely more complex and warrants further exploration; however we demonstrated a close correlation between the RoR and IoR, and robust findings in multiple models. Furthermore, this data will fuel future endeavors to explore factors contributing to reduced and late detection that will ultimately lead to enhanced CHD detection rates.

An inherent limitation to our data collection was potential lack of data regarding cases where fetal demise occurred prior to detection or referral for fetal echo or neonatal demise occurred without a definitive CHD diagnosis; however, we believe these would represent very small numbers and would not substantially impact the findings of this work. Finally, we used a neighborhood level measure of SES, which may lose resolution when compared to individual SES data and may have incorrectly categorized some pregnancies/patients.

4.7 Conclusion

In a large population-based cohort of major CHD in a jurisdiction with access to universal health care, we found that SES did not have an impact on rate of PreDx but did influence the timing of PreDx of CHD. Remoteness was associated with lower rates of and later gestational age at PreDx of CHD in Alberta. Future endeavors will focus on the factors that contribute to these discrepancies, ultimately leading to strategies to reduce these gaps in obstetrical care that importantly impact clinical outcomes of affected neonates.

Table 4.1: Socioeconomic, Demographic and Obstetrical Ultrasound View Characteristics of the Cohort, by Prenatal and Postnatal diagnosis

		Prenatal and postnatal diagnosis n (%, 95% CI)		
	Total	**Prenatal Diagnosis**	**Postnatal diagnosis**	**p-value**
No. of Participants	1405	814 (58, 55-60)	591 (42, 39-44)	
Location of residence*				0.032
<100km	1065	634 (60, 56-62)	431 (40, 37-43)	
>100Km	340	180 (53, 47-58)	160 (47, 41-52)	
Chan Index SES Quintile				0.74
1 (lowest)	332	175 (53, 47-58)	150 (45, 39-50)	
2	257	149 (58, 51-64)	108 (42, 35-48)	
3	236	128 (54, 47-60)	108 (46, 39-52)	
4	256	145 (56, 50-62)	111 (44, 37-49)	
5 (highest)	222	130 (59, 51-65)	92 (41, 34-48)	
Maternal age (median, IQR)		31, 27-34	30, 36-34	
Ultrasound View				<0.0001
Four-chamber	434	356 (82, 78-85)	78 (17, 14-21)	
Outflow tract	479	314 (66, 61-69)	165 (34, 30-38)	
Three-vessel / non-standard	279	102 (37, 30-42)	177 (63, 57-69)	
Septal View	213	42 (19, 14-25)	171 (80, 74-85)	

Legend: *Distance of residence from closest tertiary care obstetrical ultrasound and fetal cardiology programs in Edmonton or Calgary. CI-confidence intervals

Table 4.2: Socioeconomic, Demographic and Obstetrical Ultrasound View Characteristics of the Cohort by Prenatal Diagnosis at <22 weeks and >22 Weeks of Gestation

Legend : *Distance of residence from closest tertiary care obstetrical ultrasound and fetal cardiology programs in Edmonton or Calgary. CI-confidence intervals

	Prenatal diagnosis at <22 weeks and >22 weeks of gestation (n, %, 95% CI)			
	Total	**<22 Weeks**	**≥22 Weeks**	**p-value**
Location of residence*				
<100 km	634	348 (55, 50-58)	286 (45, 41-49)	<0.001
>100 km	180	62 (34, 27-41)	118 (66, 58-72)	
Chan Index SES quintile				0.021
1 (lowest)	175	79 (45, 37-52)	96 (55, 47-62)	
2	149	62 (42, 33-49)	87 (58, 50-66)	
3	128	72 (56, 47-64)	56 (43, 35-52)	
4	145	71 (48, 40-57)	74 (51, 42-59)	
5 (highest)	130	76 (58, 49-67)	54 (41, 32-50)	
Ultrasound View				0.062
Four-chamber	356	189 (53, 47-58)	167 (47, 41-52)	
Outflow tract	314	163 (52, 46-57)	151 (48, 42-53)	
Three-vessel / non-standard	102	42 (41, 31-51)	60 (58, 48-68)	
Septal views	42	16 (38, 23-54)	26 (61, 45-76)	

Table 4.3: Association of Socioeconomic Quintiles and Remoteness of Residence with Rate of Missed Prenatal Diagnosis of CHD

Legend: Both models adjusted for year of birth, distance from tertiary care centre, OB US view. IoR: Index of Remoteness measured on scale of 0 – 1, with higher values representing greater remoteness.

	Unadjusted RR (95% CI)	Model 1 RR (95% CI)	Model 2 RR (95% CI)
Chan Index SES quintiles			
1 (Lowest)	1.11 (0.92-1.35)	1.10 (0.93-1.31)	1.09 (0.92-1.29)
2	1.01 (0.82-1.25)	0.99 (0.82-1.19)	0.98 (0.82-1.17)
3	1.10 (0.90-1.36)	1.16 (0.96-1.39)	1.15 (0.95-1.39)
4	1.05 (0.85-1.29)	1.03 (0.86-1.24)	1.03 (0.85-1.24)
5 (Highest)	Ref.	Ref.	Ref.
Year of birth	0.95 (0.93-0.96)	0.95 (0.93-0.96)	0.95 (0.93-0.96)
Distance from tertiary care centre			
RoR – distance per 100km	1.038 (0.99-1.09)	1.048 (1.001-1.10)	
IoR (0 – 1 scale)	1.62 (0.87-3.03)		1.82 (1.05 – 3.16)
Ultrasound View			
Four-chamber	Ref.	Ref.	Ref.
Outflow tract	1.9 (1.5-2.4)	1.9 (1.5-2.4)	1.9 (1.5-2.4)
Three-vessel / non-standard	3.5 (2.8-4.4)	3.3 (2.7-4.2)	3.4 (2.8-4.3)
Septal views	4.5 (3.6-5.5)	4.2 (3.4-5.2)	4.3 (3.4-5.2)

Table 4.4: Association of Socio-economic status and Remoteness of Residence with Prenatal diagnosis of CHD after 22 weeks

	Unadjusted RR (95% CI)	Model 1 RR (95%CI)	Model 2 RR (95% CI)
Chan Index SES quintiles			
1(lowest)	1.32 (1.03-1.69)	1.34 (1.06-1.71)	1.34 (1.05-1.70)
2	1.41 (1.10-1.79)	1.37 (1.08-1.76)	1.37 (1.07-1.76)
3	1.05 (0.79-1.40)	1.04 (0.79-1.38)	1.06 (0.80-1.40)
4	1.22 (0.95-1.59)	1.21 (0.94-1.56)	1.22 (0.95-1.58)
5 (highest)	Ref.	Ref.	Ref.
Year of birth	0.96 (0.94-0.98)	0.96 (0.93-0.98)	0.96 (0.93-0.98)
Distance from tertiary care centre			
RoR – distance per 100km	1.09 (1.04-1.14)	1.13 (1.08-1.19)	
IoR (0 – 1 scale)	3.78 (2.05-6.95)		4.2 (2.2-8.2)
Ultrasound View			
Four-chamber	Ref.	Ref.	Ref.
Outflow tract	1.03 (0.87-1.20)	1.04 (0.88-1.22)	1.04 (0.88-1.22)
Three-vessel / non-standard	1.25 (1.03-1.52)	1.17 (0.96-1.44)	1.19 (0.97-1.47)
Septal views	1.32 (1.01-1.71)	1.35 (1.00-1.83)	1.38 (1.02-1.86)

Legend: Adjusted for year of birth, distance from tertiary care centre (Model 1) or Index of Remoteness (IoR) (Model 2), obstetrical ultrasound view

Table 4.5: Adjusted prediction of missed prenatal diagnosis and late prenatal diagnosis

Distance from tertiary care (km)	Missed prenatal diagnosis %, (95% CI)	Diagnosis after 22 weeks, %, (95% CI)
6	41 (38,45)	43 (38,48)
11	42 (42,45)	46 (42,50)
16	43 (41,46)	48 (44,52)
59	45 (43,48)	55 (51,59)
100	46 (43,50)	57 (53,62)
234	48 (44,53)	62 (55,70)

Legend: CI-confidence intervals

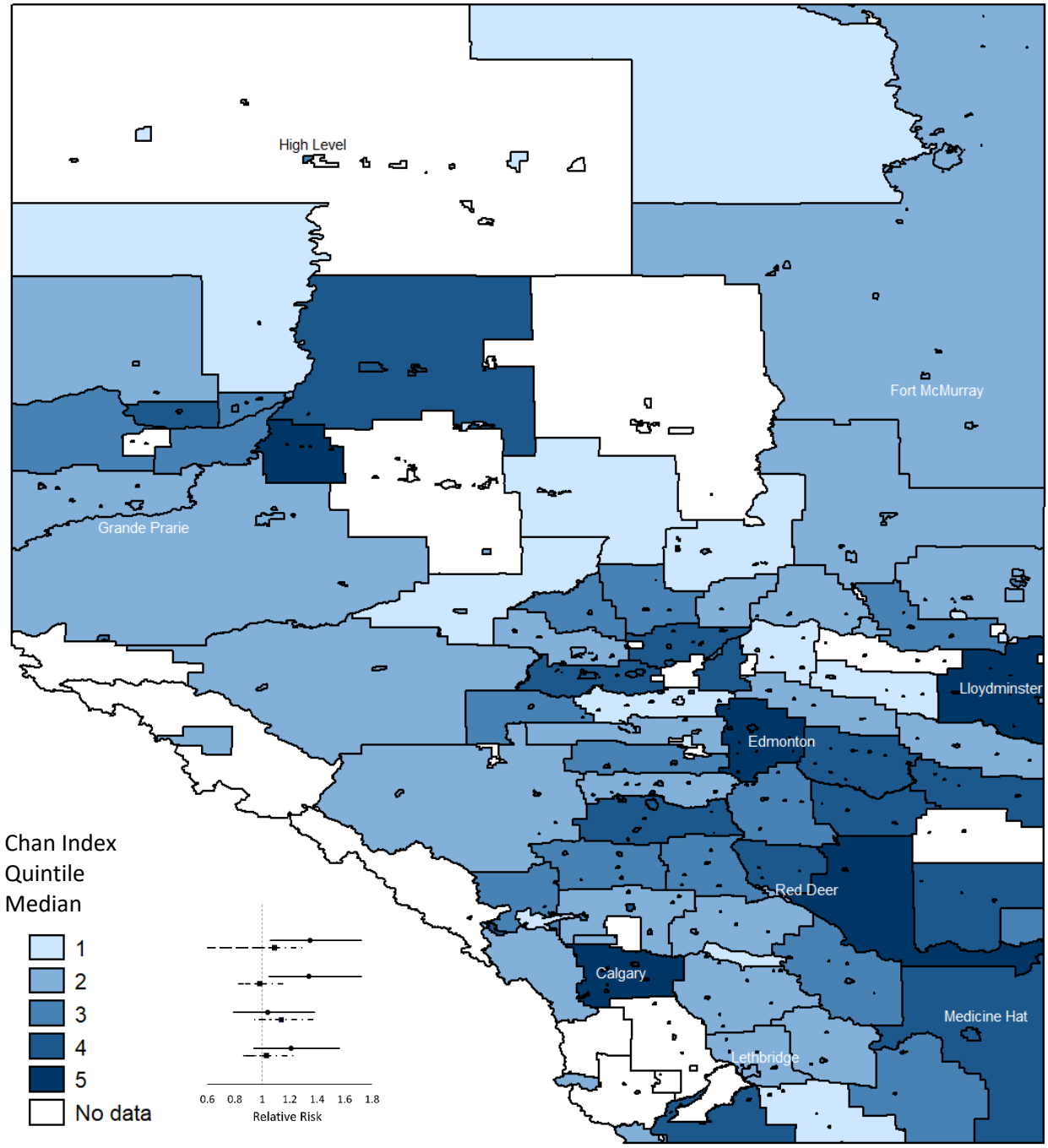

Figure 4.1. Chan Index median quintile by census subdivisions in Alberta.

Legend: Major population centres are indicated, with Calgary and Edmonton representing the only sites of tertiary Fetal Cardiology care. The relative risks by Chan Index quintile adjusted for remoteness of residence, ultrasound view group and year of birth are shown (solid bar: risk of prenatal diagnosis of major CHD after 22 weeks gestation, dashed bar: risk of missed prenatal diagnosis). Quintile 5 is reference category.

CHAPTER 5:
OVERVIEW OF THE FINDINGS & FUTURE DIRECTIONS

5.1 Trends in Prenatal Detection of Congenital Heart Disease

5.1a Summary of Findings

The prenatal detection of congenital heart disease (CHD) has clearly improved over the past two decades based on the published literature from jurisdictions around the world[142]. This is further supported by our current population study in the province of Alberta[89]. In our investigation of trends in prenatal detection of major CHD in Alberta based on OB US views, we found over the study period rates of detection of lesions associated with an abnormal four-chamber view (e.g. hypoplastic left heart syndrome, single ventricle lesions, Ebstein's anomaly and atrioventricular septal defects) to be among the highest from 2008 but also to have continued to show improvement. Mirroring the earlier work of our fetal cardiology program examining d-TGA[89], we found rates of prenatal diagnosis of lesions associated with outflow tract abnormalities (e.g. transposition, conotruncal anomalies, semilunar valve obstruction) to temporally relate to changing OB US guidelines, achieving the highest rates in more recent years. These findings suggest current fetal cardiac screening guidelines are effective in enhancing recognition of cardiac outlet pathology**.** The cardiac outlet pathology detected includes critical CHD that warrants early postnatal intervention, and thus specialized delivery planning. Some of these lesions also have a high association with genetic syndromes and extracardiac pathology, that, when discovered, should prompt further testing. Thus, improvements in their detection ultimately will enhance the care of affected pregnancies and newborns.

Although prenatal detection rates for CHD associated with abnormal four-chamber and outflow tract views have increased significantly, CHD associated with abnormalities primarily of the 3 vessel/3 vessel-tracheal views (3VV/3VT) and other nonstandard views, as well as ventricular septal defects (VSDs) remain challenging to detect. Although we witnessed some improvement in their detection, the rates even in more recent years remain suboptimal. Specific lesions that continue to demonstrate suboptimal prenatal detection include coarctation of the aorta, anomalous pulmonary venous connections and VSDs, specifically those warranting intervention in the first year.

5.1b Future Directions

The prenatal detection of CHD, particularly more severe pathology, has well-recognized benefits for both the pregnant woman and her family as well as the affected baby[143]. It has long been appreciated, however, that most affected pregnancies are among low-risk populations[43,44,45], and thus they would generally not be referred for specialized fetal echocardiography services that provide a detailed examination of the fetal heart. Thus, prenatal screening of the fetal heart relies on the performance of personnel engaged in general routine OB US, both to acquire adequate images and to be able to interpret those images. Definition of simple strategies including the use of standard views that are technically simple to acquire and interpret are key to enhanced fetal cardiac screening.

Knowledge of the trends in prenatal detection and recognition of CHD subtypes that remain a challenge to detect provides a target to enhance education and to fine-tune guidelines that will ultimately lead to ongoing improvements in the rates of prenatal detection. Maintenance of

databases/registries of major CHD diagnoses, including such factors as were collated in the two studies presented in this thesis, facilitates regular reporting of prenatal detection without a requirement for extensive retrospective data mining.

Several potentially modifiable factors likely continue to limit the success of fetal cardiac screening. Studies have demonstrated that the experience of the sonographer is a critical factor[144]. Focused training programs for sonographers performing screening ultrasounds in the United Kingdom and Sweden have demonstrated a significant improvement in the detection of CHD[123,145]. As an example, Tegnander et al[146] reported that sonographers with previous experience of more than 2,000 examinations of the fetal heart had a 52% detection rate of CHD as compared to a 32.5% detection rate of operators performing fewer than 2,000 cardiac examinations. Wong et al compared prenatal detection rates of CHD in a non-tertiary and tertiary institution. The overall detection rate of CHDs for routine ultrasound scans performed in the tertiary institution was significantly higher than that for scans performed in non-tertiary institutions (61% vs 21%)[147]. More work is required to better determine the skills and experience required to provide adequate fetal cardiac screens which could be further explored in our province.

Other strategies which would remove the need for an experienced sonographer include use of remote telemonitoring and artificial intelligence (AI). Over the past 1-2 decades, several groups have explored the role of telemedicine in prenatal screening of the fetal heart using 2D and 3D fetal imaging[148,149,150]. In this context, fetal cardiac screening images are acquired by ultrasound personnel in a remote site with transmission of the images to a site where there are experienced personnel who are best able to interpret the findings. While this approach is increasingly used, it requires sufficient training of the sonographers with the patient to ensure adequate images are acquired, and the availability of sufficient expert reviewers in the central site as well as telehealth

connections. More recently, several groups have begun to explore the possibility of AI application in fetal cardiac screening[148,151,152,153]. Using this approach, the sonographer provides 2D or 3D images that then undergo automated analysis of specific views for signs of pathology[149]. Training datasets and machine learning are used to develop algorithms which recognize differences from normal, or specific pathology. While this approach holds promise, its evolution is only in its infancy.

An additional challenge in prenatal detection of CHD relates to the evolution of some CHD that may have more subtle findings early in gestation. Coarctation of the aorta and semilunar valve obstruction are such lesions[92,154,155,156,157,125]. Although coarctation of the aorta may be associated with left versus right heart discrepancy early in gestation, this is not a consistent feature[158] and may be a feature of other cardiac pathologies and abnormalities of the fetal circulation[159]. Transverse and distal arch hypoplasia, a small aortic to ductal arch diameter ratio and the presence of as posterior shelf are more reliable features[92]; however, these too are not consistently identified particularly early in gestation but may become more evident by the 3rd trimester. For semilunar valve obstruction, some affected fetuses have very severe lesions presenting early that are associated with an abnormality of the four-chambers. Others, however, even with critical valve disease, only evolve obstruction with time, and thus may not be recognized at the routine mid trimester OB US exam[160]. A 3rd trimester fetal cardiac screen, at the very least in pregnancies undergoing OB US for other reasons, could improve rates of prenatal detection of such lesions.

Finally, for lesions such as total anomalous pulmonary venous return (TAPVC) and ventricular septal defect (VSD), screening views or features that specifically identify such CHD are likely necessary. In the normal heart, the posterior wall of the left atrium and the descending aorta are juxtaposed. The descending aorta as well sits in close proximity to the left pulmonary

veins. These features can be demonstrated in the four-chamber view. The presence of a gap between the posterior wall of the heart and the descending aorta is a feature of TAPVC, whether or not the confluence of veins is visible[161]. This confluence of pulmonary veins has also been recognized as a "twig sign" which may further draw attention to the pathology[162,163]. Training of sonographers in performing the four-chamber view should include assessment for these specific features which may improve detection of TAPVC. With respect to assessing the heart for ventricular septal defect**s (**VSD), the four-chamber view sweeps with the ventricular septum perpendicular to the plane of imaging, sweeping from the diaphragm towards the fetal outflows permits 2D evaluation for VSDs. Such an evaluation can also be done using sagittal sweeps. Color flow imaging in these same views with sufficiently low Nyquist levels can further confirm the presence of VSDs. Whether color Doppler should be a part of routine fetal cardiac screening, however, remains controversial[164].

5.2 Impact of Socioeconomic Status and Remoteness of Residence on Prenatal CHD Detection

5.2a Summary Findings

Canada has a universal healthcare system that, in theory, offers health coverage for all its citizens regardless of race, socioeconomic status (SES), educational level, and location of residence. This universal care also includes prenatal care services including fetal ultrasound screening[165]. Prenatal ultrasound is a service offered to essentially all pregnant Canadians[166]. However, whether in practice, the quality and availability of this service is equal in all pregnancies requires evaluations such as reported in this thesis.

In a multicenter North America study, Krishnan et. al[32] demonstrated that lower SES and rural residence to be associated with decreased prenatal diagnosis of dextro-transposition of the great arteries (d-TGA), with lower SES also being associated with decreased prenatal diagnosis of hypoplastic left heart syndrome (HLHS). Interestingly, while they found greater RoR to negatively impact prenatal detection of these critical lesions in both US and Canadian jurisdictions, including Alberta, lower SES was associated with reduced prenatal detection of d-TGA in 18 US regions but not in their Canadian counterparts. Our work further supports these findings for a full spectrum of major CHD. SES does not appear to have a significant impact on the rate of prenatal detection of major CHD, which could suggest the type of healthcare in Canada, or at least Alberta, may be somewhat protective for more vulnerable, lower SES populations. Although SES did not have an impact on prenatal detection rates of CHD, greater remoteness of residence from a tertiary care centre was found to negatively impact prenatal detection of CHD. In the current study, maternal residence greater than >100 Km from the tertiary care centre was associated with a 40% greater probability of having a postnatal diagnosis and with a 42% higher adjusted probability of prenatal diagnosis of CHD later than 22 weeks gestation.

Lack of a prenatal diagnosis has been shown to importantly impact the perioperative condition and, in some cases, risk of mortality[143,167] of the newborn with critical CHD. In addition, greater RoR, with delivery in outlying, largely community hospitals, may be associated with delay in postnatal diagnosis, and necessitates transport to the regional or tertiary care center often prior to when a definitive CHD diagnosis is made. This has the potential to compound the negative effects of a postnatal diagnosis on the neonate[77]. In addition, requirement for neonatal transport is specialized, labor and cost intensive compared to delivery at a tertiary centre[168].

Finally, among pregnancies with a prenatal diagnosis of CHD, both lower SES and greater RoR were associated with delays in prenatal diagnosis of CHD in Alberta with a larger proportion of both being diagnosed after 22 weeks. Such delays result in less time for additional testing and decision making and even restrict the options for the patient with respect to termination versus continuation of the pregnancy.

5.2b Future Directions

Our findings suggest there is inequality in OB US screening and referral practices despite universal health care, particularly for Albertans who live in more remote communities. As underlying causes of these findings, we speculate firstly that health care personnel working in rural areas may be poorly supported in acquisition of the new skills required to adequately evaluate the outflow tracts or other complex views. Secondly, a possible lack of sufficient personnel to screen places time-pressure on sonographers performing screening ultrasound, and also limits the number of patients who can be seen at an appropriate gestational age. Thirdly, inadequate equipment may contribute both to lack of and delays in prenatal diagnosis. Additional system factors such as delayed triaging of referrals for higher level OB US by maternal fetal medicine specialists and fetal echo services may play a role. Finally, patient related issues including lack of transportation and/or childcare, lost wages and difficulties with navigating the tertiary care facility and health system, in general, may also contribute.

Understanding the factors that contribute to lack of and delays in prenatal diagnosis of major CHD are critical first steps towards identifying effective strategies that will narrow this gap in prenatal care. Identification of the median gestation at first anatomical screening ultrasound by provincial location of residence would be a straightforward first step. Questionnaires disseminated to obstetric sonographers regarding knowledge of fetal cardiac screening guidelines, and/or direct

observation of cardiac screening view acquisition quality would be instructive. The time from initial screening ultrasound to referral to tertiary care is also an important variable that can be collected. If ultrasound personnel in remote practices are found to lack the necessary skills, training programs for those performing OB US could be developed as successfully achieved in other jurisdictions [8, 145,122,169]. With this strategy, improvements in prenatal detection of CHD have been demonstrated with minimal investment of time, with some single training initiatives occurring within 1-3 days[145,169]. Limitations in ultrasound personnel availability and lack of sufficient equipment could be addressed through collaboration with health authorities as well as through novel digital alternatives, with training of front-line clinical personnel to do basic imaging. Facilitative algorithms for referral to tertiary care OB US and fetal echocardiography programs that limit delays in definitive diagnosis and counseling would likely result in more timely diagnoses. Understanding the hardships our more remote residents and those of lower SES face in attending appointments, critical for a timely prenatal diagnosis, should also prompt innovative approaches to facilitating appropriate and equal care.

This research focused on the experience of the population of pregnancies and infants with major CHD encountered in Alberta. Whether our findings entirely translate to other provinces and other jurisdictions with government funded universal health services is not clear and warrants further study.

5.3 Conclusions

In this body of work we demonstrate, in a comprehensive provincial population of major CHD, the improvement in rates of fetal diagnosis of major CHD over the past decade. The greatest improvements were for lesions associated with an abnormal outflow tract view, suggesting that updates to guidelines mandating imaging of the outflow tracts are effective. Recent focus on the

three-vessel and three-vessel trachea view in imaging guidelines and sonographic education will likely yield similar improvements. In order to further optimize rate and timing of fetal diagnosis of CHD, attention to health system and socioeconomic factors is also likely to be of significant benefit.

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