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SEVERITY OF CONGENITAL HEART DEFECTS AS A PREDICTOR FOR PRETERM BIRTH

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SEVERITY OF CONGENITAL HEART DEFECTS AS A PREDICTOR FOR PRETERM BIRTH

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Bachelor of Arts

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An abstract of

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

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Abstract

SEVERITY OF CONGENITAL HEART DEFECTS

AS A PREDICTOR FOR PRETERM BIRTH

By Jennifer Lowe

Purpose:
To examine if preterm birth risk varies by congenital heart defect (CHD) severity.

Methods:
This study is a retrospective cohort design analyzing pregnant and non-pregnant female patients with CHD who were identified by encounters occurring between 1/1/2011-12/31/2013 in an existing Emory CHD surveillance repository. Women were linked to Georgia birth certificates during this time to examine the association between severity of CHD and preterm birth.

Results:
Among the initial cohort of 2,523 women aged 12-55, 1,525 (60.4%) had at least one pregnancy diagnosis code in their administrative record, but did not match to a birth certificate; 129 (5.1%) women matched to a birth certificate, but had no pregnancy diagnosis codes in their record; and 869 (34.4%) women had both pregnancy diagnosis codes and a matched birth certificate. After excluding women without a birth certificate match, without a pregnancy diagnosis code, or who only had a 745.5 code in isolation, we retained 823 women for further analyses. Overall, 23.9% (197/823) births were preterm and 43.4% (357/823) had a severe CHD. Both crude and adjusted analyses revealed that preterm birth was not significantly different for women who had a severe compared to those who had a not severe CHD.

Conclusion:
CHD severity may not be associated with preterm birth risk. However, failure to match a large segment of this sample with their birth outcomes may have biased the results towards the null. Further, a real difference in preterm birth risk may have been masked with differential misclassification of exposures because of issues with either the Marelli severity classification schema not sufficiently categorizing important CHD diagnoses for adverse pregnancy outcomes, or with administrative data using ICD-9-CM codes that comprise certain CCS categories that may not adequately differentiate obstetrical complications and comorbidities such as hypertension. To explore these hypotheses, integrated records are vital for patients with CHD, especially for women with CHD who are of reproductive age, to better manage their care and understand their risks during pregnancy.

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TABLE OF CONTENTS

List of Abbreviations

ACHD	Adult Congenital Heart Defect
AS	Aortic Stenosis
ASD	Atrial Septal Defect
ASD2	Secundum Atrial Septal Defect
AVSD	Atrioventricular Septal Defect
BC	Birth Certificate
CVD	Cardiovascular Disease
CHD	Congenital Heart Defect
CHF	Congestive Heart Failure
FGR	Fetal Growth Restriction
MS	Mitral Stenosis
NYHA	New York Heart Association
PAVSD	Pulmonary Atresia with Ventricular Septal Defect
PDA	Patent Ductus Arteriosus
PFO	Patent Foramen Ovale
RSPH	Rollins School of Public Health
RV	Right Ventricle
SES	Socioeconomic Status
TOF	Tetralogy of Fallot
TGA	Transposition of the great arteries
VSD	Ventricular Septal Defect

CHAPTER I: BACKGROUND

Introduction

Congenital Heart Defects (CHD)

A congenital heart defect (CHD) is a type of birth defect affecting both the structure and function of the heart (1). CHD is the most common birth defect in the United States, occurring in up to 1% of births annually, and also the leading cause of birth defect-related illness and death among infants (1-3). Some common signs of CHD are: a hole in the heart, obstructed blood flow, abnormal blood vessels, or heart valve abnormalities (4). Symptoms often include trouble breathing, discoloring of nails or lips, or feelings of tiredness (4). CHD severity ranges from simple (mild or moderate) to complex (severe), and infants born with severe CHD require surgery between birth and their first year of life to correct their life-threatening condition (4). Improvements in diagnosis and treatment have increased life expectancy for those with CHD (5). With mortality on the decline for those born with a CHD, over 90% of babies born with a CHD now survive into adulthood (2). Those born with a mild to moderate CHD are expected to have a 95% survival rate until adulthood, while those born with a severe CHD have a 69% expected survival to 18 years of age (4).

In the U.S, approximately 1.5 million adults 18 years old and older are living with CHD, which is more than a 63% increase in the adult CHD population since 2000 (1, 5). With a growing population of adults with CHD, there are increasing concerns regarding their medical management. In 2004, CHDs accounted for hospital costs close to $1.4 billion in the United States (5). Those with simple CHDs are recommended to follow up with their physician every 3-5 years, but those with the most severe CHD are recommended to follow up with their physician every 6-12 months.

Types of CHD and Classification

The current investigation initially used a modified Marelli five level severity hierarchy that utilized ICD-9-CM CHD-related diagnostic codes (Appendix A) (6). The first level is most severe and includes transposition of the great arteries (TGAs), Common Truncus, Tetralogy of Fallot (TOF) or pulmonary valve atresia. The other not severe levels are classified into one of the following four buckets: shunt, valve, valve+shunt or other. Some of the CHD abnormal shunt conditions include atrial septal defect (ASD), ventricular septal defect (VSD), and patent ductus arteriosus (PDA); among the valve-related anomalies are stenosis, insufficiencies and anomalies pertaining to the pulmonary arteries, and lastly, some of the conditions classified as 'Other' include unspecified anomalies of the heart, circulation and aorta (see Appendix A) (6).

CHD and Pregnancy

More women than men in the United States live with CHD with a reported estimated prevalence of 8.03 per 1000 women compared to 7.67 per 1000 men (5). As such, the proportion of women of reproductive age with CHD has also increased (5). From 2000 to 2010, among all delivery hospitalizations, delivery hospitalizations for women with CHD increased from 6.4 (95% CI 6.2–6.7) per 10,000 to 9.0 (95% CI 8.7–9.3) per 10,000, indicating more women with CHD are becoming pregnant and delivering babies (7). While men and women with CHD both require continuous, specialized healthcare and surveillance throughout their lifespan, women with CHD who become pregnant are at increased prenatal and obstetrical risk and require careful healthcare planning and management.

Obstetric and Delivery Complications for Pregnant Women with CHD

Compared to pregnant women without CHD, pregnant women with CHD are more often diagnosed with perinatal, obstetric and delivery complications including gestational diabetes,

placental abruption, postpartum hemorrhage, chorioamnionitis (intra-amniotic infection), rupture of membranes, premature labor, cesarean section deliveries, premature birth, stillbirths, and infant mortality (7). In a national study using 2000-2010 data from the Nationwide Inpatient Sample, investigators assessed the prevalence of delivery types and pregnancy-related complications in women with CHD and without CHD. Their data included over 8 million hospital discharges from more than 1,000 U.S.-based hospitals. General and cesarean deliveries as well as obstetric and medical complications (outcomes) were identified using the *International Classification of Diseases, 9th Revision, Clinical Modifications* (ICD-9-CM) codes and Diagnosis-related Groups (DRGs). Data revealed that women with CHD who were hospitalized after delivery had 10.5-35.5 times higher odds of cardiovascular complications due to their pregnancy than women without CHD (7). These women also had at least 20% more obstetric complications than women without CHD; these complications included stillbirth, preterm labor, placental abruption, hemorrhage, and fetal growth restriction (FGR) (7).

Hypertensive Disorders for Pregnant Women with CHD

Women with CHD are also at increased risk for hypertensive disorders during pregnancy (8). Untreated or uncontrolled hypertension in pregnant women increases the risk of adverse neonatal events like preterm birth and delivery (8). Preeclampsia is common among women with CHD, and cardiovascular disease (CVD) which, combined with eclampsia, contributes to a significant amount of obstetrical complications, including preterm birth (9). Pregnant women with CHD may also have impaired uteroplacental flow related to their cardiac disease that is also associated with a high prevalence of adverse perinatal events (10, 11). While some studies have identified predictors of adverse neonatal events among pregnant women with CHD, there is

modest predictive value for relevant risk factors to impact the development of adverse birth outcomes such as preterm birth or low birth weight among the offspring of CHD mothers (10).

Severe CHD and Pregnancy Complications

Since the number living with a severe CHD lesion has increased primarily due to surgical advancements in treatment, it is important for CHD survivors to be aware of risk factors associated with pregnancy. Preeclampsia and eclampsia have high rates among pregnant women with severe CHD likely due to changing pathophysiology induced by the pregnancy (12). Additionally, pregnant women with severe CHD have high rates of adverse cardiac and neonatal complications (13). A systematic review of the literature on pregnancy complications for women with severe CHD lesions revealed a 4% infant mortality rate and a 16% premature birth rate; these rates are higher than the national average with 5.9 deaths per 1000 births and 10% prematurity, respectively (12, 14, 15).

The most common congenital lesions in women of childbearing age are ASDs. If not repaired, ASDs often cause left-to-right shunting, leading to an enlargement of the right atria and ventricle. Unrepaired ASDs have been linked to an increased risk for preeclampsia, low birthweight, and neonatal mortality, but those with repaired ASDs are likely to have a decrease of these risks unless there are other underlying preexisting heart conditions (9). However, women with ASDs, whether repaired or not, are still at increased risk for preterm labor, preterm birth, and low birthweight compared to women without CHDs (16).

Another common, severe CHD occurring in women of reproductive age is Tetrology of Fallot (TOF). TOF is a cyanotic CHD with a superior infundibular septal displacement leading to potential long-term hypertrophy in the right ventricle (RV) (17). During pregnancy, women with repaired lesions are watched for RV dilation or dysfunction, which can cause increased blood

volume. Women with unrepaired TOF are advised to avoid pregnancy due to the potential for cyanosis or a crossed embolism due to the burden of extra blood volume (9). Even among women with a repaired TOF, studies indicate that pregnant patients with TOF are more likely to have a spontaneous abortion (17). With respect to preterm birth among repaired TOF patients, one study looking at 112 pregnancies reported only one preterm delivery which was pre-scheduled due to maternal risk suggesting that preterm birth may not be more prevalent among women with repaired TOF (17).

Cyanotic heart disease can occur in women with CHD, and has been seen mainly among those with severe CHD, and most commonly reported among those with a TOF diagnosis (17, 18). While women with cyanotic CHD can tolerate pregnancy at low risk to themselves, studies have indicated a high incidence of fetal cardiac complications, preterm birth and spontaneous abortion, which are reduced once the pregnant patient receives integrated care (18). Women with cyanotic CHD typically have high hemoglobin levels and low arterial oxygen saturation which can lead to prematurity (18). One study indicated that women with this condition had a low percentage of live births, delivered prematurely 34% of the time, and also had a high spontaneous abortion rate (18).

Endocardial cushion defects, or atrioventricular septal defect (AVSD), occur when holes exist between the left and right chambers of the heart. This can cause more blood to flow where it should not, overworking the heart and lungs, potentially leading to congestive heart failure (CHF) if not fully treated (19). Increased size of AVSD and unrepaired VSD increase the risk of preeclampsia and other obstetric complications during pregnancy (9). If left unrepaired, AVSD could advance to Eisenmenger physiology, where pressure in the left heart is greater than the right, and blood flows through the hole from left to right (9). This aberrant flow pattern can

cause a combination of cyanosis, high pressure in the lungs, and increasing numbers of red blood cells due to less oxygen (9). Pregnancy is not advised for women with Eisenmenger's syndrome because it may be detrimental not only to the mother, but also may cause fetal complications due to the effects of low oxygen levels in the blood (20). The rate of miscarriages among pregnant women with Eisenmenger's syndrome has been reported to be as high as 30% with maternal death occurring in about 40-50% of these patients (9, 21). As such, Eisenmenger patients who conceive are often excluded from analyses regarding cyanotic CHD outcomes due to the elevated risk of complex and serious complications to both mother and fetus (18).

CHD patients with Transposition of the Great Arteries (TGA) have an increased risk of volume and pressure of the systemic ventricle, which can lead to eventual ventricular dysfunction. This condition can worsen during pregnancy due to the burden placed on the heart, and can cause cardiac complications during pregnancy (9). Due to medical innovations, however, women who have had TGA repairs in childhood are no longer discouraged from getting pregnant, but there is little published information on the rate of preterm birth for those with specific repair procedures (22, 23). High rates of cardiac deterioration have been reported in women during pregnancy with previous TGA repair (22, 23).

Pregnant women treated with a Fontan circulation for their single ventricle are also at increased risk for maternal and neonatal complications. Fontan repair is done such that blood bypasses the right heart and enters directly into the pulmonary artery, creating a normal pulmonary arterial pressure (21). Fontan patients who become pregnant are more likely than those without Fontan physiology to end in miscarriage, heart failure, arrhythmia and hemorrhage (9). Women with this condition have also reported a delay in fertility, and it has been reported that pregnancies in women with Fontan have an increased prevalence of infertility (24, 25). Low

birth weight and preterm birth have also been associated with pregnancies in women with Fontan (9). Preterm labor is often spontaneous, leading to an increase in spontaneous preterm delivery (24).

Valvular heart disease, including tricuspid stenosis, increases both heart rate and cardiac output in pregnant women, and this condition leads to an increased risk for cardiac complications due to pregnancy. Pregnant patients with valvular conditions have impaired cardiac flow and, as a result, this increases the risk of low birthweight and preterm delivery (9). Pregnant women are at risk of developing cyanosis if tricuspid stenosis is paired with an ASD, which is associated with heart failure, arrhythmia, and adverse perinatal events (26).

A systematic literature review by Drenthen et al. (2006) captured 48 papers looking at pregnancy complications by CHD type in hospital deliveries (12). On average, the rate of premature birth was assessed at 16%, in part due to premature labor, and was reported more often among those with severe CHD conditions including hypoplastic left heart syndrome or hypoplastic right heart syndrome, Ebstein anomaly, transposition of the great arteries (TGA), Pulmonary atresia with ventricular septal defect (PAVSD), Fontan, cyanotic CHD, and Eisenmenger syndrome (5). Preterm birth was most common among women with Eisenmenger Syndrome at close to 70%, followed by women who were diagnosed with a combined category classified as cyanotic CHD with close to 50% of them experiencing preterm births (12). Drenthen et al. (2006) suggest that obstetric intervention may contribute to the higher premature labor rate in women diagnosed with more severe CHD conditions (27). Women with TGA and Fontan are at high risk for premature rupture of membranes (27). However, among all CHD pregnancies and births examined, spontaneous preterm birth occurred most often before 34 weeks gestation (12).

Drenthen et al.'s (2006) review was limited by the populations in captured articles, as well as varying exposures in the populations, each presumably defined differently from study to study. Each study also looked at different outcomes, so the total number of patients with certain CHDs did not carry over to each outcome category. Because most of the studies reviewed were case series, they had no control group. Although this review attempted to compare rates of different outcomes between women with CHD and healthy women without CHD, these studies spanned different populations and so, comparison numbers may not be easily interpretable based on the combined populations. Despite these limitations, there is valuable information in combining populations with certain CHDs to see how risk factors for certain comorbid conditions perform in general and to specific study populations.

Conversely, other studies have indicated it may not be the type of CHD a woman has that predicts pregnancy complications, but rather the hemodynamic changes that occur during pregnancy such as pulmonary regurgitation or dysfunction (28). These specific hemodynamic changes are individually monitored and can be difficult to apply at a broader population level. However, some have noted that pregnancy-related hemodynamic changes may be a better indicator than CHD severity (29). Nonetheless, differences in pregnancy outcomes are reported by CHD complexity (10, 11).

Functional classes are used to stratify congestive heart failure (CHF) in patients according to the severity of their symptoms which range across varying levels of physical activity (30). According to the New York Heart Association (NYHA), there are four categories of CHF symptoms that range from those who are least symptomatic (Class I) to those who are most symptomatic (Class IV): ***Class I*** **-** No evidence of CHF symptoms; ***Class II*** **–** CHF symptoms appear with moderate exertion like walking at least two city blocks or climbing at

least two flights of stairs; ***Class III –*** CHF symptoms appear with minimal exertion like walking a single city block or climbing a single flight of stairs. No CHF symptoms are evident at resting state; and ***Class IV:*** Symptoms of CHF are evident at resting state (31). For pregnant women with CHD compared to pregnant women without CHD, functional class deterioration, or a drop in functional class group, occurs more often which may indicate that women with CHD may have a more difficult time adapting to hemodynamic changes during pregnancy (11, 32). Adverse obstetric events have been associated with number of surgical procedures, and adverse neonatal outcomes have been associated among women with a NYHA functional Class II condition (33). A strong association is observed between maternal cardiac events and neonatal outcomes (10, 13).

Not severe CHD and Pregnancy Complications

There has been an increase in prevalence of less severe CHD in the overall population due to better technology and diagnosis, affecting the distribution of disease and potential outcomes in the current cohort of reproductive aged women (34). While there are many studies that report pregnancy complications among women with severe CHD (9, 18, 22-25, 27), there is less published work on pregnancy complications among women with not severe CHD conditions. Some of the most common not severe CHD conditions include those with pulmonary valvar stenosis, ventricular septal defect (VSD), aortic valve and mitral stenosis (4).

A study examining outcomes of 108 pregnancies among women with congenital pulmonary valvar stenosis revealed an increased risk for miscarriage, preterm birth, and offspring mortality compared to the general population. The rate of preterm birth was reported at 16%, similar to the preterm birth rate among women with severe CHD (27). However, data showed that women with mild to moderate CHD were less likely to develop premature

membrane rupture, and therefore had a lower rate of premature labor (32). Some studies have reported incidence of preterm birth among pregnant women with mild to moderate CHD to be comparable to pregnant women without CHD (8).

VSD is a common condition that is typically repaired in childhood. The larger the defect, the more significant left ventricular volume overload in adulthood, which ultimately leads to heart failure (21). In a retrospective cohort study of 88 women with 202 pregnancies, 147 of which were completed, the risk of premature labor among women with repaired VSD was found to be almost 4 times greater compared to women without a repaired VSD (35). Pregnant women with unrepaired VSD were 4.59 times more likely to develop preeclampsia than controls (35).

Congenital aortic stenosis (AS), an obstruction to the outflow of blood, has been found to be more common in males, , however, women diagnosed with AS are now living to childbearing age (21, 32). Sometimes women may not know they have this defect until symptoms develop in pregnancy due to the added burden on cardiac output (21). In a retrospective study using a tertiary care database, 35 women with AS not only reported 53 successful pregnancies but also were more likely to have had obstetric and perinatal complications than cardiac complications (32). Preterm birth occurred 13% of the time, however, women older than 30 had over 4 times the risk of an adverse perinatal event (i.e., premature delivery, small for gestational age, and low birthweight) compared to younger women (32). Maternal age was the only significant predictor of adverse perinatal events in this study, even when comparing differences in severity of aortic stenosis (32). Women with AS tolerate pregnancy well, but have a higher rate of obstetric and perinatal complications such as hemorrhage, preterm labor, low birth weight compared to pregnant women without CHD (32). These conditions, especially preterm labor and preterm birth, appear more often among women with more severe forms of AS (32).

The most common CHD valve lesion in reproductive-aged women is rheumatic mitral stenosis (MS). It is also the most commonly presented cardiac condition in pregnant women (36). Sometimes, MS will present itself for the first time during pregnancy. Women with MS can generally tolerate pregnancy well with follow-up care (37) . However, with increasing severity of MS, adverse obstetrical outcomes increase including arrhythmia, need for cardiac medication, pulmonary edema, and hospitalization (36).

Ebstein anomaly is an anomaly in the tricuspid valve. Pregnant women with this condition have less than a 5% risk of CHF or arrhythmia; however, if arrhythmia does occur, it can decrease cardiac function resulting in potential obstetric complications including neonatal mortality, preterm birth, low birth weight, and CHD in the fetus (38, 39).

745.5

Patent foramen ovale (PFO) is a condition present in over 25% of the population (40). Depending on CHD severity, the shunts could be clinically insignificant (41). Adults with repaired or present secundum atrial septal defects (or ASD2) have a greater mortality rate than those without, but risk increases in conjunction with other heart conditions (42). These two conditions are coded together under 745.5 in ICD-9-CM. A study examining the specificity of this code in a CHD database found this code only correlated with ASD2 pathology in 24% of cases (43). Among those aged 21 to 64, Rodriguez and colleagues also found a true ASD was coded as 745.5 only 20.6% of the time, indicating a poor validation of this code as an indicator for CHD (43). These data suggest it is important to look at this code separately from other ICD-9-CM codes or groupings.

Preterm Birth and Pregnant Women with CHD

Labor and delivery complications often associated with CHD include premature birth, defined as birth occurring prior to 37 completed weeks' gestation (44, 45). Preterm birth is the leading cause of infant morbidity and mortality in the United States among births to women of child bearing age unaffected by CHD (32, 44). Preterm infants have a higher risk of mortality than those born full term, and this risk increases with decreasing gestational age and birthweight (46). Complications due to premature birth can have lifelong health, growth, and developmental consequences (46). Late preterm births, birth occurring between 34 and 36 weeks gestation, have more perinatal and neonatal complications compared to full term births (46). Annually, the cost of preterm birth exceeds $26 billion dollars, making it not only a leading cause of infant mortality, but also a costly health outcome (46). While national preterm birth rates decreased between 2007 to 2014 (47), after 2014, preterm births increased nationally again, largely due to a rise in late preterm births (14). This increase differs by racial group, ethnicity, and plurality (14).

Some reviews have specifically indicated fetal outcomes like premature birth vary by CHD type (12). For instance, among a cohort of pregnant women with CHD followed by the Boston Adult Congenital Heart Service, premature births were the most common outcomes among 20% of births to women with a CHD (28). In another study using the same cohort, but adding another year of data, 46.4% of preterm births occurred from spontaneous preterm labor, and 27.7% occurred due to a premature membrane rupture (29).

Other Factors

Maternal Age and Preterm Birth among Pregnant Women with CHD

Maternal age can affect cardiac, obstetric, and neonatal outcomes in women with CHD (33). Preterm birth rates vary depending on maternal age and are highest among the youngest and oldest mothers (47). Maternal age is not causal, but rather is associated with preterm birth (47, 48). Among women with CHD, women younger than 30 have less risk for adverse perinatal events than do women older than 30 (16, 32). Maternal age over 30 has previously been indicated as the only significant predictor of adverse perinatal events among women with congenital AS (32). Because of variation in age-specific rates like with AS, it is recommended to analyze perinatal events like preterm birth based on age categorization (47).

Racial and Socioeconomic Disparities in Preterm Birth and CHD

Environmental exposures disproportionately affect minority communities, affecting all aspects of health, and have been attributed to both CHD prevalence and preterm birth in minority communities (49). Preterm birth rates among all women increased more than 20% from 1990 to 2006 (50). In 2016, preterm births were reported in 14% of African American women which was almost 50% higher than the 9% rate for white women (14). Preterm births are reported by race even when controlling for age, smoking, amount of prenatal care, and socioeconomic status including social capital and support, supporting the concept that social and physical environments contribute to this disparity (49).

A large racial gap in infant mortality exists and had not narrowed from 1968 to 1997 with the overall decrease in mortality (34). Black infants have a 20% higher mortality than white infants with CHD, holding steady between 1979 and 1997 (2, 34). This greatly influences the demographics of the population of persons with CHD Non-Hispanic black and Hispanic females

have lower rates of severe CHDs such as AVSD, TOF, and VSD compared to non-Hispanic white females (51); there are varying rates of specific CHDs by racial and ethnic groups. A study of CHD prevalence in metro-Atlanta over a 30-year period revealed increases in prevalence for all races for mild to moderate CHDs (34). Rates for peripheral pulmonary stenosis, one of the less severe defects, increased 10-fold overall, and increased faster among blacks than whites (34). Racial variations in CHDs correspond with geographic distributions of disease, indicating race, residence, and other social factors could increase risk for certain CHDs (34). For certain types of defects such as TGA, TOF, and VSD, the mortality among blacks is much higher than among whites, with blacks often dying at half the age as their white counterparts (52). Additionally, in the National Inpatient Database used to compare delivery hospitalizations between women with and without CHD, race/ethnicity data were missing for up to 17% of patients, indicating potential biases when comparing race data based on certain records (7). Women with CHD were more likely to be white, and minority populations were less prevalent compared to the population without CHD (7).

Socioeconomic status (SES) is measured differently across studies attempting to quantify this association with varying outcomes. As such, it can be difficult to compare SES in relation to outcomes across studies; however, a meta-analysis comparing SES and CHDs revealed a possible association between lower maternal SES (ascertained from education, income, and/or occupation) and an increased risk of CHD in offspring (53). A Canadian study found that for mild to moderate CHDs, low maternal income and education were significant risk factors, while severe CHDs were associated with low maternal education (54). This then affects the distribution of persons living to adulthood with CHD.

Biases in CHD and Pregnancy Outcome Research

Counseling is important for reproductive aged women with CHD as they may not be aware of the potential obstetric risks associated with their condition (24). Women with CHD should seek advice and care at experienced Adult Congenital Heart Defect (ACHD) Centers that can provide maternal and fetal expertise as changes during pregnancy often expose or aggravate their CHD conditions (9). In addition, unless in exceptional good health, women with certain types of CHD, such as unrepaired TOF, Eisenmenger physiology, and some Fontan conditions are typically advised against becoming pregnant, and this may contribute to a negative bias toward becoming pregnant in studies of pregnancy outcomes of women with CHD (13). Healthy women with CHDs who do become pregnant often have a greater likelihood for better perinatal and delivery outcomes than women with CHD who are not as healthy; thus, counseling women with certain severe CHD against becoming pregnant may lead to an underestimation overestimation of positive obstetric and delivery outcomes for women with CHD.

It may also be the case that miscarriages are more likely in certain CHD groups than others, and this likely affects the accuracy of estimating the likelihood of negative and positive birth outcomes for women with CHD. Therefore, it is important to assess the validity of reporting systems because we may not be getting the full picture of perinatal risks and outcomes solely based on medical advice and surveillance systems. Previous analysis looking at reliability and validity of birth certificates call into question how much information can accurately be pulled from these sources (55). These authors found information regarding maternal risk, labor and delivery methods, as well as maternal health behaviors, prenatal visits, and complications during pregnancy and birth are not reliable, indicating administrative data may be more robust to determine situations (55). Certain information, however, such as maternal demographic

information including insurance, birthweight, gestational age, and Apgar score are more reliable than other information provided, indicating birth certificates have inherent biases in and of themselves (55).

CHAPTER II: METHODS

Research Questions

1. Do pregnant women with a severe CHD have a higher prevalence of preterm birth compared to pregnant women with a not severe CHD?
2. Does the availability of a birth certificate vary by CHD severity?
    a. If we restrict the comparison to women with pregnancy codes?
    b. If we link Georgia birth certificates to all women in the dataset, do we pick up more pregnancies?

Specific Aims

1) Determine the prevalence for preterm birth by maternal CHD severity (severe/not severe)
2) Describe pregnant women with CHD with and without Georgia birth certificates by severity status, maternal age, race, ethnicity, insurance status, and residence.
3) Characterize CHD women with linked Georgia birth certificates for pregnancy outcome looking specifically at preterm delivery, CHD severity, and demographic information including age, race, ethnicity, insurance status, and residence.

Study Design

This is a retrospective cohort of female patients with CHD who were identified by at least one CHD encounter occurring between 1/1/2011-12/31/2013 in the existing Emory CHD surveillance repository. GA birth certificates were linked to patient medical records to examine the association between CHD severity and preterm birth. Administrative and vital records data were used to examine how race, maternal age, residence, hypertension, obstetrical complications, pregnancy complication, hemorrhage, anemia, and diabetes are associated with this relationship.

Population

This study uses data from the congenital heart disease (CHD) repository that was created as part of a larger life span surveillance project (NU50DD004932-01) funded by the Centers of Disease Control and Prevention in collaboration with Emory University Schools of Medicine and Public Health. The repository includes patients who have at least one of the 55 CHD-related ICD-9-CM codes (see Appendix A), who were at least one year of age, and who sought healthcare and had at least one encounter in at least one of the following healthcare facilities: Emory Healthcare, Grady Health, Sibley Heart Center, Children's Health Care of Atlanta (CHOA), Piedmont Health, Wellstar, and CMS Medicaid claims.

Data Management and IRB

The parent study had approval from Emory University's Institutional Review Board (IRB#0000064051), and the current study was approved as an amendment to the initial study (#IRB000006405). Data were housed and analyzed in a secure, private, Federal Information Security Management Act (FISMA)-compliant network directory at the Emory University, Rollins School of Public Health in the school's Department of Technology; the system is maintained by authorized IT personnel and only study researchers have access to the specific secure drive. Prior to analysis, specific PHI identifiers were replaced with a proxy unique identifier for each patient, and no Protected Health Information (PHI) was included in the analytic dataset to maintain confidentiality. The dataset was cleaned and de-duplicated prior to construction of the analytic dataset.

While the aim of the parent project was to enhance a CHD population-based surveillance system to better understand the survival, healthcare utilization, and long-term outcomes of patients living with CHD in the state of Georgia, the current study contributes to the larger CHD

surveillance project and the literature by examining CHD severity as a predictor of preterm birth within a pregnant adult CHD (ACHD) population, aged 12 to 55 years.

Inclusion and Exclusion Criteria

Men and female patients who were outside the 12-55 age range were excluded from an;aysis. Pregnant women whose only CHD code was a fetal echo (CPT code) in the 2011-2013 repository, including, but not limited to: 76825-76828, 93325, were also excluded, as a previous analysis indicated these codes administratively attach a fetal code to the mother, and our data cannot differentiate if the code belongs to the fetus or mother.

Data Set Construction

Information on female patients between 12-55 years of age seen between 2011-2013 were extracted from the CHD repository if they had one or more pregnancy-related encounters defined by specific pregnancy-related CCS codes that fall within 177-196, 218-220, 222-224, 661 and 670 (Appendix B). Records for all women aged 12-55 years were linked, where possible, to Georgia birth certificates by last name, first name, gender, and date of birth, and some manual matching occurred.

Some women had a pregnancy diagnosis code (see below), but did not match to a birth certificate. Another group had no pregnancy diagnosis code in their administrative record, but they matched to a Georgia birth certificate. The last group had both a pregnancy diagnosis code in their record and matched to a Georgia birth certificate. This group was used for further analyses.

Variables

Pregnancy Status: Women were identified as pregnant if they had at least one of the specific pregnancy-related CCS codes in any record from 2011-2013 that fell within 177-196, 218-220, 222-224, 661 and 670. A pregnant woman was coded as '1' for 'Yes' and '0' for 'No'.

ICD-9-CM 745.5: Women with ICD-9-CM code 745.5 in isolation were grouped and considered separately, and coded as "2". Those with a 745.5 code in isolation were not considered in any analyses apart from that presented in Table 1; 79.6% of these cases were previously determined to not have true CHD (43).

CHD Severity: Severity of CHD was operationalized applying a modified Marelli scheme, a five-category scheme (refer to Appendix A for operational definition). Not severe diagnoses were coded '1' for 'Yes' and '0' for 'No' and included shunt, valve, shunt + and 'other' and the "severe" category was also coded as '1' for 'Yes' and '0' for 'No'. These five categories were collapsed into two categories: not severe and severe, where severe was coded as '1' for 'Yes' and not severe was coded as '0' for 'No'.

Maternal Age: Maternal age was obtained from Georgia birth certificates for those women with linked records. We subtracted the date of birth (DOB) of the mother from the DOB of the child to determine maternal age. Under failed linked conditions, we used the woman's age from the date of diagnosis of the pregnancy code. There is not much impact for using this strategy in order to calculate age as age may be one year off, not indicating clinical significance in birth outcomes. A new categorical variable was created to categorize maternal age as follows: <20, 20-29, 30-39, 40 and higher years and these age categories were coded as '1', '2', '3', and '4', respectively.

Maternal Race: This variable was extracted from the patient's medical records and had 7 categories: white, black, American Indian or Alaska Native, Asian, Native Hawaiian or Other

Pacific Islander, Other, and Unknown. For the analysis, race was collapsed into four categories: white, African American/black, other, and unknown, and coded as '1', '2', '3 and '4, respectively. From the Georgia birth certificate, if a mother indicated she was "Hispanic", she was categorized as "white." Other categories besides white or African American/black were categorized as "other." From administrative data, if an individual record contained different race answers, the person was categorized as "multi-racial." A supplemental analysis was conducted with five race categories from the Georgia birth certificate and six race categories from the administrative data to see how often there is a difference in race from patient record to linked Georgia birth certificate, and how often the Georgia birth certificate supplements a missing value of race in a patient's medical record.

Residence: Residence was categorized dichotomously as those residing within the five-county metro-Atlanta areas of Fulton, DeKalb, Gwinnett, Cobb, and Clayton coded and coded as "1" for 'Yes', and those residing outside of these five counties as '2' for 'No'. If at any time a patient lived in those five counties, they were considered living within the metro-Atlanta catchment counties.

Preterm Status: First, gestational age was obtained using the obstetric estimate from the Georgia birth certificate, and the variable 'preterm' was created to classify births as either <37 completed weeks of gestation for preterm birth and coded as '1', or term birth for gestation ≥37 weeks and coded as '0'.

Timing of Comorbidity (occurring before or during pregnancy): CCS codes for comorbidities were flagged as a `1' or 'Yes' if present at the time of diagnosis or before/during pregnancy or after pregnancy using date of diagnosis and child's DOB. Only flags indicating before/during pregnancy were used in the analysis as potential mediators or confounders between

severity of CHD and preterm birth. These also account for potential complications in previous pregnancies for women with more than one pregnancy in the dataset.

Hypertension: CCS codes 98, 99, and 183 for essential hypertension, non-essential hypertension, and hypertension that complicated pregnancy (including pre-eclampsia) were combined to create an overall Yes ('1') or No ('0') flag for a diagnosis of hypertension that occurred before or during pregnancy.

Anemia: CCS codes 59 and 60 were used to determine if a woman had (coded as '1') or did not have (coded as '2') a diagnosis for anemia before or during pregnancy, respectively.

Other Obstetrical Complications: CCS code 195 was used to determine Yes, coded as '1', or No, coded as '0', on obstetrical complications before/during pregnancy. This condition included thromboembolic events (stroke, PE), obstetrical death, other complications of pregnancy/ delivery/puerperium, spontaneous abortion, infectious disease, infant complications, hemorrhage, obstetric complications, cervical incompetence, fetal malformation, Rh, fetal growth restriction (FGR), Abo isoimmunization, maternal heart complications, and cardiomyopathy in pregnancy.

Hemorrhage: CCS code 182 was used to classify individuals as having a diagnosis of hemorrhage as '1' or not having a diagnosis of hemorrhage as '0' before or during pregnancy.

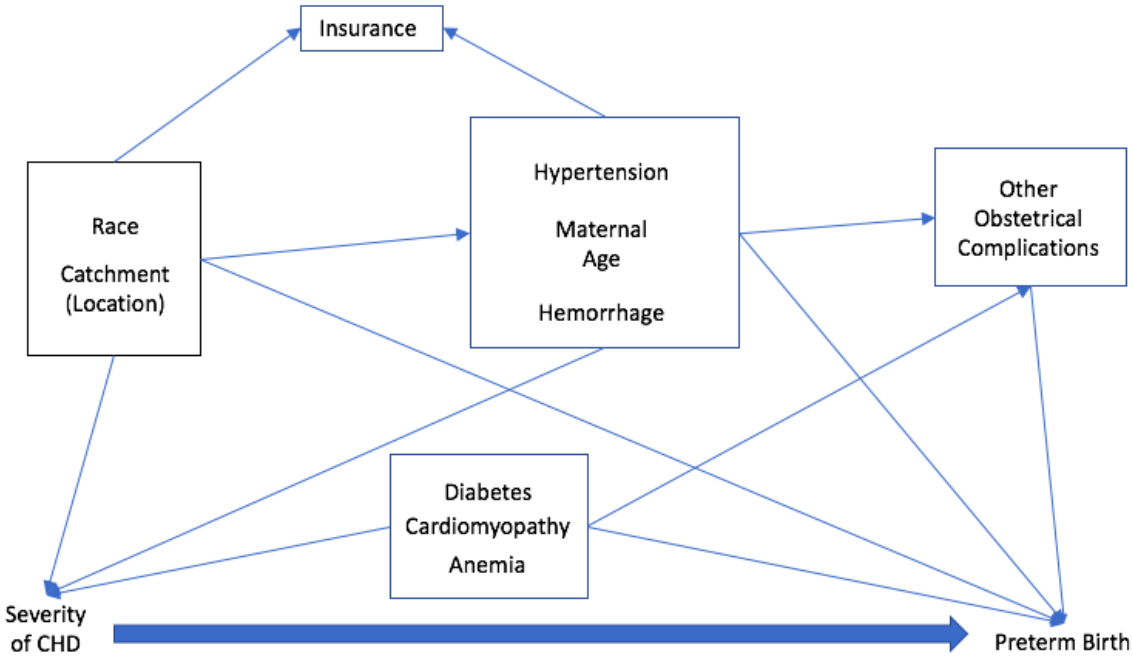
Diabetes: CCS codes 49, 50, and 186 were combined to classify individuals as having a diagnosis of diabetes without complications, diabetes with complications, or diabetes that complicated pregnancy, childbirth or puerperium occurring before or during pregnancy as '1' or not having a diabetes diagnosis as '0'.

Cardiomyopathy: CCS code 97 for cardiomyopathy was used to determine if an individual was diagnosed with cardiomyopathy before or during pregnancy as '1' or '0' if the individual was not diagnosed with cardiomyopathy.

Directed Acyclic Graph (DAG)

We built a DAG to determine the associations between severity of CHD (exposure) and preterm birth (outcome) and potential covariates. As examined in the literature, both race and the location where people live (catchment area) can affect the CHD prevalence in the population due to environmental stressors, as well as selective births between white and black women. Race and catchment area are interrelated based on institutional barriers and are thus grouped together in the DAG. Race and location have also been shown to impact preterm birth with black and rural mothers having an increased risk of preterm birth. These factors also affect insurance status for minorities and for births that occur in places without expanded Medicaid.

Race and residence can also affect hypertension and hemorrhage that occur during or before pregnancy and serve as environmental factors or factors that may be associated with race. Compared with less severe CHD cases, more severe CHD cases may be associated with increased hypertension, risk of peripartum hemorrhage, and other pregnancy complications. Likewise, older mothers may be associated with pregnancy risk factors that lead to preterm births. Having a CHD may not only increase the risk of diabetes, cardiomyopathy, and anemia, but also increase the risk of other obstetrical problems and preterm birth.



Statistical Analysis

From the onset, we defined three cohorts of women with CHD: 1) those who had both a pregnancy-related code in the encounter data and matched to a Georgia birth certificate (n=869); 2) those who matched to a Georgia birth certificate, but who did not have a corresponding pregnancy code in the encounter data (n=129); and 3) those who had a pregnancy-related ICD-9-CM code in their encounter history from 2001-2013, but who did not match to a Georgia birth certificate (n=1,525). We compared these cohorts to examine whether demographic characteristics and health status varied among them.

For the cohort with both a pregnancy-related ICD-9-CM code and a matching Georgia birth certificate, we excluded those who had a 745.5 code in isolation (n=46), and retained a sample of 823. Bivariate analyses for preterm birth (outcome) and CHD severity (exposure) were performed separately for each of the ten covariates of maternal age, maternal race, insurance status, residence, hypertension, hemorrhage, diabetes, anemia, cardiomyopathy, and other obstetrical complications (predictors). We conducted chi-square tests to determine if there

was a significant difference in these predictors for the preterm and term groups (outcome) and for the severe and the not severe CHD groups (exposure). We also computed prevalence ratios (PR) with 95% confidence ratios (95%CI) for the ten covariates in relation to both CHD severity (exposure) and preterm birth (outcome), and calculated crude and adjusted PRs with 95%CIs for preterm birth with multivariate log-binomial regression analysis.

Additional analysis comparing maternal race reported in the administrative data compared to maternal race reported on the Georgia birth certificate was conducted. Flags were created to track when maternal race agreed, when the race data did not agreed, and when Georgia birth certificate race supplemented the administrative data. Both a quantitative and qualitative analyses listing of non-matches was conducted. All statistical analyses were conducted using SAS 9.4 (Cary, NC).

Results

From 2011 to 2013, a total of 2,523 women with CHD aged 12-55 were identified as pregnant either by an ICD-9-CM pregnancy-related code in our CHD clinical/administrative repository or by matching to a Georgia birth certificate that belonged to the index case's offspring (Table 1). Overall, for these 2,523 cases, 23.5% (n=593) were classified as having a severe CHD, 63.9% (n=1,611) were classified as having a severe CHD lesion, and 12.6% were categorized with 745.5 in isolation (exposure). The largest age group was the 20-29 year group which accounted for 41.4% (n=1,044) of the sample followed by the 30-39 year old group with 31.1% (n=785). The less than 20 years old group accounted for 19.6% (n=494) of the CHD pregnancy cohort and the last age group, the >=40 year olds accounted for the remaining 7.9% (n=200). Those with public insurance coverage accounted for 67.8% (n=1,710) of the group with the remaining 32.1% (n=810) covered by private insurance. The majority of race

information for the overall cohort was unknown at 60.6% (n=1,530), followed by whites at 23.7% (n=598) and blacks at 13.8% (n=349). A small percentage, 1.8% (n=46) of the overall pregnant CHD patients classified themselves as 'other' race which combines American Indians and Native Americans, Asians, Hawaiians or other Pacific Islanders, and multi-racial. About 59.7% (n=1,505) of women resided outside the five county metro-Atlanta area, with the remaining 40.3% living inside the five county catchment area. In the overall sample of CHD pregnant women, with respect to comorbid conditions, 13.8% (n=349) reported having hypertension, 10.7% (n=271) diabetes, 12.9% (n=325) anemia, 4.4% (n=110) cardiomyopathy, 69.1% (n=1,744) obstetrical complications, and 13.5% (n=341) hemorrhage.

Table 1 also presents frequencies and percentages for demographics and CHD severity (severe/not severe/ICD-9-CM 745.5 in isolation) (exposure) for the three cohorts. There were 869 (34.4%) CHD women who had both a pregnancy-related code and a matched Georgia birth certificate, 129 (5.1%) CHD women who did not have a pregnancy–related code but who linked to a Georgia birth certificate, and 1525 (60.4%) women with CHD who had a pregnancy–related code but did not link to a Georgia birth certificate; note that Table 1 includes patients who had a 745.5 ICD-9-CM code in isolation, while all later analyses (Tables 2 and 3) omit these cases.

In Table 1, for the cohort who had both a coded pregnancy and a matched Georgia birth certificate, 41.1% (n=357) had a severe CHD, 53.6% (n=466) had a not severe CHD, and 5.3% (n=46) were classified with having a 745.5 ICD-9-CM code in isolation. Mean maternal age was 29.5 years, with 3.3% were <20 years, 41.0% were 20-29, 47.4% were 30-39, and 8.3% were >=40. Public insurance covered 38.9% (n=338) of the women and private insurance covered 61.1% (n=531). Most of the women were white (59.5%), followed by black (35.3%) and other or unknown (5.2%). Most women resided within the five counties (51.3%). Obstetrical

complications were reported in 88.3% (n=767), but specific complications and comorbid conditions were not commonly listed with 8.7% (n=76) reporting hypertension, 6.7% (n=58) diabetes, 8.7% (n=76) anemia, 3.8% (n=33) cardiomyopathy, and 5.8% (n=50) hemorrhage.

The association of preterm birth (outcome) with the CHD severity (exposure), along with the series of covariates including maternal age, insurance, race, residence, hypertension, diabetes, anemia, cardiomyopathy, obstetrical complications, and hemorrhage, and the association of the covariates with CHD severity are presented in Tables 2a, 2b, and 2c. Among the 197 (23.9%) patients who had a preterm birth, 44.7% (n=88) had a severe CHD (ns). The 30-39 year olds were the largest age group (48% (n=395)); 54.8% of them had preterm birth (n=108), and 46.5% of them had a severe CHD (n=166). However, age group was not significant in relation to either preterm birth or CHD severity.

Maternal race was not significantly associated with CHD severity (exposure) or preterm birth (outcome). The cohort was comprised of 59.3% (n=488) whites, and 35.2% (n=290) blacks. Furthermore, 38.1% of mothers who experienced preterm birth were black, and 33.3% of them had a severe CHD.

Preterm birth and residence were not significant with 50.8% of women experiencing preterm birth living outside the metro Atlanta area, and 50.6% of them residing outside the metro area. However, 54.9% of women with severe CHD lived outside the metro, while 47.4% (n=221) of women with not severe CHD lived outside the metro ($p<.05$).

Hypertension was significantly associated with both CHD severity ($p<.0001$) and preterm birth ($p<.05$). In addition, 4.8% (n=17) of mothers with severe CHD experienced hypertension, but 11.4% of mothers with not severe CHD experienced hypertension (n=53). There were 12.2% of mothers with preterm birth (n=24) who had hypertension and 7.3% of mothers with term

births (n=46) who had hypertension. Hypertension was 46% less prevalent (PR=0.54 (95%CI 0.35-0.82)) among mothers with severe CHD compared to not severe CHD, but 49% more prevalent among mothers with preterm birth (PR=1.49 (95%CI 1.05, 2.12)) (Table 2c).

Diabetes was more prevalent among women experiencing preterm births compared to those with term births (PR=1.58 (95%CI 1.09- 2.29)). However, this relationship was not significant when comparing those with severe and not severe CHD (PR=0.92 (95%CI 0.66, 1.28)).

While the association between hemorrhage and CHD severity was not significant, there was a significant relationship between preterm birth and hemorrhage with 9.1% of women (n=18) with preterm birth experiencing hemorrhage and only 4.2% of women with term births (n=26) experiencing hemorrhage. Women experiencing preterm birth were 78% more likely to experience hemorrhage than women who had term births (PR= 1.78 (95%CI 1.22- 2.60)).

Cardiomyopathy did not significantly vary between women who had a preterm birth vs a term birth (4.6% versus 3.7%, respectively). However, while we did find a significant relationship between cardiomyopathy and CHD severity, cell size was small for women with a severe CHD (n=6, 1.7%); among those with not severe CHD, 5.6% of them had a cardiomyopathy code (n=26) (p=0.0041). Cardiomyopathy was 58% less prevalent among women with a severe CHD compared to those with a not severe CHD (PR=0.42 (0.20, 0.87)).

Other obstetrical complications were significantly different by CHD severity and preterm birth status. Among women with severe CHD, 93.8% had other obstetrical complications (n=335) compared to 85.2% with not severe CHD (n=397) ($p<0.001$). Women with other obstetrical complications were 89% more likely to have severe CHD ((PR=1.89 (95%CI 1.30-2.75)). In comparison, among those with preterm birth, 93.9% had other obstetrical

complications (n=185) compared to 87.4% (n=547) with pregnancies to term ($p<0.01$). The prevalence ratio for those with other obstetrical complications and prevalence of preterm birth was 1.92 (95%CI 1.12- 3.29).

A full model log-binomial regression revealed no association between CHD severity and preterm birth (PR=1.02 (95%CI 0.79-1.31)) (Table 3). However, pregnant women between 30-39 years old showed an increase risk of preterm birth (PR= 1.42 (95%CI 1.07-1.88)). Women who reported hemorrhage before or during pregnancy, controlling for all other predictors, had a 73% increased risk for preterm birth (PR=1.73 (95%CI 1.13-2.63)). Controlling for all other factors, pregnant women with an obstetrical complication before or during pregnancy were 92% more likely to have a preterm birth compared to women without obstetric complications (PR=1.92 (95%CI 1.11-3.31)).

When comparing the full-model to an empty model, the empty model did not reveal a significant association between severe CHD and preterm birth ((PR=1.03 (95% CI 0.81-1.32)) (Table 3). The less than 1% difference between the crude and full model estimates likely suggests that none of the included covariates were important confounders attributing to the lack of association of CHD severity with preterm birth.

CHAPTER III: MANUSCRIPT

SEVERITY OF CONGENITAL HEART DEFECTS

AS A PREDICTOR FOR PRETERM BIRTH

By Jennifer Lowe

Abstract

Purpose:
To examine if preterm birth risk varies by congenital heart defect (CHD) severity.

Methods:
This study is a retrospective cohort design analyzing pregnant and non-pregnant female patients with CHD who were identified by encounters occurring between 1/1/2011-12/31/2013 in an existing Emory CHD surveillance repository. Women were linked to Georgia birth certificates during this time to examine the association between severity of CHD and preterm birth.

Results:
Among the initial cohort of 2,523 women aged 12-55, 1,525 (60.4%) had at least one pregnancy diagnosis code in their administrative record, but did not match to a birth certificate; 129 (5.1%) women matched to a birth certificate, but had no pregnancy diagnosis codes in their record; and 869 (34.4%) women had both pregnancy diagnosis codes and a matched birth certificate. After excluding women without a birth certificate match, without a pregnancy diagnosis code, or who only had a 745.5 code in isolation, we retained 823 women for further analyses. Overall, 23.9% (197/823) births were preterm and 43.4% (357/823) had a severe CHD. Both crude and adjusted analyses revealed that preterm birth was not significantly different for women who had a severe CHD compared to those who had a not severe CHD.

Conclusion:
CHD severity may not be associated with preterm birth risk. However, failure to match a large segment of this sample with their birth outcomes may have biased the results towards the null. Further, a real difference in preterm birth risk may have been masked with differential misclassification of exposures because of issues with either the Marelli severity classification schema not sufficiently categorizing important CHD diagnoses for adverse pregnancy outcomes, or with administrative data using ICD-9-CM codes that comprise certain CCS categories that may not adequately differentiate obstetrical complications and comorbidities such as hypertension. To explore these hypotheses, integrated records are vital for patients with CHD, especially for women with CHD who are of reproductive age, to better manage their care and understand their risks during pregnancy.

Introduction

Congenital Heart Defect (CHD) is a type of birth defect affecting both the structure and function of the heart (1). CHD is the most common birth defect in the United States, occurring in up to 1% of births annually, and also the leading cause of birth defect-related illness and death among infants (1-3). In the U.S, approximately 1.5 million adults 18 years old and older are living with CHD, which is over a 63% increase in adult CHD population since 2000 (1, 5). With an increasing population of adults with CHD, there are increasing concerns for their medical management.

Women with CHDs, as do their male counterparts, require continuous, specialized healthcare and surveillance throughout their lifespan, especially once they are pregnant as they often experience increased prenatal and obstetrical risks. From 2000 to 2010, in nationwide hospital discharge data, prevalence of deliveries for women with CHD increased from 6.4 to 9.0 per 10,000 deliveries, accompanied by an increased burden of necessary medical and pregnancy-related care (7).

The prevalence of severe CHD has increased likely due primarily to surgical advancements, and it is important for this cohort to be aware of risk factors associated with pregnancy. Women with certain types of severe CHD are advised to avoid pregnancy due to the potential for cyanosis or embolism due to the extra blood volume burden (9). Adverse cardiac and neonatal complications have been associated with more severe CHD, along with a history of cardiac complications among pregnant women (13).

There has also been an increase in prevalence of less severe CHD in the overall population due to better technology and diagnosis, affecting the distribution of disease and potential outcomes in the current cohort of reproductive aged women (34). While there are many

studies that report pregnancy complications among women with severe CHDs (9, 18, 22-25, 27), there is less published work on pregnancy complications among women with not severe CHD conditions. Some of the most common not severe CHD conditions include those with pulmonary valvar stenosis, ventricular septal defect (VSD), aortic valve and mitral stenosis (4).

Labor and delivery complications often associated with CHD include premature birth, defined as birth occurring prior to 37 completed weeks' gestation (44, 45). Preterm birth is the leading cause of infant morbidity and mortality in the United States among births to women of child bearing age unaffected by CHD (32, 44). Complications due to premature birth can have lifelong health, growth, and developmental consequences (46).

Study Design

This is a retrospective cohort of female patients with CHD who were identified with encounters occurring between 1/1/2011-12/31/2013 in the existing Emory CHD surveillance repository. We linked Georgia birth certificates to patient medical records to examine the association between CHD severity and preterm birth. We used administrative and vital records data to examine how race, maternal age, residence, hypertension, obstetrical complications, pregnancy complication, hemorrhage, anemia, and diabetes are associated with this relationship.

Population

We used data from an already established CHD repository that included patients with at least one of the 55 CHD-related ICD-9-CM codes (see Appendix A) who were at least one year of age and who were seen at least once in one of the following healthcare facilities: Emory Healthcare, Grady Health, Sibley Heart Center, Children's Health Care of Atlanta (CHOA), Piedmont Health, Wellstar, and CMS Medicaid claims.

Data Management and IRB

The parent study and data repository had approval from Emory University's Institutional Review Board (IRB#0000064051) with later approval for the current study by amendment (#IRB000006405). Data were housed and analyzed on a private, Federal Information Security Management Act (FISMA)-compliant server located at the RSPH at Emory University in the Department of Information Technology (IT); the system is maintained by authorized IT staff and only study researchers have access to the specific secure drive. Specific PHI identifiers were replaced with a proxy unique identifier for each patient prior to analysis, and to maintain confidentiality, no Protected Health Information (PHI) was included in the analytic dataset. The dataset was cleaned and de-duplicated prior to construction of the analytic dataset.

Exclusion Criteria

Men were excluded from analysis as well as female patients outside the 12-55 age range. Pregnant women whose only CHD code was a fetal echo (CPT code) in the 2011-2013 repository (including, but not limited to: 76825-76828, 93325) were also excluded, as a previous analysis indicated these codes administratively attach a fetal code to the mother, and our data cannot separate if the code belongs to the fetus or mother.

Predictor Variables

Severity of CHD was operationalized by the modified Marelli scheme, a five-category scheme (refer to Appendix A for operational definition). Category 1 was considered "severe" and we collapsed the 2-5 categories to "not severe". Pregnant women with ICD-9-CM code 745.5 in isolation were grouped and considered separately. Preterm birth was determined by the obstetrical estimate on the birth certificate and as defined as birth <37 completed weeks of gestation. We chose the following predictors in examining the relationship between severity of

CHD and preterm birth: maternal age (continuous and categorical <20, 20-29, 30-39, 40+), residence (inside the metro Atlanta counties/outside metro Atlanta counties), maternal race from Georgia birth certificate (white, African American/black, other), hypertension before/during pregnancy (yes/no), hemorrhage before/during pregnancy (yes/no), other obstetrical complications (broad categories include: thromboembolic events (stroke, PE), obstetrical death, other complications of pregnancy/ delivery/puerperium, spontaneous abortion, infectious disease, infant complications, cervical incompetence, fetal malformation, Rh, fetal growth restriction (FGR), Abo isoimmunization, maternal heart complications, cardiomyopathy in pregnancy complications) before/during pregnancy (yes/no), anemia before/during pregnancy (yes/no), diabetes before/during pregnancy (yes/no).

Statistical Analysis

We conducted all statistical analyses using SAS 9.4 (Cary, NC). We report frequencies and percentages with descriptive statistics, for demographic information, and for categorization of age and severity of CHD (severe/not severe/ICD-9-CM 745.5) for women with a pregnancy diagnosis code and a matched birth certificate, for women with a matched birth certificate and no coded pregnancy in the medical record, and for women with a coded pregnancy diagnosis, but no matched birth certificate. For subsequent analysis, women without a coded pregnancy diagnosis and women without a birth certificate match were excluded from the analytic dataset due to large missing values of determined predictors. Women with a 745.5 code for CHD were excluded from all analyses after Table 1. A sample of 823 women was retained in the analytic cohort. We compared CHD severity and a series of predictors including maternal age, maternal race, residence, hypertension, hemorrhage, diabetes, anemia, and other obstetrical complications by preterm and term birth. We used a chi-square test to determine if there was a significant

difference in these predictors between the severe/not severe CHD groups. Log-binomial regression analysis was conducted comparing the crude (empty) and full models relating CHD severity to preterm birth.

Results

In the initial cohort, 2,523 women with CHD were identified. Of them, 1,525 had a coded pregnancy diagnosis in the medical record, but did not match to a Georgia birth certificate, 129 women matched to a birth certificate, but had no pregnancy diagnosis codes in their records, and 869 women had both pregnancy diagnosis codes and matched birth certificate. Women with 745.5 ICD-9-CM code in isolation were included. These three cohorts differed with respect to CHD severity, age, insurance, residence and comorbid conditions (Table 1). Among those with severe CHD, 60% had a pregnancy diagnosis code and a birth certificate match, whereas 66% of those who did not have a severe CHD had a coded pregnancy diagnosis, but no birth certificate match ($p<0.001$). Maternal race and maternal age when considered as a continuous variable did not significantly differ among the three groups, but maternal age group, when treated categorically, did differ, with 91.9% of those <20 years old in the cohort not matching to a birth certificate ($p<0.001$). This group also had larger percentages of women aged 20-29 and >=40 compared to women with a pregnancy diagnosis and birth certificate match. Most women residing outside the metro area (65.9%) did not match to a birth certificate. Among those with a diabetes code, 78.6% did not have a birth certificate match. A larger percentage of women with codes for anemia, cardiomyopathy, and hemorrhage did not match to a birth certificate. Also, 70.4% of women without other obstetrical complications code did not match a birth certificate. Among women with public insurance, 78.3% did not match to a birth certificate.

After excluding women with a 745.5 code in isolation, there were 823 women who had both a coded pregnancy in their medical record and matched to a Georgia birth certificate. These women were retained for further analyses. Overall, 23.9% (197/823) births were preterm. About 43% of the cohort had a diagnosis code for severe CHD (Table 2). Between the severe and not severe CHD groups, maternal age group, insurance type, maternal race, diabetes, anemia, and hemorrhage were not significantly different. Women with severe CHD were more likely to live outside the metro Atlanta area compared to those with a not severe CHD ($p<.05$). Hypertension (5% v. 11%, $p=0.001$) and cardiomyopathy (2% v. 6%, $p<0.04$) were less likely to have a severe CHD than a not severe CHD, but coded obstetrical complications were more frequent among women with severe than not severe CHD (94% v. 85%, $p<0.0001$).

CHD severity, maternal age, insurance status, maternal race, residence, anemia and cardiomyopathy were not significantly associated with preterm birth. However, hypertension significantly varied, with 12.2% of women with preterm birth having hypertension compared to just 7.3% of women with term births ($p=0.03$). A code for diabetes occurred significantly more among women experiencing preterm birth. Other obstetrical complications were coded more often in women with preterm birth, as was hemorrhage ($p<0.01$ for both) (Table 2a).

Preterm birth was not significantly different between those with severe and not severe CHD (Table 2b). A full-model log-binomial regression did not reveal an association of severe CHD and preterm birth (Table 3), and there was no significant difference in the estimated association of CHD severity with preterm birth between the crude and adjusted models. Certain parameters in the adjusted model, however, indicated significant risk of preterm birth among certain covariate groups, controlling for all other predictors. Women 30-39 years old were at increased risk of preterm birth (PR= 1.42 (95%CI 1.07-1.88)). Women who reported hemorrhage

during their pregnancy had a 73% increased risk for preterm birth (PR=1.73 (95%CI 1.13-2.63)). Women with an obstetrical complication code were 92% more likely to have preterm birth compared to women without this code (PR=1.92 (95%CI 1.11-3.31)).

Discussion

Overall, no significant association was found between severity of CHD and preterm birth. However, proportionately more women with a severe CHD were matched compared with women with a not severe CHD (60.2% v. 28.9%). This suggests that many women with a less severe CHD and no complications may have been seen only once and then cared for outside the healthcare network in this repository, whereas women with more severe CHD or with complications in their pregnancy may have been followed by healthcare providers within the repository network. Women living within the metro Atlanta area were more likely to be matched (41.6%) compared to women living outside that area (29.6%). Not all delivery hospitals in the metro Atlanta area are included in the repository, and none of the delivery hospitals outside the metro Atlanta area are included in the repository. While linking to a birth certificate is not predicated on the birth having occurred in a network hospital, it is possible that the variables used for linking were less accurate when the birth occurred outside the repository network. Also of note is the large discrepancy in proportion of women whose pregnancy was covered by public insurance (Medicaid) who were not matched to a birth certificate (65.5%) compared with women with private insurance (19.8% not matched). If there is a difference in birth outcomes by CHD severity associated with socioeconomic status, this discrepancy would likely bias the results. Problems with matching to a birth certificate were greater for women with Medicaid coverage, because the Medicaid database did not include names, and the Georgia birth certificate database did not include Social Security numbers (56). Some women whose records indicated that they

were pregnant might have delivered outside of the 2011-2013 time-frame, and others might have had spontaneous abortions. Pregnancy loss might be more likely among women with severe complications, such as hemorrhage, which might help explain why the code for hemorrhage was much more prevalent among women without a matched birth certificate. Without examining medical records, we could not determine if all administrative pregnancy codes were accurate.

Women with a pregnancy code and birth certificate match had a code for cardiomyopathy less often than women without a birth certificate match. This could indicate a potential healthy woman bias into our analysis sample, or possibly indicate women with both a pregnancy code and birth certificate match received more treatment for their CHD than women without a birth certificate match.

The overall preterm birth prevalence, 23.9%, is much higher than the national average, 9.9% (14), and was comparable to reported preterm birth in other studies looking at severe CHDs (18, 28, 29). While preterm birth prevalence did not differ by CHD category in our study, other predictors varied significantly between those with severe and not severe CHD. Women with severe CHD had significantly less cardiomyopathy codes than women with not severe CHD, which could again indicate a healthy woman bias for those in the severe CHD category, or these women could have more stringent follow up with physicians to manage their CHD. Overall, all women had a high percentage of at least one code for obstetrical complications; however, women with this code were 89% more likely to have severe CHD. This CCS category is large and encompasses many codes and categories, including cardiomyopathy complications during pregnancy. In relation to the low prevalence of cardiomyopathy codes among women with severe CHD, this could be explained if physicians only coded cardiomyopathy complications with the ICD-9-CM code that falls into the obstetrical complications CCS

category. This category should be further examined to determine what in this category is most important in the relationship between severity of CHD and preterm birth.

This study illuminates the need for integrated records for women with CHD both inside and outside the metro area by including birth outcomes in their record, as matching administrative and vital records was difficult in this large dataset. Managing women with high risk pregnancies, women with CHD, is important to their care, as is knowing the outcome of their birth for large datasets such as this.

Strengths and Limitations

This was a large cohort study of patients with CHD. Matching allowed us to examine birth outcomes, which a woman's administrative record does not include. However as indicated above, a limitation is that we could not match 1,525 women to birth certificates when their administrative data indicated pregnancy. This led to an exclusion of a large group of women with significantly different characteristics compared to the women who did match to a birth certificate

In terms of the codes pulled from the administrative records, while we had diagnosis codes, which are derived from billing records. If a comorbid condition or complication was present during pregnancy but seen outside the repository network, it might not be noted in the repository. Further, diagnosis codes may be inaccurate. While CCS code categories have been validated in other studies, the categories used in this paper have overlap, but with various ICD-9-CM codes in each category. Obstetrical complications included many different overarching variables included in other CCS categories and further investigation is necessary to determine what is driving the obstetrical complications category.

Conclusion

The overall preterm birth prevalence in this cohort was 23.9% and much higher than the United States average rate in 2016 which was 9.9% (14). Other obstetrical complications and hypertension significantly differed by CHD severity and preterm birth outcome and should be further examined to see what ICD-9-CM codes drives these categories. Failure to match a large segment of this sample with their birth outcomes however, may have biased the results towards the null, and a true difference in preterm birth risk may have been masked with differential misclassification of exposures because of issues with either the Marelli severity classification schema not sufficiently categorizing important CHD diagnoses for adverse pregnancy outcomes, or with administrative data using ICD-9-CM codes that comprise certain CCS categories that may not adequately differentiate obstetrical complications and comorbidities such as hypertension. To explore these hypotheses, integrated records are vital for patients with CHD, especially for women with CHD who are of reproductive age, to better manage their care and understand their risks during pregnancy.

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TABLES

Table 1: Demographics for women* aged 12-55 years, who had at least one healthcare encounter with a congenital heart defect (CHD) diagnosis between 2011-2013 in Georgia, by whether they had a coded pregnancy diagnosis and a matched Georgia birth certificate (BC)

	Pregnancy Dx, BC Match (N=869)		No Pregnancy Dx, BC Match (N=129)		Pregnancy Dx, No BC Match (N=1525)		Total (N=2523)		X^2
	N	%	N	%	N	%	N	%	p-value
CHD Severity									<.0001
Severe	357	41.1%	14	10.9%	222	14.6%	593	23.5%	
Not Severe	466	53.6%	79	61.2%	1066	69.9%	1611	63.9%	
745.5	46	5.3%	36	27.9%	237	15.5%	319	12.6%	
Maternal Age (Mean)	858	29.54	129	29.12	-	-	987	-	0.4987
Maternal Age									<.0001
< 20	29	3.3%	11	8.5%	454	29.8%	494	19.6%	
20-29	356	41.0%	47	36.4%	641	42.0%	1044	41.4%	
30-39	412	47.4%	56	43.4%	317	20.8%	785	31.1%	
>= 40	72	8.3%	15	11.6%	113	7.4%	200	7.9%	
Insurance Type									<.0001
Public	338	38.9%	33	25.6%	1339	87.8%	1710	67.8%	
Private	531	61.1%	96	74.4%	183	12.0%	810	32.1%	
Unknown	-	-	-	-	3	0.2%	3	0.1%	
Maternal Race									0.8005
black	307	35.3%	42	32.6%	-	-	349	13.8%	
white	517	59.5%	81	62.8%	-	-	598	23.7%	
other	40	4.6%	6	4.7%	-	-	46	-	
unknown	5	0.6%	-	-	1525	100.0%	1530	60.6%	
Residence									<.0001
Outside Metro	446	51.3%	66	51.2%	993	65.1%	1505	59.7%	
Inside Metro	423	48.7%	63	48.8%	532	34.9%	1018	40.3%	
Hypertension									<.0001
Yes	76	8.7%	3	2.3%	270	17.7%	349	13.8%	
No	793	91.3%	126	97.7%	1255	82.3%	2174	86.2%	
Diabetes									<.0001
Yes	58	6.7%	-	-	213	14.0%	271	10.7%	
No	811	93.3%	129	100.0%	1312	86.0%	2252	89.3%	
Anemia									<.0001
Yes	76	8.7%	-	-	249	16.3%	325	12.9%	
No	793	91.3%	129	100.0%	1276	83.7%	2198	87.1%	

Cardiomyopathy									0.0484
Yes	33	3.8%	1	0.8%	76	5.0%	110	4.4%	
No	836	96.2%	128	99.2%	1449	95.0%	2413	95.6%	
Obstetrical Complications									<.0001
Yes	767	88.3%	-	-	977	64.1%	1744	69.1%	
No	102	11.7%	129	100.0%	548	35.9%	779	30.9%	
Hemorrhage									<.0001
Yes	50	5.8%	-	-	291	19.1%	341	13.5%	
No	819	94.2%	129	100.0%	1234	80.9%	2182	86.5%	

*All cohorts include women who have a 745.5 ICD-9-CM code in isolation

Table 2a: Chi-square test for the association of CHD severity and select predictors by preterm birth status* for women^ who had at least one healthcare encounter with a CHD diagnosis between 2011-2013 in Georgia, and who had a coded pregnancy and a matched Georgia birth certificate (BC)

	Preterm Birth		Term Birth		Total		X^2
	N	%	N	%	N	%	p-value
Severity of CHD							0.675
Severe	88	44.7	269	43.0	357	43.4	
Not Severe	109	55.3	357	57.0	466	56.6	
Maternal age, years							0.143
<20	7	3.6	20	3.2	27	3.3	
20-29	70	35.5	266	42.5	336	40.8	
30-39	108	54.8	287	45.8	395	48.0	
40+	12	6.1	53	8.5	65	7.9	
Insurance Status							0.888
Public	76	38.6	238	38.0	314	38.2	
Private	121	61.4	388	62.0	509	61.8	
Maternal Race							0.519
African American/black	75	38.1	215	34.3	290	35.2	
White	109	55.3	379	60.5	488	59.3	
Other	11	5.6	29	4.6	40	4.9	
unknown	2	1.0	3	0.5	5	0.6	
Residence							0.976
Outside Metro	100	50.8	317	50.6	417	50.7	
Inside Metro	97	49.2	309	49.4	406	49.3	
Hypertension							0.034
Yes	24	12.2	46	7.3	70	8.5	
No	173	87.8	580	92.7	753	91.5	
Diabetes							0.025
Yes	20	10.2	35	5.6	55	6.7	
No	177	89.8	591	94.4	768	93.3	
Anemia							0.508
Yes	18	9.1	48	7.7	66	8.0	
No	179	90.9	578	92.3	757	92.0	
Cardiomyopathy							0.571
Yes	9	4.6	23	3.7	32	3.9	
No	188	95.4	603	96.3	791	96.1	

Other Obstetrical Complications							0.007
Yes	185	93.9	547	87.4	732	88.9	
No	12	6.1	79	12.6	91	11.1	
Hemorrhage							0.007
Yes	18	9.1	26	4.2	44	5.3	
No	179	90.9	600	95.8	779	94.7	

* Preterm: <37 completed weeks' gestation; Term: >=37 completed weeks' gestation
^ N=823; excludes women with ICD-9-CM 745.5 in isolation

Table 2b: Chi-square test for association of preterm birth and select predictors by CHD severity* for women^ who had at least one healthcare encounter with a CHD diagnosis between 2011-2013 in Georgia, and who had a coded pregnancy and a matched Georgia birth certificate (BC)

	Severe CHD		Not Severe CHD		Total		X^2
	N	%	N	%	N	%	p-value
Preterm Birth							0.6748
Preterm	88	24.6	109	23.4	197	23.9	
Term	269	75.4	357	76.6	626	76.1	
Maternal Age							0.5627
< 20	11	3.1	16	3.4	27	3.3	
20-29	155	43.4	181	38.8	336	40.8	
30-39	166	46.5	229	49.1	395	48.0	
>= 40	25	7.0	40	8.6	65	7.9	
Insurance Type							0.5425
Public	132	37.0	182	39.1	314	38.2	
Private	225	63.0	284	60.9	509	61.8	
Maternal Race							0.2587
African American/black	119	33.3	171	36.7	290	35.2	
white	222	62.2	266	54.5	488	59.3	
Other	13	3.6	27	5.8	40	4.9	
Unknown	3	0.8	2	0.4	5	0.6	
Residence							0.0335
Outside Metro	196	54.9	221	47.4	417	50.7	
Inside Metro	161	45.1	245	52.6	406	49.3	
Hypertension							0.0008
Yes	17	4.8	53	11.4	70	8.5	
No	340	95.2	413	88.6	753	91.5	
Diabetes							0.6008
Yes	22	6.2	33	7.1	55	6.7	
No	335	93.8	433	92.9	768	93.3	
Anemia							0.3473
Yes	25	7.0	41	8.8	66	8.0	
No	332	93.0	425	91.2	757	92.0	
Cardiomyopathy							0.0041
Yes	6	1.7	26	5.6	32	3.9	
No	351	98.3	440	94.4	791	96.1	

Other Obstetrical Complications							p<.0001
Yes	335	93.8	397	85.2	732	88.9	
No	22	6.2	69	14.8	91	11.1	
Hemorrhage							0.7341
Yes	18	5.0	26	5.6	44	5.3	
No	339	95.0	440	94.4	779	94.7	

* Severe vs. Not Severe (includes shunt, valve, shunt+valve and other)
^ N=823; excludes women with ICD-9-CM 745.5 in isolation

Table 2c: Prevalence ratios and 95%CIs for the occurrence of CHD severity and preterm birth* by select covariates for women^ who had at least one healthcare encounter with a CHD diagnosis between 2011-2013 in Georgia, and who had a coded pregnancy and a matched Georgia birth certificate (BC)**

	CHD Severity			Preterm Birth		
Covariate	**PR**	**Lower Limit**	**Upper Limit**	**PR**	**Lower Limit**	**Upper Limit**
Maternal Race						
white[b]	1.00			1.00		
African American/black	0.90	0.76	1.07	1.16	0.90	1.50
Other	0.71	0.45	1.13	1.23	0.72	2.09
Insurance Type						
Private[b]	1.00			1.00		
Public	0.95	0.81	1.12	1.02	0.79	1.31
Maternal age, years						
20-29[b]	1.00			1.00		
<20	0.88	0.55	1.41	1.24	0.64	2.43
30-39	0.91	0.77	1.07	**1.31**	**1.01**	**1.71**
40+	0.83	0.60	1.16	0.89	0.51	1.54
Residence						
Inside Metro[b]	1.00			1.00		
Outside Metro	**1.19**	**1.01**	**1.39**	1.00	0.79	1.28
Anemia						
No[b]	1.00			1.00		
Yes	0.86	0.63	1.19	1.15	0.76	1.75
Diabetes						
No[b]	1.00			1.00		
Yes	0.92	0.66	1.28	**1.58**	**1.09**	**2.29**
Hypertension						
No[b]	1.00			1.00		
Yes	**0.54**	**0.35**	**0.82**	**1.49**	**1.05**	**2.12**
Hemorrhage						
No[b]	1.00			1.00		
Yes	0.94	0.65	1.35	**1.78**	**1.22**	**2.60**
Other Obstetrical Complications						
No[b]	1.00			1.00		
Yes	**1.89**	**1.30**	**2.75**	**1.92**	**1.12**	**3.29**

Cardiomyopathy						
No[b]	1.00			1.00		
Yes	**0.42**	**0.20**	**0.87**	1.18	0.67	2.09

* Preterm: <37 completed weeks' gestation; Term: >=37 completed weeks' gestation
** Severe vs. Not Severe (includes shunt, valve, shunt+valve and other)
^ N=823; excludes women with ICD-9-CM 745.5 in isolation

Table 3. Crude and adjusted prevalence ratios and 95%CIs for the occurrence of preterm birth* by CHD severity and select covariates among women^ who had at least one healthcare encounter with a CHD diagnosis between 2011-2013 in Georgia, and who had a coded pregnancy and a matched Georgia birth certificate (BC)**

	Crude Model 1 (No Confounders)			Full Model 2 (all confounders)		
	PR	**95%CI**		**PR**	**95%CI**	
Exposure						
Severity of CHD	1.03	0.81	1.32	1.02	0.79	1.31
Covariates						
Maternal Race						
white [b]				1.00		
African American/black				1.18	0.89	1.56
Maternal age, years						
20-29[b]				1.00		
<20				1.27	0.65	2.48
30-39				**1.42**	**1.07**	**1.88**
40+				0.87	0.48	1.56
Residence						
Inside Metro [b]				1.00		
Outside Metro				0.89	0.69	1.15
Diabetes						
No [b]				1.00		
Yes				1.38	0.89	2.13
Hypertension						
No [b]				1.00		
Yes				1.41	0.92	2.17
Hemorrhage						
No [b]				1.00		
Yes				**1.73**	**1.14**	**2.63**
Other Obstetrical Complications						
No [b]				1.00		
Yes				**1.92**	**1.11**	**3.31**
Cardiomyopathy						
No [b]				1.00		
Yes				0.86	0.49	1.52
Insurance Type						
Private [b]				1.00		
Public				0.82	0.60	1.13

Anemia			
No [b]	1.00		
Yes	1.04	0.67	1.62

[b] Reference group
* Preterm: <37 completed weeks' gestation; Term: >=37 completed weeks' gestation
** Severe vs. Not Severe (includes shunt, valve, shunt+valve and other)
^ N=823; excludes women with ICD-9-CM 745.5 in isolation

CHAPTER IV: EXTENDED ANALYSIS

Characteristics of the Cohort

Maternal race was extracted from the patient's administrative records and had seven categories: white, black, American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, Other, and Unknown. From administrative data, if an individual had more than one encounter, her race may have been recorded differently at different times. When the record contained different race answers, we categorized her as "multi-racial." We then conducted a supplemental analysis with the original six race categories from the birth certificate (white, black, Hispanic, Asian or Pacific Islander, American Indian or Alaska Native, Unknown) and six race categories from the administrative data (white, black, Asian or Pacific Islander, American Indian or Alaska Native, Multi-racial, and Unknown) to see how often there was a difference in race from patient record to linked birth certificate, and how often the birth certificate fills in race when that is not in her healthcare encounter record.

We did this supplemental analysis to determine if administrative records and birth certificate records matched. We used maternal race on the birth certificate as the "gold standard."

Using SAS, we chose a random sample of 100 women with both an administrative pregnancy code and a birth certificate match. We developed frequency tables for these records with respect to maternal race, by whether they matched or did not match or were missing on the administrative dataset. The results, both quantitative and qualitative, are below.

Of our 100 cases, 65 known records for maternal race matched between the birth certificate and administrative data but 2 records for both administrative data and birth certificate data were missing; 5 did not match, and for 28 women, race was missing in the administrative record but available from the birth certificate record. In the administrative data, no individuals were in the category American Indian/Alaska Native. This sample indicates birth certificate

information on maternal race can be used, when available, to fill in administrative data regarding race. Two of the mismatched records displayed a black/white difference between birth certificate and administrative data. Directions for completing information on the birth certificate specify that the mother be asked her race. It is possible that administrative records sometimes rely on provider assessment of race rather than self-report. One person was categorized as white in administrative data, but she self-reported as Hispanic on the birth certificate. This could be due to provider assessment of race differing from maternal self-identification. It is also possible this woman identifies as both Hispanic and White, but has only chosen one to list on the birth certificate. Finally, two administrative data records indicated a woman was multi-racial and the birth certificate indicated Hispanic. The administrative data were collapsed by analysts so if an individual listed multiple races/ethnicity, she was categorized as multi-racial. The birth certificate information available in this analysis only listed one race for mothers. In these instances, administrative data is helpful; however, overall birth certificate information on maternal race was either the only information for maternal race available (28%) or matched administrative data (65%). Analytically, using birth certificate data for maternal race allows for a most robust dataset, with a chance of 5% variance from administrative records.

	Number
Birth Certificate/ Admin Data Match	65
Birth Certificate/Admin Data Missing Match	2
Birth Certificate/ Admin Data Do not Match	5
Admin Data Missing with no missing Birth Certificate Data	28

Non-matches

Birth Certificate Race	Admin Data Race	Reasoning?
white	black	Self-report for the BC; possibly not for Administrative record
black	white	Self-report for the BC; possibly not for Administrative record
Hispanic	white	This woman may have only identified one race/ethnicity but may identify as both
Hispanic	Multi-racial	(2 of these) If indicate >1 race coded as multiracial for admin data by the analysts

CHAPTER V: PUBLIC HEALTH IMPLICATIONS AND FUTURE TRENDS

Due to problems with matching women with administrative records to Georgia birth certificates, missing values prevented a robust examination of pregnant women in this cohort. Of 2,394 women with a pregnancy code in their administrative record, 1525 (63.7%) could not be matched to a birth certificate. Without such a match, we could not determine pregnancy outcome such as gestational age. Of note 1339 of the 1525 women (87.8%) had public insurance (i.e. Medicaid) at the date of the pregnancy code. The deterministic linkage between encounter and birth certificate used the woman's first name, last name, and date of birth. Unless there was additional information from other medical records we could access, it was impossible to link pregnant women insured by Medicaid because our source for Medicaid data (from CMS via ResDAC) provided Social Security numbers (SSN), but not beneficiary names (59). Birth certificate data had names, but not the mother's SSN. Other possible reasons for not matching were births occurring outside Georgia, outside the time window of 2011-2013, or pregnancy losses (spontaneous or induced abortion or stillbirth) for which there would be no live birth certificate. It is of concern that women differed by CHD severity and whether their pregnancy could be matched to a birth certificate (Table 1), particularly since in the subset who could be matched, there was no difference in preterm risk between severe and not severe CHD cases.

Another possibility is misclassification of women's pregnancy status using the CCS categories and ICD-9-CM codes. Future analysis of the entire medical records (rather than the encounter codes) could help assess the value of specific CCS and ICD-9-CM codes for categorizing pregnancy status.

Spontaneous abortions have also has been shown to occur more often in women with severe CHD (17, 18). These codes are considered pregnancy-related codes, and could help determine if a pregnancy occurred; these codes are not always coded in a non-obstetric medical

record, but could add to the comprehensiveness of diagnostic codes used to determine pregnancy. Examining birth certificate information comparing previous number of pregnancies with number of live births could give a better indication the number of miscarriages or stillbirths among women with matched records. For a large cohort such as this, this may be a feasible strategy to look at other pregnancy indicators that may not be included in a patient's record.

This study classified CHDs using an existing five category scheme that was later collapsed into two categories initially based on Marelli's five classifications. Classifying CHDs into severe and not severe may not be the best way to classify CHDs as previous unpublished manuscripts using this severity categorization failed to yield significant CHD severity differences (57, 58) despite literature indicating severe CHD should have more complex and complicated health implications. Assessing outcomes by specific CHDs may provide a more clinical significance for pregnant women with particular CHDs, as other papers have shown (12, 13, 27). Other severity classification schemes may reveal greater group differences or allow researchers to determine more specifically the predictors modifying the relationship between CHD and preterm birth. However, an ongoing multi-site investigation of comorbidities and complications among pregnant women with CHD may find some comorbidities and complications to be associated with the Marelli severity classification. If so, the problem with linking these data with pregnancy outcomes is even more concerning.

Among the third of pregnant women who could be matched with birth certificates at this site, the preterm birth rate of 23.9% was much higher than the national US average. It is also at the high end of other CHD studies looking at preterm birth (12, 14, 18, 28, 29), which may suggest bias in this sample, in that women who have more complicated pregnancies were more likely to be seen by the providers in this network of clinical sites.

In regards to age, the 30-39 age group were significantly more likely to experience preterm birth. This group was also more likely to have been linked to a birth certificate (52.5% v. 37.8% for the rest), suggesting that they may have been more closely monitored during their pregnancies.

The hemorrhage category within the CCS was significantly associated with preterm birth. However, hemorrhage ICD-9-CM codes are also part of the CCS category of other obstetrical complications and this CCS category was also associated with preterm birth. Such confusing and overlapping CCS categories makes it impossible to determine the true association of hemorrhage with preterm birth for these cases. The CCs category of other obstetrical complications differed significantly between those with severe and not severe CHD. This was a large, all-encompassing category that included codes both prior to birth and after birth. By only using codes from patient files occurring before or during pregnancy by date, we made an attempt to exclude potential complications occurring post-birth. Even so, as a significant category with so many varying complications, future study should examine which ICD-9-CM codes and corresponding complications drive the relationship between CHD and preterm birth. Examining which ICD-9-CM codes contribute to these categories would further define the most frequently seen complications in women with severe CHD and among those experiencing preterm birth.

This study and its results indicate in order to move forward with large cohort studies of women in this CHD repository and their birth outcomes, an integrated data set is vital. Data from smaller cohort studies of women with CHD are available that investigate women with specific CHDs and longitudinal studies from countries with integrated medical records are now available. Having an integrated data set would provide a more comprehensive look at pregnant women with CHD and their birth outcomes as medical records do not have all the birth information that birth

certificates have. Women with CHD have higher risk pregnancies and require different pregnancy and birth management than women without CHD. Given the significant differences in matching available inside versus outside the metro area, the integrated data should include women both inside and outside the metro area. Having an integrated data set with all this information is important to fully understand the pregnancy outcomes of women with CHD.

APPENDICES

Appendix A

Congenital Heart Defect Severity Ratings Using a Modified Marelli Scheme

Severity	SevCod	ICD-9-	ICD-9-CM Description
Severe	1	745.0	Common Truncus
Severe	1	745.1	Transposition of the Great Arteries (TGA)
Severe	1	745.10	Complete TGA (dextro-TGA), NOS or classical
Severe	1	745.11	DORV, or incomplete TGA
Severe	1	745.12	Corrected TGA (levo-TGA)
Severe	1	745.19	TGA OS
Severe	1	745.2	Tetralogy of Fallot
Severe	1	745.3	Single Ventricle, or cor triloculare
Severe	1	745.6	Endocardial Cushion Defect (aka AVSD)
Severe	1	745.60	Endocardial Cushion Defect (aka AVSD)
Severe	1	745.61	ASD-1 (primum)
Severe	1	745.69	Endocardial Cushion Defect (aka AVSD) Other
Severe	1	746.01	Pulmonary valve atresia or absence
Severe	1	746.1	Tricuspid atresia, stenosis or absence
Severe	1	746.7	HLHS
Severe	1	747.11	Interrupted aortic arch
Severe	1	747.41	Total anomalous pulmonary venous return
Shunts	2	745.4	VSD
Shunts	2	745.5	ASD2 or PFO
Shunts	2	745.8	Other specified defect of septal closure
Shunts	2	745.9	Unspecified defect of septal closure
Shunts	2	747.0	PDA
Shunts	2	747.1	Coarctation of aorta
Shunts+Valve	3		(depends on ICD codes of the combination)
Valve	4	746.0	Anomalies of pulmonary valve
Valve	4	746.00	Pulmonary valve anomaly, unspecified
Valve	4	746.02	Pulmonary valve stenosis
Valve	4	746.09	Pulmonary valve anomaly, other
Valve	4	746.2	Ebstein Anomaly
Valve	4	746.3	Aortic valve stenosis
Valve	4	746.4	Aortic insufficiency or bicuspid/unicuspid aortic
Valve	4	746.5	Mitral stenosis or mitral valve abnormalities
Valve	4	746.6	Mitral insufficiency
Valve	4	747.3	Anomalies of Pulmonary artery
Valve	4	747.31	Pulmonary artery atresia, coarctation, or hypoplasia
Valve	4	747.39	Anomalies of Pulmonary artery, other
Other	5	745.7	Cor biloculare
Other	5	746.8	Other Specified anomalies of heart

Other	5	746.81	Subaortic stenosis
Other	5	746.82	cor triatrium
Other	5	746.83	Infundibular or subvalvar pulmonary stenosis
Other	5	746.84	Obstructive anomalies of heart
Other	5	746.85	Coronary artery anomaly
Other	5	746.87	Malposition of heart or apex
Other	5	746.89	Other specified anomaly of heart (various types)
Other	5	746.9	Unspecified defect of heart
Other	5	747.2	Other anomaly of the aorta
Other	5	747.20	Anomalies of aorta, unspecified
Other	5	747.21	Anomaly of aortic arch
Other	5	747.22	Atresia or stenosis of aorta
Other	5	747.29	Other anomaly of aorta
Other	5	747.4	Anomalies of great veins
Other	5	747.40	Anomalies of great veins, unspecified
Other	5	747.42	Partial anomalous venous return (PAPVR)
Other	5	747.49	Other anomalies of great veins
Other	5	747.9	Unspecified anomalies of circulatory system

Appendix B

Pregnancy-related Complications defined by ICD-9_CM codes as Defined by Clinical Classification Software (CCS)

CCS CAT	CCS CAT DESC	PREGCOMPL	PREG COMPL DESC	ICD-9-CM					
184	Early labor	01	**Preterm Labor**	64400	64403	64410	64413		
184	Early labor	02	**Preterm Delivery**	64420	64421				
219	Low birth wt	02		76500	76501	76502	76503	76504	76505
				76506	76507	76508	76509	76510	76511
				76512	76513	76514	76515	76516	76517
				76518	76519	76521	76522	76523	76524
				76525	76526	76527	76528	7650	7651
				76400	76401	76402	76403	76404	76405
				76406	76407	76408	V2131	V2132	V2133
222	Perint jaund	02		V2134	V2135	7742			
186	DM in preg	03	**Gestational Diabetes**	64800	64801	64802	64803	64804	64880
				64881	64882	64883	64884		
183	HTN in preg	04	**Gestational Hypertension**	64230	64231	64232	64233	64234	64290
				64291	64292	64293	64294	64200	64201
				64202	64203	64204	64210	64211	64212

				64213 64214 64220 64221 64222 64223 64224					
183	HTN in preg	05	**Pre-Eclampsia**	64240 64241 64242 64243 64244 64250 64251 64252 64253 64254 64260 64261 64262 64263 64264 64270 64271 64272 64273 64274					
97	Carditis	06	**Heart Failure**	4250 4251 4252 4253 4254 4257 4258 4259 4280 4281 4289 39891					
108	chf;nonhp	06	**Heart Failure**	42820 42821 42822 42823 42830 42831 42832 42833 42840 42841 42842 42843					
105	Conduction	07	**Arrhythmias**	4260 4262 4263 4264 4266 4267 4269 42610 42611 42612 42613 42650 42651 42652 42653 42654 42681 42682 42689 V450 V4500 V4501 V4502 V4509					
106	Dysrhythmia	07	**Arrhythmias**	V533 V5331 V5332 V5339 4270 4271 4272 4279 7850 7851 42731 42732 42760 42761 42769 42781 42789					
107	Cardia arrst	07	**Arrhythmias**	4275 42741 42742					
117	Ot circul dx	07	**Arrhythmias**	V1253					
100	Acute MI	08	**Myocardial Infarction**	4100 4101 4102 4103 4104 4105 4106 4107 4108 4109 41000 41001 41002 41010 41011 41012 41020 41021 41022 41030 41031 41032 41040 41041					

				41042	41050	41051	41052	41060	41061
				41062	41070	41071	41072	41080	41081
				41082	41090	41091	41092		
101	Coron athero	08	**Myocardial Infarction**	4110	4111	4118			
103	Pulm hart dx	09	**Pulmonary HTN**	4160					
103	Pulm hart dx	10	**Thromb Events (Stroke, PE)**	4150	4151	4162	4179	41512	41513
				41519	430	431	436	4320	4321
109	Acute CVD	10	**Thromb Events (Stroke, PE)**	4329	4340	4341	4349	34660	34661
				34662	34663	43301	43311	43321	43331
				43381	43391	43400	43401	43410	43411
				43490	43491				
110	Precere occl	10	**Thromb Events (Stroke, PE)**	4330	4331	4332	4333	4338	4339
				43300	43310	43320	43330	43380	43390
111	Other CVD	10	**Thromb Events (Stroke, PE)**	4370	4371	4373	4374	4375	4376
				4377	4378	4379	4350	4351	4352
112	TIA	10	**Thromb Events (Stroke, PE)**	4353	4358	4359			
116	Art embolism	10	**Thromb Events (Stroke, PE)**	4440	4441	4449	44401	44409	44421
				44422	44481	44489	44501	44502	44581
				44589					
195	Ot compl bir	10	**Thromb Events (Stroke, PE)**	67150	67151	67152	67153	67154	67320

238	Complic proc	10	**Thromboembolic Events (Stroke, PE)**	67321 67383 67404 41511	67322 67384 99702	67323 67400	67324 67401	67381 67402	67382 67403
259	Unclassified	11	**Cardiac Death**	7981	7982	7989			

195	Ot preg comp	12	**Obstetrical Death**	65640	65641	65643	67490	67492	67494
220	Birth asphyx	12	**Obstetrical Death**	7680	7681				
224	Ot perint dx	12	**Obstetrical Death**	7616					
		13	**Other death within a year of delivery**						
181	Ot preg comp	14	**Other Compl of Preg/ Del/ Puerperium**	64690 64873 64894 64962	64691 64874 64950 64963	64693 64890 64951 64964	64870 64891 64953 V2342	64871 64892 64960 V2387	64872 64893 64961
189	Prev c-sectn	14	**Other Compl of Preg/ Del/ Puerperium**	65420	65421	65423			
191	Amnios dx	14	**Other Compl of Preg/ Del/ Puerperium**	7923					
193	OB-related perin trauma	14	**Other Compl of Preg/ Del/ Puerperium**	66400 66420 66440 66460 66490	66401 66421 66441 66461 66491	66404 66424 66444 66464 66494	66410 66430 66450 66480	66411 66431 66451 66481	66414 66434 66454 66484
194	Forceps del	14	**Other Compl of Preg/ Del/ Puerperium**	66950	66951				
195	Ot compl bir	14	**Other Compl of Preg/ Del/ Puerperium**	677 65401 65412	64970 65402 65413	64971 65403 65414	64973 65404 65430	65183 65410 65431	65400 65411 65432

				65433	65434	65440	65441	65442	65443
				65444	65470	65471	65472	65473	65474
				65480	65481	65482	65483	65484	65490
				65491	65492	65493	65494	65520	65521
				65523	65540	65541	65543	65560	65561
				65563	65570	65571	65573	65600	65601
				65603	65660	65661	65663	65670	65671
				65673	65680	65681	65683	65690	65691
				65693	65900	65901	65903	65910	65911
				65913	65970	65971	65973	66530	66531
				66534	66540	66541	66544	66550	66551
				66554	66560	66561	66564	66570	66571
				66572	66574	66580	66581	66582	66583
				66584	66590	66591	66592	66593	66594
				66700	66702	66704	66710	66712	66714
				67100	67101	67102	67103	67104	67110
				67111	67112	67113	67114	67120	67121
				67122	67123	67124	67130	67131	67133
				67140	67142	67144	67180	67181	67182
				67183	67184	67190	67191	67192	67193
				67194	67480	67482	67484	67500	67501
				67502	67503	67504	67510	67511	67512
				67513	67514	67520	67521	67522	67523
				67524	67580	67581	67582	67583	67584
				67590	67591	67592	67593	67594	67600
				67601	67602	67603	67604	67610	67611
				67612	67613	67614	67620	67621	67622
				67623	67624	67630	67631	67632	67633
				67634	67640	67641	67642	67643	67644
				67650	67651	67652	67653	67654	67660
				67661	67662	67663	67664	67680	67681
				67682	67683	67684	67690	67691	67692
				67693	67694	67900	67901	67902	67903
				67904					
219	Low birth wt	14	**Other Compl of Preg/ Del/ Puerperium**	7640	7641	7642	7649		
220	Birth asphyx	14	**Other Compl of Preg/ Del/ Puerperium**	7682	7683	7684	7685	7686	7687
				7689	76870	76871	76872	76873	77088
222	Perint jaund	14	**Other Compl of Preg/ Del/ Puerperium**	7730	7731	7732	7733	7734	7735
				7740	7741	7744	7745	7746	7747
				77430	77431	77439			
223	Birth trauma	14	**Other Compl of Preg/ Del/ Puerperium**	7670	7671	7672	7673	7674	7675
				7676	7677	7678	7679	76711	76719

224	Ot perint dx	14	**Other Compl of Preg/ Del/ Puerperium**	04041	7600	7601	7602	7603	7604
				7605	7606	7608	7609	7610	7611
				7612	7613	7614	7615	7617	7618
				7619	7620	7621	7622	7623	7624
				7625	7626	7627	7628	7629	7630
				7631	7632	7633	7634	7635	7636
				7637	7638	7639	7660	7661	7662
				7700	7701	7702	7703	7704	7705
				7706	7707	7708	7709	7710	7711
				7712	7713	7714	7715	7716	7717
				7718	7720	7721	7722	7723	7724
				7725	7726	7728	7729	7750	7751
				7752	7753	7754	7755	7756	7757
				7758	7759	7760	7761	7762	7763
				7764	7765	7766	7767	7768	7769
				7771	7772	7773	7774	7775	7776
				7778	7779	7780	7781	7782	7783
				7784	7785	7786	7787	7788	7789
				7790	7791	7792	7793	7794	7797
				7798	7799	7897	76061	76062	76063
				76064	76070	76074	76076	76077	76078
				76079	76381	76382	76383	76384	76389
				76621	76622	77010	77011	77012	77013
				77014	77015	77016	77017	77018	77081
				77082	77083	77084	77085	77086	77087
				77089	77182	77183	77189	77210	77211
				77212	77213	77214	77581	77589	77750
				77751	77752	77753	77931	77932	77933
				77934	77981	77982	77983	77984	77985
				77989	78091	78092	V137	V502	V502
180	Ectopic preg	15	**Ectopic Pregnancy**	6330	6331	6332	6338	6339	63300
				63301	63310	63311	63320	63321	63380
				63381	63390	63391			
177	Spont abortn	16	**Spont abortn**	63400	63401	63402	63410	63411	63412
				63420	63421	63422	63430	63431	63432
				63440	63441	63442	63450	63451	63452
				63460	63461	63462	63470	63471	63472
				63480	63481	63482	63490	63491	63492
181	Ot preg comp	16	**Spont abortn**	630	631	632	6310	6318	64600
				64601	64603				
195	Ot compl bir	16	**Spont abortn**	65130	65131	65133	65140	65141	65143
				65150	65151	65153	65160	65161	65163
178	Induc abortn	17	**Induc abortn**	6380	6381	6382	6383	6384	6385

				6386	6387	6388	6389	63500	63501
				63502	63510	63511	63512	63520	63521
				63522	63530	63531	63532	63540	63541
				63542	63550	63551	63552	63560	63561
				63562	63570	63571	63572	63580	63581
				63582	63590	63591	63592	63600	63601
				63602	63610	63611	63612	63620	63621
				63622	63630	63631	63632	63640	63641
				63642	63650	63651	63652	63660	63661
				63662	63670	63671	63672	63680	63681
				63682	63690	63691	63692	63700	63701
				63702	63710	63711	63712	63720	63721
				63722	63730	63731	63732	63740	63741
				63742	63750	63751	63752	63760	63761
				63762	63770	63771	63772	63780	63781
				63782	63790	63791	63792		
196	Nml preg/del	17	**Induc abortn**	65170	65171	65173			
224	Ot perint dx	17	**Induc abortn**	7796					
179	Abort compl	18	**Other, Specify**	6390	6391	6392	6393	6394	6395
				6396	6398	6399			
181	Ot preg comp	19	**Anemia in Pregnancy**	64820	64821	64822	64823	64824	
181	Ot preg comp	20	**Hyperemesis**	64300	64301	64303	64310	64311	64313
				64320	64321	64323	64380	64381	64383
				64390	64391	64393			
181	Ot preg comp	21	**Edema**	64610	64611	64612	64613	64614	
181	Ot preg comp	22	**Renal Disorder**	64620	64621	64622	64623	64624	64670
				64671	64673				
181	Ot preg Comp	23	**Habitual Aborter**	64630	64631	64633			
181	Ot preg Comp	24	**Neurologic/ CNS**	64640	64641	64642	64643	64644	64940
				64941	64942	64943	64944		
181	Ot preg Comp	25	**Infectious Disease**	64650	64651	64652	64653	64654	64700
				64701	64702	64703	64704	64710	64711
				64712	64713	64714	64720	64721	64722
				64723	64724	64730	64731	64732	64733
				64734	64740	64741	64742	64743	64744
				64750	64751	64752	64753	64754	64760
				64761	64762	64763	64764	64780	64781
				64782	64783	64784	64790	64791	64792
				64793	64794				
191	Amnios dx	25	**Infectious Disease**	65840	65841	65843			

195	Ot compl bir	25	**Infectious Disease**	65530	65531	65533	65920	65921	65923
				65930	65931	65933	67000	67002	67004
				67010	67012	67014	67020	67022	67024
				67030	67032	67034	67080	67082	67084
				67200	67202	67204			
181	Ot preg Comp	26	**GU/GYN**	64660	64661	64662	64663	64664	
181	Ot preg Comp	27	**Infant Complications**	64680	64681	64682	64683	64684	
195	Ot compl bir	27	**Infant Complications**	67800	67801	67803	67910	67911	67912
				67913	67914				
181	Ot preg Comp	28	**Other Endocrine (Non-Diabetes)**	64810	64811	64812	64813	64814	
181	Ot preg Comp	29	**Congenital Heart**	64850	64851	64852	64853	64854	
181	Ot preg Comp	30	**Stroke, Thrombosis, & Other Cardiovascular**	64860	64861	64862	64863	64864	
181	Ot preg Comp	31	**Smoking in Pregnancy**	64900	64901	64902	64903	64904	
181	Ot preg Comp	32	**Obesity**	64910	64911	64912	64913	64914	64920
				64921	64922	64923	64924		
181	Ot preg Comp	33	**Fetal Death - Stillbirth**	V271	V273	V274	V276	V277	
182	Hemorr preg	34	**Hemorrhage**	64000	64001	64003	64080	64081	64083
				64090	64091	64093	64130	64131	64133
				64180	64181	64183	64190	64191	64193
				66600	66602	66604	66610		
195	Ot compl bir	34	**Hemorrhage**	66612	66614	66620	66622	66624	66630
				66632	66634				
182	Hemorr preg	35	**Hemorrhage**	64100	64101	64103	64110	64111	64113
				64120	64121	64123			
185	Long pregncy	36	**Prolonged Pregnancy**	64500	64501	64503	64510	64511	64513
				64520	64521	64523			
187	Malposit ion	37	**Malposition**	65200	65201	65203	65210	65211	65213
				65220	65221	65223	65230	65231	65233
				65240	65241	65243	65250	65251	65253
				65260	65261	65263	65270	65271	65273

				65280	65281	65283	65290	65291	65293
				66000	66001	66003			
188	Pelvic obstr	38	**Pelvic Obstruction**	65300	65301	65303	65310	65311	65313
				65320	65321	65323	65330	65331	65333
				65340	65341	65343	65350	65351	65353
				65360	65361	65363	65370	65371	65373
				65380	65381	65383	65390	65391	65393
				66010	66011	66013	66020	66021	66023
				66030	66031	66033	66040	66041	66043
				66050	66051	66053	66060	66061	66063
				66070	66071	66073	66080	66081	66083
				66090	66091	66093	67810	67811	67813
190	Fetal distrs	39	**Fetal Distress**	65630	65631	65633	66100	66101	66103
				66110	66111	66113	66120	66121	66123
				66130	66131	66133	66140	66141	66143
				66190	66191	66193	66200	66201	66203
				66210	66211	66213	66220	66221	66223
				66230	66231	66233			
191	Amnios dx	40	**Obstetric Complications**	65700	65701	65703	65800	65801	65803
				65810	65811	65813	65820	65821	65823
				65830	65831	65833	65880	65881	65883
				65890	65891	65893			
192	Umbil cord	40	**Obstetric Complications**	66300	66301	66303	66310	66311	66313
				66320	66321	66323	66330	66331	66333
				66340	66341	66343	66350	66351	66353
				66360	66361	66363	66380	66381	66383
				66390	66391	66393			
195	Ot compl bir	40	**Obstetric Complications**	65980	65981	65983	65990	65991	65993
				66500	66501	66503	66510	66511	66512
				66514	66520	66522	66524	66800	66801
				66802	66803	66804	66820	66821	66822
				66823	66824	66880	66881	66882	66883
				66884	66890	66891	66892	66893	66894
				66900	66901	66902	66903	66904	66910
				66911	66912	66913	66914	66920	66921
				66922	66923	66924	66930	66932	66934
				66940	66941	66942	66943	66944	66960
				66961	66980	66981	66982	66983	66984
				66990	66991	66992	66993	66994	67300
				67301	67302	67303	67304	67310	67311
				67312	67313	67314	67330	67331	67332
				67333	67334	67380	67410	67412	67414
				67420	67422	67424	67430	67432	67434
				67440	67442	67444			

195	Ot compl bir	41	**Cervical Incompetence**	65450	65451	65452	65453	65454	65460
				65461	65462	65463	65464		
195	Ot compl bir	42	**Fetal Malformation**	65500	65501	65503	65510	65511	65513
				65580	65581	65583	65590	65591	65593
195	Ot compl bir	43	**Rh**	65610	65611	65613			
195	Ot compl bir	44	**ABO ISOIMMUNIZAT**	65620	65621	65623			
195	Ot compl bir	45	**Fetal Growth Restriction**	65650	65651	65653			
219	Low birth wt	45	**Fetal Growth Restriction**	76409	76410	76411	76412	76413	76414
				76415	76416	76417	76418	76419	76420
				76421	76422	76423	76424	76425	76426
				76427	76428	76429	76490	76491	76492
				76493	76494	76495	76496	76497	76498
				76499	V2130				
195	Ot compl bir	46	**Maternal Heart Complications**	66810	66811	66812	66813	66814	
195	Ot compl bir	47	**Cardiomyop in Pregnancy**	67450	67451	67452	67453	67454	
661	Substance-related disorders	48	***Maternal Drug Use***	64830	64831	64832	64833	64834	65550
				65551	65553	76072	76073	76075	
670	Miscellaneous mental disorders	49	**Mental Disorder in Pregnancy**	64840	64841	64842	64843	64844	
181	Ot preg comp	50	**No Complications**	V272	V275	V279			
195	Ot compl bir	50	**No Complications**	64981	64982	65103	65113	65123	65193
				65940	65941	65943	65950	65951	65953
				65960	65961	65963	66970	66971	V230
				V231	V232	V233	V234	V2341	V2349
				V235	V237	V238	V2381	V2382	V2383

196	Nml preg/del	50	**No Complications**	V2384	V2385	V2386	V2389	V239	
				650	65100	65101	65110	65111	20
				65121	65180	65181	65190	65191	V220
				V221	V222	V240	V241	V242	V270
				V7242	V9100	V9101	V9102	V9103	V9109
				V9110	V9111	V9112	V9119	V9120	V9121
				V9122	V9129	V9190	V9191	V9192	V9199

LITERATURE REVIEW TABLE

Author/Year	Title	Description of Study Population
Thompson, 2015	Medical and Obstetric Outcomes Among Pregnant Women With Congenital Heart Disease	2000-2010 Inpatient Sample of Women with delivery-related discharges
Drenthen, 2007	Outcomes of Pregnancy in Women with CHD- A Literature Review	Females with CHD; Articles in English, German, or French;
Drenthen, 2010	Pregnancy Outcomes in Women with Congenital Heart Disease	Female patients 18-58 with CHD enrolled in CONgenital CORivitia (CONCOR) registry and a Belgian tertiary medical center adult CHD database between 1980 and 2007
Ouyang, 2010	Obstetric outcomes in pregnant women with congenital heart disease	All women with CHD followed by Boston Adult Congenital Heart (BACH) service and delivering at Brigham and Women's Hospital between 1/1998-12/2005
Khairy, 2006	Pregnancy Outcomes in Women with Congenital Heart Disease	All women with CHD followed by Boston Adult Congenital Heart (BACH) service and delivering at Brigham and Women's Hospital between 1/1998-11/2004
Presbitero; 1994	Pregnancy in Cyanotic Congenital Heart Disease	Women with CHD seen in the Royal Brompton National Heart and Lung Hospital, London, and Hospital Giovanni Bosco, Torino, Italy

Exclusions	Sample	Type of Study	Exposed
Those with 74.91 delivery code	Database of hospital deliveries- largest all-payer inpatient care database; 12,524,118 women included	Cohort	Women with delivery discharge code and CHD
	Literature review; 1,413 pregnancies with information on preterm birth	Literature Review	Journal articles identified by using CHD and pregnancy/delivery by type of CHD
Excluded miscarriages and abortions	CHD tertiary database. 1803 women with 1302 completed pregnancies	Cohort	Pregnant female patients with CHD as seen in database
Women with acquired heart disease, primary arrhythmia diagnoses without underlying CHD, isolated mitral valve prolapse	65 women with 112 pregnancies	Cohort	Women with CHD who delivered between 1998 and 2005
Women with acquired heart disease, primary arrhythmia diagnoses without underlying CHD, isolated mitral valve prolapse	90 pregnanices in 53 women; Hospital based	Case series	Women with CHD followed by BACH
(1) patients with previous surgical repair who were no longer cyanotic, (2) pregnancies intentionally interrupted, (3) patients with the Eisenmenger reaction, and (4) patients whose notes had been destroyed or lost	Hospital based: 44 women with 96 pregnancies	Case series	Women with pregnancies with cyanotic CHD

Non-exposed	Definition of Exposure
Women with delivery discharge without CHD	Women with ICD-9-CM codes 745.x-747.x, 648.5x and a delivery code 74.x [except 74.91] V27, 72.x, 73.x, and 650–659
Women without CHD; healthy population	Varied depending on study, pregnant patient identified with CHD by type of CHD: Atrial septal defect, atrioventricular septal defect [AVSD], ventricular septal defect, aortic stenosis, aortic coarctation, pulmonary valve stenosis, [PS], pulmonary atresia, tetralogy of Fallot [TOF], transposition of the great arteries/vessels [TGA], Ebstein's, cyanotic heart disease, Eisenmenger, and Fontan
N/A	CHD classified as: ASD, Aortic coarctation, VSD, PVS, TOF, Marfan, AVSD, AVS, TGA, Ebstein, Congenital corr TGA, pulmonary atresia, pulmonary hypertension or Eisenmenger, complex cyanotic heart disease, other
N/A	Women with CHD who became pregnant during 1/1998-12/2005, excluding women with acquired heart disease, primary arrhythmia diagnoses without underlying CHD, isolated mitral valve prolapse
N/A	Women with CHD who became pregnant during 1/1998-11/2004, excluding women with acquired heart disease, primary arrhythmia diagnoses without underlying CHD, isolated mitral valve prolapse
	Group 1 was single-ventricle and/or tricuspid atresia (10 patients with 26 pregnancies); group 2, tetralogy of Fallot or pulmonary atresia with aortopulmonary collaterals (21 patients with 46 pregnancies); group 3, Ebstein's anomaly and atrial septal defect (8 patients with 14 pregnancies); and group 4, corrected transposition of the great arteries, ventricular septal defect, and pulmonary stenosis (5 patients with 10 pregnancies).

Definition of Outcome	Details of Outcomes
Preterm Labor (no specific definition in paper)	Odds of preterm labor (CHD vs no CHD): 1.66 (1.56-1.77)
Premature delivery at <37 weeks	224 events, 15.2% prevalence; compared to expected occurrence between 10-12%
Cardiac, obstetric complications, offspring outcome; premature labor (<37 weeks), premature delivery at <37 weeks	Premature birth: 12% prevalence; Corrected and uncorrected cyanotic heart disease as a predictor for neonatal complications (OR: 2.0 [1.4-2.9])
Preterm delivery at <37 weeks	19 (20.7%) prevalence; 42.1% PPROM 47.4% indicated delivery
Preterm delivery at <37 weeks	15(20.8%) prevalence
Premature birth <37 weeks gestation	15(37%) premature

Comments
This article found lots of differences between outcomes of women with CHD and without CHD. It did not look at every outcome based on CHD classification, but instead grouped together outcomes into cardiac complications and obstetric complications. Such a large sample size it's difficult to look at everything.
This literature review does not cover less severe CHD and is limited by the articles used in published preterm birth information. Does not differentiate between surgical status, as not given in all papers. Gives statistics for premature labor and premature birth, however does not link the two. Also looks at PROM, which is more prevalent in certain types of CHD. Strength in allowing us to look at each CHD included and combined outcomes in one paper, although combining data from different sources and different exclusions may bias these results.
No separation of indicated PTD or spontaneous. Missing some severe CHDs in which pregnancy is contraindicated, which may bring prevalence down. There is also no control group for the general population.
Categorizes the reason for preterm delivery which is important in understanding why this population had a different rate of preterm delivery
Allowed for follow of spontaneous and induced abortions, very complete data on a number of variables
Grouped different "severe" CHD to see individual group data as well as overall for cyanotic heart conditions. Strength that contains information on spontaneous abortion and live birth %. Those in group 1 had lowest % of live births