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The Influence of Maternal Contexts on Infant Outcomes, Secondary Analysis of WPCR Data 2000-2010

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THE INFLUENCE OF MATERNAL CONTEXTS ON INFANT OUTCOMES,
SECONDARY ANALYSIS OF WPCR DATA 2000-2010

by

Mary R. Butler

A Dissertation Submitted in Partial Fulfillment of the Requirements for the Degree of

Doctor of Philosophy

In Nursing

at

The University of Wisconsin, Milwaukee

May 2014
ABSTRACT

THE INFLUENCE OF MATERNAL CONTEXTS ON INFANT OUTCOMES,
SECONDARY ANALYSIS OF WPCR DATA 2000-2010

by

Mary R. Butler

The University of Wisconsin-Milwaukee, 2014
Under the Supervision of Professor Dr. Kathleen Sawin

Congenital heart defects (CHD) are the most prevalent birth defect in the world and occur in approximately 6-8 of every 1,000 live births (Hoffman & Kaplan, 2002). CHD continues to be one of the leading causes of infant morbidity and mortality today. Five to ten percent of all cases of CHD can be attributed to a chromosomal abnormality, 3%-5% are linked to single gene defects, and approximately 2% are a result of known environmental factors (Clark, 2001). With only 10%-15% of the causes of CHD are understood, the remaining 85%-90% of all CHD cases, the etiologies remain unknown. The purpose of this study was to examine the relationships of select maternal variables to the type of CHD (simple vs. complex), birth weight and gestational age in infants born with CHD participating in the Wisconsin Pediatric Cardiac Registry (WPCR). This study was a secondary analysis of 1,687 parent/child questionnaires using the data within the WPCR database from 2000-2010. A life course perspective was used to organize the maternal context variables and illustrate the relationships to the birth outcomes of the infants with CHD. The findings in this study included two maternal variables as risk
factors for having a child with complex CHD. Personal maternal history of CHD (OR: 2.382; 95% CI: 1.424-3.984) and history of serious health condition (OR: 1.537; CI: 1.085-2.178) increased the risk for complex CHD in these infants. The predictors of birth weight included; maternal history of hypertension, serious health condition six months prior/during pregnancy, CHD, obesity and income ($R^2 = 0.049, p < 0.05$). The predictors of gestational age included; maternal history of hypertension, flu, and serious health conditions 6 months prior/during pregnancy, and type of housing ($R^2 = 0.045, p < 0.05$). Nurses and healthcare providers can identify risk factors prior to pregnancy and provide education to women and their partners in anticipation for a future pregnancy to reduce risk of complex CHD in their infant. This study reinforces the multifaceted nature of CHD and need for further investigation of maternal and paternal exposures to help identify other risk factors for complex CHD.
DEDICATION

With all my love, to my family:

My husband James

My son Dominic

My mom Teresa,

My sister and her family, Sue, Tony, Abby and Gabby

And my late grandmother Leonella, a visionary and inspiration.

You have all supported me in the journey during the tough times and the joyous times. I could not have completed this without each and every one of you. Words cannot express the appreciation and love I have for you all. Thank you.
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I would like to express my deepest appreciation to Dr. Kathleen Sawin, my major professor, for guiding me in this journey. We both have learned so much in this process about CHD. Your in-depth knowledge and expertise in research have given me the skills and ability to push forward as a nurse leader in this field. I am forever indebted to you as I continue in my career.

My dissertation committee has been a gift from the beginning. I would like to thank Dr. Teresa Johnson and Dr. Michael Carvan for sharing their expertise and knowledge to develop this dissertation and assist me in improving my ability to present these findings. You both have been active members of my committee from the beginning, providing guidance and constructive criticism to challenge my writing and understanding of these concepts. Dr. Strasburger, you have been a wonderful mentor and colleague urging me to pursue higher education. I am forever grateful for your ability to push me to a level of expertise I would have never envisioned for myself. Thank you, Dr. Morin for your critique and suggestions on the final dissertation. It was a privilege and honor to work with each of you.

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Finally, I would like to express my gratitude to the Herma Heart Center for allowing me the use of the WPCR data to conduct this study in my dissertation. I could not have completed this study without the generous assistance of the WPCR coordinators and research team.
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CHAPTER ONE

The Influence of Maternal Contexts on Infant Outcomes

Congenital heart defects (CHD) are the most prevalent birth defect in the world and occur in approximately 6-8 of every 1,000 live births (Hoffman & Kaplan, 2002). CHD continues to be one of the leading causes of infant morbidity and mortality today. Five percent to ten percent of all cases of CHD can be attributed to a chromosomal abnormality. And another 3%-5% are linked to single gene defects, and approximately 2% are a result of known environmental factors (Clark, 2001). With only 10%-15% of the causes of CHD are understood, the remaining 85%-90% of all CHD cases, the etiologies remain unknown.

CHD is the most common birth defect in the United States in children and adults with approximately 1,040,106 new patients are diagnosed each year (Gibson, Burns, Walker, Cross, & Leslie, 2010). Understanding and identifying the risk factors associated with CHD is critical in reducing the financial and social constraints placed on the individual and society and the individual (Jacobs, Wernovsky, & Elliot, 2007) and decreasing the prevalence of CHD. There are many types of CHD, with many being simple such as an atrial septal defect (ASD) to the very complex, hypoplastic left heart syndrome (HLHS). As children with complex CHD survive into adulthood as a result of advances in treatment and diagnosis respectively the numbers of adults with complex CHD are increasing twofold as well. It is estimated a lifetime cost for children in the U.S. with complex CHD can be in excess of $1.2 billion (CDC, 2010). In 2004 it was estimated that hospital care for all patients with CHD, children and adults, exceeded $2.6 billion (AHA, 2009). As the adult CHD population grows, researchers predict that
numbers of adults with CHD will surpass the number of children with CHD in the next decade. The cost of care for complex CHD produces significant financial strains on families, healthcare systems and society that have been recognized as a public health problem. These issues have led researchers to gain greater understanding of the etiology of CHD development in the fetus thus try to decrease the prevalence.

Although treatment for CHD has evolved dramatically over the years, it’s etiology continues to be elusive. In the past, children born with cyanotic heart disease (causing low blood oxygen levels) were treated only with palliative measures with most children dying early in infancy. Of those children who survived, most had significantly shorter life spans before diagnostic and surgical technologies were available. Cardiac angiography was the first diagnostic tool developed in the 1930’s to visualize cardiac malformations. Shortly after catheterizations, surgical ductus ligation, surgical correction, and palliative surgical techniques followed for treatment of cyanotic heart defects with great success in the 1940’s (Emmanouilides, 2001). The first cardiopulmonary bypass procedure was successfully performed in 1953. This novel procedure was one of the first doors to be opened for surgical care and treatment of congenital heart disease. These ground breaking diagnostic and surgical techniques created a new group of complicated children and adults with a chronic health condition to care for in our society (Emmanouilides, 2001).

Over the last 75 years, successful advances in the identification of the many structural forms of CHD, methods for surgical correction, and palliative procedures have dramatically decreased mortality from 50% to almost 15% (Emmanouilides, 2001). Although many milestones have been accomplished in the diagnosis and treatment of
CHD, the etiology remains elusive. Epigenetics, the study of the biological processes in which heritable genetic changes not found in DNA sequencing influence gene function at various stages of development is a growing area of interest in the study of CHD. The environmental exposures incurred over generations and the genetic predispositions to specific health conditions such as CHD are areas of great interest for research. Identification of biologic, physical and social risk factors for giving birth to an infant with CHD in women of childbearing are goals of many researchers and clinicians.

Through use of animal models and the recent ability to sequence the human genome, a greater understanding of the molecular and genetic influences during fetal development of the heart has allowed researchers and clinicians the ability to identify critical times of vulnerability and target potential interventions. Pre- and inter-conception timeframes are now understood as critical times to focus in the mother’s exposures and their influence during fetal cardiac development (Sartiani et al, 2009). The epigenetic factors influencing the activation or inactivation of cardio-specific genes during cardiac development are being studied and are better understood. Therefore the environmental exposures that are potentially triggering these cellular processes are of great interest for researchers and clinicians due to the multifactorial nature of CHD.

Although the exact mechanism of CHD development during pregnancy when a woman are exposed to some medications, vitamins, alcohol or tobacco use, and some environmental toxins is not well understood, there has been an observed risk for CHD development in the fetus from these agents (Brent, 2004). Due to the heterogeneity of CHDs in humans and ethical considerations in human studies, understanding the exact mechanisms in cardiac formation and CHD development have been complicated. Several
cardio specific genes (GATA, Nkx, Hand, EGFR, Wnt5a), transcription factors (ZIC3, NKX2.5, TNX5, GATA4, TFAP2B, TBX1 and FOG2) (Clark, Yutzey & Benson, 2006) and epigenetic processes (histone modifications, RNA modifications, and DNA methylation) are known to be essential in normal cardiac development. Researchers have identified errors occurring in several genes, transcription factors, chromosomes, and single nucleotide polymorphisms that are responsible for specific CHDs in both animal models and humans (Bentham & Bhattacharya, 2008; Hinton, Yutzey, & Benson, 2005; Huang, Liu, & Lv, 2010; McFadden & Olson, 2002; Reamon-Buettner, Spanel-Borowski, & Borlak, 2005).

Cardiac development is a complicated process of cell proliferation, differentiation, migration and morphogenesis creating the potential for disruption of one or many of the multiple pathways. The gene-environmental interaction theory (Nora, 1968) and its influence of CHD development is complex due to the multifactorial nature complicating identification of specific etiological sources of CHD. Researchers and clinicians cannot underestimate the various exposures a woman encounters throughout her lifetime and the potential impact it may have on her developing infant. As further genetic and environmental research is conducted, greater understanding of these complex processes may provide nurses and clinicians recommendations for treatments promoting preventative prenatal health care practice guidelines for the reduction of CHD and the costs associated with its care.

Specific biologic, physical, and social variables during various times of pre-and inter-conception and pregnancy are areas for researchers and practitioners alike to intervene and study. The Centers for Disease Control and Prevention have published
routine updates on the Public Health Action Plan to Prevent Heart Disease and Stroke including investigation of the environmental causes of CHD and cardiovascular disease (CVD) (CDC, 2011). The National Heart, Lung, and Blood Institute (NHLBI) created a task force in 2001 specifically focusing on pediatric cardiovascular disease identifying research priorities, and scientific opportunities to address the growing public health problem of CHD in children and adults (NHLBI, 2002).

Etiological and epidemiological research are important when trying to identify causal sources of CHD. This type of research has implications for prenatal, pediatric, and adult care in counseling and identification of risk factors associated with CHD in these groups. However, this research is also instrumental when transitioning these children with CHD into a healthy adulthood. Health care providers (HCPs) need to provide adequate counseling for their reproductive health as some forms of CHD are familial. Continued epidemiologic, environmental, and genetic CHD research will assist in the identification of the risk factors and causal factors associated with CHD to significantly decrease or eliminate CHD in humans (Weinhold, 2004).

Study Problem and Purpose

During the review of literature several reviews of maternal risk factors for CHD were discovered. These investigators identified specific maternal risk factors for CHD but, none of which contained all of the maternal contexts of interest in one study (Gorini, Chiappa, Gargani, & Picano, 2013; Luteijn, Brown, & Dolk, 2013; Patel & Burns, 2013; Stothard, Tennant, Bell & Rankin, 2009; Jenkins at al., 2007; Thulstrup & Bonde, 2006; Watson, Jacobson, Williams, Howard & DeSesso, 2006; Lin & Ardinger, 2005). The genetic research was extensive; however the understanding between environmental risk
factors and genetic risk factors remains unknown. The Baltimore Washington Infant Study (BWIS) was the only study identified which separated the type of CHD into categories of severity and evaluated biologic and environmental risk factors (Ferencz, Loffredo, Correa-Villaseñor & Wilson, 1997).

Pediatric cardiologists around the state of Wisconsin became aware of the increasing number of infants born with single ventricle physiology in the late 1990’s. After much discussion and review, these cardiologists, and a large interdisciplinary team, created the Wisconsin Pediatric Cardiac Registry (WPCR) in 2000. This database, modeled after the BWIS (Ferencz et al., 1997), was created to help identify and track data associated with CHD in infants born in Wisconsin. The goal for creation of this comprehensive database was to gain a greater understanding of the influences of maternal and paternal exposures before and during the pregnancy that might increase the risk of CHD development in the infant. This database includes the temporal, epidemiological, and demographic variables that may reflect risk factors for the birth of an infant with CHD. The WPCR project has collected environmental exposure history, family history and genetic data for analyzing to aid in understanding the etiology of CHD.

The WPCR was the first large heart defect database-registry to collect subjective and genetic information from histories of mothers, fathers, and infants born in Wisconsin with various forms of CHD (Hanson-Morris, Pelech, 2006). The WPCR was created with three overarching goals (Harris et al., 2011):

1. Ascertain all families with an infant/child born with a congenital heart defect in the state of Wisconsin and provide a detailed phenotypic description of the anomaly.
2. Obtain both DNA samples and complete questionnaires from all ascertained families and also a control group.

3. Initiate and promote collaborative research into genetic and environmental etiologies of CHDs, utilizing data and specimens from the WPCR (p. 24).

Over the last 15 years several publications using the data from the WPCR have been presented. An overview of the structure of the WPCR and goals for the collection of the data and potential for studies using the data within the WPCR were published by Cronk et al. (2003), Hanson-Morris and Pelech (2006), and Harris et al. (2011). In Cronk et al.’s two studies (2004, 2011) geographical distribution of several types of CHD were explored in Wisconsin using data from the WPCR database. Presently, there are no published studies using the maternal data from the WPCR.

The first goal of the WPCR was most pertinent to this study. It is estimated that CHD prevalence is 0.5%-0.8%, or approximately 400-600 new cases each year occur in Wisconsin (Hanson-Morris & Pelech, 2006). In this study the completed questionnaire data were used to evaluate relationships between maternal demographics and exposures prior to and during the pregnancy and the type of CHD of their infants. There have been no published results from 2000-2010 using WPCR data examining maternal factors for risk of type of CHD. In the literature the majority of studies have identified maternal risk factors for CHD development for the general population. Few studies have identified risk factors associated with the type of CHD.

The BWIS was the first large population based study to examine the risk factors of CHD development in the general population. This study also examined the relationships between the genetic and environmental risk factors and the various CHD
phenotypes (Ferencz et al., 1997). The BWIS found evidence of increased risk with
certain types of CHD and hypothesized that certain risk factors may be more prevalent
during particular times of cardiac formation. The BWIS demonstrated an increased risk
for laterality/looping defects (OR 8.3, 95% CI 3.0-23.0), atrioventricular septal defects,
nonchromosomal (OR 10.6, CI 3.7-30.6), and cardiomyopathy (OR 11.5, CI 4.4-29.8)
when maternal diabetes was present (Ferencz et al., 1997). They also found increased risk
for specific types of CHD when several other maternal variable were present including
history of fever, influenza, family history of CHD, maternal age > 30years, and use of
diazepam.

The current study examined maternal risk factors related to complex CHD in
these infants as this question has not been examined to date. A power analysis based on
the work of Peduzzi et al. (1996) was performed to determine adequacy of size of the
sample. Using the formula of \( N=10^k/p \) (k=number of covariates) (p=the smalls of the
proportion of negative or positive cases) \( N=10(15)/.3, N= 500; 500 \) cases were required
for this study. With 1,687 completed questionnaires available adequate power to
determine relationships among the variables was present. Hypotheses were derived from
a review of literature and review of the information collected by the WPCR. This study
may provide identifiable and modifiable risk factors for women with history of an infant
with CHD to decrease the risk for having a subsequent pregnancy affected by CHD.

Maternal health and exposures have also been associated other birth outcomes
including birth weight and gestational age. Low birth weight and early gestational age
have been associated with certain maternal risk factors such as chronic health conditions
(Palmer, Bonzini, Harris et al., 2013), history of smoking (Ashford et al., 2010; Rogers,
2009), and socioeconomic status (Blumenshine, Egerter, Barclay, Cubbin, & Braveman, 2010; Jansen et al., 2008; Messer et al., 2008). In this group of infants with various types of CHD, it is hypothesized that these maternal risk factors are also associated with the infants’ birth weight and gestational age as well as type of CHD. It is important for women to optimize their health prior to and during pregnancy to decrease the risk for low birth weight and premature birth. Infants with complex CHD were also believed to be at greater risk for low birth weight and prematurity due to the complexity of CHD diagnosis (Williams et al., 2010; Malik, Cleves, Zhao, Hobbs, & NBDS, 2007).

The same questionnaire was used consistently from 2000-2010, thus providing large amounts of data to be explored. In 2006 a control group was initiated to provide comparisons of children without CHD. However, there were never enough control subjects to meet the goal of the registry. The majority of the comparison groups were older children or teenagers found to have normal cardiac structures on echocardiography, with approximately 270 controls available. There were approximately 50 controls who completed a questionnaire that was an abbreviated version if over the age of two years. These children were older therefore their parents were less likely able to complete the questionnaire accurately, due to recall issues. Therefore in this study the control group was not used. The genetic information collected was not used for this study.

A secondary analysis of the maternal context variables in the WPCR was completed using this large data set collected over the last 10 years. Through identification of the relationships between these maternal context variables and the outcome or type of CHD nurses and researchers may be provided with new evidence of risk factors in this population. From a critical review of literature of the contextual and
genetic maternal risk factors for CHD development, a specific aim was developed with two hypotheses to be tested and one exploratory research questions to be posed. The specific aim of this study was to examine the relationships of select maternal context variables to the type of CHD (simple or complex), birth weight and gestational age in infants born with CHD participating in the WPCR.

**Theoretical Framework**

The central tenets of nursing include person, environment, health, and nursing (Flaskerud & Halloran, 1980; Yura & Torres, 1975). Nursing has a goal to provide a holistic model of healthcare delivery incorporating research findings to guide practice. Both nursing and the life course theory have a goal of improving health and understanding disease processes. Therefore a life course perspective on health was chosen as a theoretical model to guide this study as this theory conceptualizes health as a reflection of an underlying developmental trajectory. The goal of the life course perspective is to understand, explain, and improve health and disease patterns across various populations (Halfon & Hochstein, 2002). The key concepts of the life course theory include:

- **Timeline** – health is cumulative and longitudinal, i.e., developed over a lifetime.
- **Timing** - health and health trajectories are particularly affected during critical/sensitive periods.
- **Environment** – the broader environment (biologic, physical, and social) affects health and development.
- **Equity** – health inequality reflects more than genetics and personal choice. (Fine & Kotelchuck, 2010).
The life course perspective uses a multidimensional approach incorporating biological, psychological, behavioral, and social contexts to explain health and disease processes allowing for intervention and education identifying risk and protective factors (Fine & Kotelchuck, 2010). This perspective acknowledges throughout the developmental trajectory, that some contexts are fixed or hard wired, and others contexts are highly flexible or plastic and amenable to change. The life course perspective fits well in the study of CHD as many of the contexts are both fixed and plastic occurring along a developmental trajectory. Although this study was cross sectional, the data provided various points in the periconceptual timeframe and throughout the pregnancy to evaluate the relationships to CHD. The life course model recognizes the epigenetic nature of diseases and appreciates how today’s experiences and exposures determines tomorrow’s health. Those health trajectories are particularly affected during critical or sensitive periods (timing) and the broader environment - biologic, physical, and social contexts – significantly affects the ability to be healthy (environment) (Kotelchuck, 2011).

A brief description of the proposed life course perspective is presented to explain the complex and overlapping relationships of maternal contexts to infant birth outcomes through the developmental trajectory of periconception to birth (Figure 1). The maternal contexts are divided into three contexts; biologic (known genetic causes associated with CHD, age, race, chronic health conditions (CHC), family history of CHD), physical (obesity, ETOH/drug use, cigarette use, medication/vitamin use, type of water consumed), and social contexts (socioeconomic status (SES), occupation, education level). The maternal contexts include fixed and modifiable factors of the maternal
environment or context both in the periconceptual phase and throughout pregnancy. It is understood that some contexts are unable to be changed such as the genetic contexts, and some contexts are amenable to change directly by choice of the mother such as the behavioral contexts. The social contexts have some ability for change in this model. However, some of the variables are influenced by a combination of maternal choices and a community level influence as well. The purpose of this study was to explore the relationships of select maternal variables to the type of CHD, birth weight and gestational age in infants born with CHD participating in the WPCR using a life course perspective. The hypotheses evaluated were:

**Hypotheses**

**Hypotheses 1:** Multiple maternal risk factors of biologic (known genetic causes associated with CHD, age, race, chronic health conditions, family history of CHD), physical (history of obesity, use of alcohol, drugs, cigarettes, medication/vitamin use, and type of water consumed), and social variables (SES, occupation, education level) influence the risk of complex CHD.

**Hypothesis 2:** Multiple maternal risk factors (biologic, physical, social) influence the risk of low birth weight or early gestational age in the infants born with CHDs.

**Definition of Terms**

**Maternal Contexts**

Maternal contextual factors are the biologic, physical and social contexts specific to the mothers of infants born with CHD. Maternal biologic context variables studied include: known genetic causes associated with CHD, maternal age, race, history of chronic health conditions, and family history of CHD.
Biologic: Biologic maternal context variables are the maternal variables which are inherent only to the mother and are not modifiable prior to or during the pregnancy. The biologic variables being studied include: Known genetic causes associated with CHD, maternal age, race, history of chronic health conditions, and family history of CHD.

- **Known Genetic Causes Associated with CHD:** There is a higher prevalence of CHD associated with specific syndromes or genetic abnormalities. In these syndromes the type of CHD is sporadic if present, degree of severity, and is related to the heterogeneous nature of CHD (Huang, Liu, Sun, Lv, Du, & Fan, 2010).

Age: Age is the part of life from birth to a given time. An individual's development measured in terms of the years requisite for like development of an average individual (Merriam-Webster Medical Dictionary, 2012).

- **Race:** Race is based on the premise of physical and biological differences, whereas ethnicity is based upon behavioral and cultural differences of groups with no biological underpinnings and can be sometimes mistakenly used interchangeably. Race is defined as a self-identification data item in which respondents choose the race or races with which they most closely identify (Federal Office of Management and Budget, 2000).

- **Chronic health conditions:** A chronic health conditions lasts longer than 3 - 6 months, is biologically based, has a significant impact on the life of a person, and requires more than usual access to healthcare services for support (The Council for Children and Adolescents with Chronic Health Conditions, 2005). Maternal
hypertension, diabetes, and epilepsy and mood disorders have been associated with greater risk for CHD (Liu et al., 2013).

- **Family history of CHD:** Having a first degree relative with a structural form of CHD increases risk for CHD in offspring (Bentham & Bhattacharya, 2008; Clark, 1996). Maternal history of CHD was significant risk factors for CHD in their infants (Liu et al., 2013).

**Physical:** Maternal physical context variables are variables which are modifiable behaviors of the mother prior to or during the pregnancy. The maternal physical variables studied include: History of obesity, ETOH and/or drug use, cigarette use, medication and/or vitamin use, and type of water consumed.

- **Obesity:** Obesity is a condition that is characterized by excessive accumulation and storage of fat in the body and is indicated by a body mass index of 30 or greater (CDC, 2012) A normal range for BMI is 18.5-24.9 (NIH, 2014).

- **Drug/alcohol use:** Alcohol and drug use is defined as consumption of alcoholic beverages including beer, wine, and spirits and/or illicit drugs on a weekly basis (Strandberg-Larson et al., 2011).

- **Cigarette use:** Cigarette or tobacco use is defined as smoking/using of cigarettes/tobacco products on a daily basis (Karatzas et al., 2011).

- **Medication/vitamin use:** According to the Food, Drug, and Cosmetic Act (2002) a drug is a substance recognized in an official pharmacopoeia or formulary; or a substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease; a substance other than food intended to affect the structure
Figure 1. Life course Conceptual Framework

Using a Life Course Perspective: The Influence of Maternal Contexts on Infant Outcomes

Maternal Contexts

Biologic
- Known Genetic Causes
- Age
- Race
- Chronic Health Conditions
- Family History of CHD

Physical
- Obesity
- ETOH use
- Drug use
- Tobacco use
- Medication/vitamin use
- Type of water consumed

Social
- Socioeconomic Status
- Occupation
- Education level

Time
- Periconception
- Early Gestation
- Mid Gestation
- Late Gestation
- Birth

Infant Outcomes

Risk of Simple or Complex CHD

Birth Weight and/or Gestational Age

Figure 1. Conceptual model of maternal contexts and the relationships to infant outcomes:
- Solid lines represent hypotheses.
- Dotted lines represent exploratory analyses.
- Simple CHD consists of isolated CHD including: atrial septal defect (ASD), ventricular septal defect (VSD), pulmonary stenosis (PS), aortic stenosis (AS), bicuspid aortic valve (BAV), coarctation of the aorta (COA), and mitral valve (MV) disease.
- Complex CHD consists of single or multiple diagnosis including: Tetralogy of Fallot (TET), atrioventricular septal defect (AVSD), transposition of the great arteries (TGA), pulmonary atresia (PA), hypoplastic left heart syndrome (HLHS), and univentricular heart disease or variants including multiple lesions.
or function of the body; or a substance intended for use as a component of a medicine but not a device or a component, part, or accessory of a device.

- *Type of water consumed:* Ingesting contaminated drinking water has been associated with increased risks for birth defects (Watson, Jacobson, Williams, Howard & DeSesso, 2006). Contaminated drinking water is a growing concern in many industrialized and industrializing nations due to increased population demands for products.

**Social:** Social maternal context variables are the social influences or immediate community variables of the mother. The social contexts can be influenced by maternal choice and/or sociological influences of the immediate community surrounding these mothers. The social maternal variables studied include: maternal socioeconomic status, occupation, and education level.

- *Socioeconomic Status:* Socioeconomic status is a combination of income level, educational level, and community income level (Luo, Wilkins, Kramer, & FIHSG, 2006).

- *Occupation:* Occupation can include paid and unpaid work history, job tasks, type of industry, and materials handled or machinery used (Shaw, Nelson, Iovannisci, Finnell, & Lammer, 2003).

- *Educational Level:* Educational level is the amount of school achieved/completed by the mother (Alverson, Strickland, Gilboa, & Correa, 2011).

**Infant Outcomes:** Infant outcomes are the birth outcomes of the infant born with CHD. Infant birth outcomes being studied include: type of CHD either simple or complex, birth weight, and gestational age. It was believed that the more complex the
CHD the greater the risk for prematurity and low birth weight would be observed. In the literature, CHD has been associated with small for gestational age and lower birth weights (Malik, Cleves, Zhao, Hobbs & NBDS, 2007).

- **Type of CHD (simple or complex):** CHD can be classified in many different methods including anatomical classifications or cyanotic heart disease (Kornosky & Salihu, 2008; Mitchell, Korones, & Berendes, 1971), pathogenic classifications (Botto & Correa, 2003; Ferencz et al., 1997; Clark, 1996; Marelli, Mackie, Ionescu-Ittu, Rahme & Pilote, 2007), structurally significant verses insignificant (Ferencz et al., 1997; Grech 1999; Pradat, Francannet, Harris & Robert, 2003; Teun van der Bom et al., 2011), with or without genetic mutation (Lin & Ardinger, 2005; Pradat, Francannet, Harris & Robert, 2003) or surgical classifications (Jacobs et al. 2007). In this study CHD was separated into either simple or complex and was identified from ICD-9 codes. Simple CHD consisted of single diagnoses of CHD, and/or did not cause significant cyanosis, and/or did not require immediate hospitalization or surgical intervention within the first year of life. Complex CHD consisted of multiple CHD diagnoses, and/or were cyanotic lesions, and/or required hospitalization or surgical intervention within the first year of life. Based upon past research simple CHD consists of isolated CHD including; atrial septal defect (ASD), ventricular septal defect (VSD), pulmonary stenosis (PS), aortic stenosis (AS), bicuspid aortic valve (BAV), coarctation of the aorta (COA) and mitral valve (MV) disease. Complex CHD consists of single or multiple diagnosis including; Tetralogy of Fallot (TET), atrioventriculoseptal defect (AVSD), transposition of the great arteries (TGA),
pulmonary atresia (PA), hypoplastic left heart syndrome (HLHS), and univentricular heart disease or variants including multiple lesions.

- **Birth Weight**: Weight at birth is defined as pounds and ounces or kilograms. Birth weight can be categorized into very low (<1500g), moderately low (1500-2499g), and normal birth weight (2500g+) (Nembhard, Salemi, Loscalzo, Wang, & Hauser, 2009).

- **Gestational Age**: Gestational age is defined as the time from conception until birth or the number of weeks from the first day of the mother's last menstrual period (LMP) until the birth (Engle, 2004). Gestational ages are assessed by the date of the LMP and by physical exam using the Dubowitz/Ballard examination score (Engle, 2004). By definition, moderate to late preterm is considered < 37 weeks gestation, very preterm (28 to < 32 week) and extremely preterm (< 28 weeks) (WHO, 2013).

**Time**: The trajectory of time includes the periods of periconception and includes all time up until the birth of the child with CHD.

**Methods**

This study was an exploratory secondary analysis of the maternal biologic, physical, and social contexts and their relationships to gestational age, birth weight and types of CHD in these infants. Using a Life course model (Fine & Kotelchuck, 2010) to guide this research, associations or relationships between the maternal variables and greater risk for complex CHD in their infants were assessed separating CHD into either simple or complex CHD. Descriptive analyses provided correlations and identification of relationships of the maternal context variables to the birth outcomes of the infants. From
these analyses logistic and multiple regression were used to test the hypotheses and answer the research questions posed. Approval was obtained from Children’s Hospital of Wisconsin (CHW) Internal review Board as an exempt study (Appendix E) as consent to participate was previously provided in the original study conducted at CHW and no patient contact was required. All data provided to the investigator were de-identified and maintained or accessed on a secure computer.

As the WPCR was adapted from the BWIS, a modified approach from the BWIS to categorize the simple and complex CHD was utilized. The dependent variable of simple or complex CHD was derived from multiple classification techniques (Calzolari et al., 2003; Hoffman, & Kaplan, 2002; Warnes, et al., 2001; Ferencz et al., 1997) used to categorize severity of CHD in both children and adults. Many struggle to classify CHD as there are countless forms of severity and CHD has a heterogeneous nature. Some forms of CHD may not be symptomatic or identified until later in life causing no health changes, whereas other forms of CHD can be life threatening and cause many health changes throughout one’s life with detrimental effects.

In the WPCR all CHD was diagnosed before 2 years of life by a pediatric cardiologist identifying various severity levels of CHD, some requiring interventions and other CHD spontaneously resolving. Therefore the various severity levels in the WPCR should be well represented over the last 10 years. In the BWIS the researchers categorized etiologic CHD into primary and secondary cardiogenesis defects and from the exposures, demographic information and medical history of the parents identified significant risk factors of CHD. In the BWIS they classified the CHD into six “pure” diagnoses and used severity ratings based upon echo results to assign case severity for
pulmonary stenosis, aortic stenosis, ventricular septal defect, and bicuspid aortic valve using echo. As an adequate control group is not available for use within the WPCR, to replicate the BWIS, and compare normal infants to infants with CHD, the independent variable of CHD was divided into either simple or complex CHD. Other studies have categorized CHD into simple, moderate and complex CHD (Calzolari et al., 2003; Hoffman and Kaplan, 2002; Warnes et al., 2001) to describe the incidence and outcomes of each type of CHD. As many of the simple CHD can go undetected it is difficult to determine precise incidence and possible risk factors.

It was hypothesized that the multiple maternal risk factors of biologic (known genetic causes associated with CHD, age, race, chronic health conditions, family history of CHD), physical (history of obesity, use of alcohol, drugs, cigarettes, medication/vitamin use, and type of water consumed), and social variables (SES, occupation, education level) would influence the risk of simple or complex CHD. A variety of statistical analyses including descriptive statistics, correlations, and regressions were used. For hypothesis 1; a logistic regression analysis was undertaken and for hypothesis 2 a multiple hierarchical was proposed and performed.

It is recognized that the data in the WPCR were collected prior the development of this study and may have limitations but also has several benefits. A significant benefit for using the data within the WPCR database was the large sample size that was collected over a decade. Pre-existing datasets may be useful to address hypotheses and research questions of interest and can provide a practical component to the researcher to advance science (Campbell, 2007). This dataset allowed investigation of the maternal risk factors not previously examined in this database. The WPCR database has been active for well
over a decade providing a robust sample which may not be available to most novice researchers. This sample provided a collection of maternal and infant variables including demographic, socioeconomic, personal health history and environmental exposure history in families affected by CHD. Using a large dataset can also have limitations such as unfamiliarity with the methods of storage, accessibility of the variables in print and electronic forms and knowledge of the maintenance practices (Aponte, 2010). Thus care should be applied in the results of the studies performed. The researcher must be cautious in the implications for inference of causal relationships between these variables in the development of CHD, as specificity and dose response cannot be elicited from the measures used in the WPCR.

A limitation of the registry was lack of a robust control group which precluded the investigation of factors related to CHD. The families in the small control group were systematically different than the families in the CHD sample. First the children in the control group were significantly older than the CHD sample; most of the children were 10 years older than those in the CHD sample. Second the recruitment of the control group was initiated in 2006 well after the original study began in 2000. Recall for questionnaires would be greatly compromised by the time interval as the comparison children were over two years of age. However, the large sample of mothers and their infants with CHD was useful in the investigation of the three outcomes, type of CHD, birth weight and gestational age. The WPCR was appropriate for this secondary analysis because of sample was large, the data were accessible and there was sufficient variability within the data to address the proposed hypothesis (Aponte, 2010).
Although the data were not collected with a specific research question in mind, the WPCR was designed to allow researchers and clinicians access to temporal, environmental, familial, and genetic data to explore relationships of potential causative factors of CHD which is congruent with my specific aim. The researcher must be cognizant of ethical and practical concerns when determining fit of the data to their research questions (Campbell, 2007). High impact questions, such as substance use, comprehensive social and medical histories, and data containing infant or child information may be out of reach of most researchers due to time or financial constraints, but can be probed by secondary analysis that may allow for discovery of problems or concerns within the original research (Smith et al., 2010). Understanding problem areas in the primary research may allow for adjustments of future research targeting a new and more focused research question.

**Study Summary**

There is undeniable evidence that CHD is the most prominent and costly birth defect in the United States. CHD significantly contributes to the infant, child, and adult morbidity and mortality rates and places substantial financial burdens upon the individuals with CHD, medical providers and intuitions, and governmental resources necessary to support treatment and care for this chronic health condition. Emphasis on primary and secondary prevention has been stressed and recommendations are necessary in the education to decrease risk factors for CHD of young child bearing aged individuals both male and female.

A review of literature was performed to gain a greater understanding and identification of the maternal risk factors for all CHD. In this review it was
acknowledged that the literature was separated into the various maternal risk factors and did not provide a comprehensive review for all the maternal context variables measured in this study. Small samples with methodological flaws and inability to accurately measure the variables relationships with greater risk for complex CHD were identified in this process. Only one study was found addressing the risk factors for simple verses complex CHD, a gap this study was designed to address. It was also recognized that the genetic influence toward CHD must be elaborated separately to best appreciate the influence on CHD development.

Nursing is a leader in prevention, education, and care of humans with various diagnoses including complex CHD. Research focusing on maternal context variables and risk for complex forms of CHD may provide knowledge for women of child bearing age to the known environmental risk factors associated with CHD and aid in early detection of complex CHD if exposed. Timing of an intervention is of essence as the fetal heart is formed within the first trimester of pregnancy, most often when the woman is unaware of the pregnancy. Education or knowledge development of young child bearing individuals during the time before conception may be key for avoidance of specific environmental exposures which may enhance the risk of giving birth to a child with complex forms of CHD.

With a greater understanding and appreciation of the mechanisms associated with gene-environment interactions during the processes prior to and during cardiogenesis (the development of the heart in the embryo) researchers and clinicians can facilitate new interventions in practice and research questions. These innovative ideas and practice changes may assist in decreasing the incidence of complex CHD. Decreasing known
environmental exposures and increasing positive health care practices may help reduce the number of children born with all forms of CHD. Data was collected with a goal to provide the ability to test for relationships amongst the genetic, epidemiologic, temporal etiologic sources for CHD development in the infant is discovered. It is anticipated that this study will provide a greater understanding of the maternal contexts associated with complex CHD, birth weight and gestational age in these infants.

**Manuscripts**

This dissertation is composed of an introductory chapter, three manuscripts (Chapters 2, 3, 4) and a chapter discussing the implication of the findings (Chapter 5). A review of literature is provided in chapter two and includes the first manuscript titled “Association of Maternal Risk Factors and Congenital Heart Defects”. This manuscript synthesizes maternal risk factors for giving birth to an infant with CHD, gaps in the literature and implications for clinical care. Chapter three is comprised of the second manuscript titled “Understanding Genetics and Pediatric Cardiac Health”. This manuscript provides a review of known genetic factors on risk of CHD formation in the infant. Future implications for study and practice are provided in this manuscript. Chapter four is the third manuscript titled, “Maternal Health and Infants Born with Congenital Heart Disease: A Secondary analysis of the WPCR”. In this manuscript the methods and results as well as study limitations are presented. Chapter five provides an in-depth discussion of the results including implications for practice and policy.
CHAPTER 2

Chapter Introduction

The purpose of this chapter is to provide a review of the literature related to the maternal context factors associated with CHD. This review was conducted to obtain a general understanding of the maternal risk factors for all CHD. The focus of this chapter will be the maternal environmental risk factors for CHD development in the infant. Using a life course perspective the maternal contexts will be arranged in a biologic, physical and social construct. This chapter is comprised of a systematic review in the format of an article to be submitted for journal submission. The referencing style of this target journal will be applied in this manuscript.

Manuscript 1: Association of Maternal Risk Factors and Congenital Heart Defects: 

State of the Science

Abstract

Aim and objective. Guided by the life course model, this review summarizes the state of the science about the contextual maternal risk factors for giving birth to an infant with congenital heart defect (CHD).

Background. CHD is the most prevalent birth defects worldwide occurring in approximately every 6-8 per 1,000 live births. Only 10-15% of the CHD etiology is known, and are primarily genetic syndromes and disorders. The remaining 85-90% of CHD is thought be influenced by the environment.

Design. Systematic literature review using PRISMA guidelines.

Method. Studies included in this review were identified through a Medline search which included studies published from 2008-2013. The articles (N=39) were analyzed to
identify the contextual maternal risk factors for CHD and were categorized into biologic, physical, and social environments using a life course perspective.

**Results.** Multiple maternal risk factors for CHD development in the infant were identified in the maternal biologic, physical and social environments.

**Discussion.** Women of childbearing age have the ability to optimize their health prior to pregnancy, thus reducing risk for CHD in their infants. Identification and discussion of risk factors is critical in early pre-conceptual and prenatal care.

**Conclusions.** This review highlighted the contextual maternal risk factors for CHD in the pre- and inter-conceptual timeframes. There are many complex genetic and environmental interactions which influence CHD development. Further research is needed to better understand the risk factors for CHD.

**Relevance and clinical practice.** The contextual maternal risk factors for CHD in the pre- and inter-conception timeframes were discussed and described allowing nurses and healthcare professionals the ability to provide education to their families of childbearing age thus reducing risk for having an infant with CHD.

**Key Words:** CHD, maternal risk factors, pre-conception, inter-conception, life course model.

**Introduction**

Congenital heart defects (CHD) are the most prevalent birth defects worldwide occurring in approximately every 6-8 per 1,000 live births (Hoffman & Kaplan, 2002). CHD is one of the leading causes for infant morbidity and mortality, with only 10% to 15% of the CHD etiologies understood. Of all CHD, 5% to 10% can be attributed to a chromosomal abnormality, 3% to 5% are linked to single gene defects, and
approximately 2% are a result of known environmental factors (Clark, 2001). For the remaining 85% to 90% of CHD cases, the etiologies remain unknown.

Although there has been extensive research on genetic risk factors for CHD, there is much less understanding of maternal environmental factors. Past and present research continues to support the gene-environment interaction theory (Nora, 1968), in which both genetic predisposition and environmental factors are responsible for the majority of CHD (Mone et al. 2004, Lin & Ardinger, 2005, Hobbs et al. 2010). Some researchers have focused on specific disease processes such as maternal diabetes (Ferencz et al. 1997, , Lisowski et al. 2010), lifestyle choices such as cigarette smoking (Grewel et al. 2008, Hackshaw et al. 2011), or other exposures such as chemical exposures within the home or workplace (Watson et al. 2006) for increased risk of CHDs. Although there is some evidence there are exposures that are related to CHD development such as rubella, thalidomide, cigarette, drug, and ETOH during early pregnancy (Brent, 2004) the exact mechanism is not well understood.

Some researchers have focused on specific exposures and the development of CHD throughout pregnancy, for examples exposures to maternal illnesses, cigarette, drug, and ETOH (Mone et al. 2004). A greater understanding of the critical time frames prior to and during CHD development have been identified; the pre-conception and inter-conception periods (Liu et al., 2013). Researchers are now appreciating the impact of the pre-conceptual exposures, particularly in the three months before pregnancy and risk for CHD development in the fetus (Jenkins et al. 2007). Several reviews specifically addressed the nongenetic (Patel et al. 2013), non inherited (Jenkins et al. 2007), effects of contaminated drinking water (Bove et al. 2002, Watson et al. 2006), environmental
exposures (Thurlstrup et al. 2006) and environmental pollution (Gorinini et al. 2014) and risks for CHD. These reviews selected specific risk factors not all with a focus on maternal risk factors for CHD therefore the present analysis was conducted to better understand the maternal context risk factors for CHD development. All of the reviews acknowledged that the risk factors of CHD development require further investigation due to several concerns such as small sample sizes, inability to perform exact measurement of exposures, and confounding variables which may have influenced results.

A Life Course Perspective

The life course perspective uses a model that helps explain the processes of health and disease patterns across populations and time (Fine & Kotelchuck, 2010). With the premise that today’s choices affect tomorrow’s health (timeline), there are critical and sensitive periods (timing), that biological, physical, and social contexts (environment) as well as healthcare access (equity) affect the outcomes of health (Fine & Kotelchuck, 2010). These multiple trajectories have complex interactions, which over a lifetime can be influenced in both positive and negative manners changing ones health and health choices. As CHD is believed to be a complex multifactorial process a life course perspective was chosen to illustrate the interactions between the contextual maternal risk factors. The genetic syndromes and chromosomal abnormalities associated CHD were not included in this review.

The maternal context variables have multidimensional relationships across time, which allows for categorizing the various risk factors into these contexts. The biologic maternal contexts are fixed and although genetically inherited, are not defined by a specifically known gene or chromosomal abnormality associated with increased risk of
CHD. These variables are thought to be preprogrammed or difficult to change with lifestyle modifications and/or choices. Physical maternal contexts are categorized by the physical influences or choices of the mothers which increase may the risk of CHD in their infant. The physical contexts are thought to be modifiable physical choices of the mothers such as alcohol or drug use as examples. Social maternal contexts are those contexts influenced both by maternal choice and the sociological influences of the immediate community surrounding these women. The social maternal contexts are usually not easily modified or quickly changed but can assist in identifying at risk populations.

Aim

The purpose of this review was to identify and summarize the current literature on contextual maternal risk factors associated with giving birth to a child with CHD. The life course perspective was used as the organizational framework used to guide this review.

Methods

Using PRISMA guidelines a review of literature was conducted. A search was conducted using three databases, Medline, CINAHL, and ESBCOhost and the MESH key terms; congenital heart defects (CHD), maternal risk factors for CHD, and congenital birth defects. Inclusion criteria were studies published in English after 2007 that provided evaluation of maternal risk factors for CHD. A total of 164 articles were identified – all from Medline database. A flow diagram of the review and inclusion process is provided (see Figure 1). To ensure the search was comprehensive the key words above were combined with the following key terms: smoking, alcohol, substance use, educational
status, occupation, socioeconomic status, and lifestyle which elicited an additional 11 articles after duplicates and articles which were not relevant were excluded. Included in the review were articles obtained from reference lists of studies from the original search or reviews which included seminal research or articles published after 2007. Case control, retrospective and prospective studies, population studies and meta-analyses were included in the final analysis. Two articles published in 2004 were retained for the review as there were limited findings in illicit drugs and water consumption. A total of 39 articles were retained for this review. In Tables 1, 2, and 3 the biologic, physical and social maternal contexts variables are summarized into the categories, author, description of the study and findings, specifically prevalence if provided and odds ratios/risk ratios. Prevalence showing relationships of these variables to risk for CHD development. Studies are presented by topic and alphabetically by first author.

Results

Biologic maternal contexts.

Maternal age. Analyses from several large congenital defect registries within the United States and Canada have identified an increased risk for infant CHD if their mother was > 35-40 years of age (Long et al. 2010, Miller et al. 2011, Liu et al. 2013). The prevalence of CHD in advanced maternal age (>35 years) was found to be about twice the normal prevalence of CHD (6-8/1,000 live births) in these studies. An as association of advanced maternal age (>35 years) and specific types of complex CHD in the infants such as Tetralogy of Fallot, truncus arteriosus, coarctation of the aorta, and transposition of the great vessels were identified in two large population studies in Atlanta and Texas (Long et al. 2010, Miller et al. 2011).
**Maternal race.** Race is based on the premise of physical and biological differences, whereas ethnicity is based upon behavioral and cultural differences of groups with no biological underpinnings. Race is defined as a self-identification data item in which respondents choose the race or races with which they most closely identify (Federal Office of Management and Budget, 2000). It is important to note in some of the studies reviewed race and ethnicity were used interchangeable.

Greater CHD prevalence was found in non-Hispanic White women in three studies (CDC 2010, Mangones et al. 2010, Miller et al., 2010). Although, these studies found greater prevalence in non-Hispanic white (NHW) women overall, Nembhard et al. (2010) reported similar rates of CHD in NHW, non-Hispanic-Black (NHB) women and Hispanic women in their retrospective study using the Florida Birth Defects data. In the CDC’s report (2010) it is important to note, the rates of CHD prevalence was less in NHB women. However, the mortality rates in term infants in this group were higher than the NHW group (1.5 per 10,000 compared to 1.3 per 10,000).

The research reviewed provided evidence of racial/ethnic differences in rates of CHD with predominance in NHW women. These studies reported these populations had higher numbers of white women and less racial diversity which may provide an explanation for their findings. It is also important to recognize the differences in birth outcomes among the groups and higher rates of mortality in the NHB women. Although higher prevalence of CHD is found in NHW women, their birth outcomes are better than NHB, and Hispanic women.

**Maternal chronic health conditions.** Maternal chronic health conditions can encompass a multitude of disease processes and several were associated with increased
risk for CHD development in the fetus. Febrile and viral illnesses were associated with 3.4 to 5 fold increased risk of CHD, particularly right sided obstructive lesions, when the mother has encountered this illness within three months prior pregnancy or within the first trimester in the infants in the Baltimore Washington Infant Study (Oster et al. 2011). Luteijn and Dolk (2013) found 1.5-2.5 fold risk for CHD if the mother had history of influenza within the first trimester of pregnancy. The use of antibiotics and antihypertensives (OR 2.6-3) in the first trimester were associated with increased risk of CHD (Zen et al. 2011).

Maternal diabetes was reported to increase risk of CHD in infants four times that of normal infants (Liu et al. 2013). Persistent truncus arteriosus, transposition of the great vessels, conotruncal abnormalities and single ventricle physiology were particularly likely to occur. These infants were found to have a two to 18 fold increased risk if the mother had poorly controlled gestational diabetes in the first trimester of pregnancy. Co-morbid conditions such as connective tissue disorders (3.01; 95%, 2.23-4.06), hypertension (OR 1.81; 1.61-2.03), and obesity (OR 1.15-1.3) have also been associated with greater risk of CHD in the infant (Lui et al. 2013, Mills et al. 2010, Stochard et al. 2011).

**Family history of CHD.** The risk of having an infant with CHD was found to be 2-4% greater if related to a first degree relative with known CHD (Fesslova et al. 2011, Fung et al. 2013, Hinton et al. 2007). If more than one family member was diagnosed with a CHD, the concordance rate was higher still (55%) in the study of probands (individual affected by a disorder) with HLHS, reporting an almost 4 fold increase of CHD in first degree relatives (Hinton et al. 2007). Swaby et al., (2011) showed similar
findings in their study of increased heritability of varying forms of CHD in relatives of adults with known 22q11.2 deletion syndrome (OR 4.43-5.88). With the greatest risk (RR 2.68-48.6) found for heritable CHD in first relatives for variable forms was found in a large Danish cohort study (Øyen et al. 2009).

**Physical maternal contexts.**

**Maternal obesity.** Obesity is a chronic condition of great public health concern in all ages. However, in pregnancy obesity has been associated with poor birth outcomes and greater risk for congenital birth defects including CHD (Arias & Brown, 2010, Hobbs et al. 2010, Mills et al. 2010, Stothard et al. 2011, Baardman, et al. 2012). Maternal obesity is a factor found to have a small to moderate risk (OR 1.1-1.43) for CHD development in the infant (Arias & Brown, 2010, Hobbs et al. 2010, Mills et al. 2010, Stothard et al. 2011, Baardman, et al. 2012). Some investigators found an associated increased risk for CHD development with obesity and smoking status (Hobbs et al. 2010, Baardman et al. 2012), which may demonstrate a change in the genetic pathways of the mother when altered by smoking status. Although obesity is a growing epidemic across the United States in all ages, data demonstrate obese women have greater complications during pregnancy than do normal weight women (Mills et al. 2010, Stothard et al. 2011).

**Maternal substance use.** Maternal history of alcohol use was identified in four studies as a modest risk for CHD development in the infant (OR 1.1-2.4). These studies found higher rates of conotruncal (disorders of the outflow tract) CHDs (OR 1.3-1.9) (Grewel et al., 2008, Strandberg-Larsen et al. 2010, Zen et al. 2011). Strandberg-Larens et al.’s (2010) Danish study did not find an associated increased risk for CHD with low to
moderate alcohol consumption. No significant risk for CHD was reported when binge drinking was present. However, Mateja et al. reported that binge drinking in the United States was associated with a two fold increase of CHD development. And when binge drinking and smoking was present in the three months prior pregnancy the risk for CHD development was significant (aOR 9.45 and 12.65).

Illicit drug use is a public health concern affecting all ages. Approximately 4% of pregnant women in the United States use illicit drugs (Substance Abuse and Mental Health Administration, 2007). Williams et al. (2004) found a twofold increased risk for VSD when the mother had history of marijuana use.

Maternal tobacco use is associated with low birth weight, prematurity, risk for stillbirth, and risk for congenital malformations (Malik et al. 2008). Six studies were found in which a modest association with increased risk for CHD in the infant when maternal smoking was present (OR 1.5-2.1) (Malik et al. 2008, Hobbs et al. 2010, Alverson et al. 2011, Patel et al. 2012, Lee & Lupo, 2013).

**Maternal medication/vitamin use.** Folic acid has been recommended to decrease risk of neural tube defects and has been shown to decrease the risk of CHD by 18% -38%, particularly VSDs in a large European study (Van Beynum et al. 2010). However, vitamin E was found to increase the risk of CHD when supplemented and consumed at high levels in the mothers diet (Smedts et al. 2009). Prescription medications are complicated to prescribe and to know if it is safe to use during pregnancy as there are limited studies and ability to test safely in humans. Alwan et al. (2010) found an increased risk for left ventricular outflow tract CHD when there was maternal history of bupropion use in the first trimester of pregnancy. And the use of antibiotics and
antihypertensive medications during the first trimester was associated with a 2.6-3 fold increased risk for CHD formation in the fetus in Brazil (Zen et al. 2011).

**Maternal drinking water.** Trichoroethylene (TCE) is a metal degreasing agent, previously used as an anesthetic, and a common persistent drinking water contaminant known to be a selective cardiac teratogen (Yauck et al. 2004). In a large case control study in Milwaukee, Wisconsin a 6 fold increased risk in older women (≥ 38 years) was found when exposed to TCE (Yauck et al. 2004). Whereas in Lithuania exposure to trihalomethane (THM) a water disinfection agent, was found to have a 1.7 fold increased risk for CHD if exposed to bromodichlormethane (BDCM) a common TMH, in the first trimester of pregnancy (Grazuleviciene et al. 2013).

**Social maternal contexts.**

**Maternal SES.** In a large population based study in the United States, low maternal income levels were associated with poorer birth outcomes, lower birth weight, prematurity or morbidity and a modest increased risk for CHD (Malik et al. 2007). Carmichael et al.’s (2009) case control study in California found no increased risk for CHD in lower income and educational level of the parents. In Lithuania, a lower education and lower status occupations was associated with a modest increased risk (OR 1.48-3.43) for CHD in the infant (Kučienė and Dulskienė, 2009).

**Maternal occupation.** Occupational exposure to chemicals, air pollution, and hazardous situations can affect the woman and unborn child’s health as has been associated with increased risk for CHD (Lin et al. 2012). Three European teams in Italy (Cresci et al. 2013), Netherlands (Snijder et al. 2012), and Russia (Vaktskjold et al. 2011) all found a moderate increased risk for CHD development in occupational exposure to
solvents (OR 1.2-2.6). Maternal exposure within the first trimester or one month prior to pregnancy to any solvents and chlorinated solvents were found to increase risk of VSD, aortic valve disorders, D-TGA, right ventricular outflow tract (RVOTO) disorders, and pulmonary stenosis (Gilboa et al. 2012). In the National Birth Defects Prevention Study (Lin et al., 2012), nurses, janitors, scientists and engineers were found to have a moderately higher risk for conotruncal CHD (OR 1.35-3.48).

**Maternal education.** Educational attainment has been associated with choice of life partner, smoking and drinking practices, and employment and has been shown to affect birth outcomes. The educational level of the mother was not significantly related to increased risk of CHD in two large population studies in the United States (Carmichael et al. 2009, Malik et al. 2009). However, a moderate risk for CHD was found in low to moderate levels of maternal education in Kučienė and Dulskienė’s (2009) study in epidemiologic study in Kaunas Lithuania (OR 3.43, 95%, CI 1.54-7.64).

**Discussion**

Through this review, the biologic, physical and social maternal risk factors for CHD were identified and presented to provide a comprehensive maternal review of risk for CHD development. Several maternal risk factors for CHD (advanced age, CHC, FH of CHD and alcohol use) were identified. However, respective of the research, often it revealed conflicting results and/or weak associations to CHD development (race, obesity, smoking, medications, water, SES, occupation, education) were present, similar to past reviews. Only one study was identified in this review regarding substance use (Williams et al. 2004).
CHD is a multifactorial process with multiple sources for alteration of fetal development. Timing and sensitive periods in cardiac development can vary. The critical time frames for CHD development were identified as pre- and inter-conception. It was also recognized that there are multiple exposures and other risk factors which can be difficult to pinpoint direct causative factors for CHD development. This review identified binge drinking in the pre-conception timeframe increased the risk 12 fold for CHD development (Mateja et al. 2012). Although current medical technology has allowed many infants, children, and adults to survive and live productive lives in society today, identification and elimination of risk factors for CHD development is critical to reduce the number of infants being born with this life threatening and life altering disease.

**Validity and Limitations of the Review**

A review of the literature describing risk, incidence and prevalence of CHD throughout the world identified several maternal risk factors for CHD. However, many of the maternal context variables were not measured or defined sufficiently to determine if there is a significant risk for giving birth to an infant with CHD. Most studies in this review were case control, retrospective studies reviewing large amounts of registry data some of which reported prevalence of CHD by types. Historical recollection and reporting of exposure or use of a substance or situation was a concern for many of the reviewed studies. Better surveillance practices during these critical times for exposures may help identify and better isolate exposures. Another major concern of the current research reviewed is the ability to obtain precise measurements of dose exposures, for example occupational hazards, contaminated water and environmental influences. It was
difficult to ensure accuracy of the data collected from the mothers, as recall bias and reporting errors were acknowledged. It is acknowledged by most researchers that the confounding variables affect many of the study variables and cannot provide conclusive causal evidence linking a specific variable to CHD. However, it is important to respect the relationships supported and identified in these research studies to guide future research in these areas. Inspection of the findings from many of the studies showed increased risks of CHD with various exposures or demographic variables in comparison to the general populations.

Most investigators encouraged further research to better isolate and identify significant relationships among variables, targeting modifiable life choices, or primary prevention techniques to decrease risk of CHD in the infant. These investigators recognized the complex interactions and inability to easily separate between variables and identify significant risk factors. It is likely impossible to isolate each maternal variable and determine cause for CHD, but studies exploring the pre- and inter-conceptual timeframes and maternal exposures may provide evidence for increased risk that can be intervened upon. As the life course perspective describes health, it is important to appreciate the multiple trajectories in one’s life; today’s choices affect tomorrow’s health.

**Relevance to Clinical Care**

Nurses are at the frontline of patient care delivery. Greater understanding of maternal risk factors for CHD development is key to reduce the most prevalent birth defect worldwide. By understanding the complex nature of CHD, and the risk factors associated, nurses can begin to identify women at risk prior to pregnancy. A thorough
knowledge of the maternal risk factors, for example the modifiable lifestyle choices, such as drug, alcohol, tobacco, and maintenance of weight, can be indentified and discussed with adolescent girls and women of child bearing age decreasing their risk of CHD in future pregnancies. These at risk women may benefit from close monitoring, fetal echocardiographic screening or genetic counseling prompted by their HCPs. Early morbidity and mortality can be prevented and decreased in infants with CHD if early identification and treatment is provided (Botto & Correa, 2003; Masmoudi & Massin, 2008). Women with fetuses found to have CHD can benefit from prenatal counseling of the options for giving birth at institutions equipped for the infant with CHD, surgical interventions or palliative procedures specific to the type of CHD or preparation for end of life considerations for the infant born with complex CHD.

Nurses can discuss in depth the known risk factors for CHD with women who have chronic conditions and necessary management of the condition. For example, early identification and screening of diabetes in pregnancy would allow for close monitoring and tight control of blood sugars of diabetic mothers, thus decreasing their risk of CHD in the developing infant. In the pre-conception time frames, medication review and clarification of safety of medication should be discussed for risk of CHD to allow for changes in care management if a pregnancy is being considered.

Central to women’s health is screening for drug, alcohol, and tobacco use from early adolescence through childbearing years and discussing the risks associated for birth defects, particularly CHD. Prevention programs are needed to address these risk factors throughout the community to have a positive impact on families planning a pregnancy. Nurses can provide education of the considerable risk of CHD associated with binge
drinking in the pre-conceptual timeframes. Because almost half of pregnancies in the US are unplanned, women's health care providers need to aggressively address these issues in all well-women’s care. Pregnancies occurring when women are in optimal health may help ameliorate these conditions. Early prenatal care in primary care settings is also crucial to identify the at risk women to provide the necessary interventions if CHD is identified. These initiatives can be used by multiple health care providers addressing health of the family in pediatric and community settings.

**Conclusion**

Through this review of maternal biologic, physical and social contexts associated with risk of CHD, identification of the associated risk factors for CHD was clarified. There were studies in which types of CHD and associated risk factors in comparison the general public were discussed. But, no studies other than the BWIS identified risk between types of CHD. Although there was conflicting results among some of the contextual variables (race, obesity, smoking, medications, water, SES, occupation, education) the risk for CHD was identified. Development of future research in these areas is necessary to not only identify potential etiological sources, but to identify families at greater risk for having a child with CHD. Nurses and healthcare providers require an understanding of the processes and mechanisms associated with CHD to decrease risk of CHD development. Although the etiology of CHD remains a mystery, scientists, nurses, and researchers continue to study potential causes appreciating and respecting the multifactorial nature of this disease.

An in depth history of biologic, physical, and social exposures of women of child bearing age should be performed to assist in identification for risk of CHD. Prompt
identification of the mother and fetus with CHD allows time for decisions, treatment, and planning to avoid adverse outcomes. Research in the environment exposures experienced among child bearing adults may provide evidence for the identification of risk factors for CHD, allowing for genetic counseling and targeting of resources for the affected individuals to maximize growth and development of the infant born. There are multiple known maternal risk factors for CHD development in the inter- and pre-conception periods in a woman’s life which requires greater study. Researchers agreed further investigation is necessary to gain understanding of the etiological sources of CHD.
References


Brent, R. L. (2004). Environmental causes of human congenital malformations: The Pediatrician’s role in dealing with these complex clinical problems caused by a


Mateja, W., Nelson, D., Kroelinger, C., Ruzek, S., & Segal, J. (2012). The association between maternal alcohol use and smoking in early pregnancy and congenital
cardiac defects. *Journal of Women’s Health, 21*(1), 26-34. doi: 10.1089/jwh.2010.2582


risk for an offspring with an isolated congenital heart defect and in particular a ventricular septal defect or an atrial septal defect. *Birth Defects Research. Part A, Clinical and Molecular Teratology*, 91, 616-622. doi:10.1002/bdra.20818;
10.1002/bdra.20818


Figure 1.

*Literature Search Process for Maternal Risk for CHD*

- Records identified in Medline database searching key words: maternal risk factors and congenital heart defects (n=164)
- Additional records identified through other sources, key words, environment, education, substance use, lifestyle choices (n=11)

Records after duplicates removed (n=167)

- Records screened (n=167)
- Records excluded: No abstract, title, publication type and relevance ruled out (n=67)

- Full-text articles assessed for eligibility (n=67)
- Full-text articles excluded, time frame for exposures not relevant, exposure not well described (n=28)

Studies included in systematic review (n=19)
### Maternal context

<table>
<thead>
<tr>
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<th>Findings: Prevalence, adjusted prevalence ratio</th>
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<td><strong>Age</strong></td>
<td>Liu et al. 2013</td>
<td>Population based cohort study (n=2,278,838 maternal infant pairs, 26,488 infants with CHD) in Canada from 2002-2010. Several chronic maternal medical conditions, including: diabetes, hypertension, connective tissue disorders, and congenital heart disease, showed an increased risk of CHD in the offspring.</td>
<td>Risk factors: Maternal age ≥ 40 yrs, aOR 1.48; 95% CI, 1.39-1.58, multi-fetal pregnancy aOR 4.53; CI, 4.28-4.80, diabetes mellitus type 1: aOR, 4.65; CI,4.13-5.24; type 2: aOR 4.12; CI, 3.69-4.60, hypertension aOR 1.81; CI, 1.61-2.03, thyroid disorders aOR, 1.45; CI, 1.26-1.67, CHD aOR 9.92; CI, 8.36-11.8, systemic connective tissue disorders aOR 3.01; CI, 2.23-4.06, and epilepsy and mood disorders aOR 1.41; CI, 1.16-1.7.)</td>
</tr>
<tr>
<td></td>
<td>Long et al. 2010</td>
<td>Large population birth defect registry- Texas 1999-2004 2,208,758 births, prevalence rates TA-0.76, dTGA-2.98, TOF-3.40/ 10,000 births. Advanced maternal age &gt;35 years showed a linear increase to risk of giving birth to a child with non-syndromic TOF, TA, d-TGA.</td>
<td>Unadjusted prevalence ratios maternal age &gt; 35 yrs: TA 2.03, 95% CI, 0.80-5.14, dTGA- 2.37, CI 0.82-1.56, TOF-1.45, CI 1.10-1.91.</td>
</tr>
<tr>
<td></td>
<td>Miller et al. 2011</td>
<td>Large population birth defects registry-Metropolitan Atlanta Congenital Defects Program (MACDP) case control 5,289/1,301,143. Possible association with advanced maternal age &gt; 35 yrs, with specific CHD phenotypes.</td>
<td>Mother 35 ≥ years of age: laterality CHD aPR=2.03, 95% CI, 1.01-4.10, conotruncal CHD aPR=1.30, CI, 1.03-2.03, VSDs aPR=1.20, CI, 1.06-1.336, ASDs aPR=1.36, CI, 1.05-1.77, DTGA aPR=1.65, CI, 1.10-2.48, COA aPR=1.54, CI.10-2.16.</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td>CDC, MMWR, 2010</td>
<td>Report: Infant birth/death data in US 2003-2006, neonatal mortality attributable to CHD was 30% lower in black mothers than white mothers. In term infants, black mothers had a 20% higher neonatal mortality rate attributed from CHD to those of white mothers.</td>
<td>Preterm infants (&lt; 37 weeks) with CHD of black mothers 4.2/10,000 compare to white mothers 6.8/10,000, Rate ratio (RR= 0.7**). Term infants with CHD of black mothers 1.5/10,000 compared to white mothers 1.3/10,000 (RR= 1.2*).</td>
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<td></td>
<td>Mangones et al. 2010</td>
<td>Population study from NYS Dept of Health Vital statistics, congenital malformations registry1992-2001, (n=2,303/235,230- 13/1000 live births. Highest prevalence among NHW followed by NHB, then Others.</td>
<td>NHW 14.4/1000 live births, NHB 12.8/1000 (Rate ratio=RR 0.89, 95%, CI, 0.80-0.99), then others 12.5/1000 (RR 0.58, CI, 050-0.69), NHB 8.8/100 (RR 0.61, CI, 0.54-0.68).</td>
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<td>Miller et al. 2011</td>
<td>Large population birth defects registry-Metropolitan Atlanta Congenital Defects Program (MACDP) case control 5,289/1,301,143. Greater prevalence in white mothers vs. non-white mothers for CHD.</td>
<td>White mothers (n=3,259) aPR=42.4/CI, 41-43.9 Non-white mother (n=2,016) aPR=38.1(RR 38.1, CI, 36.5-39.8)</td>
</tr>
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</table>

**Note:** TA, truncus arteriosus, dTGA, d-transposition of the great arteries, TOF, Tetralogy of Fallot, NHW, non-Hispanic White, NHB, non-Hispanic Black
### Table 1 (Continued)

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<td><strong>Race</strong></td>
<td>Nembhard et al. 2010</td>
<td>Retrospective cohort using data from the Florida Birth Defects Registry-1998-2003, ( n=9,352/1,216,142 ). Prevalence for specific and all CHD among non-Hispanic (NH)-white, NH-black and Hispanic infants was similar.</td>
<td>CHD prevalence per 10,000 live births- Hispanic-80.09/10,000; NH-white 79.11/10,000; NH-black 77.67/10,000.</td>
</tr>
<tr>
<td><strong>Chronic health conditions</strong></td>
<td>Lisowski, et al. 2010</td>
<td>Multicenter retrospective clinical study, literature review and meta analysis comparing the study population and in the literature of the offspring of type 1 DM mothers. Study showed an increased likelihood of specific heart anomalies, transposition of the great arteries (TGA), persistent truncus arteriosus (PTA), visceral heterotaxia and single ventricle (SV), among offspring of diabetic mothers particularly in the first trimester. This study was in accordance with the distribution in the literature.</td>
<td>TGA OR 2.85, 95%, CI, 1.92-4.23, PTA OR 4.72, CI 2.21-10.08, SV OR 18.24, CI, 7.13-46.63. Visceral heterotaxia OR 6.22, CI, 2.17-17.86.</td>
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<td>Liu et al. 2013</td>
<td>Population based cohort study (( n=2,278,838 ) maternal infant pairs, 26,488 infants with CHD) in Canada from 2002-2010. Several chronic maternal medical conditions, including: diabetes, hypertension, connective tissue disorders, and congenital heart disease, showed an increased risk of CHD in the offspring.</td>
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<td>Luteijn et al. 2010</td>
<td>Meta-analysis of influenza and congenital anomalies. Including neural tube defects, hydrocephaly, CHD, cleft lip, digestive system and limb reduction defects. First trimester maternal influenza exposure was associated with increased risk of CHD.</td>
<td>aOR 1.56; 95%, CI, 1.13-2.14, aortic valve disorder aOR 2.59, CI, 1.21-5.54, VSD aOR 1.59 CI, 1.24-2.14.</td>
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<td></td>
<td>Oster et al. 2011</td>
<td>Case-control study using data from BWIS, cases ( n= 2,361 ) controls 3,435. Greater risk for CHD infants when mother had history of fever pre-and during 1st 3 months of pregnancy.</td>
<td>Infants born with CHD -Fever: OR, 2.04; 95% CI, 1.27-3.27; influenza: OR 1.75; CI, 1.16-2.62.</td>
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<td>Zen et al. 2011</td>
<td>Prospective case-control study in Brazil- 302/303 controls. Risk factors for CHD included, maternal antibiotic use, ETOH use, anti-hypertensive med use in the 1st trimester</td>
<td>Use in 1st trimester of anti-hypertensive OR 2.62; 95% CI, 1.00–6.87, Antibiotic OR 3.17, CI 1.55-6.49.</td>
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<td>Maternal context</td>
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<td><strong>Family history of CHD</strong></td>
<td>Fesslova et al. 2011</td>
<td>Prospective study with 1634 pregnant women with FH of CHD 1,477 cases with single FH, 157 with multiple FH. 157 women were rescanned for multiple pregnancies. Increased recurrence risk for CHD 3.98% when positive FH of CHD.</td>
<td>Risk for CHD in offspring with 1 or more FH of CHD, 1 CHD- 4.06%, 2 CHD- 2.9%, multiple CHD 5% recurrence rates.</td>
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<td>Fung et al. 2013.</td>
<td>Prospective case control study in Canada 2008-20111 ( (n=2339 ) cases/199 controls). Family history, frequency of extra-cardiac anomalies (ECAs), and antenatal risk factors were assessed using questionnaires and genetic testing.</td>
<td>Family history of CHD and frequency of major extra cardiac anomalies was higher in cases versus controls. Left heart lesions OR 2.8, 95%, CI 1.5-5.1, PDA OR 2.3, CI, 1.1-4.5, right heart lesions OR 2.1, CI, 1.1-3.9, septal defects OR 2.1, CI, 1.1-3.9. Only 9.5% of cases with CHD had a confirmed genetic diagnosis. Later year of birth, family history of CHD, presence of major ECAs, maternal smoking during pregnancy, and maternal medication exposure were associated with increased odds of CHD.</td>
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<td>Øyen et al. 2009</td>
<td>National cohort study, Danish residents, 1,763,591/18,708 1977-2005. Specific CHD showed variable but strong familiar clustering in 1st degree relative ranging from 3-80 fold increased prevalence of CHD compared to the general population.</td>
<td>Among first-degree relatives, recurrence risk ratio 79.1 (95% CI; 32.9-190), heterotaxia, 11.7 ( CI, 8.0 - 17.0), conotruncal defects, 24.3 (CI,12.2 - 48.7), atrioventricular septal defect, 12.9 (CI, 7.48-22.2) for left ventricular outflow tract obstruction, 48.6 (CI, 27.5-85.6) for right ventricular outflow tract obstruction, 7.1 (CI, 4.5-11.1) for isolated atrial septal defect, and 3.4 ( CI, 2.2-5.3) for isolated ventricular septal defect. The overall recurrence risk ratio for the same defect was 8.15 (CI, 6.95-9.55), 2.68 (CI, 2.43-2.97) for different heart defects</td>
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<td>Swaby et al. 2011</td>
<td>Convenience sample of 104 probands with 22q11.2 deletion syndrome were compared to the general population prevalence of CHD in their 1st-3rd degree relatives. 4-5 fold increased risk for varying forms of CHD in these family members.</td>
<td>15 (0.9%) of 1,663 relatives had CHD, increase prevalence compare to general population, (OR 4.43, 95%, 1.03-40). Relatives with severe CHD had significantly higher prevalence compared to the general population (OR 5.88, CI 2.16-12.85).</td>
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| Maternal context | Article | Description | Findings: Prevalence, adjusted prevalence ratio Odds ratio, risk ratio (values are significant, $p <0.05$, $p < 0.001$**)

**CHD** | **All CHD:** In obese (BMI >30) women aOR 1.43(95%, CI, 1.05-1.95), conotruncal CHD, aOR 1.88(CI, 1.09-3.24).

**Adjusted OR 2.65 (95% CI, 1.20 to 5.87) for all CHD.**

**Obese BMI ≥ 30, OR 1.15 (95%, CI 1.07-1.23). Morbidly obese ≥ 40 OR 1.33 (CI 1.15-1.54).**

| Obesity | Arias & Brown, 2010. | Case-control study in Rhode Island 2007-2009, N=995 cases, N=2344 controls. Pre-pregnancy obesity was associated with increased risk of giving birth to an infant with CHD, specifically conotruncal abnormalities. | All CHD: In obese (BMI >30) women aOR 1.43(95%, CI, 1.05-1.95), conotruncal CHD, aOR 1.88(CI, 1.09-3.24).

**Adjusted OR 2.65 (95% CI, 1.20 to 5.87) for all CHD.**

**Obese BMI ≥ 30, OR 1.15 (95%, CI 1.07-1.23). Morbidly obese ≥ 40 OR 1.33 (CI 1.15-1.54).**

| Baardman et al. 2012 | Case-control study in the Northern Netherlands, n= 658 cases/322 controls. Smoking or high BMI alone, the risk for CHA in the offspring of women with high BMI (≥25 kg/m(2)) who also smoked was significantly increased. | Adjusted OR 2.65 (95% CI, 1.20 to 5.87) for all CHD. | Obesity (carriers of 2 copies *MTHFR 677 TT*) 4.62 time (95% CI, 1.54, 13.83) > risk for CHD, Smoked (G allele in TCII polymorphism) 1.81(CI, 1.06, 3.11) > risk for CHD, ETOH (GC or GG genotype in TCII polymorphism) OR 1.71 (CI, 1.00- 2.92).

**Obese BMI ≥ 30, OR 1.15 (95%, CI 1.07-1.23). Morbidly obese ≥ 40 OR 1.33 (CI 1.15-1.54).**

| Mills et al. 2010 | Population based nested case-control study. N= 7392 cases, 56,304 control. Obese but not overweight women had increased risk of bearing children with CHD. | All CHD: In obese (BMI >30) women aOR 1.43(95%, CI, 1.05-1.95), conotruncal CHD, aOR 1.88(CI, 1.09-3.24).

**Adjusted OR 2.65 (95% CI, 1.20 to 5.87) for all CHD.**

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| Hobbs et al. 2010 | Population case-control study 575/363 cases of mothers in Arkansas 1998-2007. Maternal obesity, smoking and ETOH use can increase risk of CHD if mother has functional SNPs in genes that encode folate-dependent pathways. | Obesity (carriers of 2 copies *MTHFR 677 TT*) 4.62 time (95% CI, 1.54, 13.83) > risk for CHD, Smoked (G allele in TCII polymorphism) 1.81(CI, 1.06, 3.11) > risk for CHD, ETOH (GC or GG genotype in TCII polymorphism) OR 1.71 (CI, 1.00- 2.92).

**Obese BMI ≥ 30, OR 1.15 (95%, CI 1.07-1.23). Morbidly obese ≥ 40 OR 1.33 (CI 1.15-1.54).**

| Stothard et al. 2011 | Meta-analysis (18 articles). Obesity was found to be a small risk factor for structural anomalies including CHDs. | BMI > 30 = obese, OR 1.30 (95%, CI 1.12-1.51) BMI 25-29 overweight OR 1.17 (CI 1.03-1.34). | BMI > 30 = obese, OR 1.30 (95%, CI, 1.12-1.51) BMI 25-29 overweight OR 1.17 (CI 1.03-1.34).**

**Obese BMI ≥ 30, OR 1.15 (95%, CI 1.07-1.23). Morbidly obese ≥ 40 OR 1.33 (CI 1.15-1.54).**

| Waller et al. 2007 | Ongoing multisite case control study in the US, 1997-2002. Overweight= BMI 25-30 171 cases/858 controls. Obese ≥ 30 137 cases/572. Modest risk for all CHDs in overweight and obese women. | Overweight aOR 1.8 (CI 1.43-2.26). Obese aOR 1.5 (CI, 1.22-1.85) | Overweight aOR 1.8 (CI 1.43-2.26). Obese aOR 1.5 (CI, 1.22-1.85).

| Alcohol | Grewal et al. 2008 | Population based case control study of California births 1999-2003. Maternal intake of ETOH less 1 day per week was associated with dTGA. | DTGA: 76 cases, 425 controls OR 1.9(95%, CI 1.1-3.2).

**Binge drinking > 1x in the 3 months before pregnancy aOR 2.99, (95% CI, 1.19-7.51). Any binge drinking or more once 3 month prior pregnancy and smoking aOR 12.65 (CI, 3.54-45.25) and aOR 9.45, (CI, 2.53-35.31).**

| Mateja et al. 2012 | Case control study extracted from the Pregnancy Risk Assessment Monitory Survey (PRAMS) linked to birth certificate data from 9 states over 10 years (1996-2005). Significant increase in CHDs among mothers who reported binge drinking > 1x in the 3 months prior to pregnancy. Significant interaction between any binge drinking or binge drinking > 1x and cigarette use. | DTGA: 76 cases, 425 controls OR 1.9(95%, CI 1.1-3.2).

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<td>Alcohol</td>
<td>Strandberg-Larsen et al. 2010</td>
<td>Cohort study using the data in the Danish National Birth Cohort 1996-2002. 477 infants with CHD, N=80,346 infant/mother pairs. No statistically significant risk was found for CHD (ASD/VSD) in the infants in women who consumed low-moderate (0-3 drinks/week) ETOH and infrequent binge drinking did not have a significant risk for isolated CHD (ASD or VSD).</td>
<td>VSD, 1/2-1 drink/wk, aPR=1.22 (95%, CI, 0.90-1.66), 2 drink/wk, aPR=1.38 (CI, 0.83-2.28), 3+ drinks/wk, aPR=1.10 (CI, 0.54-2.23). Test trend was 0.29.</td>
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<td>Zen et al. 2011</td>
<td>Case control study in Brazil- 302/303 controls. Risk factors for CHD included, maternal illness-fever, UTI, ETOH use, antihypertensive med use,</td>
<td>UTI-  p&lt;0.001, Infection- p&lt;0.001, Antihypertensive med use-  p=0.011, antibiotic use p&lt;0.001, ETOH use in 1st trimester p=0.066</td>
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<tr>
<td>Illicit drugs</td>
<td>Williams et al. 2004</td>
<td>Atlanta Birth Defects Case control study found a 2 fold increase risk of VSD with maternal self-reported marijuana use.</td>
<td>RR for CHD; Marijuana- VSD 1.9; Ebsteins 2.4.</td>
</tr>
<tr>
<td>Smoking</td>
<td>Alverson et al. 2011</td>
<td>BWIS case controlled large study. Statistically significant associations for CHD and maternal smoking in the 1st trimester. n=2525 case, 3435 control infants.</td>
<td>ASDs OR 1.36 (95%, CI, 1.04-1.78), RVOT OR 1.32 (CI, 1.06-1.65), PVS OR 1.5 ( CI, 1.05-1.74), TA OR 1.90 (CI, 1.04-3.45), LTGA OR 1.79 (CI, 1.04-3.10)</td>
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<td></td>
<td>Hobbs et al. 2010</td>
<td>Population case-control study 575/363 cases of mothers in Arkansas 1998-2007. Maternal obesity, smoking and ETOH use can increase risk of CHD if mother has functional SNPs in genes that encode folate-dependent pathways.</td>
<td>Obesity (carriers of 2 copies MTHFR 677 TT) 4.62 time (95% CI, 1.54, 13.83) &gt; risk for CHD, Smoked (G allele in TCII polymorphism) 1.81(CI, 1.06, 3.11) &gt; risk for CHD, ETOH GC or GG genotype in TCII polymorphism 1.71 (CI, 1.00, 2.92).</td>
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<td></td>
<td>Lee &amp; Lupo, 2013</td>
<td>Systematic review and meta analysis. The authors observed a positive association between maternal smoking during pregnancy and the risk of CHDs as a group. Women who smoked during pregnancy were more likely to have a child with 12 (71 %) of 17 CHD subtypes analyzed compared with women who did not smoke. Highest risk was for septal defects,</td>
<td>Smokers (RR, 1.11; 95 %, CI, 1.02-1.21. n = 18,282). Smokers and risk for septal defects RR, 1.44 (CI, 1.16-1.79). n = 2977.</td>
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<td></td>
<td>Malik et al.2008</td>
<td>Population based case control n= 3,067 non syndromic CHD. Found an association with right sided obstructive CHD and maternal smoking.</td>
<td>OR 2.1 (95%, CI, 1.2-3.5)</td>
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<td></td>
<td>Patel et al. 2012</td>
<td>Multi site large population study 1997-2005, US. Case control study, n=187 cases/6703 controls, he association was strongest in mothers who smoked &gt;25 cigarettes/day. Mothers with periconceptional passive smoke exposure were more likely to have infants with AVSDs than unexposed mothers, independent of maternal age, active periconceptional smoking, infant gestational age, and family history of CHDs</td>
<td>Smoker (aOR 1.5, 95% CI, 1.1-2.4), Passive smoke exposure (aOR 1.4, CI, 1.0-2.0).</td>
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<tr>
<td>Maternal context</td>
<td>Article</td>
<td>Description</td>
<td>Findings: Prevalence, adjusted prevalence ratio Odds ratio, risk ratio (values are significant, ( p &lt; 0.05 ), ( p &lt; 0.001 ))</td>
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<td>Medication, vitamin use</td>
<td>Kučienė &amp; Dulskienė, 2009</td>
<td>Epidemiologic case control study in Kaunas 1999-2005, 187 cases/643 controls. Low and moderate maternal education significantly increased the risk of CHDs. Housewives and workers had a higher risk of delivering a newborn with CHDs than the office workers. Maternal smoking during pregnancy tended to increase the risk of CHDs by 48%.</td>
<td>Low-moderate maternal education level OR=3.43; 95% CI, 1.54-7.64 OR=1.56; CI, 1.00-2.45. Housewives, workers higher risk OR=2.34; CI, 1.34-4.10 and office workers OR=1.28; CI, 0.79-2.07. Maternal smoking OR=1.48; CI, 0.82-2.67.</td>
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<td></td>
<td>Alwan et al. 2010</td>
<td>Retrospective case control study of birth defects and risk factors. ( n=6853 ) infants with CHD, ( n=5869 ) controls born in 1997-2004 in the US. Positive association between early pregnancy bupropion use and left outflow tract heart defects.</td>
<td>Any CHD and folic acid supplementation OR=0.82 (95%, CI, 0.68-0.997), septal defects, OR 0.62 (CI, 0.47-0.82)</td>
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<td></td>
<td>Van Beynum et al. 2010</td>
<td>Large regional registry (EUROCAT-Northern Netherlands), 1996-2005, case-control study. ( n=611 ) cases/2401 controls. Mothers who used periconceptual folic acid had an 18% reduced risk of delivering an infant with any CHD; a 38% reduced risk for VSD.</td>
<td>Dietary vitamin E intake, OR 13.3 (CI 95%, 8.1-20.4) and OR 12.6 (8.5-19.8) mg/day. Supplemental vitamin E intakes, Odds ratios at the highest quartiles of vitamin E intake were OR 9.1, (CI 2.0-41.4) and OR 4.8, (CI 1.1-20.2).</td>
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<td></td>
<td>Smedts et al. 2009</td>
<td>Case control study. Food frequency questionnaires were administered. 276 cases/324 controls in the Netherlands. Dietary vitamin E intake was higher in case mothers than in controls. CHD risk increased with rising dietary vitamin E intake. Periconception use of vitamin E supplements plus a high dietary vitamin E intake above 14.9 mg/day had a up to nine-fold increased CHD risk. Retinol intakes were not significantly different between the groups and not associated with CHD risk.</td>
<td>Dietary vitamin E intake, OR 13.3 (CI 95%, 8.1-20.4) and OR 12.6 (8.5-19.8) mg/day. Supplemental vitamin E intakes, Odds ratios at the highest quartiles of vitamin E intake were OR 9.1, (CI 2.0-41.4) and OR 4.8, (CI 1.1-20.2).</td>
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<td></td>
<td>Zen et al. 2011</td>
<td>Case-control study in Brazil- 302/303 controls. Risk factors for CHD included, maternal illness-fever, UTI, ETOH use, antihypertensive med use,</td>
<td>UTI- ( p&lt;0.001 ), Infection- ( p&lt;0.001 ), Antihypertensive med use- ( p=0.011 ), antibiotic use ( p&lt;0.001 ), ETOH use in 1st trimester ( p=0.066 )</td>
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<td>Water</td>
<td>Grazuleviciene et al. 2013</td>
<td>Prospective cohort study 2007-2009 in Kaunas Lithuania. Cases ( n=57 ) CHD, musculoskeletal ( n=37 ), urogenital ( n=23 ), 3,074 women participated in questionnaire. A dose response relationship for BDCM, DCBM both THMs in the 1st month of pregnancy was noted for CHD.</td>
<td>OR increased by 70% (OR 1.70, 95% 1.06-2.66) for every 0.1 ( \mu )g/d increase in the internal dose of BDCM and by 26% (OR 1.26, CI 1.01-1.54) for every 0.01 ( \mu )g/d increase in the internal dose of DCBM.</td>
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*Note:* THM, trihalomethane, BDCM, bromodichloromethane, DBCM, dibromochloromethane.
| Maternal context | Article | Description | Findings: Prevalence, adjusted prevalence ratio
<p>| Odds ratio, risk ratio (values are significant &lt;0.05*, p &lt; 0.001**) |
| Water | Yauck et al. 2004 | Case control study, Milwaukee, WI. n= 4025 infants. Older mothers ≥ 38 yrs and had TCE exposure had greater risk of CHD in their infants than that of the control group. | Older mothers &amp; TCE exposure had 6 fold greater CHD in case infants and control infants 3.3%, 95%, CI 8.245 vs. 0.5% 19.3780. Non exposed older mothers OR 3.2, CI 1.2-8.7. |
| SES | Carmichael et al. 2009 | Case-control study-California population n= 277 conotruncal defects, 608 orofacial cleft cases/ 617 controls. No increased risk for conotruncal defects in lower/poor SES or educational levels. | Maternal education high school to college OR 1.0-1.9 (95%, CI 0.6-3.4), paternal education 1.0-1.6 (CI 0.6-2.8). |
| | Kučienė &amp; Dulskienė, 2009 | Epidemiologic case control study in Kaunas 1999-2005, 187cases/643 controls. Low and moderate maternal education significantly increased the risk of CHDs. Housewives and workers had a higher risk of delivering a newborn with CHDs than the office workers. Maternal smoking during pregnancy tended to increase the risk of CHDs by 48%. | Low-moderate maternal education level OR=3.43; 95% CI, 1.54-7.64 OR=1.56; (CI, 1.00-2.45). Housewives, workers higher risk OR=2.34; (CI, 1.34-4.10) and office workers OR=1.28; (CI, 0.79-2.07). Maternal smoking OR=1.48; (CI, 0.82-2.67). |
| | Malik et al. 2007 | Large population based birth defect registry (8 US states), case control study, n=3,395 cases, n=3,924 controls. No statistically significant association between maternal educational level or SES and SGA in the case or control groups. SGA and CHD were significant. | SGA 516(15.2%), adjusted OR for state of residence 2.07(95% CI, 1.78-2.40), adjusted for infant race parity, maternal age at conception, education, pre-pregnancy BMI, weight gain during pregnancy, cocaine use 3 mo before pregnancy to end, smoking and ETOH status 1 mo before pregnancy to end, maternal HTN, and state of residence. OR 2.09 (CI 1.78-2.46). |
| Occupation | Cresci et al. 2013 | Case control study in Italy. n=190 cases/190 controls, maternal questionnaires collected on preconception exposures and lifestyle practices. Higher frequency of mothers of children with CHD (38 %) reported a positive history of exposure to toxicants (occupational and environmental) than mothers of healthy children (23 %) (p = 0.0013). | OR 2.6; (95 % CI, 1.6-4.2). |</p>
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<tr>
<td>Occupation</td>
<td>Gilboa et al. 2012</td>
<td>Multi site population study in the US. Case control study. 2951 controls, 2047 cases. Associations were observed for exposure to any solvent and any chlorinated solvent with perimembranous ventricular septal defects, aortic stenosis, D-TGA, RVOTO defects and pulmonary valve stenosis.</td>
<td>Solvents, chlorinated solvents, VSD (OR 1.6, 95%, CI 1.0 to 2.6 and OR 1.7, CI 1.0 to 2.8; any solvent exposure with aortic stenosis (OR 2.1, CI, 1.1 to 4.1); and Stoddard solvent exposure with D-TGA (OR 2.0, CI ,1.0 to 4.2), RVOTO defects (OR 1.9, CI, 1.1 to 3.3) and PV stenosis (OR 2.1, CI, 1.1 to 3.8).</td>
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<td></td>
<td>Lin et al. 2012</td>
<td>Multi center case-control study of National Birth Defects Prevention Study data-United States (10 states), 1997-2004. n=4132 case/controls. Higher risk for LVOTO defects in Nurses, septal defects in janitors and higher risk for scientists-chemical, and engineers had higher risk for conotruncal defects.</td>
<td>Nurses- LVOTO defects OR 1.35, 95%, CI, 1.03-1.77, Janitor -septal defects OR 2.19, CI, 1.10-4.36. Chemical scientist - conotruncal defect, OR 2.44, CI, 1.01-5.91, engineer- conotruncal defects OR 3.48, CI, 1.45-8.37.</td>
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<td>Occupation</td>
<td>Snijder et al. 2012</td>
<td>Age matched European case-control study 2003-2010 of cases 424 mothers, 421 fathers, controls 480 mothers, 477 fathers. No maternal exposure to specific chemicals and increased risk of CHD was found. Increased risk for CHD and exposure to specific chemicals in the father was found.</td>
<td>Mother OR 0.92, 95%, CI, 0.26-3.25. Fathers: OR 1.23, CI, 0.39-3.91.</td>
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<td>Vaktskjold et al. 2011</td>
<td>Prospective cohort study, Russia, 1973-2005, included were mothers employed as painters, painter-plasterers, and spoolers (all have exposures to solvents), higher risk for circulatory system malformations in these groups.</td>
<td>Circulatory system (primarily aortic and mitral valve disorders) OR 2.03 (95%, 0.85-4.84)</td>
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<td>Educational level</td>
<td>Carmichael et al. 2009</td>
<td>Case-control study-California population n= 277 conotruncal defects, 608 orofacial cleft cases/ 617 controls. No increased risk for conotruncal defects in lower/poor SES or educational levels.</td>
<td>Maternal education high school to college OR 1.0-1.9, 95%, CI, 0.6-3.4, paternal education 1.0-1.6, CI, 0.6-2.8.</td>
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<td>Kuciene &amp; Dulskiene, 2009</td>
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<td>Total case subjects (3,395), SGA 516(15.2%), adjusted OR for state of residence 2.07(95%, CI, 1.78-2.40), adjusted for infant race parity, maternal age at conception, education, pre-pregnancy BMI, weight gain during pregnancy, cocaine use 3 mo before pregnancy to end, smoking and ETOH status 1 mo before pregnancy to end, maternal HTN, and state of residence. OR 2.09(CI, 1.78-2.46).</td>
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CHAPTER 3

Chapter 3 Introduction

The purpose of this chapter is to provide a review of the literature related to the known genetic risk factors associated with CHD. The focus of this chapter will be the known maternal genetic risk factors for CHD development in the infant. This chapter is a review of the literature in the format of an article to be submitted for journal submission. The referencing style of this target journal will be applied in this manuscript.

Manuscript 2: Understanding Genetics and Pediatric Cardiac Health

Abstract

Purpose: Congenital heart defects (CHD) continue to be the most prevalent birth defect that occurs worldwide in approximately 6-8 of every 1,000 live births. High rates of morbidity and mortality in infants, children, and adults living with CHD place a growing need for health care professionals (HCPs) to better understand potentially modifiable genetic and environmental influences. This paper will present examples of research and governmental initiatives that support genetics education and research and a review of known genetic factors associated with CHD development.

Organizing Construct: A review the known genetic factors on risk for CHD formation in infants will be provided to help health care professionals gain a greater understanding of the genetic influences on pediatric cardiac health.

Conclusions: There are known genetic pathways and risk factors that contribute to development of CHD. This paper is a primer for nurses and HCPs providing information of the genetics and inheritance patterns of CHD to useful in daily clinical practice.
**Clinical Relevance:** Nurses work in multiple communities where they are uniquely positioned to educate and provide information about research and current models of care with families affected by CHD. Nurses and HCPs who better understand genetic risk factors associated with CHD development can more promptly refer and offer treatment for these children and families thus providing individuals of childbearing age with the necessary resources and information about risk factors.

**Key Words:** Congenital heart defects, genetics, epidemiology, etiology, cardiac development.

**Introduction**

Congenital heart defects (CHD) are the most prevalent birth defect in the world and occur in approximately 6-8 of every 1,000 live births (Hoffman & Kaplan, 2002). It is important to identify etiological factors of CHD as CHD is one of the leading causes of infant morbidity and mortality. Only 10-15% of the etiologies for CHD are understood or known. In 2001 The National Heart, Lung, and Blood Institute (NHLBI) convened a task force in Pediatric Cardiovascular Disease to identify research priorities, and scientific opportunities to address the growing public health problem of CHD in children and adults (NHLBI, 2002). This task force identified eight research priorities that varied from supporting basic science studies of the heart and blood vessel formation to transitional research to enhance clinical care.

In 2012 the American Heart Association (AHA) publically recognized the impact of genetics in diagnosing and directing treatment of cardiovascular disease (Ashley et al, 2012). The AHA published a policy statement and recommendations that prompt clinicians to better understand and incorporate genetic technology and modalities into the
care of children and adults with cardiovascular disease or increased risk of CHD. This report addresses the following and provides recommendations for use of genetic information in healthcare:

- Legal ability and ramifications of patenting personal genetic material
- Patient protection against genetic discrimination, regulation and monitoring of genetic testing materials to deliver reliable and valid testing
- Expert consensus on clinical involvement in recommending and selecting appropriate current and next generation genetic testing
- Multidisciplinary and multi-institutional involvement in adaptation for the use of pharmacogenetics in disease treatment and management
- Use of common variant and risk prediction genetic testing of the general population-feasibility and risk for discrimination,
- Reimbursement and insurance coverage for genetic testing,
- Private and public access to genetic testing and storage of genetic material-ability to monitor and protect
- Education of “Core Competencies in Genetics and Genomics” for all healthcare professionals (HCP’s)

Technology to identify genetic markers specific to heart disease continues to evolve and is an innovative part of research and clinical care. Thus, greater knowledge of genetics is required of HCP’s who care for individuals with or with increased risk of CHD. This article is a primer for nurses and HCP’s providing a review of known genetic factors associated with increased risk of CHD for use in daily clinic practice. The implications for nursing research and clinical care will be presented in the conclusion.
The Basic Building Blocks of Life

During the last two decades, scientists’ ability to map the human genome has evolved and the complex molecular processes sustaining daily life continues to be critically studied. As a central concept of molecular biology, the Central Dogma of Molecular Biology describes the one-way directional flow of genetic information; deoxyribonucleic acid (DNA) produces ribonucleic acid (RNA) which then produces proteins (Strachan & Read, 2011). Although there are many complex processes and components to the creation of genetic material, scientists noted that these essential processes are needed by all cellular organisms to sustain life. Over the last several years, scientists have appreciated that these processes and DNA are not the only factors responsible for expressing our genetic makeup, but include more complex interactions between various environmental, prenatal, and chemical exposures throughout an individuals’ life. During this rapid evolution of molecular genetics, a new area of study called epigenetics has developed to promote knowledge generation about the influences the environment has on our genetic makeup.

Epigenetics is a rapidly evolving field of study that focuses on the interactions and factors that influence chemical changes that switch parts of the genome off and on. Epigenetic is defined as “Heritable (from mother cell to daughter cell, or sometimes from parent to child), but is not produced by a change in DNA sequence” (Strachan & Read, 2011, pg. 724). The epigenetic mechanisms that influence changes in gene expression in cardiac development include histone modifications, RNA interferences, and DNA methylation (Chang & Bruneau, 2012; Vallaster, Vallaster & Wu, 2012; Weerd, Koshiba-Takeuchi, Kwon & Takeuchi, 2011). These mechanisms occur within the cells that either
silence or activate specific genes thus causing a cascade of events, which eventually change the expression of the genetic material (Kim, Ryan, Marshboom, & Archer, 2011).

Epigenetic changes appear to be influenced by environmental conditions that include famine, chemicals, and diet to name a few in which these exposure induced changes may be passed to children and grandchildren (Perera & Herbstman, 2011). Exposures to environmental disasters, chemical spills, or other naturally occurring events disrupting the current conditions or environment over time may provide an explanation for the increase in specific phenotypes that contribute to obesity, cancer or increased birth defects as examples (Hou, Zhang, Wang & Baccurelli, 2011). As the human race has learned to manufacture and sustain resources of water, food, and healthcare, the human genome has also learned to adapt to the ever changing environment turning genes off and on, sometimes with adverse effects.

As HCPs acquire a greater understanding of the complexity of molecular genetics, this information will be important when exploring genetic factors influencing embryonic and fetal development of the heart in relation to formation of congenital heart defects (CHD). Of all cases of CHD in live births, 5%-10% can be attributed to a chromosomal abnormality, and 3%-5% are linked to single gene defects (Botto & Correa, 2003; Brent, 2004). Therefore the majority of CHDs are thought to be of a multifactorial etiology, resulting from a combination of environmental and gene interactions. Normal cardiac development is a complex process and is influenced by many transcription factors and cardiac-specific genes. CHD can develop at various times in embryonic/fetal development during which teratogenic or chemical exposures may create varying types of
CHD that include but are not limited to valve disorders, muscular dysfunction, septal defects or circulatory disorders resulting in cyanosis.

The classification and description of cardiac defects has been difficult due to the complexity and multiple forms they come in. Categorizing CHDs genetically is also difficult as some CHDs are heterogeneous with varying degrees of pathology. A description of the multifactorial nature of CHDs and phenotype variability within humans is discussed in the descriptions of each disorder and its associated CHD.

**Genetics of CHD**

The heart is formed during embryonic development -frequently before the mother is aware she is pregnant. The primitive heart tube begins to form as early as embryonic day 15 (Srivastava, & Olson, 2000). Various transcription factors signal cardiac genes to begin cellular development and specification, creating the beginning of the cardio-specific regions and chambers of the heart seen around embryonic day 21. Through embryonic day 28, the heart tube segments, ventricular chambers differentiate, and early valvar regions begin to form. By embryonic day 50 the fully formed heart is visible with each chamber, valve and vessel designated to support further fetal development of the other body systems. Cardiogenesis is a complex process. Figure 1 illustrates the structural changes that occur within the specific regions of the developing heart in the first 7-8 weeks of gestation. Each color illustrates the specification and differentiation during the stages that form the fully developed heart. For example the purple and orange colors represent the ventricular formation and specification of the right and left ventricles. Through the process of looping (Days 21-28) the primitive heart tube begins differentiating the atria, ventricles, conduction systems, arterial and venous circulation.
systems, each with specific regions and genetic material signaling the next process. If there are genetic mutations or miscommunications along these routes various CHD formations may occur. (INSERT FIGURE 1).

**Single Gene Mendelian Mutations**

Single gene Mendelian mutations account for approximately 3-5% of CHD in live human births (Botto & Correa, 2003; Brent, 2004). Single gene Mendelian mutations are those mutations occurring at a single locus or the unique chromosomal location which defines the position of the individual gene or DNA sequence (Strachan & Read, 2011). There are a small number of children and adults affected by familial inherited CHD, thus it remains important to identify these individuals to assure proper allocation of resources. The patterns of inheritance are classified into five categories: autosomal dominant (AD), autosomal recessive (AR), X-linked dominant, X-linked recessive and Y-linked. The basic Mendelian patterns of inheritance (Figure 2) can be complicated by other factors, including penetrance of a trait, later presentation of a disease, and variable expression. Although the probability of inheritance of a specific disease linked mutation can be calculated, many other factors affect gene expression and the risk for disease. Referral to an expert in genetics is appropriate for pre- and interconception counseling for families with increased risk.

Autosomal dominant inheritance patterns are those in which either parent can pass the affected gene to the offspring. There is a 50% risk in every pregnancy if one parent carries the affected allele that the offspring will express the trait. Male and female offspring have an equal risk of being affected. In autosomal recessive inheritance patterns, if both parents are unaffected carriers, there is a 75% risk in each pregnancy that
they will receive the abnormal gene but only a 25% risk that they will be homozygous for the diseased allele. Where one parent is an unaffected carrier of the autosomal recessive faulty gene, and the other parent is affected by the condition, there is a 50% risk in each pregnancy that the child will inherit both copies of the faulty gene.

In X-linked disorders, males will be affected if they inherit a faulty gene since they only have one X chromosome. The male with an X-linked disorder pass their Y chromosome to their male offspring thus none of their sons will be affected. However, all of their female offspring will inherit the faulty gene, and present the disease if the trait is dominant. In X-linked recessive disorders, the female is often a carrier of the trait, and each female carrier has a 50% risk in each pregnancy that the male offspring will be affected with the trait, and a 50% risk of passing the faulty gene to a female offspring. In X-linked dominant traits, all female offspring are affected, and will pass the defect to each of their offspring. Y-linked disorders affect only males, the affected father will produce male offspring affected by the disorder (Strachan & Read, 2011). (INSERT FIGURE 2)

Although there are only a small number of children and adults affected with inherited CHDs; the developmental, physical, and financial impact can be substantial to the child and family. HCPs need to be aware of the patterns and risk of inheritance for the CHD disorders when women and men of childbearing age receive pre- and interconception counseling. HCPs may have the ability to provide pre- and interconception counseling so that individuals are able to make decisions about planning a pregnancy with information about potential risk of having a pregnancy with a mutation or birth/cardiac defect. Once a woman becomes pregnant, she should have access to
genetic testing for single gene disorders through amniocentesis or chorionic villus sampling. If a CHD is diagnosed, an early diagnosis allows time to screen with fetal echocardiography and considerations for delivery plan of an infant affected with a CHD. Since individuals with a genetic defect have up to a 50% chance of passing the genetic defect in each pregnancy, pre- and interconception genetic counseling and screening should be available in order to plan care for each pregnancy and infants with CHDs (Lin & Garver, 1988).

Some examples of single gene disorders associated with CHD include Alagille syndrome (AD), Duchene muscular dystrophy (X-linked), Noonan’s syndrome (AD), Holt-Oram syndrome (AD), Marfan’s syndrome (AD), Char syndrome (AD), Williams syndrome (AD) and Ellis-van Crevald syndrome (AR) (Carey, 2002; Hinton, Yutzey, & Benson, 2005; Lin & Ardinger, 2005). Individuals with these disorders exhibit other physical features which may include CHDs. It is important that HCP pay attention to dysmorphic appearances in parents, siblings or the newborn, so that families receive prompt genetic referrals, analysis and/or consultation with a genetic specialist. Although, these disorders are linked to a single genetic pattern of inheritance, the type of CHD can vary in degree of severity, again reiterating the multifactorial nature of CHD and role exposures that can lead to epigenetic changes during one’s lifetime.

**Chromosomal Abnormalities**

Chromosomal abnormalities occur in approximately 1 in 150 live births (ACOG, 2007; ACOG, 2001; Cary, 2003). In this group of children with chromosomal disorders, 5-10% will have a CHD. Thus children with chromosomal disorders require prompt cardiovascular evaluation to decrease or manage risk of morbidity and mortality
associated with CHD. Many infants with chromosomal disorders will exhibit other physical features prompting early genetic analysis to diagnose or determine if a disorder is present.

Chromosomes are thread-like molecular materials of DNA and proteins that contain genes which determine individual traits such as hair color or height. Humans normally have 46 chromosomes, 23 chromosomes from each parent. Chromosomal abnormalities are a result of large-scale mutations within the sperm or ova that occur before fertilization. These mutations can occur from deletions (absence of a segment of a chromosome), replications (extra copy or segment of a chromosome), mosiacisms (two or more populations of cells with different genetic or chromosomal constitutions), or translocations (a whole chromosome or segment of a chromosome becomes attached to or interchanged with another whole chromosome or segment) resulting in varying forms of diseases and disorders dependent upon the chromosomal region affected (Genetics Home Reference, 2013). Certain chromosomal abnormalities will result in early fetal demise or miscarriage.

There are several chromosomal abnormalities associated with varying forms of CHD. For example, Turner’s syndrome, William’s syndrome, Trisomy 21, and DiGeorge syndrome (Carey, 2002; Huang, Liu & Lv, 2010) may have varying forms of CHD or may not exhibit any CHD. Trisomy 21 is the most frequent chromosomal abnormality that occurs in 1 in 660 live births (Carey, 2002). Of the infants born with Trisomy 21, approximately 40% will be affected with a form of CHD, and are most commonly an atrioventricular canal defect, ventricular septal defect, and/or atrial septal defect.
DiGeorge syndrome, 22q11.2 deletion, is found commonly in patients with conotruncal defects such as Tetralogy of Fallot, aortic arch anomalies, truncus arteriosus, and malaligned ventricular septal defects (Clark, Yutzey, & Benson, 2006). The region of chromosome affected is the DiGeorge critical region (DGCR), where 30 genes are deleted in this region. There can be varying degrees of CHD, cognitive function and other syndromes such as velocardio-facial and conotruncal anomaly face syndrome seen in the DGCR abnormality.

**Multifactoral Inheritance**

The human genome is complex and the genetic processes which make up human development are dependent on multiple complex reactions. Cardiac development is just as intricate and complex which has made it difficult to isolate the exact mechanism of CHD development with the many varying forms of CHD. Therefore with the multifactorial nature of CHD, a genetic mechanism cannot be the sole focus as an etiology. However, understanding possible genetic pathways and vulnerable stages to specific exposures may allow individuals to experience decreases in risk of CHD.

The genetic mechanisms of the majority of CHDs, as well as many other disease processes is thought to be a polygenic process; where multiple loci or areas on the chromosome cause various effects on the phenotype (Strachan & Read, 2011). The genetic environmental theory postulates that specific genotypes will produce or react, dependent upon either optimal or suboptimal conditions in the environment, thus affecting the phenotype (Falconer, 1952). As researchers uncover the intricate relationships between the molecules of DNA, RNA, and epigenetic processes (e.g. DNA
methylation, histone modification and RNA interference) and their roles in abnormal heart development, the genetic environmental theory can be supported.

As there are multiple interactions between genetic materials and environmental factors in males and females of childbearing age, women during pregnancy, and during the first few weeks of fetal development, they should be aware of the known risk factors for CHD. Understanding the potential risk factors for development of CHD is a goal for both bench and clinical researchers working together to gain insight into the formation and early identification of CHDs (Kaltman, Schramm, & Pearson, 2010). A summary of the most common CHDs with known genetic causes, the genes and chromosomes that are affected, and the modes of inheritance are provided in Table 1. It is important that scientists and HCPs develop greater understanding of the epigenetic pathways in order to provide information about risk for the heritable patterns across generations for non-Mendelian disease.

**Research Implications**

The NHLBI has designed the Bench to Bassinet research program to encourage and accelerate the discovery and translation of basic research of CHD etiology into clinical studies through large scale collaborations of four large research centers in the United States (Kaltman, Schramm, & Pearson, 2010). The NHLBI’s first goal in their strategic plan is, “To improve understanding of the molecular and physiological basis of health and disease, and to use that understanding to develop improved approaches to disease diagnosis, treatment and prevention” (as cited in Kaltman, Schramm, & Pearson, 2010, pg 1264). The Bench to Bassinet Program is comprised of two research consortia: the Pediatric Cardiac Genomics Consortium (PCGC) and the Cardiovascular
Development Consortium (CvDC), administered through a common Coordinating Center (CC), and aligns with the Pediatric Heart Network, which has been funded by NHLBI since 2001. These groups are working on studies to accelerate the translation of basic research findings into clinical studies and trials, and to provide clinical input on pressing needs for basic research.

Multidisciplinary research in pre- and interconception care, prenatal health and prevention of potentially harmful exposures to women and men of childbearing age is important for nurses in the context of health promotion through the lifespan. Nurses are uniquely positioned in the community and health care settings with readily available access to young women and men of childbearing age. Engaging in further research to address barriers or deficits in access to preventative and pre- and interconception healthcare practices may provide another avenue to decrease CHD in infants. Nurses can also identify “hot spots” or locations of multiple cases of CHD or other genetic syndromes when employed in public health agencies, as well as various in- and outpatient settings. Nurses have a unique opportunity to collect data and vital statistics to promote further research of the multifactorial factors that contribute to CHD in infants.

Clinical Implications

With over three million nurses in various clinical, educational and research settings across the United States, and over 19.3 million nurses worldwide (World Health Statistics, 2011) nurses have strong potential to influence patient centered care and research. Understanding genetic influences, resources and genetic testing to better understand a disease process are necessary to provide comprehensive and preventative care to children and families affected by and at risk for CHD and other genetic disorders.
This initiative on genetic education in nursing is being promoted as a priority by the American Association of Colleges of Nursing and the Council on Cardiovascular Nursing of the American Heart Association (Ashley et al., 2012). Providing genetic education for the nursing profession is essential to support and offer appropriate counseling and care for this a growing number of individuals with and at increased risk for CHD. As the infant with CHD grows into adolescence and adulthood, transition of care and education of healthy lifestyles and informed reproductive choices are crucial to improve the lives of our patients and families affected by and at increased risk for CHD. Several clinical exemplars are presented in Figure 3 providing practical application of the modes of inheritance (INSERT FIGURE 3).

These exemplars in Figure 3 illustrate different modes of inheritance from figure 1 of specific genetic cardiac conditions that nurses and HCPs may encounter in practice. All members of the healthcare team must remain aware and knowledgeable about physical characteristics, clinical results, and family history which may help determine an increased risk for a genetic disease. Although, all nurses and HCPs may not all have a comprehensive knowledge of all genetic disorders, it is important for nurses and HCPs to provide a thorough health history and exam which may save a life and potentially decrease the risk of CHD through informed reproductive choices of future generations. There are many other genetic syndromes with various modes of inheritance outside of CHD, and HCP’s need to be aware of the patterns of inheritance as they provide pre- and interconception counseling to family members of childbearing age. The nurses and HCP’s caring for children and families with genetic disorders or increased risk of genetic disorders are not be solely responsible for the genetic expertise in various disorders, but
must have, an adequate understanding of genetic transmission and risk in order to appropriately refer individuals with questions or an increased risk of genetic diseases to a genetic specialist and their team.

**Conclusion**

Nurses and other HCPs have a responsibility to obtain current knowledge about genetics through education, research and review of current clinical practices in order to provide multiple resources for individuals and families with CHD and increased risk for other genetic disorders to optimize health outcomes. As the science of genetics is quickly evolving, members of all health disciplines including nursing must maintain currency in the research, clinical care, and education in the field of genetics. While genetic testing may provide specific information to tailor individual care, pre- and interconception counseling are critical to include with individuals at increased risk of a genetic disorder. An understanding of basic genetics, genomics and resources available to nurses and all HCP’s are critical to care for and promote health of individuals and families affected by or at increased risk of CHD.
References


http://www.who.int/gho/publications/world_health_statistics/EN_WHS2011_Full.pdf?ua=1
Figure 1. Cardiac development

From the following article: A genetic blueprint for cardiac development. Srivastava, D. & Olson, E. (2000). Bilaterally symmetrical aortic arch arteries (III, IV and VI); aortic sac (AS); conotruncal (CT) and atrioventricular valve (AVV); A, atrium; Ao, aorta; DA, ductus arteriosus; LA, left atrium; LCC, left common carotid; LSCA, left subclavian artery; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RCC, right common carotid; RSCA, right subclavian artery; RV, right ventricle; V, ventricle. Used with permission from Macmillan Publishers Ltd: Nature, Srivastava, D. & Olson, E.N. A genetic blueprint for cardiac development. Nature, 407, 221-226A doi:10.1038/35025190, 2000.
**Figure 2.** Patterns of inheritance for disease linked to a single gene polymorphism or mutation.

<table>
<thead>
<tr>
<th><strong>Type</strong></th>
<th><strong>Genotypes</strong></th>
<th><strong>Risk</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autosomal Dominant</strong></td>
<td><img src="https://via.placeholder.com/150" alt="" /></td>
<td>50% risk of having an affected child in each pregnancy</td>
</tr>
<tr>
<td>Affected parent Aa</td>
<td>a</td>
<td></td>
</tr>
<tr>
<td>Unaffected parent aa</td>
<td>a</td>
<td></td>
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<tr>
<td></td>
<td>Aa</td>
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<th><strong>Type</strong></th>
<th><strong>Genotypes</strong></th>
<th><strong>Risk</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>Autosomal Recessive</strong></td>
<td><img src="https://via.placeholder.com/150" alt="" /></td>
<td>25% risk of having an affected child in each pregnancy</td>
</tr>
<tr>
<td>Carrier parent Aa</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>Carrier parent Aa</td>
<td>a</td>
<td>50% risk of having a carrier child in each pregnancy</td>
</tr>
<tr>
<td></td>
<td>AA</td>
<td></td>
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<tr>
<td></td>
<td>Aa</td>
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<td></td>
<td>aa</td>
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<th><strong>Genotypes</strong></th>
<th><strong>Risk</strong></th>
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<tbody>
<tr>
<td><strong>X linked-Dominant</strong></td>
<td><img src="https://via.placeholder.com/150" alt="" /></td>
<td>50% risk of having an affected daughter in each pregnancy</td>
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<tr>
<td>Affected father XY</td>
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</tr>
<tr>
<td>Unaffected mother XX</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>XX</td>
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<td></td>
<td>XY</td>
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<th><strong>Type</strong></th>
<th><strong>Genotypes</strong></th>
<th><strong>Risk</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>X linked Dominant</strong></td>
<td><img src="https://via.placeholder.com/150" alt="" /></td>
<td>25% risk of having an affected daughter or affected son in each pregnancy</td>
</tr>
<tr>
<td>Unaffected father XY</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Affected mother XX</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
<td>XY</td>
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<th><strong>Genotypes</strong></th>
<th><strong>Risk</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>X linked Recessive</strong></td>
<td><img src="https://via.placeholder.com/150" alt="" /></td>
<td>50% risk of having a carrier daughter in each pregnancy</td>
</tr>
<tr>
<td>Carrier father XY</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Unaffected mother XX</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
<td>XY</td>
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<tr>
<th><strong>Type</strong></th>
<th><strong>Genotypes</strong></th>
<th><strong>Risk</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>X linked Recessive</strong></td>
<td><img src="https://via.placeholder.com/150" alt="" /></td>
<td>50% risk of having a carrier daughter, 50% chance of an affected son in each pregnancy</td>
</tr>
<tr>
<td>Carrier mother XX</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Unaffected father XY</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>XX</td>
<td></td>
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<tr>
<td></td>
<td>XY</td>
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</tbody>
</table>

*Note: Patterns of genetic inheritance discussed in the text. Characters in red indicate a chromosome with a disease-associated allele.*
Figure 3. Clinical Exemplars.

A 32 year old women is expecting a child, her husband has a diagnosis of Marfan’s syndrome, an autosomal dominant syndrome. She is concerned for her risk of having a child with Marfan’s. She also wonders if her sister-in-law who does not have Marfan’s is at risk. How would you address these concerns?

- She and her husband have a 50% chance of having an affected child in each pregnancy due to her husband’s genetic history.
- A child with Marfan’s may not exhibit cardiac problems initially at birth and thus requires lifelong follow-up with a cardiologist to monitor for mitral valve prolapse and ascending aortic dilation.
- You would also advise your patient that her sister-in-law needs to address her risk with her physician because you know that a comprehensive evaluation is needed to rule out the syndrome. However, you also know that because this is an autosomal dominant syndrome one biological parent has to have the condition to pass it on to their child. If her sister-in-law does not have the genetic condition she cannot pass Marfan’s on to her offspring.

An Amish couple is at the cardiologist to discuss care of their child with common atrium and Ellis-van Creveld syndrome, an autosomal recessive condition. She is concerned her next pregnancy may be at risk for this syndrome. What is her chance of another child with Ellis-van Creveld syndrome?

- She and her husband have a 25% of having a child with this condition, and a 50% chance of having child who is a carrier in this pregnancy and in each subsequent pregnancy.
- If they have a child with Ellis-van Creveld syndrome, this child will have physical attributes of dwarfism (short stature, short limbs) and can be at risk for an atrial septal defect or common atrium.

An 18 year old girl with Turner’s syndrome, an X-linked syndrome, comes in for follow-up of her surgically repaired coarctation of the aorta. Her mother is concerned as she is entering adulthood and thinking about having children, what is her risk for passing Turner’s syndrome on to her children. What are her chances of having a daughter or son with Turner’s syndrome?

- She has a 50% chance of having a female child with Turner’s in each pregnancy.
- If her child is genetic positive for Turner’s syndrome a full cardiac evaluation is necessary as some children with Turner’s do not have a cardiac condition. Coarctation of the aorta and bicuspid aortic valve are most common CHDs.
- Hypertension is a common condition in Turner’s syndrome which can manifest later in life.

In each of these cases, if a child does not inherit the genetic condition from his or her parents, the child will have the same risk for CHD due to the multifactorial causes. The risk for CHD in a child is 6-8/1,000 live births. Because the risk of inheritance with each of these conditions is the same in each pregnancy, a family with a family history of each of these conditions and two children could have 1, 2 or no children with the condition.

Note: Clinical exemplars of genetic inheritance patterns for CHD.
Table 1

*Genetic Causes of CHD in the Human (congenital and adult CHD)*

<table>
<thead>
<tr>
<th>Types of CHD or Syndromes Associated with CHD</th>
<th>Pattern of Inheritance</th>
<th>Associated Genes or Chromosomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial CHD (ASD, AV-block, TOF, HCM, TV abnormality)</td>
<td>MF</td>
<td>NKX2.5</td>
</tr>
<tr>
<td>D-TGA, DORV</td>
<td>MF</td>
<td>CFC1</td>
</tr>
<tr>
<td>D-TGA</td>
<td>MF</td>
<td>PROSIT240</td>
</tr>
<tr>
<td>Tetrology of Fallot (TOF)</td>
<td>MF</td>
<td>ZFPM2, NKX2.5, JAG1, FOG2</td>
</tr>
<tr>
<td>ASVD</td>
<td>MF</td>
<td>CRELD1</td>
</tr>
<tr>
<td>ASD/VSD, ASVD, PV dysplasia</td>
<td>MF</td>
<td>GATA4</td>
</tr>
<tr>
<td>Heterotaxy</td>
<td>MF</td>
<td>ZIC3, CFC1, ACVR2B, LEFTY A, ELN</td>
</tr>
<tr>
<td>Supravalvar AS</td>
<td>MF</td>
<td>GATA</td>
</tr>
<tr>
<td>T/PAPVR, TA, PS</td>
<td>MF</td>
<td></td>
</tr>
<tr>
<td>ASD, AVSD, AVB, TOF</td>
<td>MF</td>
<td></td>
</tr>
<tr>
<td>Syndromes Associated with CHD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Holt-Orem syndrome</td>
<td>AD</td>
<td>TBX5</td>
</tr>
<tr>
<td>Alagile syndrome, PS/PPS</td>
<td>AD</td>
<td>JAG1</td>
</tr>
<tr>
<td>Char syndrome, PDA</td>
<td>AD</td>
<td>TFAP2B</td>
</tr>
<tr>
<td>Noonan syndrome, PS, PV dysplasia, ASD, AVSD</td>
<td>AD</td>
<td>PTPN2, KRAS, SOS1, CHD7</td>
</tr>
<tr>
<td>CHARGE syndrome</td>
<td>AD</td>
<td>CHD7</td>
</tr>
<tr>
<td>Ellis-van Creveld, (ASD, common atrium)</td>
<td>AR</td>
<td>EVC, EVC2</td>
</tr>
<tr>
<td>Marfan syndrome</td>
<td>AD</td>
<td>FBN1, TFGBR2</td>
</tr>
<tr>
<td>Connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiofaciocutaneous syndromes</td>
<td>MF</td>
<td>KRAS, BRAF, MEK1, MEK2</td>
</tr>
<tr>
<td>Costello syndromes</td>
<td>AD</td>
<td>HRAS</td>
</tr>
<tr>
<td>Turner’s syndrome</td>
<td>X-linked</td>
<td>SHOX</td>
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<tr>
<td>William’s syndrome</td>
<td>AD</td>
<td>CLIP2, ELN, GTF2IRD1, GTF2I, IMK1</td>
</tr>
<tr>
<td>Trisomy 21, 18, 13</td>
<td>MF</td>
<td>Additional chromosome</td>
</tr>
<tr>
<td>DiGeorge</td>
<td>MF</td>
<td>DGCR, TBX1, 22q-11.2</td>
</tr>
</tbody>
</table>

*Note.* AD, Autosomal dominant; AR, Autosomal recessive; ASD, atrial septal defect; AVB, atrioventricular block; AVSD, atrioventricular septal defect; Chrom-Chromosome; D-TGA, dextro-transposition of the great arteries; DORV, double outlet right ventricle; HCM, hypertrophic cardiomyopathy; MF, multifactorial; PDA, patent ductus arteriosus; PS, pulmonary stenosis; PPS, peripheral pulmonary stenosis; T/PAPVR, total/partial anomalous venous return; TV, tricuspid valve. Adapted from “Molecular mechanisms of congenital heart disease,” by Huang, Liu, Sun, Lv, Ming, and Fan, 2010, *Cardiovascular Pathology*, 19, e185. Copyright 2010 by Elsevier Inc.
CHAPTER 4

Chapter Introduction

The purpose of this chapter is to provide a presentation and discussion of the results from this dissertation study. The focus of this chapter will be findings from the study including the risk factors for complex CHD and factors related to gestational age and birth weight in this population. This chapter presents the outcomes of the study in the format of an article to be submitted for journal submission. The referencing style of this target journal will be applied in this manuscript. Supplemental data will include correlation tables for both the dissertation as well as the journal submission.

Manuscript 3: Maternal Health and Infants Born with Congenital Heart Disease: A Secondary Analysis of the WPCR

Abstract

Objective: Examine the relationships of select maternal variables to the type of CHD, birth weight and gestational age in infants born with CHD participating in the Wisconsin Pediatric Cardiac Registry (WPCR).

Design: Descriptive secondary analysis.

Setting: Wisconsin Pediatric Cardiac Registry

Participants: 1,687 parent/child participants

Methods: Descriptive analysis, correlations, logistic and multiple regression.

Results: Maternal history of CHD, OR 2.382 (95 % CI 1.424-3.984) and history of serious health conditions OR 1.537 (CI 1.085-2.178) were found to increase the risk for complex CHD in their infants. Predictors of birth weight included; maternal history of hypertension, serious health condition six months prior or during pregnancy, CHD, obesity and income ($R^2 = 0.049, p < 0.05$). Predictors of gestational age included;
maternal history of hypertension, flu, and serious health conditions six months prior or during pregnancy, and type of housing \( (R^2 = 0.045, p < 0.05) \).

**Conclusion:** Maternal history of CHD and chronic health conditions were associated with increased risk for complex CHD in this sample. Nurses can identify risk factors of CHD prior to pregnancy and provide education to women and their partners when planning a future pregnancy. The findings from this study reinforces that there are risk factors for complex CHD. It also illustrates the multifaceted nature of CHD and need for further investigation of maternal and paternal exposures to help identify other risk factors for complex CHD.

Key words: Congenital heart defects, pregnancy, cardiac, maternal exposures.

Congenital heart defects (CHD) are the most common type of birth defect occurring in approximately 6-8/1,000 live births in the United States and continue to be a leading cause of illness and death in infants (Hoffman & Kaplan, 2002). Although, healthcare has made great strides in recognition and diagnosis of CHD, CHD prevalence appears to be increasing (Botto, Correa, & Erickson, 2001). In 2004, an estimated $1.4 billion was spent for hospitalizations of individuals with CHD in the United States, of that $511 million was used to treat complex CHD (Russo & Elixhauser, 2007).

During pregnancy a woman has many exposures within her environment of which she may or may not be aware that can influence cardiac formation in her fetus. She, in fact, may not be aware she is pregnant as cardiac formation occurs within the first 50 days of pregnancy (Sartiani et al, 2010). There is an increasing awareness of the sensitive timeframe prior to and early in pregnancy and the influences of maternal health.
The Wisconsin Pediatric Cardiac Registry (WPCR) was created in 1999 to collect subjective and genetic information on the parents and infants of children born in Wisconsin with various forms of CHD (Hanson-Morris, Pelech, 2006). It is estimated that 400-600 new cases of CHD are diagnosed each year in Wisconsin (Hanson-Morris & Pelech, 2006) or 6-7/1,000 live births (Harris et al., 2011). By studying the demographic and subjective information provided from these families it was hoped to identify risk factors for having an infant with complex CHD.

Maternal health and exposures have also been associated other birth outcomes including birth weight and gestational age. Low birth weight and early gestational age have been associated with maternal risk factors such as chronic health conditions (Palmer, Bonzini, Harris, Linaker, & Bonde, 2013), history of smoking (Ashford et. al, 2010; Rogers, 2009), and socioeconomic status (Blumenshine, Egerter, Barclay, Cubbin, & Braveman, 2010; Jansen et al., 2009; Messer et al., 2008). In this group of infants with various forms of CHD, it is hypothesized that these maternal risk factors are also associated with the infants’ birth weight and gestational age as well as type of CHD. It is important for women to optimize their health prior to and during pregnancy to decrease the risk for low birth weight and premature birth. These infants with complex CHD were also believed to be at greater risk for low birth weight and prematurity due to the complexity of CHD diagnosis (Williams et al., 2010; Malik, Cleves, Zhao, Hobbs, & NBDS, 2007).

This study was developed to address the relationships between the maternal contextual factors and exposures prior to and during pregnancy to their birth outcomes using the data in the WPCR database. Understanding the relationships of maternal health
and contextual factors may identify risk factors for having an infant with CHD in this sample.

**Conceptual Framework**

A life course perspective on health was chosen as a theoretical model to guide this study as this theory conceptualizes health as a reflection of an underlying developmental trajectory. The goal of the life course perspective is to understand, explain, and improve health and disease patterns across various populations (Halfon & Hochstein, 2002). The life course model uses a multidimensional approach incorporating the biological, psychological, behavioral, and social contexts to better explain health and disease processes of the person or community, allowing for the development of interventions and education practices to identify risk and protective factors (Fine & Kotelchuck, 2010).

This model acknowledges throughout the developmental trajectory, some contexts are fixed, or hard wired, and others contexts are highly flexible or amenable to change. The life course model fits well in the study of CHD as many of the contexts are both fixed and plastic occurring along a developmental trajectory. The life course model reflects the epigenetic nature of diseases, or the heritable process of disease development (from mother cell to daughter cell, or sometimes from parent to child), which is not produced by a change in DNA sequence (Strachan & Read, 2011, pg. 724) and how today’s experiences and exposures determines tomorrow’s health. Those health trajectories are particularly affected during critical or sensitive periods (timing) and the broader environment - biologic, physical, and social contexts – significantly affects the ability to be healthy (Kotelchuck, 2011). Included in the study model were the maternal contextual and risk factors identified through a review of the current literature (Butler,
Johnson, & Cavan, 2014) (see Figure 1). The purpose of this study was to explore the relationships of select maternal variables to the type of CHD, birth weight and gestational age in infants born with CHD participating in the WPCR from 2000-2010. The hypotheses evaluated were:

**Hypothesis 1:** Multiple maternal risk factors of biologic (genetic causes associated with CHD, age, race, chronic health conditions, family history of CHD), physical (history of obesity, use of alcohol, drugs, cigarettes, medication/vitamin use, and type of water consumed), and social variables (SES, occupation, education level) influence the risk of complex CHD.

**Hypothesis 2:** Multiple maternal risk factors (biologic, physical, social) influence the risk of low birth weight or prematurity in the infants born with CHDs.

**Methods**

**Design**

Although, the original data were not collected with a specific research question in mind, the WPCR was designed to allow researchers and clinicians access to temporal, environmental, familial, and genetic data to explore relationships of potential causative factors of CHD, which is congruent with the specific aim and hypotheses of this study. A secondary analysis of preexisting data was used in this study. Approval was obtained from Children’s Hospital of Wisconsin (CHW) Internal review Board for an exempt study. Consent to participate was provided in the original study conducted at CHW and no patient contact was required. All data was de-identified, maintained and accessed on a secure computer. This sample represented approximately 1/3 of the infants with CHD.
and their caregivers who were consented and participated in the WPCR (1,687/4,919) during this timeframe (Harris et al., 2011).

**Setting and participants**

Data for this secondary analysis were obtained from the WPCR database. The original study included children that were conceived and born in Wisconsin after January 1, 2000, and diagnosed with a structural heart defect. Participants were identified and recruited from pediatric cardiac referrals in Wisconsin. The cardiac defect was confirmed from echocardiography, catherization procedures or autopsy. Exclusions included: isolated patent foreman ovale, patent ductus arteriosus, electrophysiological disturbances, and acquired heart diseases. The sample was limited to children under the age of two years in order to reduce caregiver’s difficulty with recall bias when answering the questionnaire (Harris et al., 2011). The present study contained 1,687 completed questionnaires from the WPCR of infant and maternal information that were used.

**Measures**

**Maternal context variables.** The maternal contexts were divided into three categories (see Figure 1); biologic (genetic causes associated with CHD, age, race, chronic health conditions (CHC), family history of CHD) physical (obesity, ETOH/drug use, cigarette use, medication/vitamin use, type of water consumed), and social contexts (socioeconomic status (SES), occupation, education level). In the WPCR questionnaire, only questions specific to the maternal context variables were used to measure these concepts delineated in the conceptual framework. Several concepts were represented by multiple questions to better capture the maternal contexts in this sample (see table 1).
**Infant outcomes.** Three infant outcomes were used in the model; simple or complex CHD, gestational age and birth weight. The type of CHD variable was created using a modified classifications schema modified from the Baltimore Washington infant study (Ferencz, Loffredo, Correa-Villaseñor, & Wilson, 1997). All CHD diagnoses were provided by ICD-9 codes which were recorded by the research coordinator. Simple CHD was defined as a single CHD diagnosis of: atrial septal defect (ASD), ventricular septal defect (VSD), pulmonary valve disorders (PV), coarctation of the aorta (COA), and bicuspid aortic valve (BAV), mitral valve disorders (MV). Complex CHD was defined as: multiple CHD diagnoses and/or the diagnoses of Tetralogy of Fallot (TOF), atrioventricular septal defect (AVSD), transposition of the great arteries (TGA), pulmonary atresia (PA), hypoplastic left heart syndrome (HLHS), univentricular heart disease or variants including multiple lesions.

**Statistical Analysis**

An initial evaluation of the dataset was undertaken to determine which items would be used to measure study concepts. After thorough evaluation of numeric, text data and cleaning of the dataset, 29 variables were chosen to measure the 14 maternal context variables proposed in this study. Variables were omitted if they included free text data, had more than 30% missing data, or were slightly different in the print or online questionnaires. A power analysis based on the work of Peduzzi et al. (1996) was performed to determine adequacy of size of the sample. Using the formula of \( N = \frac{10k}{p} \) (\( k = \) number of covariates) (\( p = \) the smalls of the proportion of negative or positive cases). \( N = \frac{10(15)}{.3}, N = 500 \); 500 cases were required for this study. A total of 1,687 cases were
available for study which was well over the 500 cases needed to identify significant relationships between the independent and dependant variables.

Characteristics of the sample were identified through descriptive analysis. Frequencies were used to describe the sample and to assess for skewness (distribution), kurtosis (clustering), central tendencies, and variability of the variable. Means, medians and standard deviations were calculated for continuous variables. Percentages were used for dichotomous and categorical variables. Demographic (race-Caucasian, water type-city, marital status-married, income->$25,000 and education-some college) categorical variables were collapsed into dummy variable (yes or no) for the regression analysis. Pearson’s correlations, Spearman rho correlations, Phi coefficient and Cramer’s V tests were used to examine relationships between predictor and outcome variables. Only the significantly correlated variables were included in the final regression models (Tabachanick & Fidell, 2013).

An assessment of the reduced dataset (text in variables eliminated) using Little’s test determined patterns of the missing data. Little’s test was significant at .885, $p < .001$, indicating the interval variables showed a pattern of data missing completely at random (MCAR) (Tsikriktsis, 2005). One categorical variable had 12.2% of missing data which remained below 15% missing and was retained. The remaining categorical variables had < 5% missing data. Because the majority of missing data was less than 10%, multiple imputations were used to impute the missing data (Tsikriktsis, 2005).

A direct logistic regression was performed to access the impact of a select number of maternal context factors (predictors) on the likelihood of having a child with complex CHD (outcome) in hypothesis 1. The logistic regression model was conducted with three
significantly correlated biologic maternal contexts (age, serious health condition six months prior or during pregnancy, and history of CHD) and two social maternal contexts (income and educational level). Correlations were noted to be small but significant (see tables 7-10).

Two hierarchical multiple regressions analyses were used to test hypothesis 2 and determine predictors for gestational age and birth weight. Preliminary analyses were conducted to ensure no violation of the assumptions of normality, linearity, multicollinearity and homoscedasticity (Tabachanick & Fidell, 2013). An exploratory correlational analysis was also undertaken to address the following question. Does type of CHD (simple or complex) influence birth weight and/or gestational age? Pearson’s correlations were used to address this exploratory research question.

Results

Sample Characteristics

This sample of 1,687 infants and mother dyads had overall normal birth weight (mean 3.178 kg/7#, 11.2 oz) and gestational age (mean 37.92 weeks) in the infants in this sample. The women in this sample were generally healthy with few chronic health conditions and healthy age for child bearing (mean 29 years). In this sample sex was equally distributed of 51% male and 49% female infants with CHD. Of these infants 73% had simple CHD, and 27% had complex CHD (see table 2).

The majority of the mothers in this sample were Caucasian, married, and educated with some college. These women were mildly overweight (mean BMI=26, overweight= 25-29.9) and 17% reported history of obesity. Most were middle to upper class living in single family homes. Many of these mothers were healthy with asthma
noted most frequently as a chronic health condition (29%). The majority of these women used multivitamins prior and/or during pregnancy (91%) and less than a 25% reported taking a prescription medication. Many women reported history of smoking (41%) and the majority consumed alcohol (70%). Few reported using illicit drugs (< 2.3%). Over 75% of the women worked prior their pregnancy and continued to work during their pregnancy (See table 3, 4).

**Predictors of complex CHD**

To test the first hypothesis a direct logistic regression was performed entering the variables by domain per the conceptual framework. The final model contained five significantly correlated maternal context variables (see tables 7-10). The model as a whole containing all predictors was statistically significant, $\chi^2 (5, N = 1687) =34.1$, $p<.001$, indicating that the model was able to distinguish between subjects with simple or complex CHD. The model explained 2% (Cox & Snell $R^2$) and 2.9% (Nagelkerke $R^2$) of the variance in type of CHD (simple/complex) and correctly classified 73.1% of complex CHD cases (Field, 2013). As shown in Table 5, two context variables made a uniquely statistically significant contribution to the final model, maternal history of serious health condition and history of CHD. The strongest predictor of having an infant with complex CHD was maternal history of CHD, ($B=.420, SE = .179; \text{Exp}(B) =2.389$), indicating that mothers who had a history of CHD were 2.4 times more likely to have an infant with complex CHD. These mothers with history of a serious health condition prior or during the pregnancy was a significant predictor of complex CHD ($B=.871, SE = .262; \text{Exp}(B) = 1.523$), were 1.5 times more likely to have an infant with complex CHD (see Table 5).

**Predictors of Birth Weight and Gestational Age.**
To test the first part of hypothesis 2, which studied the predictors of birth weight, nine significantly correlated maternal variables to birth weight were into the regression using the domains in the conceptual framework (see tables 7-9). The significant correlations were small ($r = < 0.1$).

A hierarchical multiple regression were performed to assess the ability of the nine maternal context variables to predict birth weight of the infant born with CHD (see Table 6). Biological variables, age, maternal race, history of respiratory infection, hypertension, serious health conditions and history six months prior or during pregnancy of CHD were entered at Step 1, and explained 3.1% of the variance of birth weight. The physical variables history of obesity, BMI, and income level entered in Step 2, explained another 1.3% of the variance and all of but history of respiratory infection, remained significant, $R^2$ change $= .013, F$ change $(2, 1592) = 10.486, p < .001$. In Step 3 the addition of social variable of income level explained .6% of the variance, $R^2$ change $= .006, F$ change $(1, 15911) = 10.125, p < 0.05$. In the final model five maternal context variables were statistically significant explaining a total of 4.9% of the variance in the final model. History of hypertension, serious health conditions, obesity, annual income and history of history of CHD remained to be significant predictors of birth weight in the final model explaining 4.9% of the variance of birth weight.

To determine predictors of gestational age, six maternal variables with significant correlations to gestational age were entered into the hierarchical regression using the domains in the conceptual framework (see table 7-9). The significantly correlated variables had small correlations ($r = < 0.1$).
Biologic variables, history of emotional disorder, hypertension, flu and serious
health conditions six months prior or during pregnancy were entered at Step 1, and
explained 3.8% of the variance of gestational age. The physical variable of alcohol use
was entered in Step 2, which explained another .2 % of the variance. In Step 3 with the
addition of a social variable, type housing, .4% of the variance was explained, \( R^2 \) change
= .004, \( F \) change (1, 1680) = 7.875, \( p < 0.05 \). In the final model four maternal context
variables (history of HTN, flu, and serious HC, and type of housing) were statistically
significant explaining 4.5% of the variance of gestational age (see table 6).

**Exploratory Analysis.**

The type of CHD was not significantly correlated with birth weight and
gestational age (BW= -.014, GA .011, \( r \)). In this study type of CHD did not influence
gestational age and birth weight.

**Discussion**

Two significant relationships were obtained between the maternal context
variables (serious health condition and history of CHD) and risk for complex CHD.
Although the model had 14 maternal context variables, only five significantly correlated
variables were retained for the logistic regression. In this sample the majority of women
were generally healthy, educated and had minimal reported substance use that would be
put them at risk. However, history of a serious health condition showed a 1.5 fold
increased risk for complex CHD in their infants.

Having a serious health condition or chronic health condition prior to or during
pregnancy has been associated greater risk for all CHD (Miller et al., 1981; Oster, Riehle-
Colarusso, Alverson, & Correa, 2011; Srinivasan, Dheen, & Tay, 2007). Although the
type of illness or serious health condition is not well delineated to type of illness or exact timing in this sample, it does support that there is a relationship with history of any chronic illness and increased risk of CHD if present prior or during pregnancy.

In this study we found an associated greater risk for complex CHD when there was maternal history of CHD, 2.4 fold increased risk. The BWIS (1997) reported an increased risk for CHD when there was first degree family history of CHD (OR 4.1, CI 1.6-10.7), however they did not find an association with greater risk complex CHD. Romano-Zelehka et al.’s (2001) study which found increased risk for CHD (aOR 1.73, CI 0.89-2.44), most commonly ASDs, when there was parental history of CHD. Although, the exact mechanism of inheritance remains unknown it is consistent with the multi-genic complex developmental process and greater propensity for producing offspring with CHD when there is family history of CHD (Ferencz et al., 1989).

The second hypotheses revealed several maternal context predictors influencing gestational age and birth weight of this sample. Although these maternal context variables were statistically significant, they only explained about 4-5% of the variance in the outcome variables (gestational age, birth weight). Gestational age and birth weight did not statistically impact risk for complex CHD in this sample and maybe be related to the socioeconomic status of this population. The findings of no relationship were not consistent with other studies. Some have found the greater the severity of the CHD the greater risk for prematurity and low birth weight are present (Malik, Cleves, Zhao, Hobbs & NBDS, 2007, BWIS, 1997).

In the model 4.4% of the variance was explained. Although, 95% if the variance was not explained by this model, this study identified specific risk factors for lower birth
weights in these infants’ born with CHD from a relatively healthy group of women. Maternal history of hypertension, serious health condition, CHD, obesity six months prior or during pregnancy were consistent with the literature finding poor birth outcomes when CHD was present (Stochard, Tennant, Bell & Rankin, 2011). Obesity in this study was significant and also has been associated with a number of congenital malformations including neural tube defects and CHD (Mills, Troendle, Conley, Carter & Druschel, 2010; Stothard, Tennant, Bell & Rankin, 2009; Watkins & Botto, 2001).

The common risk factors associated with CHD and other birth defects, such as alcohol (Jenkins et al, 2007; Matok, Pupco, Koren, 2011), illicit drug use, smoking (Alverson, Strickland, Gilboa & Correa, 2011; Gianicolo, Cresci, Ait-Ali, Foffa & Andresassi, 2010; Sartiani et al, 2010) and teratogenic exposures did not significantly correlate with type of CHD or poor birth outcomes. Although, these risk factors are associated not only with CHD but other birth defects, if the mother does not report such exposures, further review of health history for chronic health conditions and social history should be reviewed as our sample had other identifiable risk factors.

There was a relationship of each of maternal contexts and one of the infant outcomes. However, in the exploratory analysis in the conceptual that were not supported by the findings of this study was the relationship between type of CHD and birth weight or gestational age. Although gestational age and birth weight were highly correlated to each other neither was correlated to type of CHD. If future research using a more diverse and larger sample supports our findings, the conceptual framework may be revised.
Statistical considerations and limitations

The large sample available in the dataset allowed for relationships to be explored comparing birth outcomes of the infants born with CHD, however these risks cannot be inferred to the infant without CHD. Alcohol, smoking and drug use questions were used in this study but from review in the literature, the accuracy of information about sensitive questions such as smoking, alcohol and drug consumption can be a problem in survey data (Van de Mortel, 2008; Del Boca & Darkes, 2002). Poor recall or bias in reporting these variables may account for the lack of relationships identified in this study. Generalizability may be limited as the sample is included only infants born in the state of Wisconsin from 2000-2010 which is a predominantly Caucasian, middle class, Midwestern state. The finding may not be representative of other demographic locations in the United States.

Most research exploring CHD risk factors and prevalence has used a control group for comparison; however, an adequate control group was unavailable for this study but not essential to test the hypotheses. The BWIS (1997) was the largest population study to identify multiple risk factors for CHD. In the BWIS, although a case control study, CHD type was classified according to severity and risk factors for the types of CHD ranging from simple, moderate and complex. More risk for complex CHD was identified when there was maternal history of chronic health conditions.

Specificity of critical time frames of exposure is limited in this study. This study uses cross sectional data collected over a decade, thus predictors must be interpreted cautiously as it does not indicate causal evidence. The maternal variables reporting history of illness, chronic health conditions, serious health conditions and obesity all were
measured using a six month prior to or during pregnancy timeframe. Some of the variables were non-specific such as the serious health condition variable. These variables which were available may have been a factor in the prediction of the model rather than a flaw in the model itself.

In this sample serious health conditions were found to be a greater risk for complex CHD. This finding may be influenced by the general health status of the sample. Due to the lack of a sufficiently robust control sample and the type of serious health condition cannot be determined, the most influence health condition affecting risk for complex CHD cannot be elicited. Additional research will be needed to clarify these relationships.

**Implications for Practice and Research**

In this study we found several significant maternal risk factors for having an infant with complex CHD. These maternal context factors were also significant predictors for birth weight and gestational age in this population. Although the sample was limited, the findings can be used to guide the assessment of women’s health history and health practices. This study supports the practice of a thorough review of health history and health practices with all women to identify potential risk factors for having an infant with CHD. In the recently published Scientific Statement for the management of fetal cardiac disease (Donofrio et al. 2014), it is recommended that women with personal history of CHD, specific CHC’s or infections (pre-gestational diabetes, lupus, hypertension- on ACE inhibitors, rubella), or history of known genetic condition have a fetal echo performed. These maternal conditions are just a few examples indicating the necessity of a prenatal cardiac evaluation due to increased risk for CHD. There are
several modalities for prenatal cardiac evaluation dependant on the maternal history and type of congenital heart disease present during pregnancy. If CHD is diagnosed promptly in the prenatal timeframes planning and/or management can be provided to ensure optimal outcomes of the infant and pregnant woman can be initiated.

The use of electronic medical record systems has been a nationwide undertaking. Many nurses are using an electronic medical record (EMR) system; accurate recording of family history, past medical history and social history may facilitate screening of women and families. A three generation genogram may be critical in the identification of cardiac risk factors for future pregnancy (Wright & Leahey, 2013). Development or training for use of an electronic version in the EMR may be helpful and resourceful for a busy practice. Review of these families educational level, occupation, and medical history can help identify at risk women and families when previewed by the health care professional. Accessing programs and obtaining suitable teaching materials may assist at risk individuals and provide opportunities to review current recommendations for healthy pregnancies. Many of the maternal risk which we have identified in this study can be identified through thorough history and physical assessment at routine health visits. The known modifiable risk factors should be discussed with all women and their partners who are contemplating pregnancy.

Inclusion of the man’s health and exposures is extremely important and often overlooked. As we learn more about epigenetic influences and the influences of generational health practices, a thorough health history for both woman and man will be necessary to identify risk factors for birth defects, particularly CHD for example when there are multiple family members reporting history of CHD. It is being better
understood the exposure history of the father may have as great of an impact on the risk for CHD development during the pre-pregnancy stage as well as at conception as the woman. Nurses and HCP’s can help identify these risks factors and provide counseling to these families and future generations for good healthcare practices prior to pregnancy to help decrease the risk of complex CHD and promote healthy infant outcomes. As our healthcare systems shift to a preventative model for healthcare delivery, nurses can excel in leading prevention and education.

The conceptual framework was generally supported by relationships between the maternal contexts and infant outcomes. However, not all relationships between maternal contexts and outcomes in the model were supported by the data; physical and social contexts were not related to type of CHD. The biological realm showed the most influence on type of CHD which could be due to the generally healthy sample. Or it may be related to a biologic predisposition occurring early in cardiogenesis that does not influence the type of CHD but rather the development of CHD in general. Interestingly the relationship between type of CHD and birth weight and gestational age were not supported as previously suggested in the literature (Williams et al., 2010; Malik, Cleves, Zhao, Hobbs, & NBDS, 2007). Future research may better clarify these relationships which then the conceptual framework could be modified accordingly.

Summary

CHD continues to be the leading birth defect occurring worldwide. There are known risk factors which can be identified to help decrease the risk of complex CHD, premature birth and low birth weight in infants. It is important to discuss the risk factors with our families of childbearing age to raise awareness for positive health practices
which may contribute to reducing the risk of complex CHD. Prenatal diagnosis of complex CHD through fetal echo and other modalities can assist in providing optimal outcomes of the infant and pregnant woman. Continued research in this area is needed but also inclusion of the paternal health practices. It is necessary to capture the entire family as one of the most significant risks for complex CHD is personal maternal history.
References


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Using a Life Course Perspective: The Influence of Maternal Contexts on Infant Outcomes

**Maternal Contexts**

- **Biologic**
  - Known Genetic Causes
  - Age
  - Race
  - Chronic Health Conditions
  - Family History of CHD

- **Physical**
  - Obesity
  - ETOH use
  - Drug use
  - Tobacco use
  - Medication/vitamin use
  - Type of water consumed

- **Social**
  - Socioeconomic Status
  - Occupation
  - Education level

**Time**

- Periconception
- Early Gestation
- Mid Gestation
- Late Gestation
- Birth

**Infant Outcomes**

- Risk of Simple or Complex CHD
- Birth Weight and/or Gestational Age

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*Figure 1: Conceptual model of maternal contexts and the relationships to infant outcomes.*

Solid lines represent hypothesis. Dotted lines represent exploratory analyses.

Simple CHD consists of isolated CHD including; atrial septal defect (ASD), ventricular septal defect (VSD), pulmonary stenosis (PS), aortic stenosis (AS), bicuspid aortic valve (BAV), coarctation of the aorta (COA), and mitral valve (MV) disease.

Complex CHD consists of single or multiple diagnosis including; Tetralogy of Fallot (TET), atrioventricular septal defect (AVSD), transposition of the great arteries (TGA), pulmonary stenosis (PA), hypoplastic left heart syndrome (HLHS), and univentricular heart disease or variants including multiple lesions.
Call outs: (3 required- no more than 25 words each)

Call out 1: After introduction

Congenital heart defects are the leading birth defect in the world. Positive prenatal maternal health practices can help decrease risk for complex CHD.

Call out 2: Before the results section

Maternal history of CHD increases risk for having a child with complex CHD.

Call out 3: Prior the discussion

Identification of at risk women prior to pregnancy is critical in reducing their risk of complex CHD for future pregnancies.
Table 1

Maternal questions used in analysis

<table>
<thead>
<tr>
<th>Domain</th>
<th>Context</th>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant</td>
<td>Gestation</td>
<td>What was mother’s expected delivery date?</td>
</tr>
<tr>
<td>Infant</td>
<td>Gestation</td>
<td>When was mother’s last menstrual period prior to this pregnancy?</td>
</tr>
<tr>
<td>Infant</td>
<td>Birth weight</td>
<td>How much did your baby weight at birth? Lbs/oz.</td>
</tr>
<tr>
<td>Biologic</td>
<td>Race</td>
<td>Please circle mother’s race or ethnic group.</td>
</tr>
<tr>
<td>Biologic</td>
<td>Age</td>
<td>What is mother’s date of birth?</td>
</tr>
<tr>
<td>Genetic causes</td>
<td>Did/does mother have any birth defect, malformation, or condition other than CHD which was present from birth?</td>
<td></td>
</tr>
<tr>
<td>Genetic causes</td>
<td>FH CHD</td>
<td>Did/does mother have a CHD, heart condition that she was born with?</td>
</tr>
<tr>
<td>Genetic causes</td>
<td>CHC</td>
<td>Has mother ever been told she has diabetes? (asthma/allergies, epilepsy, thyroid, peptic ulcer, eating disorder, cancer, other)</td>
</tr>
<tr>
<td>Genetic causes</td>
<td>CHC</td>
<td>Has mother ever been told that she has any of the following illnesses?</td>
</tr>
<tr>
<td>Genetic causes</td>
<td>CHC</td>
<td>In the 6 months prior to or during this pregnancy did mother have any of the following illnesses or conditions? (high blood pressure, obesity, bladder or kidney infections, emotional, vaginal infections, arthritis, headaches, colds, sinus infection, bronchitis)</td>
</tr>
<tr>
<td>Genetic causes</td>
<td>CHC</td>
<td>In the 6 months prior to or during pregnancy did mother or was mother exposed to anyone with the following infections? (influenza, mumps, measles, rubella, chicken pox, hepatitis, AIDS/HIV)</td>
</tr>
<tr>
<td>Genetic causes</td>
<td>CHC</td>
<td>In the 6 months prior to or during pregnancy did mother have any other serious health problems or was she hospitalized for any reason, excluding delivery?</td>
</tr>
<tr>
<td>Physical</td>
<td>Med/vit</td>
<td>Did mother take vitamins or multi-vitamins during this pregnancy?</td>
</tr>
<tr>
<td>Physical</td>
<td>Med/vit</td>
<td>During this pregnancy did mother regularly take medications not mentioned above?</td>
</tr>
<tr>
<td>Physical</td>
<td>Obesity</td>
<td>Mothers height</td>
</tr>
<tr>
<td>Physical</td>
<td>Obesity</td>
<td>What was mother’s pre-pregnancy weight?</td>
</tr>
<tr>
<td>Physical</td>
<td>Tobacco</td>
<td>Did mother ever smoke cigarettes?</td>
</tr>
<tr>
<td>Physical</td>
<td>Alcohol</td>
<td>In the 6 months prior to or during pregnancy did mother drink any alcoholic beverages?</td>
</tr>
<tr>
<td>Physical</td>
<td>Alcohol</td>
<td>On average, how often did mother drink alcoholic beverages during the 6 months prior to or during pregnancy?</td>
</tr>
<tr>
<td>Physical</td>
<td>Drug</td>
<td>During this pregnancy, did mother use any of the following drugs? (cocaine, marijuana, hash/hashish, amphetamines, pain killers, glue sniffing, crack, heroin, barbiturates, valium, other)</td>
</tr>
<tr>
<td>Social</td>
<td>SES</td>
<td>Select the category that best represents the total annual family income.</td>
</tr>
<tr>
<td>Social</td>
<td>SES</td>
<td>What is mother’s marital status</td>
</tr>
<tr>
<td>Social</td>
<td>SES</td>
<td>In what type of house did mother live?</td>
</tr>
<tr>
<td>Social</td>
<td>Education</td>
<td>What was the highest grade of schooling mother has completed?</td>
</tr>
<tr>
<td>Social</td>
<td>Occupation</td>
<td>Was mother working during the 6 months before she became pregnant?</td>
</tr>
<tr>
<td>Social</td>
<td>Occupation</td>
<td>Was mother working during this pregnancy?</td>
</tr>
</tbody>
</table>

Note: CHC, chronic health condition, FH CHD, family history of congenital heart defect, SES, socioeconomic status.

Table 2

Infant Demographic Characteristics

<table>
<thead>
<tr>
<th>Infant outcomes</th>
<th>Mean</th>
<th>Range</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age</td>
<td>37.92 weeks</td>
<td>24-45 weeks</td>
<td>1,687</td>
<td></td>
</tr>
<tr>
<td>Birth weight</td>
<td>3.17 kg</td>
<td>.54-5.37 kg</td>
<td>1,687</td>
<td></td>
</tr>
<tr>
<td>simple</td>
<td></td>
<td></td>
<td>1,232</td>
<td>73</td>
</tr>
<tr>
<td>complex</td>
<td></td>
<td></td>
<td>453</td>
<td>26.9</td>
</tr>
</tbody>
</table>

### Table 3

*Maternal Characteristics (n=1,687)*

<table>
<thead>
<tr>
<th>Maternal Context</th>
<th>Maternal Context Variables</th>
<th>Demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biologic</td>
<td>Age</td>
<td>Mean 29.19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD 5.739</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range 14-48</td>
</tr>
<tr>
<td></td>
<td>Race</td>
<td>4.2 % African American</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.4 % Asian</td>
</tr>
<tr>
<td></td>
<td></td>
<td>86.2 % Caucasian</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.4 % Hispanic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.6 % Native American</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.2 % Other</td>
</tr>
<tr>
<td>Physical</td>
<td>BMI</td>
<td>Mean 26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD 6.26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range 15.19-56.57</td>
</tr>
<tr>
<td></td>
<td>Water type</td>
<td>62.8 % city</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20.3 % well</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13.6 % bottle</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.3 % other</td>
</tr>
<tr>
<td>Social</td>
<td>Marital</td>
<td>17.7 % single, widowed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>78.9 % married</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.3% divorced, separated</td>
</tr>
<tr>
<td></td>
<td>Housing</td>
<td>69 % single family</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12.8 % row/duplex/townhouse</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13.1 % apartment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.4 % trailer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.6 % other</td>
</tr>
<tr>
<td></td>
<td>Income</td>
<td>7.5 % &lt; $10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7.1 % $10-19999</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7.2 % $20-24999</td>
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Table 4

Maternal Health and Substance History (n=1,687)

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<tr>
<td>CHD</td>
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<td>Diabetes</td>
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<tr>
<td>Bladder</td>
<td>11%</td>
</tr>
<tr>
<td>HTN</td>
<td>11.4%</td>
</tr>
<tr>
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<td>13.8%</td>
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<td>Emotional disorder</td>
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<td>Flu or exp</td>
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*Note: HA=headache, HTN=hypertension, SHC=Serious health condition, CHD=congenital heart defect

Table 5

Logistic regression for predictors of type of CHD (simple complex or complex)

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*Note: SHC=Serious health condition, CHD=Congenital heart defect
*p < .05, **p < .001
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</table>

*Note: Resp inf= respiratory infection, HTN=hypertension, SHC=Serious health condition, CHD=congenital heart defect, BMI=body mass index

*p < .05, **p < .001
Table 7 (supplemental material)

*Correlations Matrix: Simple/complex CHD and BW and GA*

*Biologic maternal context variables*

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<th>Resp</th>
<th>HA</th>
<th>Emotion</th>
<th>HTN</th>
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*Note:* Comparisons were two-tailed and (1) Pearson’s r statistics, Spearman’s rho (2) or Phi Coefficient (3)

* Correlation is significant at the 0.05 level (2-tailed) **Correlation is significant at the 0.01 level (2-tailed)

*p<.05, **p<.0006.
Table 8

*Correlations Matrix: Simple/complex CHD and BW and GA
Physical Maternal context variables

<table>
<thead>
<tr>
<th></th>
<th>BW</th>
<th>GA</th>
<th>S/C</th>
<th>BMI</th>
<th>Obesity</th>
<th>Presdrug</th>
<th>MVI</th>
<th>H2O</th>
<th>Marij</th>
<th>Painkill</th>
<th>Smoke</th>
<th>ETOH 6 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>BW¹</td>
<td>1</td>
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<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>GA¹</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>S/C³</td>
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<td>.011</td>
<td>1</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Obesity³</td>
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<td>-.007</td>
<td>.018</td>
<td>-.645**</td>
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<td>.024</td>
<td>-.047</td>
<td>.063*</td>
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<tr>
<td>MVI³</td>
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<td>.005</td>
<td>.051*</td>
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<td>-.018</td>
<td>-.036</td>
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<td>.012</td>
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</tr>
<tr>
<td>marij³</td>
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<td>-.011</td>
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<td>.019</td>
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<td>painkill³</td>
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<td>-.028</td>
<td>.019</td>
<td>.094**</td>
<td>-.128**</td>
<td>-.107*</td>
<td>-.009</td>
<td>-.025</td>
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<td>-.029</td>
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<td>-.050*</td>
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<td>.056*</td>
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<td>.024</td>
<td>-.036</td>
<td>.014</td>
<td>.164**</td>
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</table>

*Note. Comparisons were two-tailed and (1) Pearson’s r statistics, Spearman’s rho (2) or Phi Coefficient (3)
* Correlation is significant at the 0.05 level (2-tailed)
**Correlation is significant at the 0.01 level (2-tailed)
*p=<.05, **p<.0006
Table 9
Correlations Matrix: Simple/complex CHD and BW and GA
Social Maternal context variables

<table>
<thead>
<tr>
<th></th>
<th>BW</th>
<th>GA</th>
<th>S/C</th>
<th>Marital</th>
<th>Annual income</th>
<th>Education</th>
<th>housing</th>
<th>Work before</th>
<th>Work during</th>
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<tbody>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>GA¹</td>
<td>.690**</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S/C³</td>
<td>-.014</td>
<td>.011</td>
<td>1</td>
<td></td>
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<tr>
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<td>-.038</td>
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<td>-.075**</td>
<td>.299**</td>
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<td>.049*</td>
<td>-.015</td>
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<td>Work before³</td>
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<td>.006</td>
<td>-.095**</td>
<td>-.173**</td>
<td>-.169**</td>
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<tr>
<td>Work during³</td>
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<td>-.191**</td>
<td>-.190**</td>
<td>.083**</td>
<td>.752**</td>
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</tbody>
</table>

Note. Comparisons were two-tailed and (1) Pearson’s r statistics, Spearman’s rho (2) or Phi Coefficient (3)
* Correlation is significant at the 0.05 level (2-tailed)
**Correlation is significant at the 0.01 level (2-tailed)
*p=.05, **p<.006.
<table>
<thead>
<tr>
<th>Birth outcomes</th>
<th>Birth weight</th>
<th>Gestational age</th>
<th>Simple/complex CHD</th>
</tr>
</thead>
<tbody>
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<td>Birth weight¹</td>
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</tr>
<tr>
<td>Gestational age¹</td>
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</tr>
<tr>
<td>Simple/complex CHD³</td>
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<td>.011</td>
<td>1</td>
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</tbody>
</table>

*Note. Comparisons were two-tailed and (1) Pearson’s r statistics, Spearman’s rho (2) or Phi Coefficient (3) *Correlation is significant at the 0.05 level (2-tailed) **Correlation is significant at the 0.01 level (2-tailed) *p<.05, **p<.001.
Chapter 5

The purpose of this study was to provide of synthesis of the manuscripts including a review of literature on the maternal risk factors for congenital heart defects CHD and the known genetic risk factors for CHD. A discussion of the findings from the dissertation study that identified significant relationships between the maternal context factors and the birth outcomes of their infants (type of CHD-simple/complex, birth weight, and gestational age) is provided. This chapter begins with a synthesis of the manuscripts and continues with a discussion, limitations, and future implications in theory, practice, education, research and policy.

Synthesis of Manuscripts

A review of literature of all CHD was performed to gain an enhanced understanding of the risk factors for CHD in the mother was the focus of the dissertation and the hypothesis. The exploratory research questions regarding birth weight and gestational age were undertaken to better understand and explain the type of CHD in this dataset. The first manuscript titled, “Association of Maternal Risk Factors and CHD” provided an examination of the current state of the science of the maternal context factors associated for having an infant with CHD. In this review of literature, identification of the maternal risk factors associated with CHD during pregnancy was analyzed and sorted into maternal context variables of biologic, physical and social contexts using a life course perspective. An abundance of literature was discovered initially and was narrowed to provide the most recent research. The majority of the literature was written by medical or epidemiological disciplines with limited literature in the nursing domain. In this review the studies consisted of population based, registry based, case control or
retrospective studies conducted worldwide. Several reviews were also discovered, which discussed specific maternal risk factors for CHD but, none of which contained all of the maternal contexts of interest in one study (Gorini, Chiappa, Gargani, & Picano, 2013; Luteijn, Brown, & Dolk, 2013; Patel & Burns, 2013; Stothard, Tennant, Bell & Rankin, 2009; Jenkins at al., 2007; Thulstrup & Bonde, 2006; Watson, Jacobson, Williams, Howard & DeSesso, 2006; Lin & Ardinger, 2005).

In the first manuscript, a review of literature of maternal CHD risk factors in pregnancy was conducted using the theoretical life course perspective as the context within which to place findings. The intention of the life course perspective is to understand, explain and improve health and disease patterns across various populations (Halfon & Hochstein, 2002). The life course perspective employs key components including timelines, timing, environment, and equity of health (Kotelcheck, 2011; Fine & Kotelcheck, 2010). These key components reflect the multilayer complexity of human life and health which is helpful when discussing a complex disease process such as CHD. Using this perspective allowed for arrangement of the risk factors identified in the literature under the realms of biologic, physical and social contexts. A conceptual framework was developed from the review of literature and framed using the life course perspective which then guided the dissertation study (see Figure 1).

In this review the maternal contexts associated with CHD identified in the literature included the biologic contexts of known genetic causes, maternal age, race, chronic health conditions, and family history of CHD; the physical maternal contexts of obesity, substance use, medication and vitamin use, and water consumption; and the social maternal contexts of socioeconomic status, occupation history, and educational
level (Gorini, Chiappa, Gargani, & Picano, 2013; Luteijn, Brown, & Dolk, 2013; Patel & Burns, 2013; Stothard, Tennant, Bell & Rankin, 2009; Jenkins et al., 2007; Thulstrup & Bonde, 2006; Watson, Jacobson, Williams, Howard & DeSesso, 2006; Lin & Ardinger, 2005). These maternal risk factors were found to be risk factors for developing CHD in their fetuses. Although, these risk factors were identified, many of the researchers recognized the limitations for accurately measuring the types of exposures, isolating the types of exposures, or identifying immediate causal relationships of the risk factors for CHD due to the multifactorial nature. Many researchers commented on the need for continued research of the etiology of CHD. Some suggested larger sample size and prospective studies to provide other perspectives to better understand the risks for CHD development in the fetus.

As a result of this review of literature, it was recognized that the current studies separated many of the maternal risk factors and did not provide a comprehensive review for all the maternal context variables. Small samples, others with methodological flaws and inability to accurately measure the variables associated with greater risk for CHD were identified in this process. It was also recognized that the genetic influence toward CHD must be elaborated separately to best appreciate the influence on CHD development. Therefore the second manuscript reviews the known genetic influences on CHD development.

The second manuscript titled, “Understanding Genetics and Pediatric Cardiac Health” was produced as the genetic association for CHD development was substantial and required further discussion. The objective of this manuscript was to provide a review of the known genetic pathways and risk factors associated with CHD development for
nurses and health care providers (HCPs). This manuscript provided an overview of inheritance patterns, identified genes associate with CHD, and discussion of the additional educational, clinical and research needed to better understand genetic CHD development. During the construction of this manuscript, limited nursing literature was found on this topic illustrating a need for greater understanding and integration of genetics into nursing practice and research. The majority of literature was found in the medical and epidemiological disciplines and well describes the known genetic influences on CHD formation.

The reviews of the maternal risk factors for having an infant with CHD helped identify the need to understand these risk factors. It was then proposed that these maternal contexts could influence the type of CHD in the infant. In this review the studies were case control with the majority studying the risk for general CHD rather than type of CHD. Some studies reviewed prevalence of the types of CHD, but no study was identified which compared risk for simple verses complex CHD, and if greater risk for complex CHD was present when more maternal contexts were present. This is the first study reviewing the maternal data from 2000-2010 in the WPCR database. Due to the lack of a robust control group a hypothesis was derived using the dependant variable-type of CHD (simple or complex) as there was an adequate sample size to provide comparison. The dissertation study was conducted using a life course perspective as this model acknowledges the multilevel interactions and trajectories of the mother. Using data within the WPCR from 2000-2010 exploration of the maternal data was performed to identify relationships to types of CHD (simple or complex). Two hypotheses and one exploratory research questions were asked.
**Hypotheses 1:** Multiple maternal risk factors of biologic (known genetic causes associated with CHD, age, race, chronic health conditions, family history of CHD), physical (history of obesity, use of alcohol, drugs, cigarettes, medication/vitamin use, and type of water consumed), and social variables (SES, occupation, education level) influence the risk of complex CHD.

**Hypothesis 2:** Multiple maternal risk factors (biologic, physical, social) influence the risk of low birth weight and/or early gestational age in the infants born with CHDs.

The third manuscript was constructed from this study, and is titled, “Maternal Health and Infants Born with Congenital Heart Disease: A Secondary Analysis of the WPCR”. This manuscript provided the study design, methodology and results of the dissertation study. In this study 1,687 completed questionnaires from 2000-2010 were used with focus on maternal and infant pre-conception and inter-conception history. The maternal history was self reported information and the infant history was a combination of reported information from the caregiver and clinical data provided by the research team. After thorough cleaning of the data, 29 questions were used to represent the 14 maternal context variables organized according to the conceptual model (see Figure 1). Descriptive analysis was conducted using these variables which provided rich demographic, health and social history information for this population. These variables were then analyzed for relationships between the maternal context variables and types of CHD and infant birth outcomes in which the significantly correlated variables were retained in the final analysis. The infant birth outcome of simple or complex CHD was developed from a model used in the larger Baltimore Washington Infant Study (Ferencz, Loffredo, Correa-Villaseñor, & Wilson, 1997) which the WPCR was modeled after. The
type of CHD was used to compare differences in this population as there was not an adequate control group available. With this large data set the comparison of risk for simple or complex CHD in this group was performed using logistic regression.

The WPCR went through several transitions over the years, moving from a print questionnaire and paper data source to completely electronic database. Due to these changes, during the cleaning of this dataset some variables were eliminated due to inconsistencies and concern for error and poor reliability. Data entry and interractor reliability was not able to be accurately assessed therefore text in variables were used cautiously. Education was the only text in variable retained in the final analysis and was re-coded into a categorical variable. All other variables for the final analysis were either continuous or categorical variables.

Another concern with using a large pre-existing data set was missing data. With guidance and constant review of the data from a statistician, missing values analysis was performed. In this dataset the variables selected did not contain significant amounts of missing data therefore a listwise deletion method was not used to preserve the entire dataset. The majority of missing data was < 10% missing, and the data missing more than 10% was well below 50%; therefore multiple imputations were used to impute the missing data (Tsikriktsis, 2005).

From the analysis of this dataset the third manuscript provided a discussion and presentation of the results of this study. The main findings of this study included two significant predictors for having a child with complex CHD. These two variables, maternal history of CHD (OR 2.382, 95 % CI, 1.424-3.984) and history of serious health condition (OR 1.537, CI 1.085-2.178) showed a greater risk for having an infant with
complex CHD. The women with reported personal history of CHD were 2.4 times more likely to have an infant with complex CHD. Although, this study was not a case control and cannot infer generalization to infants without CHD. The findings in this study was consistent with the literature, in which first degree family members with history of CHD had a 2-4 fold increased risk of any CHD in their offspring (Hinton et al., 2007; Lin & Ardinger, 2005; Ferencz et al., 1989). In Caputo et al. (2005) large case control study, they did not find a significant risk relationship in simple CHD (atrial septal defects). However, in Nora et al. (1969) study of atrial septal defect (ASD) and ventricular septal defect (VSD) inheritance risk, a 2.6-3.7% higher risk was noted. The majority of infants in this study (73%) had simple CHD, with about 1/3 of the infants having complex CHD (27%). This study supports the findings of having a first degree relative as a risk factor for complex CHD.

In the current study, history of a serious health condition was a significant predictor for complex CHD in the infant and is supported as a risk factor for CHD in the literature. This group of women was 1.5 times more likely to have an infant with complex CHD if the mother reported a serious health condition prior to or during the pregnancy. This variable was measured as a yes or no answer with the ability to text in the type of serious health. When the text comments were reviewed this variable was described by the mother with many different serious health conditions provided. The mother reported what they felt as a serious health condition. With this in mind this variable must be interpreted cautiously as the serious health conditions were defined loosely by some of the mothers in this study and may be difficult to accurately define a serious health condition. For example some mothers reported history of gestational diabetes, pre-
eclampsia, and falls as a serious health condition. Others did not specify the type of serious health condition.

Serious health conditions and several other chronic health conditions were included in the maternal context variable of chronic health conditions; which included history of hypertension, diabetes, flu, bladder infections, history of emotional disorders, chicken pox, and headaches as the literature found these conditions to be risk factors for CHD. Only the significantly correlated variables in this study were retained for the final logistic regression. History of a serious health condition six months prior or during pregnancy was the only significantly correlated chronic health condition found in the analysis. The finding from the current study supports the previous conclusions in the literature of having a serious health condition as a risk factor for having a child with a complex CHD. In the literature many serious and chronic health conditions were combined or grouped together, such as history of fever, diabetes, hypertension, and viral illnesses. Two studies identified that the timing of the serious health condition particularly early in pregnancy was important, as greater risk for CHD was observed (Oster, Riehle-Colarusso, Alverson, & Correa, 2011; Zen et al, 2011). Serious and chronic health conditions were noted to be risk factors for CHD including fever, diabetes, hypertension, and viral illnesses (Oster, Riehle-Colarusso, Alverson, & Correa, 2011, Stothard, Tennant Bell, & Rankin, 2011, Zen et al, 2011). This study did not support the history of diabetes, fever, hypertension or viral illness specifically; however, some mothers in the text descriptions of serious health conditions reported these conditions. Timing of the serious health condition is important to note. When illnesses occur either in the pre- or inter-conception timeframes, or first trimester can be important to determine
risk for CHD. Febrile illnesses in the first trimester have been associated with increased risk of all CHD (Oster, Riehle-Colarusso, Alverson, & Correa, 2011; Zen et al, 2011).

Maternal self report of serious health conditions was identified in this study to be a greater risk for having an infant with complex CHD. However, some caution should be made in this finding as the specificity of the serious health condition is not present. Also, when looking at the timing of the illness or serious health condition the timeframe of the questions is quite broad (6 months prior to or during the pregnancy) in which some of the serious health conditions may be a chronic problem and not accurately represented.

A second hypothesis was tested to determine if predictors for gestational age and birth weight were present in this study. To test this hypothesis hierarchical multiple regressions were used. Predictors of birth weight included; maternal history of hypertension, serious health condition six months prior/during pregnancy, CHD, obesity and income level. In the final regression model 4.4% of the variance of birth weight of these infants with CHD was explained, $R^2$ change = .044, $F$ change (1, 15911) = 10.125, $p < 0.05$.

In this sample of infants with CHD, the maternal context variables that had the most influence on birth weight in the regression model included; maternal chronic health conditions of hypertension or serious health conditions, history of maternal CHD, history of obesity and income level. This study supports the literature and risk for having a low birth weight infant if specific maternal context variables are present such as obesity and lower incomes levels (Messer et al., 2008). In pregnancy, maternal chronic health conditions are important to address as they can be predictors for the birth outcomes of gestational age and birth weight (CDC, 2011; UNICEF & WHO, 2002). This study was
consistent with the literature describing maternal risk factors of having an infant with low birth weight but the relationship was small as only 4.4-4.5% of the variance was described in the model. There are many influences of gestational age and birth weight in this sample that were not elicited from this model.

A hierarchical multiple regression was performed to assess predictors of gestational age in the group of infants with CHD. Predictors of gestational age included; maternal history of hypertension, flu, and serious health conditions 6 months prior/during pregnancy, and type of housing. In the final model 4.5% of the total variance of gestational age was explained, $R^2$ change = .004 $F$ change (1, 1680) = 7.875, $p < 0.05$.

Findings from the current study support the literature that associated maternal history of chronic health conditions (diabetes, hypertension, obesity) as a greater risk for having a premature infant as described above (Di Renzo, et al., 2011; Magnussen, Jatten, Myklestad, Salvesen, & Romundstad, 2011). Maternal history in the preconception period of diabetes (OR -0.6, CI; -2.1 to 0.8), hypertension (OR -1.8, CI; -3.2 to -0.5) and high cholesterol (OR -1.8 CI; -3.2 to -0.3) were associated with preterm birth < 37 weeks (Magnussen et al., 2011). The type of housing was also found to be a variable influencing the risk for prematurity and is consistent with the findings in Messer et al.’s (2008) census data study finding a small association between poor housing and preterm birth (OR 1.1-1.7). The majority women in this study with both simple and complex CHD infants predominantly lived in single family homes, educated and had middle to upper class income levels. However, the remainder of the participants may have been representative of a lower SES, with risk for nutritional deficiencies and environmental exposures which may explain the poorer birth outcomes. There were no reports of
homelessness, although this was not an option in the questionnaire. The BWIS (Ferencz et al. 1997) found in the women with lower SES a greater risk for CHD, particularly laterality and looping defects. The findings of this study supports the literature in which maternal health history and SES is crucial in the infants’ birth outcomes of birth weight, gestational age, and risk for CHD (Patel, 2012; Kučienė & Dulskienė, 2009). However the majority of the variance in this sample was not described in the model with ~95% of the predictors for gestational age and birth weight unable to be determined from this study.

The exploratory research question was posed, “Does the type of CHD (simple or complex) influence birth weight, and gestational age in infants born with CHD?” It was believed that the more complex the CHD the greater the risk for prematurity and low birth weight would be observed. However, in this study group of infants with CHD, type of CHD (simple or complex) was not significantly correlated to birth weight and gestational age, BW= -.014, GA .011, r). In this study, gestational age and birth weight were not found to influence type of CHD. The complex CHD infants did not overall have lower birth weights (simple, mean BW 3.18 kg vs. complex 3.16 kg) or history of prematurity (simple mean GA 37.91 weeks vs. complex 37.96 weeks) in this sample. In fact this group of infants with CHD was found to have generally normal mean birth weights and normal gestational ages.

In the literature, CHD has been associated with small for gestational age and lower birth weights (Malik, Cleves, Zhao, Hobbs & NBDS, 2007). Malik et al.’s (2007) study was a case control study which compared the severity of the heart defect and risk for low birth weight and gestational age. In Malik et al’s (2007) study, a system which
categorized simple CHD as a single lesion verses associated CHD which combined several CHD diagnoses was used. They found a significant difference in the small for gestational age in the simple (OR 1.96, CI; 1.67-2.30) versus the associated CHD groups (OR 2.54; CI; 1.99-3.23). The simple CHD cases represented 82.4% of the cases, whereas the associated cases represented less than 20% of the cases in this study.

**Limitations**

Using a large data set has many positive features; access to large samples, and cost-effective to the novice researcher as the data has already been collected, access multiple variables to analyze, and access to data which may not otherwise have been easily collected by nursing (Aponte, 2010; Pollack, 1999). As with the benefits of secondary analysis come limitations. The data was collected prior to the development of the hypothesis or research question, and congruency of the questions asked or tested can be compromised or may need to be altered dependent on the data (McCall & Appelbaum, 1991).

A major limitation of the WPCR was the lack of specific data on the timing of exposures. There were many variables included in this study; however, the dose response to exposure could not be elicited. The questions in the WPCR were not specific enough to isolate a critical time period prior or during pregnancy for exposures. Many of the maternal co-morbid conditions were collected as a yes/no question to having or being exposed six months prior to or during the pregnancy and text in variables avoided due to inability to accurately or reliably code.

Recall is a significant concern in the collection of maternal data. The questions were all asked, “Did an event occur prior or during pregnancy?” The WPCR tried to
decrease recall bias by enrolling infants less than two years of age and their caregivers to the study. Variables were chosen to avoid large amounts of missing data. But because of this there is limited information. Text in variables was not used therefore this study loses some ability to understand the complexity of CHD and use of sensitivity of this information.

From review of the literature, sensitive questions such as smoking, alcohol and drug consumption are known to be variables of bias and may not be accurately answered by the participants (Polit & Beck, 2008). Smoking, drug and alcohol history were included in this study and used with caution in the interpretation of results. Even though this study chose these variables with little missing data, sensitive questions are still problematic. In the analysis of missing data; these questions had more missing data than the other variables particularly if there were several questions associated with that variable. Therefore only yes/no questions were included in the analysis.

Generalizability of the results may be limited as the sample included only mothers of infants born in the state of Wisconsin from 2000-2010. Wisconsin was a predominantly Caucasian, middle class, Midwestern state during the data collection period, which may not be representative of other demographic locations in the United States. The sample in this study represented approximately 1/3 of the known infants and children with CHD who were approached to participate in the WPCR (1,687/4,919) and thus even the generalizability of findings to families in the state of Wisconsin may be limited (Harris et al., 2011).

In this study comparison between types of CHD (simple and complex) were used due to lack of a robust control group. The sample was large and provided the power to
answer the hypotheses. Although the WPCR began collecting a control group in 2007, the majority of the controls enrolled were adolescents seen for chest pain, syncope or murmur. Financial ability was a concern initially to enroll a control group. The control group when started was used to compare the genetic component, which the control group did not provide the type of data which would be useful for comparison to this data.

However, after a decade of collection the WPCR changed the questionnaire dramatically to adjust for concerns of reliability, consistency, and inability to draw conclusions from some of the questions asked. This poses concerns of the reliability of some questions used for the analysis in this study. Although, these concerns and limitations are present, this study was able to identify several maternal risk factors for type of CHD and the birth outcomes of these infants. Although the relationships in this study were small, these maternal context variables were associated with greater risk for complex CHD, lower birth weight and prematurity. The multiple and logistic regression results must be interpreted with caution as they do not imply causality (Pallent, 2007). More importantly this study provided a descriptive analysis of the maternal and infant data collected from 2000-2010.

**Implications**

**Implications for Theory**

The conceptual model was generated using literature that identified variables associated with risk for CHD development prior to and during pregnancy in women. From this review of literature sufficient gaps regarding the factors associated with the risk for developing a complex CHD were found and therefore this study undertaken to test these relationships
The results of this study generally supported the relationships of the maternal context variables to risk for infant outcomes delineated in the conceptual framework. However the study did not support every domain (biologic, physical, or social) or every variable in these domains. The biologic domain was the only category predicting risk for complex CHD. The physical and social domains did not reveal significant relationships. Similarly, the physical domain did not predict gestational age. These findings may be related to the positive health practices of the sample, the measurement of the variables, or to the lack of diversity in the sample. For CHD, this lack of relationship could also be related to the timing of the CHD development in which the other domains are not as influential for affecting type of CHD, as CHD development occurs early in gestation. It is possible that once the CHD occurs it is only biological factors that determine the type of CHD. Measurement of context variables available for the study may also have been problematic. Variables with greater specificity as well as objective measures of the concepts should be considered for future studies. The lack of diversity could have also limited the findings of social variables on outcomes.

An interesting finding was the lack of support for greater risk of low birth weight or prematurity in the infant with complex CHD. This finding differs from others in the literature where having CHD and particularly, complex CHD has been found to be a risk factor for premature birth and low birth weight in other studies (Williams et al., 2010; Malik, Cleves, Zhao, Hobbs, & NBDS, 2007). It is possible that once the CHD occurs it is only biological factors that determine the type of CHD

This was the first test of the proposed conceptual model. Although five relationships were not supported (physical and social to CHD; physical to gestational age
and CHD to birth weight and gestational age it is premature to revise the model based only this study. This is particularly true for the lack CHD to birth weight and gestational age where evidence of a relationship exists in the literature. Further research with demographically, geographically and ethnically diverse samples would be important to conduct for a robust test of the model.

**Practice**

The findings of this study have several implications for practice. The study showed an increased risk for complex CHD when the mother reported personal history of CHD or history of a serious health condition prior to or during the pregnancy. HCP’s should pay particular attention to women with a serious health condition and discuss with women of childbearing age the importance of alerting their HCP of any significant health care concern when it occurs. HCP’s can have a discussion with these women if a pregnancy is being planned and these risk factors are present to allow planning. In the recent publication from the AHA regarding management of fetal cardiac disease, parameters for intervention and scanning increased prenatal risk of CHD are provided (Donofrio et al, 2014). For example, if a mother has personal history of CHD, history of rubella, diabetes, or specific medication taken during the beginning of the pregnancy a fetal echo is recommended between 18-22 weeks gestation to screen for CHD. The findings of this study which is now concluding are in concert with the recommendations published within the Scientific Statement for the care of fetal cardiac disease. This study supports the recommendations for thorough screening of family history, maternal health history particularly history of CHD, CHC’s and/or infections to identify fetuses at risk for complex CHD and CHD in general. Early fetal diagnosis is critical in the prevention of
the increased morbidity and mortality associated with undiagnosed fetal CHD. A fetal echocardiogram may be performed in such cases when maternal history of CHD or serious health conditions are present, thus allowing for referral to perinatology, delivery coordination, or options for continuation of the pregnancy to be discussed.

Although, this study focuses on risk for type of CHD (simple or complex), maternal risk factors were identified in the literature review (Butler et al., 2014) identifying risks for all CHD. Identification of maternal CHD risk factors should become regular part of women’s care. Nurses and HCPs, whether at the beginning of their career or those who are experienced require continuing education in maternal health and promotion of healthy pregnancies. There is an expectation to maintain competency in these areas of healthcare, we must provide these resources for success. Continuing education may include case studies, case review, and morbidity and mortality discussions among the healthcare team as a regularly scheduled commitment to maintain up to date competency.

This study found that serious health conditions and maternal history of CHD to be risk factors for complex CHD. So recognition of serious health conditions and chronic health conditions (Liu et al., 2013; Oster, Colarusso, Alverson & Correa, 2011) and first degree family history (Romano-Zelekha et al., 2001) are important as the literature identified these maternal contexts as risk factors for all CHD development. It is important for HCPs to be aware of their patients’ health and family history as this information may alert the HCP of risk factors for CHD which could be flagged on the electronic health records when planning of future pregnancies.
Investigators continue to study the influences of epigenetic factors and generational health practices in the risk for CHD development. A thorough health history of the mother and father may provide the ability to identify risk factors for birth defects, particularly CHD and should be expected as a standard of care (Seibert, 2010). HCPs can identify these risks and counsel families and future generations of good healthcare practices prior to pregnancy to help decrease the risk of CHD and other infant diseases. As healthcare systems shift to a prevention model for healthcare delivery, nurses are uniquely positioned to identify and educate these men and women of childbearing age and can convey this information to decrease risk of CHD.

**Education**

In this study maternal history of serious health conditions and history of CHD showed an increased risk for complex CHD in the infant. Nurses requires educational resources which encompass the pre-conceptual health promotion practices for both women and men of childbearing age to identify risk for complex CHD and CHD in general. Education strategies to promote a greater understanding of the complexity of the environmental and genetic risk factors for CHD must be incorporated at all levels of education. Interactive dialogues and examples between instructors and students of normal pregnancy recommendations followed by the abnormal findings associated with CHD to illustrate the importance to be aware and ask questions to elicit information which can impact the care.

In 2001 the American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI) recognized that a greater understanding by all HCPs of the environmental and genetic influences was essential. An expert panel produced a policy
statement to share recommendations for education, research, and need for creation of interdisciplinary teams in the study of genetics and CHD (Ashley et al., 2012). This panel provided recommendations to address each discipline of HCP’s separately but recognizing a need all HCP’s to receive education in genetics. Therefore the “Core Competencies in Genetics for Health Professionals” was published in 2007. As only 10-15% of CHD etiologies are attributed to chromosomal or single gene mutations (Brent, 2004; Botto & Correa, 2003) with new research discoveries occurring rapidly the educational resources for HCPs require updates to reflect the new knowledge acquired.

**Future Research**

CHD is an elusive birth defect affecting multiple families worldwide. This study revealed two maternal context factors influencing the risk for complex CHD. However, as only 5% of the variance of the model was described by these contexts additional research is needed to understand the 95% of unexplained relationships. The majority of the influences of CHD were unexplained in this study; similar to much of the literature reviewed when studying non-genetic risk factors for CHD all which suggested the need for continued research (Fung et al., 2013; Patel & Burns, 2013; Jenkins et al., 2007). The NHLBI supports new research when studying CHD. A task force was created with focus on several areas of basic research, clinical outcomes research, and translational research with the hope of reducing CHD (NHLBI, 2001). Using a model which compared type of CHD may provide a different lens to view the risk factors for CHD. All of these women in this study appeared generally healthy but had infants with various forms of CHD, and approximately 1/3 with complex CHD. Future studies may also increase delineation
between severity of CHD and these risk factors between these groups in the analysis as well.

This study identified significant relationships between the maternal context variables and infant outcomes in this sample. There were several maternal context variables identified which influenced birth outcomes, however the majority of the variance in the models was not explained. Future research needs to include the paternal contexts which may provide a greater understanding of risk for CHD. The risk of complex CHD in this sample provided another perspective on CHD development other than case control methods. This may allow understanding of the subtle differences in the mother’s health when all had an infant with CHD. Most research stressed the need for more research isolating variables and exposures. This study may provide another method to view affects of health practices on the severity of CHD.

**Policy**

Secondary analysis may provide and avenue to advance science and the science of understanding CHD. However, attention to the quality and maintenance of the data must be acknowledged. The WPCR was helpful providing a glimpse of the maternal and infant data. In a time limiting funding opportunities secondary analysis can be advantageous method of research. As new researchers, locating large repositories of data may provide resources, previously unavailable to aid in the answers to research questions or development of new hypotheses. This study helped to recognize the needed skills, resources and expertise to use a large dataset is important in the success of the study. A multi-disciplinary team approach would be recommended to better understand the dataset to recognize the strengths and limitations of particular variables.
The AHA created an expert policy statement which highlights the relationship between genetics and cardiovascular disease (AHA, 2012). Congenital heart disease is a multifactorial process that requires a comprehensive approach recognizing the genetic and environmental interactions. The AHA recently published recommendations for fetal diagnosis and treatment of cardiac disease (Donofrio et al. 2014) that identified several maternal and paternal health conditions or history that can increase risk for CHD in their infants. These recommendations provide structured guidelines for nurses and HCP’s to help identify and treat families who may be at greater risk for complex CHD and CHD’s in general. This study and these guidelines may assist nurses and HCP’s in the treatment, screening and counseling of families affected by CHD.

Conclusion

CHD continues to be the leading birth defect in the world leading with extremely high rates of morbidity and mortality. Although, there have been immense advances in the understanding of cardiac formation in the fetus, the majority of CHD etiology remain unknown. This study identified maternal risk factors for having an infant with complex verses simple CHD. These findings of maternal history of CHD and history of a serious health conditions during pregnancy enhanced the understanding of the increased risk for complex CHD in their infants. Because of numerous exposures during pregnancy the importance of obtaining a complete health history is critical for identifying greater risk. It is critical for nurses and healthcare professions to become aware of these risk factors when caring for women of childbearing age so identification and interventions can proceed. It is essential to continue the search for risk factors associated with CHD, pinpointing the critical time frame for CHD development. Nurses and HCPs must remain
active in CHD research, education and evidence based practice techniques to improve the care provided to those affected by CHD. The findings of this study reinforce the necessity to intensively and accurately review family history, medical history and social history of all women of childbearing age. This particular cohort of women was overall healthy with few co-morbid conditions or risky behaviors reported and still gave birth to infants with CHD. Women are at risk for CHD, as nurses and healthcare professionals it is our responsibility to promote positive health practices and be aware of risk factors providing this valuable information to these patients.
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APPENDICES
Appendix A

August 7, 2013

Mary Butler
Medical College of Wisconsin
Department of Pediatrics, Cardiology
8701 Watertown Plank Road
Milwaukee, WI 53226

Dear Ms. Butler,

I am writing in response to your letter requesting use of Wisconsin Pediatric Cardiac Registry (WPCR) data for your dissertation project, The Influence of Maternal Context on Infant Outcomes: Secondary Analysis of WPCR data 2009-2010. We have reviewed your study proposal and a copy of the letter you obtained from the CHW Institutional Review Board giving your proposal (613/133) expedited approval as of July 25, 2013. The WPCR Scientific Advisory Committee recently reviewed your request. I am pleased to inform you that the committee has granted its approval, with the condition that any publications resulting from this work cite the WPCR as a data source.

Per your request, we will provide you with data on maternal environmental risk factors, infant diagnostics, and demographics for the years 2009-2010. Jennifer Yasch, WPCR Research Coordinator, will assist you in obtaining these data.

I look forward to the results of your study.

Sincerely,

Andrew Pelczak, MD
Director, Wisconsin Pediatric Cardiac Registry

Lead agency: Children's Hospital of Wisconsin - PO Box 1097, Milwaukee, WI 53201-1097
(414) 809-WPCR (877-809-9727) • (414) 266-2326 • wpcr@chw.org

Participating Institutions: Dean Medical Center, Milwaukee, Children's Hospital Medical Center, La Crosse,
Methodist South, Milwaukee Medical College, Milwaukee, Froedtert Clinic, Green Bay, St. John's Hospital, Marshfield, St. Mary's Hospital Madison, University of Wisconsin Hospitals and Clinics, Madison
Appendix B

Wisconsin Pediatric Cardiac Registry
Questionnaire (abbreviated)
(Maternal and infant variables used in the study)

INSTRUCTIONS: This comprehensive questionnaire is being given to the families of infants born with congenital heart defect in the state of Wisconsin. The information is important to our continuing efforts to discover if there are identifiable causes of these defects. All information is strictly confidential. Prior to completing this questionnaire you must have agreed to participate in the study and completed the required consent form. The questionnaire will take approximately 1 hour to complete. Completing this survey is voluntary. You may skip questions or quit at any time. You do not need to complete the entire questionnaire at one session. Please return both the consent form and the questionnaire to the address on the cover page. Once we receive your questionnaire, if there are questions that are left unanswered, the Registry Coordinator will follow-up with a telephone call to obtain the information. If you have indicated that you decline to complete those questions, we will not contact you further. Medical terms are defined in a glossary at the back of this questionnaire.

If you need help answering any of the questions, please call the Registry Coordinator at:
(877) 809-9727 or 414-266-2325

2. Sex:  male  female

4. What is your child’s birth date?  ____ / ____ / ____
   month day year

5. What was mother’s expected delivery date?  ____ / ____ / ____
   month day year

6. When was mother’s last menstrual period prior to this pregnancy?  ____ / ____ / ____
   month day year

Now we would like to ask you some questions about the baby’s mother and her health and family.

8. Please circle mother’s race or ethnic group:
   (a) African-American
   (b) Asian
   (c) Caucasian
   (d) Hispanic
   (e) Native American
   (f) Other, please specify: ________________________________

9. What is mother’s date of birth?  ____ / ____ / ____
   month day year

10. What is mother’s marital status?
    (a) Single (never married)
    (b) Married
    (c) Divorced
    (d) Separated
    (e) Widowed

12. Did/does mother have a congenital heart defect, a heart condition that she was born with?
    Yes*  No  Don’t Know

* If yes, please circle the correct answer below or write in the diagnosis.

a) Ventricular septal defect
b) Patent ductus arteriosus
f) Atrial septal defect
g) Coarctation of the aorta
c) Pulmonary valve stenosis h) Aortic valve stenosis
d) Tetralogy of Fallot i) Transposition of the great arteries
e) AV canal/endo cardiac cushion defect j) Bicuspid aortic valve

k) Other (please specify):

14. Did/does mother have any birth defect, malformation, or condition other than heart disease which was present from birth?
Yes* No Don't Know
*If yes, specify: ___________________________________________________________

Now we are going to ask about some illnesses that can last over a period of time and may sometimes have an effect on pregnancy.

33. Has mother ever been told she has diabetes?
Yes No* Don't Know

a) Did mother have diabetes only during this pregnancy? Yes No Don't Know
b) During the 6 months before this pregnancy or during this pregnancy did mother take insulin? Yes No Don't Know
c) During the 6 months before this pregnancy or during this pregnancy did mother take oral hypoglycemic pills or capsules? Yes No Don't Know

34. Has mother ever been told that she has any of the following illnesses?

<table>
<thead>
<tr>
<th>Illness</th>
<th>Has mother ever had:</th>
<th>Age at onset (year)</th>
<th>Duration (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Asthma or allergies</td>
<td>Illness: Yes* No</td>
<td>Treatment: Yes* No</td>
<td></td>
</tr>
<tr>
<td>b) Epilepsy (seizures)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c) Thyroid disease (specify)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d) Systemic lupus (SLE)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e) Peptic ulcer disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>f) Eating disorder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>g) Cancer (specify)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>h) Other (specify)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

35. In the 6 months prior to or during this pregnancy did mother have any of the following illnesses or conditions?

<table>
<thead>
<tr>
<th>Illness</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) High blood pressure</td>
<td></td>
</tr>
<tr>
<td>b) Obesity (overweight)</td>
<td></td>
</tr>
</tbody>
</table>
c) Bladder or kidney infections

d) Emotional (psychiatric) problems, including depression - please specify:

___________________________

e) Vaginal infection:
   gonorrhea
   syphilis
   herpes
   other, please specify:

f) Arthritis

g) Headaches

h) Colds, sinus infections, bronchitis, pneumonia (please circle whichever apply)

---

36. In the **6 months prior to or during this pregnancy** did mother have or **was mother exposed** to anyone with the following infections (if yes, check the appropriate time period):

<table>
<thead>
<tr>
<th>Infection</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza (flu)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mumps</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rubella</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chicken pox or shingles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIDS or HIV</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

39. During this pregnancy did mother ever have a **fever** of 101°F or higher?

Yes*  No  Don't Know

42. In the **6 months prior to or during this pregnancy** did mother have any other **serious health problem** or was she hospitalized for any reason, excluding delivery?

Yes*  No  Don't Know

*If yes, please specify:

43. Did mother take **vitamins or multi-vitamins** during this pregnancy?

Yes*  No  Don't Know
44. Did mother take any other “over-the-counter” health food or herbal supplements during this pregnancy?

Yes*  No  Don't Know

*If yes, please list the brand name:

46. During this pregnancy, did mother regularly take any medication not mentioned above?

Yes*  No  Don't Know

*If yes, please specify:

47. What is mother's height? ______ ft. ______ in.

48. What was mother's pre-pregnancy weight? _______ lbs.

49. How much weight was gained during this pregnancy? ______ lbs.

55. Did mother ever smoke cigarettes?

Yes  No*  Don't Know

a.) Did mother smoke during the 6 month period prior to this pregnancy?

Yes**  No  Don't Know

b.) Did mother smoke during this pregnancy?

Yes**  No  Don't Know

59. During the 6 months prior to this pregnancy or during this pregnancy, did mother drink any alcoholic beverages (beer, wine, or liquor)?

Yes  No*  Don't Know

64. During this pregnancy, did mother use any of the following drugs?

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine</td>
<td>Never</td>
</tr>
<tr>
<td>Marijuana</td>
<td></td>
</tr>
<tr>
<td>Hash or Hashish</td>
<td></td>
</tr>
<tr>
<td>Amphetamines (uppers, speed)</td>
<td></td>
</tr>
<tr>
<td>Pain Killers (Percocet, Percodan, etc.)</td>
<td></td>
</tr>
<tr>
<td>Glue Sniffing</td>
<td></td>
</tr>
<tr>
<td>Crack</td>
<td></td>
</tr>
<tr>
<td>Heroin</td>
<td></td>
</tr>
<tr>
<td>Barbiturates (Downers)</td>
<td></td>
</tr>
<tr>
<td>Valium</td>
<td></td>
</tr>
<tr>
<td>Other Drugs (please specify)</td>
<td></td>
</tr>
</tbody>
</table>
69. In what **type of house** did **mother** live?
   a) Individual (unattached) house
   b) Row, duplex, or townhouse
   c) Apartment
   d) Trailer
   e) Other:________________________(specify)

72. What was the **source of mother's drinking water** during this pregnancy?
   a.) City water
   b.) Well water
   c.) Bottled water
   d.) Other, please specify: ________________________________

75. Please look at the table and select the category that best represents the total annual family income (before taxes):

<table>
<thead>
<tr>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>a.) Less than $10,000</td>
</tr>
<tr>
<td>b.) 10,000 - 19,999</td>
</tr>
<tr>
<td>c.) 20,000 - 24,999</td>
</tr>
<tr>
<td>d.) 25,000 - 49,999</td>
</tr>
<tr>
<td>e.) 50,000 - 99,999</td>
</tr>
<tr>
<td>f.) Greater than 100,000</td>
</tr>
</tbody>
</table>

77. What is the **highest grade of schooling** mother has completed? __________

79. **Was mother working during the 6 months before** she became pregnant?
   Yes      No*     Don't Know*

84. **Was mother working during** this pregnancy?
   Yes      No*     Don't Know

**Now we would like to ask for some information about the baby.**

131. How much did he/she **weigh** at birth? ___ ___ lbs. ___ ___ oz.
Appendix C

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| Author of this NPG article | no |
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| Title of your thesis / dissertation | The Influence of Maternal Contexts on Infant Outcomes, Secondary Analysis of WPCR data 2000-2010 |
| Expected completion date | May 2014 |
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Appendix E

July 26, 2013
Mary Butler, MS - PV
Kathleen Sones, PhD, RN - MS 300

Dear Ms. Butler and Dr. Sones,

Please be advised that your protocol entitled The Influence of Maternal Contexts on Infant Outcomes, Secondary Analysis of WPCR data 2000-2010 was given expedited approval on July 25, 2013 for Children’s Hospital of Wisconsin (CHW).

1. Clinical studies of drugs and medical devices only when condition(s) or (b) is met. (a) Research on drugs for which an investigational new drug application (IND) is not required. (Note: Research on marketed drugs that increases the risk or decreases the acceptability of the risk is not eligible for expedited review). (b) Research on medical devices for which (a) an investigational device exemption application (IDE) is not required, or if the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows: (a) from healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amount drawn may not exceed 50 ml in an 8 week period and collection may not occur more frequently than 1 times per week, or (b) from other adults and children considering the age, weight, and health of the subject; the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects the amount drawn may not exceed the lesser of 30 ml or 3 ml per site in an 8 week period and collection may not occur more frequently than 1 times per week.

3. Prospective collection of biological specimens for research purposes by noninvasive means. Examples: (a) Hair and nail clipping; (b) venous blood at time of enrollment or if routine patient care indicates a need for extraction; (c) mesentery and external abortions (including those accumulated saliva; (f) sputum collected after saline instillation.

4. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microphones. Where medical devices are employed, they must be cleared/approved for marketing and used in accordance with its cleared/approved labeling. Examples: (a) Physical features that are applied either to the surface of the body or at a distance and do not involve insertion of significant amount of energy into the subject or an invasion of the subject’s privacy; (b) weighing or talking heavy objects, (c) magnetic resonance imaging; (d) electrocardiography, electromyography, echocardiography, electroencephalography, electroretinography, or radiography; (e) moderate exercise, mastectomy, gynecologic screening, barium enema, intravenous pyelography, transabdominal ultrasound imagining, Doppler blood flow, and echoradiography; (g) moderate exercise, mastectomy, gynecologic screening, barium enema, intravenous pyelography, transabdominal ultrasound imagining, Doppler blood flow, and echoradiography; (g) moderate exercise, mastectomy, gynecologic screening, barium enema, intravenous pyelography, transabdominal ultrasound imagining, Doppler blood flow, and echoradiography; (f) moderate exercise, mastectomy, gynecologic screening, barium enema, intravenous pyelography, transabdominal ultrasound imagining, Doppler blood flow, and echoradiography; (f) moderate exercise, mastectomy, gynecologic screening, barium enema, intravenous pyelography, transabdominal ultrasound imagining, Doppler blood flow, and echoradiography.

5. Research involving materials (data, documents, records, or specimens) that have been collected as part of research purposes (such as medical treatment or diagnosis).

   • ALL DATA TO BE USED FOR THIS STUDY MUST EXIST AS OF THE DATE OF THE IRB APPROVAL. ANY PROSPECTIVE DATA NEEDS CONSENT, ASSENT AND HIPAA FORMS WITH A DIFFERENT APPLICATION.

   • DATA LIKE MEDICAL RECORD NUMBER, NAME, DATE OF BIRTH, CASE NUMBERS, SHOULD BE KEPT ON SEPARATE FORM OR FILE FROM CLINICAL DATA.

   • BASED ON OUR REVIEW, THE WAIVER OF HIPAA AUTHORIZATION FORM HAS BEEN ACCEP TED. THIS WAIVER HAS ONLY BEEN REVIEWED TO ENSURE ALL REQUIRED ITEMS HAVE BEEN COMPLETED. IT IS THE RESPONSIBILITY OF THE RESEARCHER TO ENSURE THE ACCURACY OF THE INFORMATION PROVIDED ON THIS FORM AND THE MINIMUM INFORMATION NEEDED TO COMPLETE THE STUDY IS REQUESTED.

   • WAIVER OF CONSENT FOR RETROSPECTIVE CHART / DATA REVIEW - THE RESEARCH INVOLVES NO MORE THAN MINIMAL RISK TO THE SUBJECTS, WILL NOT ADVERSELY AFFECT THE RIGHTS AND WELFARE OF THE SUBJECTS AND THE RESEARCH COULD NOT PRACTICALLY BE DONE WITHOUT THE WAIVER.

6. Collection of data from voice, video, digital, or image recordings made for research purposes.
7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

For purposes of identification, this research has been assigned the following number: 13/133.

This protocol is approved for 1-year from the date of the Board meeting and a continuing review is scheduled for July 24, 2014. A Continuing Review Form will be forwarded three months prior to this review date. Failure to submit the Continuing Review Form in a timely manner may result in the termination of your research approval.

Children’s Hospital of Wisconsin and the Medical College of Wisconsin require that all prospectively assigned and intervention or comparison studies be registered according to Public Law 110-85 (also known as the FDA Amendment Act). This was enacted on September 27, 2007 amending the Public Health Service Act to mandate registration and results reporting of applicable clinical trials. Please go to clinicaltrials.gov to register your study.

Any changes to this study and any serious adverse reactions, or death, must be reported immediately to the Children’s Hospital of Wisconsin’s Institutional Review Board.

Federal regulations require that if any advertising is involved in the initiation of this protocol, prior approval must be obtained from Children’s Hospital’s IRB.

If this is a sponsored research project, it is incumbent upon the Principal Investigator to be aware of the Quality Assurance requirements of the sponsor and to carry out the project accordingly.

When the above work is completed or discontinued, the Board must be notified in order to maintain an accurate record of all current projects.

If you leave the staff of the hospital, you are expected to notify the Board in writing to whom the protocol should be transferred; otherwise, the protocol will be terminated.

Sincerely,

Robert Schum, PhD, Chair
Institutional Review Board #2

cc: Glenda Watkins
Curriculum Vitae
Mary R. Butler

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Journal of Pediatric Nursing 2010
Referred Journal Publications/Original Papers:


