Mothers of Infants with Heart Defects and Increased Long-Term Risk of Cardiovascular Disease

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Abstract
Background: Cardiovascular disease (CVD) is responsible for approximately 1 in every 3 deaths of women in the United States. Recognizing the symptoms and predicting presentation is extremely difficult, particularly for women. If providers are able to determine risk factors early on, preventative measures or treatment can be initiated. This review assesses the evidence of whether having an infant with heart defects increases a woman's long-term risk of developing CVD. Methods: A comprehensive literature search was conducted using MEDLINE-PubMed, Web of Science, and CINAHL. The following keywords were utilized in the search: women, maternal health, mothers, cohort study, mortality, cardiovascular, infant, long term and congenital. These articles were assessed for quality using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) guidelines. Results: Two studies that met inclusion criteria were included in this literature review. One retrospective observational study found that there was an increased risk of mothers of infants with critical or noncritical heart defects had an increased risk of developing CVD when compared to mothers of infants without heart defects. The other retrospective observational study concluded that mothers of infants born with a major congenital anomaly had a minor but statistically significant increased risk of mortality when compared to mothers of infants born without congenital anomalies. Conclusion: Mothers of infants with heart defects have an increased long-term risk of CVD. This information can be utilized to help increase screening and adjust treatment plans for women in this category who are at an increased risk for CVD. Additional research would determine if the risk further increased in post-menopausal women who are already at a higher risk of developing CVD.

Degree Type
Capstone Project

Degree Name
Master of Science in Physician Assistant Studies

Keywords
Women, maternal health, cardiovascular disease, infant, congenital anomaly, heart defect

Subject Categories
Medicine and Health Sciences

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Mothers of Infants with Heart Defects and Increased Long-Term Risk of Cardiovascular Disease

Anne Crowl

A Clinical Graduate Project Submitted to the Faculty of the
School of Physician Assistant Studies
Pacific University
Hillsboro, OR
For the Masters of Science Degree, August 10, 2019
Faculty Advisor: Annjanette Sommers, PA-C, MS
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

Anne Crowl is an Idaho native who graduated from Idaho State University with a Bachelor’s of Science degree in Biology with a concentration in Biomedical Sciences. She worked as a medical scribe and volunteered as part of a medical team providing care to underserved populations in Peru prior to starting Physician Assistant school.
Abstract

**Background:** Cardiovascular disease (CVD) is responsible for approximately 1 in every 3 deaths of women in the United States. Recognizing the symptoms and predicting presentation is extremely difficult, particularly for women. If providers are able to determine risk factors early on, preventative measures or treatment can be initiated. This review assesses the evidence of whether having an infant with heart defects increases a woman’s long-term risk of developing CVD.

**Methods:** A comprehensive literature search was conducted using MEDLINE-PubMed, Web of Science, and CINAHL. The following keywords were utilized in the search: women, maternal health, mothers, cohort study, mortality, cardiovascular, infant, long term and congenital. These articles were assessed for quality using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) guidelines.

**Results:** Two studies that met inclusion criteria were included in this literature review. One retrospective observational study found that there was an increased risk of mothers of infants with critical or noncritical heart defects had an increased risk of developing CVD when compared to mothers of infants without heart defects. The other retrospective observational study concluded that mothers of infants born with a major congenital anomaly had a minor but statistically significant increased risk of mortality when compared to mothers of infants born without congenital anomalies.

**Conclusion:** Mothers of infants with heart defects have an increased long-term risk of CVD. This information can be utilized to help increase screening and adjust treatment plans for women in this category who are at an increased risk for CVD. Additional research would determine if the risk further increased in post-menopausal women who are already at a higher risk of developing CVD.

**Keywords:** Women, maternal health, mothers, mortality, cardiovascular disease, infant, long term, congenital anomaly, heart defect
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<td>CAD</td>
<td>Coronary artery disease</td>
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<td>CI</td>
<td>Confidence interval</td>
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<td>CVD</td>
<td>Cardiovascular disease</td>
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<td>FRS</td>
<td>Framingham risk score</td>
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<tr>
<td>HR</td>
<td>Hazard ratio</td>
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<td>Myocardial infarction</td>
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Mothers of Infants with Heart Defects and Increased Long-Term Risk of Cardiovascular Disease

BACKGROUND

Cardiovascular disease (CVD) is a catastrophic condition plaguing both men and women worldwide. It is the foremost cause of mortality for females and is responsible for approximately one in every three deaths of woman in the United States.¹ Cardiovascular disease is a condition that affects the heart and surrounding vessels and encompasses many disease processes including myocardial infarction (MI), arrhythmias, cerebrovascular accident (including transient ischemic attacks), and heart valve defects.² Some of these disease processes are more prevalent in one sex versus the other, making it vastly important for healthcare providers as well as individuals to know what disease process each sex is more likely to be at risk for. For example, the coronary syndromes seen more frequently in women than men include coronary artery dissection, MI associated with non-obstructive coronary arteries, cardiomyopathy (pregnancy-associated and stress/Takotsubo cardiomyopathy), and heart failure with preserved ejection fraction.¹

Cardiovascular disease can be difficult to detect as well as predict in women compared to men since their symptoms and presentations are typically not as straightforward. For instance, the most common and classic presenting symptoms of a MI in men are chest pain, shoulder pain, arm pain and jaw pain. In contrast, the most common presenting symptoms of a MI in women are chest pain, nausea,
back pain, dizziness, and palpitations.\textsuperscript{3} Cardiovascular disease is not only elusive in presentation to healthcare providers, but also to the patients potentially experiencing the symptoms. When surveyed about the warning signs of a MI, only 56\% of women identified the commonly recognized symptoms of chest pain along with shoulder, arm and neck pain that comes with the most identifiable symptoms.\textsuperscript{4} Just 29\% of women acknowledged shortness of breath, 17\% chest tightness, 15\% nausea, and 7\% fatigue.\textsuperscript{4} Recognition and the decision to seek treatment can be a large barrier in women with CVD.

Although women can have entirely different presentations as well as risk factors for CVD than men, the same screening tools are used to determine the need for preventative measures and treatment. The Framingham risk score (FRS) is among the most commonly utilized screening tools to predict a patients’ 10-year risk of death due to coronary artery disease (CAD), specifically a MI.\textsuperscript{5} Treatment for the prevention of CVD, like a MI, is based on the percentage calculated by the FRS. Yet when using the FRS to determine cardiovascular risk, >90\% of women are classified as “low risk” and hardly any are deemed “high risk” before age seventy.\textsuperscript{6} This makes the clinical detection of any predisposing risk factors crucial for the prevention of CVD related mortality in women.

Certain risk factors have a known association with increased risk for CVD including diabetes, hypertension, smoking obesity, and dyslipidemia.\textsuperscript{7} If a woman is determined to have a predisposing risk factor for CVD, her medical provider can initiate preliminary prevention tactics and treatment. Treatment options for a patient at risk for CVD include lifestyle modifications, daily aspirin, antihypertensive medication, and statin therapy. A newly proposed possible risk factor for increased risk of long-term
CVD is women who give birth to infants with heart defects. If the research is legitimate, this could mean a change in screening and potentially initiate earlier treatment plans for the women of this specific population. The objective of this literature review is to explore if mothers of infants with heart defects have a correlated increased long-term risk of CVD.

**METHODS**

A comprehensive literature search was conducted using MEDLINE-PubMed, Web of Science, and CINAHL. The following keywords were utilized in the search: women, maternal health, mothers, cohort study, mortality, cardiovascular, infant, long term and congenital. Studies were included that monitored the health of mothers of infants with congenital defects, particularly cardiac, and examined subsequent cardiac-related complications, hospitalizations, and mortality of these women. Additional inclusion criteria required articles to be published in English. Publications were assessed for qualification and quality using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) guidelines.8

**RESULTS**

The primary literature search yielded 22 articles for review. After screening the titles and abstracts for eligibility and eliminating any duplicate studies, a total of 2 articles met inclusion criteria. These articles were retrospective observational studies.7,9 See Table 1. An additional study10 that was a meta-analysis of prenatal diagnosis of
major congenital heart disease was considered, but ultimately excluded because it did not include specific follow-up of the mothers.

**Auger et al**

In this retrospective observational study of 1084 251 women in Quebec, Canada from 1989 to 2013 who had given birth to infants with heart defects were evaluated for cardiovascular hospitalizations later in their lives. Of the woman evaluated, 1516 had infants with critical heart defects and 14 884 has infants with noncritical heart defects. The defects were considered critical based on the interventions and treatment required post-delivery to prevent sequelae, whereas noncritical defects required less intervention and treatment could potentially be delayed for longer periods of time or not required at all. The authors considered the following heart defects to be critical: transposition of the great vessels, tetralogy of Fallot, truncus arteriosus, coarctation of the aorta, hypoplastic left heart syndrome, common ventricle, as well as congenital defects that included total anomalous pulmonary venous return such as Ebstein anomaly and pulmonary/tricuspid atresia. The authors considered the following heart defects to be noncritical: atrial septum defect, ventricular septum defect, valve anomaly, endocardial cushion defect, pulmonary artery anomalies, heterotaxy, and aorta anomalies.

Women in the study were categorized into 3 groups: 1) women who delivered at least 1 infant with a critical heart defect, 2) women who delivered at least 1 infant with a noncritical heart defect, and 3) women who delivered infants with no heart defects. If a woman gave birth to an infant with both a critical and noncritical heart defect, the infant was categorized as having a critical heart defect. The authors made a separate category for women who gave birth to infants that had multiple heart defects that were exclusively
either critical or noncritical. The authors used both diagnostic and procedure codes to detect all women who were hospitalized and given a diagnosis that is categorized under CVD, or underwent a cardiovascular procedure in the 25 year follow-up timeframe. Women that were found to have more than one cardiovascular diagnosis were entered into all outcome categories. The possible confounders that the authors considered were the following: maternal age at initial delivery (<20, 20-24, 25-29, 30-34, 35-39, ≥40), time of initial delivery (1989-1996, 1997-2004, 2005-2012), preeclampsia (yes, no), mothers total parity (1, 2, ≥3), comorbidity or subsequent admission during pregnancy (depression, obesity, diabetes mellitus, dyslipidemia), and maternal deprivation (socioeconomic deprived neighborhoods).  

In the authors’ analysis of their data, the incidence of cardiovascular hospitalization was estimated per 1000 person-years and the cumulative incidence was calculated after 25 years of follow-up for women in 1 of the 3 allocated groups stated above. The cumulative incidence was estimated using the cumulative incidence function\(^{11}\) to account for death being a competing outcome. The authors then used the counting process method\(^ {16}\) to compute 95% confidence intervals (CIs). Time modules including the Weibull distribution and the Cox model\(^{6}\) were used to calculate the median time, measured in years, necessary to acquire a cumulative incidence of 5 cardiovascular hospitalizations for every 10 000 women. The Weibull distribution was used to determine proportional hazards and the Cox model was utilized to calculate the hazard ratio and 95% CIs. These calculations were employed to determine the HR and 95% CI for the association between mothers of infants born with heart defects and the subsequent risk of hospitalization for cardiovascular etiology.\(^{7}\)
The authors found that the incidence to cardiovascular hospitalization for mothers of infants with heart defects was increased. There was a >25% increased risk of any cardiovascular hospitalization occurring later in life for mothers of infants born with heart defects, critical or noncritical. For woman of infants with critical heart defects there were 3.38 cardiovascular hospitalizations per 1000 person-years (95% CI of 2.67-4.27), for woman of infants with a noncritical heart defect there were 3.19 (95% CI of 2.96-3.45), and for infants with no heart defects there were 2.42 (95% CI of 2.39-2.44). In the adjusted models, when compared to woman whose infants did not have any heart defects, the adjusted HR was 1.43 (95% CI of 1.13-1.82) for critical defects and an adjusted HR of 1.24 (95% CI of 1.15-1.34) for noncritical defects. According to the authors, the was no evidence that the difference between specific heart defects was statistically significant.

The authors also discovered that mothers of infants with heart defects were at an increased risk for specific causes of CVD. The specific causes of CVD that they measured included: heart failure, ischemic heart disease, MI, angina, cardiac arrest, inflammatory heart disorder, conduction disorder, valve disorder, cardiomyopathy, pulmonary embolism, pulmonary vascular disease, ischemic stroke, hemorrhage, hypertension, other atherosclerosis, aortic aneurysm/dissection, deep vein thrombosis, arterial embolism and aneurysm of other vessels. They also followed the women’s need for any cardiac-related interventions including: coronary angioplasty, coronary artery bypass graft, pacemaker insertion, valve surgery, cardiac transplant, coronary care unit or any intervention. Some of the significant findings for women of infants with noncritical heart defects were that they had 2.08 times increased risk of heart failure (95% CI of
1.53-2.82), 2.13 times the risk of having a pacemaker inserted (95% CI of 1.29-3.52), and 2.52 times the risk of pulmonary vascular disease (95% CI of 1.54-4.11). The findings for mothers of infants with critical heart defects included a 2.61 times the risk of MI (95% CI of 1.31-5.20), 3.04 times the risk of other atherosclerotic disease (95% CI of 1.72-5.36), and 43.2 times the risk of cardiac transplant (95% CI of 6.41-291.7). Although the authors discovered that the critical heart defects had an often stronger association than the noncritical heart defects, they concluded that there was not a statistically significant difference between the two groups.7

Cohen et al

In this retrospective observational study9 conducted in Denmark, the outcomes of 455 250 women who had given birth to an infant with a congenital abnormality were assessed to determine if there was an increased risk of mortality in this population. The median follow-up for the mothers was 21 years (ranging from 12-28 years). The authors utilized the Medical Birth Registry,11 which includes information about all deliveries that take place in Denmark, to initially identify mothers who had given birth between 1979-2010. They then narrowed the study to women who survived at minimum 1 year post-delivery, to exclude possible mortality due to pregnancy-related complications, and who had at least 2 years of health data records prior to delivery, to adjust for any preexisting comorbidities. Twin pregnancies and stillbirths were also excluded from the data. The authors created a comparison cohort by randomly sampling up to 10 mothers of infants without any congenital anomalies for every mother in the congenital anomaly group that was matched by parity, maternal age, and the infant’s birth year. This comparison cohort consisted of 413 742 mothers.9
The authors identified infants with major congenital abnormalities using the Danish National Patient Registry,\textsuperscript{12} which has information regarding all Danish hospitalizations since 1977 as well as all emergency department and outpatient information since 1995. The congenital anomalies were then defined by using the European Surveillance of Congenital Anomalies classification system,\textsuperscript{13} and both major congenital anomalies diagnosed in the outpatient setting or any that were caused by hip dysplasia or dislocation were excluded from the study due to inadequate accuracy of their diagnoses in the Danish registry data.\textsuperscript{14} The authors subdivided the major congenital anomalies into 2 groups: single-organ which accounted for 37,406 and 90.1\% of the infants, or anomalies that affect more than 1 organ system which accounted for 4102 or 9.9\% of the infants with a congenital anomaly. For mothers that gave birth to more than one infant with a major congenital anomaly, only the first infant born with the anomaly was counted in the study. The mean age at delivery of the 2 cohorts of mothers was 28.9 with a standard deviation 5.1.\textsuperscript{9}

In the authors’ data analysis, their primary outcome was considered to be all-cause mortality with the secondary outcomes being cause-specific mortality. The authors adjusted for many variables including the following: pregnancy complications, prior spontaneous abortion, marital status, immigration status, modified Charlson comorbidity index score, diabetes mellitus, hypertension, history of any alcohol-related disease, depression, income quartile (starting 1980), level of education (starting 1981), smoking (starting 1991) and body mass index (starting 2004). The authors then performed a survival analysis utilizing a time-to-event Cox proportional hazard regression analysis.
with HRs and 95% CIs so they could compare mortality risk between mothers of infants with congenital anomalies and mothers of infants without congenital anomalies.\textsuperscript{9}

The authors found that mothers who gave birth to infants with a major congenital anomaly had an increased risk for mortality than mothers of infants born without congenital anomalies. There were 1275 deaths among the 41 508 mothers of infants with a major congenital anomaly (3.1%), which equated to 1.60 per 1000 person-years at a mean age of 49.2 years (standard deviation of 9.4 years). In comparison, there were 10 112 deaths among the 413 742 mothers of infants born without congenital anomalies (2.4%), which equated to 1.27 per 1000 person-years at the mean age of 49.2 years (standard deviation of 9.4 years). The calculated absolute mortality rate difference between mothers of children born with a major congenital anomaly and without was 0.33 per 1000 person-years (95% CI of 0.24-0.42), with an unadjusted HR of 1.27 (95% CI of 1.20-1.35), and an adjusted HR of 1.22 (95% CI of 1.15-1.29). The data for mothers of infants with a major congenital anomaly that affected a single organ was a rate difference of 0.32 (CI of 0.22 to 0.41), with an unadjusted HR of 1.26 (CI of 1.18 to 1.34), and an adjusted HR of 1.21 (CI of 1.14 to 1.29). In comparison, the rate difference for mothers of infants born with a congenital anomaly that affected more than one organ was 0.49 (CI of 0.18 to 0.80), with an unadjusted HR of 1.40 (CI of 1.16 to 1.69), and an adjusted HR of 1.31 (CI of 1.08 to 1.59).\textsuperscript{9}

When the authors compared the causes of mortality between the 2 groups, they found that mothers of infants born with a major congenital anomaly were more likely to die of certain diseases when compared to mothers of infants born without a congenital anomaly. The data indicated these mothers were more likely to die of cardiovascular
disease with a rate difference of 0.05 per 1000 person-years (95% CI of 0.02-0.08), and an adjusted HR of 1.26 (95% CI of 1.04-1.53), specifically including MI with a rate difference of 0.02 per 1000 person-years (95% CI of 0.01-0.04), and an adjusted HR of 1.97 (95% CI of 1.28-3.02). They also were more likely to die of respiratory diseases with a rate difference of 0.02 per 1000 person-years (95% CI of 0.00-0.04) with an adjusted HR of 1.45 (95% CI of 1.01-2.08), as well as other natural causes with a rate difference of 0.11 per 1000 person-years (95% CI of 0.07-0.15) and an adjusted HR of 1.50 (95% CI of 1.27-1.76). Deaths caused by cancer were also slightly increased among the mothers of infants with a major congenital anomaly with a rate difference of 0.06 per 1000 person-years (95% CI of 0.00-0.12) and an adjusted HR of 1.11 (95% CI of 1.00-1.22). In contrast, women whose infants were born with a major congenital anomaly were not more likely to die from unnatural, meaning nonmedical, causes with the data to show a rate difference of 0.03 per 1000 person-years (95% CI, 0.00-0.06) and an adjusted HR of 1.12 (95% CI, 0.92-1.36).  

**DISCUSSION**

Cardiovascular disease (CVD) can be a detrimental diagnosis that affects millions of people worldwide. One of the aspects that makes CVD so dangerous, particularly for women, is the fact that it is difficult to predict or diagnose. Since CVD can be so elusive, it is essential to determine any predisposing risk factors for CVD and incorporate them into the patient’s care plan as early as possible. This systematic review was performed to investigate if giving birth to an infant with heart defects could be one of the potential predisposing risk factors to a woman developing CVD later on in life.
The results of the retrospective observational studies reviewed\textsuperscript{7,9} concluded that there was both an increased risk of CVD in woman of infants born with heart defects as well as an increased risk of overall mortality in woman who have given birth to infants with a major congenital anomaly. In the study conducted by Auger et al\textsuperscript{7} there was minimal difference in results between mothers of infants born with critical or noncritical heart defects, although infants with critical heart defects had a stronger association with increased CVD risk, they both were important. Both groups of women were found to have an increased risk of developing CVD and were hospitalized sooner for CVD than women whose infants did not have a heart defect.\textsuperscript{7} In the study conducted by Cohen et al\textsuperscript{9} that focused on major congenital anomalies as a whole, it is important to recognize that although they were not specifically examining heart defects, a large portion of major congenital anomalies overall are cardiac in nature. It is essential to note that when the Cohen et al\textsuperscript{9} authors evaluated overall mortality of the women in their study, the mothers of infants born with a major congenital anomaly were more likely to die of cardiovascular disease.

There are limitations in each study that are important to consider. In the study conducted by Auger et al\textsuperscript{7} many confounding variables were accounted for, yet there were still some possible CVD contributions that the study could not account for in their results. One of the possible CVD contributions that the authors could not account for were some behavioral and lifestyle factor such as smoking, increased stress due to having a child with a heart defect, as well as increased maternal anxiety. The authors did adjust for maternal depression as a comorbidity during the pregnancy or subsequent admissions within the study. In the study conducted by Cohen et al,\textsuperscript{9} although the authors went to
great length to limit the selection bias by conducting a study that had a population-based cohort design, it is important to note that the study took place solely in Denmark where the groups had access to free universal healthcare and were given comprehensive family support. The study could have yielded different results if it were done in another country with contrasting resources and population. The authors believe that the limitations of the study being done in Denmark with the groups having access to free universal healthcare, the outcomes were potentially better than another country that for example did not have access to healthcare and the extensive support that was given to the families over the post-delivery course. The Cohen et al\textsuperscript{9} study also did not account for the increased incidence of chronic stress in families that have a child with a major congenital anomaly. This could potentially have contributed to the health of the mothers in the study. The authors also could not adjust for any unknown genetic or behavioral factors that could potentially confound the data.

The follow-up done in both studies\textsuperscript{7,9} was sufficient at greater than 20 years post-delivery in both studies, yet one aspect to consider is that not every woman in the study was followed into menopause. This is important because younger woman who have not yet reached menopause are less likely to have CVD than a post-menopausal woman. The Auger et al\textsuperscript{7} team felt that their data analysis was most likely underpowered due to this fact and that they were detecting associations that had rare outcomes overall since the women in their study had not yet reached menopause. Longer patient follow-up, specifically into the post-menopause years, would be helpful in strengthening the data as well as the association between increased risk of CVD and infants born with heart defects.
Even with their limitations, these studies\textsuperscript{7,9} are extremely important because they could change the way that mothers who give birth to infants with a heart defect are both screened and treated for CVD. Knowing that having an infant with a heart defect is a predisposing risk factor for CVD could prompt providers to start earlier screening or treatment plans. Counseling mothers of infants born with heart defects earlier about lifestyle changes such as increased exercise, weight loss, tobacco cessation, and decreasing alcohol consumption could be one way of increasing primary prevention. This research could also potentially prompt earlier treatment in these mothers with medications such as daily aspirin, antihypertensive medications, or statin therapy. With CVD being so difficult to detect in women, any increased chance of preventing an CVD event from occurring is worth acknowledging.

\textbf{CONCLUSION}

Cardiovascular disease is a detrimental, dangerous disease with often unreliable risk factors. There appears to be an increased long-term risk of CVD for mothers of infants born with a heart defect based on the 2 retrospective observational studies evaluated in this literature review. Although both studies had limitations and would benefit from longer follow-up in future research, the findings were statistically significant. This information has the potential to change the way that providers treat mothers of infants with heart defects based on the possibility that they are at an increased risk of developing CVD. Treatment plans could be changed by doing increased yearly screening, starting preventative measures like lifestyle modifications earlier than previously planned, and even starting interventions such as aspirin, antihypertensive medications, and statin therapy. This new information could be significant for both
healthcare providers and women alike.
References


### Table 1: Quality Assessment of Reviewed Articles

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*a Comprehensive adjustment for confounders done in the article*
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<td>Retrospective observational study</td>
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