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ORIGINAL RESEARCH

CONGENITAL HEART DISEASE

The Ongoing Relationship Between Offspring Congenital Heart Disease and Preeclampsia Across Pregnancies

Isabel Katlaps, MD,[a,*] Christina Ronai, MD, MSED,[b,*] Bharti Garg, MBBS, MPH,[c] Ava Mandelbaum, BA,[a] Afsoon Ghafari-Saravi, MD,[a] Aaron B. Caughey, MD, PHD,[c] Erin Madriago, MD[a]

ABSTRACT

BACKGROUND Prior literature has described an association between preeclampsia and offspring congenital heart disease (CHD), while suggesting there may be a stronger relationship in individuals with early preeclampsia.

OBJECTIVES The authors sought to explore the relationship between offspring CHD and preeclampsia among pregnancies in a population-based study.

METHODS Retrospective cohort study all singleton pregnancies delivered in the state of California 2000 to 2012. We included singleton births with gestational ages of 23 to 42 weeks and excluded pregnancies complicated by pre-existing diabetes or identified fetal chromosomal anomalies. We used multivariable logistic regression to estimate ORs for associations between offspring CHD and preeclampsia. Further subanalyses examined the relationships in deliveries <34 weeks and >34 weeks to analyze if there was a difference according to timing of preeclampsia development.

RESULTS Preeclampsia was strongly associated with offspring CHD (aOR: 1.38; 99% CI: 1.29-1.49) in the same pregnancy. Among patients with preeclampsia in the index pregnancy, there was an increased risk of fetal CHD in the subsequent pregnancy (aOR: 1.39; 99% CI: 1.20-1.61). Among patients with offspring CHD in the index pregnancy, there was an increased risk of preeclampsia in the subsequent pregnancy (aOR: 1.39; 99% CI: 1.15-1.68). In all 3 analyses, results remained significant when stratified by <34 weeks and ≥34 weeks.

CONCLUSIONS Our findings suggest a need for further investigation into the etiology of preeclampsia and its relationship to embryologic development of cardiovascular structures. (JACC Adv 2024;3:101009) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Department of Pediatrics, Oregon Health & Science University, Portland, Oregon, USA; [b]Department of Cardiology, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts, USA; and the [c]Department of Obstetrics and Gynecology, Oregon Health & Science University, Portland, Oregon, USA. *Drs Katlaps and Ronai have contributed equally and are considered co-joint first authors.

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ABBREVIATIONS AND ACRONYMS

CHD = congenital heart disease

ICD = International Classification of Diseases

Congenital heart disease (CHD) is the most common congenital disorder in newborns affecting approximately 1% of live births in the United States per year[1,2] and is the leading cause of birth defect-related infant deaths.[3] For pregnant patients, an estimated 10% of fetal loss is due to severe forms of CHD.[4] Despite advancements in surgical treatment portending toward better prognoses in this population of prenatally diagnosed fetuses, concern about outcomes remains significant for both the pregnant patient and infant.

Given that the heart is the first organ to develop, it has the longest exposure time to pregnancy environmental risk factors like nutritional deficiencies, drugs and chemical exposure,[5-7] as well as pregnant patient factors like obesity, diabetes, advanced age, and tobacco use.[8,9] Hypertension and its spectrum of disorders, which affects nearly 8% of women of reproductive age,[10] has also been identified as a potential risk factor for the developing fetal heart.[11] While numerous studies have confirmed an increased risk of other types of congenital anomalies in pregnancies complicated by preeclampsia,[12-14] few have looked at the risk of CHD. Given the shared developmental pathways for the placenta and embryo and the fact that impaired placental angiogenesis leads to alterations in pregnant patient blood flow and deranged embryonic development of the fetal cardiovascular system,[4,15] further evaluation of this association is warranted. Specifically, we investigated the relationship between preeclampsia and CHD in the same pregnancy. Furthermore, we investigated whether preeclampsia in a prior pregnancy was associated with offspring CHD in the subsequent pregnancy and if CHD in a prior pregnancy was associated with preeclampsia in the subsequent pregnancy.

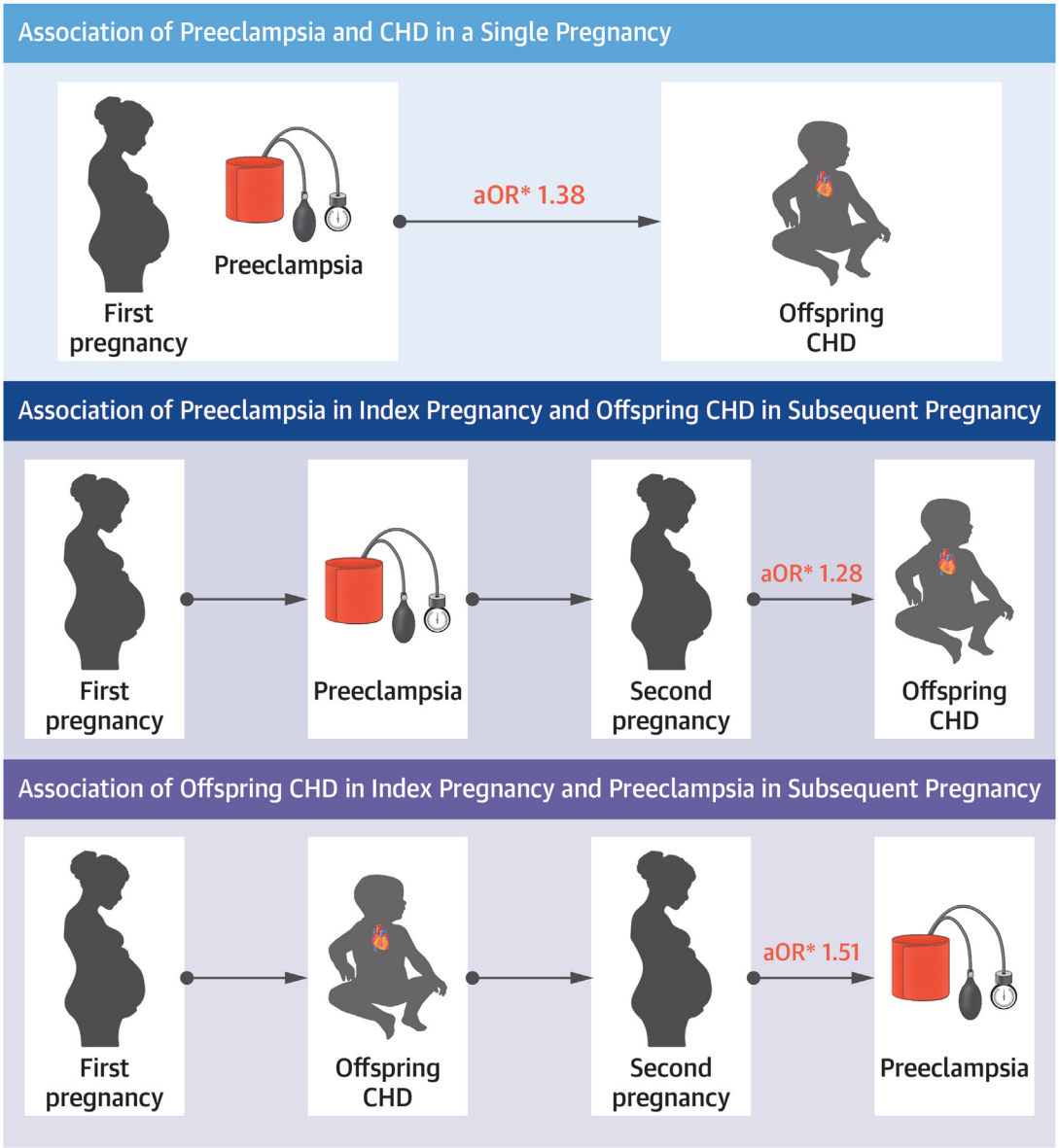
METHODS

We performed a retrospective cohort study that included all pregnancies delivered in the state of California from 2000 to 2012. Patients were identified from linked California Vital Statistics Birth Certificate Data, infant Vital Statistics Death Certificate Data, California Patient Discharge Data, and Vital Statistics Fetal Death File. Data linkage is performed by the California Office of Statewide Health Planning and Development Healthcare Information Resource Center, under the California Health and Human Services Agency, which used a unique "record linkage number" unique to the mother-infant pair. Institutional Review Board approval was obtained from the Institutional Review Board at Oregon Health and Science University, the California Office of Statewide Health Planning and Development, and the California Committee for the Protection of Human Subjects. Since the linked data set did not contain potential patient privacy and identification information, informed consent was exempted.

We included deliveries with singleton births with gestational age of 23 to 42 weeks. We excluded preexisting diabetes which was identified using birth certificates and using International Classification of Diseases (ICD-9) diagnosis codes (250.×) from hospital discharge data. Other exclusions were chromosomal abnormalities such as Down syndrome (ICD-9 diagnosis code: 758.0), trisomy 18 (758.2), trisomy 13 (758.1), DiGeorge syndrome (279.11), Turner syndrome (758.6), and Noonan syndrome (759.89). The variables of interest were neonatal CHD which was identified using ICD-9 diagnosis codes (listed in Supplemental Table 1), and preeclampsia (birth certificate and ICD-9 diagnosis code: 642.4, 642.5). We assessed numerous demographics as confounders such as maternal race and ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, non-Hispanic Asian, non-Hispanic Native American, or other/multiracial). Age was categorized as <20, 20 to 34, and ≥35 years. Educational attainment was categorized as attendance at some college vs less than college, and insurance was categorized into public vs nonpublic insurance. In addition, gestational diabetes mellitus was assessed using birth certificates and ICD-9 codes (648.0, 648.8), and preterm delivery (<34 weeks) was captured using gestational age.

We examined the demographics in the entire cohort and then the association between CHD and preeclampsia in the incident and subsequent pregnancies. Multivariable logistic regression models were utilized to assess the association between preeclampsia and CHD. Prior studies have suggested that there may be a difference in the mechanism behind the development of early preeclampsia (defined as preeclampsia <34 weeks) and late preeclampsia (defined as preeclampsia ≥34 weeks).[13,16] Furthermore, preeclampsia falls upon a spectrum of severity with patients who are delivered prior to 34 weeks more likely to be preeclampsia with severe features.[17] To examine these differences in type of preeclampsia, we conducted subanalyses to examine the relationships in deliveries before and after 34 weeks for all 3 analyses described below. Given the restraints of our retrospective data set, we were unable to ascertain the exact gestational age at which a patient was diagnosed with preeclampsia, however, we can

CENTRAL ILLUSTRATION **Relationship Between Offspring Congenital Heart Disease and Preeclampsia**



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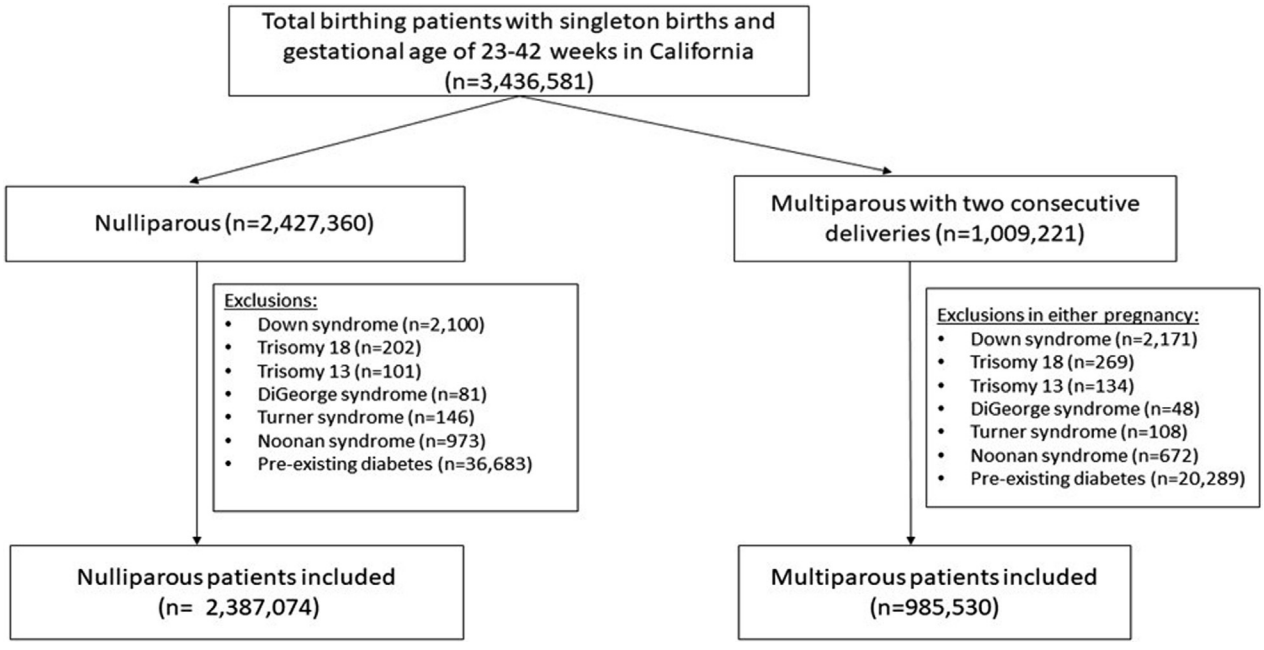
*Adjusted for maternal race and ethnicity, age, education, insurance, and gestational diabetes mellitus. Abbreviation as in Figure 2.

assume that those with known preeclampsia who delivered prior to 34 weeks had early preeclampsia. Those with known preeclampsia who delivered after 34 weeks either had late preeclampsia or earlier preeclampsia without severe features. In reality, this was likely an underestimate of the prevalence of pregnant patients with severe preeclampsia, as there may have been a small subset of patients who were diagnosed with severe preeclampsia after 34 weeks and thus, miscategorized.

Statistical analyses were conducted in 3 different ways (Central Illustration):

1) Group 1: Examined the association between offspring CHD and preeclampsia in the same pregnancy. For this, we utilized all nulliparous

FIGURE 1 Inclusion and Exclusion Criteria for the Entire Cohort of Birthing Patients in California (2000-2012)



patients and assessed the association of offspring CHD (independent variable) and preeclampsia (dependent variable) in the same pregnancy. The association between offspring CHD and preeclampsia was further assessed in deliveries <34 weeks and deliveries ≥34 weeks. Type of CHD was categorized as obstructive, mixing, regurgitant, or other based on the ICD-9 diagnosis codes. The subtype of CHD and timing of delivery was examined.

2) Group 2: Evaluated the association of preeclampsia in the index pregnancy with CHD in the subsequent pregnancy. This analysis utilized multiparous patients with 2 consecutive deliveries in California. Further stratified analysis was done in deliveries <34 weeks and deliveries ≥34 weeks in the index pregnancy.
3) Group 3: Examined the association of offspring CHD in the index pregnancy with preeclampsia in the subsequent pregnancy. This analysis also utilized all multiparous patients with 2 consecutive deliveries in California, and stratified analysis was done in deliveries <34 weeks and deliveries ≥34 weeks in the subsequent pregnancy.

All logistic regression models were adjusted for maternal age, education, insurance status, race and ethnicity, and gestational diabetes mellitus. A number of sensitivity analyses were then performed to affirm our results. While examining the association of preeclampsia in the index pregnancy with offspring CHD in the subsequent pregnancy, we excluded pregnancies complicated by preeclampsia in the subsequent pregnancies. Similarly, while assessing the association of CHD in the index pregnancy with preeclampsia in the subsequent pregnancy, we excluded CHD in the subsequent pregnancy. Statistical significance was set at 0.01. All analyses were done using Stata 17 (Stata Corp).

RESULTS

A total of 3,436,581 (72% nulliparous and 28% multiparous) pregnant patients were identified (Figure 1). The majority of the participants were Hispanic (47.9%), 20 to 34 years old (70.5%), and attended some college (51.9%). After excluding chromosomal abnormalities and pre-existing diabetes, a total of 3,372,604 nulliparous and

TABLE 1 Demographics of All the included Pregnant Patients (N = 3,372,604)

Race/ethnicity	
Non-Hispanic White	1,058,993 (31.8%)
Non-Hispanic Black	186,918 (5.6%)
Hispanic	1,565,747 (46.9%)
Non-Hispanic Asian	458,465 (13.7%)
Non-Hispanic American Indian and Alaska Native	11,274 (0.3%)
Other/Multiracial	53,888 (1.6%)
Maternal age, y	
<20	610,533 (18.1%)
20-34	2,439,931 (72.3%)
≥35	322,140 (9.6%)
Education	
No college	1,591,251 (48.5%)
Some college	1,691,995 (51.5%)
Insurance	
Private	1,903,129 (57.6%)
Public	1,400,339 (42.4%)
Prepregnancy body mass index, kg/m^2	
<18.5	1,086 (0.1%)
18.5-24.9	164,938 (14.2%)
25-29.9	472,717 (40.6%)
≥30	526,698 (45.2%)
Chronic hypertension	25,115 (0.7%)
Gestational hypertension	103,460 (3.1%)

Values are n (%).

multiparous patients were included demographics are described in Table 1.

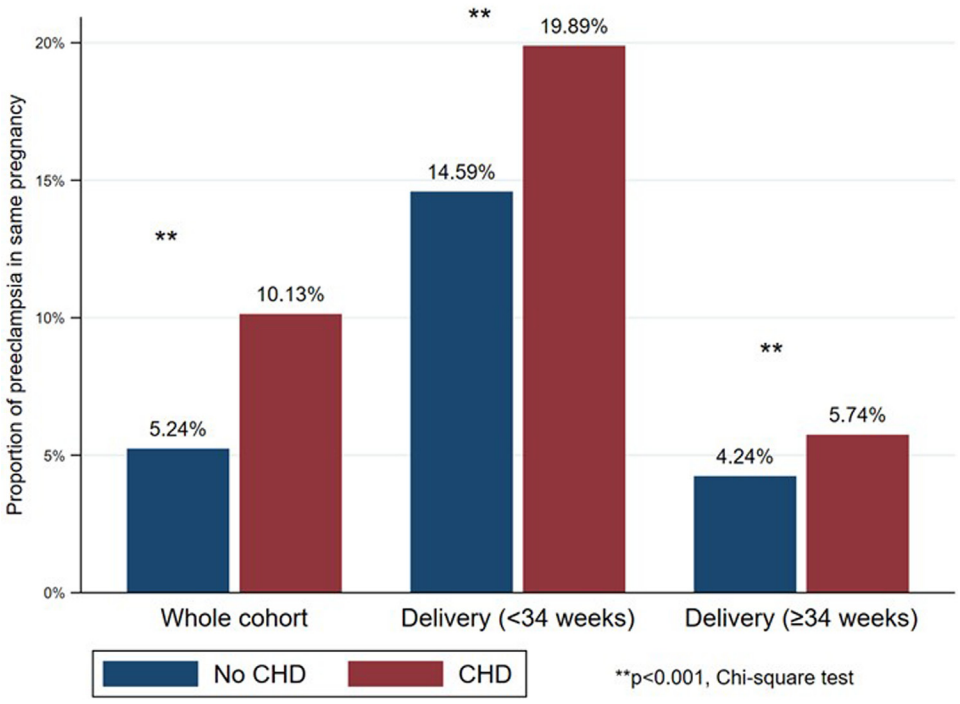
GROUP 1: PREECLAMPSIA AND CHD IN THE SAME PREGNANCY. Among 2,387,074 included nulliparous pregnant patients (aged 25.7 ± 6.3 years), 125,829 patients had pre-eclampsia. The proportion of pre-eclampsia was significantly higher among patients whose offspring had CHD as compared to pregnancies without CHD in offspring (10.13% vs 5.24%, $P < 0.001$, Figure 2). After adjusting for potential confounders, multivariable logistic regression analyses demonstrated that patients with offspring who had CHD had an increased risk of having preeclampsia (aOR: 1.38; 99% CI: 1.28-1.49) compared to those without offspring with CHD (Table 2). The results stayed the same when the association between preeclampsia and CHD was examined in <34 weeks delivery (aOR: 1.42; 99% CI: 1.29-1.58) and delivery ≥34 weeks (aOR: 1.32; 99% CI: 1.18-1.49).

Specific CHD diagnoses were categorized as obstructive, mixing, regurgitant, or other (Table 3). Among 239,881 pregnant patients with preeclampsia, 0.2% of fetuses had obstructive CHD, 0.7% had mixing CHD, 0.04% had regurgitant CHD, and 0.1% had other CHD. After controlling for maternal age, race/ethnicity, body mass index, and insurance, we found a higher odds of preterm delivery among obstructive CHD (aOR: 5.95; 99% CI: 4.96-7.77), mixing CHD (aOR: 3.58; 99% CI: 3.10-4.13), regurgitant CHD (3.32 (1.82-6.04), and other CHD (aOR: 2.29; 99% CI: 1.54-3.42) (Figure 3) compared to fetuses without CHD.

GROUP 2: PREECLAMPSIA IN THE INDEX PREGNANCY AND CHD IN THE SUBSEQUENT PREGNANCY. Among 985,530 included multiparous pregnant patients, the proportion of patients having offspring with CHD in the subsequent pregnancy was significantly higher in patients with preeclampsia in the index pregnancy, compared to those without preeclampsia (0.83% vs 0.55%, $P < 0.001$) (Figure 3). After adjusting for confounders, there was an increased risk of fetal CHD in the subsequent pregnancy among patients with preeclampsia in the index pregnancy (aOR: 1.39; 99% CI: 1.20-1.61). Association between pre-eclampsia in the index pregnancy and CHD in the subsequent pregnancy stayed when assessed among the population who delivered at <34 weeks (aOR: 1.34; 99% CI: 1.03-1.75) and ≥34 weeks (aOR: 1.42; 99% CI: 1.19-1.70) in the index pregnancy. Sensitivity analyses after excluding pregnancies with preeclampsia in the subsequent pregnancy showed similar results. After excluding pregnant patients with preeclampsia in the subsequent pregnancy (given a past history of preeclampsia increases future risk of preeclampsia), the odds of CHD in the subsequent pregnancy remained significant (aOR: 1.28; 99% CI: 1.07-1.54).

GROUP 3: CHD IN THE INDEX PREGNANCY AND PREECLAMPSIA IN THE SUBSEQUENT PREGNANCY IN MULTIPAROUS PATIENTS. Among 985,530 pregnant patients, higher rates of preeclampsia in the subsequent pregnancy were seen among those with fetal CHD in the index pregnancy, as compared to those without a baby with CHD in the index pregnancy (4.07% vs 2.58%, $P < 0.001$) (Figure 4). After adjusting for potential confounders, we continued to observe an increased risk of preeclampsia in the subsequent pregnancy in patients with offspring CHD in the index pregnancy (aOR: 1.39; 99% CI: 1.15-1.68). Association between CHD in the index pregnancy and preeclampsia in the subsequent pregnancy stayed when assessed in <34 weeks deliveries (aOR: 1.39; 99% CI: 1.02-1.90) and ≥34 weeks deliveries (aOR: 1.40; 99% CI: 1.10-1.78) in the subsequent pregnancy. Sensitivity analyses

FIGURE 2 Percentage of Preeclampsia in Pregnancies With and Without Offspring CHD



For the whole group, preeclampsia was significantly more prevalent in those with offspring CHD no matter the delivery timing.
CHD = congenital heart disease.

TABLE 2 Association of Preeclampsia and congenital heart Disease in Single as Well as Multiple Pregnancies

	Unadjusted OR (99% CI)	Adjusted OR (99% CI)[a]
Preeclampsia with CHD in the same pregnancy (nulliparous)		
Whole cohort (n = 2,387,074)	2.04 (1.89-2.19)	1.38 (1.28-1.49)
Delivery <34 wk (n = 233,843)	1.45 (1.31-1.61)	1.42 (1.29-1.58)
Delivery ≥34 wk (n = 2,153,231)	1.38 (1.23-1.54)	1.32 (1.18-1.49)
Preeclampsia and CHD in 2 consecutive pregnancies (multiparous)		
Whole cohort (n = 985,530)	1.52 (1.31-1.76)	1.39 (1.20-1.61)
Delivery <34 wk in index pregnancy (n = 89,707)	1.31 (1.01-1.70)	1.34 (1.03-1.75)
Delivery ≥34 wk in index pregnancy (n = 895,823)	1.43 (1.20-1.71)	1.42 (1.19-1.70)
CHD and preeclampsia in 2 consecutive pregnancies (multiparous)		
Whole cohort (n = 985,530)	1.60 (1.34-1.93)	1.39 (1.15-1.68)
Delivery <34 wk in subsequent pregnancy (n = 89,695)	1.44 (1.06-1.94)	1.39 (1.02-1.90)
Delivery ≥34 wk in subsequent pregnancy (n = 895,835)	1.43 (1.13-1.81)	1.40 (1.10-1.78)

[a]Adjusted for maternal race and ethnicity, age, education, insurance, and gestational diabetes mellitus. Analyses with the entire cohort also include adjustment for preterm delivery.
CHD = congenital heart disease.

after excluding pregnancies with offspring CHD in the subsequent pregnancy showed similar results. After excluding patients with offspring CHD in the subsequent pregnancy (given a past history of offspring CHD increases future risk of offspring CHD), odds of preeclampsia in the subsequent pregnancy remained significant (aOR: 1.51; 99% CI: 1.25-1.83).

DISCUSSION

The results of our study demonstrate a relationship between preeclampsia and CHD that persists beyond a single pregnancy. Firstly, we demonstrated that there is an increased risk of preeclampsia in pregnancies complicated by offspring CHD. We also found that a past history of preeclampsia increased future risk of a pregnancy complicated by fetal CHD, and vice versa. Finally, we demonstrated that these associations continued to be significant when stratifying by delivery timing.

TABLE 3 Congenital Heart Disease Subcategories

Obstructive
- Anomalies of pulmonary valve
- Atresia of pulmonary valve
- Stenosis of pulmonary valve
- Tricuspid atresia and stenosis
- Congenital stenosis of aortic valve
- Congenital mitral valve stenosis
- Hypoplastic left heart syndrome
- Subaortic stenosis
- Infecund pulmonary stenosis
- Obstructive abnormalities of heart
- Coarctation of aorta
- Interruption of aortic arch
- Atresia and stenosis of aorta
- Pulmonary artery atresia

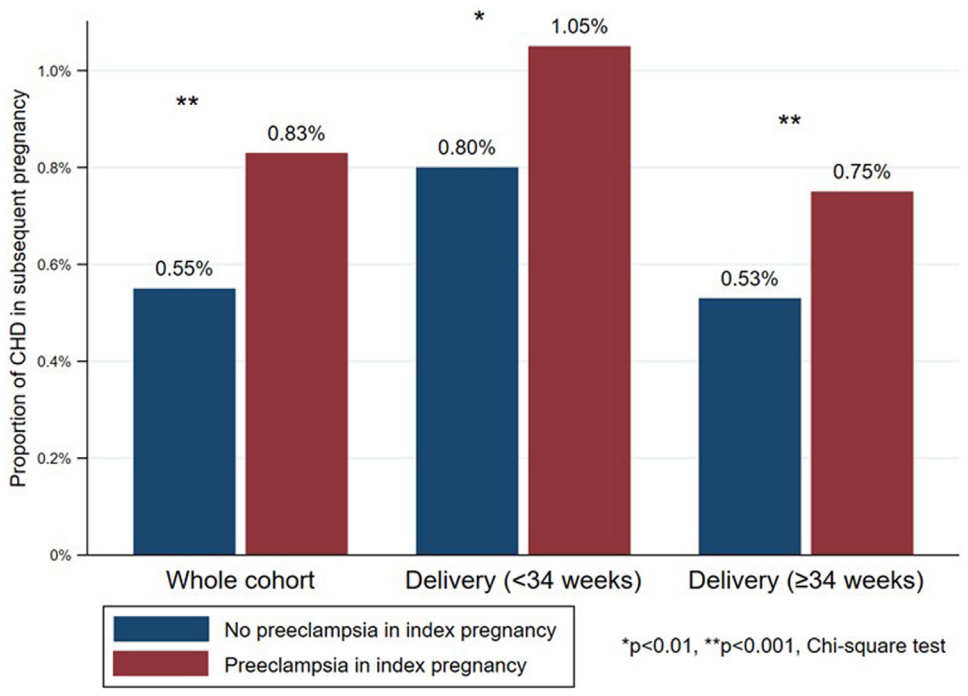
Mixing
- Common truncus arteriosus
- Transposition of great vessels
- Double outlet right ventricle
- Tetralogy of Fallot
- Common ventricle
- Ventricular septal defect
- Ostium secundum type atrial septal defect
- Endocardial cushion defect
- Ostium primum defect
- Cor biloculare
- Other bulbous abnormalities
- Defects of septal closure

Regurgitant
- Ebstein anomaly
- Congenital insufficiency of aortic valve
- Congenital mitral valve insufficiency

Other
- Cor triatriatum
- Coronary artery abnormalities
- Congenital heart block
- Malposition of cardiac apex
- Other anomalies of aorta
- Aortic arch anomalies
- Congenital anomaly of pulmonary artery
- Other anomalies of pulmonary artery
- Congenital anomalies of great veins

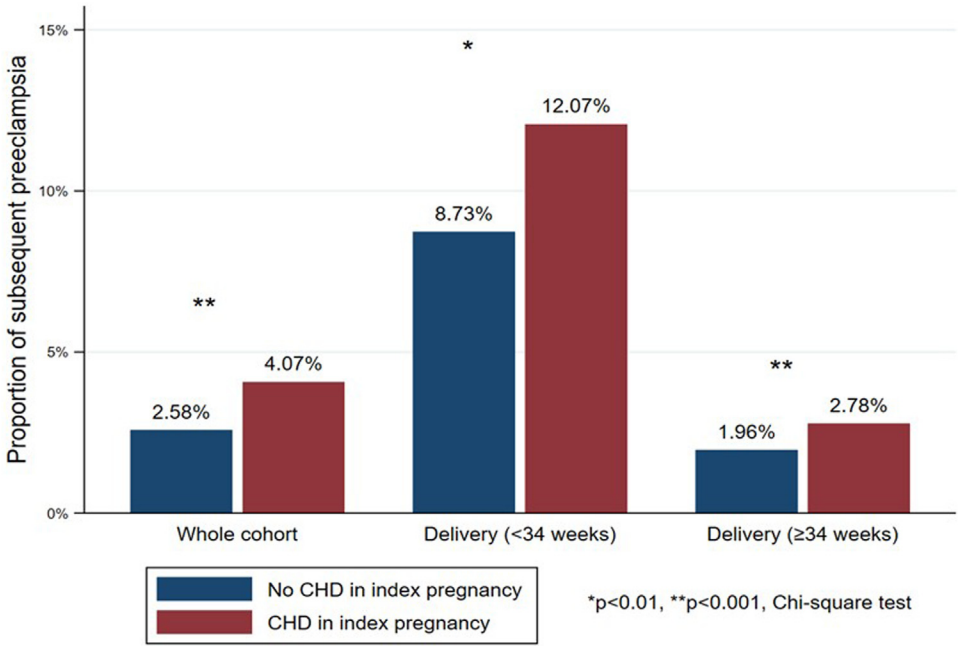
As we understand more the developmental origins of health and disease, scrutinizing the critical concept of the "placental-cardiovascular axis" is increasingly important. Chronologically, the vascularized placenta and embryonic heart grow simultaneously and are concurrently affected by underlying genetics,[18] hormonal influences, and common molecular signaling pathways.[19,20] Physiologically, the "feto-placental unit" provides adequate oxygen transfer between the pregnant patient and the growing fetus. Any impairment of this process simultaneously has a direct effect on both. Diminished oxygen leads to antiangiogenic signaling factors, gene inactivation and, as studies have shown, the subsequent development of fetal CHD.[14] Mechanically, the placenta and fetal heart are directly connected through complex vitelline and chorionic circulatory circuits. Changes in volume and resistance as the placenta and fetal heart vascularize and grow have a synergistic effect on the development of each. Studies have

FIGURE 3 Percentage of Congenital Heart Disease in Subsequent Pregnancy Among Those With and Without Preeclampsia in the Index Pregnancy



For the whole group, offspring CHD in the subsequent pregnancy was significantly more prevalent in those with preeclampsia in the index pregnancy no matter the delivery timing. Abbreviation as in Figure 2.

FIGURE 4 Percentage of Preeclampsia in Subsequent Pregnancy Among Patients With and Without Offspring CHD in the Index Pregnancy



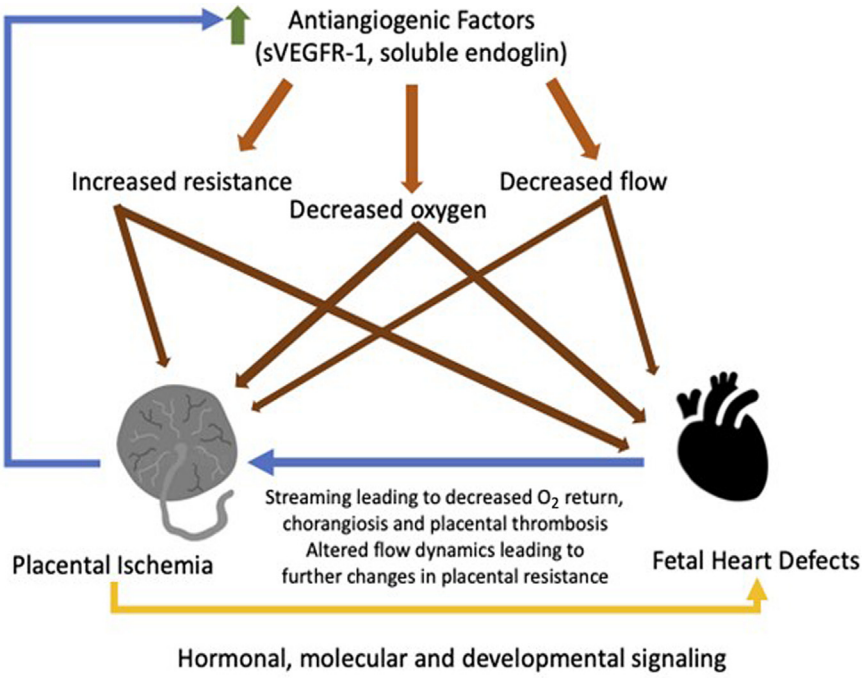
For the whole group, preeclampsia in the subsequent pregnancy was significantly more prevalent in those with offspring CHD in the index pregnancy no matter the delivery timing. Abbreviation as in Figure 2.

shown that alterations in blood flow (from pressure loading the heart with iatrogenic banding or diminishing venous return by ligating the vitelline vein) create abnormal hemodynamic forces which directly lead to dose-dependent malformed hearts early in gestation.[21-23] This has also borne out clinically in pathologic conditions of placental flow (ie, twin-twin transfusion and abnormal cord insertion) where there is an associated increase in the frequency of congenital heart defects.[24] Simultaneously, the fetal heart impacts the placenta. Fetuses with transposition of the great arteries have smaller placentas and higher chorangiosis, potentially due to abnormal streaming and diminished umbilical arterial oxygen return to the developing placenta. Increased chorangiosis and placental thrombosis in up to 40% of placentas of fetuses with CHD may also represent a pro-thrombotic state perpetuated or exacerbated by the underlying fetal heart condition.[25]

Within the framework of the placenta-cardiovascular axis, preeclampsia exemplifies a state of increased resistance, increased hypoxia from abnormal angiogenesis, and abnormal hormonal effects that leads to mechanical, molecular, and developmental signaling changes for both the placenta and the fetal heart. Preeclampsia, due in part to local placental ischemia, leads to aberrant signaling and an excess of antiangiogenic factors.[26] As antiangiogenic factors, including soluble vascular endothelial growth factor receptor 1 and soluble endoglin increase,[27] a resulting imbalance leads to generalized endothelial cell dysfunction,[28] diminished formation of new blood vessels, increased vascular resistance, changes in flow dynamics and increased hypoxia that alter flow dynamics in the developing fetal heart and lead to the development of CHD (Figure 5). While the pathophysiologic mechanisms predisposing one to preeclampsia are thought to occur before 20 weeks, the impact on fetal cardiac formation suggests that they are likely there even earlier (as early as 4-6 weeks), during early cardiac formation.

The association between preeclampsia and CHD in the same pregnancy has been studied[12,13,16,29] and previous studies have shown a relationship specifically between early preeclampsia and offspring CHD. While our study was limited in the ability to definitively call "early" or "late" preeclampsia and was instead dependent upon early or late delivery, we also demonstrated that the association was present

FIGURE 5 Placental-Fetal Heart Factors in Preeclampsia and Fetal CHD



There is a complex interplay between flow, resistance, and oxygenation in addition to vascular factors, hormonal factors, and various signaling molecules all posited to interact and affect the placental-cardiovascular axis. sVEGFR-1 = soluble vascular endothelial growth factor 1.

for both early and late deliveries. In addition, we demonstrated that the risk for delivery <34 weeks was highest in obstructive type CHD. Whether this is because early-onset clinical disease represents a more severe form of placental abnormality or that early preeclampsia represents an etiologically different mechanism from late-onset preeclampsia is unclear. Most interesting, given our findings of the association across pregnancies with support from data in prior studies, is the possibility that there is an underlying mechanism that starts earlier than either preeclampsia or fetal heart development, which is influenced and adapted during each pregnant patient/fetal event, and then persists into subsequent pregnancies. Identifying a reciprocal association between fetal CHD and preeclampsia can have significant clinical implications. Pregnant patients with a history of offspring CHD may be at an increased risk for the development of preeclampsia and should be monitored closely. Early identification of these patients can allow for earlier interventions, such as low-dose aspirin prophylaxis, that may prevent or mitigate the severity of preeclampsia.[30,31] On the other hand, identifying preeclampsia as a risk factor for offspring CHD has clinical implications related to prenatal screening and identification. Perhaps a history of preeclampsia as a risk factor for fetal CHD should prompt a screening fetal echocardiogram. Early detection of CHD in fetuses can provide several benefits, including allowing for appropriate prenatal counseling and strategic planning for delivery and postnatal care. As improved methods for evaluating placental flow are established, a more direct hemodynamic assessment of the fetal-placental unit in both normal and malformed fetal hearts will be crucial to developing a more complete understanding of how conditions like preeclampsia alter cardiogenesis. As this understanding evolves, there may be additional opportunity to evaluate the effect of interventions like aspirin prophylaxis on placental outcomes.

STUDY STRENGTHS. The strengths of our study include the large and diverse population evaluated, the time period which allowed for serial pregnancy evaluation, and the selection of patients without preexisting diabetes or chromosomal abnormalities that could influence the development of CHD.

STUDY LIMITATIONS. The limitations of this study were also inherent to the constraints imposed by a large population database. Due to the limited retrospective data set, we could not ascertain the specific gestational age when a pregnant person was diagnosed with preeclampsia. We assumed that those with known preeclampsia who delivered prior to 34 weeks were diagnosed with early severe preeclampsia and those who delivered after 34 weeks had non-severe preeclampsia, however that assumption may have been incorrect for some patients. We did not have access to clinical charts, and therefore did not have information regarding pregnant patient medications (including low-dose aspirin or antihypertensive use), family histories (include pregnant patient or partner history of CHD), ultrasound reports, other reasons for early delivery or additional clinical information. Given the retrospective data set, we could not exclude the possibility of a missed diagnosis, leading to non-differential misclassification bias occurring toward the null hypothesis. Finally, while we did our best to be as inclusive as possible, it is possible we missed potential confounders that could have affected our results.

CONCLUSIONS

Our findings demonstrate that there is an association between preeclampsia and offspring CHD that persists beyond a single pregnancy. These results suggest that there may be a complex common mechanistic pathway that is responsible for both the predisposition to preeclampsia and CHD, respectively. Further investigation into the specific mechanistic pathway causing the development of these diseases is imperative to our understanding of the placental-cardiovascular axis, which will help inform clinicians and improve screening approaches and potentially outcomes in this population.

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The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Christina Ronai, Department of Cardiology, Boston Children's Hospital, 300 Longwood Avenue, Boston, Massachusetts 02115, USA. E-mail: Christina.ronai@cardio.chboston.org.

PERSPECTIVES

COMPETENCY IN PATIENT CARE: There is an association between preeclampsia and CHD. Understanding that a prior pregnancy complicated by a fetus with CHD confers an increased risk of preeclampsia in a subsequent pregnancy may impact prenatal care and monitoring during future pregnancies.

TRANSLATIONAL OUTLOOK: Further studies are needed to investigate the complex interplay between the placenta and fetal cardiac development.

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APPENDIX For a supplemental table, please see the online version of this paper.