# Placental Abruption as a Risk Factor for Heart Failure

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**Complications of pregnancy present an opportunity to identify women at high risk of cardiovascular disease (CVD). Placental abruption is a severe and understudied pregnancy complication, and its relationship with CVD is poorly understood. The California Healthcare Cost and Utilization Project database was used to identify women with hospitalized pregnancies in California between 2005 and 2009, with follow-up through 2011. Pregnancies, exposures, covariates, and outcomes were defined by International Classification of Diseases Ninth Revision codes. Cox proportional-hazards regression was used to examine the association between placental abruption and myocardial infarction (MI), stroke, and heart failure (HF). Multivariate models controlling for age, race, medical co-morbidities, pregnancy complications, psychiatric and substance use disorders, and socioeconomic factors were employed. Among over 1.5 million pregnancies, placental abruption occurred in 14,881 women (1%). Median follow-up time from delivery to event or censoring was 4.87 (interquartile range 3.54 to 5.96) years. In unadjusted models, placental abruption was associated with risk of HF, but not MI or stroke. In fully-adjusted models, placental abruption remained significantly associated with HF (Hazard ratio 1.44; 95% confidence interval 1.09 to 1.90). Among women with placental abruptions, hypertensive disorders of pregnancy and preterm birth respectively modified and mediated the association between placental abruption and HF. In conclusion, placental abruption is a risk factor for HF, particularly in women who also experience hypertensive disorders of pregnancy and preterm birth. Placental abruption is a specific adverse pregnancy outcome associated with risk of HF.**  **(Am J Cardiol 2020;131:17−22)**

Contemporary guidelines on primary prevention of cardiovascular disease (CVD) have begun to recognize the opportunity pregnancy provides for identification of high-risk women.[1] Growing evidence suggests that maternal placental syndromes either precipitate subsequent CVD or, more likely, placental syndromes and CVD share a common pathophysiology.[2] While placental abruption is one of the most severe placental vascular diseases, its relationship with CVD is understudied in comparison to other pregnancy disorders. Placental abruption occurs when the placenta prematurely detaches from the uterus due to rupture of blood vessels in the decidua basalis, or the maternal portion of the placenta.[3] CVD and placental abruption share many common pathophysiologic features, including uncontrolled coagulopathy, endothelial dysfunction, and acute on chronic vascular compromise.[3] Despite their pathophysiologic similarities, placental abruption has not been widely studied in relation to CVD. Prior studies have suggested that placental abruption may confer an increased risk of CVD[4−7]; however, the evidence is mixed.[8−10] Well-powered and robustly-controlled studies in multiethnic populations are required to better characterize the relationship between placental abruption, covariates, and CVD subtypes. Here, we investigated the association between placental abruption and risk of myocardial infarction (MI), stroke, and heart failure (HF) in a large demographically diverse cohort. This is the first large U.S.-based study to report on the relationship between placental abruption and CVD subtypes.

## Methods

The California Healthcare Cost and Utilization Project (HCUP) database includes state-specific information on all inpatient, emergency, and ambulatory visits − including demographics, expected payer, dates of admission and discharge, and International Classification of Diseases Ninth Revision (ICD-9) diagnoses. The HCUP database includes information on approximately 97% of all U.S. community discharges and captures over 95% of all deliveries in California.[11] This study is considered exempt by the University of California, San Francisco Institutional Review Board and was conducted in accordance with the HCUP Data Use Agreement.

Women California residents in the HCUP database with inpatient hospitalizations for deliveries between 2005 and 2009 were initially included. Only first pregnancy from the indexed period was included for each woman. Women

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were excluded if there was missing covariate data, such as age or race/ethnicity, or if they had pre-existing ICD-9 codes corresponding to MI, HF, stroke, peripartum cardiomyopathy, hypertensive urgency, or congenital or valvular heart disease. With the exception of hypertensive urgency, both primary and secondary diagnoses were considered for exclusion criteria. Hypertensive urgency was defined as emergency department visit or hospital admission in which hypertension was the primary diagnostic code. ICD-9 codes were obtained from prior studies and are included in supplemental Table 1.[12–15] The final sample for this study included 1,555,596 women with deliveries from 2005 to 2009 (Figure 1), which represented 7.4% of all deliveries in the U.S. during this period.[16] Follow-up began 6 months after delivery in index pregnancy to avoid overlap in counting of exposures and outcomes. The HCUP database contains encounter-level data, and so outcomes are recorded when they occurred during follow-up encounters with the health system. Follow-up continued until 2011.

Exposure (placental abruption) and outcomes (MI, stroke, HF) were identified by ICD-9 codes; both primary and secondary diagnoses were included (supplemental Table 1). CVD outcomes were emergency department visits or admissions for MI, stroke, or HF. ICD-9 codes used to identify HF included HF related to hypertensive heart disease, as well as systolic and diastolic HF of unspecified etiology. Subgroup outcomes with less than 10 events are annotated as "≤10" in accordance with HCUP policy, in order to protect patient confidentiality.

To account for potential confounding, covariates known to be associated with both placental abruption and CVD were identified from baseline descriptive statistics and adjusted for in multivariate models. Covariates were grouped into categories including (1) age at admission and race (2) medical co-morbidities including diabetes, hypertension, obesity, chronic kidney disease, hyperlipidemia, and smoking, (3) pregnancy-related conditions including gestational diabetes and hypertensive disorders of pregnancy (composite of gestational hypertension, pre-eclampsia, and eclampsia), (4) psychiatric disorders including schizophrenia, depression/bipolar, anxiety, and substance use disorders (alcohol, stimulant, marijuana, or other depressant use disorder), and (5) markers of social determinants of health including physical or sexual abuse, insurance, and median income for zip code. Preterm birth is known to be associated with both placental abruption and CVD.[17] However, abruption-associated prematurity occurs as a consequence of decidua basilis bleeding, with placental abruption being the antecedent event.[18] Therefore, preterm birth was considered to be a mediator (not a confounder) of the relationship between placental abruption and CVD outcomes, and so preterm birth was not included in multivariate models. All covariates and mediators were defined by ICD-9 codes (supplemental Table 1).

Descriptive statistics were conducted on baseline demographic data. Continuous variables are reported as mean and standard deviation. Categorical values are expressed as absolute and relative frequencies. Two-tailed *t* tests were used to compare continuous variable means and Chi-square tests were used to compare categorical variables. Cox regression analysis was used to examine the association between placental abruption and CVD outcomes. Outcomes demonstrating a statistically significant association with placental abruption on univariate analysis were examined in multivariate models adjusting for all 5 covariate groups listed above. Mediation analysis of the relationship between placental abruption and CVD outcomes by preterm delivery was assessed by comparing the fully adjusted log hazard ratios for placental abruption before and after additional adjustment for preterm birth. Finally, modification of the relationship between placental abruption and CVD outcomes was assessed by adding interactions between placental abruption and race as well as pregnancy conditions to the fully adjusted Cox models. For evaluation of effect modification, hypertensive disorders of pregnancy were analyzed as a composite of gestational hypertension, pre-eclampsia, and eclampsia. Analyses were performed using

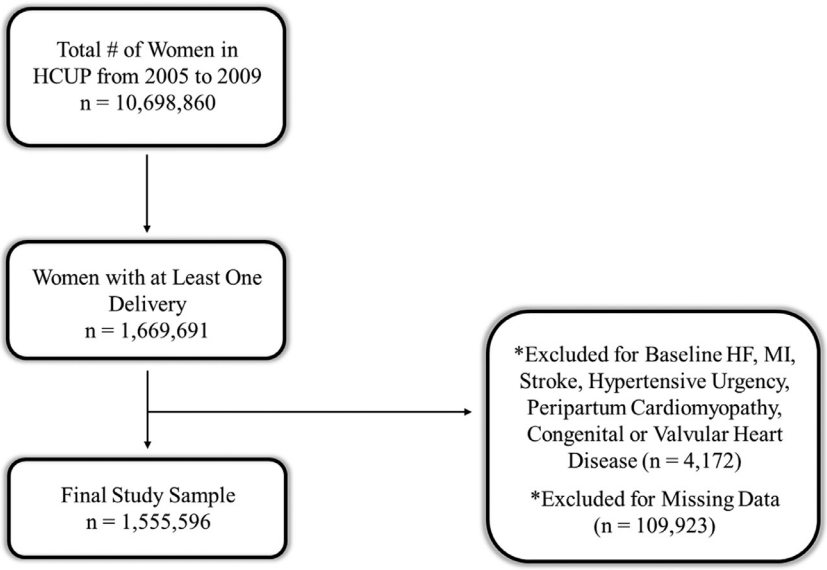


Figure 1. Study cohort creation and exclusion criteria.

SAS version 9.4X and STATA versions 14.2 and 15.1. p values of <0.05 were considered statistically significant.

## Results

The primary cohort consisted of over 1.5 million women. Table 1 displays baseline characteristics. Over 60% of the cohort was nonwhite. Approximately 7% of the study population had a pre-existing medical co-morbidity, and over 20% experienced a pregnancy-related complication.

Placental abruption occurred in 1% of pregnancies. Compared with women without placental abruptions, women who experienced abruptions were older and more likely to be of Asian/Pacific Islander or black race. Women who experienced a placental abruption were more likely to have co-morbid medical conditions, and were more likely to experience other pregnancy-related complications, such as a hypertensive disorder of pregnancy. Placental abruption was also associated with increased risk of several psychiatric disorders and substance use disorders (Table 1).

Approximately 8,724 (5.6%, exact number redacted per HCUP policy) women developed a CVD outcome during the study period. During the follow-up period, there were ~480 MIs, 1,353 strokes, and 2,143 women with emergency room visits or admissions for HF (Table 2). Median follow-up time from delivery to event or censoring was 4.87 (interquartile range 3.54 to 5.96) years. There were 0.66, 1.84, and 2.98 cases of MI, stroke, and HF, respectively, per 10,000 person-years. For women with placental abruptions, the event rates for stroke and HF per 10,000 person-years were 2.68 and 7.19, respectively (rate for MI redacted per HCUP policy). In univariate Cox proportional-hazards models, placental abruption was significantly associated with near-term risk of HF (Hazard Ratio [HR] 2.45, 95% confidence interval [CI] 1.86 to 3.23), but not MI or stroke (Table 2).

Table 1
Characteristics of study population

| Variable | Total Cohort (n = 1,555,596) | Placental abruption | | p value |
|---|---|---|---|---|
| | | No (n = 1,540,715) | Yes (n = 14,881) | |
| **Age**, Mean (SD) (years) | 28.5 (6.5) | 28.4 (6.4) | 29.2 (6.8) | p < 0.0001 |
| White | 616,668 (39.6%) | 611,165 (39.7%) | 5,503 (37.0%) | p < 0.0001 |
| Hispanic | 605,786 (38.9%) | 600,188 (39.0%) | 5,598 (37.6%) | |
| Asian/Pacific Islander | 189,158 (12.2%) | 187,221 (12.2%) | 1,937 (13.0%) | |
| Black | 101,117 (6.5%) | 99,717 (6.5%) | 1,400 (9.4%) | |
| Other or Unknown | 42,867 (2.8%) | 42,424 (2.8%) | 443 (3.0%) | |
| Diabetes mellitus | 12,958 (0.83%) | 12,774 (0.83%) | 184 (1.24%) | p < 0.0001 |
| Hypertension | 12,893 (0.83%) | 12,622 (0.82%) | 271 (1.82%) | p < 0.0001 |
| Obesity | 44,129 (2.84%) | 43,719 (2.84%) | 410 (2.76%) | ns |
| Chronic Kidney Disease | 339 (0.02%) | 324 (0.02%) | 15 (0.10%) | p < 0.0001 |
| Hyperlipidemia | 1,317 (0.08%) | 1,305 (0.08%) | 12 (0.08%) | ns |
| Smoker | 37,258 (2.40%) | 36,626 (2.38%) | 632 (4.25%) | p < 0.0001 |
| **Pregnancy Conditions** | | | | |
| Gestational Diabetes | 103,316 (6.64%) | 102,248 (6.64%) | 1,068 (7.18%) | p < 0.01 |
| Gestational Hypertension | 39,017 (2.51%) | 38,520 (2.50%) | 497 (3.34%) | p < 0.0001 |
| Pre-eclampsia | 58,199 (3.74%) | 56,858 (3.69%) | 1,341 (9.01%) | p < 0.0001 |
| Eclampsia | 1,283 (0.08%) | 1,236 (0.08%) | 47 (0.32%) | p < 0.0001 |
| Preterm Delivery | 109,323 (7.03%) | 103,360 (6.71%) | 5,963 (40.1%) | p < 0.0001 |
| Psychiatric diseases | | | | |
| Schizophrenia | 824 (0.05%) | 809 (0.05%) | 15 (0.10%) | p < 0.05 |
| Depression/Bipolar | 18,269 (1.17%) | 18,019 (1.17%) | 250 (1.68%) | p < 0.0001 |
| Anxiety | 6,255 (0.40%) | 6,184 (0.40%) | 71 (0.48%) | ns |
| Alcohol Use Disorder | 1,305 (0.08%) | 1,266 (0.08%) | 39 (0.26%) | p < 0.0001 |
| Stimulant Use Disorder | 8,764 (0.56%) | 8,296 (0.54%) | 468 (3.14%) | p < 0.0001 |
| Marijuana Use Disorder | 7,071 (0.45%) | 6,882 (0.45%) | 189 (1.27%) | p < 0.0001 |
| Other Depressant Use Disorder | 1,917 (0.12%) | 1,850 (0.12%) | 67 (0.45%) | p < 0.0001 |
| Socioeconomic factors | | | | |
| Physical or Sexual Abuse | 746 (0.05%) | 735 (0.05%) | 11 (0.07%) | ns |
| Insurance | | | | p < 0.0001 |
| Private | 938,539 (60.3%) | 930,304 (60.4%) | 8,235 (55.3%) | |
| Medicaid | 565,524 (36.4%) | 559,592 (36.3%) | 5,932 (39.9%) | |
| Self-Pay | 20,827 (1.34%) | 20,442 (1.33%) | 385 (2.59%) | |
| Medicare | 4,868 (0.31%) | 4,792 (0.31%) | 76 (0.51%) | |
| Other | 25,838 (1.66%) | 25,585 (1.66%) | 253 (1.70%) | |
| Median Income for Zip Code (quartile) | | | | p < 0.0001 |
| First | 415,286 (26.7%) | 410,885 (26.7%) | 4,401 (29.6%) | |
| Second | 403,611 (26.0%) | 399,696 (25.9%) | 3,915 (26.3%) | |
| Third | 373,988 (24.0%) | 370,655 (24.1%) | 3,333 (22.4%) | |
| Fourth | 362,711 (23.3%) | 359,479 (23.3%) | 3,232 (21.7%) | |

Table 2
Cardiovascular outcomes in women with a placental abruption

| | Number of outcomes | | | | Univariate hazard ratio (95% CI) |
|---|---|---|---|---|---|
| | Total cohort (n = 1,555,596) | No placental abruption (n = 1,540,715) | Placental abruption (n = 14,881) | p value | |
| Outcomes | | | | | |
| Myocardial Infarction | ~480 (0.03%) | 480 (0.03%) | ≤10 (<0.1%) | ns | 1.28 (0.57-2.86) |
| Stroke | 1,353 (0.09%) | 1,334 (0.09%) | 19 (0.13%) | ns | 1.47 (0.93-2.30) |
| Heart Failure | 2,194 (0.14%) | 2,143 (0.14%) | 51 (0.34%) | p < 0.0001 | 2.45 (1.86-3.23) |

Adjustment for pregnancy-related conditions led to the greatest reduction from the univariate hazard ratio (Hazard ratio [HR] decreased from 2.45, 95% confidence interval [CI] 1.86-3.23 to 1.97, 95% CI 1.49 to 2.61, Figure 2). In fully-adjusted models accounting for all covariates, placental abruption remained significantly associated with HF (HR 1.44, 95% CI 1.09 to 1.90, Figure 2).

Placental abruption had a significant interaction with hypertensive disorders of pregnancy (composite of gestational hypertension, pre-eclampsia, and eclampsia) on the risk of HF ($p < 0.05$). Placental abruption was associated with an even higher risk of HF among women with hypertensive disorders of pregnancy (HR 1.79, 95% CI 1.30 to 2.48) compared with women without hypertensive disorders of pregnancy (HR 0.90, 95% CI 0.52 to 1.60). Mediation analysis found that after adjustment for preterm birth, the fully adjusted hazard ratio for the association of placental abruption with HF was attenuated from 1.44 (95% CI 1.09 to 1.90) to 1.21 (95% CI 0.91 to 1.61).

## Discussion

In a large diverse cohort of patients in California, placental abruption was associated with risk of HF, but not with MI or stroke, at a median follow-up of about 5 years. The relationship between placental abruption and HF was modified by hypertensive disorders of pregnancy such that women with both placental abruption and hypertensive disorders of pregnancy had the greatest HF risk. Preterm birth co-occurred in 40% of pregnancies complicated by placental abruption, and was a significant mediator of the relationship between placental abruption and HF. These results suggest that placental abruption is a risk factor for subsequent development of HF, and that hypertensive disorders of pregnancy and preterm birth respectively modify and mediate this risk.

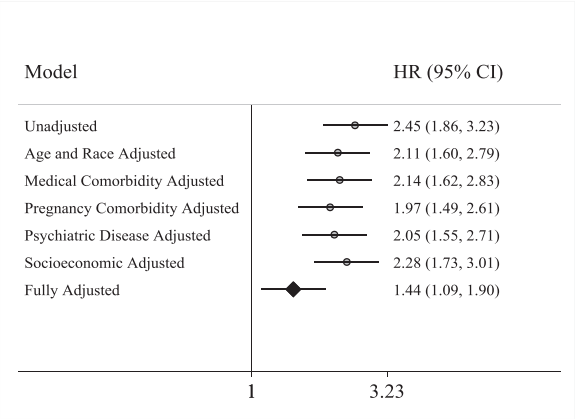


Figure 2. Univariate, partially-adjusted, and fully-adjusted multivariate models for association between placental abruption and heart failure.

Previously, there have been conflicting data on the association between placental abruption and CVD. A prior study in Denmark found that placental abruption was associated with increased all-cause mortality, but not increased CVD-specific mortality.[10] Similarly, the only prior U.S.-based study found no increased risk of CVD morbidity among women with placental abruptions.[8] Larger studies from Denmark, Canada, and Norway and Sweden have found associations between placental abruption and CVD mortality, and have estimated a 1.7- to 2.7-fold increased risk.[4,5,7] Although we did not examine CVD mortality, we found a significant association between placental abruption and subsequent HF. Only one prior study has examined the effect of placental abruption on subtypes of CVD; this study found significant associations between placental abruption and ischemic heart disease (HR 1.6, 95% CI 1.4 to 1.9), acute MI (HR 1.9, 95% CI 1.4 to 2.4), and HF (HR 1.7, 95% CI 1.2 to 2.3) with a median follow-up of 16 years.[5] In contrast, we examined risk at near-term follow-up. We similarly describe a relationship between placental abruption and HF, although did not find a significant association between placental abruption and MI or stroke. It is possible that MI and stroke present as late manifestations of CVD in patients with placental abruption, and so may not have been captured in our study.

The relationship between placental abruption and HF may be mediated by a shared predisposition to endothelial and vascular dysfunction. HF and placental abruption share similar risk factors, including cocaine use, smoking, hypertension, and African-American race.[19–21] The majority of placental abruptions are caused by subacute vascular inflammation and uteroplacental insufficiency which leads to hemorrhage at the decidual-placental interface.[3,22] Pathologic examination has found that the placental beds of women with abruptions have notable abnormalities, including (1) absence of physiologic remodeling of spiral arteries, (2) intimal and/or subintimal thickening, and (3) vascular malformations such as dilation, thrombosis, or hemorrhage.[23] The changes in the spiral arteries of patients with placental diseases, including fatty change in intimal cells and myointimal hyperplasia, have shown notable similarities to atherosclerosis seen in systemic blood vessels.[24] Women who experience placental abruptions may have an underlying predisposition to vascular injury making them

particularly vulnerable to the adverse effects of other HF risk factors, such as hypertension. In accordance with this theory, we showed that women with both hypertensive disorders of pregnancy and placental abruptions are at particularly high risk.

Prior studies have found that preterm birth is associated with CVD, although the impact of placental abruption on the relationship between preterm birth and CVD has not previously been examined.[17] Placental abruption causes thrombin release from decidual tissue, which triggers premature labor and delivery; 10% of preterm births are thought to result from bleeding events, often at the decidua basilis.[18] We found that hypertensive disorders of pregnancy, placental abruption, preterm birth, and HF are all closely interrelated. Additional research should quantify the extent to which placental abruption is responsible for the increased CVD risk which has been described with preterm birth.

Strengths of our study include use of a large, multiethnic sample which represents the vast majority of deliveries in California for our defined study period. A limitation of our study is reliance on ICD-9 coding for identification of exposures, covariates, and outcomes. As with all research relying on administrative claims data, there is a risk of misclassification or under-identification. A prior validation study found that the ICD-9 codes used for placental abruption have high concordance with placental abruption identified by medical record review (sensitivity of 89%).[25] We felt further reassured that the prevalence of abruption reported in our study (1%) corresponds to the prevalence reported in the U.S.-based National Hospital Discharge Survey (NHDS) dataset from the same time period.[26] Similarly, ICD-9 codes corresponding to cardiovascular outcomes and risk factors such as HF, diabetes, hypertension, and stroke have been previously shown to have high sensitivity for detection of these conditions, although there are limitations in specificity.[14] Limitations in the specificity of ICD-9 codes would most likely have led to under-identification of exposures and outcomes and random misclassification which would have biased the study toward the null; it is thus likely that the described findings are conservative. While under-identification of covariates could have led to incomplete adjustment of potential confounders, this is the most robustly controlled study to date examining this question.

Nearly half of the 6.5 million Americans with HF are women, although underrepresentation of women in research has limited our understanding of sex-specific predisposing factors.[27] Pregnancy complications have emerged as important risk factors for HF in women. Prior studies have shown that hypertensive disorders of pregnancy are associated with up to a 4-fold increased risk of development of HF.[28] Hypertension is known to be a particularly strong risk factor for HF in Hispanic and black women, and we similarly demonstrate a link between hypertensive disorders of pregnancy, placental abruption, and HF in this multiethnic cohort.[27,29] This study contributes to a growing body of research which demonstrates the important link between placental diseases and subsequent HF risk. An appreciation for the link between pregnancy-related conditions and HF could allow for early identification and risk factor modification of women at high-risk. Women with placental abruptions should be considered at risk of HF, especially if they also experience other pregnancy-related conditions such as hypertensive disorders of pregnancy and/or preterm birth.

## Authors Contribution

Jacqueline T. DesJardin: participated in development of design and methodology, investigation process, data presentation, and writing of the paper. Michael J. Healy: participated in conceptualization, development of design and methodology, investigation process, and reviewing of the paper. Gregory Nah: participated in data curation and data analysis. Eric Vittinghoff: participated in design and data analysis. Anushree Agarwal: participated in reviewing and editing of the paper. Gregory M. Marcus: participated in provision of study resources and reviewing and editing of the paper. Juan M. Gonzalez Valez: participated in reviewing and editing of the paper. Zian H. Tseng: participated in reviewing and editing of the paper. Nisha I. Parikh: participated in conceptualization, development of design and methodology, provision of study resources, supervision, and reviewing and editing of the paper.

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## Supplementary materials

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