ORIGINAL RESEARCH

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Pulmonary Hypertension and Pregnancy Outcomes: Insights From the National Inpatient Sample

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***Background*—**Pregnant women with pulmonary hypertension (PH) are at risk for adverse cardiac outcomes, particularly at the time of labor and delivery. The purpose of this study is to define the impact of PH on pregnancy outcomes and the risk of major adverse cardiac events (MACE).

***Methods and Results*—**The National Inpatient Sample was screened for hospital admissions of women delivering during the years 2003 to 2012. The primary outcome was MACE, a composite of death, cardiac arrest, cardiogenic shock, myocardial infarction, respiratory failure, arrhythmia, stroke, and embolic event. Data on 1519 patients with PH and 6 757 582 without heart disease or PH were available. There were 59.6% with isolated PH; 10.7% with PH and congenital heart disease; 18.1% with PH and valvular heart disease; 3% with PH and valvular heart disease and congenital heart disease; 6.6% PH and cardiomyopathy; and 1.9% with PH and cardiomyopathy and valvular heart disease. Compared with women without heart disease or PH, women with PH experienced significantly higher MACE (24.8 versus 0.4%, $P<0.0001$). Among the subsets of women with PH, the highest MACE was noted in women with the combination of PH and cardiomyopathy and valvular heart disease, and PH and cardiomyopathy, primarily because of heart failure and arrhythmia. Women with PH were significantly more likely to experience eclampsia syndromes, preterm delivery, and intrauterine fetal demise ($P<0.0001$ for all). PH subtype was significantly associated with MACE in multivariable analysis ($P<0.001$).

***Conclusions*—**In a contemporary data set of pregnant women in the United States, PH was associated with an increase in MACE during the hospitalization for delivery, with an exceptionally elevated risk among women with associated cardiomyopathy. **(*J Am Heart Assoc*. 2017;6:e006144. DOI: 10.1161/JAHA.117.006144.)**

Key Words: cardiomyopathy • congenital heart disease • pregnancy • pulmonary hypertension

Pulmonary hypertension (PH) is a disease characterized by debilitating symptoms and an overall diminished life expectancy because of narrowing of the pulmonary vasculature, often leading to right heart failure. Pregnancy in women with PH has long been regarded as high risk for maternal and neonatal complications, including maternal death,[1–3] particularly during labor and delivery and the period immediately postpartum. Often, PH is considered a contraindication to pregnancy.[4–6] This is largely because of an inability of the right ventricle to adapt to the volume shifts and hemodynamic changes associated with pregnancy, labor, and delivery, such as the marked increase in plasma volume and cardiac output, decrease in systemic vascular resistance, and increased susceptibility to thromboembolic events because of hypercoagulability.[7] Recent data from the United States suggest that incidence of pregnancy in women with PH is increasing,[8] a rather alarming finding given the risks in pregnancy. Women with PH do become pregnant,[1,8] whether planned or unplanned, and may choose to continue with a pregnancy often despite adequate counseling. A substantial number of women are opting to enter into such pregnancies, likely because of recent advancements in diagnosis and medical

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An Accompanying Data S1 is available at http://jaha.ahajournals.org/content/6/10/e006144/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- Pregnant women with pulmonary hypertension (PH) are at risk for adverse cardiac outcomes, particularly at the time of labor and delivery.
- PH was associated with an increase in major adverse cardiac events during the hospitalization for delivery compared with those without, largely related to heart failure and arrhythmia.
- Maternal mortality was low overall, and lower than previously reported, but multifold higher than women without PH. PH associated with left heart disease experience substantially higher adverse cardiac events than isolated PH or PH associated with congenital heart disease.

What Are the Clinical Implications?

- Women with PH are at substantial risk during pregnancy and delivery.
- The etiology of PH as well as its association with other forms of heart disease, particularly left heart disease, should be included in risk stratification before and during pregnancy.
- Women with PH who become pregnant warrant a multidisciplinary approach for management of pregnancy, labor, and delivery.
- Prepregnancy counseling can help inform patients and providers regarding their reproductive choices and substantial risks involved.

therapies that have allowed more women with PH to live through child-bearing age, as well as a growing number of adults with congenital heart disease who may be complicated by PH.

PH can be primary in pathogenesis or the result of congenital heart disease (CHD), valvular heart disease (VHD), cardiomyopathy, or related to chronic thromboembolic disease or other systemic disease.[9] We aimed to characterize the adverse maternal cardiac outcomes in pregnant women with PH resulting from multiple different causes or associated conditions during the hospitalization for delivery in the United States and to determine the risk factors associated with adverse maternal cardiac events.

Methods

Data Source

We utilized data from the 2003 to 2012 National Inpatient Sample (NIS), collected by the Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project, which is the largest all-payer inpatient publicly available database in the United States. The NIS provides annual information on approximately 8 million inpatient stays estimated from a stratified sample of hospitals (2003–2011) or hospital discharges (2012) that are nationally representative of all hospital discharges from US acute hospitals. Discharge records related to labor and delivery from years 2003 to 2012 were included in the study. *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes were utilized to ascertain hospitalizations for delivery, defined as any discharge record with a normal delivery or other indications for care in pregnancy-, labor-, and delivery-related diagnoses or delivery-related procedure as previously described (Data S1).[10] Our analysis was limited to delivery-associated hospitalizations. Clinical Classifications Software codes for *ICD-9* were utilized to identify the VHD and CHD cohorts[11]; for PH and cardiomyopathy, *ICD-9* codes were used. The remaining codes utilized in the study can be found in Data S1. Because the NIS consists of publicly available de-identified data files, this current study was exempted from Institutional Review Board approval, per the US Department of Health and Human Services guidelines.

Study Population

From 2003 to 2012, a total of 8 438 681 records were extracted for delivery-related analysis (Figure 1). Deliveries with missing data on race or insurance were excluded (n=1 679 574). Deliveries with subtype PH+CHD+cardiomyopathy or PH+CHD+cardiomyopathy+VHD were also excluded because NIS does not allow for reporting of events with n<10 so as to protect individuals' privacy, as <10 patients were available for study. Similarly, for records with multiple codes for eclampsia status, eclampsia status was assigned according to the priority rule: eclampsia complication>severe preeclampsia>mild preeclampsia>preeclampsia/eclampsia with preexisting hypertension, in order to divide the levels of preeclampsia present in cases where multiple diagnoses were coded.

Patient Characteristics and Outcome Measures

All patient and hospital characteristics were obtained from the NIS. Demographics, medical history, and other covariate data associated with hospital admission extracted included maternal age, race, and insurance status. Delivery at teaching hospital, location and region of hospital, length of stay, and total hospital charges, which represent absolute total hospital charge, were extracted. The primary outcome of interest was major adverse cardiac events (MACE), defined as a composite of outcomes that relate to cardiac complications of delivery and include in-hospital death, acute myocardial infarction, heart failure, arrhythmia, cerebrovascular events, pulmonary

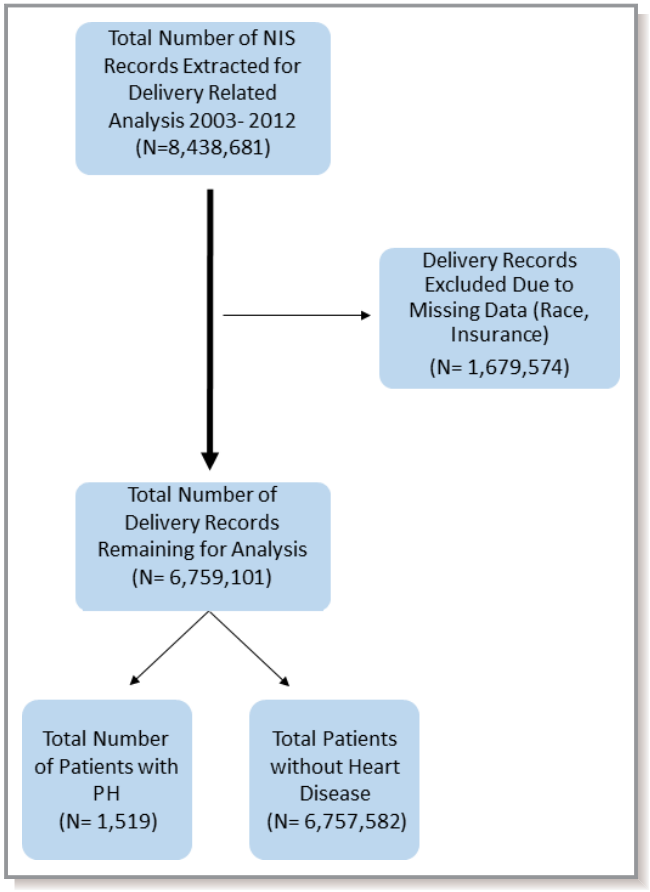

Figure 1. Extraction of study population. This figure illustrates the manner in which records were extracted from the NIS data set. After extraction, there was a total of 1519 patients with PH and 6 757 582 patients without heart disease. HCUP NIS does not allow reporting of <10 events in order to protect individuals' privacy. HCUP indicates Healthcare Cost and Utilization Project; NIS, National Inpatient Sample; PH, pulmonary hypertension.

embolism, arterial embolism, atheroembolism, obstetrical pulmonary embolism, and cardiac complications of anesthesia or other sedation in labor and delivery as previously described.[10] Potential confounding factors for MACE included diabetes mellitus, multiple gestation, transient hypertension of pregnancy, eclampsia status (including mild preeclampsia, severe preeclampsia, eclampsia complicating pregnancy/childbirth, preeclampsia/eclampsia with preexisting hypertension, postpartum hemorrhage, acute renal failure, cardiorespiratory failure or shock, respiratory failure, and cesarean delivery.

Statistical Analysis

Data were summarized by descriptive statistics. For all descriptive analysis, χ^2 tests with exact *P* values based on Monte Carlo simulation were used to compare unadjusted marginal differences for categorical variables among groups.

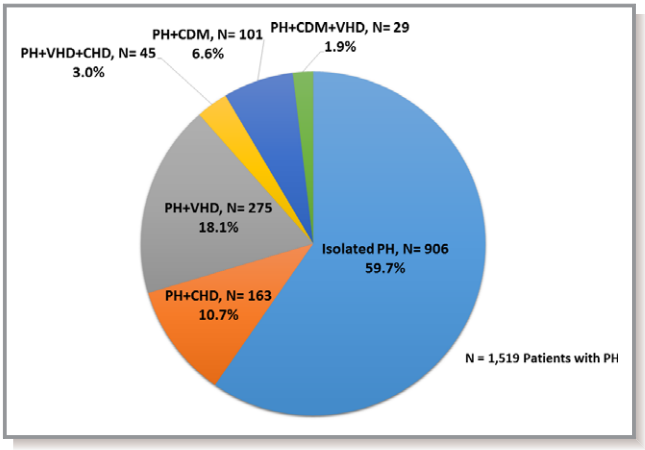

Figure 2. Prevalence of pregnancy and PH. This figure shows the breakdown of subclasses among the total 1519 patients with PH. CDM indicates cardiomyopathy; CHD, congenital heart disease; PH, pulmonary hypertension; VHD, valvular heart disease.

Welch's ANOVA tests were used to compare unadjusted marginal differences for continuous variables such as age, length of stay, and total charges. Predictors of adverse cardiac outcomes examined included variables related to patients' demographic information, specific comorbidities, and pregnancy-related complications. Variables with a $P<0.1$ in univariate descriptive analyses, together with age, race, and PH type were included in the multivariable logistic regression. Firth bias correction was used because of sparse count issue.[12] A *P* value <0.05 was considered statistically significant and all analysis was performed using SAS 9.3.[13]

Results

Study Population

Data on 1519 patients with PH and 6 757 582 without heart disease or PH were available for study (Figure 2). Among the 1519 pregnant women diagnosed with PH, 906 had isolated PH (59.7%). The remainder of the sample had combined disease patterns as follows: 163 (10.7%) had PH with CHD (PH+CHD); 275 (18.1%) had PH with VHD (PH+VHD); 101 (6.6%) had PH with cardiomyopathy; 45 (3.0%) had PH along with VHD and CHD (PH+VHD+CHD); and 29 (1.9%) had PH along with cardiomyopathy and VHD.

Demographic and clinical characteristics of women with PH and those without heart disease or PH were obtained (Table 1). Compared with women with no heart disease (n=6 757 582), patients with PH were on average older by 2 years, more than twice as likely to be black, had twice as long hospital stays, accumulated greater than 3-fold charges, were more likely to be insured by Medicare or Medicaid, and were more likely to deliver at a teaching hospital (all

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Table 1. Characteristics of Women With and Without PH, and Associated Subtype

Variable	PH (N=1519)	No Heart Disease (N=6 757 582)	*P* Value*	Isolated PH (N=906)	PH+CHD (N=163)	PH+VHD (N=275)	PH+VHD+CHD (N=45)	PH+CDM (N=101)	PH+CDM+VHD (N=29)	*P* Value†
Age at admission, y, n±SD	30.1±6.3	28.1±5.9	<0.0001	30.4±6.4	28.0±5.6	30.3±6.3	28.0±4.6	31.7±6.2	30.1±6.3	<0.0001
Race, n (%)										
White	552 (36.3)	3 539 607 (52.3)	<0.0001	344 (38.0)	54 (33.1)	95 (34.6)	15 (33.3)	37 (36.7)	<10	<0.0001
Black	460 (30.2)	912 339 (13.5)		304 (33.6)	29 (17.8)	71 (25.8)	<10	36 (35.6)	14 (48.3)	
Hispanic	339 (22.3)	1 583 335 (23.4)		186 (20.5)	56 (34.4)	64 (23.3)	18 (40.0)	11 (10.9)	<10	
Asian or Pacific Islander	75 (4.9)	344 673 (5.1)		30 (3.3)	12 (7.4)	23 (8.4)	<10	<10	<10	
Native American	17 (1.1)	50 894 (0.8)		<10‡	<10	<10	0	<10	0	
Other	76 (5.0)	326 734 (4.8)		34 (3.8)	10 (6.1)	20 (7.3)	<10	<10	<10	
Primary payer										
Medicare	59 (3.9)	39 798 (0.6)	<0.0001	40 (4.4)	<10	<10	<10	<10	<10	0.3062
Medicaid	783 (51.6)	2 853 438 (42.2)		451 (49.8)	87 (53.4)	147 (53.45)	27 (60.00)	53 (52.48)	18 (62.07)	
Private including HMO	571 (37.6)	3 446 689 (51.0)		357 (39.4)	59 (36.2)	99 (36.0)	11 (24.4)	37 (36.6)	<10	
Self-pay	41 (2.7)	234 407 (3.5)		19 (2.1)	<10	12 (4.4)	<10	<10	0	
No charge	14 (0.9)	17 705 (0.3)		<10	<10	<10	<10	<10	0	
Other	51 (3.4)	165 545 (2.5)		34 (3.8)	<10	<10	0	<10	<10	
Length of stay, d	6.7±8.8	2.7±2.6	<0.0001	6.3±7.8	6.3±10.8	7.2±9.5	7.7±12.3	8.6±9.3	7.9±10.6	0.1446
Total charges, in dollars	41 171.3±74 258.1	12 036.7±12 275.8	<0.0001	37 977.4±59 355.1	45 362.7±121 932.3	40 539.7±66 112.6	58 803.8±131 359.5	49 815.1±58 943.1	68 512.1±129 877.1	0.2973
Location/teaching status of hospital										
Rural	61 (4.1)	650 583 (9.7)	<0.0001	41 (4.6)	<10	<10	<10	<10	0	0.3325
Urban nonteaching	363 (24.1)	2 952 479 (44.0)		232 (26.0)	30 (18.4)	67 (24.5)	<10	21 (20.8)	<10	
Urban teaching	1082 (71.9)	3 114 281 (46.4)		621 (69.5)	127 (77.9)	200 (73.0)	36 (80.0)	75 (74.3)	23 (79.3)	
Teaching hospital	1143 (75.3)	3 764 864 (55.7)	<0.0001	662 (73.1)	133 (81.6)	207 (75.3)	38 (84.4)	80 (79.2)	23 (79.3)	0.1061
Region of hospital										
Northeast	326 (21.5)	1 324 827 (19.6)	<0.0001	203 (22.4)	30 (18.4)	66 (24.0)	12 (26.7)	12 (11.9)	<10	0.3192
Midwest	193 (12.7)	962 383 (14.2)		124 (13.7)	18 (11.0)	28 (10.2)	<10	13 (12.9)	<10	
South	675 (44.4)	2 712 729 (40.1)		395 (43.6)	77 (47.2)	124 (45.1)	20 (44.4)	47 (46.5)	12 (41.4)	
West	325 (21.4)	1 757 643 (26.0)		184 (20.3)	38 (23.3)	57 (20.7)	<10	29 (28.7)	<10	

Continued

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Table 1. Continued

Variable	PH (N=1519)	No Heart Disease (N=6 757 582)	*P* Value*	Isolated PH (N=906)	PH+CHD (N=163)	PH+VHD (N=275)	PH+VHD+CHD (N=45)	PH+CDM (N=101)	PH+CDM+VHD (N=29)	*P* Value†
Comorbidities										
Diabetes mellitus	84 (5.5)	69 130 (1.0)	<0.0001	65 (7.2)	<10	<10	0	10 (9.9)	<10	0.0004
Gestational diabetes mellitus	52 (3.4)	46 943 (0.7)	<0.0001	45 (5.0)	0	<10	0	<10	<10	0.0071
Multiple gestation	75 (4.9)	127 693 (1.9)	<0.0001	54 (6.0)	0	15 (5.5)	0	<10	<10	0.0238
Systemic lupus erythematosus	29 (1.9)	7413 (0.1)	<0.0001	23 (2.5)	<10	<10	0	<10	<10	0.0508
Systemic sclerosis	<10	359 (0.0)	<0.0001	<10	0	<10	0	0	0	0.7184
Rheumatoid arthritis	<10	5330 (0.1)	<0.0001	<10	0	0	0	0	0	0.7986
Sickle cell disease	11 (0.7)	1970 (0.0)	<0.0001	<10	<10	<10	0	<10	0	1
Thyroid disease	0	3186 (0.1)	0.3973	0	0	0	0	0	0	
Portal hypertension	<10	78 (0.0)	<0.0001	<10	0	0	0	0	0	0.8074
Chronic thromboembolic disease	1335 (87.9)	0	<0.0001	771 (85.1)	150 (92.0)	255 (92.7)	38 (84.4)	93 (92.1)	28 (96.6)	0.0021
HIV	<10	1839 (0.0)	<0.0001	<10	0	<10	0	0	0	1
Obstructive sleep apnea	45 (3.0)	1590 (0.0)	<0.0001	39 (4.3)	0	<10	<10	<10	<10	0.0142
Preexisting hypertension	110 (7.2)	55 225 (0.8)	<0.0001	71 (7.8)	<10	13 (4.7)	<10	15 (14.9)	<10	0.0049
Eisenmenger syndrome	45 (3.0)	0	<0.0001	0	33 (20.3)	0	12 (26.7)	0	0	<0.0001

CDM indicates cardiomyopathy; CHD, congenital heart disease; HIV, human immunodeficiency virus; HMO, health maintenance organization; PH, pulmonary hypertension; VHD, valvular heart disease.
*P value was based on χ^2 test for categorical variables and Welch test for continuous variables to compare healthy women and women with PH. Column percentage was reported.
†P value was based on χ^2 test with exact value from Monte Carlo simulation for categorical variables and Welch test for continuous variables. Column percentage was reported.
‡Healthcare Cost and Utilization Project (HCUP) National Inpatient Sample does not allow reporting of <10 events in order to protect individuals' privacy.

$P<0.0001$). They were also more likely to have multiple gestations and be diabetic. Associated comorbidities are listed in Table 1, and include a higher likelihood of having associated systemic lupus erythematosus, sickle cell disease, chronic thromboembolic disease, obstructive sleep apnea, and preexisting hypertension (all $P<0.0001$). Chronic thromboembolic disease was a common comorbidity, present in 87.9% of cases. A small group of women had coexisting Eisenmenger syndrome (3%). Of the women with isolated PH, 88 (5.8%) had a diagnosis of primary/idiopathic PH. Among the subclasses of PH, those with PH+cardiomyopathy had the longest length of stay and those with PH+cardiomyopathy+VHD had the highest total inpatient hospital charges.

Prevalence of Maternal Adverse Cardiac Events, Respiratory and Renal Failure

MACE among women with PH and those with no heart disease are compared in Table 2 and Figure 3. MACE was more frequent among patients with PH compared with those with no heart disease (24.8% versus 0.4%); heart failure and arrhythmia were the most common presentations of MACE. Overall maternal mortality was low in the PH cohort, although multifold higher than in the women without any heart disease. Respiratory failure, including use of mechanical ventilation and noninvasive positive pressure ventilation, as well as renal failure were more frequent among women with PH compared with those with no heart disease ($P<0.0001$).

Among the PH subgroups in Table 2, women with PH+cardiomyopathy+VHD, as well as those with PH+cardiomyopathy, experienced the highest MACE rates (62.1% and 59.4%, respectively), while women with PH+CHD exhibited the lowest MACE rate (15.3%). Again, heart failure and arrhythmia were the most common components of MACE among the PH subgroups. Not unexpectedly, heart failure was most common among the PH+cardiomyopathy+VHD cohort (55.2%, $P<0.0001$); arrhythmias were most common among the PH+cardiomyopathy cohort (19.8%, $P=0.0013$). Mechanical ventilation was most utilized among the PH+cardiomyopathy cohort (10.9%), while women with isolated PH developed the highest rate of acute renal failure (1.9%) among all the PH subgroups.

Obstetric Outcomes in Pregnant Women With PH

Women with PH more frequently developed preeclampsia/eclampsia syndrome, including severe preeclampsia (6.7% versus 1.2%), mild preeclampsia (5.3% versus 2.2%), and eclampsia with preexisting hypertension (8.0% versus 0.5%) compared with those women without any heart disease ($P<0.0001$, Table 3). Women with PH had substantially higher rates of cesarean delivery (49.7% versus 31.7%, $P<0.0001$). Women with PH had higher rates of obstetric bleeding, postpartum hemorrhage, postpartum infarction, and intrauterine fetal demise (all $P\leq0.0004$). The incidence of preterm delivery was multifold higher than in those without HD (21.5 versus 7.1%, $P<0.0001$).

Among the PH subclasses in Table 3, women with PH+cardiomyopathy most commonly had severe preeclampsia and eclampsia with preexisting hypertension (9.9% and 11.9%, $P<0.01$). The incidence of preterm delivery was common, and was highest among the PH+cardiomyopathy+VHD and PH+cardiomyopathy subgroups (37.9 and 57.4%, $P=0.0148$); the incidence of cesarean delivery was common, and highest among the isolated PH, PH+cardiomyopathy, and PH+cardiomyopathy+VHD subgroups.

Associations With Maternal Adverse Cardiac Events

Multivariable regression analysis examining independent risk factors associated with MACE are shown in Figure 4. Several PH subclasses had a higher risk of MACE as compared with the PH+CHD group (selected since it was the lowest risk group among those studied). Among all patients with PH, those with PH+VHD had an increased odds of MACE (odds ratio [OR] 1.83, 95% confidence interval [CI], 1.08–3.09) compared with those with PH+CHD; PH+VHD+CHD (OR 2.83, 95% CI, 1.32–6.08); PH+cardiomyopathy (OR 6.94, 95% CI, 3.76–12.82); and PH+cardiomyopathy+VHD (OR 6.56, 95% CI, 2.68–16.04). Those with isolated PH had similar risk for MACE as those with PH+CHD group (OR 1.22, 95% CI, 0.76–1.98).

Discussion

In a large national contemporary data set of pregnant women in the United States, PH was associated with a high prevalence of maternal adverse cardiac events during the hospitalization for delivery, with an exceptionally elevated risk among women with associated cardiomyopathy. This study is the largest-known characterization of PH and pregnancy to date. While inpatient maternal mortality was low overall, it was multifold higher than in women with no heart disease. Women with PH associated with left heart disease experienced substantially higher MACE than women with isolated PH or PH associated with CHD. Preeclampsia/eclampsia and preterm delivery were common in women with PH, as were fetal demise, obstetric and postpartum bleeding, and cesarean delivery.

Pregnancy in women with PH has been historically associated with prohibitive maternal mortality, upwards of

Table 2. Prevalence of MACE, Respiratory and Renal Failure in Women With PH

Variable	PH (N=1519)	No Heart Disease (N=6 757 582)	*P* Value*	PH (N=906)	PH+CHD (N=163)	PH+VHD (N=275)	PH+VHD+CHD (N=45)	PH+CDM (N=101)	PH+CDM+VHD (N=29)	*P* Value†
MACE, n (%)	376 (24.8)	25 128 (0.4)	<0.0001	183 (20.2)	25 (15.3)	75 (27.3)	15 (33.3)	60 (59.4)	18 (62.1)	<0.0001
Mortality (maternal)	12 (0.8)	475 (0.0)	<0.0001	10 (1.1)	<10	<10	0	0	0	0.6379
Acute myocardial infarction	<10	181 (0.0)	<0.0001	<10‡	0	<10	0	0	<10	0.1823
Heart failure	188 (12.4)	1390 (0.0)	<0.0001	74 (8.2)	11 (6.8)	25 (9.1)	10 (22.2)	52 (51.5)	16 (55.2)	<0.0001
Arrhythmia	175 (11.5)	21 004 (0.3)	<0.0001	84 (9.3)	15 (9.2)	47 (17.1)	<10	20 (19.8)	<10	0.0013
Cerebrovascular events	<10	583 (0.0)	<0.0001	<10	0	0	0	0	0	1
Arterial embolism	<10	53 (0.0)	<0.0001	<10	0	0	0	0	0	1
Obstetrical pulmonary embolism	44 (2.9)	1675 (0.0)	<0.0001	32 (3.5)	<10	<10	0	<10	0	0.3584
Cardiac complications of anesthesia or other sedation in labor and delivery	<10	474 (0.0)	<0.0001	<10	0	<10	0	0	0	0.6353
Cardiorespiratory shock	<10	313 (0.0)	<0.0001	<10	0	<10	0	0	0	0.4888
Shock unspecified	0	36 (0.0)	0.9283	0	0	0	0	0	0	–
Cardiogenic shock	<10	35 (0.0)	<0.0001	<10	0	<10	0	0	0	0.2967
Other shock without trauma	<10	242 (0.0)	<0.0001	<10	0	0	0	0	0	1
Other non-MACE outcome measures										
Respiratory failure	117 (7.7)	4213 (0.1)	<0.0001	71 (7.8)	<10	20 (7.3)	<10	11 (10.9)	<10	0.3121
Mechanical ventilation	71 (4.7)	3287 (0.1)	<0.0001	42 (4.6)	<10	10 (3.6)	<10	11 (10.9)	<10	0.0166
Noninvasive positive pressure ventilation	18 (1.2)	534 (0.0)	<0.0001	13 (1.4)	<10	<10	0	0	<10	0.2936
Acute renal failure	26 (1.7)	1978 (0.0)	<0.0001	17 (1.9)	0	<10	<10	<10	<10	0.039

CDM indicates cardiomyopathy; CHD, congenital heart disease; MACE, major adverse cardiovascular events; PH, pulmonary hypertension; VHD, valvular heart disease.

*P value was based on χ^2 test for categorical variables and Welch test for continuous variables to compare healthy women and women with PH. Column percentage was reported.

†P value was based on χ^2 test with exact value from Monte Carlo simulation for categorical variables and Welch test for continuous variables. Column percentage was reported.

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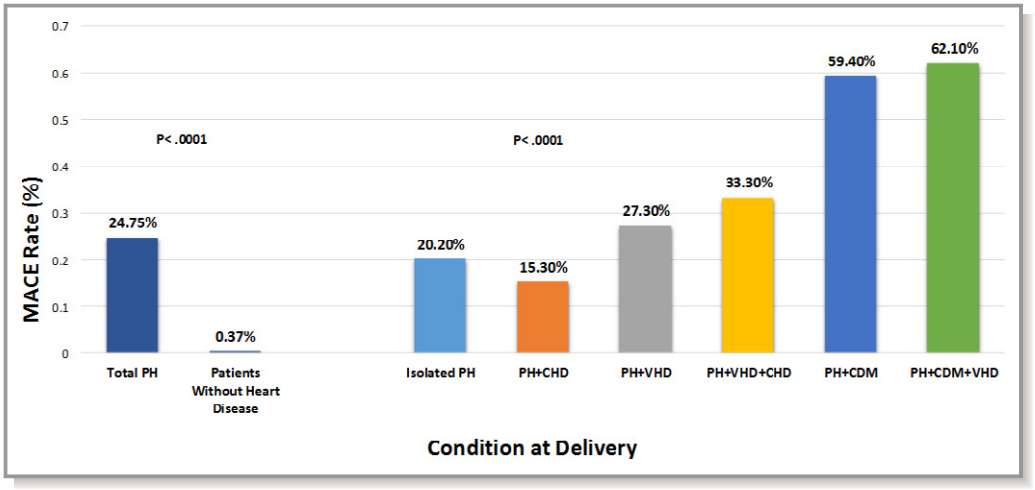

Figure 3. MACE rates in pregnant women with pulmonary hypertension. This figure compares the MACE rates of women with PH and women without any heart disease, as well as the MACE rates among the PH subclasses. CDM indicates cardiomyopathy; CHD, congenital heart disease; MACE, major adverse cardiac events; PH, pulmonary hypertension; VHD, valvular heart disease.

50%.[1,3] In the past 15 years, advances in medical therapy and treatment of PH have developed, improving overall quality of life and prognosis.[14] The incidence of PH in pregnancy is increasing in the United States,[8] a finding that we find particularly alarming given the risk of maternal mortality and morbidity. Recently, there have been reports of lower mortality (3%[2]), although still multifold higher than what would be considered acceptable to most mothers. The lower mortality herein may be attributable to differences in length of follow-up, since we measure inpatient mortality from the index hospitalization for delivery, and cannot capture deaths that could have occurred later, a period of particularly high risk for postpartum women with PH because of ongoing hemodynamic changes associated with pregnancy.[5] Data suggest these changes persist for up to 6 months postpartum.[5] The length of stay and total hospital charges are high, as well as a high prevalence of heart failure and arrhythmia, reflecting complicated and high-level patient care in the PH group. Herein, we may be capturing a larger number of patients whose degree of PH may not be severe and whose pregnancy outcome may be slightly more favorable. However, the rate of obstetric complications is also high and comparable with existing literature. Nonetheless, it seems that progress in the care of pregnant women with PH has been made, for reasons that are not entirely clear, whether related to improvements in recognition of the disorder and its risk in pregnancy, management in pregnancy, or management of labor and delivery with a multidisciplinary approach.[5] However, one should not be overly reassured by the reported lower mortality herein, since women tended to have heart failure and arrhythmias quite frequently (overall MACE ranging between 15% and 62%), particularly when PH was seen in combination with left heart disease such as cardiomyopathy. Recent research from our group[8,10] and that of others[9,15] has shown that cardiomyopathy predicts adverse cardiac events in pregnant women.

Women with PH associated with congenital heart disease had the lowest MACE in our study. This may be because the disease was known and monitored and controlled before pregnancy. The population with PH and CHD is expected to be a highly variable disease population. Eisenmenger syndrome, found in only 3% of the entire PH group, occurs when the pulmonary vascular resistance exceeds the systemic vascular resistance and prompts reversal of the systemic-to-pulmonary shunt; it is considered the most hazardous form of pulmonary arterial hypertension in CHD patients, particularly in pregnancy. Women with Eisenmenger syndrome are strongly advised against pregnancy because they are not able to withstand the prolonged hemodynamic stress of pregnancy, including increased blood volume, heart rate, and cardiac output.[16] However, paradoxically, our study did not find Eisenmenger syndrome to be an independent predictor of MACE upon multivariable analysis. This may be a function of the cohort not being well represented in this study because the incidence of Eisenmenger syndrome was relatively low in the examined population, though this is reflective of its presence in the general population as Eisenmenger syndrome is uncommon. It is also plausible that the lower than expected MACE rate is because of preservation of right ventricular function.[17]

Obstetric complications were high in the PH group, including preeclampsia and eclampsia syndromes, preterm delivery, as were fetal demise, obstetric and postpartum bleeding, and the use of cesarean delivery. However, these

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Table 3. Obstetric Outcomes in Women With PH During Hospitalization for Delivery

Variable	PH (N=1519)	No Heart Disease (N=6 757 582)	*P* Value*	PH (N=906)	PH+CHD (N=163)	PH+VHD (N=275)	PH+VHD+CHD (N=45)	PH+CDM (N=101)	PH+CDM+VHD (N=29)	*P* Value†
Transient HTN, n (%)	47 (3.1)	212 697 (3.2)	0.9051	34 (3.8)	<10	<10	0	<10	0	0.0812
Eclampsia status										
Eclampsia	<10	4961 (0.1)	<0.0001	<10‡	<10	0	0	<10	0	0.0099
Severe preeclampsia	102 (6.7)	83 781 (1.2)		65 (7.2)	<10	17 (6.2)	<10	10 (9.9)	<10	
Mild preeclampsia	80 (5.3)	147 957 (2.2)		55 (6.1)	<10	10 (3.6)	<10	<10	<10	
Preeclampsia or eclampsia with preexisting HTN	121 (8.0)	33 202 (0.5)		84 (9.3)	10 (6.1)	12 (4.4)	<10	12 (11.9)	<10	
Obstetric bleeding	44 (2.9)	116 052 (1.7)	0.0004	26 (2.9)	<10	<10	0	<10	0	0.1838
Postpartum hemorrhage	90 (5.9)	182 156 (2.7)	<0.0001	55 (6.1)	<10	13 (4.7)	<10	<10	<10	0.9037
Postpartum infection	47 (3.1)	26 444 (0.4)	<0.0001	32 (3.5)	<10	<10	<10	<10	<10	0.4181
Laceration	13 (0.9)	165 550 (2.5)	<0.0001	<10	<10	<10	<10	0	<10	0.3946
Premature rupture of membrane	53 (3.5)	260 156 (3.9)	0.465	30 (3.3)	<10	11 (4.0)	<10	<10	<10	0.9343
Preterm delivery	327 (21.5)	478 012 (7.1)	<0.0001	187 (20.6)	29 (17.8)	57 (20.7)	10 (22.2)	33 (32.7)	11 (37.9)	0.0148
Intrauterine fetal demise	19 (1.3)	27 627 (0.4)	<0.0001	14 (1.6)	0	<10	<10	<10	<10	0.0471
Cesarean delivery	755 (49.7)	2 143 724 (31.7)	<0.0001	460 (50.8)	71 (43.6)	127 (46.2)	22 (48.9)	58 (57.4)	17 (58.6)	0.1837
Vaginal delivery										
Vaginal delivery alone	759 (50.0)	4 544 928 (67.3)	<0.0001	444 (49.0)	91 (55.8)	148 (53.8)	23 (51.1)	43 (42.6)	10 (34.5)	0.0183
Vacuum assisted	<10	66 375 (0.9)		<10	<10	0	0	0	<10	
Failed vacuum	<10	2288 (0.0)		<10	0	0	0	0	0	

CDM indicates cardiomyopathy; CHD, congenital heart disease; HTN, hypertension; PH, pulmonary hypertension; VHD, valvular heart disease.

*P value was based on χ^2 test for categorical variables and Welch test for continuous variables to compare healthy women and women with PH. Column percentage was reported.

†P value was based on χ^2 test with exact value from Monte Carlo simulation for categorical variables and Welch test for continuous variables. Column percentage was reported.

‡Healthcare Cost and Utilization Project (HCUP) National Inpatient Sample does not allow reporting of <10 events in order to protect individuals' privacy.

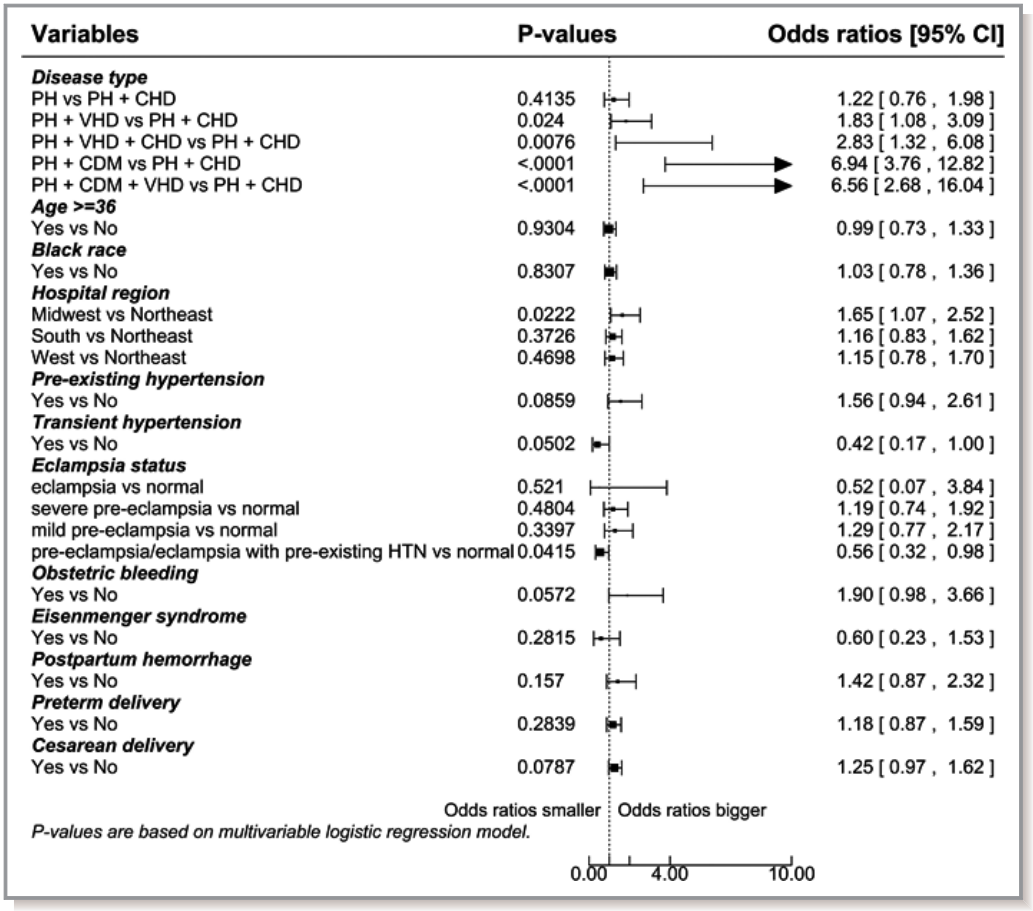

Figure 4. Multivariable analysis comparing individual predictors of MACE. Multivariable regression analysis was performed for those factors in which $P<0.1$ in univariate analysis. "PH and CHD" and "Northeast" were used as references for the disease type and hospital region analysis because they exhibited the lowest MACE rates in descriptive statistics. The following variables were independent predictors for MACE: PH and VHD ($P=0.024$), PH and VHD and CHD ($P=0.0076$), PH and CDM ($P<0.0001$), and PH and CDM and VHD ($P<0.0001$). CDM indicates cardiomyopathy; CHD, congenital heart disease; CI, confidence interval; HTN, hypertension; MACE, major adverse cardiac events; PH, pulmonary hypertension; VHD, valvular heart disease.

rates are similar to those found in a recent multinational registry.[2] Postpartum hemorrhage, obstetric bleeding, and cesarean section have all been associated with adverse outcomes during pregnancy in women with PH. The optimal mode of delivery remains controversial; however, the literature favors the use of cesarean delivery[1,2] and even recommends it.[18] Nonetheless, it is essential that these women be managed optimally by a multidisciplinary team of cardiologists, anesthesiologists, and obstetricians regarding the method and timing of their delivery.

Over a contemporary period of time, over 1500 women with PH became pregnant and carried a pregnancy to delivery. While there were likely others who miscarried early, or were not captured by this data set for other reasons, it is alarming that this a rather large number of high-risk group of women who achieved a pregnancy and delivery. This information suggests that there may be gaps in adequate healthcare access and/or preconception counseling in the United States that should be further explored. Because PH pregnancies are extremely high risk, the quality of preconception counseling, contraception methods, and risk counseling made available by the medical community is of paramount importance. One study of adult CHD patients documented that patients often cannot remember ever receiving counseling regarding pregnancy risks or contraception,[19] despite this being a Class I recommendation by Society Guidelines.[5,20]

Study Limitations

Our study has several important limitations. The NIS was especially valuable in studying PH, which has a low incidence in pregnancy, because it allowed for a large, representative US sample. This data set has been utilized in the past to study hospitalization trends and its predictors in patients with heart

disease, as well to assess outcomes in PH without pregnancy,[14] pregnant women with preexisting cardiomyopathy, CHD, and myocardial disorders.[10,21–24] However, the data are restricted to inpatient, delivery-related hospitalizations, and maternal data on medication use, disease severity, and neonatal complications are not available. Late maternal mortality is a real and devastating issue.[2,25] Another important limitation was the exclusion of approximately 20% of data because of missing information on race or insurance status, in order to achieve a more uniform data set; however, exclusion of a large number of records could have had implications on the study results. Despite these limitations, it is validating that our data substantiated existing paradigms about PH, including cardiac and obstetric complications.

Conclusions

Utilizing a national, all-payer inpatient data set, we found that women with PH endured a significantly higher rate of MACE than women without heart disease, largely related to heart failure and arrhythmia. Maternal mortality was low overall, and lower than previously reported, but multifold higher than women without PH. PH associated with left heart disease experience substantially higher MACE than isolated PH or PH associated with CHD. Preeclampsia/eclampsia and preterm delivery were common in women with PH, as were fetal demise and obstetric and postpartum bleeding. Women with PH who become pregnant warrant a multidisciplinary approach for management of pregnancy, labor, and delivery. Prepregnancy counseling can help inform patients and providers regarding their reproductive choices.

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Disclosures

None.

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