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Elevated cardiovascular disease risk in low-income women with a history of pregnancy loss

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ABSTRACT

Objective Pregnancy is associated with elevated risk of cardiovascular diseases (CVD), but little is known regarding the association between CVD and specific types of pregnancy losses. The aim of this study is to investigate the effects of pregnancy loss on the risk of subsequent CVD of any type.

Methods This prospective longitudinal study examines medical records between 1999 and 2014 for Medicaid beneficiaries born after 1982 who lived in a state that funds all reproductive health services, including induced abortion. Unique pregnancy outcomes, history of diabetes, hyperlipidaemia or CVD (International Classification of Diseases, Ninth Revision (ICD-9): 401–459) prior to their first pregnancy outcome for each woman. Cumulative incidence rates of a first CVD diagnosis following a first pregnancy were calculated for the observed period, exceeding 12 years.

Results A history of pregnancy loss was associated with 38% (OR=1.38; 95% CI=1.37 to 1.40) higher risk of a CVD diagnosis in the period observed. After controlling for history of diabetes, hyperlipidaemia, age, year of first pregnancy, race, state of residence, months of eligibility, number of pregnancies, births, number of losses before and after the first live birth, exposure to any pregnancy loss was associated with an 18% (adjusted OR=1.18; 95% CI=1.15 to 1.21) increased risk of CVD. Our analyses also reveal an important temporal relationship between the CVD and pregnancy loss. Immediate and short-term increased CVD risk is more characteristic for women whose first pregnancy ended in live birth while a delayed and more prolonged increased risk of CVD is associated with a first pregnancy loss.

Conclusions Our findings corroborate previous research showing that pregnancy loss is an independent risk factor for CVD, especially for diseases more chronic in nature. Our research contributes to understanding the specific needs for cardiovascular health monitoring for pregnant women and developing a consistent, evidence-based screening tools for both short-term and long-term follow-up.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Pregnancy is a risk factor for many cardiovascular diseases (CVD), but relatively little research has been done on the effects of pregnancy loss on cardiovascular risk.

WHAT THIS STUDY ADDS

⇒ Our study of a large population of low-income women revealed that compared with women who carry a first pregnancy to term, women whose first pregnancy ends in a pregnancy loss face an elevated cumulative risk of CVD from 2 through 12 years following their first pregnancy outcome. Thus, our analysis provides a better understanding of the association between a first pregnancy outcome and CVD risk over longer periods of time.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ Clinician's should consider pregnancy history when advising and evaluating patients. Our analyses of the full range of pregnancy-related CVD diagnoses indicates opportunities for developing more specific cardiovascular health monitoring for pregnant women based on their complete pregnancy histories, including their pregnancy losses.

INTRODUCTION

Profound physiological changes including significant hormonal, metabolic and haemodynamic shifts and their impact on cardiovascular and pulmonary systems during pregnancy are widely recognised. Studies have found that women with any history of pregnancy have increased long-term risk of hypertension,[1] ischaemic heart disease (IHD),[1] myocardial infarction (MI),[2–4] ischaemic stroke and intracerebral haemorrhage,[5–9] venous and arterial thromboembolism.[10 11]

However, research examining the association between history of pregnancy loss and cardiovascular disease (CVD) is limited. Further, the existing research has focused narrowly on several select CVDs such as coronary heart disease (CHD) and MI.

Increased risk of MI and CHD in later life among women with a history of miscarriage and recurring episodes of miscarriage has been suggested in studies linking miscarriage with future risk of CVD.[12–17] Positive association has been reported between stillbirth and the risk of subsequent MI and CHD as well.[12 17]

Relatively little evidence exists regarding any association between induced abortion and risk of future CHD.[12 14] Research linking death certificates with the Medicaid records of women who had an induced abortion or delivery did find a significantly higher age-adjusted risk of death from all causes, including circulatory diseases and cerebrovascular disease in women who had an induced abortion or a delivery compared with women with completed pregnancy and delivery.[18]

There is a need for further research to determine the frequency and type of cardiovascular complications associated with pregnancy loss, including both natural losses and induced abortions. Our study examines the hypothesis that pregnancy loss of any type is a risk factor for cardiovascular diseases.

MATERIALS AND METHODS

Study population

Data were obtained from the US Centers for Medicare & Medicaid Services (CMS) using the data submitted to CMS from 16 states (Alaska, Arizona, Connecticut, Hawaii, Illinois, Maryland, Massachusetts, Minnesota, Montana, New Jersey, New Mexico, New York, Oregon, Vermont, Washington and West Virginia) for the years 1999–2014. These states both (1) provided coverage for all reproductive healthcare options, including induced abortion, during the years 1999 through at least 2012, and (2) have reported all reproductive health services to CMS. California was excluded because most state-funded Medicaid abortions are not reported to CMS.

The study was limited to young women born in 1983 or later who had at least one pregnancy outcome before 2013 and had been eligible for Medicaid for at least 12 months between 1999 and of 2015 inclusive. To maximise identification of first pregnancy outcomes, data for each beneficiary was rolled in beginning in the year of her 14th birthday or in 1999, whichever was later, giving us a cohort wherein the oldest beneficiaries were 16 years of age in 1999 and 29 years of age in 2012.

Study variables

The primary outcome variable was any treatment for cardiovascular disease (CVD), defined as any treatment code associated with International Classification of Diseases, Ninth Revision (ICD-9) codes 401–459. The date of a first CVD code, if any, was identified for each woman. In addition, diagnosis codes were identified for diabetes (ICD-9: 250) and hyperlipidaemia (ICD-9: 272.4) were identified along with the first date of diagnosis for each of these known risk factors for CVD.

All pregnancy outcomes were identified for each woman. Pregnancy outcomes were identified using diagnostic ICD-9 codes and clarified with Current Procedural Terminology (CPT) and Healthcare Common Procedure Coding System (HCPCS) codes. Pregnancy outcomes were segregated into two categories: live birth or pregnancy loss, the latter including both natural losses (ICD-9: 446–450), and induced abortions (ICD-9: 451). Our study groups were divided into women whose first pregnancy ended in a loss and women whose first pregnancy ended in a live birth and who had no subsequent known pregnancy losses.

To address coding errors or other conflicts within the data, multiple pregnancy outcome codes within 4 weeks of the first pregnancy outcome code in that time period were collapsed into a single pregnancy outcome using the first date associated with that cluster of Medicaid claims. In addition, codes indicating an abortion within 36 weeks prior to a live birth was excluded, as well as any data indicating an abortion or natural loss 2 weeks before through 4 weeks after a confirmed code for an induced abortion.

In addition, each woman's year of birth, age at first pregnancy, state of residence at first pregnancy outcome, months of eligibility, and race were extracted for use as control variables.

Statistical analyses

Logistic regression analyses were conducted to compare subsets of women who experienced CVD to those women who did not. Covariates included the age; race; history of diabetes or hyperlipidaemia; state of residence at time of first pregnancy outcome; year of first pregnancy, total number of months of eligibility; total number of pregnancies, live births and losses prior to and subsequent to a first live birth, and an interaction term for age at first pregnancy and total months of eligibility.

RESULTS

Our population consisted of 1 157 980 Medicaid beneficiaries who had at least one pregnancy outcome. In this population, 5.32% had a history of CVD prior to their first pregnancy and 11.44% had a first diagnosis of CVD after their first pregnancy. Characteristics of this study population are shown in table 1. The first treatment for CVD was over twice as common after a first pregnancy than prior to the first pregnancy. Compared with women without any CVD, women who had their first CVD following their first pregnancy had more pregnancies overall, including more live births, more abortions and more natural losses. Also, women with any history of CVD were eligible for Medicaid for a longer period of time overall and for a longer period of time following their first pregnancy outcome.

After excluding women with CVD prior to their first pregnancy, table 2 shows the differences in the rates of a first CVD diagnosis segregated by first pregnancy outcome, comparing women whose first pregnancy ended in a loss with women whose first pregnancy was a live birth and who had no known subsequent history of pregnancy loss. Overall, women with a history of first pregnancy loss were 38% more likely to develop a CVD than those who had only live births. As would be expected, the percentage of women with a first diagnosis of CVD following their

Table 1 Characteristics of study population. All women and subgroups with and without history of a cardiovascular disease (CVD) treatment

	All	No CVD	1st CVD before 1st Pg	1st CVD after 1st Pg
N (%)	1 157 980 (100)	963 972 (83.25)	61 574 (5.32)	132 434 (11.44)
Avg ages				
Avg age at 1st pregnancy	21.4	21.4	22.4	21.3
Avg age at 1st cardio diagnosis	21.8	N/A	22.9	24.2
Avg months eligibility				
Avg # months of eligibility	94.2	89.1	130.4	114.7
Avg # months of eligibility in years after 1st pregnancy outcome	35.5	32.9	37.4	53.0
Avg # of pregnancy outcomes				
Avg # live births	1.2	1.2	1.3	1.3
Avg # abortions	1.4	1.3	1.4	1.5
Avg # natural losses	1.0	1.0	1.1	1.1
Prior to 1st pregnancy				
History of diabetes %	11 571 (1.00)	6890 (0.71)	2594 (4.21)	2087 (1.58)
History of hyperlipidaemia %	8818 (0.76)	5621 (0.58)	1962 (3.19)	1235 (0.93)
After 1st pregnancy				
History of diabetes %	13 568 (1.17)	7401 (0.77)	1551 (2.52)	4616 (3.49)
History of hyperlipidaemia %	11 313 (0.98)	6558 (0.68)	1013 (1.65)	3472 (2.62)

Avg, average; Pg, pregnancy.

first pregnancy was higher for women with a history of diabetes or hyperlipidaemia.

Figure 1 shows that the rate of a first diagnosis of CVD in the months following the first pregnancy outcome and the relative increase in first CVD diagnosis in each subsequent 6-month period. In the first 6 months following a live birth 3.6% of women who had given a live birth were diagnosed with CVD compared with 2.0% of women whose first pregnancy was lost. But after the first 6-month period, the semiannual risk of a first CVD diagnosis following a first pregnancy loss was higher, and remained higher over a period of at least 12 years.

Table 3 shows the adjusted ORs (Adj OR) of the logistic regression analysis. The strongest effects on a first diagnosis of CVD after a first pregnancy were a history of diabetes (Adj OR=2.01) or a history of hyperlipidaemia (Adj OR=1.55) prior to the first pregnancy. The second strongest predictor was age, with older women more likely than younger women to experience CVD following their first pregnancy.

Compared with women with only live births women whose first pregnancy ended in a loss were 18% more likely (Adj OR=1.18, 95% CI=1.15 to 1.21) to be subsequently diagnosed with CVD. There was also a small but significant increased risk associated with the number of pregnancy losses that occurred prior to each woman's first live birth, and the number of losses subsequent to the first live birth, and also to the number of live births.

Racial differences were most notable in regard to Hispanics, who had lower CVD rates following a first pregnancy than all other racial groups. The results relative to the state of residency and the year of first pregnancy outcome reveal significant variances that are not easily explained. These may be due to differences in state regulations not only between states but over the 15 years examined.

Finally, table 4 shows the frequency of each CVD diagnosis disaggregated according to three-digit ICD codes. Unlike the previous analyses, this table is not restricted to first CVD diagnosis. Each patient with any occurrence of the specific diagnosis following the first pregnancy was counted. Table 4 shows the total number of each CVD diagnosis in the study population, the percentage of women in each group experiencing that diagnosis, and Adj OR for each diagnosis showing the elevated risk of each diagnosis associated with a first pregnancy loss compared with no history of pregnancy loss. The four diseases most strongly associated with a first pregnancy ending in a loss were aortic aneurysm and dissection, atherosclerosis, subarachnoid haemorrhage and old MI.

DISCUSSION

We analysed the risk of a first CVD diagnosis in women with a history of pregnancy loss across 59 ICD-9 CVD diagnosis codes. In line with the existing research, our

Table 2 CVD rates and ORs of women with a history of pregnancy loss compared with only live births, segregated by age groups, year of first pregnancy, race, history of risk factors and state

	Live birth only		First pregnancy lost		Unadjusted OR
	N	% with CVD	N	% with CVD	OR (95% CI)
Total	743 743	10.93	352 663	14.51	1.38 (1.37 to 1.40)
Age at first pregnancy					
14–19	160 554	11.75	117 664	16.14	1.45 (1.42 to 1.48)
20–24	371 807	12.72	147 122	17.83	1.49 (1.47 to 1.51)
25–29	130 128	11.62	36 697	16.21	1.47 (1.43 to 1.52)
Year of first pregnancy outcome					
1999–2000	4442	13.57	5630	19.48	1.54 (1.39 to 1.70)
2001–2002	19 492	13.44	18 706	19.54	1.56 (1.49 to 1.65)
2003–2004	51 163	13.72	38 278	19.13	1.49 (1.44 to 1.54)
2005–2006	90 923	13.28	53 138	18.05	1.44 (1.40 to 1.48)
2007–2008	134 263	12.20	63 315	16.06	1.38 (1.34 to 1.41)
2009–2010	192 999	10.55	80 066	13.25	1.30 (1.27 to 1.33)
2011–2012	250 461	8.86	93 530	9.33	1.06 (1.03 to 1.09)
Race					
White	247 789	11.37	82 174	13.23	1.19 (1.16 to 1.22)
Black	113 592	14.87	84 713	17.36	1.20 (1.18 to 1.23)
Hispanic	172 494	8.89	65 716	14.84	1.78 (1.74 to 1.83)
Other	209 868	9.93	120 060	13.20	1.38 (1.35 to 1.41)
State of residence					
Alaska	2583	6.16	1130	8.41	1.40 (1.09 to 1.80)
Arizona	110 470	7.93	13 270	13.22	1.77 (1.68 to 1.86)
Connecticut	13 462	10.42	10 287	11.37	1.10 (1.02 to 1.19)
Hawaii	6143	10.11	4329	14.28	1.48 (1.32 to 1.66)
Illinois	176 099	16.11	30 434	20.76	1.36 (1.33 to 1.40)
Massachusetts	28 596	11.26	11 449	14.42	1.33 (1.25 to 1.41)
Maryland	55 678	9.38	28 128	14.87	1.69 (1.62 to 1.76)
Minnesota	33 320	9.43	9293	14.49	1.63 (1.53 to 1.74)
Montana	10 581	4.95	1414	8.20	1.72 (1.40 to 2.10)
New Jersey	12 526	16.66%	31 155	18.55	1.14 (1.08 to 1.20)
New Mexico	37 583	5.08	13 825	7.56	1.53 (1.42 to 1.65)
New York	154 687	11.87	125 359	17.03	1.52 (1.49 to 1.56)
Oregon	35 638	6.23	15 867	8.96	1.48 (1.39 to 1.58)
Vermont	6067	11.59%	1273	17.83	1.66 (1.43 to 1.92)
Washington	51 203	7.24	50 818	7.28	1.01 (0.96 to 1.05)
West Virginia	9107	9.39	4632	8.66	0.91 (0.81 to 1.03)
Prior diabetes					
No	739 528	10.84	349 988	14.35	1.38 (1.36 to 1.39)
Yes	4215	26.41	2675	36.41	1.60 (1.46 to 1.74)
Prior hyperlipidaemia					
No	740 281	10.88	350 504	14.46	1.39 (1.37 to 1.40)
Yes	3462	21.29	2159	23.07	1.11 (0.99 to 1.24)

CVD, cardiovascular disease .

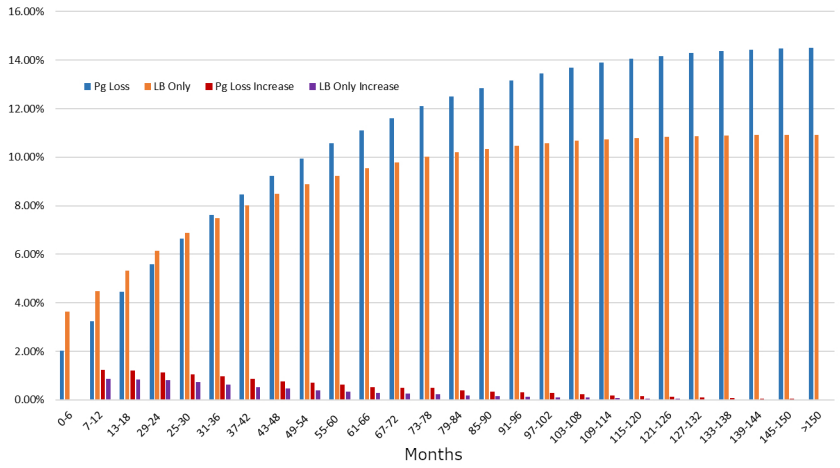

Figure 1 Cumulative rate of first cardiovascular disease diagnosis in 6-month increments following a first pregnancy outcome. LB, live birth; Pg, pregnancy.

findings show that overall, pregnancy loss is associated with elevated CVD risk. In this population of young Medicaid patients, 5.32% had experienced a CVD diagnosis prior to their first pregnancies, as compared with 11.44% who had a first CVD diagnosis after their first pregnancy outcome. This twofold increase in CVD diagnosis after the first pregnancy reflects a cascade of massive haemodynamic, hormonal and metabolic shifts placing a demand on cardiovascular and pulmonary systems in response to increased blood volume, changes in cardiovascular parameters such as heart rate and stroke volume, increase in cardiac output, decrease in systemic and pulmonary vascular resistance, pregnancy-related coagulopathies and vascular changes due to pressure the uterus applies to the vein system. It has also been observed that these changes may unmask previously undiagnosed heart disease and exacerbate a pre-existing disease.[19] Our finding that essential hypertension (ICD 401), cardiac dysrhythmias (ICD 427) and haemorrhoids (ICD 455) were the most common first CVD diagnoses can be explained by the above described shifts and add to the existing body of research indicating that hypertensive disorders in pregnancy, including pre-eclampsia/eclampsia (PE/E) are associated with long-term CVD risk.[1]

However, in our analysis the association between a first pregnancy loss and CVD became clearer over longer periods of time. Specifically, the temporal view of first CVD diagnosis shown in figure 1 shows that a first pregnancy ending in live birth is more likely to be associated with higher first time CVD diagnoses within the first 6 months after a first pregnancy outcome compared with the rate of CVD in the first 6 months following a first pregnancy ending in a loss. But the same figure shows that in every period following the first 6 months the increased rate of CVD diagnoses following a pregnancy loss is higher and persists longer. Combined with the disaggregated analysis of all CVD diagnoses following a first pregnancy outcome (table 4) these results offer a picture of two different clinical manifestations relative to pregnancy outcome: immediate and delayed. Immediate and short-term increased CVD risk is more characteristic for women whose first pregnancy ended in live birth while a delayed and more prolonged increased risk of CVD is associated with pregnancy loss.

Our findings related to the live birth group shows a clinical picture of pregnancy-related overload of cardiovascular and pulmonary systems and acute complications related to metabolic, haemodynamic and hormonal shifts. For example, cardiomyopathy (ICD 425), phlebitis and thrombophlebitis (ICD 451), other acute and subacute forms of IHD (ICD 411) may be caused by increased blood volume (almost 50% above the non-pregnant level during the second and third trimesters of pregnancy) and pregnancy-related hypercoagulability, which increases the risk of arterial and venous thrombosis[7] and IHD.[1] Some of these CVDs can be also characterised as the 'conditions of the third trimester', for example, other diseases of pericardium (ICD 423), which could be manifested as hydropericardium—the most frequent form of pericardial involvement in pregnancy with clinically silent pericardial effusion present in the third trimester in approximately 40% of healthy pregnant women.[20]

In addition, many of these CVDs have interconnected aetiological mechanisms. The hormonal and metabolic changes of normal pregnancy are intertwined with insulin resistance, hypercoagulability, and immunological dysfunction each playing important roles in fetal development while potentially contributing as risk factors for CVD diagnosis.[21] For example, acute and subacute endocarditis (ICD 421) and septic arterial embolism (ICD 449) may be linked as suggested by the existing evidence of association between septic embolism with infective endocarditis, which among other factors may be caused by pregnancy-related infection events. The risk of arterial thromboembolism is increased threefold to fourfold in pregnant women compared with women who are not pregnant.[20]

In contrast, CVD diagnoses that are more chronic in nature (eg, other forms of chronic IHD (ICD 414)

Table 3 The adjusted ORs* and CIs for risk factors associated with cardiovascular disease following a first pregnancy outcome

	Adj OR (95% CI)
Any exposure to pregnancy loss	
No	ref
Yes	1.18 (1.15 to 1.21)
Age at first pregnancy	
14–19	ref
20–24	1.25 (1.23 to 1.27)
25–29	1.47 (1.44 to 1.50)
Year of first pregnancy outcome	
1999–2000	ref
2001–2002	1.32 (1.24 to 1.42)
2003–2004	1.50 (1.41 to 1.60)
2005–2006	1.78 (1.67 to 1.90)
2007–2008	2.04 (1.92 to 2.18)
2009–2010	2.33 (2.19 to 2.49)
2011–2012	2.59 (2.42 to 2.76)
Race	
White	ref
Black	1.03 (1.01 to 1.05)
Hispanic	0.88 (0.86 to 0.89)
Other	0.91 (0.89 to 0.92)
State of residence at first pregnancy outcome	
New York	ref
Alaska	0.69 (0.61 to 0.78)
Arizona	0.64 (0.62 to 0.65)
Connecticut	0.79 (0.76 to 0.83)
Hawaii	0.63 (0.59 to 0.67)
Illinois	1.30 (1.28 to 1.32)
Massachusetts	0.76 (0.74 to 0.79)
Maryland	0.83 (0.80 to 0.85)
Minnesota	0.69 (0.67 to 0.72)
Montana	0.63 (0.58 to 0.69)
New Jersey	1.17 (1.14 to 1.21)
New Mexico	0.44 (0.43 to 0.46)
Oregon	0.55 (0.53 to 0.58)
Vermont	0.77 (0.71 to 0.82)
Washington	0.55 (0.53 to 0.56)
West Virginia	0.71 (0.67 to 0.75)
Prior diabetes	
No	ref
Yes	1.94 (1.84 to 2.04)
Prior hyperlipidaemia	
No	ref
Yes	1.47 (1.38 to 1.56)
Number of months of eligibility in years following first pregnancy outcome	1.03 (1.03 to 1.03)
Number of losses prior to live births	1.07 (1.06 to 1.09)
Number of subsequent losses	1.00 (1.00 to 1.01)
Number of pregnancies	0.09 (0.92 to 0.97)
Number of live births	1.16 (1.13 to 1.19)

*Logistic regression controlling for the categorical variables: exposure to pregnancy loss, age, race, year of first pregnancy, state of residence at time of first pregnancy, history of diabetes or hyperlipidaemia, and the continuous variables of: total number of months of eligibility, total number of pregnancies, number of live births and number losses prior to and subsequent to a first live birth, and an interaction term for age at first pregnancy and total months of eligibility.
Adj OR, adjusted OR.

hypertensive heart disease (ICD 402), cardiac dysrhythmias (ICD 427), and essential hypertension (ICD 401)) are more common among women with any history of pregnancy loss, occur more often after 6 months and continue with prolonged duration (ie, remained higher over a period of 12 years). The underlying mechanisms leading to these CVD complications are unclear. However, existing research has proposed several plausible explanations such as shared metabolic and hormonal changes contributing to both adverse pregnancy outcomes and the development of CVD,[12] vascular pathology contributing to poor placenta implantation and subsequent pregnancy loss and CHD in later life,[22] elimination of a protective effect of high level of oestrogen on cardiovascular health due to shorter duration of pregnancy and specific genetic or epigenetic features predisposing women to both pregnancy loss and CHD. In addition, grief and other mental health issues associated with pregnancy loss may also contribute to increased levels of stress and behavioural changes, including substance use and eating disorders, that may increase cardiovascular risks.[23]

We also note that the total number of pregnancies was slightly negatively associated with CVD risk in this model, but this is most likely due to the effect of the number of pregnancies being distributed across the overlapping continuous variables including the count for the number of live births and number of losses before and after the first live birth.

In addition, the results relative to the state of residency and the year of first pregnancy outcome reveal significant variances that are not easily explained. These may be due to differences in Medicaid eligibility not only between states but also over the 15 years examined. For example, for women with their first pregnancy in 2011–2012, the small unadjusted difference between women with and without a history of pregnancy loss shown in table 2 was magnified to an Adj OR of 2.59 in table 3. In part this

Table 4 The incidence rate (%) of women experiencing each International Classification of Diseases, Ninth Revision (ICD-9) code following a first pregnancy outcome for the entire period examined with adjusted OR comparing first pregnancy loss to no pregnancy loss

Three digit ICD-9 code	ICD-9 description	N, total with disease	ICD% no Pg loss	ICD% yes Pg loss	Adjusted OR* (95% CI)
401	Essential hypertension	37 878	3.00	4.42	**1.15 (1.11 to 1.20)**
402	Hypertensive heart disease	1769	0.11	0.27	**1.20 (1.03 to 1.41)**
403	Hypertensive chronic kidney disease	1524	0.10	0.22	**1.26 (1.05 to 1.50)**
404	Hypertensive heart and chronic kidney disease	145	0.01	0.02	1.30 (0.71 to 2.39)†
405	Secondary hypertension	0	0	0	N/A
410	Acute myocardial infarction	746	0.06	0.09	1.09 (0.84 to 1.42)
411	Other acute and subacute forms of ischaemic heart disease	1572	0.15	0.12	0.88 (0.71 to 1.10)
412	Old myocardial infarction	488	0.04	0.06	**1.66 (1.19 to 2.31)**
413	Angina pectoris	1523	0.10	0.21	**1.49 (1.25 to 1.77)**†
414	Other forms of chronic ischaemic heart disease	2605	0.16	0.40	**1.24 (1.09 to 1.41)**
415	Acute pulmonary heart disease	2151	0.11%	0.38%	**1.30 (1.14 to 1.47)**
416	Chronic pulmonary heart disease	867	0.07	0.10	1.14 (0.88 to 1.47)
417	Other diseases of pulmonary circulation	83	0.01	0.01	1.34 (0.62 to 2.91)†
420	Acute pericarditis	713	0.06	0.07	1.17 (0.88 to 1.55)
421	Acute and subacute endocarditis	2607	0.26	0.18	0.98 (0.81 to 1.19)
422	Acute myocarditis	102	0.01	0.01	1.30 (0.64 to 2.66)
423	Other diseases of pericardium	1889	0.18	0.16	0.98 (0.80 to 1.20)†
424	Other diseases of endocardium	8357	0.68	0.94	1.08 (0.99 to 1.17)
425	Cardiomyopathy	2233	0.20	0.22	1.14 (0.97 to 1.33)
426	Conduction disorders	2603	0.19	0.34	**1.28 (1.12 to 1.46)**
427	Cardiac dysrhythmias	30 179	2.27	3.77	**1.31 (1.25 to 1.36)**
428	Heart failure	2829	0.20	0.37	**1.32 (1.16 to 1.51)**
429	Ill-defined descriptions and complications of heart disease	4320	0.32	0.55	**1.22 (1.09 to 1.36)**
430	Subarachnoid haemorrhage	795	0.06	0.09	**1.75 (1.34 to 2.29)**
431	Intracerebral haemorrhage	844	0.06	0.11	**1.34 (1.06 to 1.74)**
432	Other and unspecified intracranial haemorrhage	837	0.06	0.10	1.25 (0.97 to 1.61)
433	Occlusion and stenosis of precerebral arteries	1399	0.09	0.20	**1.31 (1.10 to 1.56)**
434	Occlusion of cerebral arteries	1806	0.14	0.21	1.14 (0.96 to 1.35)
435	Transient cerebral ischaemia	1843	0.14	0.23	**1.18 (1.01 to 1.38)**
436	Acute, but ill-defined, cerebrovascular disease	1265	0.09	0.16	**1.41 (1.17 to 1.71)**
437	Other and ill-defined cerebrovascular disease	1885	0.15	0.22	1.17 (0.99 to 1.38)
438	Late effects of cerebrovascular disease	1776	0.14	0.20	1.14 (0.10 to 1.36)†
440	Atherosclerosis	2144	0.14	0.31	**1.72 (1.49 to 2.00)**
441	Aortic aneurysm and dissection	912	0.06	0.12	**2.12 (1.65 to 2.73)**
442	Other aneurysm	2414	0.25	0.15	**1.45 (1.14 to 1.85)**
443	Other peripheral vascular disease	2963	0.20	0.42	**1.36 (1.20 to 1.54)**
444	Arterial embolism and thrombosis	466	0.04	0.06	1.33 (0.97 to 1.83)
445	Atheroembolism	18	0.00	0.00	1.82 (0.11 to 30.34)
446	Polyarteritis nodosa and allied conditions	407	0.04	0.04	0.96 (0.64 to 1.45)
447	Other disorders of arteries and arterioles	947	0.08	0.10	1.00 (0.79 to 1.28)
448	Disease of capillaries	1701	0.15	0.16	1.02 (0.82 to 1.26)

Continued

Table 4 Continued

Three digit ICD-9 code	ICD-9 description	N, total with disease	ICD% no Pg loss	ICD% yes Pg loss	Adjusted OR* (95% CI)
449	Septic arterial embolism	148	0.02	0.01	1.39 (0.50 to 3.91)
451	Phlebitis and thrombophlebitis	8490	0.82	0.67%	1.02 (0.93 to 1.13)
452	Portal vein thrombosis	163	0.02	0.01	1.80 (0.84 to 3.86)
453	Other venous embolism and thrombosis	4637	0.37	0.54%	**1.32 (1.18 to 1.47)**
454	Varicose veins of lower extremities	5323	0.47	0.51	0.96 (0.86 to 1.08)
455	Haemorrhoids	20 743	1.74	2.22	**1.12 (1.06 to 1.18)**
456	Varicose veins of other sites	673	0.06	0.07	1.00 (0.72 to 1.40)
457	Non-infectious disorders of lymphatic channels	708	0.06	0.08	1.13 (0.85 to 1.51)
458	Hypotension	4134	0.34	0.47	**1.36 (1.21 to 1.53)**
	Total	176 624	14.09	20.37	

Bold font indicates statistical significance, lower confidence interval greater than 1.
*Logistic regression controlling for the categorical variables: exposure to pregnancy loss, age, race, year of first pregnancy, state of residence at time of first pregnancy, history of diabetes or hyperlipidaemia, and the continuous variables of: total number of months of eligibility, total number of pregnancies, number of live births and number losses prior to and subsequent to a first live birth, and an interaction term for age at first pregnancy and total months of eligibility.
†Low outcome sample.
Pg, pregnancy.

reflects a magnification of the differences in the age groups. By 2011–2012, the contingent of women having a first pregnancy outcome was older than in those in 1999–2000. Similarly, the proportion of teenagers and women over 25 having each type of first pregnancy outcome (delivery or live birth) was also different.

There were interesting racial differences in our findings, most notably among Hispanic women among whom the greatest difference CVD rates was observed between those whose first pregnancy was delivered (8.89%) and those whose first pregnancy was a loss (14.94%). At the same time, however, Hispanics had the lowest rate of CVD (Adj OR=0.88) of all four racial groups analysed. These findings could be another expression of so-called Latina paradox. This paradox is examined in a systematic review[24] of a large number of studies showing that, despite lower economic status, less access to medical care, Latina's appear to have fewer complications and better pregnancy outcomes compared with other minority groups. This paradox is not well understood. But nation of birth and documentation status may play a significant role.[24] Unfortunately, the data set used for our analysis does not allow us to shed any additional light on these questions.

CMS data has many limitations which restricted our ability to analyse the data more carefully. For example, there is no information on height, weight, body mass index (BMI), or patient adherence to prescribed treatments. In addition, ICD coding practices may vary across different states and hospital systems, though it is unlikely that such variations would be so systematically biased as to change the direction of our results. Most importantly, our data also did not allow for further investigation of the underlying mechanisms of CVD. Therefore, we recognise that this exploratory study provides only a first step in a general characterisation of CVD diagnoses associated with a first pregnancy loss. As such, it underscores the importance of additional research to better identify CVD risk profiles based on pregnancy duration, pregnancy outcomes, and the underlying mechanisms that explain the long-term effects of pregnancy loss on CVD risk in order to provide better recommendations for screening and guidance. As an additional limitation of our research, we note our inability to control for major CVD risk factors such as unhealthy diet, BMI, family history of heart disease, physical activity and smoking.

However, we believe that our analysis of a full range of pregnancy-related CVD complications provides a window into understanding the twofold impact of duration of pregnancy. As noted above, such understanding may be critical in (1) revisiting cardiovascular health monitoring for pregnant women and (2) developing a consistent, evidence-based screening tools for both short-term and long-term follow-up, which are currently lacking.[25]

The underlying pathophysiological mechanisms for the association between pregnancy loss and development of CVD are unclear. Further research is needed to examine whether proposed hypotheses such as shared metabolic and hormonal changes contributing to both adverse pregnancy outcomes and the development of CVD,[12] vascular pathology contributing to poor placenta implantation and subsequent pregnancy loss and CHD in later life[22 26] elimination of a protective effect of high level of oestrogen on cardiovascular health due to shorter duration of pregnancy[27] and specific genetic or epigenetic features predisposing women to both pregnancy loss and CHD[28 29] will hold.

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REFERENCES

1 Black MH, Zhou H, Sacks DA, *et al*. Hypertensive disorders first identified in pregnancy increase risk for incident prehypertension and hypertension in the year after delivery. *J Hypertens* 2016;34:728–35.
2 Kealey A. Coronary artery disease and myocardial infarction in pregnancy: a review of epidemiology, diagnosis, and medical and surgical management. *Can J Cardiol* 2010;26:e185–9.
3 James AH, Jamison MG, Biswas MS, *et al*. Acute myocardial infarction in pregnancy: a United States population-based study. *Circulation* 2006;113:1564–71.
4 Baris L, Hakeem A, Moe T, *et al*. Acute coronary syndrome and ischemic heart disease in pregnancy: data from the EURObservational Research Programme-European Society of Cardiology registry of pregnancy and cardiac disease. *J Am Heart Assoc* 2020;9:e015490.
5 Liu S, Chan WS, Ray JG. Stroke and cerebrovascular disease in pregnancy: incidence, temporal trends, and risk factors. *Stroke* 2019;50:13–20.
6 Tate J, Bushnell C. Pregnancy and stroke risk in women. *Womens Health* 2011;7:363–74.
7 Lanska DJ, Kryscio RJ. Stroke and intracranial venous thrombosis during pregnancy and puerperium. *Neurology* 1998;51:1622–8.
8 Lanska DJ, Kryscio RJ. Risk factors for peripartum and postpartum stroke and intracranial venous thrombosis. *Stroke* 2000;31:1274–82.
9 James AH, Bushnell CD, Jamison MG, *et al*. Incidence and risk factors for stroke in pregnancy and the puerperium. *Obstet Gynecol Surv* 2006;61:4–5.
10 James AH. *Venous thromboembolism in pregnancy*. . Lippincott Williams & Wilkins, 2009: 29. 326–31.
11 Heit JA, Kobbervig CE, James AH, *et al*. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. *Ann Intern Med* 2005;143:697.
12 Kharazmi E, Dossus L, Rohrmann S, *et al*. Pregnancy loss and risk of cardiovascular disease: a prospective population-based cohort study (EPIC-Heidelberg). *Heart* 2011;97:49–54.
13 Kharazmi E, Fallah M, Luoto R. Miscarriage and risk of cardiovascular disease. *Acta Obstet Gynecol Scand* 2010;89:284–8.
14 Smith GCS, Pell JP, Walsh D. Spontaneous loss of early pregnancy and risk of ischaemic heart disease in later life: retrospective cohort study. *BMJ* 2003;326:423–4.
15 Parker DR, Lu B, Sands-Lincoln M, *et al*. Risk of cardiovascular disease among postmenopausal women with prior pregnancy loss: the women's health Initiative. *Ann Fam Med* 2014;12:302–9.
16 Wagner MM, Bhattacharya S, Visser J, *et al*. Association between miscarriage and cardiovascular disease in a Scottish cohort. *Heart* 2015;101:1954–60.
17 Parikh NI, Jeppson RP, Berger JS, *et al*. Reproductive risk factors and coronary heart disease in the women's health Initiative observational study. *Circulation* 2016;133:2149–58.
18 Reardon DC, Thorp JM. Pregnancy associated death in record linkage studies relative to delivery, termination of pregnancy, and natural losses: a systematic review with a narrative synthesis and meta-analysis. *SAGE Open Med* 2017;5:205031211774049.
19 Stuart JJ, Tanz LJ, Missmer SA, *et al*. Hypertensive disorders of pregnancy and maternal cardiovascular disease risk factor development: an observational cohort study. *Ann Intern Med* 2018;169:224–32.
20 Ristić AD, Seferović PM, Ljubić A, *et al*. Pericardial disease in pregnancy. *Herz* 2003;28:209–15.
21 Martinez SC, Hayes SN, Cardiovascular Division, Mayo Clinic, Rochester, MN. Ischemic complications of pregnancy: who is at risk? *US Cardiol Rev* 2016;10:14–20.
22 Germain AM, Romanik MC, Guerra I, *et al*. Endothelial dysfunction: a link among preeclampsia, recurrent pregnancy loss, and future cardiovascular events? *Hypertension* 2007;49:90–5.
23 Reardon DC. The abortion and mental health controversy: a comprehensive literature review of common ground agreements, disagreements, actionable recommendations, and research opportunities. *SAGE Open Med* 2018;6:205031211880762.
24 Richardson DM, Andrea SB, Ziring A, *et al*. Pregnancy outcomes and documentation status among Latina women: a systematic review. *Health Equity* 2020;4:158–82.
25 Melchiorre K, Thilaganathan B, Giorgione V, *et al*. Hypertensive disorders of pregnancy and future cardiovascular health. *Front Cardiovasc Med* 2020;7:59.
26 Ranthe MF, Andersen EAW, Wohlfahrt J, *et al*. Pregnancy loss and later risk of atherosclerotic disease. *Circulation* 2013;127:1775–82.
27 Mahendru AA, Everett TR, McEniery CM, *et al*. Cardiovascular function in women with recurrent miscarriage, pre-eclampsia and/or intrauterine growth restriction. *J Matern Neonatal Med* 2013;26:351–6.
28 Hastie CE, Smith GCS, Mackay DF, *et al*. Maternal risk of ischaemic heart disease following elective and spontaneous pre-term delivery: retrospective cohort study of 750 350 singleton pregnancies. *Int J Epidemiol* 2011;40:914–9.
29 Smith GCS, Wood AM, Pell JP, *et al*. Recurrent miscarriage is associated with a family history of ischaemic heart disease: a retrospective cohort study. *BJOG An Int J Obstet Gynaecol* 2011;118:557–63.