European Heart Journal (2020) **41**, 4234–4242
doi:10.1093/eurheartj/ehaa497

CLINICAL RESEARCH
Vascular biology and medicine

Pregnancy-associated arterial dissections: a nationwide cohort study

Sebastian E. Beyer [1], Andrew B. Dicks[1], Scott A. Shainker [2], Loryn Feinberg [3], Marc L. Schermerhorn [4], Eric A. Secemsky[3,5], and Brett J. Carroll[3]*

[1]Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, 185 Pilgrim Road, Palmer 4, Boston, MA 02215, USA; [2]Department of Obstetrics and Gynecology, Beth Israel Deaconess Medical Center, Harvard Medical School, 185 Pilgrim Road, Palmer 4, Boston, MA 02215, USA; [3]Division of Cardiovascular Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, 185 Pilgrim Road, Palmer 4, Boston, MA 02215, USA; [4]Division of Vascular and Endovascular Surgery, Department of Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, 185 Pilgrim Road, Palmer 4, Boston, MA 02215, USA; and [5]Smith Center for Outcomes Research in Cardiology, Beth Israel Deaconess Medical Center, Harvard Medical School, 185 Pilgrim Road, Palmer 4, Boston, MA 02215, USA

Received 2 March 2020; revised 8 May 2020; editorial decision 20 May 2020; accepted 28 May 2020; online publish-ahead-of-print 30 July 2020

See page 4243 for the editorial comment on this article (doi: 10.1093/eurheartj/ehaa754)

Aims Pregnancy is a known risk factor for arterial dissection, which can result in significant morbidity and mortality in the peripartum period. However, little is known about the risk factors, timing, distribution, and outcomes of arterial dissections associated with pregnancy.

Methods and results We included all women ≥12 years of age with hospitalizations associated with pregnancy and/or delivery in the Nationwide Readmissions Database between 2010 and 2015. The primary outcome was any dissection during pregnancy, delivery, or the postpartum period (42-days post-delivery). Secondary outcomes included timing of dissection, location of dissection, and in-hospital mortality. Among 18 151 897 pregnant patients, 993 (0.005%) patients were diagnosed with a pregnancy-related dissection. Risk factors included older age (32.8 vs. 28.0 years), multiple gestation (3.6% vs. 1.9%), gestational diabetes (14.3% vs. 0.2%), gestational hypertension (6.0% vs. 0.6%), and pre-eclampsia/eclampsia (2.7% vs. 0.4%), in addition to traditional cardiovascular risk factors. Of the 993 patients with dissection, 150 (15.1%) dissections occurred in the antepartum period, 232 (23.4%) were diagnosed during the admission for delivery, and 611 (61.5%) were diagnosed in the postpartum period. The most common locations for dissections were coronary (38.2%), vertebral (22.9%), aortic (19.8%), and carotid (19.5%). In-hospital mortality was 3.7% among pregnant patients with a dissection vs. <0.001% in patients without a dissection. Deaths were isolated to patients with an aortic (8.6%), coronary (4.2%), or supra-aortic (<2.5%) dissection.

Conclusion Arterial dissections occurred in 5.5/100 000 hospitalized pregnant or postpartum women, most frequently in the postpartum period, and were associated with high mortality risk. The coronary arteries were most commonly involved. Pregnancy-related dissections were associated with traditional risk factors, as well as pregnancy-specific conditions.

Keywords Dissection • Arterial • Pregnancy • Peripartum • Mortality

Introduction

Cardiovascular disease is the leading cause of maternal mortality in the USA, accounting for 15.5% of pregnancy-related deaths.[1] Most cardiovascular events are due to thromboembolism, cardiomyopathy, or stroke,[2] which are thought to be caused by haemodynamic, hormonal, and structural vascular changes.[3–5] Though far less common, pregnancy is also a risk factor for acute arterial dissections,[4,6,7] suspected to be related to arterial changes during pregnancy.

Arterial dissections associated with pregnancy have been described in all arterial beds, but the best-studied are acute aortic dissections and spontaneous coronary artery dissections (SCADs). In a

*Corresponding author. Tel: 617-632-7493, Fax: 617-632-7620, Email: bcarrol2@bidmc.harvard.edu

cohort-crossover study including over 6 million hospitalizations and emergency department visits of pregnant women, Kamel *et al.*[6] determined that the incidence rate of aortic dissection or rupture was four times as high in pregnant compared with non-pregnant women. An evaluation of pregnancy-associated SCAD patients from a Mayo Clinic registry demonstrated that multiparity, infertility therapies, and pre-eclampsia were associated with SCAD.[7] Most cases of SCAD occurred within the first 5 weeks of delivery. Both studies, however, only included a relatively low number of cases (36 and 54, respectively), limiting their ability to identify patient characteristics or outcomes associated with arterial dissections. Furthermore, it is unknown if pregnancy is also associated with other arterial dissections.

The goals of our study were to determine the risk factors, timing, distribution, and outcomes of acute arterial dissections during pregnancy, delivery, and the postpartum period using a large population-based database.

Materials and methods

National Readmissions Database

We obtained data from the Nationwide Readmissions Database (NRD) between 1 January 2010 and 30 September 2015. In 2015, the NRD collected discharge data from 27 geographically dispersed states, accounting for 57.8% of the total US resident population and 56.6% of all US hospitalizations.[8] The database is populated with data from all payers as well as uninsured persons and is comprised of more than 100 clinical and non-clinical variables for each hospital stay. These data include patient demographics, payment source, and diagnosis and procedure codes from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), and Procedure Coding System (ICD-9-PCS). Trained analysts at each healthcare facility use automated online reporting to provide discharge data to data organizations in participating states which process the data to ensure quality and accuracy.[9] Data are then shared with the Healthcare Cost and Utilization Project (HCUP) through a Federal-State-Industry partnership for the development of HCUP databases including the NRD. October through December 2015 did not contribute to the analysis because of the transition from ICD-9 to ICD-10 coding system in October 2015. Methods are briefly described here, with complete details provided in the Supplementary material online.

Ethical approval

The Institutional Review Board (IRB) at Beth Israel Deaconess Medical Center waived the need for IRB approval because the NRD contains de-identified aggregate data.

Study population

We identified all female patients ≥12 years of age who were hospitalized during pregnancy or delivery using ICD-9-CM codes (Supplementary material online, *Table S1*).[6] Similar to prior reports using administrative claims databases,[3] we defined a pregnancy admission as any record with a pregnancy-related code or a delivery-related code. We defined antepartum as an admission associated with a pregnancy-related ICD-9-CM code, but not with delivery-related code. When multiple labour-related admissions occurred, delivery was defined as the latest hospitalization in order to exclude visits not resulting in delivery as previously described.[6] The postpartum period was defined as the first 42 days after discharge from the delivery hospitalization.[10] All hospitalizations following the delivery-associated admission were defined as postpartum admissions.

Data from November and December of the years 2010–2014 and from August and September of 2015 did not contribute admissions to the analysis, allowing every patient to have at least 60 days of follow-up to assure consistent 42-day follow-up during the postpartum period.[10]

We excluded admissions for delivery if the discharge date was missing or if the hospitalization occurred in a state other than the patient's primary residence, because any postpartum admission occurring in a different state from that of the index hospitalization would not be captured by the NRD.

Patient characteristics

Patient characteristics included hypertension, dyslipidaemia, diabetes mellitus, tobacco use (former or current), bicuspid aortic valve, coarctation of the aorta, Marfan syndrome, Ehlers-Danlos syndrome, Turner syndrome, fibromuscular dysplasia of the renal artery, and trauma (motor vehicle accident) [all identified using ICD-9-CM codes reported at the time of admission (Supplementary material online, *Table S1*)], as well as alcohol use, illicit drug use, heart failure, chronic kidney disease, chronic liver disease, obstructive sleep apnoea, rheumatoid arthritis, and depression (as included in the NRD). We also identified complications during pregnancy and delivery including high-risk pregnancy, multiple gestation, haemorrhage, gestational hypertension, gestational diabetes, and pre-eclampsia/eclampsia, as well as the mode of delivery (vaginal, caesarean section) in patients admitted for delivery or during the postpartum period using diagnosis and procedure codes, as listed in Supplementary material online, *Table S1*.

Study outcomes

The primary outcome was any pregnancy-related (pregnancy, delivery, and postpartum period) dissection. We identified arterial dissections using ICD-9-CM codes (Supplementary material online, *Table S1*). Studies have shown that ICD-9 codes for cardiovascular diagnoses and procedures such as myocardial infarction, cardiac angiography, percutaneous transluminal coronary angioplasty, and coronary artery bypass graft surgery have high sensitivities and specificities (>90% for all).[11] The positive predictive value of aortic dissection, coded according to ICD-10, was 92% when previously validated.[12] All available discharge diagnoses (i.e. primary and secondary) were included.[5] Secondary outcomes were (i) the timing of the dissection (antepartum/delivery vs. postpartum), (ii) the location of the individual dissections (aorta, carotid artery, coronary artery, iliac artery, renal artery, vertebral artery, or other artery), (iii) the trend of the incidence of the dissections over the course of the study period, (iv) in-hospital mortality associated with arterial dissections, and (v) the rate of invasive diagnostic and therapeutic procedures.

Statistical analysis

All metric and normally distributed variables are reported as mean ± standard deviation; non-normally distributed variables are presented as median (interquartile range). Categorical variables are presented as frequency and percentage. Cell sizes ≤10 were reported as '≤10' per HCUP guidelines.[13]

We stratified patients according to the presence of a pregnancy-related dissection and compared baseline characteristics using Fisher's exact or χ^2 tests for categorical variables and Student's *t* or Wilcoxon rank-sum tests for continuous variables. In addition, we compared baseline characteristics using standardized differences, which compare the differences in means in units of the pooled standard deviations.[14] We examined independent predictors of a pregnancy-associated dissection with a multivariable logistic regression model. Variables included in the multivariable model were statistically significant ($P < 0.05$) on univariate analyses. Dyslipidaemia was not included in the final model because of a strong correlation with gestational diabetes.

We then stratified patients with a pregnancy-related dissection according to the timing (pregnancy/delivery vs. postpartum) of the dissection. Among patients with an arterial dissection after delivery, we estimated the time from delivery (day of discharge) to the time of readmission for the dissection using the Kaplan–Meier method. Patients were censored at the end of each year as the NRD does not track patients across years. To evaluate incidence trends, logistic regression models were used. Trends were assumed to be linear on the log-odds scale. All statistical analyses were performed by using the weighted values of observations as provided by the NRD to obtain national estimates. A two-sided $P < 0.05$ was considered significant. We used STATA v.16 (StataCorp, College Station, TX, USA) for all statistical analyses.

Results

Study cohort

Between January 2010 and September 2015, 22 393 805 women were hospitalized for pregnancy or delivery. After applying the exclusion criteria, 4 241 908 patients were removed from the analysis, resulting in 18 151 897 patients included in our study (*Figure 1*). Of these patients, 993 (0.005%) were diagnosed with a pregnancy-related arterial dissection. The incidence of which increased with higher maternal age (*Figure 2*).

Patient characteristics

Patients with a pregnancy-related dissection were older (32.8 vs. 28.0 years of age, $P < 0.001$) than patients without a dissection. Chronic hypertension (19.0% vs. 3.1%, $P < 0.001$), dyslipidaemia (2.3% vs. 0.2%, $P < 0.001$), tobacco use (13.5% vs. 7.8%, $P < 0.001$), alcohol use (1.2% vs. 0.2%, $P < 0.001$), obesity (7.8% vs. 5.6%, $P = 0.046$), heart failure (2.1% vs. 0.04%, $P < 0.001$), chronic liver disease (≤1% vs. 0.2%, $P < 0.001$), arthritis (1.8% vs. 0.3%, $P < 0.001$), depression (6.1% vs. 2.3%, $P < 0.001$), Marfan syndrome (4.6% vs. 0.01%, $P < 0.001$), and Ehlers-Danlos syndrome (≤1% vs. 0.01%, $P < 0.001$) were more common in patients with a dissection than in those without a dissection. Complications of pregnancy or delivery including multiple gestation (3.6% vs. 1.9%, $P = 0.006$), gestational hypertension (6.0% vs. 0.6%, $P < 0.001$), gestational diabetes (14.3% vs. 0.2%, $P < 0.001$), and pre-eclampsia/eclampsia (2.7% % vs. 0.4%, $P < 0.001$) were also more common in patients with a dissection (*Table 1*).

On multivariable analysis, the following predictors were independently associated with a higher risk of a pregnancy-related dissection: higher age, chronic hypertension, tobacco use, alcohol use, chronic heart failure, Marfan syndrome, Ehlers-Danlos syndrome, and gestational diabetes (Supplementary material online, *Table S2*).

Timing of dissection

Dissections occurred in the antepartum period in 150 (15.1%) patients, during the admission for delivery in 232 (23.3%) patients, and in the postpartum period in 611 (61.5%) patients (*Figure 3A*). Most postpartum readmissions associated with a dissection occurred within 30 days of delivery (3.2/100 000 deliveries at 30 days vs. 4.7/100 000 deliveries at 180 days) (*Figure 3B*). The timing was similar among all types of dissections.

Compared to patients with a dissection prior to or during delivery, those with a dissection in the postpartum period were older (34.0 vs. 30.7 years of age, $P < 0.001$). High-risk pregnancy (4.7% vs. 10.8%,

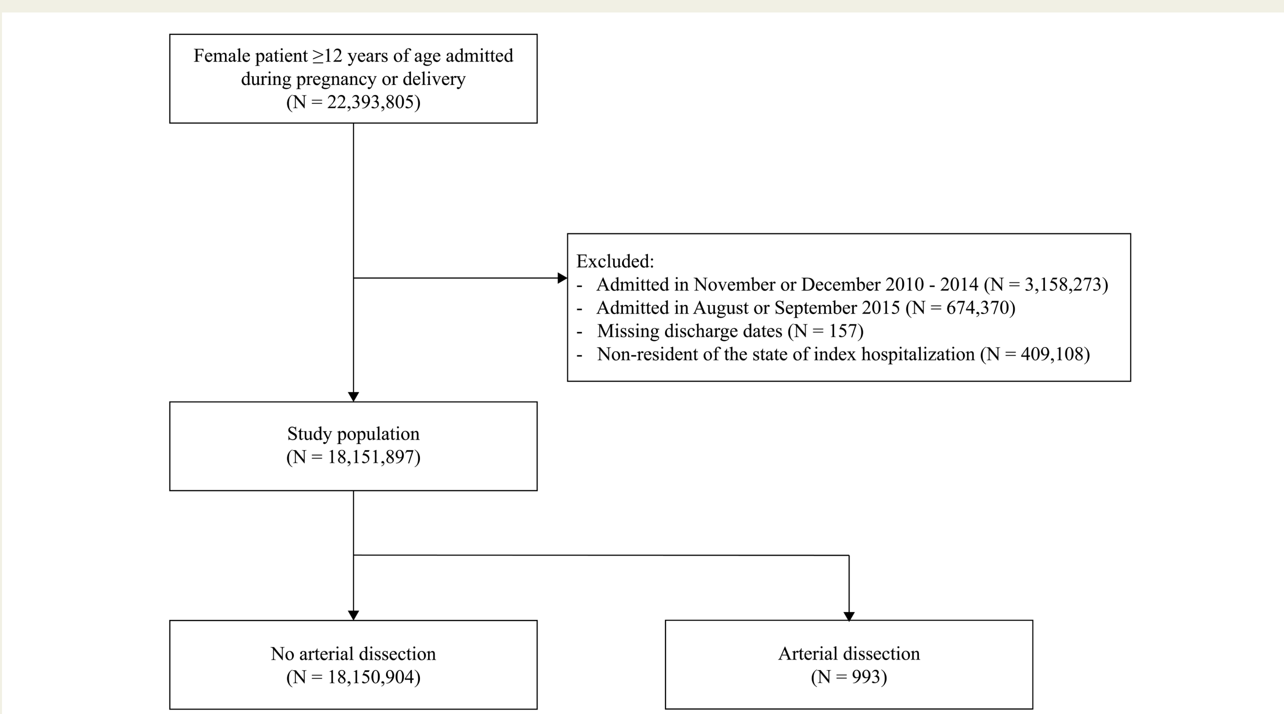


Figure 1 Study population.

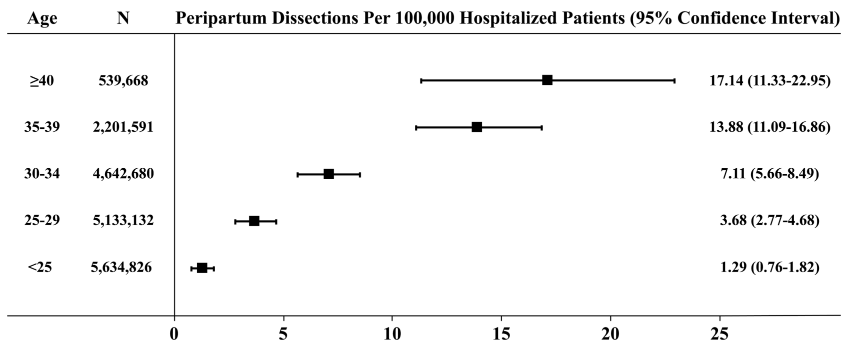


Figure 2 Incidence of arterial dissections, stratified by age category. The figure shows the incidence of dissections per 100 000 hospitalized pregnant or postpartum patients by maternal age.

Table 1 Characteristics comparing patients with and without pregnancy-related dissections

Characteristic	Arterial dissection (*N* = 993)	No arterial dissection (*N* = 18 150 904)	*P*-value	Standardized difference
Age, years	32.8 ± 5.5	28.0 ± 6.0	<0.001	0.828
Comorbidities				
Hypertension	188 (18.96)	565 329 (3.11)	<0.001	0.528
Dyslipidaemia	23 (2.32)	32 452 (0.18)	<0.001	0.196
Diabetes mellitus	15 (1.50)	187 745 (1.03)	0.536	0.042
Tobacco use	134 (13.48)	1 412 532 (7.78)	<0.001	0.187
Alcohol use	12 (1.16)	28 122 (0.15)	<0.001	0.126
Illicit drug use	22 (2.17)	345 240 (1.90)	0.715	0.019
Obesity	77 (7.76)	1 007 754 (5.55)	0.046	0.089
Heart failure	21 (2.12)	7467 (0.04)	<0.001	0.204
Chronic kidney disease	≤10	10 833 (0.06)	0.267	0.033
Chronic liver disease	≤10	31 628 (0.17)	<0.001	0.099
Rheumatoid arthritis	17 (1.75)	52 444 (0.29)	<0.001	0.147
Depression	60 (6.05)	423 217 (2.33)	<0.001	0.188
Bicuspid aortic valve	0 (0.00)	291 (0.00)	—	—
Coarctation of the aorta	0 (0.00)	421 (0.00)	—	—
Marfan syndrome	46 (4.64)	961 (0.01)	<0.001	0.315
Ehlers-Danlos syndrome	≤10	2711 (0.01)	<0.001	0.074
Turner syndrome	0 (0.00)	549 (0.00)	—	—
Fibromuscular dysplasia of renal artery	0 (0.00)	35 (0.00)	—	—
Trauma (Motor vehicle accident)	0 (0.00)	0 (0.00)	—	—
Complications during pregnancy or delivery				
High-risk pregnancy	70 (7.05)	944 849 (5.21)	0.155	0.077
Multiple gestation	36 (3.62)	338 273 (1.86)	0.006	0.109
Haemorrhage	11 (1.10)	91 063 (0.50)	0.151	0.067
Gestational hypertension	59 (5.95)	101 439 (0.56)	<0.001	0.311
Gestational diabetes	142 (14.30)	40 638 (0.22)	<0.001	0.570
Pre-eclampsia/eclampsia	27 (2.71)	70 319 (0.39)	<0.001	0.191

Numbers are mean ± SD or *N* (%), unless otherwise stated.
OR, odds ratio.

$P = 0.041$), haemorrhage during pregnancy (0% vs. 2.9%, $P = 0.024$), gestational hypertension (≤1.6% vs. 14.0%, $P < 0.001$), pre-eclampsia/eclampsia (≤1.6% vs. 5.3%, $P = 0.008$), as well as traditional cardiovascular risk factors were less common in patients with a dissection in the postpartum period. Conversely, gestational diabetes was more common in patients with a dissection in the postpartum

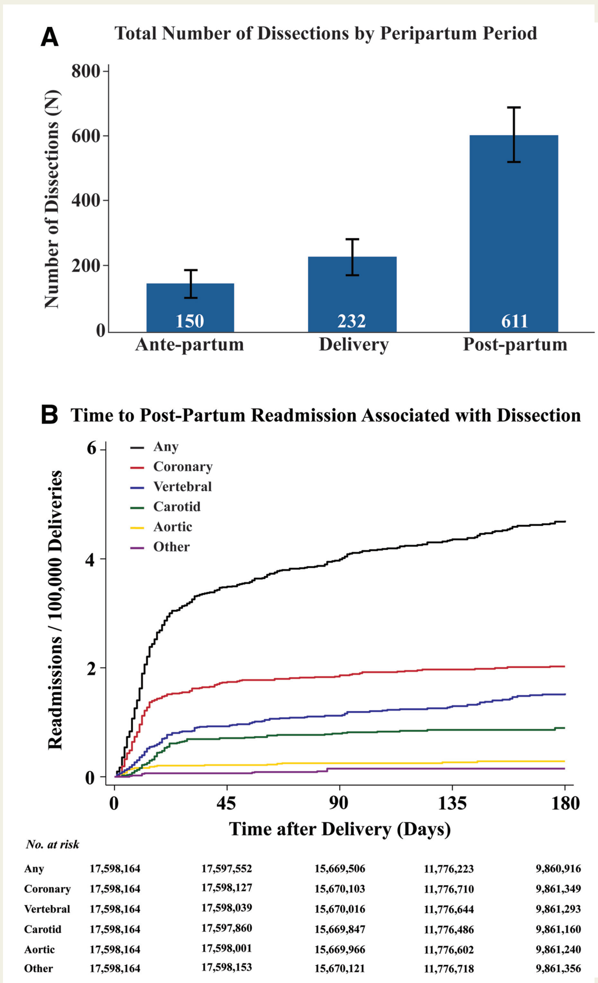


Figure 3 Timing of arterial dissections. The figure shows the total number of dissections according to the peripartum period (*A*) and the time from delivery (day of discharge) to the postpartum re-admission associated with a dissection (*B*). Most dissections occurred in the postpartum period, and of those most occurred within the first 30 days of delivery.

period (19.5% vs. 6.0%, $P < 0.001$) (*Table 2*). Of patients with a dissection during the admission for delivery, 84.8% underwent a caesarean section, while only 32.6% of patients with a dissection in the postpartum period delivered by caesarean section.

Location of dissections and temporal trend during the study period

Overall, the most common dissections were coronary (38.2%), vertebral (22.9%), aortic (19.8%), and carotid (19.5%) (*Take home figure*). Multiple arteries were involved in 4.4% of patients. 57.9% of aortic dissections occurred in the thoracic aorta, 15.7% in the thoracoabdominal aorta, and 10.7% in the abdominal aorta. 15.7% were coded as 'unspecified' aortic location. 30.5% of aortic dissections were presumed type A dissections, while 69.5% were presumed type B dissections. The most common dissections prior to or during delivery were aortic (41.4%), followed by coronary (19.9%), carotid (18.1%), and vertebral (16.8%). This differed from the postpartum period, where coronary artery dissection was the most common site (49.6%), followed by vertebral (26.7%) carotid (20.5%), and aortic (6.4%) (*Figure 4A*). The distribution of aortic dissection subtypes was similar across peripartum periods.

During the study period, the incidence of dissections per 100 000 hospitalized pregnant or postpartum patients increased from 4.46 (95% confidence interval 3.01–5.92) in 2010 to 6.20 (4.47–7.94) in 2015 ($P_{trend} = 0.062$). This was driven by an increase in the rate of vertebral dissections from 0.81 (0.36–1.25) to 2.31 (1.08–3.54) ($P_{trend} < 0.001$). The rates of the other arterial dissections remained stable (*Figure 4B*).

Interventions and mortality associated with dissection

Overall, 501 (50.4%) patients with a dissection underwent invasive diagnostic angiography. The rate was higher among patients with a dissection in the postpartum period (66.2% vs. 25.2%, $P < 0.001$). Cardiovascular interventions were performed in 379 (38.2%) patients. Interventions included percutaneous coronary interventions (PCIs) and cardiac surgery in 199 (20.0%) and 191 (19.2%) patients, respectively. The rate of PCIs was higher in patients with dissections in the postpartum period (27.8% vs. 7.6%, $P < 0.001$), whereas the rate of cardiac surgeries did not differ by peripartum periods (*Table 3*). Further details on invasive diagnostic and therapeutic procedures by type of dissection are provided in the Online Supplement (Supplementary material online, *Tables S3–S8*).

Of patients with a pregnancy-related dissection, 37 (3.7%) died during the hospitalization compared to 2531 (0.0001%) pregnant patients without a dissection ($P < 0.001$). Deaths were isolated to those with an aortic [17 (8.6%)], coronary [16 (4.2%)], carotid ($\leq$10), or vertebral ($\leq$10) dissection. No deaths occurred in those with an iliac, renal, or 'other' dissection.

Discussion

In this nationwide cohort analysis, we demonstrate that arterial dissections occur in approximately 5.5/100 000 hospitalized pregnant or postpartum women. Arterial dissections were associated with multiple gestation, gestational hypertension, pre-eclampsia, and eclampsia, in addition to traditional cardiovascular risk factors. The majority of dissections occurred during the postpartum period and of those, most occurred within 30 days of the hospitalization for delivery. While coronary artery dissections were most common overall, vertebral artery dissections were the most common dissections in the postpartum period.

Prior studies have shown an association between connective tissue disorders, hypertension, and pre-eclampsia with aortic dissection during pregnancy.[6] Our study extends those findings by demonstrating the importance of pregnancy-specific characteristics, such as multiple gestation, gestational hypertension, gestational diabetes, and pre-eclampsia/eclampsia, which are associated with maternal vascular remodelling.[15] Traditional cardiovascular risk factors were also more common in patients with a peripartum dissection. However, the rates were lower than in non-pregnant patients with an arterial

Table 2 Characteristics comparing patients with a dissection during pregnancy or delivery and patients with a dissection during the postpartum period

Characteristic	Dissection during pregnancy or delivery (*N* = 382)	Dissection during postpartum period (*N* = 611)	*P*-value	Standardized difference
Age, years	30.7 ± 5.6	34.0 ± 5.1	<0.001	-0.614
Comorbidities				
Hypertension	128 (33.58)	60 (9.80)	<0.001	0.611
Lipid disorder	17 (4.33)	≤10	0.015	0.206
Diabetes mellitus	15 (3.90)	0 (0.00)	0.034	0.289
Tobacco use	74 (19.28)	60 (9.85)	0.017	0.273
Alcohol use	≤10	≤10	0.077	0.169
Illicit drug use	14 (3.78)	≤10	0.158	0.171
Obesity	54 (14.04)	23 (3.83)	0.000	0.369
Heart failure	19 (4.94)	≤10	0.002	0.294
Chronic kidney disease	≤10	0 (0.00)	0.208	0.096
Chronic liver disease	≤10	0 (0.00)	0.012	0.220
Rheumatoid arthritis	15 (4.01)	≤10	0.008	0.257
Depression	40 (10.52)	20 (3.25)	0.004	0.294
Bicuspid aortic valve	0 (0.00)	0 (0.00)	—	—
Coarctation of the aorta	0 (0.00)	0 (0.00)	—	—
Marfan syndrome	42 (10.94)	≤10	<0.001	0.455
Ehlers-Danlos syndrome	≤10	0 (0.00)	0.075	0.129
Turner syndrome	0 (0.00)	0 (0.00)	—	—
Fibromuscular dysplasia of renal artery	0 (0.00)	0 (0.00)	—	—
Trauma (motor vehicle accident)	0 (0.00)	0 (0.00)	—	—
Pregnancy or delivery characteristics				
High-risk pregnancy	41 (10.79)	29 (4.71)	0.041	0.232
Multiple gestation	11 (2.78)	25 (4.15)	0.431	-0.076
Haemorrhage	11 (2.85)	0 (0.00)	0.024	0.246
Gestational hypertension	54 (14.01)	≤10	<0.001	0.523
Gestational diabetes	23 (5.98)	119 (19.51)	<0.001	-0.419
Pre-eclampsia or eclampsia	20 (5.31)	≤10	0.008	0.246

Numbers are mean ± SD or *N* (%), unless otherwise stated.

dissection,[16] further highlighting the importance to understand how pregnancy-specific changes lead to an increased risk.

Pregnancy results in haemodynamic changes including increased heart rate, stroke volume, cardiac output, and left ventricular dimensions,[17] as well as large fluctuations in oestrogen and progesterone levels. Oestrogen has been shown to have both cardioprotective effects via release of nitric oxide leading to up-regulation of vascular smooth muscle relaxation as well as destructive effects via release of matrix metalloproteinase leading to degradation of extravascular structural support.[18–22] The alterations in hormone levels likely alter this protective-destructive balance with evidence by arterial histology from the pregnant state demonstrating reticular fibre fragmentation, elastic fibre disorganization, hypertrophy, and hyperplasia of smooth muscle cells.[23,24] Our findings suggest that the presence of additional risk factors, such as gestational diabetes or pre-eclampsia, may compound the underlying baseline risk during pregnancy.

Notably, most of the dissections were associated with labour or occurred in the postpartum period shortly after delivery. These findings are consistent with prior reports in patients with pregnancy-associated SCAD demonstrating that most dissections occur in the early postpartum period.[7] Our analysis adds to those results by demonstrating differences in patient characteristics between patients who develop a dissection in the antepartum period compared with those with dissections in the postpartum period. Dissections in the postpartum period were not only less commonly associated with traditional cardiovascular risk factors, but also less commonly with high-risk pregnancy characteristics, such as gestational diabetes, gestational hypertension, pre-eclampsia, or eclampsia. It is possible that dissections in the postpartum period are more commonly due to the numerous stressors on the vasculature surrounding delivery, such as Valsalva efforts and rapid volume shifts in the systemic circulation shortly after delivery.[25]

In evaluating the distribution of dissections, there are several differences in the location of dissection between the antepartum and postpartum populations. While the distribution of aortic dissections drops from 41.4% in the antepartum group to 5.2% in the postpartum group, the percentage of coronary dissections increases from 19.9% to 49.8%. The rationale for these changes in distribution likely reflects

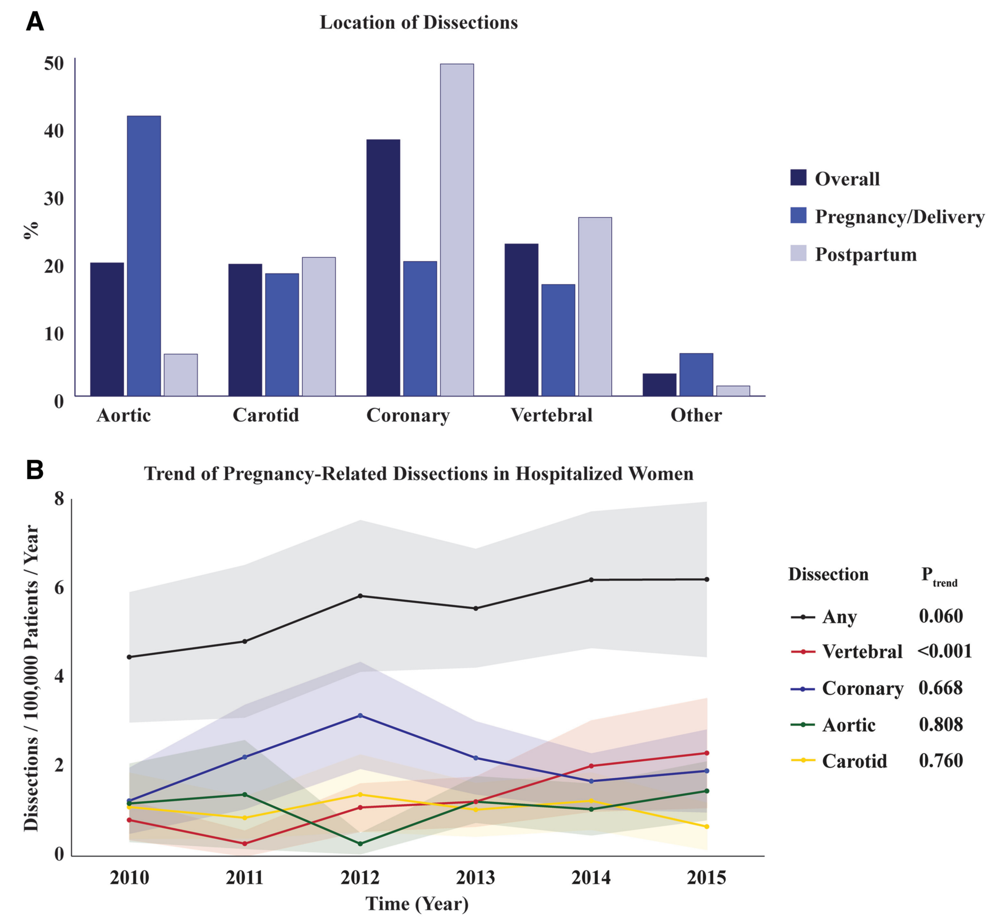
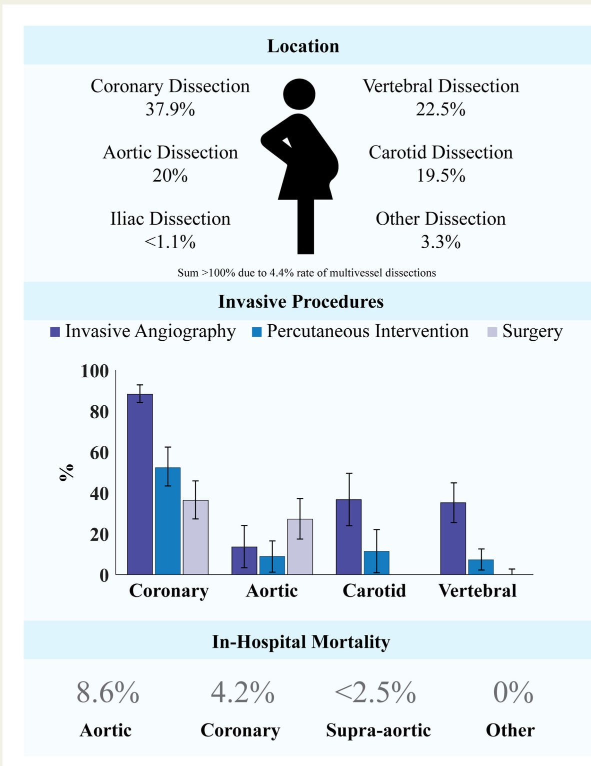


Figure 4 Location of arterial dissections. (*A*) The location of dissections stratified by the timing during the peripartum period (pregnancy/delivery vs. postpartum). The sum is >100% due to a 4.4% rate of multivessel dissections. During pregnancy and delivery, aortic dissection is most common, while coronary dissection was the most common dissection in the postpartum period. (*B*) The incidence trends of dissections over the course of the study period. Shaded areas represent 95% confidence intervals. There is a small overall increase over time, which is primarily due to an increase in vertebral dissections.

the differences in the pregnancy-associated hormonal and haemodynamic changes on specific vascular beds. For example, the aorta may be more prone to the haemodynamic stresses of increased cardiac output during pregnancy compared with the cerebrovascular bed. Given cardiac output peaks late in pregnancy this may partially explain the relative higher rate of aortic dissection during pregnancy/delivery compared with postpartum period.[26] In comparison, the heart and coronary arteries appear to be particularly susceptible during the early postpartum period, likely related to the dramatic increase in systemic circulation related to return of blood volume after delivery and post-delivery uterine contraction. The increase in distribution of coronary artery dissections in the postpartum period corresponds with peak timing of other cardiac pathology in pregnancy, including pregnancy-associated myocardial infarction from any cause and peripartum cardiomyopathy, with the majority of these cases occurring within the first postpartum week.[27,28]

Vertebral artery dissection is an important cause of ischaemic stroke in young adults, accounting for ~15% of strokes in adults 15–49 years old.[29] It primarily affects the extracranial segments and is frequently associated with cervical manipulation or hyperextension of the neck, as well as traditional cardiovascular risk factors including age, hypertension, and diabetes mellitus.[30] With fewer than 20 cases reported in the largest series,[31] little is known about pregnancy-associated vertebral dissections. In our study, most of vertebral dissections were diagnosed shortly after delivery, suggesting that changes in postpartum hormones leading to transient arterial wall abnormalities and increases in blood pressure[32] as well as labour itself might play a role. Interestingly, however, many vertebral dissections after the 6-week postpartum period, raising the concern that the diagnosis may be delayed in some cases because of the sometimes mild and non-specific presentation.[32] The higher rate of vertebral dissection postpartum may also be related to postpartum hormonal changes could specifically effect the posterior circulation. Such an association has been hypothesized with postpartum cervical artery dissection in the setting of reversible cerebral vasoconstriction syndrome and reversible posterior encephalopathy syndrome.[32,33] Furthermore, our results show the incidence of vertebral artery dissection has increased during the study period, a finding that may be



Take home figure Coronary artery dissection is the most common arterial dissection in the peri-partum period and also has the highest rate of invasive angiography and intervention. Mortality is highest among those with an aortic dissection.

related to higher maternal age, a decreased rate of caesarean sections, as well as improved and more widely available diagnostic procedures.

Prior data for interventions in pregnancy-related arterial dissection are limited in the current literature. The most abundant data available are for SCAD. In a previous detailed collection of 750 patients with SCAD, 4.7% were associated with pregnancy.[34] The overall rate of percutaneous intervention was 14% and 0.7% underwent coronary artery bypass graft surgery; in-hospital major adverse events were 8.8% with death occurred in 0.1%. Peripartum-associated SCAD was an independent risk factor for in-hospital major adverse event (OR 2.9, CI 1.2–7.1; $P = 0.02$) with increased rates of high-risk presentation, depressed ejection fraction, and multivessel SCAD. Data were not available regarding treatment for those with peripartum SCAD specifically. The higher risk features of pregnancy-related SCAD may account for the greater rates of intervention in our study compared with overall rate in SCAD. Our results are similar to a prior small report of 45 cases of peripartum SCAD with 34% undergoing PCI and 36% undergoing CABG[35] and a prior report utilizing the National Inpatient Sample.[36] Cervical artery dissection is generally managed conservatively and interventions are generally reserved for those with recurrent ischaemia despite antithrombotic therapy.[37] Thus, data regarding interventions in non-pregnancy-related cervical dissection are also limited to case series.[38] Our rate of endovascular intervention of 8.8% is similar to a prior report of patients with vertebral dissection in the presence of fibromuscular dysplasia.[39]

Billing codes do not differentiate type A from type B aortic dissection, but using prior algorithms, over two-thirds of pregnancy-related aortic dissections were type B dissections, of which 14% underwent thoracic endovascular aortic repair (TEVAR). In a prior analysis of all patients with presumed type B dissection in the NRD, the rate of TEVAR was similar at 16%.[40] There was a comparably lower rate of TEVAR from data of a similar timeframe in the International Registry of Acute Aortic Dissections (IRAD) (30.9%), which is likely reflective of judicious utilization of TEVAR in younger patients with possible genetic predisposition to dissection.[26]

The mortality associated with any type of aortic dissection in our study was 8.6%. Prior reports of mortality estimates have been limited by very small sample sizes and have therefore ranged from 0%[41] to 50%[42]. Our results are most consistent with the findings of the largest series so far, a study of 25 patients published in 2017.[43] The authors report a mortality rate of 20% among patients with a type A dissection and of 0% in patients with a type B dissection.[44] It is, however, important to note that these are only estimates of the inpatient mortality. The overall mortality is likely higher with estimates that 50% of patients with a type A aortic dissection and ∼4% of patients with a type B aortic dissection have previously been found to die prior to hospital admission.[45]

Our study also showed an inpatient mortality of 4.2% among patients with an SCAD, a mortality of <2.5% among patients with a supra-aortic dissection, and no deaths in those with other types of arterial dissections. While the relatively low mortality associated with coronary artery dissection is in contrast to earlier reports, more recent series have indicated that mortality rates associated with pregnancy-associated SCAD have dramatically changed over the last 50 years. Our findings are consistent with a recent review that highlighted a drop in maternal mortality from 85% to 4%,[46] further emphasizing the importance of contemporary management with emergent angiography, reduced thrombolysis, and increasingly conservative or percutaneous management.[26] Data are lacking regarding mortality rates related to vertebral and carotid artery dissections in pregnancy. Case studies have thus far reported a mortality rate of 0%.[31,32,47] Our results confirm the mortality rate to be low, albeit greater than 0%.

This study must be interpreted within the limitations of analyses of administrative claims data. The data are limited to the accuracy of billing by the providers making it possible for comorbidities to be under-recognized and/or under billed, especially in those patients who have uncomplicated antepartum and postpartum periods. Thus, our analysis may have been susceptible to misclassification. However, positive predictive values of codes for aortic dissection and other cardiovascular diagnoses have previously found to be upwards of 90%.[11,12] In addition, details of out-of-hospital death are not available in the NRD, thus our incidence of some dissections, particularly aortic dissection, may be underestimated. However, in studies of patients with aortic dissection the prevalence of cardiovascular risk factors was similar in patients who did and those who did not experience out-of-hospital death. Therefore, the distribution of risk factors in our study is unlikely to be affected. No data are available on out-of-hospital mortality for patients with other types of arterial dissections. Furthermore, granular data from imaging studies to evaluate

Table 3 Diagnostic and therapeutic procedures in patients with any dissection

	Overall (*N* = 993)	Dissection during pregnancy or delivery (*N* = 382)	Dissection during the postpartum period (*N* = 611)	*P*-value
Diagnostic procedures				
Any diagnostic invasive angiography (coronary and non-coronary)	501 (50.4)	96 (25.2)	404 (66.2)	<0.001
Coronary angiography	340 (34.2)	56 (14.6)	284 (46.5)	<0.001
Non-coronary angiography	194 (19.5)	44 (11.6)	149 (24.4)	0.012
Therapeutic procedures				
Any cardiovascular intervention (percutaneous and surgical)	379 (38.2)	108 (28.2)	271 (44.4)	0.005
PCI	199 (20.0)	29 (7.6)	170 (27.8)	<0.001
PCI with stent placement	145 (14.6)	19 (4.9)	127 (20.8)	<0.001
Percutaneous intervention of non-coronary artery	58 (5.8)	28 (7.5)	29 (4.8)	0.417
Cardiac surgery	191 (19.2)	57 (14.8)	134 (21.9)	0.149
CABG	119 (12.0)	23 (6.0)	96 (15.7)	0.065
Non-cardiac surgery	52 (5.3)	41 (10.7)	11 (1.9)	<0.001

Numbers are mean ± SD or *N* (%), unless otherwise stated.
CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.

underlying mechanisms of dissections, such as bicuspid aortic valves, are not available in the NRD.

Conclusion

Arterial dissection remains a rare complication of pregnancy, but is associated with a significantly increased risk of mortality. Most events occur shortly after delivery, and the distribution of the vascular bed involved differs based on the peripartum period. High-risk pregnancy-specific characteristics likely play an important role in addition to traditional cardiovascular risk factors.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Conflict of interest: Dr S.A.S. reports grants and salary support from the Charles Koch Foundation, outside the submitted work. Dr M.L.S. reports consulting fees from Abbott Vascular, Cook Medical, Endologix, Medtronic, and Philips, outside the submitted work. Dr E.A.S. reports grants to the institution from AstraZeneca, BD Bard, Boston Scientific, Cook Medical, Cardiovascular Systems, Inc, Medtronic, Philips, and UC San Francisco. Dr E.A.S. further reports consulting fees from BD Bard, Cardiovascular Systems, Inc, Medtronic, Janssen, and Philips, as well as speaking bureau fees from BD Bard, Cook Medical, and Medtronic, outside the submitted work. The remaining authors have no disclosures.

References

1. Wolfe DS, Hameed AB, Taub CC, Zaidi AN, Bortnick AE. Addressing maternal mortality: the pregnant cardiac patient. *Am J Obstet Gynecol* 2019;**220**:167.e1–167.e8.
2. Creanga AA, Berg CJ, Syverson C, Seed K, Bruce FC, Callaghan WM. Pregnancy-related mortality in the United States, 2006-2010. *Obstet Gynecol* 2015;**125**:5–12.
3. James AH, Jamison MG, Biswas MS, Brancazio LR, Swamy GK, Myers ER. Acute myocardial infarction in pregnancy: a United States population-based study. *Circulation* 2006;**113**:1564–1571.
4. De Martino A, Morganti R, Falcetta G, Scioti G, Milano AD, Pucci A, Bortolotti U. Acute aortic dissection and pregnancy: review and meta-analysis of incidence, presentation, and pathologic substrates. *J Card Surg* 2019;**34**:1591–1597.
5. Elgendy IY, Gad MM, Mahmoud AN, Keeley EC, Pepine CJ. Acute stroke during pregnancy and puerperium. *J Am Coll Cardiol* 2020;**75**:180–190.
6. Kamel H, Roman MJ, Pitcher A, Devereux RB. Pregnancy and the risk of aortic dissection or rupture: a cohort-crossover analysis. *Circulation* 2016;**134**:527–533.
7. Tweet MS, Hayes SN, Codsi E, Gulati R, Rose CH, Best P. Spontaneous coronary artery dissection associated with pregnancy. *J Am Coll Cardiol* 2017;**70**:426–435.
8. NRD Overview. https://www.hcup-us.ahrq.gov/nrdoverview.jsp (3 February 2020).
9. HCUP Partners. https://www.hcup-us.ahrq.gov/partners.jsp (9 April 2020).
10. Romano M, Cacciatore A, Giordano R, La Rosa B. Postpartum period: three distinct but continuous phases. *J Prenat Med* 2010;**4**:22–25.
11. Petersen LA, Wright S, Normand SL, Daley J. Positive predictive value of the diagnosis of acute myocardial infarction in an administrative database. *J Gen Intern Med* 1999;**14**:555–558.
12. Sundbøll J, Adelborg K, Munch T, Frøslev T, Sørensen HT, Bøtker HE, Schmidt M. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. *BMJ Open* 2016;**6**:e012832.
13. Requirements for Publishing with HCUP Data. https://www.hcup-us.ahrq.gov/db/publishing.jsp (3 February 2020).
14. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009;**28**:3083–3107.
15. Myatt L, Webster RP. Vascular biology of preeclampsia. *J Thromb Haemost* 2009;**7**:375–384.
16. Howard DPJ, Banerjee A, Fairhead JF, Perkins J, Silver LE, Rothwell PM; Oxford Vascular Study. Population-based study of incidence and outcome of acute aortic dissection and premorbid risk factor control: 10-year results from the Oxford Vascular Study. *Circulation* 2013;**127**:2031–2037.
17. Immer FF, Bansi AG, Immer-Bansi AS, McDougall J, Zehr KJ, Schaff HV, Carrel TP. Aortic dissection in pregnancy: analysis of risk factors and outcome. *Ann Thorac Surg* 2003;**76**:309–314.
18. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SAA, Howard BV, Johnson KC, Kotchen JM, Ockene J; Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA* 2002;**288**:321–333.
19. Prentice RL, Langer R, Stefanick ML, Howard BV, Pettinger M, Anderson G, Barad D, Curb JD, Kotchen J, Kuller L, Limacher M, Wactawski-Wende J; Women's Health Initiative Investigators. Combined postmenopausal hormone

therapy and cardiovascular disease: toward resolving the discrepancy between observational studies and the Women's Health Initiative clinical trial. *Am J Epidemiol* 2005;**162**:404–414.
20. Wolinsky H. Effects of estrogen and progestogen treatment on the response of the aorta of male rats to hypertension. Morphological and chemical studies. *Circ Res* 1972;**30**:341–349.
21. Pompei LM, Steiner ML, Theodoro TR, Souza PZ, Romanini ACA, Coulson-Thomas V, Pinhal MAS, Fernandes CE. Effect of estrogen therapy on vascular perlecan and metalloproteinases 2 and 9 in castrated rats. *Climacteric* 2012;**16**: 147–153.
22. Lu T, Achari Y, Rattner JB, Hart DA. Evidence that estrogen receptor beta enhances MMP-13 promoter activity in HIG-82 cells and that this enhancement can be influenced by ligands and involves specific promoter sites. *Biochem Cell Biol* 2007;**85**:326–336.
23. Manalo-Estrella P, Barker AE. Histopathologic findings in human aortic media associated with pregnancy. *Arch Pathol* 1967;**83**:336–341.
24. Rajagopalan S, Nwazota N, Chandrasekhar S. Outcomes in pregnant women with acute aortic dissections: a review of the literature from 2003 to 2013. *Int J Obstet Anesth* 2014;**23**:348–356.
25. Practice Guidelines for Obstetric Anesthesia: an Updated Report by the American Society of Anesthesiologists Task Force on Obstetric Anesthesia and the Society for Obstetric Anesthesia and Perinatology. *Anesthesiology* 2016;**124**: 270–300.
26. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, Blomström-Lundqvist C, Cífková R, De Bonis M, Iung B, Johnson MR, Kintscher U, Kranke P, Lang IM, Morais J, Pieper PG, Presbitero P, Price S, Rosano GMC, Seeland U, Simoncini T, Swan L, Warnes CA; ESC Scientific Document Group. 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy: the Task Force for the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *Eur Heart J Oxford Academic* 2018;**39**:3165–3241.
27. Kamel H, Navi BB, Sriram N, Hovsepian DA, Devereux RB, Elkind M. Risk of a thrombotic event after the 6-week postpartum period. *N Engl J Med* 2014;**370**: 1307–1315.
28. Elkayam U. Clinical characteristics of peripartum cardiomyopathy in the United States: diagnosis, prognosis, and management. *J Am Coll Cardiol* 2011;**58**:659–670.
29. Park K-W, Park J-S, Hwang S-C, Im S-B, Shin W-H, Kim B-T. Vertebral artery dissection: natural history, clinical features and therapeutic considerations. *J Korean Neurosurg Soc* 2008;**44**:109–115.
30. Metso TM, Debette S, Grond-Ginsbach C, Engelter ST, Leys D, Brandt T, Pezzini A, Bersano A, Kloss M, Thijs V, Lyrer PA, Tatlisumak T, Metso AJ. Age-dependent differences in cervical artery dissection. *J Neurol* 2012;**259**:2202–2210.
31. Shanmugalingam R, Reza Pour N, Chuah SC, Vo TM, Beran R, Hennessy A, Makris A. Vertebral artery dissection in hypertensive disorders of pregnancy: a case series and literature review. *BMC Pregnancy Childbirth* 2016;**16**:164.
32. Arnold M, Camus-Jacqmin M, Stapf C, Ducros A, Viswanathan A, Berthet K, Bousser MG. Postpartum cervicocephalic artery dissection. *Stroke* 2008;**39**: 2377–2379.
33. Baffour FI, Kirchoff-Torres KF, Einstein FH, Karakash S, Miller TS. Bilateral internal carotid artery dissection in the postpartum period. *Obstet Gynecol* 2012;**119**: 489–492.
34. Saw J, Starovoytov A, Humphries K, Sheth T, So D, Minhas K, Brass N, Lavoie A, Bishop H, Lavi S, Pearce C, Renner S, Madan M, Welsh RC, Lutchmedial S, Vijayaraghavan R, Aymong E, Har B, Ibrahim R, Gornik HL, Ganesh S, Buller C, Matteau A, Martucci G, Ko D, Mancini G. Canadian spontaneous coronary artery dissection cohort study: in-hospital and 30-day outcomes. *Eur Heart J* 2019;**40**: 1188–1197.
35. Higgins GL, Borofsky JS, Irish CB, Cochran TS, Strout TD. Spontaneous peripartum coronary artery dissection presentation and outcome. *J Am Board Fam Med* 2013;**26**:82–89.
36. Faden MS, Bottega N, Benjamin A, Brown RN. A nationwide evaluation of spontaneous coronary artery dissection in pregnancy and the puerperium. *Heart* 2016;**102**:1974–1979.
37. Biller J, Sacco RL, Albuquerque FC, Demaerschalk BM, Fayad P, Long PH, Noorollah LD, Panagos PD, Schievink WI, Schwartz NE, Shuaib A, Thaler DE, Tirschwell DL; American Heart Association Stroke Council. Cervical arterial dissections and association with cervical manipulative therapy: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014;**45**:3155–3174.
38. Serkin Z, Le S, Sila C. Treatment of extracranial arterial dissection: the roles of antiplatelet agents, anticoagulants, and stenting. *Curr Treat Options Neurol* 2019; **21**:48.
39. Kadian-Dodov D, Gornik HL, Gu X, Froehlich J, Bacharach JM, Chi Y-W, Gray BH, Jaff MR, Kim ESH, Mace P, Sharma A, Kline-Rogers E, White C, Olin JW. Dissection and aneurysm in patients with fibromuscular dysplasia: findings from the U.S. Registry for FMD. *J Am Coll Cardiol* 2016;**68**:176–185.
40. Carroll BJ, Schermerhorn M, Kennedy KF, Swerdlow N, Soriano KM, Yeh RW, Secemsky EA. Readmissions after acute type B aortic dissection. *J Vasc Surg* 2019;Online ahead of print.
41. Lind J, Wallenburg HC. The Marfan syndrome and pregnancy: a retrospective study in a Dutch population. *Eur J Obstet Gynecol Reprod Biol* 2001;**98**:28–35.
42. Lipscomb KJ, Smith JC, Clarke B, Donnai P, Harris R. Outcome of pregnancy in women with Marfan's syndrome. *Br J Obstet Gynaecol* 1997;**104**:201–206.
43. Zhu J-M, Ma W-G, Peterss S, Wang L-F, Qiao Z-Y, Ziganshin BA, Zheng J, Liu Y-M, Elefteriades JA, Sun L-Z. Aortic dissection in pregnancy: management strategy and outcomes. *Ann Thorac Surg* 2017;**103**:1199–1206.
44. McClure RS, Brogly SB, Lajkosz K, Payne D, Hall SF, Johnson AP. Epidemiology and management of thoracic aortic dissections and thoracic aortic aneurysms in Ontario, Canada: a population-based study. *J Thorac Cardiovasc Surg* 2018;**155**: 2254–2264.e4.
45. Tanaka Y, Sakata K, Sakurai Y, Yoshimuta T, Morishita Y, Nara S, Takahashi I, Hirokami M, Yamagishi M. Prevalence of type A acute aortic dissection in patients with out-of-hospital cardiopulmonary arrest. *Am J Cardiol* 2016;**117**: 1826–1830.
46. Paratz ED, Kao C, MacIsaac AI, Somaratne J, Whitbourn R. Evolving management and improving outcomes of pregnancy-associated spontaneous coronary artery dissection (P-SCAD): a systematic review. *Int J Cardiol Heart Vasc* 2018;**18**:1–6.
47. Kelly JC, Safain MG, Roguski M, Edlow AG, Malek AM. Postpartum internal carotid and vertebral arterial dissections. *Obstet Gynecol* 2014;**123**:848–856.

Corrigendum

doi:10.1093/eurheartj/ehz825
Online publish-ahead-of-print 14 November 2019

Corrigendum to: 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes [*Eur Heart J* (2019); doi:10.1093/eurheartj/ehz425].

The following post-publication corrections have been made to these Guidelines:

In Figure 4, the arrow leading from 'invasive coronary angiography' to 'non-invasive testing for ischaemia' has been corrected to point clockwise;
and Figure 8 has been updated to clarify the second and third step rows.