Pregnancy and the Risk of Aortic Dissection or Rupture: a Cohort-Crossover Analysis:

Kamel, Pregnancy and Aortic Dissection or Rupture

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Abstract

Background—Case series have described aortic dissection and rupture in pregnancy. Few population-based data exist to support an association.

Methods—We performed a cohort-crossover study using data on all emergency department visits and acute care hospitalizations at nonfederal healthcare facilities in California, Florida, and New York. We included women 12 years of age with labor and delivery or abortive pregnancy outcome between 2005 and 2013. Our outcome was a composite of aortic dissection or rupture. Based on the timing of reported aortic complications during pregnancy, we defined the period of risk as 6 months before delivery until 3 months after delivery. We compared each patient's likelihood of aortic complications during this period to an equivalent 270-day period exactly 1 year later. Incidence rates and incidence rate ratios were computed using conditional Poisson regression with robust standard errors.

Results—Among 6,566,826 pregnancies in 4,933,697 women, we identified 36 cases of aortic dissection or rupture during the pregnancy or postpartum period and 9 cases during the control period 1 year later. The rate of aortic complications was 5.5 (95% confidence interval [CI], 4.0-7.8) per million patients during pregnancy and the postpartum period, compared with 1.4 (95% CI, 0.7-2.9) per million during the equivalent period 1 year later. Pregnancy was associated with a significantly increased risk of aortic dissection or rupture (incidence rate ratio, 4.0; 95% CI, 2.0-8.2) compared to the control period 1 year later.

Conclusions—The risk of aortic dissection or rupture is elevated during pregnancy and the postpartum period.

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Keywords

Aorta; aneurysm; pregnancy

Pregnancy significantly increases the risk of vascular events. Pregnant women face a several-fold higher risk of venous thromboembolism,[1] myocardial infarction,[2] and stroke[3] compared with nonpregnant women of childbearing age. These risks extend for several months into the postpartum period.[4]

Besides these relatively common vascular disorders, pregnancy may also increase the risk of rarer vascular events. Aortic dissection and aortic rupture are uncommon but potentially life-threatening conditions that often result in death without prompt treatment. Aortic complications are particularly common in those with connective tissue disorders and in those with a family history, but may also occur in the absence of these risk factors. A number of case reports and case series over several decades suggest that pregnancy may trigger aortic dissection or rupture.[5] Aortic complications in pregnancy have been described in Marfan syndrome,[6, 7] Loeys-Dietz syndrome,[8] the vascular type (Type 4) of Ehlers-Danlos syndrome,[9] Turner syndrome,[10] and congenital aortic malformations such as a bicuspid aortic valve.[11] However, aortic complications have also been reported in pregnant women without any other known risk factors.[12-14]

Besides these suggestive case studies, few population-based data exist to support an association between pregnancy and aortic complications. Of note, three prospective observational studies involving a total of 145 pregnancies in 78 patients with Marfan syndrome failed to find an obviously elevated risk of aortic complications during pregnancy in the absence of significant aortic enlargement.[15-17] In the absence of an appropriate control group, it remains uncertain whether pregnancy is actually associated with aortic complications or whether publication bias has resulted in more frequent reporting of complications during pregnancy.[18] To better assess the relationship between pregnancy and aortic complications, we performed a cohort-crossover analysis in a large population-based sample of patients.

Methods

Design

Using administrative claims data on all emergency department (ED) visits and acute care hospitalizations at nonfederal healthcare facilities in California, Florida, and New York from 2005 through 2013, we performed a cohort-crossover analysis in which the risk of aortic dissection or rupture for each pregnant woman was compared with her risk during the equivalent period 1 year later. Since each patient served as her own control, this design reduced the risk of residual confounding compared with traditional case-control or cohort studies.[19] We chose these three states because they are demographically heterogeneous, comprise three of the four most populated U.S. states and approximately 25% of the U.S. population, and provide deidentified administrative claims data that permit tracking of individual patients across visits over multiple years. All patients are included regardless of

insurance status. Trained analysts at each healthcare facility use automated online reporting software to provide these data in a standardized format to the respective state health department, which then performs a multistep quality assurance check to identify invalid or inconsistent records. We obtained these data in a deidentified format from the Healthcare Cost and Utilization Project.[20] Our institutional review board approved our analysis of these deidentified and publicly available data.

Patients

Following standard methods, we identified pregnant women ≥12 years of age by noting all encounters with an *International Classification of Diseases, 9th Revision, Clinical Modification* (*ICD-9-CM*) discharge code for labor or an abortive outcome.[4, 21] When multiple labor-related hospitalizations occurred during a single 40-week period, we defined delivery as the latest hospitalization during that time so as to exclude visits for false labor.[4] Since we did not have precise data on when each pregnancy began, we assumed that labor or an abortive outcome occurred at 40 weeks of gestation; this was a conservative approach because it overestimated the duration of exposure to pregnancy and therefore underestimated the risk of aortic complications during pregnancy versus nonpregnant periods. In our primary analysis, we included all recorded pregnancies for each patient; in a sensitivity analysis, we focused on the first-recorded pregnancy because women who have already completed a first pregnancy without an aortic complication may be at a lower risk of subsequent aortic complications than the general population of women of child-bearing age.[22]

Measurements

Our outcome was a composite of aortic dissection or rupture, defined by *ICD-9-CM* codes 441.0× (dissection of aorta), 441.1 (ruptured thoracic aortic aneurysm), 441.3 (ruptured abdominal aortic aneurysm), 441.5 (ruptured aortic aneurysm of unspecified site), and 441.6 (ruptured thoracoabdominal aneurysm). Only events resulting in hospitalization were included in our outcome. To focus on incident outcomes, we excluded any diagnoses of aortic dissection or rupture recorded after an index diagnosis. In our primary analyses, we used both principal and secondary diagnosis codes to define outcomes, but in sensitivity analyses, we limited our outcomes to only principal diagnoses of an aortic complication or only aortic complications accompanied by a concomitant procedure code for surgical (*ICD-9-CM* procedure codes 38.44 or 38.45) or endovascular (39.71 or 39.73) aortic repair.

To perform analyses stratified by the baseline risk of aortic complications, we noted comorbidities that were definable by *ICD-9-CM* codes and have been reported in association with aortic complications during pregnancy: Marfan syndrome (*ICD-9-CM* code 759.82),[6] Ehlers-Danlos syndrome (756.83),[7] Turner syndrome (758.6),[10] and hypertension (401-405) or pre-eclampsia or eclampsia (642).[13]

Statistical Analyses

Based on the temporal pattern of reported cases of aortic complications during pregnancy, we defined the period of risk to extend from 6 months prior to delivery or abortive outcome through the postpartum period.[23, 24] Following the approach of prior studies, we defined the

postpartum period as the 12 weeks after delivery (rather than the traditional 6 weeks) to ensure comprehensive capture of any events that could be related to a preceding pregnancy.[1, 4] We then compared each patient's likelihood of aortic dissection during this period to the equivalent 270-day period exactly 1 year later. We performed exploratory analyses limited to outcomes in the antepartum or the postpartum period; in cases where both dissection and labor or abortive outcome were documented during the same hospitalization, we used previously validated present-on-admission codes to determine the relative timing of events.[25] We performed subgroup analyses stratified by the presence or absence of a documented connective tissue disorder, the presence or absence of documented hypertension, and cesarean versus vaginal delivery. In a sensitivity analysis, we limited our sample to patients with at least one ED visit or hospitalization after the end of their crossover period, thus ensuring that they were alive and resident within the state throughout follow-up. Since women who have an aortic complication before a pregnancy may be less likely to become pregnant in the future, falsely reducing the control-time risk estimates in a cohort of only women who were pregnant, we also performed a sensitivity analysis using a case-crossover design in which the odds of pregnancy prior to an aortic complication were compared to the odds of pregnancy in the corresponding 270-day period 1 year earlier. Incidence rates and incidence rate ratios (IRR) were calculated using conditional Poisson regression for matched data and robust standard errors to account for clustering among patients with multiple pregnancies. In a confirmatory analysis, we combined data on hospitalizations with demographic data from the U.S. Census Bureau[26] to compare age-standardized rates of aortic complications in pregnant patients versus nonpregnant controls. All analyses were performed using Stata/MP version 13 (College Station, TX).

Results

Among 6,566,826 pregnancies in 4,933,697 women (Table 1), we identified 36 cases of aortic dissection or rupture during the pregnancy or postpartum period and 9 cases during the control period 1 year later. The incidence of dissection or rupture was 5.5 (95% confidence interval [CI], 4.0-7.8) per million patients during pregnancy and the postpartum period, compared with 1.4 (95% CI, 0.7-2.9) per million during the equivalent period 1 year later (IRR, 4.0; 95% CI, 2.0-8.2). The rate of 5.5 aortic complications per million pregnancies was also significantly higher than the rate of 1.7 (95% CI, 1.5-1.9) aortic complications per million during an equivalent 270-day period among nonpregnant controls (IRR, 3.2; 95% CI, 2.4-4.3).

All 36 pregnancy-related complications occurred during the first- or second-recorded pregnancy. The incidence during a first-recorded pregnancy (5.1 [95% CI, 3.5-7.7] per million) did not differ appreciably from the rate during a second-recorded pregnancy (8.2 [95% CI, 4.6-15.9] per million). There was no obvious difference in risk when considering events only in the antepartum period (IRR, 4.0; 95% CI, 1.6-10.2) or considering events only in the 3-month postpartum period (IRR, 3.5; 95% CI, 1.2-10.6) as compared to the equivalent nonpregnant period 1 year later.

The absolute increase in the risk of aortic dissection or rupture was much higher in patients with a documented connective tissue disorder (4,960.6 [95% CI, 1,870.1-17,746.3] per

million) compared to the remaining patients (4.9 [95% CI, 3.5-7.0] per million) (P<0.001 for interaction). However, even in patients without documented connective tissue disease, the risk was higher during pregnancy than outside of pregnancy (IRR, 3.6; 95% CI, 1.7-7.3). Although the relative increase in the risk of aortic complications during pregnancy was similar for patients with and without pre-existing hypertension (P= 0.54 for interaction), both the baseline risk and the absolute risk increase associated with pregnancy appeared higher in those with hypertension: 106.2 (95% CI, 44.9-317.1) per million during pregnancy versus 42.6 (95% CI, 9.2-428.3) during the crossover period. Both the estimates for connective tissue disease and hypertension were based on small numbers of patients (Table 1). We found no interaction between pregnancy and the mode of delivery in relation to the risk of aortic complications (P= 0.76 for interaction), nor an interaction between pregnancy and the presence or absence of pre-eclampsia/eclampsia (P= 0.45).

Our findings were similar in sensitivity analyses limited to each patient's first-recorded pregnancy (IRR, 3.1; 95% CI, 1.4-6.9), limited to patients with at least one visit after the end of their crossover period (IRR, 3.4; 95% CI, 1.5-8.0), limited to outcomes defined by principal diagnosis codes (IRR, 2.9; 95% CI, 1.4-5.8), or limited to outcomes accompanied by a procedure code for aortic repair (IRR, 2.8; 95% CI, 1.1-7.2).

In a case-crossover design assessing the likelihood of labor during time intervals prior to an aortic complication, we identified 14,999 cases of aortic dissection or rupture. Of these cases, 62.4% were admitted to the intensive care unit, 30.6% had a documented surgical or endovascular treatment, and 28.1% died. In a case-crossover analysis limited to women who were pregnant either around the time of their aortic complication or during the same period 1 year prior to their aortic complication, the association between pregnancy and aortic dissection or rupture (IRR, 3.5; 95% CI, 2.0-5.9) was similar to the association in our primary analysis above.

Discussion

In a cohort-crossover analysis of a large, population-based sample of patients, we found a strong association between pregnancy and the risk of aortic dissection or rupture. Relative risks were increased to a similar extent in both the antepartum and postpartum periods as compared with the control period 1 year later. We found that pregnancy was associated with an increased risk of aortic complications among both women with and without documented connective tissue diseases such as Marfan syndrome, although the risk was significantly greater in those with connective tissue diseases. Absolute risks were also higher in those with hypertension, a potentially modifiable risk factor that may be amenable to more intensive risk factor management during pregnancy among high-risk women.

Our finding that pregnancy can trigger aortic complications has important implications for pre-pregnancy counseling and peripartum care. Women without documentation of established risk factors for aortic complications (such as pre-existing Marfan syndrome) appear to have an increased relative risk, but the absolute risk remains low. A scarcity of data exists to guide women with conditions such as Marfan syndrome regarding their risks of serious aortic complications if they become pregnant.[22] The available studies have reported

conflicting findings about whether pregnancy results in an increase in aortic root diameter.[15-17, 27] Furthermore, prior studies appear to have lacked sufficient statistical power to evaluate the association between pregnancy and the clinical outcome of aortic dissection or rupture.[16] In this context, our findings provide firm support for the current practice of counseling patients at high baseline risk of aortic complications (such as those with certain connective tissues diseases) that pregnancy is likely to increase the risk of aortic complications,[28, 29] and may provide a more precise estimate of the magnitude of the increase in relative risk. Furthermore, our findings indirectly support current guideline recommendations for intensification of monitoring of the aortic root during pregnancy in patients with connective tissue disorders.[28, 29] Lastly, our findings suggest that clinicians should have a lower threshold for initiating diagnostic testing for symptoms of a possible aortic dissection or rupture in pregnant or postpartum patients—especially those with connective tissue disorders or hypertension—than in nonpregnant women of similar age.

Our findings may reflect prevalent but undiagnosed or undocumented connective tissue disorders, or they may indicate that the physiological changes of pregnancy can cause aortic injury even in otherwise healthy women. The mechanisms by which pregnancy may trigger aortic complications are uncertain. Pregnancy and the postpartum state cause hemodynamic changes—such as increases in heart rate, stroke volume, cardiac output, and left ventricular dimensions[11]—that may affect the forces on the aortic wall. This may be exacerbated by increased outflow resistance in the distal aorta due to compression by the gravid uterus.[30] Pregnancy also causes hormonal and biochemical changes that may modify the ability of the aorta to withstand the hemodynamic effects placed on it. The importance of dysregulated signaling (e.g., by TGF-beta) in the genesis of a number of conditions associated with aortic aneurysms[8] suggests one pathway by which the hormonal and biochemical effects of pregnancy may mediate the risk of aortic complications. Estrogen receptors are present in aortic tissue and may mediate the effect of pregnancy-induced hormonal changes on the weakening of elastic fibers.[31] These pathways may result in the type of medial degeneration often seen in patients with aortic disease,[31, 32] although in one series only two of six pregnant women with aortic dissection had clear evidence of medial degeneration on histologic examination of surgical specimens.[33]

The findings of this study must be interpreted in the context of several limitations. First, the lack of detailed clinical data precluded an assessment of the risk of aortic complications in relation to patients' aortic root diameter prior to pregnancy. Therefore, we cannot comment on whether pregnancy increases the risk of aortic complications in women with an aortic root diameter <40 mm or <45 mm, which are the thresholds currently recommended for deciding on the safety of pregnancy in women with Marfan syndrome or other connective tissue disorders.[28, 29, 34] Second, we defined our outcomes using *ICD-9-CM* codes with unknown sensitivity and specificity. If these codes have randomly low sensitivity or specificity, the resulting nondifferential misclassification of outcomes would have falsely attenuated the relationship between pregnancy and aortic dissection. On the other hand, if providers document aortic complications more reliably in young pregnant women than in young nonpregnant women, or systematically miscode other pregnancy-related complications using these codes, then the resulting differential misclassification would have upwardly biased the apparent association between pregnancy and aortic complications. We

think such differential misclassification is unlikely because we found a similarly elevated risk during the 3-month postpartum period as during pregnancy itself. Furthermore, diagnosis codes for major illnesses have been validated to have good sensitivity and specificity in these administrative claims data.[35] Also, the outcomes of patients with diagnoses of aortic complications in our study are consistent with modern series based on detailed clinical data,[36] further supporting the validity of the diagnosis codes used in our study, and our findings were similar in an analysis limited to patients with a documented aortic repair procedure. Third, our subgroup analyses should be interpreted with caution, because it is possible that only more severe cases of hypertension or connective tissue disease were documented, thereby inflating the apparent risks of aortic complications in these groups. Fourth, we did not have precise data about the timing of gestation. We addressed this by taking a conservative approach that likely overestimated the duration of pregnancy. Similarly, aortic complications resulting in death early in pregnancy may have been missed. These limitations would be expected to attenuate our estimates of risk during pregnancy, suggesting that the true risk of aortic complications during pregnancy may be somewhat higher than what we found.

Conclusion

We found that the absolute increase in the risk of aortic dissection or rupture attributable to pregnancy was approximately 4 per million pregnancies. This may be helpful when counseling patients about the risks of pregnancy, when formulating multidisciplinary plans of care for high-risk patients, and when evaluating symptoms concerning for aortic dissection or rupture in pregnant or postpartum patients.

Acknowledgments

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Clinical Perspective

What Is New?

- Case series suggest that pregnancy may trigger aortic dissection or rupture, but few population-based data exist to support an association between pregnancy and aortic complications.

- Using administrative data from a large population, we compared the risk of aortic complications during pregnancy and the postpartum period with a control period 1 year later.

- The incidence of aortic complications was 5.5 per million patients during pregnancy and the postpartum period versus 1.4 per million during the control period (incidence rate ratio, 4.0; 95% CI, 2.0-8.2).

- The availability of a control period in this study supports an association between pregnancy and aortic complications.

What Are the Clinical Implications?

- These findings can be used to counsel patients at high baseline risk of aortic complications about the risks of pregnancy. In our study, absolute risks were particularly elevated in those with a documented diagnosis of hypertension or a connective tissue disease.

- Furthermore, our findings suggest that clinicians should have a lower threshold for initiating diagnostic testing for symptoms of a possible aortic dissection or rupture in pregnant or postpartum patients— especially those with connective tissue disorders or hypertension—than in nonpregnant women of similar age.

Table 1

Baseline Characteristics of Patients At Time of First Pregnancy, Stratified by the Occurrence of Aortic Complications During Pregnancy

Characteristic[*]	Aortic Complication (N = 36)	No Aortic Complication (N = 4,933,661)	P Value
Age, mean (SD), y	29.2 (7.0)	27.3 (6.8)	0.11
Age <35 years	27 (75.0)	4,027,057 (81.6)	0.31
White race[†]	11 (30.6)	2,121,171 (43.0)	0.13
Private insurance	15 (41.7)	2,732,249 (55.4)	0.10
Vascular risk factors			
Absence of pre-existing hypertension	31 (86.1)	4,895,363 (99.2)	<0.001
Absence of pre-eclampsia	21 (58.3)	4,505,942 (91.3)	<0.001
Absence of eclampsia	36 (100.0)	4,929,694 (99.9)	0.87
Absence of connective tissue disorder[§]	32 (88.9)	4,933,033 (99.9)	<0.001

Abbreviations: SD, standard deviation.

[*] Data are presented as number (%) of participants unless otherwise specified. Comparisons were made using the chi-square test or t-test.

[†] Self-reported by patients or their surrogates.

[§] Marfan, Turner, or Ehler-Danlos Syndromes.