Aortic Dissection During Pregnancy and Postpartum: A Systematic Review

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Abstract

Patients with aortic dissection during pregnancy and postpartum period exhibit high mortality. At present, a complete overview of aortic dissection during pregnancy and postpartum period is lacking. This systematic review includes 80 reports published from 2000-2020, comprising a total study population of 103 patients with aortic dissection. It was suggested that Stanford Type A aortic dissection is more likely to occur in the third trimester, while Stanford Type B is more likely to occur within 12 weeks postpartum. The most common risk factor was connective tissue disease, with no other known risk factors. Mode of delivery has no significant effect on the type of postpartum aortic dissection. Reduced maternal and fetal mortality was observed when patients with Stanford Type A aortic dissection occurring after 28 gestational weeks underwent aortic replacement after cesarean section. Patients with Stanford Type B aortic dissection were treated mainly with medication and/or endovascular repair. Contemporary management of patients during pregnancy and within 12 weeks postpartum requires multidisciplinary cooperation and includes serial, non-invasive imaging, biomarker testing, and genetic risk profiling for aortopathy. Early diagnosis and accurate treatment are essential to reduce maternal and fetal mortality.

Introduction

Aortic dissection is a rare but potentially lethal condition caused by a tear in the intimal layer of the aortic wall. The Standard classification is used to classify aortic dissections into two subtypes: Stanford Type A dissections involve the ascending aorta, and Stanford Type B dissections involve the descending but not the ascending aorta[1]. Most aortic dissections occur in patients between 65–75 years of age, with an incidence of 3-5 cases per 100,000 people per year[2]. Previous studies have shown that developing aortic dissection during pregnancy is even rarer, mostly occurring from 6 months prior to delivery and 12 weeks postpartum[3]. Aortic complications are particularly common in patients with hypertension, genetic disorders that involve the connective tissue, such as Marfan syndrome, and a history of familial thoracic aneurysm/dissection. However, this condition may also occur in the absence of these risk factors.

As a result of increased cardiovascular stress during pregnancy, pathologic changes occur in the arterial wall and the risk of aortic dissection or rupture increases with gestational age. In pregnant patients with connective tissue disorders or familial history of aneurysms/dissections, pre-existing medial degeneration of the aorta, such as a weakened aortic wall and intrinsic abnormalities of aortic media, is an important risk factor of aortic dissection. Therefore, the condition of the patient's aorta should be carefully evaluated before pregnancy and guiding her to pregnant at an appropriate time. It is important to have reliable information about aortic dissection occurring during pregnancy and early postpartum because this may lead to better insight into its pathophysiology and management. In addition, dedicated care could be better planned

and provided. But the emergency nature of this problem does not lend itself easily to study by randomized controlled trials. Although many case reports have been reported, a complete overview is still missing. The aim of this review is to provide a comprehensive overview of aortic dissection during pregnancy and early postpartum pooled from the literature since the year 2000, concentrating on risk factors, management, and outcomes.

Methods

Search Strategy.

We conducted a PubMed literature search on April 20, 2020, using the following search terms: “pregnancy” and “postpartum” and “aortic dissection”. The search was limited to original research papers and case reports with English abstracts. All titles and abstracts were screened for study population (prepartum, postpartum), type of aortic dissection, and occurrence time. Studies were eligible if they reported aortic dissection from 6 months prior to delivery to 12 weeks postpartum. According to Christoph et al.[4], aortic dissection was characterized by rapid development of an intimal flap, which is caused by blood flowing into the media and forcing the intima and the adventitia apart. Papers focused on traumatic aortic dissection or research in animal models were excluded. After exclusion on the basis of the title and abstract, full papers were carefully read and reconsidered by three authors independently using the above-mentioned inclusion and exclusion criteria. In the case of disagreement, an agreement between authors was negotiated. References of the selected papers were cross checked with the

same inclusion and exclusion criteria.

The study protocol was approved by the local ethics committee; written informed consent was obtained from all patients prior to their enrolment.

Data Extraction.

Selected papers were reviewed and the study characteristics were tabulated in Microsoft Excel for Windows. We focused on the following variables: age; diagnosis (Type A dissection; Type B dissection); time of occurrence; risk factors (hypertension, connective tissue disorders, congenital aortic malformation, familial thoracic aneurysm or dissection, and absence of risk factors); diameter of aortic root; aortic regurgitation; mode of delivery (spontaneous vaginal or cesarean section); management; maternal outcome, and fetal outcome.

Statistical Analysis.

The normally distributed study variables are presented as mean ± standard deviation, and non-normally distributed data as median and first and third quartiles. Categorical variables are presented as percentages. One-way analysis of variance (ANOVA) and Student's t-test with post hoc Bonferroni correction were used to compare continuous variables with a normal distribution among the four groups and between two groups, respectively. Comparisons of frequencies of events were performed using Fisher's exact test. Statistical analyses were performed using SPPS version 16.0. Differences among

variables were considered significant at $p < 0.05$.

Results

Search Results.

The systematic literature search yielded 465 potential eligible studies. After exclusion, cross-referencing, and reaching agreement on 3 studies, 80 studies were included in this systematic literature review[5-84] (Figure 1). This resulted in a total study of 103 patients with aortic dissection during 6 months prior to delivery to 12 weeks postpartum.

Patient Characteristics.

Patient characteristics are summarized in Table 1. There was no significant difference in age between patients with Type A and Type B dissections($p>0.05$). Chest pain was the most common first symptom (44/103,42.7%). There was a significant difference at the time of occurrence time of dissection between Type A and Type B dissections. Type A was more likely to occur 6 months before delivery, while Type B was more likely to occur within 12 weeks postpartum ($p=0.007$). The average diameter of the aortic root was larger in patients with Type A than Type B at the time of dissection （Type A: 52.9±13.0 cm [N=30]; Type B: 38.1±7.6cm [N=9]; $p<0.0001$). The distribution of aortic regurgitation was not significantly different between the dilated aortic root group and the normal group（$p=0.056$). Aortic dissection is more common in pregnant patients with connective tissue disease and with no other known risk factors. These two risk factors were present in similar percentages of patients with aortic dissection (35.9% and 26.2%, respectively), with a significantly difference when compared with other risk

factors such as pre-eclampsia, congenital aortic malformation and familial history of aneurysm or dissections ($p<0.05$). Mode of delivery (i.e. cesarean section or vaginal delivery) has no significant difference on the type of aortic dissection within 12 weeks postpartum ($p=0.274$).

Management and Outcome.

Management and outcome of patients with Type A aortic dissection are summarized in Table 2. Fifteen patients under 28 weeks of gestation, the mortality of the fetus who continued to be pregnant after aortic replacement was lower ($P= 0.002$). Forty-five pregnant women with gestation ≥28 weeks, both maternal and fetal mortality who underwent aortic replacement surgery followed cesarean section was reduced ($P<0.001$); Seventeen cases of postpartum patients that occurred within 12 weeks after delivery all had a good prognosis.

Management and outcome of patients with Type B aortic dissection are summarized in Table 3. Among 13 pregnant women, one of the fetus died in utero cause of demise. Fourteen patients occurred aortic dissection within 12 weeks postpartum, one patient died of infection six months after implantation of the stent because of delayed diagnosis and combined with superior duodenal artery dissection; one patient died attribute to ineffective drug treatment and one patient died immediately before receiving any treatment.

Discussion

The principal findings of this review are as follows: 1) in pregnant women with aortic dissection, chest pain is the most common first symptom. However, some patients may take a long time to confirm the diagnosis due to the diverse presentation and atypical nature of first symptoms, thereby missing the best treatment opportunity and resulting in a poor prognosis; 2) Type A aortic dissection is more likely to occur in the third trimester of pregnancy, and Type B aortic dissection is more likely to occur within 12 weeks after delivery. In addition, the aortic root is often dilated in patients with Type A aortic dissection, which does not appear to be related to whether the aortic regurgitation is complicated; 3) the most common risk factor for pregnant women with aortic dissection is connective tissue disease, with no other known risk factors for aortic dissection during pregnancy and postpartum, and; 4) Pregnant women with Type A aortic dissection occurring before 28 gestational weeks have lower fetal mortality who continued to be pregnant after aortic replacement, and pregnant women with Type A aortic dissection occurring after 28 gestational weeks have lower mortality rates for maters and fetuses undergoing aortic replacement followed cesarean section. Type B aortic dissection is mainly treated with medication and/or endovascular repair. Early, rapid, and accurate diagnosis is an important factor for helping improve the prognosis of mothers and their fetuses.

In this review, Type B aortic dissection occured less frequently than Type A aortic dissection. Similar results have been previously described by Rutherford et al[85]. One reason for this might be related to the easily overlooked systolic jet from the left ventricular or distal dissection. On the other hand, compared with Type A aortic

dissections, Type B aortic dissection might be underestimated in the literature because of its atypical symptoms and not requiring immediately surgery. At present, the reason for the increased incidence of aortic dissection during pregnancy is unclear. Previous studies have suggested that it is may be due to the increase in heart rate, stroke volume, cardiac output, and left ventricular wall mass and end-diastolic dimension[86,87] during pregnancy and postpartum, which might trigger the development of an intimal tear. In addition, estrogen and progesterone induce histological structural changes of the aortic walls early in pregnancy that remodels the tunica media and intima. These all result in an increased risk of dissection due to fragmentation of the reticulum fibers, diminished amount of acid mucopolysaccharides, and loss of the corrugation of elastic fibers in the vessel[88,89]. As these modifications occur in every pregnancy, it may be assumed that those afflicted by aortic dissection have some additional etiologic factors, such as Marfan syndrome and hypertension, which have been shown to predispose the aorta to become fragile[90]. Patients with Marfan syndrome have a mutation in the FBN1[91] or FBN2 gene ('Marfan-like' syndrome)[92] that encode fibrillin-1 and fibrillin-2, respectively, which are components of elastin-associated microfibrils that are located mainly in the medial layer of the aorta, resulting in a secondary phenotypical change in the vascular smooth muscles, release of matrix-degrading enzymes, and inflammation[91]. In patients with hypertension, an increase in pro-inflammatory cytokines and matrix metalloproteinases (MMPs) may lead to excessive degradation of the extracellular matrix and an increased risk of aortic dissection[93].

Up to half of all aortic dissections and ruptures in women younger than 40 years of age

are associated with pregnancy[94]. Aortic dissection is associated with a high risk of mortality and, if prepartum, fetal demise. About 21% of patients died before reaching the hospital, as high as 50% within 24 hours of hospital admission, and the mortality rate increases by about 1% per hour for the first 48 hours [95]. In this review, 5 patients with Type A aortic dissection died, all of which were related to the delay in diagnosis and treatment. One case was diagnosed 24 hours after the onset of symptoms and died after surgery. Two cases were confirmed by autopsy after 24 hours of the onset of symptoms. The other 2 cases refused surgery, and died due to ineffective medical therapy. Therefore, prompt diagnosis and treatment are essential. However, the clinical symptoms of aortic dissection are often non-specific and occur in pregnant women with an absence of known risk factors, which are also easily confused with other diseases, such as acute myocardial infarction and pulmonary embolism. Therefore, aortic dissection should be suspected in patients presenting with acute chest pain, back pain, or abdominal pain that is abrupt in onset, and described as severe, ripping, tearing, stabbing, or sharp pain. Risks were particularly elevated in pregnancies with a documented diagnosis of hypertension or a connective tissue disease. Compared with nonpregnant women of similar age, clinicians should reduce the standard for initiating diagnostic testing for symptoms of a possible aortic dissection or rupture in pregnant or postpartum patients with risk facors.

The key factor in aortic dissection management is the early detection and identification of individuals who are at risk of death or progression of disease. Until now, it has been shown that lacking of vascular smooth muscle and inflammation is not a central feature

of Type B aortic dissections, suggesting the pathological processes in Type A and Type B are distinct, affecting the ascending and descending aorta, respectively[4]. However, there are no studies focused on the differences in the cellular and molecular mechanisms between the two subgroups. Improved understanding of the underlying mechanisms that cause aortic dissection during pregnancy and early postpartum may help identify new targets for treatment and remove the limitation of antihypertensive agents therapy. Indeed, in the near future, understanding the underlying processes of extracellular matrix degradation and cellular inflammation is expected to lead to more targeted therapies. Monitoring for key pathophysiological regulators, such as the TGFβ pathway[96], in combination with metabolic technologies will help identify effective clinically biomarkers for the rapid diagnosis of aortic dissection at the bedside[97-99]. The use of biomarkers might also promote the development of individualized endovascular treatment strategies and initiate the first steps in precision therapy for patients with aortic dissection[90,100].

Several limitations of this study should be noted when interpreting the findings. First, the main defect of this study is the missing data of some patients, which may lead to less statistically significant differences between subgroups. Adequate data collection will be helpful for more accurate statistical analysis in the future. Second, the lack of detailed clinical data hindered an assessment of the risk of aortic complications in relation to patients' aortic root diameter prior to pregnancy. Therefore, we cannot analyze whether pregnancy increases the risk of aortic dissection in women with physiologically normal aortic root diameter. Third, subgroup analyses should be

divided with caution, as previous studies tend to report more severe cases of Type A dissections, leading to an overestimation of the apparent risks of Type A aortic dissection with others groups. Lastly, we need large community-based disease and control groups to assess whether the features present in patients with aortic dissection are truly risk factors. Unfortunately, no such population studies exist.

Conclusion

The most common underlying cause for the development of aortic dissection in pregnant woman was connective tissue disease, such as Marfan syndrome, followed by pregnancy itself in previously healthy pregnant woman without known risk factors. Preconception evaluation and consultation with specialists in maternal-fetal medicine, cardiology, and genetics are essential. Proper timing of pregnancy helps to reduce complications in pregnancy, further decreasing maternal and fetal morbidity and mortality. The aorta should be assessed during pregnancy and early postpartum period. Once an abnormality is found, a team approach of obstetricians, cardiac surgeons, cardiologists, and vascular interventionists will result in the best patient outcome.

Statements

Data: Availability

Conflict of Interest: None

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