Aortic Disease and Dissection in Pregnancy: Caring for Women with Connective Tissue Disorders

Melissa L. Russo, M.D.
Assistant Professor of Medicine
Maternal Fetal Medicine and Human & Molecular Genetics
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OBJECTIVES
Aortic Disease and Dissection in Pregnancy: Caring for Women with Connective Tissue Disorders

1) Define a connective tissue disorder and medical implications and diagnosis of Marfan and Loeys-Dietz syndrome.

2) Review the risks and warning signs for aortic aneurysm and dissection in pregnancy.

3) Discuss current management guidelines in pregnancy for Marfan and Loeys-Dietz syndrome.
What is your role as a nurse?
OVERVIEW
Aortic Disease and Dissection in Pregnancy: Caring for Women with Connective Tissue Disorders

- Background: Connective tissue disorders and implications in pregnancy
- Risk factors for Aortic Dissection
- Clinical signs and management for Aortic Dissection
- Nursing implications & interventions
Definition of Connective Tissues Disorder

A **connective tissue disorder** involves ligaments, bones, blood vessels.

- Connective tissues - extensive extracellular matrix framework - collagen & elastin
- Connective tissue = Heart, blood vessels, eyes, skeleton
Definition of Aortopathy

The aorta is the main artery that carries blood to entire body.

- Aorta has different parts- embryologically made from different cells
- Aneurysm- pathologic dilation of the three vessel wall layers resulting in 50% increase in diameter
- Dissection- Tear in intima layer and creates false lumen and bleeds into false lumen

Aortopathy is disease with aortic pathology
Aortic Dissections

- There are two types of aortic dissection
- Stanford Type A (involve ascending aorta and root) & B (beyond the great vessels)
- Type A Dissections- High Mortality Rate & Type B Dissections- Lower Mortality Rate
Aortic Dissections

Signs of Aortic Dissection:
Chest Pain, Back Pain - between scapula
  • Abrupt in onset, most severe at onset
  • Ripping or tearing sensation
  • Progression to abdominal pain and flank pain
Dyspnea
Syncope
Weakness on One Side of Body
Aortic Dissections

Clinical and Exam Findings:
Decreased pulsations in radial, femoral, carotid pulses
Systolic BP differential >20 mmHg in limbs
Focal neurological deficits
Hypertension or Hypotension

Table 4 – Symptoms and physical findings in aortic dissection.

- Pulse deficit
- Systolic blood pressure limb differential > 20 mmHg
- Focal neurological deficits
- Aortic regurgitation
- Pericardial tamponade
- EKG—ST-segment elevation
- Syncope

Smok DA. Semin Perinatology. 2014
Aortic Dissections

Diagnosis:
Echocardiogram
CT angiogram
MR angiogram
Who is at Risk for Aortic Dissection:

Specific Genetic Syndromes:
- Marfan syndrome
- Loeys-Dietz syndrome
- Vascular Ehlers-Danlos syndrome
- Bicuspid Aortic Valve
- Familial Thoracic Aortic Aneurysm and Dissection (FTAAD)
- Turner syndrome
Who is at Risk for Aortic Dissection?

Specific Genetic Syndromes:
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Marfan Syndrome

- Mutations in Fibrillin-1 Gene \((FBN1)\)
- Autosomal Dominant Disorder
- Characterized by: Cardiovascular, Musculoskeletal, Ocular Features
Marfan Syndrome

- Revised Ghent Criteria for Diagnosis (Systemic Score of $\geq 7$)
**Marfan Syndrome: Revised Ghent Criteria**

**In the absence of family history:**

1. Aortic root diameter (Z-score ≥2) and ectopia lentis = MFS
2. Aortic root diameter (Z-score ≥2) and causal \( FBN1 \) mutation = MFS
3. Aortic root diameter (Z-score ≥2) and systemic score ≥7 points = MFS
4. Ectopia lentis and causal \( FBN1 \) mutation with known aortic root dilatation = MFS

**In the presence of family history:**

5. Ectopia lentis and family history of MFS (as defined above) = MFS
6. Systemic score ≥7 points and family history of MFS (as defined above) = MFS
7. Aortic root diameter (Z-score ≥2 above 20 years old, ≥3 below 20 years) and family history of MFS (as defined above) = MFS

*Caveat: without discriminating features of Shprintzen–Goldberg syndrome, Loeys–Dietz syndrome or vascular form of Ehlers–Danlos syndrome AND after \( TGFBRII/II \), collagen biochemistry, \( COL3A1 \) testing if indicated.

**Scoring of systemic features of MFS**

1. Wrist and thumb sign = 3 points (wrist or thumb sign – 1 point)
2. Pectus carinatum deformity = 2 points (pectus excavatum or chest asymmetry – point)
3. Hindfoot deformity = 2 points (plain pes planus – 1 point)
4. Protrusio acetabuli = 2 points
5. Reduced upper segment/lower body segment ratio and increased arm/height and no severe scoliosis = 1 point
6. Scoliosis or thoracolumbar kyphosis = 1 point
7. Reduced elbow extension = 1 point
8. Facial features (3/5) = 1 point (dolichocephaly, enophthalmos, downsloping palpebral fissures, malar hypoplasia, retrognathia)
9. Pneumothorax = 2 points
10. Skin striae = 1 point
11. Myopia >3 diopters = 1 point
12. Mitral valve prolapse (all types) = 1 point
13. Dural ectasia = 2 points
Loeys Dietz Syndrome

- Mutations in TGFBR1/2, TGFB2, SMAD3 - Autosomal Dominant

- Characterized by: Cardiovascular, Craniofacial, Cutaneous, Skeletal Features

- Widespread arterial involvement, vascular tortuosity, high risk of aneurysm and dissection of aorta and throughout arterial tree
Loeys Dietz Syndrome

- Characterized by: Cardiovascular, Craniofacial, Cutaneous, Skeletal
  - Aortic Aneurysm
  - Arterial Tortuosity
  - Pes Planus
  - Translucent, Soft Skin
  - Hypertelorism
  - Bifid Uvula
  - Arachnodactyly
  - Pectus Deformity
Loeys Dietz Syndrome

Increased Vertebral Artery Tortuosity Index Is Associated With Adverse Outcomes in Children and Young Adults With Connective Tissue Disorders

Shaine A. Morris, MD; Darren B. Orbach, MD, PhD; Tal Geva, MD; Michael N. Singh, MD; Kimberlee Gauvreau, ScD; Ronald V. Lacro, MD
The Effect of Pregnancy on Connective Tissue Disorders
The Effects of Pregnancy on the Cardiovascular System

Hemodynamic Changes
• Blood volume increases 30-40%
• Increased Cardiac Output
• Increased Heart Rate

These effects peak in the 3rd trimester.
The Effects of Pregnancy on the Cardiovascular System

Hormonal Changes
- Estrogen & Progesterone Increase through a pregnancy
- Histological changes in layers of large arteries:
  - Loss of reticulin
  - Decreased muccopolysaccharides
  - Loss of normal corrugation fibers
  - Hypertrophy of smooth muscle

Does Pregnancy Increase the Risk of Aortic Dissection and Rupture?

• Population-based Study-New York, California and Florida
• Cohort-crossover analysis- 6.5 million pregnancies in 4.9 million women
• 36 Cases aortic dissection in pregnancy
• Rate of aortic complications 5.5 per million (1.4 per million control)
• **Pregnancy associated with significantly increased risk of aortic dissection/rupture especially in women with CTD and HTN**
  • Absolute risk increase 4960 per million vs 4.9 million in controls
  • Absolute risk increase 106 per million in HTN

Kamel, Roman, Pticher, Devereux Circulation 2016
Pregnancy affects Long-Term Prognosis in Women with Connective Tissue Disorders

• Comparison Women with pregnancies vs. no pregnancies
  • Increase in long-term adverse outcomes- greatest in those with multiple pregnancies
    • Elective Surgery (13 vs 6.5 %)
    • Adverse CV outcomes (23 vs 0 %)-death, aortic dissection, severe AI, urgent surgery
  • Larger increase in aortic diameter during pregnancy-> increased risk long-term adverse outcomes

Table 2
Risk factors for long-term outcome after pregnancy in women with Marfan syndrome. Modified from Donnelly et al.21

<table>
<thead>
<tr>
<th>Associated factors with long-term adverse outcome:</th>
<th>Odds ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic size</td>
<td>1.3 (1.11-1.61)</td>
</tr>
<tr>
<td>Number of pregnancies</td>
<td>1.5 (1.15-1.97)</td>
</tr>
<tr>
<td>Prospective care</td>
<td>0.1 (0.05-0.39)</td>
</tr>
<tr>
<td>Medication</td>
<td>0.3 (0.14-0.92)</td>
</tr>
<tr>
<td>Aorta &gt; 4 cm</td>
<td>3.8 (1.11-13.3)</td>
</tr>
<tr>
<td>Independent correlates</td>
<td></td>
</tr>
<tr>
<td>Initial aortic size</td>
<td>1.8 (1.07-3.07)</td>
</tr>
<tr>
<td>Rate of aortic change (log)</td>
<td>7.4 (1.32-41.22)</td>
</tr>
</tbody>
</table>

Donnelly et al. JACC 2012
# Aortic Dissection Risk during Pregnancy: Marfan Syndrome

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th># Patients/# Pregnancies</th>
<th>Aortic Dissection Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyeritz et al. 1981</td>
<td>26 Women / 80</td>
<td>No Dissections</td>
</tr>
<tr>
<td>Rossiter et al. 1995</td>
<td>21 Women / 45</td>
<td>4.4 %</td>
</tr>
<tr>
<td>Lipscomb et al. 1997</td>
<td>36 Women / 75</td>
<td>4.3 %</td>
</tr>
<tr>
<td>Lind et al. 2001</td>
<td>45 Women / 95</td>
<td>4.5 %</td>
</tr>
<tr>
<td>Meijboom et al. 2006</td>
<td>63 Women / 111</td>
<td>0.9 %</td>
</tr>
<tr>
<td>Pacini et al. 2009</td>
<td>85 Women / 160</td>
<td>4.4 %</td>
</tr>
<tr>
<td>Goland et al. 2009</td>
<td>350 pregnancies*</td>
<td>3 %</td>
</tr>
<tr>
<td>Curry et al. 2014</td>
<td>21 Women / 29</td>
<td>10 %</td>
</tr>
<tr>
<td>Hassan et al. 2015</td>
<td>339 Deliveries/ ICD9 codes</td>
<td>1.8 %</td>
</tr>
</tbody>
</table>
Pregnant Women with MFS & LDS have an elevated risk of aortic dissection in peripartum period

Overall Rate of Aortic Dissection in Pregnancy/ Post partum Period 5-6%

• Majority of aortic complications occur in the 3rd trimester or post partum period

Aortic Root Size significantly affects risk of dissection
• ≥ 4 cm risk of dissection 10 %
• < 4 cm risk of dissection 1%

Aortic Dissection Rate in LDS 1-19%* Loeys et al. 2006
Pregnancy Related Complications for Women with CTD

Cardiovascular Complications:
• Aortic Root Growth 
• Aortic Dissection 
• Arrhythmias

Preterm Rupture of Membranes/Preterm Birth

Fetal Growth Restriction

Spontaneous Pneumothorax
Anesthesia Complications
Venous Thromboembolism (Blood Clots)
Known Risk Factors for Aortic Dissection in Pregnancy Women with Connective Tissue Disorders

- Aortic Root Size
  - ≥ 4 cm risk of dissection 10%
  - < 4 cm risk of dissection 1%

- HTN Disorders and Preeclampsia

- Aortic Root Replacement
Risk of Aortic Dissection in Pregnancy with Aortic Root Replacement (ARR)

• Dr. Braverman & Dr. Wilkins- Washington University in St Louis

• 29 Women with MFS, 38 pregnancies after Aortic Root Replacement

• 4 acute type B dissections (10.5%) and no type A dissections

• Prophylactic vs Acute Aortic Dissection- Risk of Future Dissection
  • 2/4 (50%) women with prior type A aortic dissection developed type B dissection
  • 2/25 (8%) women with ppx ARR developed type B dissections
Risk of Aortic Dissection in Pregnancy with Aortic Root Replacement (ARR)

• Prophylactic aortic root replacement protects against type A dissections however these patients are still at risk for type B dissections

• Women who have had ARR as a result of dissection vs. prophylactic replacement are different in terms of their risks for future dissection and this information will be important in counseling women about risks for future dissection in pregnancy
The Quest for New Risk Factors for Aortic Dissection in Pregnancy
Pathogenesis of Aortic Aneurysm in MFS and LDS: Excessive TGFβ Signaling through non-canonical ERK activation

Latent Complex

Normal Fibrillin-1

Excessive TGFβ Activation

Marfan Syndrome Mutated Fibrillin-1

TGFβ

cytoplasm

SMAD2/3

SMAD4

ERK

MEK

TF

nucleus

Phenotypic Consequence
Aortic Aneurysm
89% of pregnant mice die within the 4 weeks after delivery.
Removal from Pups

Postpartum Survival Improves 11 to 74%

Mouse Model of Marfan Syndrome
Pup Removal at Birth Protects from Death via Aortic Dissection

Postpartum Day

Percent Survival

mgR-/-preg (n=49)  p<0.0001
mgR-/-female, pups removed (n=27)
Are there similar effects in humans???
Oxytocin levels rise through pregnancy, peaking in the third trimester and remain elevated with lactation.

Stock et al. 1991
Oxytocin levels rise through pregnancy, peaking in the third trimester and remain elevated with lactation.

Stock et al. 1991
Management Guidelines in Pregnancy for Women with Connective Tissue Disorders
Preconception Counseling:

- Titration off of Angiotensin-Receptor Blocker (ARB) onto Beta-Blocker
- Genetic Counseling of Heritability Risk, Genetic Testing Options
- Imaging Studies- CV imaging (CTA) and Spinal Imaging
- Counseling about Risks of Pregnancy, CV complications and effects on long term health

- Discussion of Contraceptive Options:
Antepartum Care: Care During Pregnancy

- Multi-disciplinary Approach
  - Maternal-Fetal Medicine, Cardiology
  - CV surgery, Anesthesia, NICU, Nursing

- Genetic Counseling of Heritability Risk - Genetic Testing Options
  - Embryo stage - Preimplantation Genetic Diagnosis (PGD) and IVF
  - 1st Trimester - Chorionic villus sampling
  - 2nd-3rd Trimester - Amniocentesis
  - Post-Delivery testing in Baby
Antepartum Care: Care During Pregnancy

• Beta-blockade during pregnancy (Avoid CCB)
  • Metoprolol (Avoid Atenolol - fetal growth restriction)

• Growth ultrasounds during the Pregnancy - every 4 weeks

• Fetal Echocardiogram 22-24 weeks (Risk of CHD if affected with LDS)
Antepartum Care: Care During Pregnancy

• Maternal CV imaging- echocardiogram and MRA
  • Echocardiogram every trimester *

• Spine imaging- cervical spine stability, scoliosis, dural ectasias
Management at Delivery

Anesthesia Considerations
- Additional monitoring of vital signs (arterial line placement)
- Type of Anesthesia - Regional (Spinal/Epidural vs General Anesthesia)
  - Presence of Dural Ectasia
  - Vascular anomalies/variants in anatomy

Timing and Mode of Delivery
- Timing of Delivery - No consensus-expert opinion - 36-39 weeks*
- Vaginal vs C-section - Depends on institution, aortic root size
  - Vaginal - Forceps or Vacuum - decreasing time/efforts for pushing
  - Threshold of Aortic Root Size of 4cm
- Vascular EDS/ Loeys-Dietz* - C-section is recommended
Management Postpartum

Recovery 24-48 hrs in CV ICU Setting
- Highest risk time for dissection in first week post-partum

CV Surveillance in Post-partum Period
- Echocardiogram in 24-48 hours
- MRA or CTA in first week post-partum
- Echocardiogram at 3 and 6 months

Breast Feeding
SUMMARY POINTS

• Women with connective tissues disorders are at higher risk for CV complications in pregnancy and when these complications exist consequences can be catastrophic.

• Identification of women who have these risks is KEY

• Most women with these disorders have favorable outcomes in pregnancy and those that usually do best are those who have a well-organized, educated, multi-disciplinary team
What is my role as a nurse?

• Knowledge is power
• Speak up if you are concerned
• Recognize those at risk
• Know the warning signs for AD
• Know how to diagnose AD
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Dionne Walker, Linda Tyer-Viola, Amanda Garey, Kaleidoscope Conference

Loeys Dietz Syndrome Foundation

The Marfan Foundation

Patients with Marfan and Loeys Dietz Syndrome
Thank you for listening!
References

References


References