Second-Trimester Pregnancy Loss: What do we know? What can be done?

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Second-Trimester Pregnancy Loss

What do we mean?
Second-Trimester Pregnancy Loss

• Intrauterine fetal demise
  – Unexplained fetal death after 10 weeks

• Spontaneous delivery
  – Cervical insufficiency/incompetence
  – Preterm Labor/PPROM
Second-Trimester Pregnancy Loss

What do we know?
Second-Trimester Pregnancy Loss

Fetal Demise
Fetal Demise

In US, 6.2 million pregnancies/yr

Martin & Hoyert, Sem Perinatol 2002
Fetal Demise

- Fetal mortality rate: 6.4 per 1000 live births plus fetal deaths
- ~50% occur in second trimester

Fetal Demise: Fetal Risk Factors

– Anomalies
  • Structural
  • Chromosomal

– Infection/inflammation
  • Ascending bacterial infection triggers cytokine cascade

– Multifetal
  • Fetal death rate 18.5 vs 6.2/1000

MMWR 2004; 53:529
Fetal Demise:
Placental/Umbilical Cord Risk factors

– Abruptio placentae

– Cord accident

– Uteroplacental insufficiency
Fetal Demise: Maternal Risk Factors

– Social habits
  • Weight (>87kg - OR 2.1)
  • Smoking (OR 1.5)
  • Marital status (single - OR 1.6)

– Age
  • >35yo (OR 3.5)

– Race
  • Black (OR 1.6)
Fetal Demise: Maternal Risk Factors

– Vascular disease
  • Diabetes
  • SLE
  • HTN
  • Renal disease

– Thrombophilia
  • Inherited
  • Acquired
Inherited Thrombophilia

- Factor V Leiden mutation
- Prothrombin G20210A gene mutation (heterozygous)
- Plasminogen activator inhibitor-1 4G/4G mutation (homozygous)
- Thermolabile variant of the Methylene-tetrahydrofolate Reductase (C677T MTHFR)
- Antithrombin III deficiency
- Protein S deficiency
- Protein C deficiency
Inherited thrombophilia in the general population

![Graph showing inherited thrombophilia in the general population.](attachment:thrombophilia_graph.png)
Inherited Thrombophilia

- ~15% of white European populations have some form of thrombophilia

- Responsible for ~50% of all maternal thromboembolic events in pregnancy

- Linked to an increased risk of fetal demise in some studies
# Inheritance, Diagnosis, Prevalence and Relative Pathogenicity of the Inherited Thrombophilias

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Genetics</th>
<th>Assay</th>
<th>Prevalence</th>
<th>Risk of VTE</th>
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<tbody>
<tr>
<td>Factor V Leiden</td>
<td>AD</td>
<td>DNA</td>
<td>2-15%</td>
<td>3 to 8-fold</td>
</tr>
<tr>
<td>PT G20210A</td>
<td>AD</td>
<td>DNA</td>
<td>2-3%</td>
<td>3-fold</td>
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<tr>
<td>ATIII</td>
<td>AD</td>
<td>Activity assay</td>
<td>0.02%</td>
<td>25-50-fold</td>
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<tr>
<td>Protein C</td>
<td>AD</td>
<td>Activity assay</td>
<td>0.2-0.3%</td>
<td>10 to 15-fold</td>
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<tr>
<td>Protein S</td>
<td>AD</td>
<td>Activity assay</td>
<td>0.1-2.1%</td>
<td>2-fold</td>
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<tr>
<td>Hyper-homocystinemia</td>
<td>AR</td>
<td>Fasting levels or DNA</td>
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<td>2.5-fold</td>
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<tr>
<td>PAI-1</td>
<td>AR</td>
<td>DNA</td>
<td>High</td>
<td>unknown</td>
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</tbody>
</table>

Inherited Thrombophilia: Adverse pregnancy outcomes

• Carriers of genetic thrombophilias have increased rates of vascular thrombosis

• The placenta is a highly vascular organ

• Many adverse pregnancy outcomes are associated with characteristic placental lesions involving thrombosis
Inherited Thrombophilia

Meta-analysis of 31 case-control, cohort and cross-sectional studies

• Factor V Leiden associated with fetal loss
  - OR 7.83, 95% CI 2.83-21.67

• PT20210A gene mutation linked to fetal loss
  - OR 2.30, 95% CI 1.09-4.87

• Protein S deficiency associated with fetal loss
  - OR 7.39, 95% CI 1.28-42.63

• Protein C and AT deficiencies not significantly associated with fetal loss

Rey et al. Lancet 2003; 361:901
Second trimester pregnancy loss

Contribution of inherited thrombophilia to pregnancy loss and the role of prophylaxis to prevent recurrence is controversial.
Absence of association of inherited thrombophilia with unexplained third-trimester intrauterine fetal death

Ron Gonen, MD, Noa Lavi, MD, Dina Attias, MD, Liliana Schlamser, MD, Zvi Borochowitz, MD, Elias Toubi, MD, Gonen Ohel, MD

Department of Obstetrics and Gynecology, Division of Hematology. The Simon Witten Inst., Division of Clinical Immunology, Blad Zion Medical Center, and Faculty of Medicine, Technion Institute of Technology, Haifa, Israel

Thrombophilia is not associated with an increase in placental abnormalities in women with intra-uterine fetal death

Leonard P. Mosterina, Joss G. Santenja and Feike Willemsen

From the "Department of Obstetrics and Gynecology, Medical Center Leeuwarden, and 5Department of Pathology, Laboratory for National Health Services Friesland, the Netherlands"
Does heparin therapy improve pregnancy outcome in patients with thrombophilias?

M. PAIDAS, D.-H. KU, E. TRICHE, C. LOCKWOOD and Y. ARKEL
The Program for Thrombosis and Hemostasis in Women’s Health, Division of Maternal & Fetal Medicine, Department of Obstetrics & Gynecology, Yale University School of Medicine, New Haven, Connecticut, USA

Thromboprophylaxis improves the live birth rate in women with consecutive recurrent miscarriages and hereditary thrombophilia

H. CARP, "‡ M. DOLITZKY" and A. INBAL‡
†Department of Obstetrics and Gynecology, ‡Institute of Thrombosis and Hemostasis, Sheba Medical Center, Tel Hashomer, Israel and Sackler Faculty of Medicine and Department of Obstetrics and Gynecology, Sackler School of Medicine, Tel Aviv University, Israel

DEBATE

Antithrombotic prophylaxis for women with thrombophilia and pregnancy complications – Yes

R. BRENNER
Thrombosis and Hemostasis Unit, Department of Haematology, Rambam Medical Center & Bruce Rappaport Faculty of Medicine, Technion, Haifa, Israel

Antithrombotic prophylaxis for women with thrombophilia and pregnancy complications – No

S. MIDDENDORP
Academic Medical Center, Department of Vascular Medicine, Amsterdam, The Netherlands
Inherited Thrombophilias: Can we prevent recurrent pregnancy loss?

*Lesser thrombogenic thrombophilia

Assess history of thromboembolism or adverse pregnancy outcomes

- No antepartum treatment
  - Treat postpartum with prophylactic anticoagulation for 4-6 weeks if:
    a) cesarean delivery
    b) affected 1st degree relative

+ A) Prior thromboembolic event:
  - Treat with prophylactic heparin ante- and postpartum
  - Use coumadin for 4-6 weeks

B) Adverse pregnancy outcome
  - Treat prophylactic heparin antepartum,
  - Treat postpartum for 4-6 weeks only if:
    a) cesarean delivery
    b) affected 1st degree relative

*Does not include AT deficiency or homozygotes or compound heterozygotes for factor V Leiden or prothrombin mutations

Acquired Thrombophilia: Antiphospholipid Syndrome

- Autoimmune disorder characterized by moderate-to-high levels of circulating antiphospholipid antibodies

- Clinical features include venous or arterial thrombosis, autoimmune thrombocytopenia, and fetal loss

- It can occur as a primary condition, or with other autoimmune diseases such as lupus
# Diagnosis of Antiphospholipid Syndrome

<table>
<thead>
<tr>
<th>Table 1. Clinical and Laboratory Criteria for the Diagnosis of Antiphospholipid Syndrome*</th>
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</thead>
<tbody>
<tr>
<td><strong>Criterion</strong></td>
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<tr>
<td>Clinical</td>
</tr>
<tr>
<td>Fetal loss</td>
</tr>
<tr>
<td>Thrombosis</td>
</tr>
<tr>
<td>Autoimmune thrombocytopenia</td>
</tr>
<tr>
<td>Other features</td>
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<tr>
<td>Laboratory</td>
</tr>
<tr>
<td>Lupus anticoagulant</td>
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<tr>
<td>Anticardiolipin antibodies</td>
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</tbody>
</table>

*Antiphospholipid syndrome is diagnosed when the patient has (1) at least one clinical feature and (2) lupus anticoagulant or medium-to-high positive immunoglobulin G anticardiolipin antibodies or both. Because antiphospholipid antibodies may appear transiently following infection, positive tests should be confirmed 8 or more weeks after initial testing.

1IgM and IgA isotypes are of uncertain significance and should not be used to diagnose antiphospholipid syndrome unless patient also has lupus anticoagulant or IgG anticardiolipin antibodies (GPL units).
Antiphospholipid Syndrome

- Women with APS are at high-risk of complications during pregnancy, including VTE, CVA, recurrent miscarriage, IUFD, IUGR, and preeclampsia

- The rate of these complications vary widely, due to differences in populations and non-standard diagnostic criteria for APS
Antiphospholipid Syndrome: Can we prevent recurrent pregnancy loss?

- Multiple studies evaluating women with recurrent miscarriage and APLS show improved outcomes with heparin/aspirin

- Recent meta-analysis concluded that anticoagulation therapy may reduce the risk of pregnancy loss by 29-71% (Cochrane Database Systematic Review 2005)
Second-Trimester Spontaneous Pregnancy Loss:

Preterm labor and cervical insufficiency
Preterm Labor

- Infection/Inflammation
  - Ascending infection
  - Post amniocentesis

- Multifetal gestation
Cervical Insufficiency

• Definition:
  – Inability of the uterine cervix to retain a pregnancy in the absence of contractions or labor (ACOG Practice Bulletin #48)
  – “Painless cervical dilation”

• US Incidence: 23,000 cases/year
  (National Center for Health Statistics 2000)
Cervical Structure

• Uterus and cervix formed from fusion of distal mullerian ducts followed by central resorption of Mullerian tissue

• Cervix consists primarily of extracellular connective tissue, including cross-linked collagens, and smooth muscle

• Changes in the biochemical structure of the cervix occur just prior to labor in normal pregnancies
Cervical Insufficiency

Once cervical ripening occurs by any etiology, the protective barrier formed by the normal cervix, mucous plug, fetal membranes, and maternal immune system is disrupted potentially leading to PPROM or PTL.
Cervical Insufficiency
Risk Factors: Congenital Factors

- Short cervix
  - Biological variation
  - Iams et al looked at 2915 pregnant women at 24 weeks and found that the RR of preterm birth was 10-fold higher if CL was $<5^{th}$%ile (NEJM 1996;334:567)
Cervical Insufficiency Risk Factors: Congenital Factors

- Mullerian duct abnormalities
  - Bicornuate or unicornuate uteri are risk factors
- DES exposure in utero
  - 25-50% of exposed women have cervicovaginal structure abnormalities
  - 6.4% risk of second trimester pregnancy loss (Kaufman et al. Obstet gynecol 2000;96:483)
- Connective tissue disorder
  - Collagen or elastin deficiency
  - Ehlers-Danlos syndrome
  - Marfan Syndrome
Cervical Insufficiency Risk Factors: Acquired Factors

- Cervical laceration following NSVD
- Cervical injury at time of CS
- Cervical conization (LEEP/LLETZ, cold knife cone biopsy)
- Cervical dilation (D&C; D&E)
Cervical Insufficiency Risk Factors: Others

- Uterine overdistention
  - Multifetal gestations
  - Polyhydramnios

- Biochemical factors
  - Elevated serum relaxin
  - Cytokines

- Environmental factors
  - Infection/inflammation
  - Toxins

- Genetic factors
  - Genetic polymorphisms in genes encoding inflammatory cells
Cervical Insufficiency: Diagnosis

- Painless cervical dilation

- Transvaginal sonography
  - Cervical shortening
  - Cervical funneling

- Nongravid diagnostic tests not helpful
  - HSG with balloon traction on cervix, cervical assessment with dilators, cervical resistance
Cervical Insufficiency

- Cervical length is inversely correlated with GA at delivery.

- Studies evaluating cervical length and the internal os indicate that cervical insufficiency and preterm labor are not discrete entities.

- Women with a short cervix are at risk for preterm labor AND second trimester loss.
Cervical Insufficiency: Diagnosis

• Early cervical changes may include “beaking” or “funneling”

• Iams has described cervical changes based on the configuration of the endocervical canal: T, Y, V, and U

Iams JD. Ultrasound Obstet Gynecol 1997;10:156
Second Trimester Pregnancy Loss:

What Can Be Done?
Second Trimester Pregnancy Loss

Evaluate history and medical records carefully

- IUFD?
- Cervical insufficiency?
- Preterm labor?
- Infection? (post amnio?)
- Overdistention? (multifetal?)
- Thrombophilia?
Second Trimester Pregnancy Loss: What Can Be Done?

- Multifetal pregnancy loss
  - Discourage multi-embryo transfers
  - Be optimistic!!
Second Trimester Pregnancy Loss: What Can Be Done?

• Infection?
  – Pre-pregnancy or antepartum antibiotics, in general, not helpful in most studies

  – Role of BV controversial
  – BV associated with pregnancy loss<22 weeks; treatment with clindamycin associated with 50% reduction in PPROM/PTL (McGregor et al. AJOG 1995;173:157)
  – Treatment of BV with clindamycin in asymptomatic pregnant women at 12-22 weeks reduces the rate of late miscarriage (Ugwumadu et al. Lancet 2003;361:2161)
  – Treatment of asymptomatic BV with metronidazole does not reduce occurrence of adverse perinatal outcomes (Carey et al. NEJM 2000;342:40)
Second Trimester Pregnancy Loss: What Can Be Done?

- Preterm labor?
  - Consider 17-OHP
    - Meis study did not evaluate patients with a history of 2nd trimester pregnancy loss (Meis et al. NEJM 2003;348:2379)
    - Da Fonseca study did not publish data on subgroup analysis of women with history of second trimester pregnancy loss (da Fonseca et al. AJOG 2003;188:419)
  - Avoid multifetal gestation
Second Trimester Pregnancy Loss: What Can Be Done?

- IUFD?
  - Review autopsy and cytogenetics report, if possible
  - Review placental pathology
  - Review available cultures
  - Maternal serum screening (PAPP-A and MSAFP)
  - Early glucola
  - Thrombophilia work-up; consider heparin/BASA
  - Fetal anatomic survey
Second Trimester Pregnancy Loss: What Can Be Done?

- Can we prevent recurrent pregnancy loss with anticoagulation?
  - Even if inherited thrombophilia is an etiologic factor, it is not known whether treatment can reduce rates of recurrence
  - Antiphospholipid syndrome must be considered separately from other forms of genetic thrombophilia
    - Treatment of this autoimmune disease with aspirin/heparin has been shown to prevent adverse obstetric outcomes
Testing for Antiphospholipid Syndrome

Indications for Testing for Antiphospholipid Antibodies

Obstetric
- Otherwise unexplained fetal death or stillbirth
- Recurrent pregnancy loss (three or more spontaneous abortions with no more than one live birth, or unexplained second- or third-trimester fetal death)
- Severe pregnancy-induced hypertension <34 weeks of gestation
- Severe fetal growth restriction or other evidence of uteroplacental insufficiency in the second or early third trimester

Medical
- Nontraumatic thrombosis or thromboembolism (venous or arterial)
- Stroke, especially in individuals <50–55 years of age
- Autoimmune thrombocytopenia
- Transient ischemic attacks or amaurosis fugax, especially in individuals <50–55 years of age
- Livedo reticularis
- Hemolytic anemia
- Systemic lupus erythematosus
- False-positive serologic test for syphilis

ACOG Ed. Bull. 1998
Second Trimester Pregnancy Loss: What Can Be Done?

- Cervical insufficiency?
  - CONTROVERSIAL!!
  
  - For decades after McDonald and Shirodkar described their procedures, prophylactic cerclages were placed in women with a history consistent with cervical insufficiency
Prophylactic Cerclage: 4 published randomized trials

- French study: 506 women; more women in the cerclage group were hospitalized and received tocolysis; no difference in rate of preterm delivery (Lazar et al. Br J Obstet Gynaecol 1984;91:731)

- South African study: 194 women; cerclage group with significantly longer hospital stay; no difference in gestational age at delivery or survival. (Rush et al. Br J Obstet Gynaecol 1984;91:724)

- UK trial: 1292 women; fewer deliveries <33 weeks in cerclage group if ≥3 losses in past; no difference in perinatal mortality; Cerclage associated with higher rates of medical intervention and postpartum fever. (MRC/RCOG. Br J Obstet Gynaecol 1993;100:516)

- Dutch study: 70 women; no difference in delivery <34 weeks or neonatal survival (Althuisius et al. Am J Obstet Gynecol 2000;183:823)
Cervical Insufficiency

Prophylactic Cerclage

• The Cochrane Library combined the data from the four trials

• Overall, no reduction in pregnancy loss or preterm delivery rates with prophylactic cerclage

• Cerclage associated with higher rates of febrile morbidity, tocolysis, and hospitalization

Cochrane Database Syst Rev. 2003;(1):CD003253
Cervical Insufficiency
Prophylactic Cerclage

“On the basis of this limited clinical information, elective cerclage should be confined to patients with 3 or more otherwise unexplained second-trimester pregnancy losses…”

ACOG Practice Bull #48, 2003
Prophylactic Cerclage: Multifetal Gestations

TWINS

• Randomized study evaluated prophylactic cerclage in 50 twin pregnancies

• In cerclage group, 45% delivered prematurely; neonatal death rate 18.2%

• In non-cerclage group, 48% delivered preterm; neonatal death rate 15.2%

Dor et al. Gynecol Obstet Invest 1982; 13:55
Prophylactic Cerclage: Multifetal Gestations

TRIPLETS

• One study reviewed triplet pregnancies from a national database and compared outcomes in those with and without prophylactic cerclage

• 248 of 3278 women (7.6%) underwent prophylactic cerclage

• No differences in GA at delivery, birth at <32 weeks, birthweight, or neonatal outcomes

Cervical Insufficiency

Prophylactic Cerclage

Insufficient data from randomized trials exist to conclude that prophylactic cerclage is beneficial
Cervical Insufficiency

Alternatives to Prophylactic Cerclage

• With the ability of TV ultrasound to evaluate the cervix in the 2nd trimester, close sonographic observation is an alternative to cerclage

• Most patients considered candidates for prophylactic cerclage who are followed with ultrasound will have normal findings, and will not undergo cerclage
Cervical Insufficiency: Urgent/Emergent Cerclage

• Four randomized studies have been conducted assessing urgent cerclage in women with sonographic findings suggestive of cervical insufficiency
  – Althuisius et al. AJOG 2001;185:1106 (CIPRACT)
  – Rust et al. AJOG 2001;185:1098
  – Berghella et al. AJOG 2004;191:1311

• Recent meta-analysis combined these 4 trials
Cervical Insufficiency: Urgent/Emergent Cerclage

- “Cerclage does not prevent preterm birth in all women with short cervical length on TV U/S. In the subgroup analysis of singleton gestations, especially those with a prior preterm birth, cerclage may reduce preterm birth...”

- Significantly higher rates of SPTB in twin pregnancies with cerclage based on ultrasound changes compared to management without cerclage

- Emergent cerclage in patients with cervical dilatation and bulging membranes is associated with high rates of adverse maternal and neonatal outcomes

Cervical Insufficiency: Urgent/Emergent Cerclage

The role of cervical cerclage in obstetric practice: Can the patient who could benefit from this procedure be identified?

Roberto Romero, a Jimmy Espinoza, a,b Offer Erez, a,b Sonia Hassan b

Perinatology Research Branch, National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services, Bethesda, MD and Detroit, MI; Wayne State University, Department of Obstetrics and Gynecology, b Detroit, MI

“...the patient with severe endocervical inflammation may have subclinical intra-amniotic inflammation/infection or extra-amniotic inflammation/infection and may be in the advanced stages of the process that culminates in the expulsion of the conceptus to enhance maternal survival.”
Cervical Insufficiency: Urgent/Emergent Cerclage

Patients should be counseled appropriately, and amniocentesis should be performed to identify those especially likely to be harmed
Cervical Insufficiency

• If midtrimester loss is truly multifactorial, different etiologies may respond differently to certain treatments
  – Cerclage may *correct* an anatomic weakness
  – Cerclage may *exacerbate* an inflammatory process

• “Cervical insufficiency” is unlikely to be a discrete entity, but part of a spectrum including spontaneous preterm birth

• Intrinsic cervical “weakness” is probably only one of many factors contributing to mid-trimester loss
Second Trimester Pregnancy Loss: Future Directions

• Better understanding of causes/risk factors
  – Genetic predisposition
  – Anatomical predisposition
  – Fetal predisposition
Second Trimester Pregnancy Loss: Future Directions

• Better understanding of therapies
  – Antibiotic therapy
  – Hormonal therapy
  – Immune therapy
    • Anticoagulation
    • Immunoglobulins/steroids
  – Herbal therapies
  – Cerclage
  – Single embryo transfer
  – Gestational surrogate
Second Trimester Pregnancy Loss: CONCLUSION

Statistically, your patient with a history of a second trimester pregnancy loss will most likely have a good outcome regardless of your management.
Second-Trimester Pregnancy Loss: What do we know? What can be done?

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