Thrombophilias, Antibodies, and Pregnancy Outcomes: Are We Overdiagnosing and Overtreating our Patients?

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Disclosures

- No disclosures or conflicts to report
Learning Objectives

At the conclusion of this presentation, the participant should be able to:

1. Identify and understand the diagnosis of recurrent pregnancy loss

2. Critically assess current guidelines for the diagnosis and management of thrombophilias and immune disorders relevant to pregnancy outcomes

3. Effectively implement current evidence-based criteria regarding thrombophilias and autoimmune issues to management of women preconceptionally and during pregnancy

4. Identify diagnostic criteria and management options for the antiphospholipid syndrome
The Roadmap

- What is recurrent pregnancy loss (RPL)?
- What are the potential causes of RPL?
- Thrombophilia testing – who, when, ever?
- Autoimmune issues/APL
- Empiric/alternative therapies: any evidence?
Case #1

- 43-yr-old G4P1112, hx lupus since age 18
- OB hx
  - 1989: term SVD; on prednisone for lupus
  - 2004: twins @ 34+ weeks for NR-FHR, no meds had PPTL with c/s
- No lupus sx or meds until 2008
- 2013: 2 IVF cycles
  - 1 loss 3 wks after transfer, 1 failed cycle
- Seen by reproductive immunologist
  - ACA, LAC, B2GP all (-), ANA, SS-A (+)
Case # 1 (cont’d)

- Further workup in immunologist’s office
  - Monthly NK cell panels and cytokine assays
  - Monthly lymphocyte surface marker assays
- Immunologist’s “protocol” pre-IVF
  - Prednisone 10 mg BID
  - Lovenox 60 mg BID
  - Humira (adalizumab) q 2 weeks for 1-2 months
  - 3 cycles of paternal leukocyte immuniz. in Mexico
- Underwent IVF with local REI
- Currently 8 weeks pregnant
  - Still on Lovenox and Prednisone
Case #2

- 38 yr-old G5 P1031

- OB history
  - 2009: full term SVD
  - 2012-13: 7 week Sab, 8 week Sab with documented aneuploidy, 6-7 week chemical pregnancy

- Seen by her naturopath
  - Workup there: (+) antiphosphatidylglycerol IgM, heterozygous (+) MTHFR mutation
  - Placed on Lovenox prior to IVF and continued

- Twin pregnancy post IVF/PGD
  - 1st visit @ 18 weeks: (+) integrated screen for T21, (-) NIPT
KEEP CALM

HELP IS ON THE WAY
Early Pregnancy: Terminology and Development

- Traditional obstetric nomenclature
  - Pregnancy loss < 20 weeks: SAb
  - Deaths in utero > 20 weeks: stillbirth
- “Spontaneous abortion” – introduced in 1500s
  - Lumps together a heterogeneous group of conditions at a broad range of gestational ages
Pregnancy Loss Classification

- Pre-implantation losses ("chemical pregnancy")
  - HCG made by blastocyst in sufficient amount to be detected by beginning of 3rd week of gestation
  - Failed pregnancy, dx’d by poor HCG progression, seen before 5th week, even if miscarriage sx not until later

- Pre-embryonic losses
  - When u/s shows gestational sac but no fetal pole, loss occurred early in, or before, gastrulation (< 6 weeks)

- Embryonic losses
  - Detectable embryo with or without pre-existing cardiac activity < 10 weeks’ size on u/s
  - Loss of formed embryo on visual inspection of POC

- Fetal losses: after 10 weeks or CRL > 30 mm

Silver RM et al. Obstet Gynecol 2011; 118: 1402-8
Pregnancy Loss: Statistics

- Properly categorizing pregnancy losses is critical both for patient management and for quality research into losses.
- Most pregnancy losses occur in pre-embryonic and embryonic periods:
  - Only 1.7% of losses in 1 series were after 9-10 weeks.
  - In U.S., 0.6% of losses after 20 weeks.
- Pregnancy loss reported to occur in almost 1/3 of all conceptions:
  - 2/3 are peri-implantation losses, often not symptomatic.

Goldstein SR, Obstet Gynecol 1994; MacDorman MF, Natl Health Ctr Stats 2009
Aneuploidy and Pregnancy Loss

Aneuploidy reported in up to 90% of pre-embryonic losses $^{1-3}$
- 50% of losses between 8-11 weeks are aneuploid
- Decreases to 30% for losses at 16-19 weeks
- Aneuploidy < 15% in stillbirths > 20 weeks
  - Rates higher in more recent studies using SNP/microarray $^{4}$

What is Recurrent Pregnancy Loss?

- **ASRM (2008)**
  - “A disease distinct from infertility, defined by 2 or more failed pregnancies” *(ASRM Practice Committee, Fertil Steril 2008)*
  - After 3 or more losses, thorough evaluation warranted

- **11th Intl. Congress on APL/APS (2006)**
  - One or more unexplained deaths of morphologically normal fetus at or beyond 10th week of gestation *(Miyakis S, J Thromb Haem 2006)*

- If RPL defined as loss of 3 or more consecutive pregnancies → 1% of couples *(Rai R, Lancet 2006)*

- Many experts consider 2 consecutive losses as sufficient for diagnosis of RPL *(Branch DW, NEJM 2010)*
  - Recurrence rate same as after 3 losses *(Boogaard, Fert Steril 2013)*
  - *Pregnancy loss is NOT a failed IVF transfer cycle*
Figure 1 Kaplan-Meier plot showing percentage of women in the recurrent miscarriage cohort who have had at least one live birth after first consultation by number of miscarriages before first consultation. (Lund et al. Recurrent miscarriage and prognosis f...
# Standard evaluation for recurrent pregnancy loss

<table>
<thead>
<tr>
<th>Diagnostic evaluation</th>
<th>Etiology</th>
<th>% abnormal</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetic analysis of both partners</td>
<td>Structural genetic</td>
<td>3%–5%</td>
<td>Genetic counseling, donor gametes, preimplantation genetic screening</td>
</tr>
<tr>
<td>Hysterosalpingogram, hysteroscopy, or sonohysterography</td>
<td>Anatomic</td>
<td>15%–20%</td>
<td>Hysteroscopic septum resection, myomectomy, lysis of adhesions</td>
</tr>
<tr>
<td>Thyrotropin, Prolactin, Hemoglobin A(_{1c})</td>
<td>Endocrinologic</td>
<td>8%–12%</td>
<td>Levothyroxine, Bromocriptine, cabergoline, Metformin</td>
</tr>
<tr>
<td>Lupus anticoagulant, Antiphospholipid antibodies, (\beta_2)-glycoprotein 1 antibodies</td>
<td>Immunologic</td>
<td>15%–20%</td>
<td>Heparin plus aspirin</td>
</tr>
<tr>
<td>Thrombophilia testing</td>
<td>Thrombophilia</td>
<td>Varies</td>
<td>None</td>
</tr>
<tr>
<td>Tobacco, alcohol use, Excessive caffeine, Obesity</td>
<td>Lifestyle issues</td>
<td></td>
<td>Eliminate exposure, Reduce consumption, Decrease body mass</td>
</tr>
</tbody>
</table>

*From: Kutteh WH; SRM, Feb 2012*
34-year old with three 1st-trimester losses at 9-11 weeks

Normal parental karyotypes
Normal TSH, Hgb A1c
Normal sonohysterogram

Autoimmune testing?
YES, but focused

Thrombophilia testing?
NO

From: Kutteh WH; SRM, Feb 2012
Inherited Thrombophilias in Pregnancy

Inherited thrombophilias are associated with an increased risk of venous thromboembolism and also have been linked to adverse outcomes in pregnancy. However, there is limited evidence to guide screening for and management of these conditions in pregnancy. The purpose of this document is to review common thrombophilias and their association with maternal venous thromboembolism risk and adverse pregnancy outcomes, indications for screening to detect these conditions, and management options in pregnancy.

Background

The Hemostatic Paradox of Pregnancy

Pregnancy poses a particularly complex hemostatic challenge. Successful pregnancy requires the avoidance of hemorrhage during implantation, endovascular cytotoxic remodeling of maternal spiral arteries, and during the third stage of labor it also requires the maintenance of a fluid uteroplacental circulation. Maintaining hemostatic balance during pregnancy requires alterations in both local uterine and systemic clotting, as well as anticoagulant and fibrinolytic proteins. The decidua layer of the uterus plays a crucial role in the prevention of hemorrhage during implantation, placentation, and the third stage of labor (1, 2). Confirmation of the crucial role that the decidua plays in the maintenance of gestational hemostasis is seen in the hemorrhage associated with obstetric conditions marked by absent or impaired decidua (eg, ectopic pregnancy and placenta accreta). Conversely, decidual tissue factor also can promote the intense hypofibrinogenemia and disseminated intravascular coagulation observed in decidual hemorrhage (ie, placental abruption).

Pregnancy is marked by increased clotting potential, decreased anticoagulant activity, and decreased fibrinolysis (3–5). The thrombotic potential of pregnancy is exacerbated by venous stasis in the lower extremities due to compression of the inferior vena cava and pelvic veins by the enlarging uterus, a hormone-mediated increase in venous capacitance, insulin resistance, and hyperlipidemia. Thus, it is not surprising that venous thromboembolism complicates approximately 1 in 1,600 births and is a leading cause of maternal morbidity in the United States (6, 7).

There is a strong association between inherited thrombophilias and venous thromboembolism, which makes detection of these mutations a logical target for prevention strategies (Table 1). However, it is controversial whether there is an association between inherited thrombophilias and uteroplacental thrombosis that lead to adverse pregnancy outcomes such as fetal loss, preeclampsia, fetal growth restriction, and placental abruption (8). This possible association has resulted in increased screening for thrombophilias in pregnancy, although there has been no confirmation of treatment benefits.

Committee on Practice Bulletins—Obstetrics. This Practice Bulletin was developed by the Committee on Practice Bulletins—Obstetrics with the assistance of Charles Lockwood, MD, George Wendel, MD, and Neil Silberman, MD. The information is designed to aid practitioners in making decisions about appropriate obstetric and gynecologic care. These guidelines should not be construed as dictating an exclusive course of treatment or procedure. Variations in practice may be warranted based on the needs of the individual patient, resources, and limitations unique to the institution or type of practice.
Evaluation and treatment of recurrent pregnancy loss: a committee opinion

The Practice Committee of the American Society for Reproductive Medicine
American Society for Reproductive Medicine, Birmingham, Alabama

The majority of miscarriages are spontaneous and most result from genetic causes that are greatly influenced by maternal age. Recurrent pregnancy loss (RPL) is defined by two or more failed clinical pregnancies, and up to 50% of cases of RPL will not have a clearly defined etiology. (Fertil Steril® 2012;98:1:1103–11. ©2012 by the American Society for Reproductive Medicine.)

Earn online CME credit related to this document at www.asrm.org/ce/earn

Discussion: You can discuss this article with its authors and with other ASRM members at http://fertsterforum.com/goldsteinj-evaluation-treatment-recurrent-pregnancy-loss-committee-opinion/

C

Clinically recognized pregnancy loss is common, occurring in approximately 15–25% of pregnancies. The majority of spontaneous losses before 10 weeks’ gestation result from random numeric chromosome errors, specifically, trisomy, monosomy, and polyplody (1). In contrast, recurrent pregnancy loss (RPL) is a distinct disorder defined by two or more failed clinical pregnancies (2). It is estimated that fewer than 5% of women will experience two consecutive miscarriages, and only 1% experience three or more (3).

WHO TO EVALUATE

The challenge for clinicians is to differentiate sporadic miscarriage from RPL. Self-reported losses by patients may not be accurate. In one study, only 71% of self-reported clinical pregnancy losses could be verified in hospital records (4). For the purposes of determining whether evaluation for RPL is appropriate, pregnancy is defined as a clinical pregnancy documented by ultrasonography or histopathological examination. Ideally, a threshold of three or more losses should be used for epidemiological studies while clinical evaluation may proceed following two first-trimester pregnancy losses.

ETIOLOGY OF RECURRENT PREGNANCY LOSS

Studies that focus on RPL have examined factors related to genetics, age, antiphospholipid syndrome, uterine anomalies, thrombophilia, hormonal or metabolic disorders, infection, autoimmunity, sperm quality, and lifestyle issues (Table 1). Several recommendations have been published (5, 6) regarding the evaluation and management of RPL. These publications do not support definitive conclusions about the causes of RPL because most studies of pregnancy loss have focused on sporadic miscarriage and not RPL. A putative diagnosis will be made and treated in approximately 50% of patients with RPL (7, 8). The following overview acknowledges that our understanding of this field is in flux.

Cytogenetic Abnormalities in Pregnancy Loss

Virtual every published set of recommendations and reviews on this topic agrees that genetic causes should be evaluated and appropriate treatments considered (4–6, 9). Unfortunately, clinical genetic testing remains rudimentary and rarely includes molecular studies which show promise in helping to elucidate mechanisms for RPL. There is a very high frequency of sporadic karyotypic abnormalities in products of conception while the incidence of karyotypic abnormalities in the parents is low.

Of the examined products of conception, approximately 60% of early pregnancy losses are associated with sporadic chromosomal abnormalities, primarily trisomies that are, in part, age related (1, 10, 11). In those losses with a normal karyotype, gross morphological abnormalities in the fetus diagnosed by transcervical embryoscopy have been described in 10% of patients (12). The risk of sporadic miscarriage between 6 and 12 weeks of gestation in women less than 35 years of age is 9% to 12% (13, 14). The risk increases in women over 35 years of age due to the markedly increased incidence of trisomic pregnancies (10). In women older than 40 years of age, the sporadic miscarriage rate approaches 50% (1, 14, 15) (Fig. 1). The risk of aneuploidy at each age is lower in women with RPL than in those who undergo sporadic miscarriages (11).
Thrombophilias in Pregnancy: VTE risks

- Pregnancy is marked by ↑ clotting potential, ↓ fibrinolysis, ↓ anticoagulant activity
  - Thrombotic potential of pregnancy exacerbated by: venous stasis in lower extremities, as well as hormone-mediated ↑s in insulin resistance and hyperlipidemia: **VTE in 1/1600 pregnancies**

- **Strong** association between thrombophilias & VTE
  - Recurrence risk ~10-12% for untreated pregnant women with such a personal hx of VTE and a thrombophilia
    
    *(Brill-Edwards P. NEJM 2000)*

- Controversial (at best) association with adverse pregnancy outcomes

  *ACOG PB # 124, September 2011*
### Prevalences and Risks of VTE with Thrombophilias

<table>
<thead>
<tr>
<th></th>
<th>Prev in Gen Pop %</th>
<th>Lifetime ↑ VTE Risk</th>
<th>% of all VTE</th>
<th>VTE Risk/Preg (No hx) %</th>
<th>VTE Risk/Preg (Prior VTE) %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low-risk thrombophilias</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVL heterozygote</td>
<td>1-15</td>
<td>3-8</td>
<td>40</td>
<td>&lt; 0.3</td>
<td>10</td>
</tr>
<tr>
<td>PTG heterozygote</td>
<td>2-5</td>
<td>3</td>
<td>17</td>
<td>&lt; 0.5</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Protein C activity (&lt;50%)</td>
<td>0.2-0.4</td>
<td>10-15</td>
<td>14</td>
<td>0.1-0.8</td>
<td>4-17</td>
</tr>
<tr>
<td>Protein S free Ag (&lt;55%)**</td>
<td>.03-0.1</td>
<td>2</td>
<td>3</td>
<td>0.1</td>
<td>0-22</td>
</tr>
<tr>
<td><strong>High-risk thrombophilias</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVL homozygote</td>
<td>&lt; 1</td>
<td>2</td>
<td>1.5</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>PTG homozygote</td>
<td>&lt; 1</td>
<td>0.5</td>
<td>2.8</td>
<td>&gt; 17</td>
<td></td>
</tr>
<tr>
<td>FVL/PTG compound</td>
<td>0.01</td>
<td>1-3</td>
<td>4.7</td>
<td>&gt; 20</td>
<td></td>
</tr>
<tr>
<td>Antithrombin III def (&lt;60%)</td>
<td>0.02</td>
<td>25-50</td>
<td>1</td>
<td>3-7</td>
<td>40</td>
</tr>
</tbody>
</table>

** Should not be tested in pregnancy or high-estrogen states.
# Thromboprophylaxis for Pregnancies with Thrombophilias

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Antepartum Management</th>
<th>Postpartum Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk thrombophilia: No personal history of VTE</td>
<td>Surveillance without anticoagulation therapy</td>
<td>Surveillance without anticoagulation therapy or postpartum anticoag if additional risk factors</td>
</tr>
<tr>
<td>Low-risk thrombophilia: 1st degree relative with VTE</td>
<td>Surveillance without anticoagulation therapy</td>
<td>Postpartum prophylactic anticoagulation therapy</td>
</tr>
<tr>
<td>Low-risk thrombophilia: Hx of single episode VTE No long-term anticoagulation</td>
<td>Prophylactic LMWH or UFH (preferred) or surveillance</td>
<td>Postpartum prophylactic anticoagulation therapy</td>
</tr>
<tr>
<td>High-risk thrombophilia: No personal history of VTE</td>
<td>Surveillance or Prophylactic LMWH or UFH</td>
<td>Postpartum prophylactic anticoagulation therapy</td>
</tr>
<tr>
<td>High-risk thrombophilia: Prior VTE in self or 1st-degree No long-term anticoagulation</td>
<td>Prophylactic LMWH or UFH</td>
<td>Postpartum prophylactic anticoagulation therapy</td>
</tr>
<tr>
<td>No thrombophilia but prior single VTE: transient risk factor of pregnancy or E2-related</td>
<td>Prophylactic LMWH or UFH (also if no associated risk factor but not long-term anticoag)</td>
<td>Postpartum prophylactic anticoagulation therapy</td>
</tr>
</tbody>
</table>

BUT.... are thrombophilias and blood clotting the root of all evil?
Can We Extrapolate from Thrombophilias and VTE?

- Diagnosis and prophylaxis against VTE is effective in lowering the risks of primary and recurrent disease.
  - Chemoprophylaxis for thrombophilias (other than APS) is heparin or LMWH, not aspirin (clotting factors, not platelets).

- Regarding adverse pregnancy outcomes:
  - Thrombophilias have been associated with adverse outcomes, including RPL, in retrospective studies.
  - Prospective intervention studies limited.
  - Large prospective studies show no association.
Thrombophilias and Pregnancy Outcomes

Since 1990s, venous prothrombotic factors explored to explain unexplained pregnancy loss and other uterine/placental problems

- First large meta-analysis: Rey R et al, Lancet 2003
  - 31 retrospective studies included, authors note significant heterogeneity

<table>
<thead>
<tr>
<th>Factor</th>
<th>RFL</th>
<th>Studies</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVL</td>
<td>7</td>
<td>2.01 (1.13-3.58)</td>
<td></td>
</tr>
<tr>
<td>NRFL</td>
<td>12</td>
<td>1.73 (1.18-2.54)</td>
<td></td>
</tr>
<tr>
<td>PTG</td>
<td>9</td>
<td>2.05 (1.18-3.54)</td>
<td></td>
</tr>
<tr>
<td>NRFL</td>
<td>5</td>
<td>2.30 (1.09-4.87)</td>
<td></td>
</tr>
<tr>
<td>MTHFR</td>
<td>8</td>
<td>0.98 (0.55-1.72)</td>
<td></td>
</tr>
</tbody>
</table>

- Similar results in subsequent meta-analyses
More Recent Evidence Refutes Association w/APOs

- Larger single studies with more stringent inclusion criteria and enrollment of appropriate controls have diminished or eradicated the association from smaller earlier studies for thrombophilias and adverse pregnancy outcomes (APOs)

  - Case-control study of 311 women with (≥ 2) RPL / 599 controls
  - FVL: 4.8% vs 4.2%; OR 1.16 (0.6-2.2)
  - PTG: 3.2% vs 2.5%; OR 1.29 (0.57-2.9)

  - Large Danish cohort of women with RPL (n = 363)
  - Live birth rates no different in 1st pregnancy after referral for FVL/PTG carriers vs non-carriers

- **Bennett SA, et al. Thrombosis Research 2014**
  - Clotting analyses in women with ≥3 unexplained losses < 14 wks
  - *No evidence of hypercoagulable state in women with unexplained RPL*
Does “Treating” Thrombophilias Improve Outcome?

- Recent review by ACMG: Bradley LA, Genet Med 2012 (Apr)
  - While some association may be present, analysis of data is adequate that anticoagulation is ineffective for this indication (except for APS), and had higher risk of harm

  - Randomized multicenter trial, 207 women with thrombophilia and RPL
  - ASA vs Lovenox/placebo vs ASA/Lovenox
  - No differences in outcomes between groups
Thrombophilias in Pregnancy: Prospective Evaluations

- 2 large prospective multicenter observational cohort studies conducted by NICHD-sponsored MFMU Network
  - 5188 unselected singleton pregnancies; 3.8% PTG (+) /2.7% FVL (+)

- The earlier FVL study was originally conceived as a prospective trial of heparin prophylaxis against VTE for FVL mutation carriers with no other risk factors
  - Since accurate information about VTE risk was found to be lacking in background calculations, study designed to more precisely estimate the true VTE risk among “incidental” mutation carriers

- PTG study was a secondary analysis of the earlier FVL study
  - Only 5 women were compound heterozygotes for FVL/PTG mutations
  - All the VTEs (4/3) in both studies were in nonmutation carriers

*Dizon-Townson D, Obstet Gynecol 2005; Silver RM, Obstet Gynecol 2010*
Table 2. Adverse Pregnancy Outcome in Maternal Carriers of the Factor V Leiden Mutation Compared With Noncarriers

<table>
<thead>
<tr>
<th>Outcome</th>
<th>FVL Carriers</th>
<th>FVL Noncarriers</th>
<th>Relative Risk (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy loss</td>
<td>8/134 (6.0)</td>
<td>264/4,751 (5.6)</td>
<td>1.1 (0.5–2.2)</td>
<td>.84</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>5/134 (3.7)</td>
<td>141/4,751 (3.0)</td>
<td>1.3 (0.4–2.8)</td>
<td>.60</td>
</tr>
<tr>
<td>Abruption</td>
<td>0</td>
<td>31/4,751 (0.7)</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>SGA &lt; 5th percentile*</td>
<td>6/124 (4.8)</td>
<td>173/4,428 (3.9)</td>
<td>1.2 (0.5–2.6)</td>
<td>.64</td>
</tr>
<tr>
<td>SGA &lt; 10th percentile*</td>
<td>10/124 (8.1)</td>
<td>403/4,428 (9.1)</td>
<td>0.9 (0.5–1.7)</td>
<td>.69</td>
</tr>
</tbody>
</table>

FVL, factor V Leiden mutation; CI, confidence interval; SGA, birth weight small for gestational age. Data are presented as n/N (%) or relative risk (95% confidence interval).

*Based on live-born singletons.
<table>
<thead>
<tr>
<th>Condition</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy loss</td>
<td>0.98</td>
<td>0.49–1.95</td>
<td>.951</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>1.30</td>
<td>0.56–3.02</td>
<td>.536</td>
</tr>
<tr>
<td>SGA 5%</td>
<td>1.39</td>
<td>0.67–2.89</td>
<td>.377</td>
</tr>
<tr>
<td>SGA 10%</td>
<td>1.34</td>
<td>0.80–2.25</td>
<td>.267</td>
</tr>
<tr>
<td>Abruption</td>
<td>2.23</td>
<td>0.52–9.58</td>
<td>.280</td>
</tr>
<tr>
<td>Oligohydramnios</td>
<td>1.18</td>
<td>0.57–2.44</td>
<td>.659</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>1.39</td>
<td>0.87–2.21</td>
<td>.165</td>
</tr>
<tr>
<td>GA at delivery</td>
<td>–</td>
<td>–</td>
<td>.941</td>
</tr>
</tbody>
</table>

CI, confidence interval; SGA, small for gestational age; GA, gestational age.

Multivariable analysis adjusted for maternal age, race, parity, prior pregnancy loss, prior SGA neonates, and family history of thromboembolism.

Prothrombin gene G20210A mutation and obstetric complications.
Silver RM; Zhao Y; Spong CY; Sibai B; Wendel G Jr; Wenstrom K; Samuels P; Caritis SN; Sorokin Y; Miodovnik M; OSullivan MJ; Conway D; Wapner RJ; Obstetrics & Gynecology. 115(1):14-20, 2010 Jan.
Testing for Common and “Other” Thrombophilias

- Current available data show no indication for testing for common thrombophilias for a history of recurrent pregnancy loss or other adverse outcomes, and no documented benefit from rx.

- No association with MTHFR polymorphism (heterozygous or homozygous) for any adverse pregnancy outcomes: including RPL and VTE.


- Less common “thrombophilias” have even less data to support either association with APOs or treatment and should not be tested (ACOG PB, 2011).

  - “Promoter mutation” in PAI-1 gene, anti-protein Z Ab’s, “protein Z deficiency”, anti-annexin ab’s.
Antiphospholipid Syndrome

Antiphospholipid syndrome (APS) is an autoimmune disorder defined by the presence of characteristic clinical features and specified levels of circulating antiphospholipid antibodies (Box 1 and Box 2). Diagnosis requires that at least one clinical and one laboratory criterion are met. Because approximately 70% of individuals with APS are female (1), it is reasonably prevalent among women of reproductive age. Antiphospholipid antibodies are a diverse group of antibodies with specificity for binding to negatively charged phospholipids on cell surfaces. Despite the prevalence and clinical significance of APS, there is controversy about the indications for and types of antiphospholipid tests that should be performed in order to diagnose the condition. Much of the debate results from a lack of well-designed and controlled studies on the diagnosis and management of APS. The purpose of this document is to evaluate the data for diagnosis and treatment of APS.

Background

Current evidence suggests that the antigenic determinant for antiphospholipid antibodies that is primarily clinically relevant is β2-glycoprotein I. This glycoprotein is a ubiquitous, multifunctional plasma protein with an affinity for negatively charged phospholipids. It has a regulatory role in coagulation, fibrolysis, and other physiologic systems (2). Antiphospholipid antibodies have been associated with a variety of medical problems, including arterial thrombosis and venous thrombosis, autoimmune thrombocytopenia, and fetal loss (3–8). In addition to fetal loss, several obstetric complications have been associated with antiphospholipid antibodies, including preeclampsia, intrauterine growth restriction, placental insufficiency, and preterm delivery (9, 10).

Antiphospholipid Antibodies

The three antiphospholipid antibodies that contribute to the diagnosis of antiphospholipid syndrome are 1) lupus anticoagulant, 2) anticardiolipin, and 3) anti-β2-glycoprotein I (Box 1). Most experts feel that testing for lupus anticoagulant, which is detected via coagulation assays in plasma, is more specific, but less sensitive than the other two tests (11, 12). Some patients with antiphospholipid syndrome have all three antibodies detected. However, many do not, indicating that the three antibodies are not identical. Thus, the different antiphospholipid antibodies are perhaps best viewed as related but distinctly different immunoglobulins. Because transient positive test results may occur, the diagnosis of APS requires two positive antiphospholipid antibody test results at least 12 weeks apart.

Lupus Anticoagulant

Lupus anticoagulant is present in many individuals without systemic lupus erythematosus and is associated not with anticoagulation but with thrombosis. The presence of lupus anticoagulant is assessed indirectly, and a series of tests are needed for the laboratory diagnosis. The...
Case #3

- 31 year-old G1 P0101
- 1st encounter was at 30+ weeks for in-house consult
  - ↑ BPs 2 weeks before admission
  - Delivered for HELLP syndrome; also IUGR, AEDF
- Labs in-house
  - (-) ACA and B2GP; “borderline” LAC
- Labs 12 weeks after discharge from hospital
  - All labs repeated and all negative
Antiphospholipid Syndrome (APS)

- Autoimmune disorder defined by presence of characteristic clinical features (including RPL) AND specified levels of circulating APL antibodies
  - Despite clinical significance and prevalence of APS, controversy has surrounded indications for and types of tests for diagnosis

- Primary clinically relevant antigenic determinant for APL antibodies is β-glycoprotein I
  -Ubiquitous, multifunctional plasma protein with a regulatory role in coagulation, fibrinolysis, and other physiologic systems

ACOG PB # 111, January 2011
Testing for APS

- Most recent criteria for APS based on 2006 consensus statement, affirmed by 13th Intl. Congress on APL Antibodies (April 2010)
  - Only the 3 APL antibodies endorsed (LAC, ACA, anti-β2GP) can and should be used to establish a diagnosis
- Some laboratories offer testing, often in a broad panel of tests, for other APL and autoimmune antibodies
- Results from such additional assays do little to improve the accuracy of diagnosing APS and testing for them is not recommended

Antiphospholipid (aPL) antibody syndrome: Diagnosis


**Clinical criteria**

1. Vascular thrombosis: One or more episodes of arterial, venous, or small vessel thrombosis in any tissue or organ

2. Morbidity in pregnancy

   One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation

   One or more premature births of a morphologically normal neonate prior to the 34th week of gestation secondary to eclampsia or severe pre-eclampsia or recognized features of placental insufficiency

   Three or more unexplained consecutive spontaneous miscarriages before the 10th week of gestation

**Laboratory criteria** (Must be present on 2 or more occasions at least 12 weeks apart)

1. Lupus anticoagulant present

2. Anticardiolipin antibody OR Anti-β2-glycoprotein: medium or high titer of IgG or IgM isotype (>40 μg of IgG or IgM phospholipid or >99th percentile)
Medical Complications of APS

- Most common and serious: venous and arterial thromboses
  - 70% are venous, in any blood vessel in body
  - Thrombosis recurrence risk 25%/yr in untreated pts
  - Increased risk of thrombosis in pregnancy (25% occur in pregnant women)\(^1\): prospective studies, 5-12% VTE risk\(^2\)
  - Arterial thromboses: unusual sites (retinal) and stroke/TIA
    - APL ab’s in 4-6% of otherwise healthy pts w/stroke < age 50\(^3\)

- Obstetric complications
  - IUFD/Recurrent Pregnancy Loss
  - Preeclampsia, esp. severe preterm (< 34 weeks)
    - Study of > 1000 women with APL had ↑ risk of both preeclampsia (OR 5.5) and severe preeclampsia (OR 8.1)\(^4\)
  - IUGR

Specific Impact of Lupus Anticoagulant

- Positive test for LAC is a stronger risk factor for thrombosis and adverse pregnancy outcomes after 12 weeks than (+) results for ACA or B2GP\(^1\)\(^{-3}\)

- Case-control study of risk factors for stroke among women in general population < age 50 \(^4\),\(^5\)
  - 17% of stroke patients vs 0.7% of controls (+) for LAC (OR 43.1)
  - Risk increased by use of OCs (OR 201.0) or smoking (OR 87.0)

Physiologic Rationale for Obstetric APS Therapy

- **Aspirin**
  - APL antibodies against β2GPI activate platelets → synthesis of thromboxane A2
  - ASA shown to ↓ placental thromboxane production in vitro and in women with RPL  
    *(Peaceman AM, AJOG 1993, Obst Gynecol 1995)*

- **Heparin**
  - Targets inflammatory reaction from interaction of APL and cellular binding
  - Impacts complement activation pathways (more than anticoagulant effect  
  - In vitro: attenuates APL-mediated trophoblast apoptosis

- **Initial treatment studies (1980s)**
  - ASA/heparin alone, small series, poorly-defined criteria and controls: largest study (1988), 42 pts, open-label ASA, 88% v 10% live vs hx
APS Treatment Trials

- **Majority opinion: ASA + Heparin**
    - 90 women with RPL (median # losses = 4) and (+) APL
    - All started ASA with (+) HCG, random allocation to UFH (5000 U BID) when +FHM on scan. Endpoint live ≥ 34 wks (or Sab)
    - Live birth rate ↑ with ASA/heparin: 71% v 42% (OR 3.4; 1.4-8.1)
  - Kutteh WH. AJOG 1996
    - Similar protocol and rates: 80% v 44%
  - Subsequent meta-analyses confirmed superiority of ASA + heparin over ASA alone (Ziakis PD, Obst Gynec 2010; Empson M, Cochrane 2005)

- **Best type of heparin: UFH vs LMWH?**
  - Majority of studies suggest LMWH equivalent to (Noble et al, Fertil Steril 2005, Laskin CA, J Rheum 2009) or superior to UFH (Stephenson, J ObGyn Can 2004) for treatment of APS
What *Doesn’t* Work for APS

- The range of immunomodulatory agents used to treat RPL in conjunction with (or without) APL have shown **no benefit at best**, and inferior outcomes at worst, when used with or instead of ASA and heparin.

- Prednisone – poorer outcomes
  - Prednisone + ASA vs placebo (RCT, n = 66)
    - No differences in live birth rates *(Laskin CA, NEJM 1997)*
    - ↑ rates of prematurity (62% v 12%, p < 0.001), HTN (13% v 5%) and diabetes (15% v 5%) in treatment group
  - In Cochrane analysis, prednisone and ASA also associated with higher rates of PTD (PPROM) and GDM compared to: (1) placebo, (2) ASA alone, and (3) ASA/heparin *(Empson et al, Cochrane 2005)*
Empiric Therapy for RPL without APS?  *(Hint: No)*

- **SPIN Study (Scotland)**
  - 294 women with ≥ 2 consecutive unexplained losses (> 10 and < 24 weeks); APL & thrombophilia (-)
  - Randomized to LMWH/ASA vs surveillance
  - Pregnancy loss rates equivalent: 22% v 20%, OR 0.91 (0.52-1.59)  *(Clark P, et al. Blood 2010)*

- **Dutch Trial (NEJM 2010)**
  - 364 women with ≥ 2 unexplained losses < 20 weeks
  - Randomized to: (1) ASA, (2) ASA/LMWH, (3) placebo
  - No treatment arm improved live-birth rates compared to placebo  *(Kaandorp SP, et al. NEJM 2010)*
### Table 2. Live-Birth Rate (Primary Outcome).*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Aspirin plus N.</th>
<th>Aspirin Only</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention-to-treat population</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>123</td>
<td>120</td>
<td>121</td>
<td></td>
</tr>
<tr>
<td>Live birth — no. (%)</td>
<td>67 (54.5)</td>
<td>61 (50.8)</td>
<td>69 (57.0)</td>
<td>0.63</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>0.96 (0.76 to 1.19)</td>
<td>0.89 (0.71 to 1.13)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Absolute difference in live-birth rate (95% CI) — %</td>
<td>−2.6 (−15.0 to 9.9)</td>
<td>−6.2 (−18.8 to 6.4)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Women who became pregnant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>97</td>
<td>99</td>
<td>103</td>
<td></td>
</tr>
<tr>
<td>Live birth — no. (%)</td>
<td>67 (69.1)</td>
<td>61 (61.6)</td>
<td>69 (67.0)</td>
<td>0.52</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>1.03 (0.85 to 1.25)</td>
<td>0.92 (0.75 to 1.13)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Absolute difference in live-birth rate (95% CI) — %</td>
<td>2.1 (−10.8 to 15.0)</td>
<td>−5.4 (−18.6 to 7.8)</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

* Absolute differences and relative risks were calculated for the comparison between patients receiving aspirin plus nadroparin (combination-therapy group) and the placebo group and between the aspirin-only group and the placebo group. P values are for all comparisons. CI denotes confidence interval.
Prior Losses and Preconception ASA?

- Commonly used with IVF despite meta-analyses showing no impact on pregnancy or livebirth rates
  
  Siristatidis CS, Cochrane 2011; Groevenfeld E, Hum Reprod Update 2011

- Recent NICHD-sponsored RPCT in women with 1-2 prior losses

- ASA (or placebo) given daily until completion of 6 cycles or 36 weeks gestation

- Slow enrollment led to “expansion” of criteria
  - 1 or 2 losses (from 1); loss > 20 weeks (from <20); losses > 1 yr before enrollment; up to 2 liveborn

- Primary outcome was livebirth
  - No differences for ASA in either overall or the sub-strata groups
  - No difference in pregnancy loss rates in any group

Effectiveness of Intravenous Immunoglobulin (IVIG) Therapy in Treatment of Recurrent Pregnancy Loss or Miscarriage

Recurrent pregnancy loss or miscarriage is often a sign of an underlying fertility problem. Depending on the cause of frequent miscarriages, fertility treatment may improve your chances of conceiving after a miscarriage & to help you maintain a positive and successful pregnancy to term.

Intravenous immunoglobulin (IVIG) is a treatment option for those who experience recurrent pregnancy loss due to autoimmune problems. It happens when your body's immune system becomes hostile to the embryo or fetus, mistaking it for a foreign body. There are many studies suggesting why IVIG therapy may work, but the exact mechanism of action is not entirely clear. It is thought that by receiving immunoglobulins in the form of a transfusion, the amount of natural killer (NK) cells in the woman's body are reduced, and/or antibodies that cause the body to attack the pregnancy might be absorbed or blocked. Thus, a woman's immune system is repressed to possibly allow embryos to implant following embryo transfer.

How often do you have to take IVIG during pregnancy?

The dosage and timing of the therapy varies by what is being treated. For those patients that are having in vitro fertilization (IVF) and have issues with NK cells and/or other harmful antibody-related issues, the IVIG is usually given 10 days before the IVF procedure. IVIG is repeated since again after the pregnancy is confirmed. For those patients attempting natural impregnation that have NK cell and/or other harmful antibody-related issues, the IVIG is usually dosed before the before the natural impregnation is attempted, then repeated again after pregnancy is confirmed. After this, most centers give further repeated doses throughout the pregnancy, but the frequency of these doses varies widely from center to center.

Are there any harmful effects of IVIG on unborn baby?

According to the FDA, IVIG falls under Pregnancy Category C which means that it is not known whether immune globulin will harm an unborn baby. The FDA Pregnancy Category C states that "Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks." One characteristic of the FDA definitions of the pregnancy categories is that the FDA requires a relatively large amount of data on a pharmaceutical for it to be defined as pregnancy category A or even Category B. Additionally, since IVIG is not FDA approved for the treatment of recurrent pregnancy loss and that there is the likelihood of significant legal cases that could result from any widespread study of IVIG impact on newborns when the IVIG was used for infertility in the mother all lead to the current status of IVIG being listed as a category C, which is where most drugs end up if there is not an exceptional amount of data to move them to Categories A or B.

Does health insurance pay for IVIG therapy for recurrent pregnancy loss?

Since there is not enough clinical data to show effectiveness of IVIG treatment in prevention of recurrent pregnancy loss, most insurance companies consider IVIG therapy as experimental and investigational and therefore do not cover the cost of the IVIG nor the nursing visits needed to infuse the drug. For those patients wishing to pay cash for the IVIG therapy for infertility treatment in the home, the costs can range from $5,000 to $20,000 per course of treatment (i.e., 35 grams of IVIG given at home daily for 5 days in a row might cost $17,000 with Drug, Nursing and IV supplies).

To talk to an expert of IVIG Infusion therapy call:

1-877-577-IVIG (4844)
IVIG and RPL

- Proposed on basis of direct antibody effects and role for immunomodulation
- Majority of use data from uncontrolled and/or retrospective open-label series
- One large multicenter RPCT (Stephenson MD, Human Reprod 2010)
  - 47 women with ≥ 3 unexplained losses, IVIG vs saline q14-21 days preconception then q4 wks until 20 wks
  - Live birth rates equivalent: 70% v 63%, OR 1.4 (0.4-4.6)
  - For pregnancies with (+) FHM @ 6 wks: 94% both arms
  - 6 RCTs included, OR live birth for IVIG 0.9 (0.55-1.54)
A systematic review of intravenous immunoglobulin for treatment of unexplained recurrent miscarriage

Fertility and Sterility Volume 95, Issue 3 2011 1080 - 1085.e2

http://dx.doi.org/10.1016/j.fertnstert.2010.12.021
A  
**Primary recurrent miscarriage**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>IVIG Events Total</th>
<th>Control Events Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>German RSA/IVIG 1994</td>
<td>20 33</td>
<td>21 31</td>
<td>48.2%</td>
<td>0.73 [0.26, 2.05]</td>
</tr>
<tr>
<td>Jablonowska 1999</td>
<td>9 11</td>
<td>8 9</td>
<td>9.0%</td>
<td>0.56 [0.04, 7.44]</td>
</tr>
<tr>
<td>Perino 1997</td>
<td>16 22</td>
<td>20 24</td>
<td>29.5%</td>
<td>0.83 [0.13, 2.22]</td>
</tr>
<tr>
<td>Stephenson 1998</td>
<td>4 8</td>
<td>5 9</td>
<td>13.3%</td>
<td>0.80 [0.12, 5.40]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>49 74</td>
<td>54</td>
<td>100.0%</td>
<td>0.67 [0.32, 1.39]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 0.18$, df = 3; $I^2 = 0\%$
Test for overall effect: $Z = 1.08$

B  
**Secondary recurrent miscarriage**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>IVIG Events Total</th>
<th>Control Events Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jablonowska 1999</td>
<td>8 11</td>
<td>7 10</td>
<td>22.7%</td>
<td>1.14 [0.17, 7.60]</td>
</tr>
<tr>
<td>Stephenson 1998</td>
<td>5 10</td>
<td>4 7</td>
<td>26.7%</td>
<td>0.75 [0.11, 5.24]</td>
</tr>
<tr>
<td>Stephenson 2010</td>
<td>16 23</td>
<td>15 24</td>
<td>50.7%</td>
<td>1.37 [0.41, 4.61]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>44 41</td>
<td>29</td>
<td>100.0%</td>
<td>1.15 [0.47, 2.84]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 0.27$, df = 2; $I^2 = 0\%$
Test for overall effect: $Z = 0.31$

Figure 2  Live birth rates stratified by type of miscarriage. (A) Primary recurrent miscarriage. (B) Secondary recurrent miscarriage.

Baris Ata, Seang Lin Tan, Fady Shehata, Hananel Holzer, William Buckett

**A systematic review of intravenous immunoglobulin for treatment of unexplained recurrent miscarriage**

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Natural Killer Cells and RPL?

- Some studies suggest differences in peripheral blood NK cell levels in women with RPL.
  - Based on uterine/endometrial NK cell data with RPL (Quenby S, et al, Hum Reprod 2002).

- However, both phenotypic and functional differences exist between uterine and peripheral NK cells.
  - Data demonstrate that peripheral blood NK testing gives no useful info on uterine NK cells (Moffett A, et al. BMJ 2004).
Natural Killer Cells and RPL? (2)

- Recent retrospective cohort study (Kitano K, Fert Steril, 12/13)
  - 1127 pts with 2 or more consecutive miscarriages
    - 180 excluded for identifiable causes, including 33 with APS
    - 323 excluded for having received any treatment
  - For 552 pts with unexplained RPL, no rx, pNK studied
    - Subsequent miscarriage rate was 22.5%
    - LB rate was 81% with 2 prior Sab, 71% with 3, 65% with 4
  - In multivariable logistic regression, elevated pNK activity not an independent risk factor for subsequent miscarriage
    - Plasma NK activity did show weak inverse correlation with age

- Testing of “NK cell profiles” should not be performed routinely in evaluation of miscarriage in general and RPL in particular 1-4

4. Wold & Arici, Cur Opin Ob Gyn 2005
Newer Thoughts on Immunity and RPL

- Goal for therapies may be to *enhance tolerance* rather than to suppress maternal immune system
  - Peripheral (extrathymic) regulatory T cells (pTregs) respond specifically to paternal antigens to induce maternal-fetal tolerance
  - Experiments in mice show that pregnancy-induced pTregs suppress *effector* T cells
    - Genetically-altered mice unable to induce pTregs: in pregnancy, activated Tcells infiltrate placenta→Sab

Willams Z, et al. NEJM 2012*
Summary (1)

- Recurrent pregnancy loss (RPL) is a specific and clinically-focused diagnosis: at least 2 embryonic losses at > 9-10 weeks.
- Common hereditary thrombophilias are not contributors to RPL (or other adverse pregnancy outcomes) and should not be tested for in this context.
- MTHFR mutation testing is not indicated for any obstetric or non-obstetric risk histories.
Antiphospholipid syndrome (APS) is a real diagnosis based on clinical and lab criteria, and warrants treatment during pregnancy.

ASA/heparin regimens are the only evidence-validated treatment for APS.

Prednisone, IVIG, and other unproven immune modulators have not been shown to have benefit for RPL in well-conducted trials and may be detrimental.

NK cell testing is not validated for screening in RPL, outside of research protocols.