به نام خدا
Recurrent Early Pregnancy Loss

Three or more (not necessarily consecutive) spontaneous miscarriages.

clinical investigation and treatment in two consecutive spontaneous miscarriages:

- Embryonic heart activity observed before any earlier pregnancy loss.
- Normal karyotype on products of conception from an earlier loss.
- Female partner age over 35 years.
- Infertility.
The Risk of Recurrent Early Pregnancy Loss in Young Women

<table>
<thead>
<tr>
<th>Number of Prior Miscarriages</th>
<th>% Risk of Miscarriage in Next Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women who have had at least one liveborn infant</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>24%</td>
</tr>
<tr>
<td>2</td>
<td>26%</td>
</tr>
<tr>
<td>3</td>
<td>32%</td>
</tr>
<tr>
<td>4</td>
<td>26%</td>
</tr>
<tr>
<td>6</td>
<td>53%</td>
</tr>
<tr>
<td>Women who have not had at least one liveborn infant</td>
<td>2 or more</td>
</tr>
</tbody>
</table>
The risk of clinically recognized spontaneous miscarriage:

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Risk Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>before age 30</td>
<td>7–15%</td>
</tr>
<tr>
<td>aged 30–34</td>
<td>8–21%</td>
</tr>
<tr>
<td>aged 35–39</td>
<td>17–28%</td>
</tr>
<tr>
<td>age 40 and older</td>
<td>34–52%</td>
</tr>
</tbody>
</table>
the prognostic value of embryonic heart activity and risk for subsequent loss

- age 35 and under: < 5%
- ages 36–39: 10%
- age 40 and over: 29%
- histories of recurrent pregnancy loss: 15–25%
Factors related to recurrent pregnancy loss

- Genetic Factors
- Anatomic Factors
- Immunologic Factors
- Inherited Thrombophilias
- Endocrine Factors
- Infectious Causes
- Environmental Factors
Genetic Factors

- 50-75% of spontaneous miscarriages result from numerical chromosomal abnormalities in the embryo or fetus and occur by chance.
- Trisomies are the most common.
- 5% of couples with recurrent pregnancy loss, karyotypes will reveal a balanced chromosomal translocation.
Aging and Gamete Aneuploidy

aneuploid oocytes is

before age 35 less than 10%

by age 40 30%

by age 43 50%

after age 45 nearly 100%
Women with a demonstrated low ovarian reserve have an extremely high rate of pregnancy loss and Down syndrome regardless of age and regardless of whether the low ovarian reserve came about naturally or resulted from ovarian surgery.
IVF with preimplantation genetic diagnosis (using FISH) for reasons of advanced maternal age or in couples with unexplained recurrent pregnancy loss can increase implantation rates and decrease miscarriage risk, but have not increased live birth rates. Consequently, the associated costs in couples without other specific indications for IVF cannot be justified.
Anatomic Factors

- Congenital Uterine Malformations
- Uterine Leiomyomas
- Intrauterine Adhesions (Asherman’s Syndrome)
Congenital Uterine Malformations (6-7%)

- unicornuate uterus
- Uterine didelphys
- bicornuate uterus
- septate uterus
- Developmental uterine abnormality related to in utero DES-exposed women
Uterine Leiomyomas

only submucous myomas and larger intramural fibroids that clearly encroach upon or displace the uterine cavity are relevant
Intrauterine Adhesions (Asherman’s Syndrome)

pregnancy outcomes are generally poor (40-80% ending in spontaneous miscarriage and approximately 25% in preterm delivery) and much improved after hysteroscopic lysis (50-90% ending in term delivery, 7-23% ending in miscarriage)
Immunologic Factors

- Autoimmune disorders
  - systemic lupus erythematosus
  - antiphospholipid syndrome
- Alloimmune disorders
Antiphospholipid syndrome

**DIAGNOSIS REQUIRES ONE OF THE CLINICAL CRITERIA AND ONE OF THE LABORATORY FINDINGS**

prevalence of antiphospholipid syndrome among all women with recurrent pregnancy loss is quite low (3-5%)
Antiphospholipid Syndrome
Clinical Criteria:

1. Vascular Thrombosis

2. Pregnancy Morbidity
   
   A. One or more losses after the 10th week of a morphologically normal fetus.

   B. One or more premature births of a normal neonate before the 34th week because of preeclampsia or eclampsia or placental insufficiency.

   C. Three or more unexplained consecutive early miscarriages
Antiphospholipid Syndrome laboratory Tests:

1. Lupus anticoagulant present on two or more occasions at least 12 weeks apart.
2. Anticardiolipin antibody of IgG or IgM isotype in medium to high titer on two or more occasions at least 12 weeks apart.
3. Anti-b2-glycoprotein 1 antibody of IgG or IgM isotype in 99th percentile titer on two or more occasions at least 12 weeks apart.
Antiphospholipid Syndrome
Treatment

combined treatment regimen includes aspirin
(75-85 mg/day), beginning with attempts at conception and unfractionated heparin (5,000-10,000 subcutaneous twice daily) beginning at first indication of pregnancy
Inherited Thrombophilias

Selected screening for the most common abnormalities in women with otherwise unexplained recurrent pregnancy loss with a suspicious loss after 8 weeks’ gestation or after detection of fetal heart activity is reasonable

but routine screening of all women with recurrent pregnancy loss cannot be justified
Thrombophilias Evaluation

- Factor V Leiden
- Prothrombin Gene Mutation
- Activated Protein C Resistance
- Homocysteine
- Protein C
- Protein S
- Antithrombin III
Endocrine Factors

- Hypothyroidism
- Diabetes Mellitus
- Polycystic Ovary Syndrome
- Luteal Phase Deficiency
Infectious Causes

Routine serologic testing, cervical cultures, and endometrial biopsy cannot be justified.

Evaluation should be limited to women with clinical cervicitis, chronic or recurrent bacterial vaginosis, or other symptoms of pelvic infection.

Empiric antibiotic treatment in women suspected of harboring a genital mycoplasma infection is less costly and less complicated than serial cultures.
Environmental Factors

Smoking    alcohol    heavy coffee    Isotretinoin
BMI equal to or greater than 25

Anesthetic gases
perchlorethylene (a dry cleaning solvent),
other organic solvents
exposure to heavy metals
(mercury, lead)
painters and factory workers
Not associated with an increased incidence of spontaneous miscarriage

- Exposure to video terminals
- Exercise program
- Dental assistants
- Laboratory or gardening workers
- Use of electric blankets and heated water beds
Unexplained Recurrent Pregnancy Loss

- more than half of all women with recurrent pregnancy loss
- 70-75% of women with unexplained recurrent pregnancy loss ultimately achieve a successful pregnancy
- Careful monitoring is warranted because women with recurrent pregnancy loss are also at increased risk for ectopic pregnancy
- Empiric treatments with exogenous progesterone or aspirin in women with unexplained recurrent pregnancy loss have no proven value
Summary of Evaluation and Treatment for Recurrent Pregnancy Loss

As a quick reference, the following table summarizes our recommended evaluation and treatments for factors known to predispose to recurrent pregnancy loss. *Established tests and treatments are shown in bold type. Tests and treatments that must be applied selectively and those not yet firmly established are shown in standard type.*

<table>
<thead>
<tr>
<th>Category</th>
<th>Evaluation</th>
<th>Treatments</th>
</tr>
</thead>
</table>
| Genetic      | Karyotype, both partners  
Ovarian reserve test  
Comparative genomic hybridization | Counseling  
Donor gametes where appropriate  
Preimplantation genetic diagnosis |
| Anatomic     | Sonohysterography or HSG  
Magnetic resonance imaging  
IVP or renal ultrasound | Hysteroscopic septoplasty  
Hysteroscopic myomectomy  
Hysteroscopic adhesiolysis  
Abdominal metroplasty  
Abdominal myomectomy  
Cervical cerclage |
| Immunologic  | Lupus Anticoagulant  
Anticardiolipin Antibody  
Anti-β2-glycoprotein 1 Antibody | Aspirin and Heparin |
| Thrombophilias | Factor V Leiden  
Prothrombin Gene Mutation  
Activated Protein C Resistance  
Homocysteine  
Protein C  
Protein S  
Antithrombin III | Heparin |
| Endocrine    | TSH  
Luteal Phase Duration  
Blood Glucose, Hgb A1c  
Prolactin | Thyroxine  
Clomiphene citrate  
Metformin  
Dopamine agonists |
| Infectious   | As indicated by symptoms | Empiric antibiotics |
| Environmental | History | Behavior modification |