Recurrent miscarriages

definitions

- **Miscarriage:**
- loss of viable uterine pregnancy prior to 24 week
  - early: ≤ 12 weeks
  - late : 13-24 weeks.
- Clinically presented as uterine bleeding and pelvic cramping
- Most common cause is chromosomal abnormalities

definitions

- Recurrent pregnancy loss:
  - Two or more failed clinical pregnancies as documented by ultrasonography or histopathologic examination.
  - Three consecutive pregnancy losses, which are not required to be intrauterine
  - The majority of RPL has no identified cause

- Incidence: 15% of pregnant women loss their pregnancies, 2% experience two consecutive pregnancy losses, just 1 percent have three consecutive pregnancy losses

Etiology … General Maternal Factors

➢ Medical disorders

- Diabetes mellitus, hypothyroidism, systemic lupus erythematosus (SLE), pcos and hyperprolactinemia are
- Up to 40% of clinical pregnancies are lost in women with SLE

➢ Maternal age

- increased incidence of chromosome abnormally fetuses in older women.
- If a live fetus is demonstrated by ultra-Sonography at 8 weeks' gestational age,

✓ fewer than 2% when the mother is younger than 30 years of age.

✓ exceeds 10% when the mother is older than 40 years.

✓ the risk may be as high as 50% at age 45 years

- Advanced paternal age has also been identified as a risk factor for miscarriage

Etiology … General Maternal Factors

- **Infections**
  - Mycoplasma, Listeria, Or Toxoplasma
- **Smoking and alcohol**
  - Associated with an incidence of chromosomally abnormal abortions
- **Psychological stress**
  - Domestic violence and other forms of stress are associated with a greater risk of pregnancy complications such as spontaneous abortion, preterm birth, and low birth weight

Etiology… local maternal factors

- Cervical incompetence
  - defined as recurrent painless cervical dilation leading to second-trimester pregnancy losses
  - usually the result of trauma (mechanical dilation of the cervix at the time of termination of pregnancy diagnostic curettage, assisted labor)
  - The diagnosis of cervical incompetence is usually made when a mid-trimester pregnancy is lost with a clinical picture of sudden unexpected rupture of the membranes, followed by painless expulsion of the product of conception.

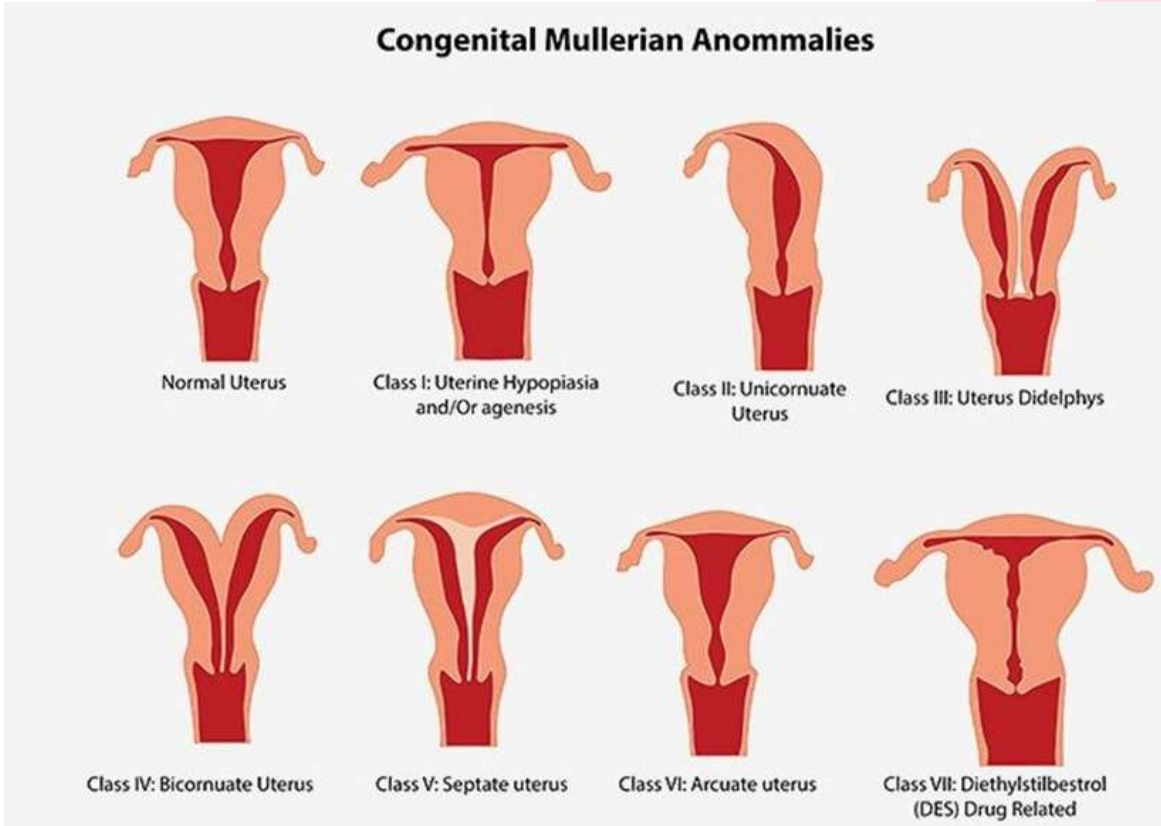
Etiology… local maternal factors

- Cervical incompetence
  - Physical examination showing advanced cervical dilation and/or effacement in the absence of labor
  - ultrasonography of the cervix indicating funneling or shortness of the cervix or widening of the lower uterine segment .
  - exclusion of relevant other diagnoses
  - Management: cerclage placement at 12 to 14 weeks of gestation in patients with recurrent (more than one) second-trimester losses preceded by painless cervical dilatation

Etiology… local maternal factors

- ➢ Congenital abnormal uterus
- septate uterus is the most common uterine abnormality associated with RPL
- Associated with pregnancy loss in both the first and the second trimesters.
- It has been reported that women with arcuate uteri tend to miscarry more in the second trimester while women with septate uteri are more likely to miscarry in the first trimester
- Evaluation: laparoscopic, hysteroscopic, and hysterographic examination
- Management: surgical repair
- There's a study showed that repair of bicornuate and septate uteri reduced the abortion rate from 84 percent (before surgery) to 12 percent (after surgery)
- ➢ Acquired abnormal uterus
- Leiomyoma, Adenomyosis and Intrauterine adhesions
- Most common cause sub mucous fibroids.

Congenital Mullerian Anommalies



Etiology… local maternal factors

- Defective endometrial receptivity
- Normal endometrial receptivity allows embryo attachment, implantation, invasion, and development of the placenta
- These processes are likely to be disturbed resulting in unexplained infertility and RPL
- research suggests that RPL is associated with uterine stem cell deficiency which then results in abnormal endometrial preparation for pregnancy

Etiology… fetal factors

- The most common cause of spontaneous abortion is a significant genetic abnormality of the conceptus.
- In spontaneous first-trimester abortions, approximately two-thirds of fetuses have significant chromosomal anomalies, with approximately half of these being autosomal trisomies.
- Fortunately, the majority of these are not inherited from either mother or father and are single nonrecurring events.
- When seen on ultrasonography before spontaneous abortion, many such pregnancies appear to consist of an empty gestational sac.

Etiology… Immunological factors

- **Antiphospholipid syndrome**
- is a systemic autoimmune disorder characterized by venous or arterial thrombosis and/or pregnancy loss in the presence of persistent expression of antiphospholipid antibodies.
- 15% of RPL cases.
- characterized by the presence of both clinical and laboratory findings

Diagnostic criteria of
ANTIPHOSPHOLIPID SYNDROME

≥1 clinical criteria + **≥1 laboratory criteria**

CLINICAL CRITERIA:

1. **≥1 arterial, venous, or small-vessel thrombosis event of any organ** (excluding superficial venous thrombosis)

2. **Pregnancy morbidity (A, B or C):**

   A. ≥1 unexplained fetal death of a morphologically normal fetus at ≥10 weeks' gestation

   B. ≥1 premature birth before 34 weeks' gestation due to eclampsia, severe pre-eclampsia, or placental insufficiency

   C. ≥3 consecutive spontaneous abortions before the 10th week of gestation (in the absence of anatomic, hormonal, or chromosomal causes)

LABORATORY CRITERIA:

1. **Lupus anticoagulant positivity** on ≥2 occasions ≥12 weeks apart

2. **IgG or IgM anticardiolipin antibodies in moderate or high titers** (>40 GPL units or >99th percentile) measured by standard ELISA on ≥2 occasions ≥12 weeks apart

3. **IgG or IgM anti-beta-2-glycoprotein I antibody in moderate or high titers** (>99th percentile) measured by standard ELISA on ≥2 occasions ≥2 weeks apart

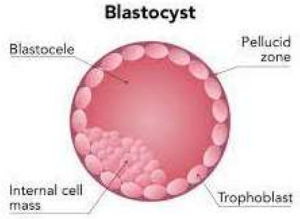
Etiology… Immunological factors

- ➢ Antiphospholipid syndrome
- Complications:
  - ✓ unexplained fetal demise after 10 weeks' gestation
  - ✓ preterm delivery before 34 weeks' gestation due to severe preeclampsia or placental insufficiency
  - ✓ recurrent miscarriages before 10 weeks' gestation
- Management: prophylactic low-molecular-weight heparin and low-dose aspirin (81 mg), unless there is a history of thrombosis, in which case a full dosage of anticoagulants is indicated

Etiology… Immunological factors

➢ Other immunological factors

- Allogeneic factors may cause RPL by a mechanism similar to that of graft rejection in transplant recipients
- f the blastocyst is developmentally normal, the embryo should be entirely protected by trophoblast cells.
- in some pregnancies, the blastocyst is genetically deformed and not fully intact. As a result, paternally-derived antigens are exposed to the maternal immune system, which leads to a graft rejection response



Etiology… others

- Placental factors
- Thrombophilia and fibrinolytic factors:

• Thrombosis of spiral arteries and the intervillous space on the maternal side of the placenta can impair adequate placental perfusion. The resulting abnormalities of the uteroplacental circulation may cause late fetal loss, intrauterine growth restriction, placental abruption, or preeclampsia

Approach

History taking

❖ Detailed history should be taken and must include :

- All the details of previous pregnancy losses, including:
  - The gestational age of prior pregnancy loss, and characteristics (eg, anembryonic pregnancy, live embryo) .
  - What information is available from previous laboratory, pathology, and imaging studies ?
  - The method of treatment of previous pregnancy loss.

History taking

- full medical and surgical history(thyroid problems, diabetes).
- menstrual history.
- Family and personal history of (venous and arterial thrombosis), (a history of congenital abnormalities or karyotypic abnormalities).
- Social history (smoking, alcohol, drugs, and exposure to environmental toxins)

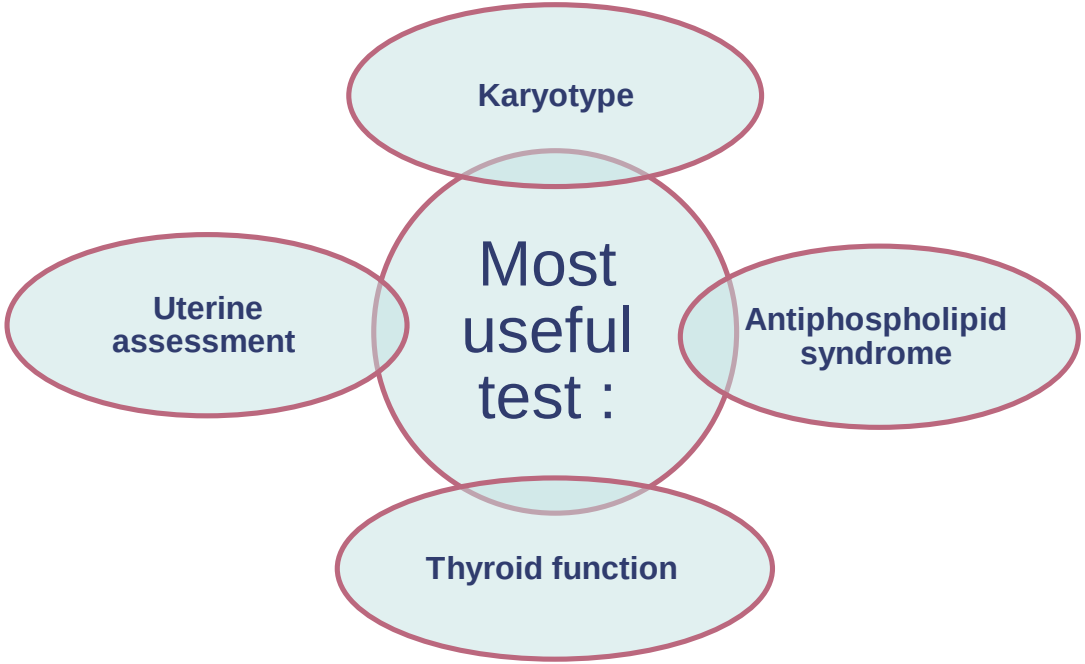
Physical examination

- Physical examination should include a :

- detailed general exam.
- and pelvic exam , for pelvic organ abnormalities (eg, uterine malformation, cervical laceration and polyps).

EVALUATION

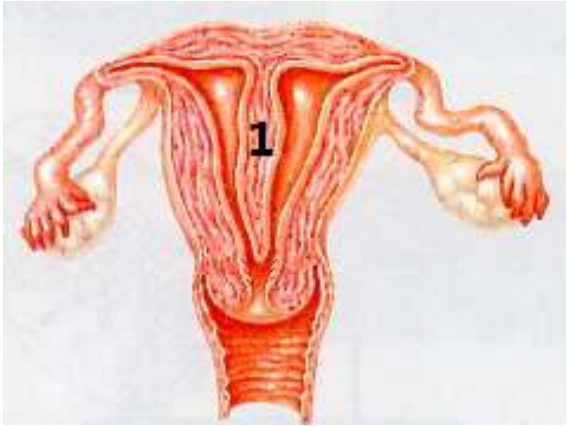
- We take a step-wise approach to the evaluation of individuals with RPL.



EVALUATION

- Karyotype – for both of the parents.
- Uterine assessment – Anatomic causes of RPL are typically diagnosed using hysterosalpingography (HSG) or sonohysterography.

- Methods of imaging can be used :
- (Sonohysterography , Hysterosalpingogram , Hysteroscopy , Ultrasound , Magnetic resonance imaging)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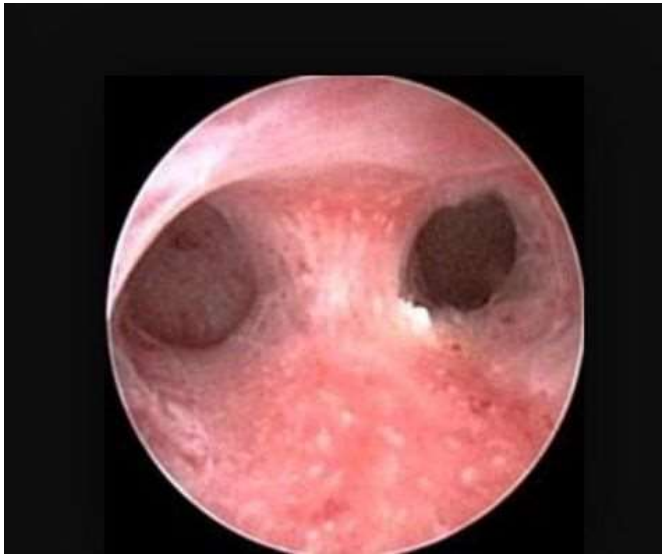

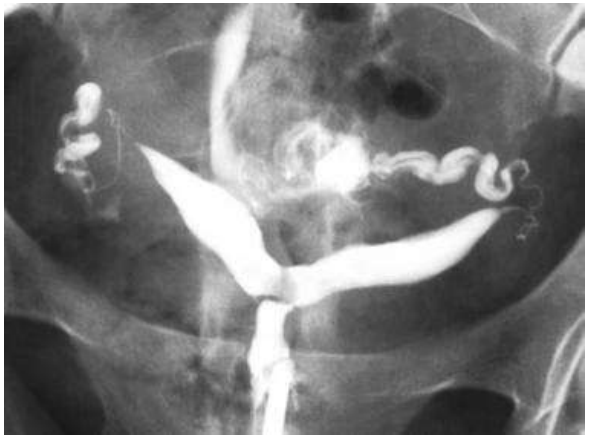

EVALUATION

- Antiphospholipid syndrome – The minimum immunology work-up for women with RPL is measurement of anticardiolipin antibody (IgG and IgM) and lupus anticoagulant. Diagnosis of antiphospholipid antibody syndrome includes testing for anti-beta2 glycoprotein I antibodies as well as anticardiolipin antibody and lupus anticoagulant.

- Thyroid function – Thyroid function should be assessed in women with clinical manifestations or a personal history of thyroid disease. Screening asymptomatic women for subclinical thyroid dysfunction is controversial .

EVALUATION

- Less useful tests :
  - Evaluation of ovarian reserve .
  - Hypercoagulable state .
  - Culture and serology .
  - Autoantibodies and immune function .
  - Screening for diabetes .
  - Progesterone level .
  - Endometrial biopsy .

- ~~Male contribution to RPL is still unclear.~~

management

- treat the underlying cause
- Over half of couples with recurrent losses will have normal findings during the standard evaluation.

❑ TREATMENT OPTIONS FOR UNEXPLAINED RECURRENT PREGNANCY LOSS

✓ Lifestyle modification:

- eliminating use of tobacco products, alcohol, and caffeine and reduction in body mass index (for obese women).

✓ Human menopausal gonadotropin

- The mechanism may be correction of a luteal phase defect or stimulation of a thicker endometrium, thus leading to a better implantation site.

✓ In vitro fertilization and preimplantation genetic diagnosis

Case scenario

- Ms. Villanova, a 29yo G3P0030 woman presents as a new patient desiring an answer for why she had three miscarriages.
- She is nervous to attempt to conceive for fear of another miscarriage

FOCUSED HISTORY

What elements of the patient's history are most relevant?

- **PMH:** Denies
- **PSH:** D&C x3 for MAB
- **POBH:** History of three first trimester SAB, all confirmed IUP on ultrasound. D&C x3. No additional assessments
- **PGYNH:** Regular menses Q28 days lasting 5 days. Denies history of STIs or abnormal paps. Up to date on pap. Last STI screening 6 months ago. Sexually active with mutually monogamous male partner for 5 years
- **MEDS:** Prenatal vitamin
- **ALL:** NKDA
- **FH:** Denies family history of miscarriage, chromosomal anomalies, congenital issues, VTE, DM, thyroid disease
- **SH:** Lives with husband. Denies tob, drug, etoh use. Denies caffeine. Exercises regularly. Denies IPV. Works as a preschool teacher. Feeling more anxious since having multiple miscarriages. Accepts blood products

PERTINENT PHYSICAL EXAM FINDINGS

What elements of the patient's physical exam are most relevant?

- **General:** Well appearing woman, VSS
- **Skin:** No acanthosis nigricans
- **Vulva:** Normal appearing external female genitalia. No lesions
- **Vagina:** Normal appearing mucosa. No abnormal discharge.
- **Cervix:** No lesions. No CMT
- **Uterus:** NT. Anteverted. Not enlarged
- **Adnexae:** NT. No masses palpable

Case scenario

- **What is the first step in the office?**

- History and Physical Examination .

- **What are other potential components of the evaluation of RPL?**
  - Karyotype
  - Thyroid function.
  - Uterine assessment.
  - Antiphospholipid Antibody Syndrome assessment

Case scenario

- **What options can you offer your patient for uterine assessment?**
  - Sonohysterography.
  - Hysterosalpingography.
  - Hysteroscopy.

- **How would you counsel your patient regarding thyroid function?**

- Asymptomatic hypothyroidism can increase the risk of RPL.
- There is an increased risk of miscarriage in women with subclinical hypothyroidism and euthyroid women with thyroid peroxidase antibodies.

Case scenario

- What tests can you offer your patient to evaluate for Antiphospholipid Antibody Syndrome?
  - Lupus anticoagulant.
  - Anticardiolipin immunoglobulin IgG and IgM.
  - Anti B2 glycoprotein 1 IgG and IgM.

References

- Hacker & Moore's Essentials of Obstetrics & Gynecology 6th
- Up To Date