Recurrent Miscarriage

Recurrent Miscarriage

- This is also referred to as *recurrent spontaneous abortion* and *recurrent pregnancy loss.* It is classically defined as three or more consecutive pregnancy losses at 20 weeks or less or with fetal weights less than 500 grams.

- Most women with recurrent miscarriage have embryonic or early fetal loss, and the minority of losses are after 14 weeks

RPL-TYPES

- Primary recurrent pregnancy loss" refers to couples that have never had a live birth,

- While "Secondary RPL" refers to those who have had repetitive losses following a successful pregnancy

INCIDENCE

- 50% of all conceptions fail (most unrecognized)
- 13-15% of recognized pregnancies are lost, 90 % of these before 12-14 weeks
- 10-20% of pregnant women have 1sporadic spontaneous abortion
- 2% have 2 consecutive Spontaneous Abortion
- 0.4-1% have 3 consecutive Spontaneous Abortion

	Prior losses	% Risk
Women who have at least 1 live birth	0	12 %
	1	24 %
	2	26 %
	3	32 %
	4	26 %
Women who have no live birth	2 or more	40-45 %

RISK FACTORS AND ETIOLOGY

- Only in 50 %, the cause can be determined
- Etiological categories:

- Immunologic(AUTIMUNE,ALLOIMMUNE)
- Endocrine(DM,PCOS,THYROID DYSFUCTION, Progesterone Deficiency
- Genetic
- Thrombophilic
- Environmental
- Anatomical
- Infection

1-ParentalChromosomal Abnormalities

these account for only 2 to 8percent of recurrent losses, karyotypic evaluation of both parents remains a critical part of evaluation

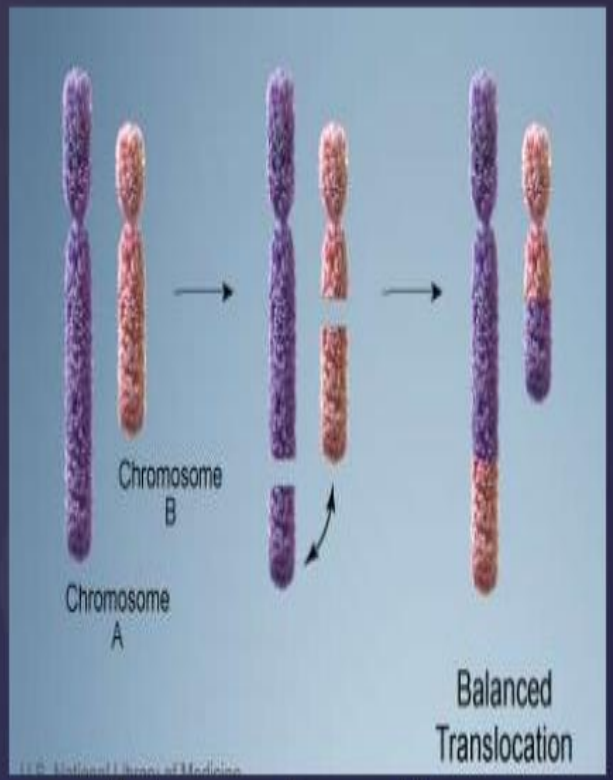
The ratio of female-to-male abnormalities was approximately 2:1.

Balanced reciprocal translocations accounted for 50 percent of identified abnormalities;

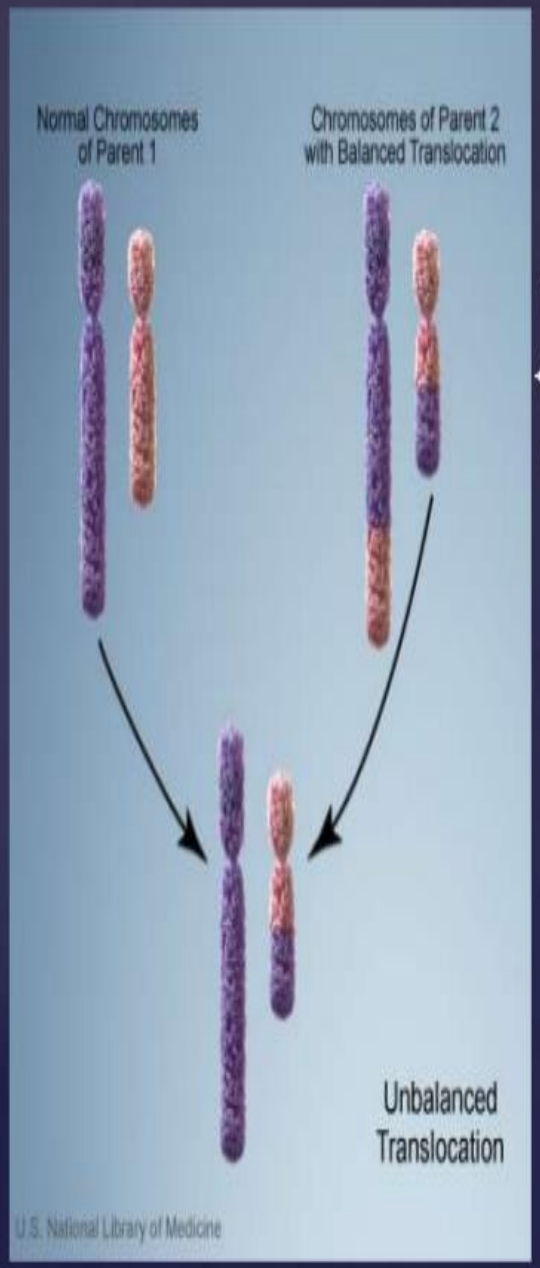
Robertson an translocations for 24 percent;

X chromosome mosaicism such as 47,XXY—*Klinefelter syndrome*—for 12 percent;

and chromosomal inversions,deletion and a variety of other anomalies comprised the remainder



Balanced translocation: carrier

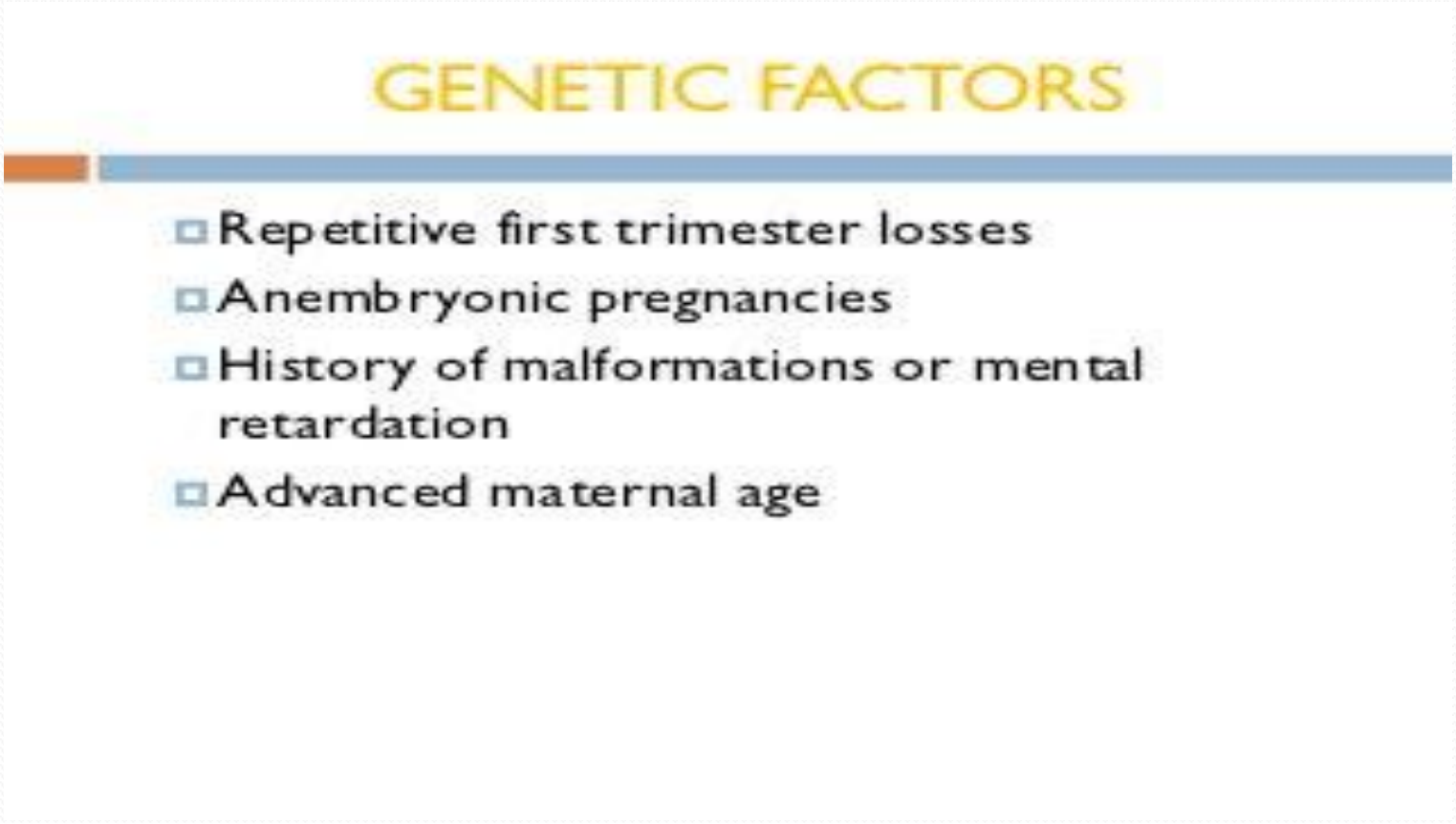


Mechanism of abnormal embryonic karyotype in offspring of carriers of balanced translocations

if one parent carries a balanced translocation, the karyotype of a resultant pregnancy may be normal, the same balanced translocation, or an unbalanced translocation. Balanced translocations are likely to cause subsequent recurrent miscarriage in the offspring. An unbalanced translocation may produce a miscarriage, fetal anomaly, or stillbirth

Thus, a history of second-trimester loss or fetal anomaly should raise the suspicion that an abnormal chromosome pattern is present in one parent. Couples with an abnormal karyotype should be offered preimplantation genetic counseling

Routine karyotyping of products of conception is costly, may not accurately reflect the fetal karyotype, and we do not recommend it. That said, some recommend routine chromosomal analysis following a second consecutive miscarriage



Fetal chromosomal abnormalities

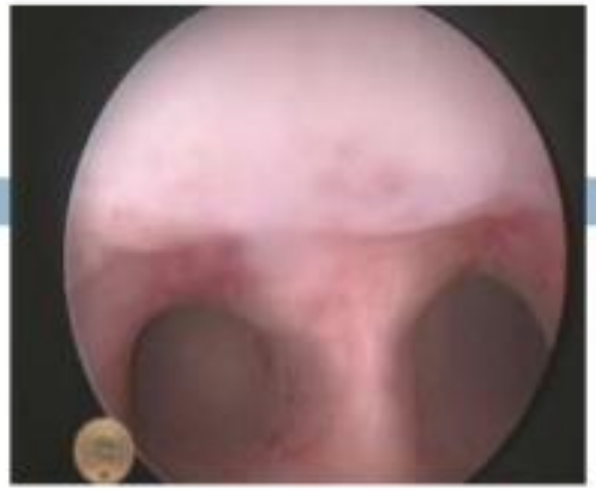
- This may be due to abnormalities in the egg, sperm or both. The most common chromosomal defects are -

- ***Monosomy:*** in vitro fertilization
  - Viable only that of X-chromosome
- ***Trisomy:*** 13, 18, 21 tolerated than monosomy

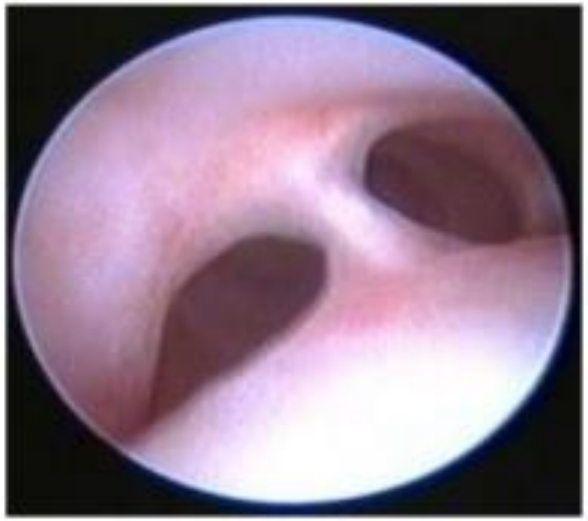
UTERINE FACTORS

- Acquired or congenital anomalies
- Congenital anomalies: 10 -15 % in women with RPL vs. 7 % in all women.
- Abnormal implantation:
  - ↓ vascularity (septum)
  - ↑ inflammation (fibroid)
  - ↓ sensitivity to steroid hormones

SEPTATE UTERUS



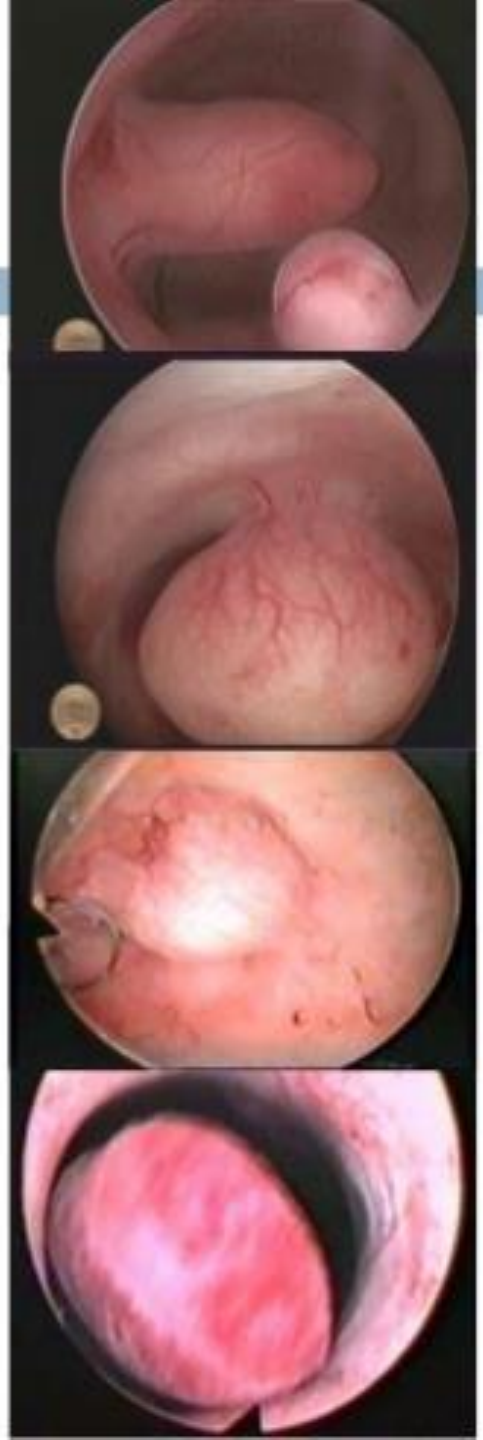
- Most common
- Poorest outcome
- Miscarriage > 60 %
- Fetal survival with untreated cases 6 to 28 %
- The mechanism
  - Not clearly understood
  - Poor blood supply



poor implantation

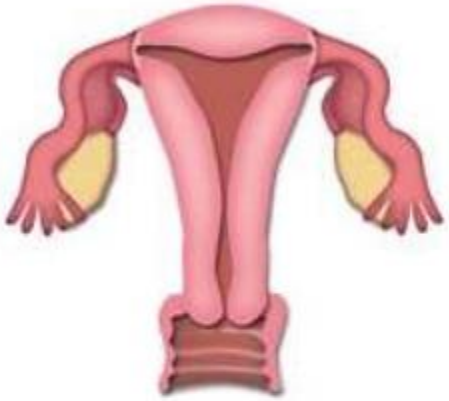
LEIOMYOMA

- Submucous
- The mechanism -
  - Their position
  - Poor endometrial receptivity
  - Degeneration with increasing cytokine production

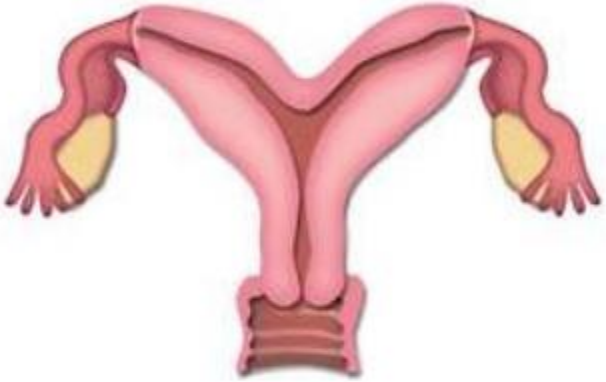


Uterine abnormalities

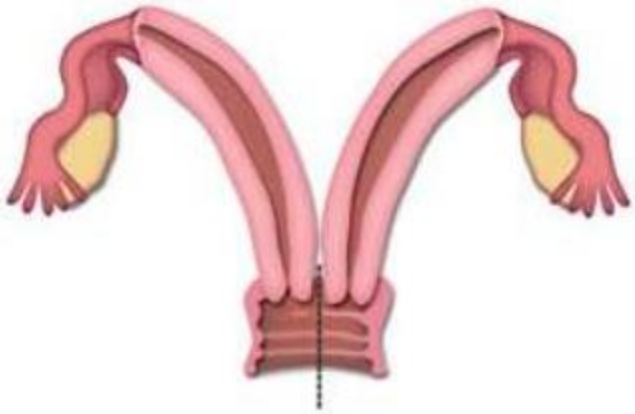
Normal Uterus

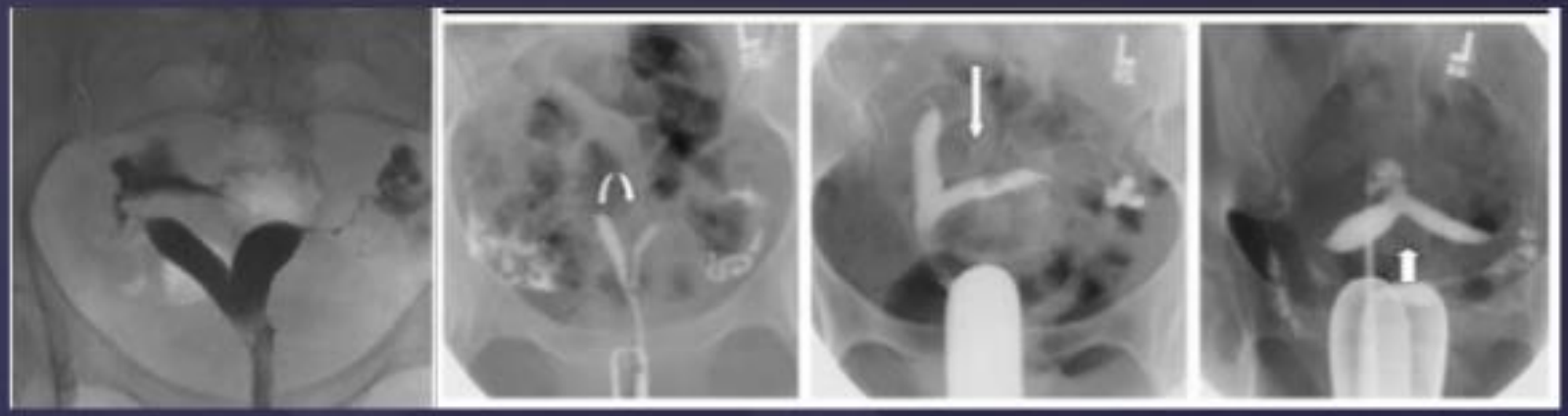


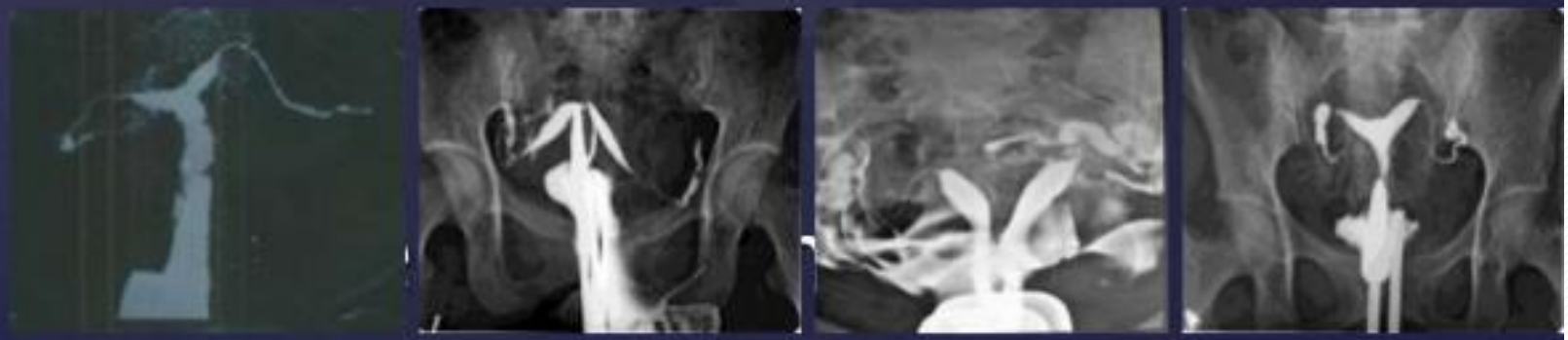
Bicornuate Uterus



Uterus didelphys







OTHER UTERINE CAUSES

- Endometrial polyps
- Intrauterine adhesions
  - Curettage for pregnancy complications (4/52)
  - Traumatize basalis layer → granulation tissue
  - Insufficient endometrium to support fetoplacental growth
  - Menstrual irregularities (hypomenorrhea, amenorrhea), cyclic pelvic pain, infertility.

OTHER UTERINE CAUSES

- Cervical insufficiency
  - Recurrent mid-trimester loss
- Other Anomalies

  DES exposure (T shaped uterus+/- cervical changes)

CERVICAL INCOMPETENCE

- Women with a history of second-trimester miscarriage and suspected cervical weakness who have not undergone a history-indicated cerclage may be offered serial cervical sonographic surveillance.
- In women with a singleton pregnancy and a history of one second-trimester miscarriage attributable to cervical factors, an ultrasound-indicated cerclage should be offered.

CERVICAL INCOMPETENCE

- **Cervical cerclage is associated with potential hazards related to the surgery and the risk of stimulating uterine contractions and hence should only be considered in women who are likely to benefit.**
- Transabdominal cerclage has been advocated as a treatment for second-trimester miscarriage and the prevention of early preterm labour in selected women with previous failed transvaginal cerclage and/or a very short and scarred cervix

UTERINE ASSESSMENT

- Sonohysterography (SIS)
  - More accurate than HSG
  - Differentiate septate & bicornuate uterus
- Hysterosalpingogram (HSG)
  - Does not evaluate outer contour
  - Not ideal for the cavity
- Hysteroscopy
  - Gold standard for Dx + Rx intrauterine lesions
  - Reserved for when no Dx is made

UTERINE ASSESSMENT

- Ultrasound
  - Presence and location of uterine myomas
  - Associated renal abnormalities
- MRI
  - Differentiate septate from bicornuate

- Hysteroscopy, laparoscopy, or MRI → second-line tests when additional information is required

TREATMENT

Surgery

- Hysteroscopy
  - Procedure of choice
  - Septum excision, polypectomy
- Laparoscopic myomectomy
  - For fibroids
- Laparotomy

IMMUNOLOGIC FACTORS

Autoimmune

(directed to self) tissues/cells)

-Systemic Lupus Erythmatosus

-Antiphospholipid Syndrome

Alloimmune

(directed to foreign

An abnormalmaternal immune response to fetal or placental

antigen.

Alloimmune mechanism

Theory: Normally pregnancy(foreign tissue graft) is tolerated by the maternal immune system through formation of **antigen blocking antibodies**.

Felt that in couples that share similar types of HLA, there is **inadequate formation of blocking antibodies** in the maternal environment.

Therefore the maternal immune system mounts an immune response to the implanting pregnancy and a spontaneous abortion occurs.

Autoimmune mechanism

Although previous studies have concluded that ther
was a higher degree of HLA sharing in couples w
recurrent abortion, multiple recent studies **have**
confirmed this.

Multiple investigators have attempted to modulate
immune response using

1) paternal WBC immunization
2) IV Immunoglobulin
3) donor seminal plasma vaginal suppositorie

NONE HAVE BEEN SHOWN TO BE

ALLOIMMUNITY

DIAGNOSIS

- HLA crossmatching

  Husband's lymphocytes + wife's serum

TREATMENT

- Transfusion of husband's lymphocytes

  Pure suspension of husband's lymphocytes

  [300ml of blood = 10ml of suspension]

  Inject 5ml IV, 1 ml subcu and 1ml intradermal

Progesterone

- Mechanism
  - inhibits Th1 immunity
  - shift from Th1-to Th2 type responses

- administered
  - intramuscularly
  - intravaginally
    - may increase local, intrauterine concentration
    - averting any adverse systemic side effects

Autoimmune

- Systemic Lupus Erythmatosus (SLE)

  -Risk for loss is 20%,mostly in 2nd and 3rd trimester of pregnancy and associated with antiphospholipid antibodies.

- Antiphospholipid syndrome (APA)
  - 5 - 15 % of womenwith RPL may have APA

    APA likely induce microthrombi at placentation site. Altered vascularity affects developing embryo, induces abortion

Antiphospholipid syndrome

- An Autoimmune disorder having specific clinical & lab criteria.
  --Sapporo criteria

Diagnosis requires at least one of each.

CLINICAL 1) Thrombolic events-arterial,venous,small vessel

2)Pregnancy loss- ≥3 losses at <10wks gestation, fetal death after 10wks,premature birth at <34wks associated with severe preeclampsia or placental insufficiency.

LABORATORY 1) Lupus Anticoagulant

2) Anticardiolipin antibodies(IgG or IgM)

Any lab test results must be observed on at least 2 separate occasions 6 wks apart.

Treatment Of APLS

There are treatment regimens for antiphospholipid syndrome that increase live birth rates

Women who received both aspirin and heparin had asignificantly greater percentage of viable infants—80 percent

The American College of Obstetricians and Gynecologists ▪ (2005a) recommends low-dose aspirin—81 mg orally per day, along with unfractionated heparin—5000 units subcutaneously, twice daily

This therapy, begun when pregnancy is diagnosed, is continued until delivery. Although this treatment may improve overall pregnancy success, these women remain at high risk for preterm labor, prematurely ruptured membranes, fetal-growth restriction, preeclampsia, and placental abruption

Inherited Thrombophilias

These are genetically determined abnormal clotting factors that can cause pathological thrombosis from an imbalance between clotting and anticoagulation pathways.

THROMBOPHILIA

- Thrombosis on maternal side of the placenta → impair placental perfusion
  - Late fetal loss, IUGR, abruption, or PIH
- Relationship with early loss is less clear
  - large and contradictory literature
  - May be restricted to specific defects not completely defined, or presence of multiple defects

THROMBOPHILIA

- Evaluate if loss > nine weeks + evidence of placental infarction or maternal thrombosis
- Antithrombin III, Protein C, Protein S, prothrombin gene, factor V leiden

Antithrombotic Therapy

- The combined use of low-dose aspirin (75-80mg/dl) and subcutaneous unfractionated heparin (5000unit twice daily)

ENDOCRINE FACTORS

Thyroid disease and antibodies

Severe iodine deficiency is associated with excessive early pregnancy loss

Thyroid hormone deficiency from an autoimmune cause is common in women, but any effects it has on miscarriage have not been adequately studied. And although thyroid auto antibodies are associated with an increased incidence of spontaneous abortion, their role in recurrent miscarriage is less convincing

Because it is not clear that thyroid disease causes recurrent miscarriage, the American College of Obstetricians and Gynecologists (2001) concludes that there is no indication for screening asymptomatic women. Conversely, overt hypothyroidism may be difficult to detect clinically, testing is inexpensive, and treatment is highly effective. Thus, we recommend thyroid-stimulating hormone (TSH) screening for women with recurrent miscarriage.

2)Diabetes mellitus

- Poorly controlled (↑Blood glucose & HbA1c levels in 1st trimester) ⟶ ↑ risk for loss.
- Miscarriage risk rises with the level of HbA1c
- Well-controlled ⟶ No ↑ risk.

Luteal phase defect

- **Progesterone is essential for implantation and maintenance of pregnancy**
- **A defect in C.L. → impaired progesterone production**

Polycystic Ovarian Syndrome

Because of oligo- or anovulation, these women are subfertile. When pregnant, there also may be an increased risk for miscarriage

- **Mechanism is unknown**
- **Insulin resistance**
- **↑ LH, Testosterone, and androstenedione → adversely affect the endometrium**

Hyperprolactinemia

Normal levels play important role in maintaining early pregnancy (in RPL

ENDOCRINE FACTORS

- Thyroid Function Tests- T3 ,T4,TSH
- S.Prolactin
- Glucose tolerance test
- HbA1c
- S.FSH
- S.LH
- S.Progesterone

- PCOS, hyperandrogenism, hyperinsullinemia
  - insulin-sensitizing agents (METFORMIN)
- overt diabetes mellitus
  - prepregnancy glycemic control
- hypothyroidism
  - thyroid hormone replacement

- Inherited thrombophilic defects,

  including activated protein C resistance (most commonly due to factor V Leiden gene mutation), deficiencies of protein C/S and antithrombin III, hyperhomocysteinaemia and prothrombin gene mutation,

- are established causes of systemic thrombosis

MISCELLANEOUS

- Environmental chemicals & stress
  - Anesthetic gases (nitrous oxide), formaldehyde pesticides, lead, mercury
    - Sporadic spontaneous loss
    - No evidence of associations with RPL
- Personal habits
  - Obesity, smoking, alcohol, and caffeine
    - Association with RPL is unclear
      - May act in a dose-dependent fashion or synergistically to ↑ sporadic pregnancy loss
- Exercise
  - does not ↑ sporadic or RPL

- Male factor
  - Trend toward repeated miscarriages with abnormal sperm (< 4% normal forms, sperm chromosome aneuploidy)
  - Paternal HLA sharing not risk factor for RPL
  - Advanced paternal age may be a risk factor for miscarriage (at more advanced age than females)
- Infection
  - Listeria, Toxoplasma, CMV, and primary genital herpes
  - Cause sporadic loss, but not RPL

RPL -When To Start Investigating ?

- Ideally after 3 losses but earlier if high risk pt, elderly, with medical disorders and known family history.
- How to Investigate ?
- Investigate commoner and treatable causes first
- Do not order a blind screen

History

- Full history including:
- Complete obstetric history
  - Year of miscarriage
  - Gestation
  - How was the pregnancy confirmed?
    - UPT? Ultrasound?
    - Assumed pregnant as missed menses?
  - Spontaneous, D&C or termination?
  - Life embryo at miscarriage?
  - Any complications
- If 2nd timester loss, ask for features of cervical incompetence

⦿ GA & characteristics (anembryonic pregnancy, live embryo) of all previous pregnancies.

History

- Any surgical history esp uterine instrumentation, cervical surgery
- Any medical illnesses
- Consanguinity?

- RPL typically occurs at a similar GA
- Most common causes of RPL vary by trimester
  - Chromosomal & endocrine earlier than anatomic or immunological causes
- Uterine instrumentation → intrauterine adhesions
- Menstrual cycles regularity → endocrine dysfunction
- Galactorrhea, Headache, Visual disturbances

- Thyroid related symptoms
- Hx of congenital or karyotypic abnormalities → heritable
- Was cardiac activity detected? If not → suggests chromosomal abnormality
- Does F.Hx display patterns of disease consistent with strong genetic influence? consanguinity
- Exposure to environmental toxins
- Hx venous thrombosis → thrombophilia or APAS
- Information from previous laboratory, pathology, and imaging studies

- Environmental factors can diagnosed by history only
  - Smoking
  - Anesthetic gases
  - Toxins, chemicals

High risk factors – Life Style

- Obesity
- Daily caffeine intake > 300 mg
- Alcohol consumption
- Use of NSAIDs

PHYSICAL EXAMINATION

- General physical
- Signs of endocrinopathy (hirsutism, galactorrhea, thyroid ,BMI)
- Pelvic organ abnormalities (uterine malformation, cervical laceration)

LABORATORY EVALUATION

- 1-Karyotype (Parental)

  Low yield & limited prognostic value → only if the other work-up was negative

- Karyotype (Embryonic)

  Not really needed

  May consider after 2nd loss

  If abnormal karyotype + normal parents → "bad luck"

2-UTERINE ASSESSMENT

- *Sonohysterography (SIS)*
  - *More accurate than HSG*
  - *Differentiate septate & bicornuate uterus*
- *Hysterosalpingogram (HSG)*
  - *Does not evaluate outer contour*
  - *Not ideal for the cavity*
- *Hysteroscopy*
  - *Gold standard for Dx + Rx intrauterine lesions*
  - *Cannot differentiate septate from bicornuate*
  - *Reserved for when no Dx is made*

- Ultrasound
  - Presence and location of uterine myomas
  - Associated renal abnormalities
- MRI
  - Differentiate septate from bicornuate

- Hysteroscopy, laparoscopy, or MRI

→ second-line tests when additional information is required

3-APAS

Dx: one lab & one clinical criteria are met

Clinical criteria:

- Venous or arterial thrmobosis
- RPL

Laboratory criteria

- Lupus anticoagulant
- Anticardiolipin antibody (IgG and IgM)
  - Medium or high titers of both
  - Low to mid positive can be due to viral illness
- Repeat twice, 6-8 weeks apart

4-THROMBOPHILIA

Evaluate if loss > nine weeks + evidence of placental infarction or maternal thrombosis

5-THYROID

TSH +/- FT4 & FT3

More important in ♀ with clinical manifestations but even in asymptomatic

Thyroid peroxidase antibody

INVESTIGATIONS

Etiology	Investigation
Genetic/Chromosomal	Karyotype both partners
Anatomical	HSG, hysterosonogram, ESI laparoscopy & hysteroscopy, MRI
Endocrine	TSH, prolactin, +/- GTT
Immunological	Anticardiolipin, lupus anticoagulant screen
Thrombophylia	Antithrombin III, Protein C, Protein S, prothrombin gene, factor V leiden
Infectious	Cervical Cultures