Recurrent abortion

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Defnition

Recurrent abortion is traditionally defined as two or more consecutive miscarriages occurring before 20 weeks.

May affect as many as 1% to 2% of women of reproductive age

An earlier evaluation(investigation) may be indicated

- **fetal cardiac activity was identified prior to a loss,**
- **Woman older than 35 years,**
- **Couple had difficulty in conceiving. (infertility)**

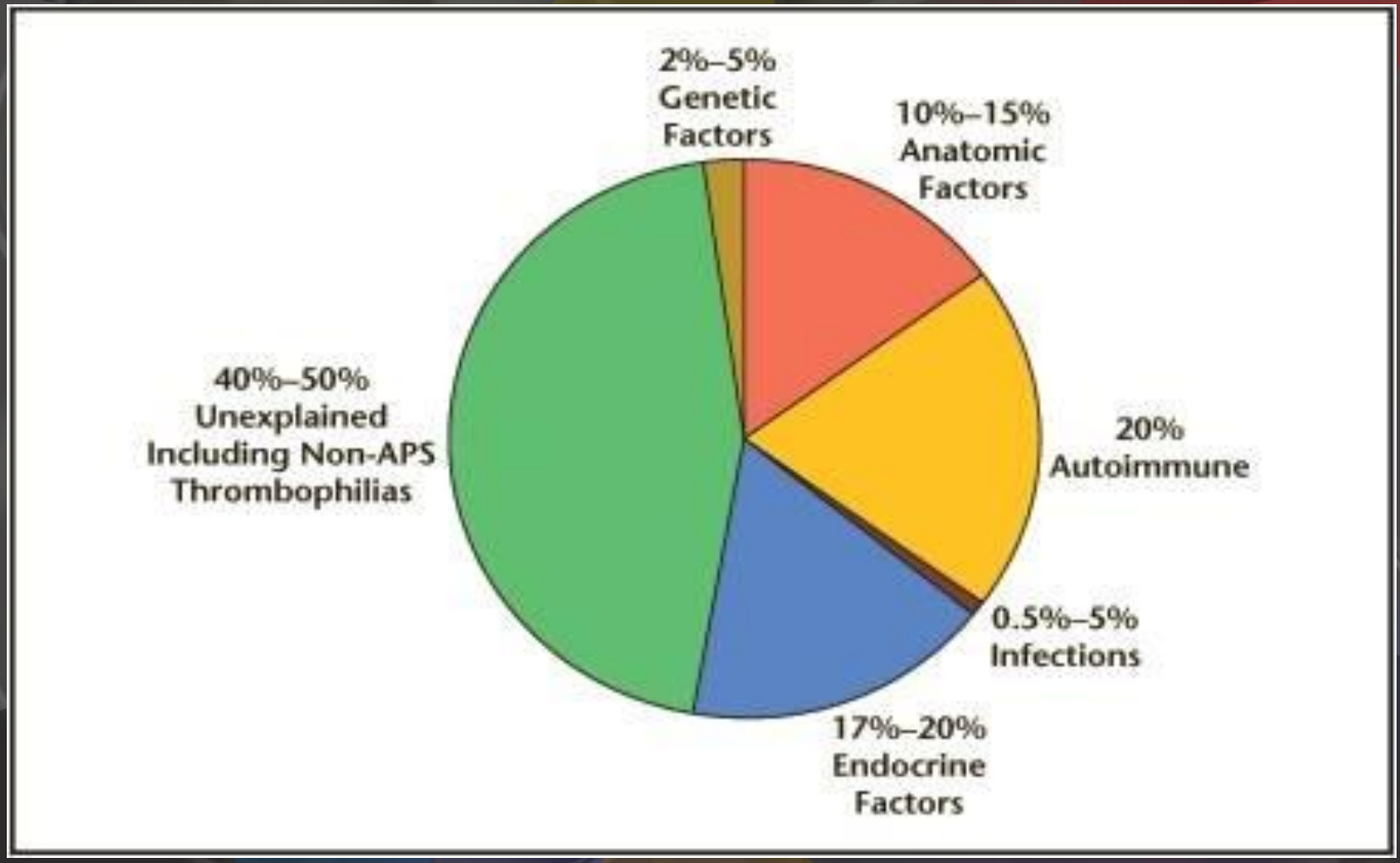
Risk factors for recurrent abortion

- Maternal age- associated with a decline in both the number and quality of the remaining oocyte(highest by ≥ 35)
- Advanced paternal age is also a risk factor

(highest by ≥ 40)

- Previous miscarriages- risk increases with each successive pregnancy loss,40% after 3 consecutive pregnancy losses
- Obesity-increases risk of both sporadic and recurrent miscarriage
- Environmental factors-Cigarette smoking caffeine and alcohol consumption (x – Ray,chemotherapy)

Causes of Recurrent Pregnancy Loss



GENETIC FACTORS

- Repetitive first trimester losses
- Anembryonic pregnancies
- History of malformations or mental retardation
- Advanced maternal age
- *Genetic etiology less likely with late first trimester or second trimester losses*

Genetic factors

- Parental Chromosomal abnormalities-

One of the partner carries a balanced structural chromosomal anomaly

Most common is balanced reciprocal and Robertsonian translocation which causes unbalanced translocation in the fetus

- Embryonic Chromosomal abnormalities-

Due to abnormalities in the egg, sperm or both .

Most common- Monosomy or trisomy

Mainly responsible for sporadic miscarriage

MANAGEMENT

- Genetic counselling
- Assisted reproductive technologies, including PGD (preimplantation genetic diagnosis)
- Use of either donor oocyte or donor sperm depending on the affected partner

ANATOMIC FACTORS– UTERINE FACTORS

- Acquired or congenital anomalies
- Congenital uterine anomalies: 6 - 7 % in women with RPL vs. 2 % in all women.
- Pathogenesis uncertain but attributed to :

Reduced intrauterine volume

Poor vascular supply

Congenital

- Septate uterus 65 %

Unicornuate uterus 50% loss

Uterus didelphys 40% loss

Bicornuate uterus 30 % loss

DES exposure - many have abnormal uterine structure (T shaped uterus+/-cervical changes)-24 %

Acquired

Uterine Leiomyomas

Intrauterine Adhesions(Asherman's Syndrome)

Incompetent 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

Ultrasound

Presence and location of uterine myomas
Associated renal abnormalities

MRI

Differentiate septate from bicornuate

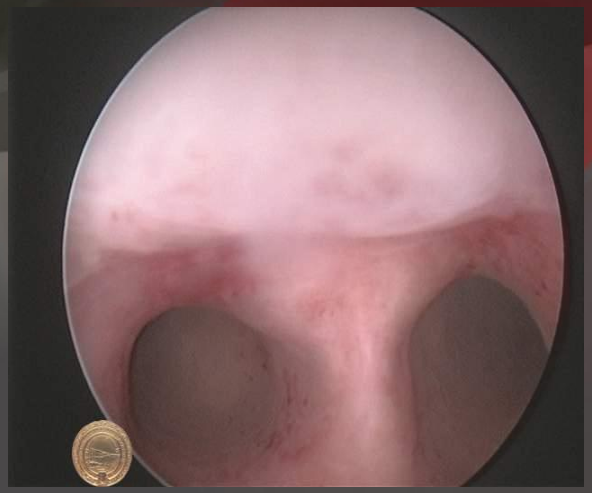
UNICORNUATE UTERUS

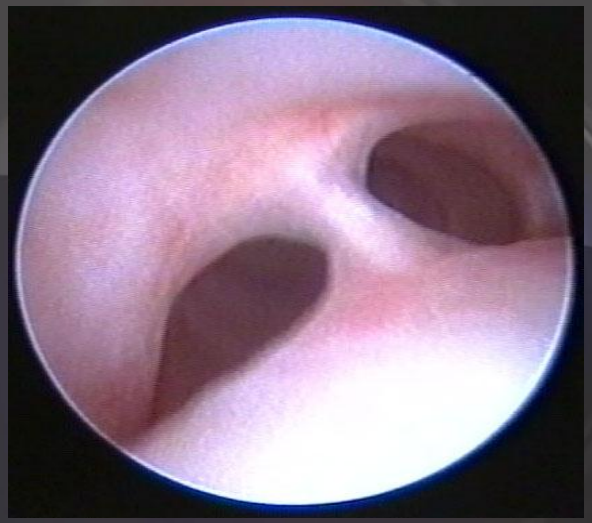
- No surgical procedure can enlarge unicornuate uterus

- Available evidence suggests most pregnancies best managed expectantly with cervical cerclage reserved for those with previous second trimester pregnancy losses or evidence of progressive cervical shortening

SEPTATE UTERUS

- Most common developmental anomaly
- Poorest outcome
- Miscarriage 65 %
- The mechanism
  Not clearly understood
  Implantation on Poorly vascularised septum

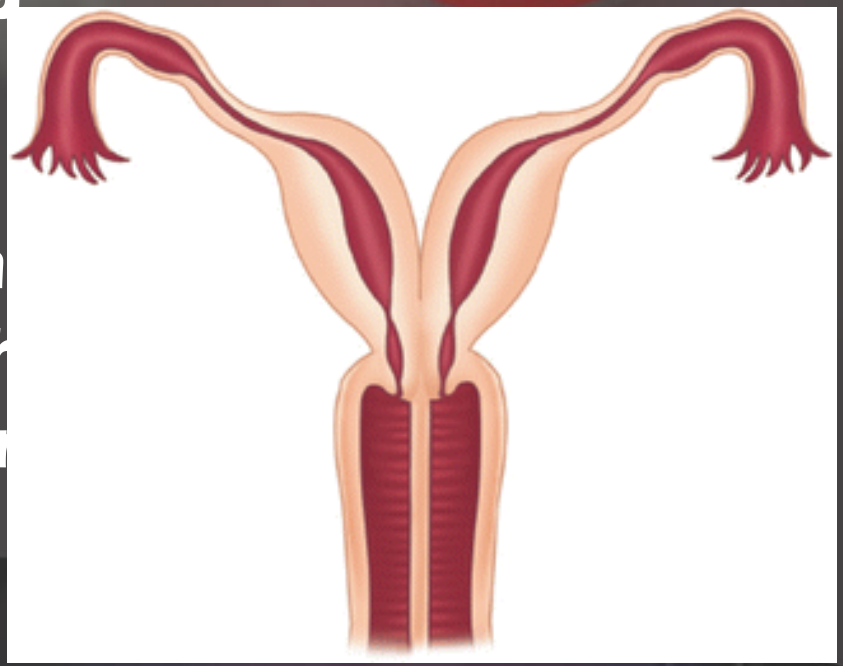




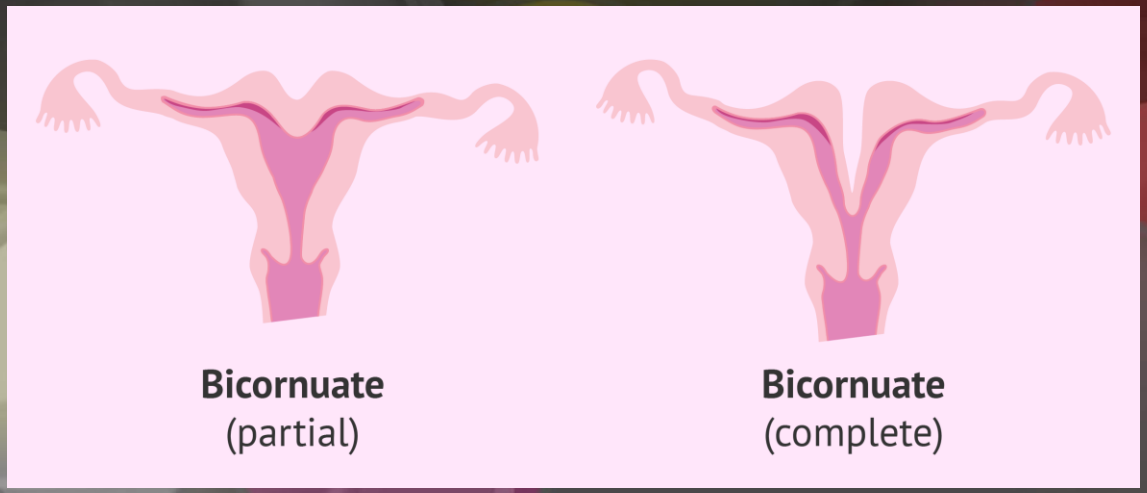
Uterine septa not always associated with a poor pregnancy outcome but their presence in a woman with RPL is an indication for surgical correction (Hysteroscopic septoplasty,usually only incision required)

UTERUS DIDELPHYS

- Only surgery indicated is removal of an obstructing longitudinal vaginal septum
- Unification procedures can benefit some women with numerous miscarriages or previable births
- The recommended technique unifies the two fundi and leaves the two cervices intact



BICORNUATE UTERUS



Surgery generally considered unnecessary and best reserved for those with a well established history of otherwise unexplained recurrent pregnancy loss or previable births

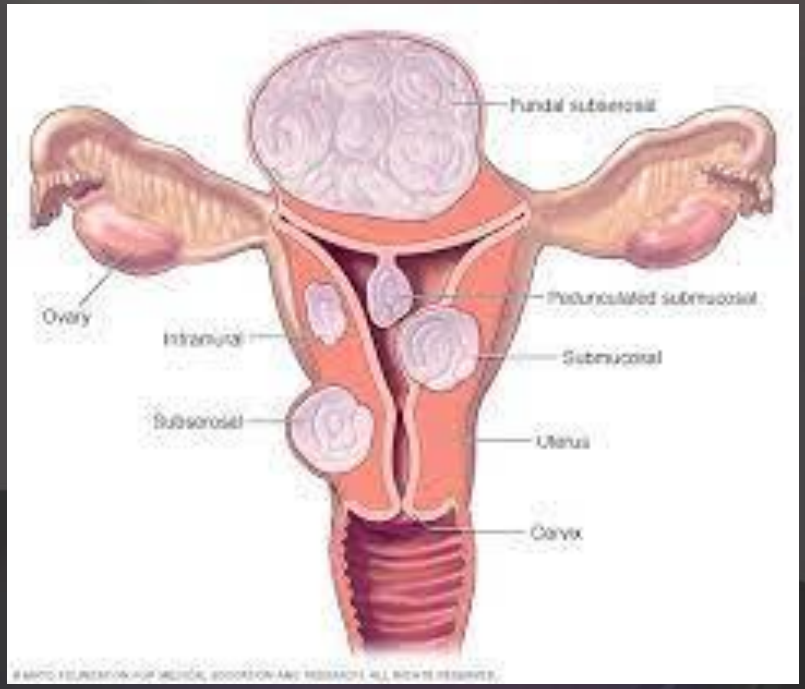
Strassman abdominal metroplasty surgical procedure of choice

Uterine leiomyoma

Unclear relationship between uterine leiomyomata and RPL

- **Pregnancy outcomes adversely affected by submucous myomas,not by subserosal or intramural myomas under 5-7 cm in size**

Large submucosal fibroids distort the cavity or occupy a large subendometrial area



Surgery not indicated when myomas do not distort the uterine cavity or when specific symptoms are not attributable to them

Treatment options:

Hysteroscopic/Abdominal myomectomy,subtotal hysteroscopic myomectomy

INTRAUTERINE ADHESIONS/ASHERMAN'SYNDROME/AMENORRHOEA TRAUMATICA

Excessive curettage for pregnancy complications

Traumatize basalis layer → granulation tissue

Insufficient endometrium to support fetoplacental growth

Menstrual irregularities (hypomenorrhea, amenorrhea), cyclic pelvic pain, infertility.

- Diagnosis primarily on high index of suspicion,based on history
- Scanty or no withdrawl bleeding after sequential treatment with exogenous estrogen and progestin
- Operative hysteroscopy primary method of treatment
- Most advocate insertion of an intrauterine balloon catheter (left in place for approx 7-10 days) after adhesiolysis

- Treatment with broad spectrum antibiotic and a non-steroidal anti inflammatory drug minimize the risk of infection and uterine cramping while catheter is in place
- High dose exogenous estrogen for approx 4 weeks after surgery encourage rapid endometrial re-epithelialization and proliferation with a progestin in the final week
- Recurrence rates 20-60%

Cervical insufficiency/Cervical incompetence

Defnition- Inability of the cervix to retain a pregnancy in the second trimester,in the absence of uterine contractions.

Presents as acute, painless dilatation of the cervix which causes recurrent mid trimester pregnancy loss

Cervical insufficiency- Causes

- **Congenital**
  - Mullerian tube defects (bicornuate uterus, septate uterus, unicornuate uterus)
  - Diethylstilbestestrol exposure in utero
  - Abnormal collagen tissue(Ehlers Danlos syndrome, Marfans syndrome)

Acquired

- Forceful mechanical cervical dilatations
- Cervical lacerations
- Cervical cone or LEEP procedure

DIAGNOSIS

Usually made in three different settings;

Women who present with sudden onset of Symptoms and signs of cervical insufficiency (acute presentation)

Women who present with history of second trimester loss consistent with diagnosis of cervical incompetence (historical diagnosis)

Women with endovaginal ultrasound findings consistent with cervical incompetence (ultrasound diagnosis)

Acute Presentation

- Women present between 18 and 22 weeks with pelvic or rectal pressure of recent onset,
- Increased mucous vaginal discharge, and no contractions.

Historical Diagnosis

- Women gives history of painless cervical dilatation treated with cerclage in the second trimester of a previous pregnancy.
- History of ruptured membranes without contractions in second trimester of pregnancy

ACOG recommends TVS cervical length screening for women with prior preterm birth .

- 16 – 24 wks of pregnancy every 2 wks if cervix – length = 25 – 29 mm then weekly screening.

  If cervical length $< 25\ mm$ cerclage recommended .
- By woman without a history of preterm birth with a short cervix incidentally identified progestrone therapy only offered .
- Cerclage not recommneded by twins pregnancy with a cx – length $< 25\ mm(\ No\ improved\ outcomes)$

SURGICAL TREATMENT

Shirodkar operation

McDonald operation

Abdominal cerclage

Cerclage

Principle-

A non absorbable encircling suture is placed around the cervix at the level of internal os

Operates by interfering with the uterine polarity and the adjacent lower segment from being taken up.

Timing of operation

Elective cerclage-In proven cases around 14 weeks or at least 2 weeks earlier than the lowest period of previous wastage as early as 10th week.

Emergency cerclage- when the cervix is dilated and the membranes are bulging.

Contraindications for cerclage

Intrauterine infections

Ruptured membranes

History of vaginal bleeding

Severe uterine irritability

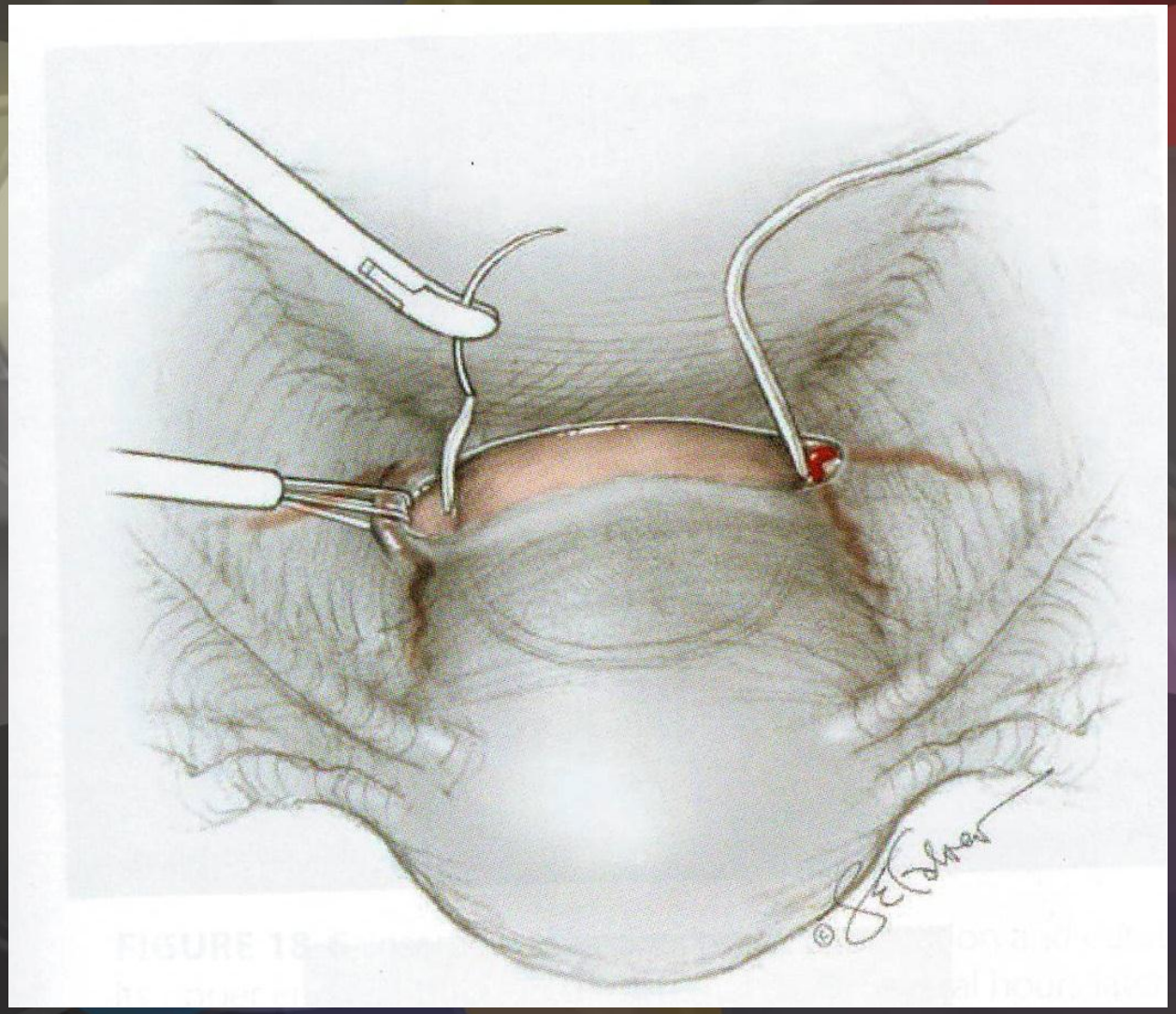
Cervical dilatation >4 cm

Cerclage operation

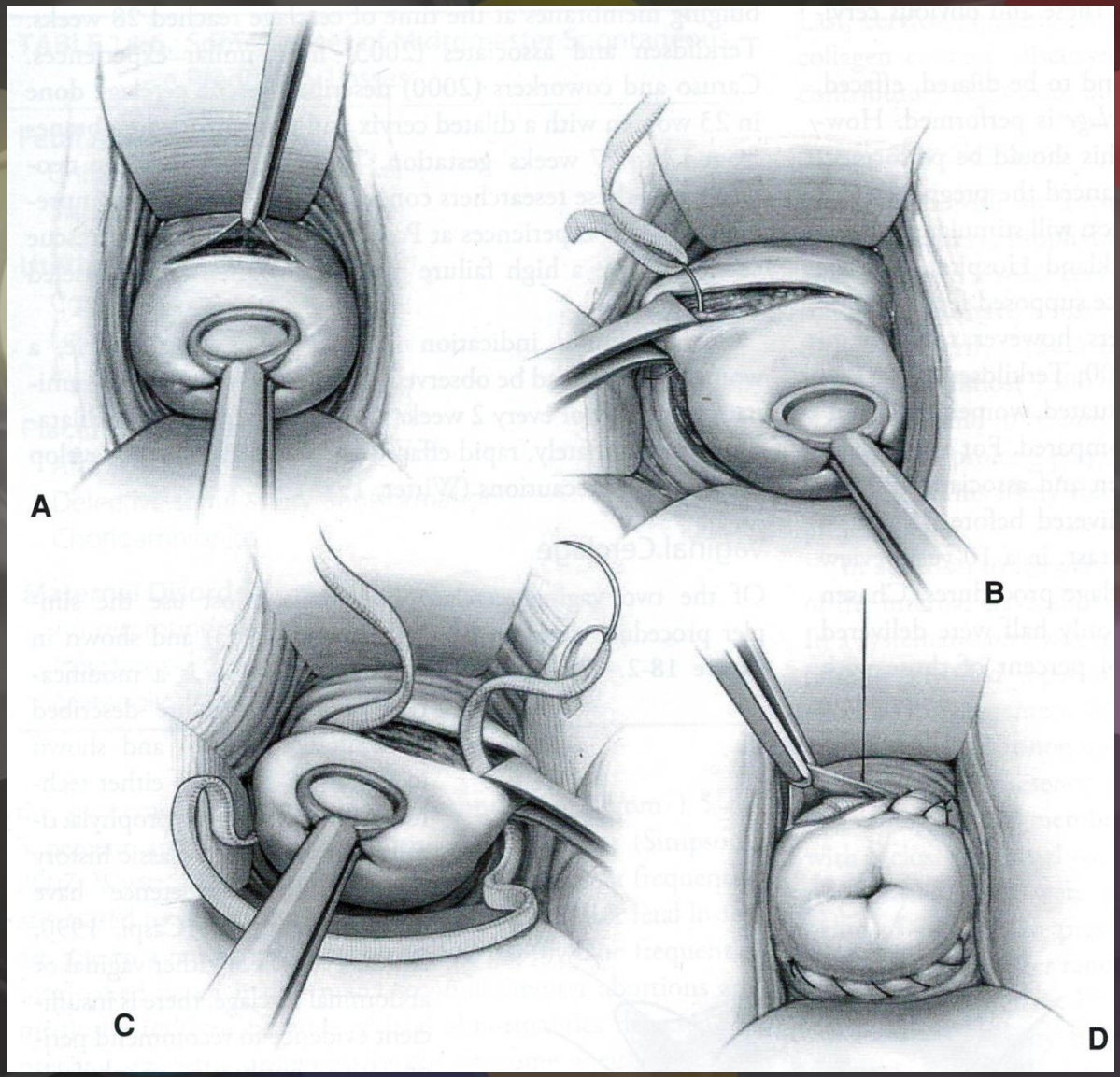
Shirodkar operation- opening the anterior fornix and dissecting away the adjacent bladder before placing the suture submucosaly, tied interiorly and the knot buried by suturing the anterior fornix mucosal opening

Mac Donald technique- requires no bladder dissection and the cervix is closed by purse string sutures around the cervix

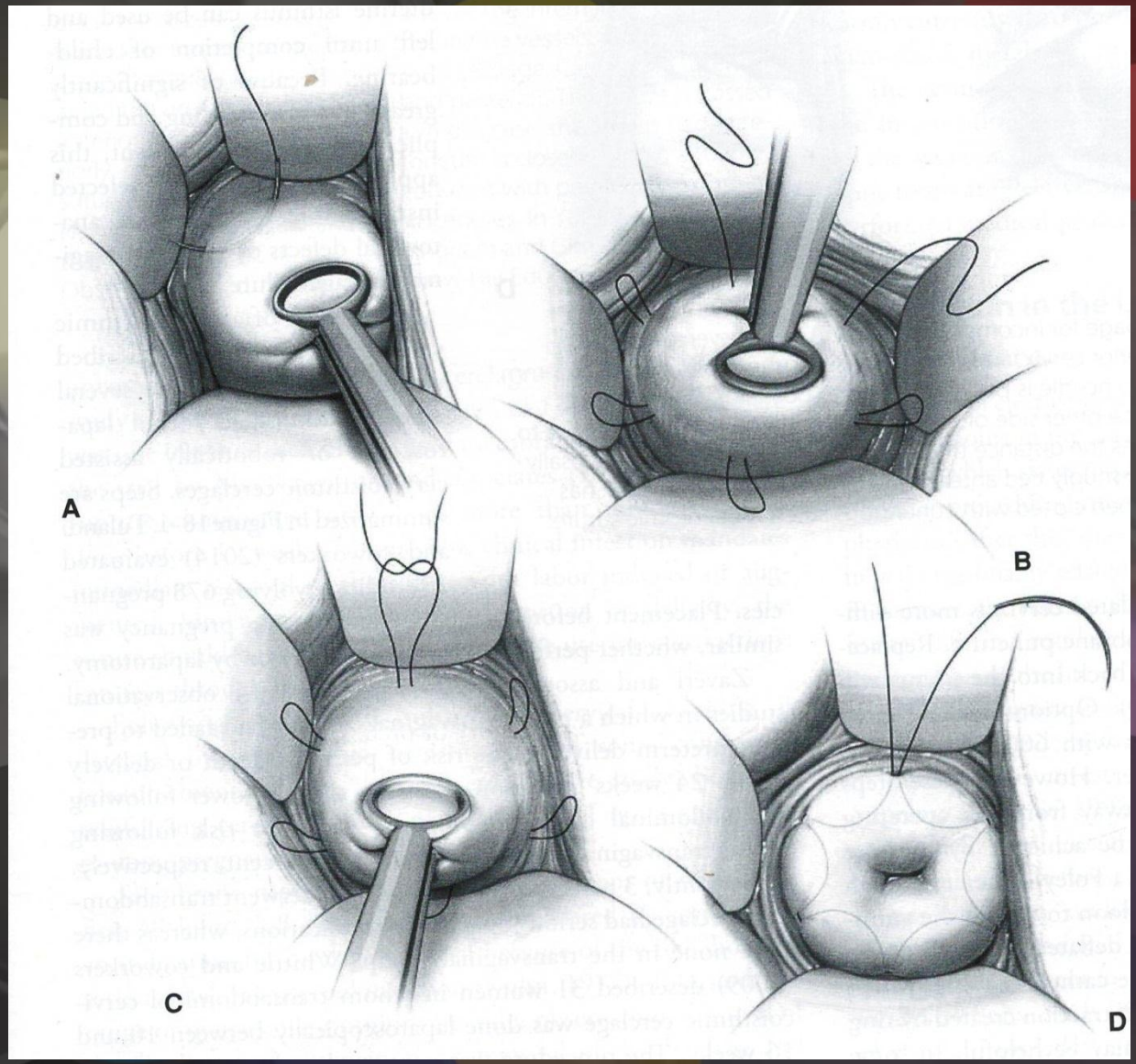
Transabominal Cerclage



Shirodkar Cerclage



McDonald Cerclage



Complications

Slipping or cutting through the suture

Chorioamniotis

Rupture of the membrane

Abortion /Preterm labour

Post operative advice

Bed rest

Tocolysis

To avoid intercourse

Report in case of leaking, bleeding, and pain

Stitch should be removed at 37 weeks or earlier when the labour starts

ENDOCRINE FACTORS

- Endocrine factors that may predispose to an increased risk of pregnancy loss include:
- Thyroid disease
- Diabetes mellitus
- Polycystic ovary syndrome
- Luteal phase deficiency

Hypothyroidism

Associated with isolated as well as RPL

- **Patients with hypothyroidism even subclinical have an increased rate of spontaneous miscarriage**
- **Subjects have concomitant reproductive abnormalities including ovulatory dysfunction and luteal phase defect**
- **Association between antithyroid antibody positivity and RPL unclear**

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.

Polycystic Ovarian Syndrome

Characterized by excessive production of androgens by the ovaries which interferes with the reproductive, endocrine, and metabolic functions.

Woman presents with oligo/anovulation,Hyperandrogenism,and polycystic ovaries on ultrasound

Increased risk of miscarriage in PCOS is due to insulin resistance, hyperinsulinaemia, and hyperandrogenemia

Metformin treatment can reduce the risk of miscarriage in PCOS woman

Luteal Phase deficency

There is inadequate growth and function of the corpus luteum which is essential for maintenance of pregnancy during the first 7 to 9 weeks of gestation

Life span of corpus luteum is shortened and there is inadequate progestrone secretion

As a result there is inadequate secretory changes in the endometrium which hinder implantation

- Gold standard for diagnosing LPD is endometrial biopsy but not preferred due to invasive nature

- An abnormally short luteal phase duration (less than 13 days),best defined by the interval from detection of the midcycle LH surge to the onset of menses ,is the most objective and reliable diagnostic criterion.

Role of progesterone in recurrent abortion

- Women with a history of miscarriage who present with bleeding may benefit from use of vaginal micronized progestron .
- Therefore in the absence of any factor ,progesterone is given till the placenta takes over the luteal function
- Type of progesterone- natural micronized progesterone/dyhydrogesterone
  Route-oral/vaginal/intramuscular
  Dose-600-800mg per day vaginally

Infections

- No infectious agent has been proven to cause recurrent pregnancy loss

- Certain infections have been associated with spontaneous loss
  - *Toxoplasma gondii*, Chlamydia trachomatis,Ureaplasma urealyticum,Mycoplasma hominis,Listeria monocytogenes,Campylobacter species
  - Rubella, HSV, CMV can directly infect the foetus and the placenta
  - Bacterial vaginosis in the first trimester can cause 2nd trimester miscarriage and preterm delivery

Immunologic factors

Autoimmune-directed to self tissue/cells

Alloimmune- directed to foreign antigen

Alloimmune

An immune response to placental and fetal antigen

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

Couples that share similar types of HLA, there is inadequate formation of blocking antibodies

Maternal production of cytotoxic antibodies

- Maternal immune system mounts an immune response to the implanting pregnancy and a spontaneous abortion occurs.

- Routine test for Human leukocyte antigen type and anti-paternal cytotoxic antibody and use of immunotherapy not beneficial

Autoimmune

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

Antiphospholipid syndrome (APA) -5%of women with RPL may have APA.

APA induces microthrombi at placentation site.Altered vascularity affects developing embryo and induces abortion

Autoimmune Abnormalities

Antiphospholipid Antibody Syndrome

- The most treatable cause of RPL which is well accepted and evidence based.
- Up to 15–20% of women with recurrent pregnancy loss have antiphospholipid antibodies (aPL).
- In 5% second or third trimester losses occur.
- About 5-10% of all pregnancies are complicated by preeclampsia or fetal growth restriction and up to 75% into preterm births.

Antiphospholipid Syndrome Criteria (Sydney revision of Sapporo criteria -2006)

Definite APS: 1 Clinical + 1 Lab criteria

CLINICAL CRITERIA

- **Vascular Thrombosis- arterial or venous**
- **Pregnancy Morbidity:**

  a) 1 omore death of normal fetus at ≥ 10 wks

  b) 1or more premature birth at ≤ 34 wks due to severe preeclampsia or placental insufficiency

  c) ≥3 consecutive abortions at <10wks with other causes being ruled out

LABORATORY CRITERA

- Anti-Cardiolipin IgG and IgM
- Lupus anticoagulant (LAC)
- Anti β2-glycoprotein1 IgG and IgM

medium - high titer(40 GPL or MPL or higher than 99th percentile) at least 12 wks apart

Positive test should be repeated at least 12 apart

When to start treatment

Heparin or Enoxiparin 4000 unit with low dose aspirin is preferred regime .

Aspirin is started when pregnancy is being attempted or documented.

Heparin is started as soon as cardiac activity is documented on TVS.

APLA/APS-Treatment dose

1. Unfractionated Heparin 5000-10000 IU subcutaneous twice a day Or Low molecular weight Heparin(Enoxiparin) is better option

+

2. Low dose Aspirin (80-100 mg/day)

INHERITED THROMBOPHILIAS

Pregnancy is a hypercoagulable state

Women with heritable or acquired thrombophilic disorders have significantly increased risks of pregnancy loss

Coagulation factors:

- Factors that favour clotting when increased
  Fibrinogen
  Factors VII, VIII, X

- Factors that favour clotting when decreased
  Antithrombin III
  Protein C
  Protein S

Inherited thrombophilic defects

- **Activated protein C resistance (most commonly due to factor V Leiden gene mutation)**
- **Deficiencies of protein C/S and antithrombin III**
- **Hyperhomocystenemia- Probably interference in embryonic development through defective chorionic villous vascularization**
- **Prothrombin gene mutation- Higher plasma prothrombin concentrations, augmented thrombin generation**

Mechanism of action

- Thrombosis on maternal side of the placenta → impaired placental perfusion
  - Late fetal loss, IUGR, abruption, or PIH
- Relationship with early loss is less clear

Antithrombotic Therapy

- The combined use of low-dose aspirin (80-100mg/dl) and subcutaneous unfractionated heparin (5000unit twice daily)
- Or better Enoxiparin 4000 unit.

INVESTIGATIONS

Etiology — **Investigation**

Genetic/Chromosomal---------- **Karyotype both partners**

Anatomical---------- **HSG or Sonohysterography or USG**

Endocrine---------- **TSH**

Luteal phase duration, Blood sugar

Immunological---------- **Anticardiolipin Antibody ,Lupus anticoagulant , Anti-**β2- glycoprotein 1 antibody

Thrombophilias---------- **Antithrombin III, Protein C, Protein S, prothrombin gene, factor V leiden,prothrombin gene mutation,Activated protein C resistance**

Infectious---------- **Endocervical swab to detect infection**

Evaluation

- *Tests NOT useful*
  - ANA
  - Maternal anti-paternal leukocyte antibodies
  - Mixed lymphocyte maternal-paternal cell cultures
  - HLA genotyping
  - Immunophenotype panels (CD56, CD16)

Management of Patient with Idiopathic Recurrent abortions

Preconception

Counselling of the couple-after 2 consecutive miscarriages chance of a successful pregnancy is high(70%)

1. Folic acid

Post conception :

1. Prophylactic aspirin
2. Prophylactic cervical circlage
   - If history of repeated D & E
3. Anticardiolipin antibodies [IgM]
4. Steroids for pulmonary maturity
5. Monitor closely near term [NST, USG]

TABLE 18-7. Various Regimens for Medical Termination of Pregnancy

First Trimester

Mifepristone/Misoprostol

[a]Mifepristone, 200–600 mg orally; followed in 24–48 hr by:
[b]Misoprostol, 200–600 μg orally or 400–800 μg vaginally, buccally, or sublingually

Misoprostol Alone

[c]800 μg vaginally or sublingually every 3 hr for 3 doses

Methotrexate/Misoprostol

[d]Methotrexate, 50 mg/m^2 BSA intramuscularly or orally; followed in 3–7 days by:
[e]Misoprostol, 800 μg vaginally. Repeat if needed 1 week after methotrexate initially given

Second Trimester

Mifepristone/Misoprostol

Mifepristone, 200 mg orally; followed in 24–48 hr by:
Misoprostol, 400 μg vaginally or buccally every 3 hr up to 5 doses

Misoprostol Alone

Misoprostol, 600–800 μg vaginally; followed by 400 μg vaginally or buccally every 3 hr up to 5 doses

Dinoprostone

20 mg vaginal suppository every 4 hr

Concentrated Oxytocin

50 units oxytocin in 500 mL of normal saline infused during 3 hr; then 1-hr diuresis (no oxytocin); then escalate sequentially in a similar fashion through 150, 200, 250, and finally 300 units oxytocin each in 500 mL normal saline

[a]Doses of 200 versus 600 mg similarly effective.
[b]Oral route may be less effective and have more nausea and diarrhea. Sublingual route has more side effects than vaginal route.
[c]Intervals 3–12 hours given vaginally; 3–4 hours given sublingually.
[d]Efficacy similar for routes of administration.
[e]Similar efficacy when given on day 3 versus day 5.
BSA = body surface area.
Pymar, 2001; Raghavan, 2009; Schaff, 2000; Shannon, 2006; von Hertzen, 2003, 2007, 2009, 2010; Winikoff, 2008.


Thank you