Recurrent Pregnancy Loss
What can we do?

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1 in 4 pregnancies ends in miscarriage

mumsnet
Miscarriage Care

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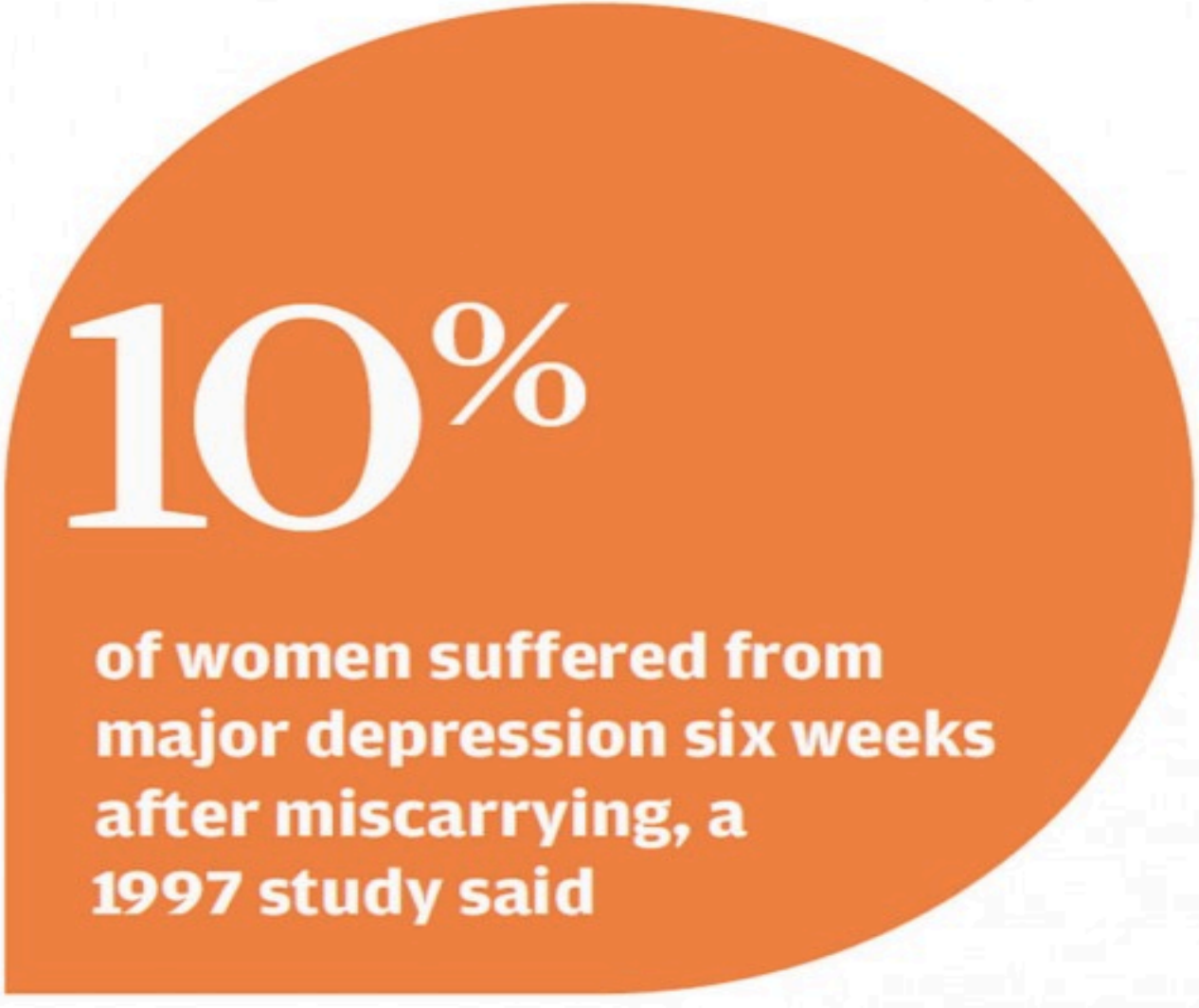

10%
of women suffered from major depression six weeks after miscarrying, a 1997 study said

Recurrent Pregnancy Loss

Defn: Recurrent Pregnancy Loss (RPL)

- Classical: 3 or more consecutive pregnancy losses before 20 weeks gestation, 1-2%
- 5% couples experience 2/> consecutive losses
- Risk of further pregnancy loss is similar for 2 and 3 consecutive losses, 43.7%, 44.6%
- Investigation may be appropriate after 2 pregnancy losses, especially in older women and if keen to be investigated

Recurrent Pregnancy loss

- Possible causes
- Investigation
- Management

Causes

- Age
- Previous pregnancy loss
- Uterine factors
  - Anomalies
  - Fibroids
  - Polyps
  - Adhesions
  - Cervical insufficiency
  - Defective endometrial receptivity

Causes

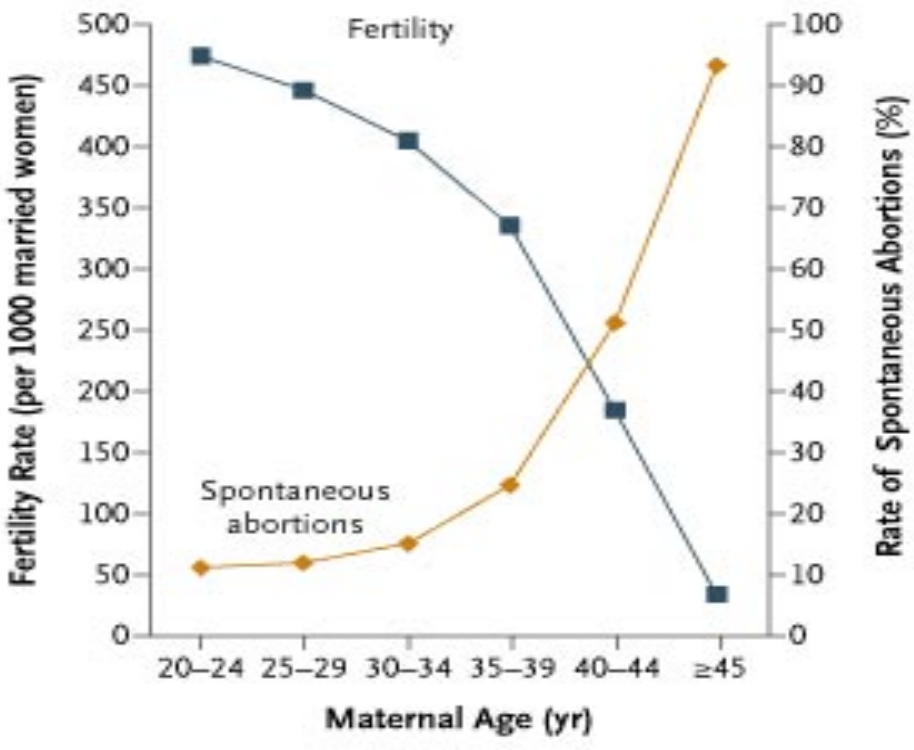
- Immunological factors
  - Antiphospholipid syndrome
  - Other immunological factors
- Endocrine factors
  - Diabetes mellitus
  - PCOS
  - Thyroid antibodies and disease
  - Hyperprolactinaemia
  - Luteal phase defects

Causes

- Chromosomal abnormality
- Genetic disorders
- Thrombophilia
- Infection
- Decreased ovarian reserve
- Personal habits
- Male factor
- Environmental chemicals and stress

Age

12-19yrs 13%
20-24yrs: 11%
25-29yrs: 12%
30-34yrs: 15%
35-39yrs: 25%
40-44yrs: 51%
>/=45yrs: 93%



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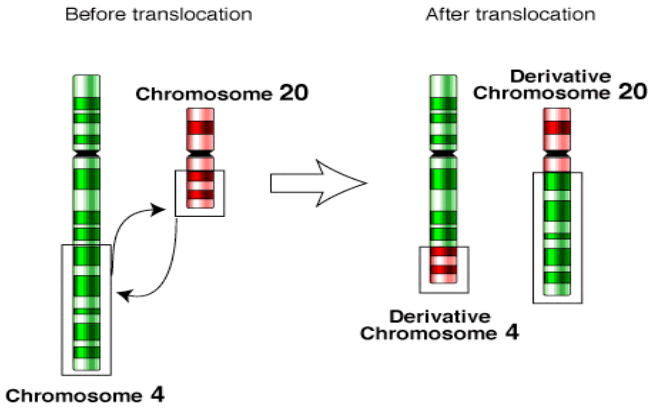
Chromosomal abnormality

% Abnormal	Gestational age
60	12
45	16
12	20
6	24
-1	40



- Increases with advancing maternal age
- Parental abnormalities in 3-5% of couples with RPL
- Balanced translocation most common
  - Reciprocal (60%) or Robertsonian (40%)
  - 25-50% risk of pregnancy loss
- Trisomy, monosomy and triploidy; 85% losses

Karyotyping

- Should be performed on products of conception (POC) of the 3rd and subsequent consecutive miscarriage(s)
- Parental peripheral blood karyotyping of both partners should be performed in couples with RPL where testing of POC reports an unbalanced structural chromosomal abnormality, or POC are not available for karyotyping
- If the karyotype of the miscarried pregnancy is abnormal, there is a better prognosis for the next pregnancy
- Role for PGD in IVF pregnancies

Antiphospholipid syndrome (APS): Hughes syndrome

- Most important treatable cause of recurrent miscarriage, 2% in normal, 15% with RPL.
- Association between antiphospholipid antibodies – lupus anticoagulant, anticardiolipin antibodies and anti-B2 glycoprotein-I antibodies – and adverse pregnancy outcome or vascular thrombosis.
- Test: on 2 or more occasions at least 12 weeks apart

APS: Adverse pregnancy outcomes

- Three or more consecutive miscarriages before 10 weeks of gestation
- One or more morphologically normal fetal losses after the 10th week of gestation
- One or more preterm births before the 34th week of gestation owing to placental disease.

APS antibodies: action

- Inhibition of trophoblastic function and differentiation
  - activation of complement pathways at the maternal–fetal interface resulting in a local inflammatory response
  - in later pregnancy, thrombosis of the uteroplacental vasculature

- In vitro studies have shown that the effect of APS antibodies on trophoblast function and complement activation is reversed by heparin.

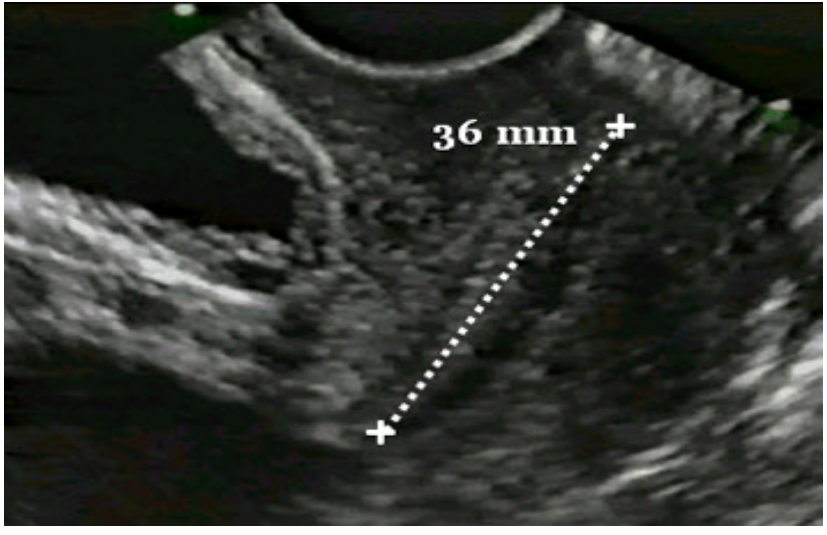
Treatment

- Strongly advise women to plan pregnancy
- Stop smoking
- Maintain good diet and healthy weight
- Regular exercise
- Aspirin
- Clexane

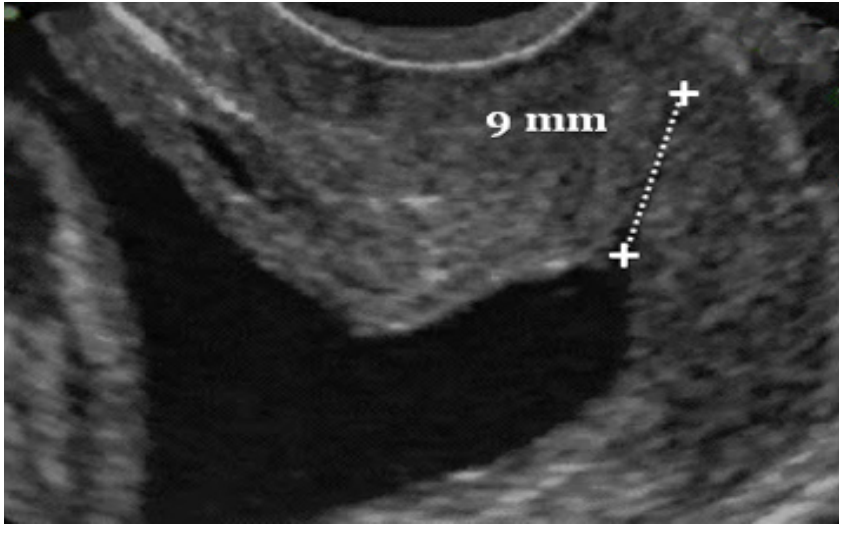
Cervical incompetence

- Look for history: Large LLETZ, cone biopsy, transcervical myomectomy, later 1st TM TOP or ERPC, painless 2nd TM loss or PPROM
- Currently no satisfactory objective test that can identify women with cervical weakness in the non-pregnant state
- In women with singleton pregnancy & one 2nd TM miscarriage attributable to cervical factors, an USS-indicated cerclage, if cervical length of </=25mm is detected by TVS before 24 wks

Normal cervix

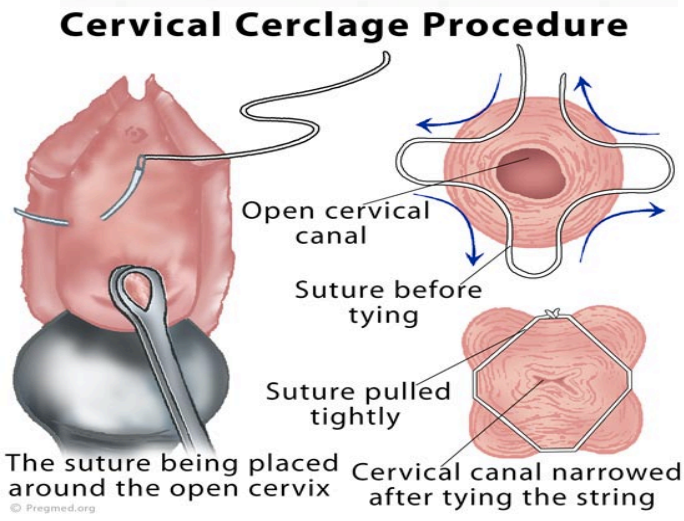


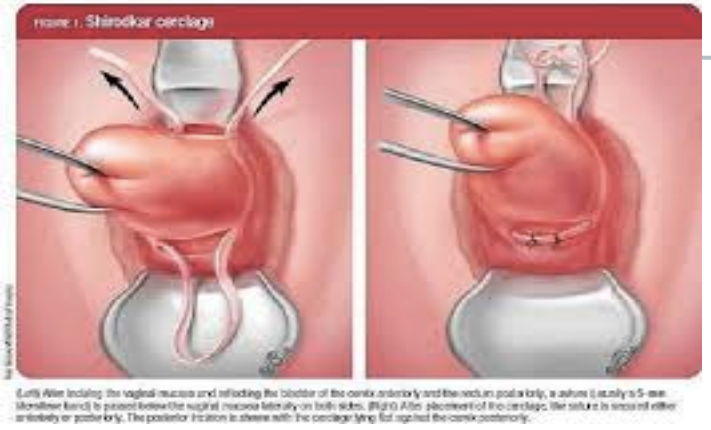
Short cervix

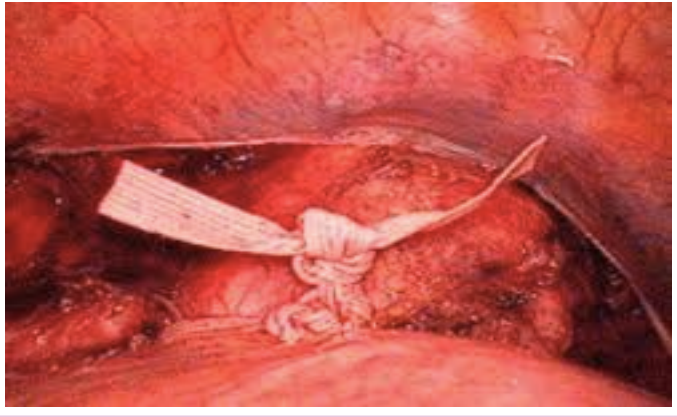


Management: cervical incompetence

- Serial cervical lengths
- Progesterone support
- Prophylactic cervical suture
  - Vaginal:
    - MacDonald's
    - Shirodkar's
  - Abdominal
    - Laparoscopic
    - Open







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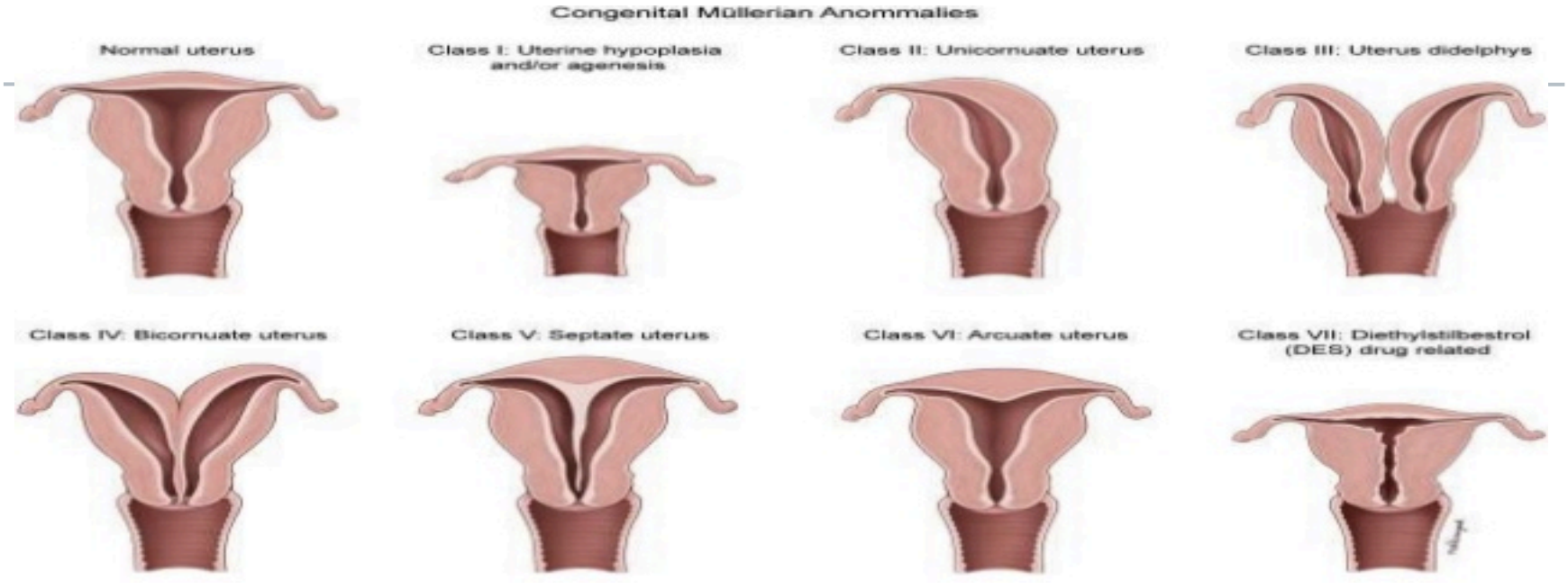
Uterine anomalies

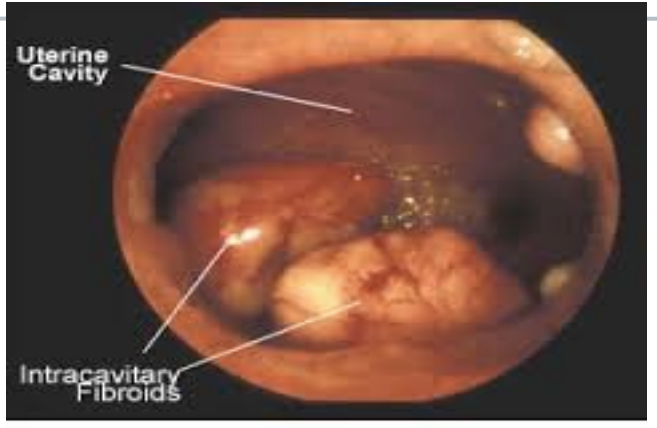
- Prevalence & implications in general is unknown
- In RPL: between 1.8% and 37.6%
- RPL may be related to cervical incompetence
- Higher prevalence with 2nd TM loss compared with 1st TM miscarriages, PTD
- Term delivery rate of only 50%



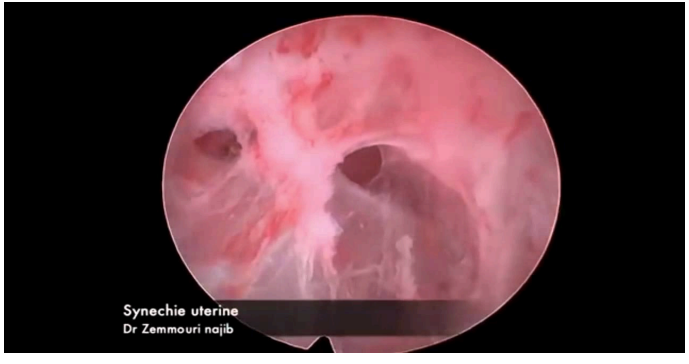
- **Unicornuate:** only one half of the uterus has developed
- **Didelphys:** the two halves of the uterus remain separate
- **Bicornuate:** an abnormal, indented external uterine surface and two endometrial cavities
- **Septate:** a normal external uterine surface but two endometrial cavities
- **Arcuate:** a normal external uterine surface with a 1 cm or less indentation into the endometrial cavity

Uterine anomalies: Treatment

- Strong history
- Pelvic USS, 3D USS, MRI
- Hysteroscopic evaluation +/- laparoscopy
- Transcervical resection of septae
- Hysteroscopic resection of:
  - polyps
  - fibroids
  - adhesions



View of uterus through a hysteroscope



Endocrine factors: DM

- Poorly controlled Diabetes mellitus has been associated with miscarriage
- Women with diabetes who have high haemoglobin A1c levels in the 1st TM are at risk of miscarriage and fetal malformation
- Pre-pregnancy counseling: Improve diet, exercise, blood glucose control, 5mg folic acid prior to pregnancy

Endocrine factors: Thyroid disease

- Thyroid dysfunction & Anti-thyroid antibodies have been linked to recurrent miscarriage
- TSH: 4-5mIU/L was considered normal but recently TSH value of over 2.5mIU/L are considered outside normal range
- Hence look for and treat subclinical hypothyroidism

Polycystic ovarian syndrome: PCOS

- Increased risk of miscarriage recently attributed to insulin resistance, hyperinsulinaemia, hyperandrogenaemia but uncertain cause (? high LH levels)
- Elevated free androgen index appears to be a prognostic factor for a subsequent miscarriage in women with recurrent miscarriage
- Treatment: Diet, Exercise, Metformin, Progesterone support

Immune factors

- No clear evidence to support human leucocyte antigen incompatibility between couples, the absence of maternal leucocytotoxic antibodies or the absence of maternal blocking antibodies
- Natural killer (NK) cells are found in peripheral blood and the uterine mucosa
- No clear evidence that altered peripheral blood NK and uterine NK cells are related to recurrent miscarriage

Infections

- Bacterial vaginosis in the 1st TM is a risk factor for 2nd TM miscarriage and PTD: oral clindamycin significantly reduces risk
- No role for routine TORCH investigations
- No role of antibiotic therapy in women with a previous 2nd TM miscarriage
- Any severe infection that leads to bacteraemia or viraemia can cause sporadic miscarriage
- Syphilis in areas of high prevalence

Thrombophilias

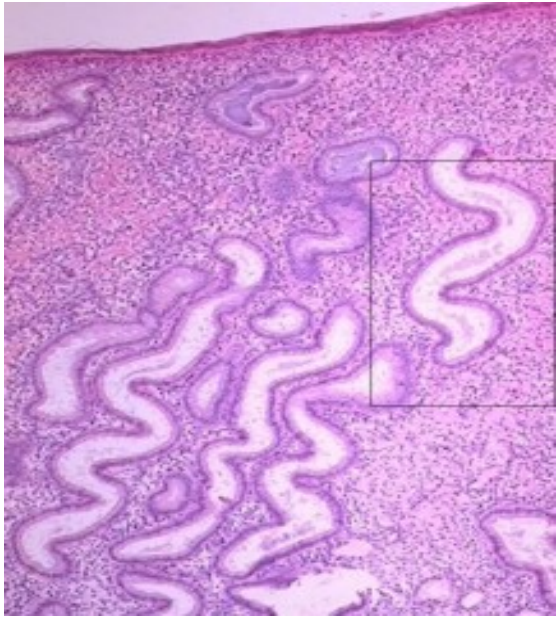
- Association between thrombophilia and late pregnancy loss has been consistently stronger than for early pregnancy loss

- Women with 2nd TM miscarriage should be screened for inherited thrombophilias

Thrombophilias: Tests

- Factor V Leiden
- Activated protein C resistance
- Prothrombin gene mutation
- Protein C and protien S deficiency
- Methylenetetrahydrofolate mutation (MTHFR)
- Carriers of factor V Leiden or prothrombin gene mutation have double the risk of experiencing recurrent miscarriage compared with women without these thrombophilic mutations

Luteal Phase Defect



- Controversial cause of RPL
  - No convincing studies showing LPD treatment improves pregnancy outcome (Lee *Semin Reprod Med* 2000;18(4):433-40)
  - 80% of women with low mid-luteal progesterone proceed to term
  - 20% of fertile women have abnormal endometrial biopsies
  - Progesterone and/or ovulation induction for LPD

Male factor

- No significant difference in semen parameters
- No difference in incidence of anti-sperm antibodies
- Aside from cytogenetic abnormalities, male factor contribution to RPL unknown (Hill ASRM 2002 Course 6 p.56)
    - Oligoasthenoteratospermia 35-74%
    - Fertile donor sperm 4-7%
- DNA Fragmentation may result in early embryo loss (Hum Reprod. 2006 Nov; 21(11):2876-81)

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Environmental Factors

Confirmed association

- Ionizing irradiation
- Organic solvents
- Alcohol
- Mercury
- Lead

Suspected association

- Caffeine (>300mg/d)
  - Fever
  - Cigarette Smoking
- Unknown association
- Pesticides

(Gardella & Hill *Semin Reprod Med* 2000;18(4):407-424)

Summary: tests

- FBC: Platelet count
- APL antibodies
- Thrombophilia screen
- FSH, LH, Day 21 progesterone, Prolactin
- Parental karyotypes
- HVS and Chlamydia
- TFT, Thyroid antibodies
- Tests for PCOS, DM if indicated
- USS
- Hysteroscopy

Summary

- More than 50% of couples with RPL have no explanation despite extensive evaluation
- Role of aspirin, progesterone supplements
- 70% live birth rates reported in couples with unexplained RPL who undertake an untreated subsequent pregnancy
    - depends on maternal age & number of prior losses
- Informative and sympathetic counseling appears to play an important role

Recurrent miscarriage package from London Gynaecology

- Our recurrent miscarriage package aims to quickly diagnose reasons for miscarriage in women
  - 30 minute consultation with a consultant gynaecologist
  - Abdominal and pelvic examination
  - Blood tests including
  - Full blood count
  - Coagulation profile
  - Antithrombin III
  - Factor V Leiden gene
  - Factor II Prothrombin gene
  - MTHFY gene
  - Activated protein C resistance
  - Lupus anticoagulant
  - Protein C and Protein S
  - Anticardioplipin antibodies
  - Chromosomal analysis
  - Comprehensive report to you and your GP
  - Direct access to consultant 24/7

Thank You

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