Genetics of Recurrent Miscarriage

Definition

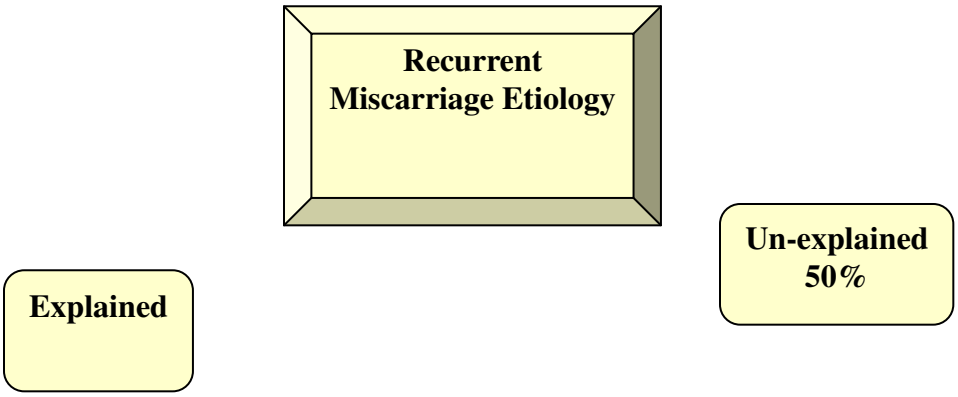
- Occurrence of 3 or more clinically recognized consecutive pregnancy losses before 20 weeks from last menstrual period
- Primary- No previous full term pregnancy
- Secondary- At least one successful pregnancy

Impact of Problem

- Couple- Extreme distress
- Doctor- Many causes and investigations but few treatment options

Incidence

- May affect as many as 1-3% of childbearing women
- First trimester losses -75%
- Second trimester loses -25%



- **Anatomic (Sporadic) 12%-16%**
- **Endocrine 17%-20%**
  - **Luteal phase deficiency**
  - **Uncontrolled DM**
  - **PCOS**
- **Immunological 10%-16%**
  - **Anti phospholipid syndrome**
- **Environmental**
  - **Alcohol, Smoking**

Chromosomal 3.5%-5%

- Fetal chromosomal abnormalities
- Parental balanced chromosomal rearrangement

- **Single gene disorders**
  - Alpha thalassemia major
  - Thrombophilia
  - X linked dominant disorders

Risk Factors for RM

- Advanced maternal age
  - affects ovarian function, giving rise to a decline in the number of good quality oocytes, resulting in chromosomally abnormal conceptions that rarely develop further.
  - **RM risk -75% in women >45years**
- Previous number of miscarriages

- Prevalence of RPL among first degree relatives of women with RPL is increased approximately sixfold compared with controls [Christiansen et al 1990]
- prognosis for subsequent pregnancies in RPL couples is better after an aneuploid miscarriage than after an euploid miscarriage

increased non random genetic abberations

- Parental chromosomal abnormality (Balanced chromosomal rearrangements)
  - General population 1 in 500(0.2%)
  - Recurrent Miscarriage- 4.1-11%
- 2-5% of couples with RSA are carriers of balanced chromosomal rearrangements

Parental Chromosomal Abnormalities

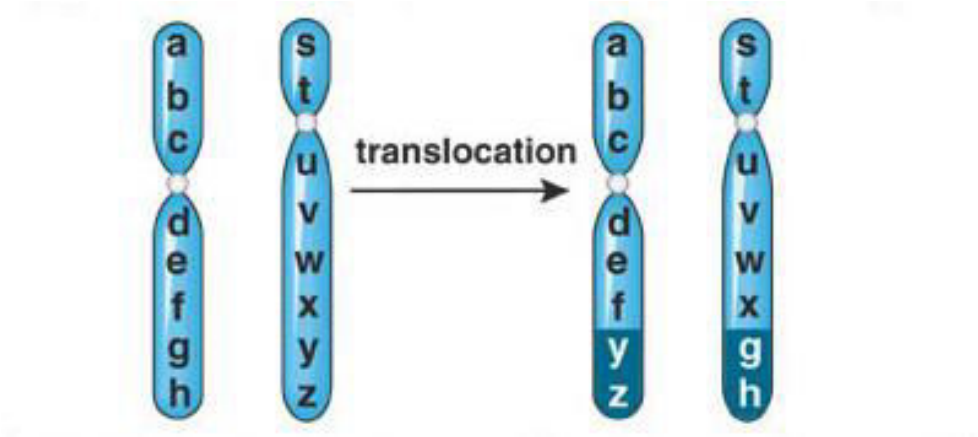
- Translocation (commonest) (1in 500)

- Reciprocal [50%]
- Robertsonian [24%]

– Mosaicism for a numeric aberration [12%]
– Inversion

Translocation

Translocation is exchange of chromosomal segments between two, non-homologous chromosomes.



Reciprocal Translocation

- two non-homologous chromosomes exchange information if no genes are broken,

individuals appears normal

(no phenotype)

- no gain or loss of genetic information

- individuals are translocation carriers t(11,22)

- if one of the breaks occurs in a gene

- gene can be disrupted

– can have a phenotype

Inversions

- A 2 breakpoint event involving one chromosome, segment between the break gets inverted, and reinserted
- **Two types-**

  Pericentric (0.12-0.7%)-

  Paracentric(0.1-0.5%)-

- **Common normal variants-**

  Inv 1,9,16,Y

Karyotype of Products of Conception

- Successful culture requires healthy cells derived from the fetus
- Unsuccessful in upto 50% of cases
  - Maternal overgrowth of fetal cells
  - Poor growth of abortus tissue esp. if there is a long time interval from the demise until the culture is performed
  - Poor chromosome morphology

Tips for chromosomal testing of products of conception-

- No definite recommendations for routinely obtaining abortus karyotype (ACOG 2001)
- Karyotype analysis of abortus tissue for couples with a subsequent second or third pregnancy loss (Hogge et al 2003)
- If abortus is aneuploid, maternal cause is excluded (ACOG, 2001)
- If POC karyotype not possible, do parental karyotype

Karyotypic abnormalities in couples with Recurrent abortions

- Total Couples n=742(1484 cases)

Sattva -Genetics of recurrent abortion

- Duration -12 years
- Chromosomal rearrangements = 52 (7%)
- Structural aberrations 22 (2.9%)
  - Reciprocal (6,8,11,18)=15 (68.2%)
  - Robertsonian (21,22,13,14)=4 (18.1%)
  - Inversion(4)=1 (9%)
  - Deletion=2
- Numerical anomalies (mosaics with XO,XXX, XXY)= 9 (1.2%)
- Chromosomal variants (para centromeric heterochromatin/fragile sites) = 21 (3.2%) [Dubey et al. Ind J Hum Genet 2005]

Genetic testing of POCs using nonculture-based techniques

array comparative genomic hybridization with or without reflex microsatellite single nucleotide polymorphism

(SNP)

- precise, more detailed, and more reliable than culture-based methods and should add to cost-efficiency and overall utility [viaggi et al 2013 Mathur et al 2014]
- Nonculture-based techniques have been used successfully in fresh and in preserved tissues [Kudesia et al 2014]
- Higher resolution- yields more genetic information
- Results - more quickly
- not require dividing cells- fetal demise or stillbirth-macerated tissue
- standardized procedure - computerized analysis

ACOG and SFM recommendations for PND - December 2013

- Limited data - clinical utility of chromosomal microarray in 1st trimester and 2nd trimester pregnancy losses - not recommended

Single Gene Disorders in Recurrent Miscarriage

- Alpha Thalassemia
- Myotonic dystrophy

X linked Dominant disorder

- Incontinentia Pigmenti
- Chondrodysplasia punctata
- Focal dermal hypoplasia of Goltz
- Rett Syndrome
- Aicardi Syndrome
- Hereditary thrombophilia
  - First and later trimester losses

- Microthrombosis in placenta ;Impaired uteroplacental circulation

Evidence based increased risk

- Factor V Leiden gene mutation
- Prothrombin G 20210A mutation
- combinations

No significant association

- Protein C,S deficiency
- Antithrombin III
- MTHFR C677T mutation

2014 Cochrane review including

- nine trials (n = 1228 women with or without inherited thrombophilia)
- authors found no evidence of an increased frequency of live birth among women with unexplained recurrent miscarriage treated with anticoagulants (asprin, heparin, LMWH or combinations of these drugs), including subgroup analysis of women with inherited thrombophilia [Dejong et al 2014]