

Recurring Miscarriage

1

Definition

Recurring miscarriage is defined as the loss of three or more consecutive pregnancies

2

Incidence

1%

3

Recurring Miscarriage

Classification

Modern-day investigators should attempt to assign each pregnancy loss into pre-embryonic, embryonic or fetal.

(Farquharson and Bricker, Oct 2000.)

4

Recurring Miscarriage

Classification

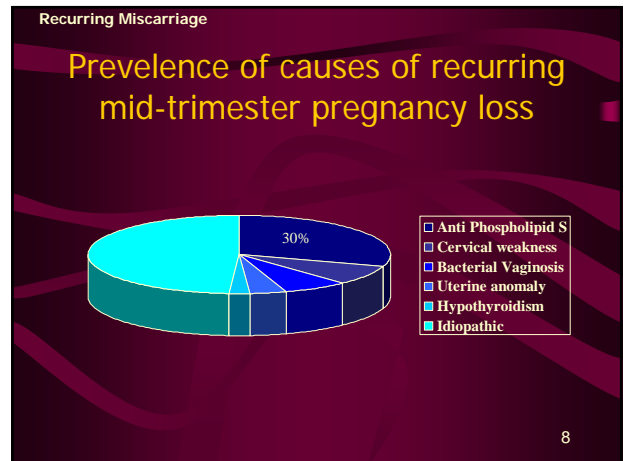
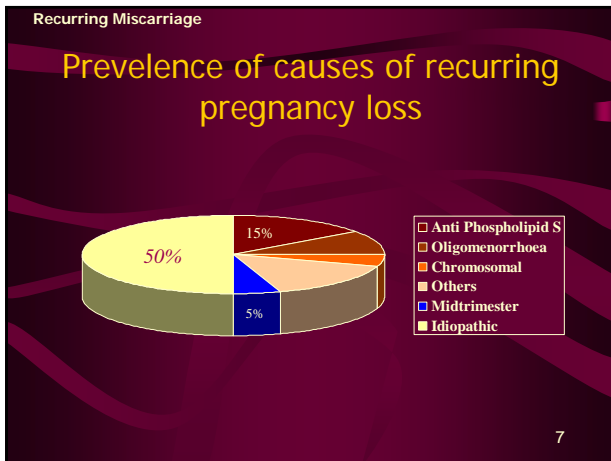
Type of loss	Typical gestation (weeks)	Fetal heart activity	Principal diagnostic group	β-hCG level
Pre-embryo	<6	Never	Idiopathic	Low then fall
Embryo	6-8	Never	Oligomenorrhoea /idiopathic	Initial rise then fall
Fetal	>8	Lost	Antiphospholipid Syndrome	Rise then static or fall

5

Ætiological Factors

- Genetic
- Anatomical
- Infective
- Endocrine
- Autoimmune
- Alloimmune
- Thrombophilic defects
- Unexplained

6



Ætiological Factors

1. Genetic factors

Although fetal chromosomal abnormalities are the commonest cause of sporadic miscarriage, they are less frequent in women with recurrent miscarriage.

9

Ætiological Factors

1. Genetic factors

3%-5% of partners presenting with recurrent pregnancy loss carry a chromosomal abnormality, most commonly a balanced reciprocal or Robertsonian translocation.

10

Ætiological Factors

1. Genetic factors

Specialist counseling offers the couple a **prognosis** for future pregnancies, as well as allowing for the investigation and counseling of **relatives** and appropriate **prenatal diagnosis** in ongoing pregnancies **(Grade C recommendation)**.

11

Ætiological Factors

2. Anatomical factors

A. Uterine Anomalies

The reported incidence of uterine septa in women with normal reproductive histories, is similar to that identified in women with a history of recurrent miscarriage.

12

Ætiological Factors 2. Anatomical factors

B. Cervical weakness

The great majority of patients with cervical weakness have a history of some preceding cervical trauma such as dilatation, TOP or cervical surgery.

13

Ætiological Factors 3. Infective factors

For an infective organism to be implicated in the aetiology of recurrent episodes of pregnancy loss, it must be capable of persisting in the genital tract and avoiding detection, or cause insufficient symptoms to disturb the woman.

14

Ætiological Factors 3. Infective factors

Toxoplasmosis, rubella, cytomegalovirus, herpes and listeria infections do not fulfil these criteria

15

Ætiological Factors 3. Infective factors

Bacterial Vaginosis in the first trimester of pregnancy has been reported as a risk factor for preterm delivery and second trimester miscarriage, but an association with first trimester miscarriage has not been shown.

16

Recurring Miscarriage

Ætiological Factors 4. Endocrine factors

- Diabetes and thyroid disease
- Luteal phase defects
- PCO
- Oligomenorrhoea

17

Recurring Miscarriage

Ætiological Factors 4. Endocrine factors

- Diabetes and thyroid disease

Systemic maternal endocrine disorders such as diabetes mellitus and thyroid disease have been associated with miscarriage. However, well controlled diabetes mellitus is not a risk factor for recurrent miscarriage, nor is treated thyroid dysfunction.

18

Ætiological Factors 4. Endocrine factors

- Luteal phase defects

These result in progesterone deficiency and may be associated with recurrent miscarriage, but in most cases it is far more likely that the fall in progesterone is an inevitable secondary effect of a pregnancy failing for other reasons.

19

Ætiological Factors 4. Endocrine factors

- PCO

The prevalence of polycystic ovaries identified using pelvic ultrasound criteria is significantly higher among women with recurrent early miscarriage (56%) when compared to the general population (22%).

20

Ætiological Factors 4. Endocrine factors

- PCO

Until very recently, it was thought that polycystic ovary syndrome predisposed to recurrent miscarriage and that hypersecretion of LH was the main factor.

21

Ætiological Factors 4. Endocrine factors

- PCO

A recent study examining PCO groups by hormonal evaluation and ultrasound criteria found no detectable effect of PCO on parity or miscarriage.

22

Ætiological Factors 4. Endocrine factors

- Oligomenorrhoea

Oligomenorrhoea is over-represented in the recurring miscarriage population (10-15%), which is in sharp contrast to the incidence in the general population (1%). The presence of oligomenorrhoea has also been shown to have a higher chance of miscarriage.

23

Ætiological Factors 5. Autoimmune factors

Primary Antiphospholipid Syndrome (PAPS) predisposes to recurring miscarriage and is implicated in the pathogenesis of a wider range of obstetric, vascular and neurological conditions.

24

Ætiological Factors 5. Autoimmune factors

Primary Antiphospholipid Syndrome (PAPS)

In women with recurrent miscarriage associated with aPL the livebirth rate in pregnancies with no pharmacological intervention may be as low as 10%.

25

Ætiological Factors 5. Autoimmune factors

Primary Antiphospholipid Syndrome (PAPS)

Pathogenesis

- Thrombosis and placental infarction
- Direct inhibition of trophoblast
- Interfere with spiral artery remodelling in second wave trophoblast invasion

26

Ætiological Factors 5. Autoimmune factors

Primary Antiphospholipid Syndrome (PAPS)

Obstetric complications

- recurrent fetal death
- severe PIH and pre-eclampsia
- fetal growth restriction
- preterm delivery
- placental abruption
- thrombosis

27

Ætiological Factors 6. Alloimmune factors

There is no clear evidence to support the concept of partner specific miscarriage or the hypothesis that some women miscarry because they lack the appropriate protective immune response to prevent rejection of their genetically dissimilar fetus.

28

Ætiological Factors 7. Thrombophilic defects

Thrombophilias such as

- Antithrombin III deficiency
 - Protein C deficiency
 - Protein S deficiency
- Hyperhomocysteinaemia
- Activated protein C resistance

seem to predispose women to recurring miscarriage as well as IUD and stillbirth.

29

Ætiological Factors 7. Thrombophilic defects

The vast majority of cases of APCR are congenital, secondary to a mutation in the factor V (Leiden) gene. Factor V Leiden is the most prevalent familial thrombophilic condition.

30

Ætiological Factors 8. Idiopathic

The importance of identifying this group is significant, since they can be reassured that the prognosis for future pregnancy with supportive care alone is in the region of 75%.

31

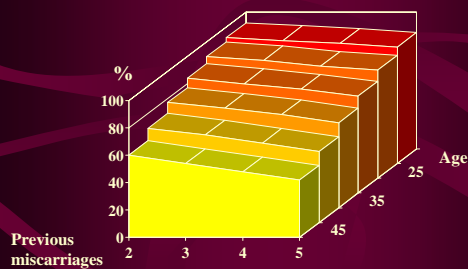
Ætiological Factors 8. Idiopathic

The most important factors affecting the predicted probability of successful pregnancy in this group are maternal age and the number of previous losses.

32

Recurring Miscarriage

Predicted probability of successful pregnancy



33

RCOG Recommendations

- What investigations to do? 📄
- What not to do? 🚫
- What treatment to use 📄
- What should be abandoned 🚫

34

RCOG Recommendations Investigations 📄

Peripheral blood karyotyping should be performed on all couples with recurrent miscarriage and the finding of an abnormality should prompt referral to a clinical geneticist. **(Grade C recommendation)**

35

RCOG Recommendations Investigations 📄

Karyotyping the products of conception in cases of recurrent miscarriage provides useful information for counseling and future management. **(Grade C recommendation)**

36

RCOG Recommendations Investigations

The routine performance of a pelvic ultrasound scan to establish **ovarian** and **uterine** morphology is a useful tool to identify women with risk factors for pregnancy loss. **(Grade C recommendation)**

37

RCOG Recommendations Investigations

Screening for antiphospholipid antibodies (both the lupus anticoagulant and anticardiolipin antibodies) is recommended but before a diagnosis of PAPS can be made it is mandatory that the patient should have two positive tests at least six weeks apart

38

RCOG Recommendations Investigations

The performance of TORCH screening is invariably uninformative. **(Grade C recommendation)**

39

RCOG Recommendations Investigations

The use of hysterosalpingography as a routine investigation is questionable since it is associated with patient discomfort, carries a risk of pelvic infection and offers the same diagnostic sensitivity as non-invasive pelvic ultrasound assessment of the uterine cavity.

40

RCOG Recommendations Investigations

Routine screening for occult diabetes and thyroid disease with oral glucose tolerance and thyroid function tests should not be performed in asymptomatic women presenting with recurrent miscarriage. **(Grade C recommendation)**

41

RCOG Recommendations Investigations

Routine tests for HLA type and anti-paternal cytotoxic antibody cannot be recommended. **(Grade B recommendation)**

42

RCOG Recommendations Investigations

A recent study has reported that testing for aPL other than LA and aCL in women with recurrent miscarriage is of no clinical value. **(Grade C recommendation)**

43

RCOG Recommendations Investigations

The place of all other investigations including a search for newly described thrombophilic defects is unproven and such tests should only be performed in the context of research studies.

44

RCOG Recommendations Treatment

The live birth rate in recurrent miscarriers with aPL treated with low dose aspirin alone (75mg acetylsalicylic acid daily) is 40% and significantly improved to 70% when they are treated with low dose aspirin together with low dose heparin (5,000 iu s.c. 12 hourly). **(Grade A recommendation)**

45

RCOG Recommendations Treatment

Treatment with metronidazole for pregnant women with bacterial vaginosis has recently been reported to reduce the risk of preterm delivery, but the benefit was only noted in those women with a history of previous preterm delivery.

46

RCOG Recommendations Treatment

Cervical cerclage should only be considered when the history of miscarriage is preceded by spontaneous rupture of membranes or painless cervical dilatation. **(Grade B recommendation)**

47

RCOG Recommendations Treatment

Open uterine surgery is associated with significant postoperative infertility and carries the risk of uterine rupture during labour. These complications are less likely after hysteroscopic surgery but randomised studies are needed.

48

RCOG Recommendations Treatment

Exogenous progesterone supplementation after conception does not improve pregnancy outcome. **(Grade A recommendation)**

49

RCOG Recommendations Treatment

Pre-pregnancy suppression of LH does not improve the live birth rate amongst ovulatory women with PCO who hypersecrete LH. **(Grade A recommendation)**

50

RCOG Recommendations Treatment

hCG supplementation should only be used in the context of ongoing randomised controlled trials

51

RCOG Recommendations Treatment

Treatment with corticosteroids in pregnancy does not improve the live birth rate and since it is associated with significant maternal and fetal morbidity should be abandoned. **(Grade C recommendation)**

52

RCOG Recommendations Treatment

The use of immunotherapy cannot be recommended. **(Grade B recommendation)**

53

RCOG Recommendations Treatment

Thrombophilic defects in women presenting with recurrent miscarriage is a promising avenue of research. However the efficacy of thromboprophylaxis during pregnancy in recurrent asymptomatic miscarriers has not been established.

54

RCOG Recommendations Treatment

The use of empirical therapy in women with no recognisable aetiological factors for their miscarriages is unnecessary and should be resisted.

(Grade C recommendation)

55

RCOG Recommendations Summary

Recurring miscarriage investigation should include

- * Peripheral blood **karyotyping** in both partners
- * **Karyotyping** of all fetal products
- * A pelvic **ultrasound scan** to assess ovarian morphology and the uterine cavity
- * Screening tests for **antiphospholipid antibodies** (both the LA and aCL) performed on two separate occasions at least six weeks apart. Discordant results should prompt the performance of a third test.

56

RCOG Recommendations Summary

In women with recurrent miscarriage who have undergone the above investigations

- * those with karyotypic abnormalities should be seen by a **clinical geneticist**
- * those with persistently positive tests for antiphospholipid antibodies should be offered treatment with **low dose aspirin** together with **low dose heparin** during pregnancy.
- * that treatments of unproven benefit should be abandoned.
- * that all future treatment options are evaluated in randomised controlled trials.

57

Thank You

58