Recurrent miscarriage

TARGET AUDIENCE	Maternity staff
PATIENT GROUP	Those affected with recurrent miscarriage

Scope

This guideline provides guidance on the diagnosis and care of women who experience recurrent miscarriage within NHS Lanarkshire. The term "recurrent early pregnancy loss" (REPL) is used interchangeably throughout this guideline with 'recurrent miscarriage'.

Definition

In this guideline, recurrent miscarriage has been defined as three or more first trimester miscarriages (up to 11+6 weeks' gestation) of a clinically-confirmed, potentially viable pregnancy. This means that such pregnancies should be confirmed on either ultrasound scan or by analysis of confirmed products of conception. These losses do not need to be consecutive. However, clinicians are encouraged to use their clinical discretion to recommend evaluation and possible treatment after two first trimester losses if there is a suspicion that the miscarriages are pathological and not of a sporadic nature.

REPL also includes two or more second trimester losses. In this guideline, a second trimester loss if the loss of a clinically-confirmed pregnancy between 12+0 and 23+6 weeks' gestation.

Criteria for Referral

- Any woman who has experienced three or more clinically-confirmed, potentially-viable pregnancy losses prior to 12+0 weeks' gestation.
- Any woman who has experienced two or more clinically-confirmed, potentially-viable pregnancy losses between 12+0 and 23+6 weeks' gestation.
- Any women aged $\geq$ 38 years who has experienced two or more clinically-confirmed, potentially-viable pregnancy losses.
- Any woman who has had three or more non-clinically-confirmed, potentially-viable pregnancy losses may be considered for review at the PEARL clinic on a case-by case basis.
- Women with a confirmed diagnosis of recurrent miscarriage can be referred to the PEARL clinic or the MOT clinic depending on the background and investigations to date.
- If there is dubiety about whether or not a woman meets the above criteria, please discuss with the PEARL clinic staff before confirming with the woman that they will be seen. If they do not meet the criteria, they will not be appointed. The PEARL clinic staff are always available to discuss individual cases prior to formal referral.

Recurrent miscarriage

Exclusion criteria

The following pregnancy outcomes should not be included when assessing for recurrent miscarriage:

- ectopic pregnancies
- pregnancies of unknown location (PUL) or biochemical pregnancies – these represent 40-80% of conceptions and reassurance is sufficient.
- molar pregnancies
- unsuccessful assisted conception pregnancies (such as IVF/ICSI) which cannot be clinically confirmed
- termination of pregnancies (social or medical reasons)

Potential causes of recurrent miscarriage

Acquired thrombophilia

- The main acquired thrombophilia implicated in recurrent miscarriage is antiphospholipid syndrome (APS) which affects 15% of women presenting with recurrent miscarriage.
- There are strict diagnostic criteria for APS which are listed below:
    - Elevated antisposholipid antibodies (APA's)
        - Significantly-elevated levels of either anticardiolipin antibodies (ACL) or lupus anticoagulant (LAC).
        - These must be **significantly-elevated** on two separate occasions at least twelve weeks apart.
        - The ranges for anticardiolipin IgG/IgM antibodies in pregnancy are as follows:
            - Negative < 10 U/mL
            - Equivocal 10-39.9 U/mL
            - Positive > 40 U/mL
        - The normal range for DRVVT (lupus anticoagulant) is 0.00 – 1.19.
        - **After the first positive test, advise the woman to use effective contraception until the test is repeated**. Conception before investigations are complete complicate the diagnosis and management of recurrent miscarriage.
    - Clinical evidence. One of the following must be present:
        - Clinical thrombosis (arterial or venous)
        - One of more pregnancy loss of ≥ 10+0 weeks' gestation of a morphologically-normal infant
        - One or more preterm birth (< 34 weeks') due to pre-eclampsia
        - Three or more CONSECUTIVE clinically-confirmed pregnancy losses < 10+0 weeks' where no other cause is identified

Inherited thrombophilia

- These include:
    - factor V leiden mutation
    - prothrombin gene G20210A mutation

  - antithrombin deficiency
  - protein C deficiency
  - protein S deficiency
- Factor V leiden mutations, prothrombin gene mutations and protein S deficiency may be associated with an increased risk of second trimester loss.
- These are weakly-associated with recurrent first-trimester miscarriage.
- Deficiencies of antithrombin, protein C and protein S may also be associated with third trimester pregnancy loss.

Genetic causes

- Fetal:
  - Up to 70% of sporadic first trimester miscarriages are due to fetal chromosomal abnormalities.
  - The presence of pregnancy loss in association with aneuploidy increases the overall risk of future aneuploidy (including fetal loss) and may influence future pregnancy first trimester screening results.
  - We have an agreement with the WOS genetic service that products of conception from the third and later confirmed pregnancy losses be sent dry with the correct paperwork for chromosomal analysis (see page 7).
- Parental:
  - **WE NO LONGER ROUTINELY TEST FOR PARENTAL KARYOTYPE**.
  - Approximately 2% of couples will demonstrate a chromosomal rearrangement that may result in unbalanced translocations in pregnancy.
  - Inheritance and consequences of unbalanced chromosomes will depend on the chromosomes involved and the size of unbalanced information.
  - Referral to Clinical Genetics is recommended when inheritance is confirmed.

Maternal uterine causes

- Congenital:
  - The commonest is a septate uterus. Others include bicorunate, subseptate, unicorunate and didelphys uteri.
  - We currently do not recommend imaging beyond a pelvic ultrasound
  - Any abnormalities should be reported during the EPAS scan.
  - If this is normal, no further scanning is required.
  - NHSL is not in a position to offer 3D ultrasound routinely.
  - Surgery has variable success and can increase risk of obstetric complications such as the placenta accreta spectrum (PAS).
- Acquired:
  - These include cervical Incompetence and other structural uterine abnormalities such as fibroids or polyps.
  - Women who have fibroids or polyps encroaching on the uterine cavity may be associated with recurrent miscarriage.

- Women with a history of second trimester miscarriage and early preterm deliveries or those with previous cervical trauma (> 1 LLETZ, cone biopsies or unrepaired cervical lacerations) may be at risk of recurrent miscarriage.

Endocrine causes

- Hypothyroidism:
  - Subclinical hypothyroidism and untreated clinical hypothyroidism have been implicated in recurrent miscarriage. However their relevance and benefit of potential therapies are yet to be confirmed.
  - Thyroid function tests (TFT's) should be offered to those presenting with recurrent miscarriage.
- Polycystic Ovarian Syndrome (PCOS):
  - there is no clear causal relationship between PCOS and recurrent miscarriage though there may be a weak association.
  - There is currently no indicated treatment for this.
  - Testing for PCOS is not routinely recommended in those presenting with recurrent miscarriage.
- Hyperprolactinaemia:
  - Significantly elevated prolactin levels are weakly associated with subfertility and miscarriage.
  - Testing prolactin levels is not routinely recommended in those presenting with recurrent miscarriage.

Immune causes

- Recurrent miscarriage has been associated with a variety of variations in immune function.
- The theoretical association of rejection of pregnancy tissue by the maternal immune system has yet to be proven.
- There may be an association with activation of peripheral and /or uterine natural killer cells. At present there is no standardised test to identify these. Research is ongoing to identify normal values and possible therapies where elevated NK/uNK cells have been implicated in recurrent pregnancy loss.
- Women with recurrent miscarriage should not be routinely offered immunological screening (such as HLA, cytokine and natural killer cell tests).

Infective causes

- Pelvic infections are associated with single miscarriages, however in the event of treated disease, no clear link has been established with recurrent miscarriage.
- Women with recurrent miscarriage should not be routinely offered infective screening.

Environmental causes

- Smoking, alcohol consumption, a high BMI and illicit substance use are all associated with pregnancy loss.
- Complete cessation of smoking should be recommended.
- Complete cessation of alcohol consumption should be recommended.
- Achieving a normal BMI should be recommended prior to attempting conception.
- Maintaining a healthy diet should be recommended.
- Taking prenatal vitamins and folic acid should be recommended.

Unexplained recurrent miscarriage

Despite these categories, there remain a significant proportion of women where a cause is not demonstrated.

Routine investigations

Women with recurrent miscarriage should be offered the following tests via the PEARL clinic:

- FBC.
- TFTs.
- Thyroid peroxidase (TPO) antibodies should not routinely be offered except if there is a history of hyperthyroidism.
- Antiphospholipid antibodies (anticardiolipin antibodies and lupus anticoagulant) testing should be offered to women with recurrent miscarriage.
- Routine testing of beta-2-glycoprotein-I levels should not be offered.
- Genetic thrombophilia screen (factor V leiden mutation, prothrombin gene mutation, antithrombin, protein C, protein S) should be offered to women with second trimester miscarriage. They have a weak association with recurrent miscarriage. Routine testing for recurrent miscarriage in early pregnancy is not recommended.
- HbA1c (if there is a history of pre-existing diabetes).
- Cytogenetic analysis should be offered on pregnancy tissue of the third and subsequent miscarriage(s) and in any second trimester miscarriage.
- Parental peripheral blood karyotyping should be offered for couples in whom testing of pregnancy tissue reports an unbalanced structural chromosomal abnormality as this is likely parental in origin.
- Absence of pregnancy tissue for whatever reason (even if the patient meets the recurrent miscarriage criteria mentioned above) is NOT an indication for requesting parental karyotyping and the genetic service will decline these requests.
- Referral to the clinical genetics service if the parents are shown to have a translocation issue etc.
- Women with previous aneuploidy will be offered routine first trimester screening.
- All scans done in EPAS should aim to determine fetal viability as well assessing for and reporting any suspected uterine anomalies.

Recurrent miscarriage

- Women with two previous LLETZ, one LLETZ with a depth of ≥ 10mm, one or more cone biopsies or a history of unexplained second trimester loss should undergo serial cervical scans in subsequent pregnancies (see separate guideline).

Treatment

- Aspirin and LMWH:
    - Women with confirmed APS should be offered LDA and LMWH from a positive test until at least 34 weeks' gestation. The dose prescribed should be 75mg daily until 7+6 followed by 150mg daily from 8+0 until 36+6.
    - Care should be provided through the MOT clinic.
    - There is limited evidence of benefit of LMWH for prevention of recurrent miscarriage in women with inherited thrombophilias.
        - These women should be referred to the PEARL clinic for counselling.
        - LMWH may be used for maternal VTE thromboprophylaxis as per current VTE risk assessment guidance (see RCOG Green Top guideline).
    - LDA and LMWH are not indicated in women with unexplained recurrent miscarriage.
- Progesterone:
    - Progestogen supplementation should be considered in women with recurrent miscarriage who present with clinical evidence of bleeding in early confirmed pregnancy.
    - The dose is 400mg micronized vaginal progesterone twice daily until 16 weeks' gestation.
    - Please see separate guideline entitled "Guideline for referral for progesterone therapy".
- Thyroxine replacement:
    - This should not be routinely recommended for euthyroid women with a history of miscarriage.
- Prednisolone:
    - This is currently being assessed for efficacy in treatment of women considered to have elevated natural killer cells.
    - At present there is no standardised protocol for their use and is restricted to administration within the confines of research.
- Intravenous immunoglobulins (IVIG) and intralipid:
    - There is little evidence of benefit of the use of IVIG in unexplained miscarriage and there are no clear clinical indications for its use outside of a research context.
    - Use of IVIG and/or intralipid is not recommended.
- Pre-implantation genetic testing (PGT) and IVF:
    - There are currently insufficient data to support the routine use of PGT for couples with unexplained recurrent miscarriage.
    - Treatment may carry a significant cost and potential risk.
    - This can be considered on a case-by-case basis and only after genetic counselling has been completed when there is a parental chromosomal abnormality.

    - The recurrence risk depends on nature of chromosomal abnormality.
- Uterine/cervical anomalies:
    - Resection of a uterine septum should be considered for women with recurrent first- or second-trimester miscarriage.
    - However, consideration for surgical intervention should therefore be reserved for case-by-case recommendations.
    - Women with a shortened cervix (<25 mm) may be considered for cervical cerclage. Progesterone has not been shown to be of clear benefit.
- Advice:
    - Women and their partners should be counselled about smoking cessation.
    - Women with recurrent miscarriage should be advised to limit alcohol consumption.
    - Women who have an ongoing history of substance misuse should be referred to LAMS.
    - Women with recurrent miscarriage should be advised to maintain a BMI between 19 and 25 kg/m^2.
    - Women with recurrent miscarriage should be advised to limit caffeine to less than 200mg/day.

Recurrent miscarriage

GENETICS TEST REQUEST FORM

West of Scotland Genetic Services (Laboratories)
Level 2, Laboratory Medicine, Southern General Hospital, Govan Road, Glasgow, G51 4TF
http://www.nhsggc.org.uk/medicalgenetics

NHS Greater Glasgow and Clyde

ENQUIRIES Tel: 0141 354 9300 Fax: 0141 232 7980 Email: geneticlabs@ggc.scot.nhs.uk

PLEASE COMPLETE THIS FORM USING BLACK INK ONLY

PATIENT DETAILS *(Printed label if available)*

Family name:

First name(s):

DOB: Sex: M ☐ F ☐ U ☐

CHI number: (mandatory)

Address:

Postcode: Pedigree/ your ref:

Hospital Number:

REFERRER DETAILS

Clinician: (please print)

Address for report:

Tel No: Fax No:

Email:

CONSENT: *It is the referring clinician's responsibility to obtain informed consent from the patient/carer for the test and for sample storage for any future diagnostic test.*

Clinicians Signature:

Print Name:

REASON FOR REFERRAL/ CLINICAL INDICATION

Is the patient clinically affected? Y ☐ N ☐

Is there a family history (if yes, give details)? Y ☐ N ☐

Is the patient pregnant? Y ☐ N ☐

If yes, how many weeks gestation? _____ weeks

TEST REQUEST		SAMPLE REQUIRED
DNA analysis (may require clinical genetics approval)	☐	*Blood EDTA*
DNA extraction and storage	☐	*Blood EDTA*
Biochemical genetics	☐	*Blood EDTA*
Microarray (may require clinical genetics approval)	☐	*Blood LiHep + EDTA*
Developmental delay	☐	*Blood LiHep + EDTA*
Chromosomes/karyotype (including QF-PCR)	☐	*Blood LiHep + EDTA*
Prenatal diagnosis (including QF-PCR)	☐	*CVS/ AF* (please circle)

SAMPLING DETAILS

Taken by: Bleep:

Date: Time:

HIGH RISK ☐ URGENT ☐

OTHER TEST REQUEST/ SAMPLE TYPE

POC/ tissue/ tumour/ FFPE tissue/ Oragene/ buccal smear (please circle and then detail test required below)

SPECIMEN CONTAINER MUST BE LABELLED WITH TWO PATIENT IDENTIFIERS, OR SPECIMEN WILL BE REJECTED

SAMPLE REQUIREMENTS:
EDTA and Lithium Heparin blood: 5ml adults/children, 1ml neonates (EDTA), 2ml neonates (LiHep). Invert tubes several times to prevent clotting.
Amniotic fluid (AF): two separate sterile universal tubes, 15ml for culture plus 5ml for QF-PCR (samples for QF-PCR must arrive ***before 2pm***).
Chorionic villi (CVS): 10-30mg in sterile transport media (samples for QF-PCR must arrive ***before 2pm***). Transport media available from laboratory.
Solid tissue: place specimen in a sterile universal tube containing 20ml of transport media. ***Products of conception (POC):*** place in a dry, sterile well sealed container. ***Tumour and lymph nodes:*** should arrive in the laboratory ***before 4pm***, if likely to arrive after this time please contact the laboratory. Fixative (e.g. formalin) should NOT be added to any tissue, POC or tumour specimens. Transport media available from laboratory.

The sample and referral card should be sealed separately in a biohazard bag, preventing paperwork contamination in the event of a leakage. All packaging must conform to UN3373(P650) standards. If a specimen is known to present an infection risk, please tick the HIGH RISK box above.

For laboratory use only:	Checks:

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This form is available from the EPAS department, Scan department or Perinatal Midwives

References

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			2
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