Recurrent Miscarriage Guideline 2017

Referral Criteria and Investigation

Scope

This guideline provides guidance on the diagnosis and care of women who experience recurrent consecutive first trimester miscarriages and/or second trimester losses within NHS Lanarkshire.

Definition

Women are classified as experiencing recurrent early pregnancy loss (REPL) if they have had three or more consecutive losses prior to 12+0 weeks' gestation of a clinically confirmed potentially viable pregnancy.

Women are classified as having had a second trimester loss if they have had a pregnancy loss of a clinically confirmed, potentially viable pregnancy of a confirmed gestation between 12+0-23+6 weeks. Two confirmed second trimester losses also fulfil the criteria for REPL.

Criteria for Referral

- Women who have experienced 3 or more consecutive pregnancy losses prior to 12+0 weeks' gestation of clinically confirmed potentially viable pregnancies are eligible for referral to the REPL clinic. (seen on scan, intrauterine, confirmed products of conception)
- Women who have experienced 2 or more pregnancy losses between 12+0 and 23+6 weeks' gestation of a potentially clinically viable pregnancy are eligible for referral to the REPL clinic.
- Women aged ≥ 38 years who have experienced 2 or more consecutive miscarriages of clinically confirmed potentially viable pregnancies are eligible for referral to the REPL clinic.
- Women who have had 3 or more pregnancy losses where clinical confirmation of potential viability cannot be confirmed for one or more loss may be considered for review at the MOT clinic on a case-by case basis.
- Women with a confirmed diagnosis of REPL should be referred to the REPL clinic at WGH or MOT clinic depending on the background and investigations to date
- Do not promise women that a REPL appointment will be sent as if the criteria are not met they will not be appointed.
    - The REPL/MOT staff are always available to discuss referrals

Exclusion criteria

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

- Ectopic pregnancy
- Pregnancy of unknown location/biochemical
    - 40-80% of conceptions: Reassurance is sufficient
- Molar pregnancy
- Unsuccessful IVF (no FH seen)
- Termination of pregnancy for social or medical reasons

Associated Causes

Thrombophilias

Acquired – This is predominantly related to Antiphospholipid syndrome (APS). This affects 15% of women who present with recurrent miscarriage.

- We test for **significantly elevated** anticardiolipin antibodies (aCL) and/or a positive Lupus Anticoagulant.
- Two positive tests taken at least 12 weeks apart are required.
- After the first positive test, advise the woman to use effective contraception until it has been repeated. Falling pregnant before investigations are complete complicate the diagnosis and management

APAS is also diagnosed when the following is present:

- either clinical thrombosis (arterial or venous),
- 1 or more pregnancy losses >10 weeks of a morphologically normal infant,
- 1 or more preterm birth <34 weeks due to pre-eclampsia or
- 3 or more miscarriages <10 weeks where no other cause is identified..

Inherited – These include Factor V Leiden, Protein C and S deficiencies.

- These are weakly associated with recurrent miscarriage.
- Factor V Leiden and Prothrombin G20210A mutation may be associated with an increased risk of late second trimester loss.
- Antithrombin, Protein S or Protein C deficiency may also be associated with pregnancy loss typically in the third trimester.

Genetic Causes

- We no longer routinely test for parental karyotype
    - We have an agreement with the WOS Genetic Services that products of conception from the third and later confirmed pregnancy losses, be sent dry with the correct paperwork for Chromosomal Analysis. (Page 7)
    - The subsequent report will inform further investigation if necessary
- 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
- 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.
- 70% of **sporadic** first trimester loss are due to chromosomal abnormalities.

Maternal uterine causes

- **Congenital** – The most common congenital association with recurrent miscarriage is septate uterus. Other congenital uterine abnormalities include bicorunate, subseptate, unicorunate and didelphys uteri.
    - We currently do not recommend imaging beyond a pelvic ultrasound
        - Any anomalies should be reported when scanned at EPAS
        - If the uterus is normal at EPAS scanning, further imaging is not recommended.
    - Surgery has variable success and can increase risk of obstetric complications such as accreta.

- **Acquired conditions** - Cervical Incompetence and Uterine Fibroids/Polyps.

    - Women who have an identified fibroid or polyp that encroaches on the uterine cavity may be associated with recurrent miscarriage.
    - Women with a history of late miscarriage (12-24 weeks) and early preterm deliveries or those with previous cervical trauma (> 1 LLETZ, cone biopsies or unrepaired cervical lacerations) may be at risk of recurrent late miscarriage.

Endocrine disorders

- Hypothyroidism
    - Subclinical hypothyroidism and untreated clinical hypothyroidism have been implicated in recurrent miscarriage; however their relevance and potential therapies for subclinical hypothyroidism are yet to be confirmed.
    - **We do not recommend thyroid function tests unless there are clinical features**
- Polycystic Ovarian Syndrome
    - there is no clear causal relationship between PCOS and recurrent miscarriage, however there may be some association. There is currently no indicated treatment for this.
    - **Testing for PCOS is not recommended in the context of REPL**
- Hyperprolactinaemia
    - Significantly elevated prolactin levels are weakly associated with reduced female fertility and miscarriage.
    - **Currently testing for prolactin is not recommended**

Immune-related

- 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 as a potential cause. Research is ongoing to identify normal values and possible therapies where elevated NK/uNK cells have been implicated in recurrent pregnancy loss.
    - **We do not recommend referral for such testing**

Infections

- Pelvic infections are associated with single miscarriages, however in the event of treated diseases, no clear link has been established with recurrent miscarriage.
    - **Bacteriological testing is not indicated in the context of REPL**

Environmental factors

- Smoking, alcohol consumption, a high BMI and illicit substance use are all associated with pregnancy loss.
    - **We recommend complete cessation of smoking**
    - **We recommend avoidance of alcohol**
    - **We recommend a healthy diet , prenatal folic acid and strongly advise a normal BMI**

Unexplained

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

Investigations

Women who attend the REPL/MOT clinic will undergo:

- Full blood count
- Antiphospholipid antibody tests (Anticardiolipin/ Lupus Anticoagulant)
- Thrombophilia screening
- TFTs (if clinical features only)
- RBG and HbA1c if there is a history of diabetes
- If tissue is available, karyotyping should be offered of pregnancy tissue after 3rd and subsequent consecutive miscarriages.
- Consideration will be given to parental karyotyping if no pregnancy tissue is available, but a pregnancy was seen on ultrasound on the third confirmed loss
    - This information must be included in the request form, or it may be declined
- Parents with demonstrated translocations etc, should be referred to clinical genetics
- Women with previous aneuploidy will be offered routine first trimester screening
- Ultrasound at EPAS should be report any suspected uterine anomalies.
- Women with two previous LLETZ, one or more cone biopsies or a history of recurrent late miscarriage should undergo serial cervical scans in subsequent pregnancies.

Treatments

- Women who have a diagnosis of Antiphospholipid syndrome should therefore be prescribed **LDA** and **LMWH** in all future pregnancies, once there are no contraindications.
- There is limited evidence of benefit with the use of LMWH in women with inherited thrombophilias.
    - Refer to MOT clinic for counselling
    - Their use may be indicated for thromboprophylaxis for the mother.
- Women who have a diagnosis of an inherited thrombophilia should be assessed regarding their thromboembolic risk and LMWH given if indicated to reduce the risk of venous thromboembolism at the appropriate gestation (Green top Guideline 37a 2015)
- There is limited evidence of a benefit to **progesterone** administration for women with unexplained recurrent miscarriage.
    - The PROMISE trial gave a clear result in that women who received progesterone where no less likely to miscarry than those who received placebo
    - We do not routinely recommend progesterone treatment
- **Prednisolone** is at present 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)
    - Women should be advised that at present there is very 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 is therefore not currently supported.

- **Pre-implantation Genetic Diagnosis and IVF**
    - 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.

- Those with demonstrated uterine anomalies should be aware that at present, there is little evidence to suggest that surgical correction improves live birth rate. Consideration for surgical intervention should therefore be reserved for case-by-case recommendation.

- Women with a shortened cervix (<15 mm) may be considered for cervical cerclage. Progesterone has not been shown to be of clear benefit

- All women and their partners should be counselled about smoking cessation. Women should be advised to avoid alcohol consumption while trying for a pregnancy. Women who have an ongoing history of substance misuse should be referred to LAMS.

- A healthy BMI improves outcome

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

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

NHS Greater Glasgow and Clyde

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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This Guideline is currently being reviewed by the Maternity Clinical Effectiveness Group in regard to any changes. It remains a current guideline until the updated version is published.