National Women & Infants Health Programme

QUICK SUMMARY DOCUMENT

Recurrent Miscarriage

This Quick Summary Document (QSD) is a resource for all clinicians working in healthcare in Ireland who are involved in the care of women/couples with Recurrent Miscarriage.

Following a comprehensive literature review a number of evidence-based recommendations for management of Recurrent Miscarriage were agreed upon.

Key Recommendations

STRUCTURE OF CARE

1. Investigation/evaluation of women/couples with RM can proceed after two consecutive pregnancy losses.
2. Couples should be referred to a RM clinic; this should have the appropriate staffing and clinical expertise, be appropriately located, with access to the required equipment and facilities.
3. Written information should be given in advance of appointments in the RM clinic, and further written information should accompany explanation of investigative findings, treatments and future pregnancy plans.

COUNSELLING AND SUPPORTIVE CARE

4. Psychological counselling and support should be offered to couples with RM and tailored to their needs.

INVESTIGATIONS

5. Medical, obstetric (for women) and family history should be used to tailor diagnostic investigations for women and men experiencing RM.
6. Maternal age and previous pregnancy history offer the best available prognostic information.
7. Advise women/couples regarding changes to potentially modifiable risk factors as relevant, including smoking cessation, maintaining a BMI between 19-25, healthy eating and physical activity (normal exercise pattern; not excessive), abstaining from alcohol and drug consumption (including caffeine, which should be reduced to <200mg/day).
8. Routine antenatal advice regarding folic acid and vitamin D supplementation should also be given.
9. Information and explanation about RM should be provided, in particular; the challenge in identifying a cause, the lack of evidence-based treatments and that there is an excellent prognosis for future pregnancy outcome without pharmacological intervention if offered supportive care alone in the setting of a dedicated early pregnancy assessment unit.

Anatomical investigations

10. As part of standard investigations for RM, women should have a pelvic ultrasound performed by an experienced ultrasonographer, with 3D ultrasound available if required to diagnose uterine anomalies.
11. Magnetic resonance imaging (MRI) is not recommended as first line option for the assessment of uterine malformations in women with RM but can be used where 3D ultrasound is not available and/or to examine complex malformations in greater detail.
12. It is recommended that imaging or imaging with hysteroscopy should be used to diagnose uterine septa rather than laparoscopy with hysteroscopy because this approach is less invasive.
13. If a Müllerian uterine malformation is diagnosed, further investigation (including investigation of the kidneys and urinary tract) should be considered.

14. At a minimum, all women should have a 2D transvaginal ultrasound to exclude any contributory gynaecological pathology.

Immunological screening

15. Women with recurrent miscarriage should not be offered routine immunological screening (such as HLA, cytokine and NK cell tests) outside of the research context.

Haematology

16. For women with RM, screening for hereditary thrombophilia should not be undertaken, unless:
    - in the context of research.
    - in women with additional risk factors and after consultation with local haematology services.
17. For women with RM, we recommend testing for antiphospholipid antibodies after two miscarriages.
18. The recommended antibodies for testing are lupus anticoagulant, anticardiolipin antibodies (IgG and IgM), and β2 glycoprotein I antibodies (IgG and IgM).

Metabolic and endocrinologic factors

19. Thyroid stimulating hormone (TSH), thyroid peroxidase antibody (TPOAb) levels and free thyroxine (FT4) levels should be tested routinely in women with RM.
20. There is insufficient evidence to support testing prolactin levels, luteal phase insufficiency, androgens, PCOS or vitamin D.
21. In select cases with a relevant menstrual or fertility history, testing 'day 2-5' hormone profile, LH, FSH, oestradiol and/or testing for ovarian reserve may be appropriate.

Infectious screening

22. Infectious screening in asymptomatic women using vaginal swab specimens is not recommended.

Screening for genetic factors

23. Cytogenetic analysis should be performed on pregnancy tissue of the third and subsequent miscarriage(s) or on the second and subsequent miscarriage if aged <35 years and not prior livebirth.
24. For genetic analysis of the pregnancy tissue, standard procedures for testing should have due regard for maternal cell contamination and risk of test failure, as well as the ability to detect chromosomal anomalies especially relevant to recurrent first-trimester miscarriage.
25. Parents should not undergo routine peripheral karyotyping. Karyotyping may be performed however after individual assessment of risk or if there is no pregnancy tissue available for testing after the third miscarriage or second miscarriage if aged <35 and no prior livebirth.
26. All individuals and couples with an atypical parental karyotype result, and a proportion of those with an atypical fetal karyotype, should be offered genetic counselling.

Histopathological Investigations

27. Any available histopathological results from previous miscarriages should be reviewed to ensure that placental pathologies with a recurrence risk, such as chronic histiocytic intervillositis or massive perivillous fibrinoid deposition, are not missed.

Investigations for male factors

28. In couples with RM, it is recommended to assess factors in the male partner that may contribute to sperm health (paternal age, smoking, alcohol consumption, medications, exercise pattern and body weight).
29. Couples with RM should not be offered routine sperm DNA fragmentation screening outside of the research context.

TREATMENT

Anatomical factors

30. There is low-quality evidence in favour of hysteroscopic uterine septum resection that suggests a reduction in miscarriage rates, but no improvement in live birth rates.
31. Metroplasty in women with bicorporeal uterus and double cervix (former American Fertility Society (AFS) didelphic uterus) and RM is not recommended due to insufficient evidence that it reduces miscarriage or improves livebirth rates.
32. Uterine reconstruction is not recommended for hemi-uterus (former American Fertility Society (AFS) unicornuate uterus) and RM due to insufficient evidence that it reduces miscarriage or improves livebirth rates.
33. Selection and treatment of women for hysteroscopic metroplasty of a uterine septum should be done by a multidisciplinary team including specialists in reproductive medicine, uterine imaging and hysteroscopic surgery.
34. Surgical management of acquired uterine anomalies are not recommended due to insufficient evidence at present, but it may be considered for select cases.

Immunological treatments

35. Immunotherapies (such as corticosteroids, intralipid, lymphocyte immunity factor, granulocyte colony-stimulating factor, tumour-necrosis factor -α blockers) are not recommended to women with unexplained RM due to insufficient evidence.
36. Paternal cell immunisation, third-party donor leucocytes, trophoblast membranes and intravenous immunoglobulin in women with previous unexplained RM are not recommended as they do not improve the live birth rate.

Treatment for thrombophilia

37. For women with hereditary thrombophilia and a history of RM, antithrombotic prophylaxis should not be used unless in the context of research, or if indicated for VTE prevention.
38. For antiphospholipid syndrome – if laboratory and clinical criteria are fulfilled, referral to local haematology service should be considered and potential for treatment with low dose aspirin (75mg) and prophylactic LMWH in next pregnancy discussed.
39. For APLS, treatment with low dose (75mg) aspirin should commence before conception and prophylactic LMWH must be initiated as soon as the pregnancy test is positive.

Treatment of endocrine factors

40. Overt hypothyroidism arising before conception or during early gestation should be treated with levothyroxine in women with RM.
41. There is low-quality evidence that levothyroxine (LT4) treatment of women with mild-moderate sub-clinical hypothyroidism (TSH levels: 4.0-10mIU/l) is associated with improved pregnancy and livebirth rates; there is insufficient evidence of benefit in women with upper normal TSH concentrations (2.5-4.0mIU/l). Treatment of women with upper normal TSH levels may reduce the risk of miscarriage, but the potential benefit of treatment should be balanced against the risks.
42. There is insufficient evidence to support treatment with levothyroxine in euthyroid women with thyroid antibodies and RM outside a clinical trial.
43. 400mg vaginal progesterone twice daily may improve livebirth rate in women with one or more miscarriages and vaginal bleeding in a subsequent pregnancy.
44. Bromocriptine treatment can be considered in women with RM and hyperprolactinemia to increase live birth rate.
45. There is insufficient evidence for HCG supplementation or metformin in the treatment of RM.

Infectious factors

46. Given the lack of prospective studies linking any infectious agent to RM, any use of antibiotics is not supported by the evidence and therefore should not be recommended.
47. There is no evidence to recommend endometrial scratching or biopsy in women with unexplained RM.

Genetic factors

48. Options for couples with chromosomal rearrangements include attempting a further natural conception, preimplantation genetic testing for structural rearrangements (PGT-SR) or gamete donation.
49. There are currently insufficient data to support the routine use of pre-implantation genetic testing for couples with unexplained recurrent miscarriage.

Male factors

50. There is no evidence to recommend treatments for male factors.

Unexplained RM and empiric treatments

51. In women with three or more consecutive miscarriages immediately preceding their current pregnancy, empiric vaginal progestogen administration of 400mg twice daily may be of some potential benefit.
52. LMWH and corticosteroids are not recommended for unexplained RM.
53. Women with RM are at increased risk of placental dysfunction and for this purpose low-dose aspirin (75mg) is recommended in a future pregnancy, with consideration of prophylactic dose LMWH based on individual risk factors and history.
54. While low dose folic acid (0.4 mg/day) is routinely started preconceptionally to prevent neural tube defects, it has not been shown to prevent pregnancy loss in women with unexplained RM.
55. Women with risk factors for folic acid deficiency, such as obesity, epilepsy or diabetes mellitus, should be considered for high dose (5mg) folic acid supplementation; in an Irish context, it should be considered for women with RM.

FUTURE PREGNANCY PLANNING

56. As part of their visit to a RM clinic, women/couples should receive written information regarding the results of investigations, treatment plans, contact numbers for available supports, (including the early pregnancy assessment unit and emergency room), in addition to necessary prescriptions and a personalised plan should a further pregnancy loss occur.
57. Provisions should be made for women to receive appropriate supportive care in terms of communication with healthcare professionals, ultrasound examinations and access to services in case of subsequent miscarriage(s).
58. At a minimum, women with an ongoing pregnancy should be booked into a consultant-led clinic for obstetric care, ideally a “high-risk” or perinatal medicine clinic whereby screening for conditions associated with RM may take place, e.g., pre-term birth, growth restriction and stillbirth.

Algorithm

Algorithm for investigations Recurrent Miscarriage

Take a complete history from the woman and her partner and consider additional investigations to those listed below accordingly

After **2 consecutive** miscarriages

Thyroid function test

Thyroid antibodies:

- Thyroid peroxidase antibodies

FBC

Antinuclear antibodies

Thrombophilia

Antiphospholipid syndrome

- Lupus anticoagulant
- Anticardiolipin antibodies (IgG and IgM)
- β2 glycoprotein I antibodies (IgG and IgM)

Consider HBA1c
(To be considered if BMI >30, family history, history of gestational diabetes, high risk ethnicity, history of polycystic ovaries)

Transvaginal Pelvic Ultrasound (with 3D imaging if necessary)

If less than 35 years and **two consecutive** miscarriage – perform cytogenetics on pregnancy tissue

If less than 35 years and **two consecutive** miscarriages and no pregnancy tissue for cytogenetic analysis – perform parental karyotypes

If **35 years or older** and **three consecutive miscarriages** – perform cytogenetics on pregnancy tissue

If **35 years or older** and **three miscarriages** with no tissue for cytogenetic analysis – perform parental karyotypes

Blood investigations and pelvic US *could* be organised in the community in advance of RM clinic appointment. Cytogenetics and karyotype must be sent from the maternity hospital.

Recurrent Miscarriage Clinic

Blood tests to investigate recurrent miscarriage

Test	Department	Bottle **
Thyroid function test	Biochemistry	Red
Thyroid antibodies: • Thyroid peroxidase antibodies	Biochemistry	Red
FBC	Haematology	Purple
Antinuclear antibodies	Immunology	Red
Thrombophilia Antiphospholipid syndrome • Lupus anticoagulant • Anticardiolipin antibodies (IgG and IgM) • β2 glycoprotein I antibodies (IgG and IgM	Haematology	Red/Purple
HBA1c **(To be considered if BMI >30, family history, history of gestational diabetes, high risk ethnicity, history of polycystic ovaries)**	Haematology	Purple

** may vary in each maternity unit according to phlebotomy/laboratory products used, verify with local laboratory prior to taking bloods

Auditable standards

Audit using the key recommendations as indicators should be undertaken to identify where improvements are required and to enable changes as necessary, and to provide evidence of quality improvement initiatives.

Auditable standards for this Guideline include:

- Percentage of women/couples receiving the recommended investigations (100%)
- Percentage of women with pregnancy outcome recorded (100%) – to include numbers who:
    - Achieve a new pregnancy
    - Achieve a new pregnancy without any form of artificial reproductive technology (ART) OR with all forms of ART
    - Go on to experience: a first trimester miscarriage/a second trimester miscarriage/fetal growth restriction/placental abruption/pre-eclampsia/baby born at ≥37 weeks' gestation/stillbirth/neonatal death (defined as: death of a live born baby occurring within 28 completed days of birth)
    - Achieve a new pregnancy within six months of their last miscarriage/≥6 months and <12 months of their last miscarriage.
- Numbers of parents with an abnormal karyotype referred for genetic counselling annually/waiting times/number who conceive without receiving counselling

Recommended reading

1. HSE Nomenclature for Clinical Audit – https://www.hse.ie/eng/about/who/nqpsd/ncca/nomenclature-a-glossary-of-terms-for-clinical-audit.pdf
2. HSE National Framework for developing Policies, Procedures, Protocols and Guidelines at https://www.hse.ie/eng/about/who/qid/nationalframeworkdevelopingpolicies/
3. Quenby S, Gallos ID, Dhillon-Smith RK, Podesek M, Stephenson MD, Fisher J, et al. Miscarriage matters: the epidemiological, physical, psychological, and economic costs of early pregnancy loss. Lancet. 2021 May 1;397(10285):1658-67. https://pubmed.ncbi.nlm.nih.gov/33915094/
4. RCOG 2021 Updated guideline Regan L, Rai R, Saravelos S. RCOG Consultation Document Oct-Nov 2021 2021;4:1-48. https://www.rcog.org.uk/media/3cbgonl0/gtg_17.pdf
5. ESHRE Early Pregnancy Guideline Development Group E. Guideline Recurrent Pregnancy Loss Update 2022. 2022. https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Recurrent-pregnancy-loss
6. Coomarasamy A, Dhillon-Smith RK, Papadopoulou A, Al-Memar M, Brewin J, Abrahams VM, et al. Recurrent miscarriage: evidence to accelerate action. Lancet. 2021 May 1;397(10285):1675-82. https://pubmed.ncbi.nlm.nih.gov/33915096/
7. RE:CURRENT Study Website – https://www.ucc.ie/en/obsgyn/plrg/plrgresearchactivity/therecurrentstudy/
8. www.pregnancyandinfantloss.ie

Authors

Linehan L, Hennessy M, Khalid A, Whelan J, O'Donoghue K. National Clinical Practice Guideline: Recurrent Miscarriage. National Women and Infants Health Programme and The Institute of Obstetricians and Gynaecologists. January 2023

https://www.hse.ie/eng/about/who/acute-hospitals-division/woman-infants/clinical-guidelines/

https://www.rcpi.ie/faculties/obstetricians-and-gynaecologists/national-clinical-guidelines-in-obstetrics-and-gynaecology/