National Women & Infants Health Programme

National Clinical Practice Guideline

# Recurrent Miscarriage

INSTITUTE OF OBSTETRICIANS & GYNAECOLOGISTS

ROYAL COLLEGE OF PHYSICIANS OF IRELAND

**Guideline Development Group**

Dr Laura Linehan (Specialist Registrar Obstetrics and Gynaecology)

Marita Hennessy, PhD (Postdoctoral Researcher)

Dr Azy Khalid (Consultant Obstetrician and Gynaecologist)

Ms Jill Whelan (Clinical Midwife Specialist in Bereavement & Loss)

Professor Keelin O'Donoghue (Consultant Obstetrician and Gynaecologist)

**Guideline Programme Team**

Prof Keelin O'Donoghue (Clinical Lead)

Ms Nicolai Murphy (Programme Manager)

**Approved by**

The National Women and Infants Health Programme (NWIHP) and the Institute of Obstetricians and Gynaecologists (IOG) Clinical Advisory Group (CAG) 2022

**Version Number:** Version 1.0

**Publication Date:** January 2023

**Date for Revision:** January 2026

**Electronic Location:**

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/

**Version control**

| Version | Date Approved | Section numbers changed | Author |
|---|---|---|---|
| | | | |
| | | | |
| | | | |

**Cite this document as:**

**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**

# Table of Contents


ALGORITHM 3

KEY RECOMMENDATIONS 4

CHAPTER 1: INITIATION 12

1.1 Purpose 12
1.2 Scope 12
1.3 Objective 12
1.4 Guideline development process 12
1.5 Stakeholder involvement 13
1.6 Disclosure of interests 14
1.7 Disclaimer 15
1.8 Use of language 16

CHAPTER 2: CLINICAL PRACTICE GUIDELINE 17

Background 17
Section 1: Structure and organisation of RM care 19
Section 2: Organisation of RM care 20
Section 3: Supportive Care 21
Section 4: Investigation of RM 23
Section 5: Treatment of RM 41
Section 6: Future Pregnancy Planning 56

CHAPTER 3: DEVELOPMENT OF CLINICAL PRACTICE GUIDELINE 59

3.1 Literature search strategy 60
3.2 Appraisal of evidence 61
3.3 AGREE II process 61
3.4 Literature review 61
3.5 Grades of recommendation 62
3.6 Future research 62

CHAPTER 4: GOVERNANCE AND APPROVAL 63

4.1 Formal governance arrangements 63
4.2 Guideline development standards 63

CHAPTER 5: COMMUNICATION AND DISSEMINATION 64

CHAPTER 6: IMPLEMENTATION 65

6.1 Implementation plan 65
6.2 Education plans required to implement the Guideline 65
6.3 Barriers and facilitators 65
6.4 Resources necessary to implement recommendations 66

CHAPTER 7: AUDIT AND EVALUATION 67

7.1 Introduction to audit 67
7.2 Auditable standards 67
7.3 Evaluation 68

CHAPTER 8: REVISION PLAN 69

8.1 Procedure for the update of the Guideline 69
8.2 Method for amending the Guideline 69

CHAPTER 9: REFERENCES 70

Reference list 70
Bibliography 88
Supporting Evidence 88

GLOSSARY (for the Purpose of this Guideline) 89

Appendix 1: Expert Advisory Group Members 2021- 90

Appendix 2: Members of the RE:CURRENT Research Advisory Group 2020-2022 92

Appendix 3: NWIHP/IOG CAG Membership (2022) 94

Appendix 4: Guideline Programme Process 96

Appendix 5: Blood Investigations Checklist 97

Appendix 6: Grades of Recommendation 98

Appendix 7: AGREE II checklist 101

Appendix 8: Policies, Procedures, Protocols and Guidelines Checklist 107

# 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
- Thyroglobulin 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.

# Key Recommendations

| No | Recommendation | Grade of recommendation* | Supporting Evidence** |
|---|---|---|---|
| **STRUCTURE OF CARE** | | | |
| **Clinical Question 1: When should women/couples with RM receive care/be investigated?** | | | |
| 1 | Investigation/evaluation of women/couples with RM can proceed after two consecutive pregnancy losses. | Best Practice | GDG |
| **Clinical Question 2: How should the care of women/couples with RM be organised?** | | | |
| 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. | Best Practice | GDG/ESHRE |
| 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. | Best Practice | GDG |
| **COUNSELLING AND SUPPORTIVE CARE** | | | |
| **Clinical Question 3: How should the psychological needs of women/couples with recurrent Miscarriage be addressed?** | | | |
| 4 | Psychological counselling and support should be offered to couples with RM and tailored to their needs. | Best Practice | GDG |

| No | Recommendation | Grade of recommendation* | Source Guideline** |
|---|---|---|---|
| **INVESTIGATIONS** | | | |
| **Clinical Question 4: What epidemiological factors are relevant for women/couples presenting with RM?** | | | |
| 5 | Medical, obstetric (for women) and family history should be used to tailor diagnostic investigations for women and men experiencing RM. | Best Practice | ESHRE |
| 6 | Maternal age and previous pregnancy history offer the best available prognostic information. | 1B | ESHRE |
| 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). | 2C | RCOG |
| 8 | Routine antenatal advice regarding folic acid and vitamin D supplementation should also be given. | Adapted | ESHRE/ RCOG |
| 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. | Best Practice | PHA NI |
| **Clinical Question 5: What are the recommended investigations for women/couples presenting with RM?** | | | |
| **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. | 2C | ESHRE |
| 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. | 2C | ESHRE |
| 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. | Best Practice | ASRM |

| No | Recommendation | Grade of recommendation* | Source Guideline** |
|---|---|---|---|
| 13 | If a Müllerian uterine malformation is diagnosed, further investigation (including investigation of the kidneys and urinary tract) should be considered. | 2C | ESHRE |
| 14 | At a minimum, all women should have a 2D transvaginal ultrasound to exclude any contributory gynaecological pathology. | 2C | ESHRE |
| **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. | 2C | RCOG |
| **Haematology** | | | |
| 16 | For women with RM, screening for hereditary thrombophilia should not be undertaken, unless:<br>• in the context of research.<br>• in women with additional risk factors and after consultation with local haematology services. | 2B | ESHRE |
| 17 | For women with RM, we recommend testing for antiphospholipid antibodies after two miscarriages. | 2C | ESHRE |
| 18 | The recommended antibodies for testing are lupus anticoagulant, anticardiolipin antibodies (IgG and IgM), and β2 glycoprotein I antibodies (IgG and IgM). | Adapted | ESHRE |
| **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. | Adapted | GDG |
| 20 | There is insufficient evidence to support testing markers for prolactin levels, luteal phase insufficiency, androgens, PCOS or vitamin D. | Adapted | GDG |
| 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. | Best Practice | PHA NI |
| **Infectious screening** | | | |
| 22 | Infectious screening in asymptomatic women using vaginal swab specimens is not recommended. | Best Practice | DGGG, OEGGG and SGGG |

| No | Recommendation | Grade of recommendation* | Source Guideline** |
|---|---|---|---|
| **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 no prior livebirth. | 2C | RCOG |
| 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. | Best Practice | GDG |
| 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. | 2C | RCOG |
| 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. | Best Practice | ESHRE |
| **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. | Best Practice | GDG |
| **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). | 2C | ESHRE |
| 29 | Couples with RM should not be offered routine sperm DNA fragmentation screening outside of the research context. | 2C | RCOG |

| No | Recommendation | Grade of recommendation* | Source Guideline** |
|---|---|---|---|
| **TREATMENT** | | | |
| **Clinical Question 6: What are the possible treatments for women/couples presenting with RM?** | | | |
| **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. | 2C | ESHRE |
| 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. | 1C | ESHRE |
| 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. | 1C | ESHRE |
| 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. | Best Practice | NICE |
| 34 | Surgical management of acquired uterine anomalies are not recommended due to insufficient evidence at present, but it may be considered for select cases. | 2C | ESHRE/GDG |
| **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. | Adapted | ESHRE |
| 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. | 1A | RCOG |
| **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. | 2C | ESHRE |

| No | Recommendation | Grade of recommendation* | Source Guideline** |
|---|---|---|---|
| 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. | Best Practice | GDG |
| 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. | 2C | ESHRE |
| **Treatment of endocrine factors** | | | |
| 40 | Overt hypothyroidism arising before conception or during early gestation should be treated with levothyroxine in women with RM. | 1C | ESHRE |
| 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. | Adapted | ESHRE/ GDG/RCOG SIP 70 |
| 42 | There is insufficient evidence to support treatment with levothyroxine in euthyroid women with thyroid antibodies and RM outside a clinical trial. | 2C | ESHRE |
| 43 | 400mcg vaginal progesterone twice daily may improve livebirth rate in women with one or more miscarriages and vaginal bleeding in a subsequent pregnancy. | 1B | ESHRE/NICE |
| 44 | Bromocriptine treatment can be considered in women with RM and hyperprolactinemia to increase live birth rate. | 2C | ESHRE |
| 45 | There is insufficient evidence for HCG supplementation or metformin in the treatment of RM. | Adapted | ESHRE/ RCOG |
| **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. | Best Practice | ASRM |
| 47 | There is no evidence to recommend endometrial scratching or biopsy in women with unexplained RM. | Best Practice | ESHRE |

| No | Recommendation | Grade of recommendation* | Source Guideline** |
|---|---|---|---|
| **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. | 2C | RCOG |
| 49 | There are currently insufficient data to support the routine use of pre-implantation genetic testing for couples with unexplained recurrent miscarriage. | 2C | RCOG |
| **Male factors** | | | |
| 50 | There is no evidence to recommend treatments for male factors. | 2C | RCOG |
| **Clinical Question 7: What are the possible treatments for women/ couples presenting with Unexplained RM?** | | | |
| **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. | Best Practice | GDG |
| 52 | LMWH and corticosteroids are not recommended for unexplained RM. | Best Practice | GDG |
| 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. | Best Practice | GDG |
| 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. | 2C | ESHRE |
| 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. | Best Practice | GDG |

| No | Recommendation | Grade of recommendation* | Source Guideline** |
|---|---|---|---|
| **FUTURE PREGNANCY PLANNING** | | | |
| **Clinical Question 8: How should women/couples with RM be cared for in a subsequent pregnancy?** | | | |
| 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. | Best Practice | GDG |
| 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). | 2C | RCOG |
| 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. | 2C | RCOG |

* The recommendations are graded using an adaption of the GRADE approach to evidence, which is further outlined in Chapter 3.

** The recommendations were compiled following a systematic review of guidelines as per the ADAPTE process and the source guideline indicates where adapted and/or adopted recommendations originated. Additional recommendations were derived following an updated review of the literature with GDG consensus and this is indicated within the table.

# Chapter 1: **Initiation**

The National Clinical Effectiveness Committee (NCEC) and Health Information and Quality Authority (HIQA) define clinical guidelines as systematically developed statements, based on a thorough evaluation of the evidence, to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances, across the entire clinical spectrum [1].

## 1.1 Purpose

The purpose of this Guideline is to provide a comprehensive, evidence-based guidance for the management of recurrent first-trimester miscarriage (RM) within the Republic of Ireland.

## 1.2 Scope

### Target Users

The Guideline is a resource for all primary, secondary and tertiary health and social care professionals who are involved in the care of women/couples with recurrent miscarriage. It may also be of interest to women/couples with RM, support and advocacy organisations and those involved in research.

### Target Population

Women, men, people and/or couples presenting with recurrent first trimester miscarriage within the Republic of Ireland.

A note on language regarding sex/gender: Throughout this document we refer to women and/or couples, noting 'people' within the target population above. In our use of the term 'women' we acknowledge that people who do not identify as cis-gender women are excluded from this descriptor, including people who identify as transgender, gender diverse and gender non-binary [2]. We also appreciate that there are risks to desexing language when describing female reproduction [3,4]. Research is needed in this area to examine the needs of people who do not identify as cis-gender women, and guideline bodies need to address this gap within current guidelines.

## 1.3 Objective

To provide evidence-based recommendations for the care of women/couples presenting with RM as well as promoting a standardised approach nationally across all maternity units regarding the structure/organisation of care, counselling and supportive care, investigations and treatments.

## 1.4 Guideline development process

The Guideline Developers agreed to undertake this work under the direction of the Guideline Programme Team (GPT). An Expert Advisory Group (EAG) was commissioned by the GPT. Their role was to critically review the Guideline prior to submission to the National Women and Infants Health Programme (NWIHP) for final approval.

See Appendix 1 for EAG membership and Appendix 3 for Clinical Advisory Group membership and Appendix 4 for Guideline Programme Process.

Many clinical guidelines regarding RM exist internationally [5]. In developing a National Clinical Guideline for Ireland, the Guideline Development Group (GDG) decided to adapt existing guidelines and/or guideline recommendations using the ADAPTE process [6].

The Guideline Developers/writing group comprised:

- Dr Laura Linehan, Specialist Registrar Obstetrics and Gynaecology, Cork University Maternity Hospital [Lead];
- Marita Hennessy PhD, Postdoctoral Researcher, Pregnancy Loss Research Group, University College Cork;
- Dr Azy Khalid, Consultant Obstetrician and Gynaecologist, University Hospital Waterford;
- Ms Jill Whelan, Clinical Midwife Specialist in Bereavement & Loss, University Hospital Waterford;
- Professor Keelin O'Donoghue, Consultant Obstetrician and Gynaecologist, Cork University Maternity Hospital.

## 1.5 Stakeholder involvement

Stakeholders are people who have a common interest in improving health services. This includes persons that are responsible for delivering and those who receive services related to the clinical Guideline.

Members of the RE:CURRENT (Recurrent miscarriage: Evaluating current services) Project [7] Research Advisory Group were consulted in regard to this Guideline. RE:CURRENT is a two-year project (2020-2022), funded by the Health Research Board, which aims to evaluate RM care in the Republic of Ireland. The RE:CURRENT Research Advisory Group was formed in 2020 and comprises 22 individuals with clinical, methodological and lived experience: healthcare and allied health professionals, representatives from advocacy and support organisations, those involved in the administration, governance and management of maternity services, academics, and women and men who have experienced RM (Appendix 2).

The RE:CURRENT Research Advisory Group were involved in a modified e-Delphi consensus study which aimed to develop guideline-based key performance indicators for RM care. As part of this process, they discussed, agreed and prioritised recommendations for RM care that had been identified within a systematic review of clinical practice guidelines for RM in high-income countries [5].

In writing this Guideline, we also incorporated the views of various stakeholders regarding services and supports for RM in Ireland which were garnered through qualitative interviews conducted by members of the RE:CURRENT Project Team between June 2020 and February 2021 [8]. Interviews were held with 42 individuals involved in the delivery and management/governance of services and supports (including consultant obstetricians and Gynaecologists, Specialist Registrars, Clinical Midwife/Nurse Bereavement Specialists, Midwives, Sonographers, Medical Social Workers, Public Health Nurses, and General Practitioners; representatives from advocacy and support organisations; those involved in the administration, governance and management of maternity services), and 13 women and seven men who had experienced at least two consecutive first-trimester miscarriages.

This GDG is also grateful to Professor Cathy Allen, Consultant Obstetrician and Gynaecologist, National Maternity Hospital, Dr Samantha Doyle, Clinical and Biochemical Geneticist, National Maternity Hospital, Dr Yvonne O' Brien, Consultant Obstetrician and Gynaecologist, Galway University Hospital

and Portiuncula University Hospital for their review of the Guideline and contribution of their expertise. We would also like to thank Jennifer Ui Dhubhgain, Secretary, Miscarriage Association of Ireland and Parent Advocate, RE:CURRENT Project for her review and insights. We are also grateful to Prof. Niamh O'Connell, National Haemophilia Director, Consultant Haematologist, National Coagulation Centre, St James's Hospital and Clinical Professor, Dept. of Haematology, Trinity College Dublin and the Coagulation Special Interest Group of the Irish Haematology Society for their review of the Guideline and subsequent recommendations.

Finally, the views of members of the RE:CURRENT Research Advisory Group and the Oversight Group for the National Standards for Bereavement Care Following Pregnancy Loss and Perinatal Death were sought on a draft version of this Guideline.

## 1.6 Disclosure of interests

Guideline developers and reviewers bring a range of experiences and perspectives to the work of the national Guideline Programme. It is likely that both Guideline developers and stakeholders/reviewers will have a variety of interests, arising from different contexts and activities done in a professional or personal capacity. These can include employment and other sources of income, speaking engagements, publications and research, and membership of professional or voluntary organisations. The involvement of individuals with relevant content expertise is essential for enhancing the value of Guideline recommendations, but these individuals may also have interests that can lead to conflicts of interest, as may peer reviewers, patient representatives and researchers.

All interests should be declared if, in the view of a reasonable person, they are relevant, or could be perceived to be relevant, to the work of the Clinical Practice Guideline in question.[1] Declaring an interest does not mean there is a conflict of interest.

It is important that interests are openly declared so they can be appropriately managed. Conflicts of interest can bias recommendations and ultimately be harmful to patients and the health system. Disclosures of interests and appropriate management of conflicts of interest, when identified, are therefore essential to producing high-quality, credible health guidelines.[2]

The Guidelines International Network (GIN), a global network of Guideline developers that aims to promote best practices in the development of high-quality guidelines, developed a set of 9 principles to provide guidance on how financial and non-financial conflicts of interest should be both disclosed and managed. It is recommended that Guideline developers follow the GIN principles.[3]

For this National Clinical Practice Guideline, all Guideline developers are asked to complete a conflict of interest declaration form. The response to declared interests will be managed by the Guideline programme team, in accordance with GIN principles. Conflicts of interest may be reported in the published Guideline and declarations of interest can be made available.

---

1 NICE (2019) Policy on declaring and managing interests for NICE advisory committees https://www.nice.org.uk/Media/Default/About/Who-we-are/Policies-and-procedures/declaration-of-interests-policy.pdf

2 Traversy G, Barnieh L, Akl EA, Allan GM, Brouwers M, Ganache I, Grundy Q, Guyatt GH, Kelsall D, Leng G, Moore A, Persaud N, Schünemann HJ, Straus S, Thombs BD, Rodin R, Tonelli M. CMAJ. 2021, 193(2):E49-E54. DOI: 10.1503/cmaj.200651 https://www.cmaj.ca/content/193/2/E49

3 Holger J. Schünemann, Lubna A. Al-Ansary, Frode Forland, *et al.*; for the Board of Trustees of the Guidelines International Network . Guidelines International Network: Principles for disclosure of interests and management of conflicts in guidelines. Ann Intern Med. 2015;163:548-553. doi:10.7326/M14-1885. https://www.acpjournals.org/doi/10.7326/m14-1885

The authors have no conflicts of interest to declare and signed a COI statement prior to embarking on guideline development.

**Funding**

LL is a PhD scholar funded through the Pregnancy Loss Research Group, Department of Obstetrics and Gynaecology, University College Cork.

MH is a Postdoctoral Researcher on a project funded by the Health Research Board Ireland [ILP-HSR-2019-011] and led by KOD, titled: "Study of the impact of dedicated recurrent miscarriage clinics in the Republic of Ireland". The funders had no role in guideline design, data collection and analysis, publication or preparation of the Guideline.

## 1.7 Disclaimer

These guidelines have been prepared to promote and facilitate standardisation and consistency of good clinical practice, using a multidisciplinary approach. Information in this Guideline is current at the time of publication.

The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the Clinician in light of clinical data presented by the patient and the diagnostic and treatment options available.

Clinical material offered in this guideline does not replace or remove clinical judgment or the professional care and duty necessary for each specific woman.

Clinical care carried out in accordance with this guideline should be provided within the context of locally available resources and expertise.

This Guideline does not address all elements of standard practice and assumes that individual clinicians are responsible for:

- Discussing care with women/couples in an environment that is appropriate and which enables respectful confidential discussion. This includes the use of interpreter services where necessary
- Advising women/couples of their choices and ensure informed consent is obtained
- Provide care with professional scope of practice, meeting all legislative requirements and maintaining standards of professional conduct
- Applying standard precautions and additional precautions, as necessary, when delivering care
- Documenting all care in accordance with local and mandatory requirements.

## 1.8 Use of language

Within this guidance we use the terms 'woman' and 'women's health'. However, it is important to acknowledge that people who do not identify as cis-gender women are excluded from this descriptor, including people who identify as transgender, gender diverse and gender non-binary[4]. We also appreciate that there are risks to desexing language when describing female reproduction[5 6]. Services and delivery of care must be appropriate, inclusive and sensitive to the needs of people whose gender identity does not align with the sex they were assigned at birth. This includes training and education regarding diverse pathways to pregnancy and the use of practices which affirm the sexual and gender identities of all people using Obstetrics and Gynaecology services.

Language use is key to effectively communicate options, recommendations, and respectfully accept a woman's fully informed decision[7]. With this in mind, the use of birth is preferable to the term delivery in all circumstances and is used consistently where possible throughout the guidelines. It is acknowledged that in some circumstances (e.g., in the case of a medically indicated intervention or surgery) and in some contexts, substituting with the term delivery is considered appropriate and this term may be used instead.

4 Moseson H, Zazanis N, Goldberg E, *et al.* The Imperative for Transgender and Gender Nonbinary Inclusion. Obstet Gynecol. 2020;135(5):1059-1068. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7170432/

5 Brotto LA, Galea LAM. Gender inclusivity in women's health research. BJOG: An International Journal of Obstetrics & Gynaecology. https://obgyn.onlinelibrary.wiley.com/doi/full/10.1111/1471-0528.17231

6 Gribble KD, Bewley S, Bartick MC, *et al.* Effective Communication About Pregnancy, Birth, Lactation, Breastfeeding and Newborn Care: The Importance of Sexed Language. *Frontiers in Global Women's Health*. 2022;3. Accessed June 9, 2022. https://www.frontiersin.org/article/10.3389/fgwh.2022.818856

7 https://blogs.bmj.com/bmj/2018/02/08/humanising-birth-does-the-language-we-use-matter/

# Chapter 2: Clinical Practice Guideline

## Background

### Prevalence

Miscarriage is generally defined as the spontaneous loss of a pregnancy before it reaches viability, that is 24 weeks of gestation, and occurs in approximately 15% of pregnancies. [9] The population prevalence of women who have had one miscarriage is 10.8%, two miscarriages is 1.9%, and three or more miscarriages is 0.7%. [9]

### Terminology and definitions

The terminology and definitions regarding RM or pregnancy loss vary across countries and professional bodies. [5] The European Society for Human Reproduction and Embryology (ESHRE) and the American Society of Reproductive Medicine (ASRM) use the term 'recurrent pregnancy loss', (RPL) [10,11] whereas the Royal College of Obstetricians and Gynaecologists (RCOG) in the UK use the term 'recurrent miscarriage' [12]. In its 2017 guideline, and in a draft revision to this Guideline to be published in 2022, ESHRE defines recurrent pregnancy loss as the loss of two or more pregnancies before viability. Disagreements amongst guideline group members were noted, however, with some stating that they would continue to use a definition of three or more consecutive losses in their clinical practice [10]. The ASRM also recommends clinical evaluation after two first-trimester clinical pregnancy losses [11]; this is supported by the American College of Obstetrics and Gynaecology [13].The RCOG retains a definition of three (non-consecutive) miscarriages, with the clinical discretion to recommend extensive evaluation after two first trimester miscarriages, if there is a suspicion that the miscarriages are of a pathological and not a sporadic nature [12].

In the present Guideline, we adopt the term 'recurrent miscarriage', which we define as two or more consecutive first trimester miscarriages. The GDG have decided to retain the definition of consecutive after consideration of the current care practices across the Republic of Ireland and the relevant resources. The focus is on recurrent first-trimester miscarriage given that this should be treated differently to second-trimester miscarriage [14,15]. We include primary RM (i.e., RM without any livebirths or pregnancies beyond 24 weeks gestation) and secondary RM (i.e., RM after one or more previous pregnancies progressing beyond 24 weeks gestation). A pregnancy within our definition includes those confirmed by either serum or urine b-hCG (i.e., biochemical pregnancies) as well as those documented by ultrasonography or histopathological examination. We include molar pregnancy in our definition of recurrent miscarriage. Although molar pregnancy is a distinct type of pregnancy loss, with a defined care pathway and follow-up, women experiencing molar pregnancy consider their loss similarly to miscarriage and 67% of clinicians would include molar pregnancy in their definition of RM.[8,16] Pregnancy losses both after spontaneous conception and after artificial reproductive technology (ART) treatments are included in the definition. We make no distinction as to whether miscarriages occurred with the same partner(s) or gamete donor(s). We exclude ectopic pregnancy, however, we acknowledge that women/couples experiencing sequential ectopic pregnancies may require additional supports in subsequent pregnancy as offered to those experiencing RM, such as that offered by Bereavement Midwives or formal counselling. This should be facilitated, in addition to early pregnancy ultrasounds.

We refer to RM in our guideline, however there are variations on this definition in the literature and there is overlap with the term RPL. The term RM will be used throughout to refer to first-trimester miscarriage, with specific variations as per the literature defined as necessary. RM refers to two or more first or second-trimester miscarriages unless specified.

### Risk factors associated with RM

Associated risk factors for RM are outlined in Table 1.

**Table 1. Risk factors associated with RM**

| Epidemiological Risk Factors associated with RM | Additional Associated Factors |
|---|---|
| Maternal age | Uterine anomalies (congenital and acquired) |
| Paternal age | Immunological factors |
| Previous obstetric history | Thrombophilias (Inherited and acquired) |
| Ethnicity | Endocrine factors |
| Smoking | Infectious agents |
| Alcohol | Genetic |
| Caffeine | Male contributory factors |
| Body mass index (BMI) | |
| Stress | |

The association of each factor with RM is discussed in detail in their relevant investigative section below.

### Significance: The clinical and economic impact of RM

Recurrent miscarriage is associated with future obstetric complications, including increased risk of preterm birth, small-for-gestational-age, fetal growth restriction, antepartum haemorrhage, placental abruption, and stillbirth. [9,17,18] It is also a predictor of longer-term health conditions, including cardiovascular disease and venous thromboembolism, and has mental health consequences. [9]

Women, and to a lesser extent, their partners, are at significant risk of symptoms of anxiety, depression and post-traumatic stress disorder after an early pregnancy loss, this is even more pronounced for people who experience RM. [19] RM has significant psychological consequences for women and their partners, including grief (which could represent a normal, uncomplicated and adaptive response to loss; 'pathological grief' can develop however), elevated anxiety and depressive symptoms [20,21] and even extend to suicidality. [22] A recent Irish study, conducted as part of the RE:CURRENT Project, found that women with RM experience a poorer health related quality of life (50% scored well below the population norm relating to mental health, indicating the likelihood of experiencing depression). [23]

Studies examining the needs and care experiences of women and/or their partners with RM highlight the need for more information, psychological support, the inclusion of partners in consultations, and appropriate follow-up care. [8,24-29]

The financial impacts of RM for women/couples in Ireland were also highlighted within the RE:CURRENT Project: women experienced decreased work productivity (70%) and substantial out-of-pocket costs for travel to RM care appointments and other medical expenses, such as additional scans and attending fertility services. [23]

# Section 1: Structure and organisation of RM care

## Introduction

As noted earlier, definitions of RM vary internationally. This can impact on when women/couples receive care for RM, including access to investigations. Some guideline bodies recommend clinical investigation after two non-consecutive losses, [10,11,13] while some continue to recommend investigation after three losses, with discretion to recommend extensive evaluation after two first trimester miscarriages [12]. Variation in referral criteria and practice in Ireland has been noted, with some maternity units/hospitals using a criterion of three consecutive miscarriages, while others adopt a criterion of two consecutive miscarriages, with or without provisions for specific circumstances, e.g. maternal age, or no living children [8,30].

In a recent study of stakeholder views on how RM is and/or should be defined, participants felt that a standardised definition of RM was needed, one which considered research evidence, individual needs, and healthcare resources [8]. They also highlighted that the definition of RM is a route to finding an answer and/or validating women/couples' experience of loss, and sometimes where RM is rigidly defined as three consecutive miscarriages, efforts are made to work around this, with associated impacts.

## Clinical Question 2.1: **When should women/couples with RM receive care/be investigated?**

### Evidence Statement

The results of a systematic review of the evidence on the prevalence of abnormal test results for RM among women with two versus three or more pregnancy losses, were supportive of investigations after two pregnancy losses in couples who had experienced RM; the authors stressed the need for additional studies on the prognostic value of test results. [31] Following their systematic review of the literature, co-authors of the recent Lancet series on miscarriage proposed a graded approach whereby women/couples are offered appropriate investigations after a second miscarriage, and a full panel of investigations following a third or subsequent miscarriage. [32] This evidence supports the guidelines, from ESHRE, American College of Obstetrics and Gynaecology (ACOG), and ASRM, respectively, which recommend clinical investigation after two miscarriages. [10,11,13].

There is some debate as to whether losses/miscarriages should be consecutive or not; however, the evidence is limited to make a firm conclusion [10], with some studies noting no reason to restrict to consecutive miscarriages [33,34]. The ACOG, ASRM and RCOG continue to recommend investigation after a defined number of consecutive miscarriages [11,13,35].

Our recommendation is to commence investigations after two consecutive miscarriages. Ultimately, the decision on when to start investigations should be decided by the Doctor and the woman/couple, taking into account their individual history and risk factors, as the result of shared decision-making, and cognisant of available resources. [10]

In keeping with the Lancet series recommendations, women/couples with any number of non-consecutive miscarriages should not be denied access to supportive care in the form of early scans, psychological supports or counselling. [32]

**Recommendations**

1. **Investigation/evaluation of women/couples with RM can proceed after two consecutive pregnancy losses.**

# Section 2: Organisation of RM care

## Clinical Question 2.2: **How should the care of women/couples with RM be organised?**

### Evidence Statement

The evidence to support this recommendation is largely derived from expert consensus, specifically from the ESHRE guidelines, [10] subject to minor wording changes when adapting to the Irish context. An additional point is made regarding interpreter services and information provision in different languages further to consensus of the RE:CURRENT Research Advisory Group.

### Clinical Practice

#### Recurrent miscarriage clinic

Couples should be referred to a RM clinic. A dedicated RM clinic is an outpatient clinic that offers specialist investigations, support and, if possible, treatment of couples with RM. It is a non-acute service, and the couples should preferably be seen and tested prior to a new pregnancy. The following are components of a RM clinic:

Staffing/expertise:

- Experienced staff members (Obstetricians/Gynaecologists/Fertility Doctors/Specialised Nurses) and with appropriate listening skills are part of the RM team.
- Ideally there should be trained and qualified staff (e.g., psychologists/social workers/counsellors/psychotherapists) either onsite or accessible, who offer support tailored to the psychological needs of the couples. Where available, this might be within a RM clinic.
- There should be experienced ultrasonographers within the early pregnancy clinic trained in the care of women with pregnancy loss, as well as in 3D ultrasound.

Location/equipment/facilities:

- The outpatient RM clinic is ideally a separate clinical space and should not be located next to an antenatal clinic, antenatal ward, or other areas where pregnant women may be seen/attend.

  If this is not possible due to the limitations of location, every effort should be made to minimise the impact on women/couples experiencing RM, for example, a separate waiting room could be made available, women could be escorted directly from the hospital entrance to the clinic or RM appointments could be provided for off-peak times.

- The team in the RM clinic should have access to the appropriate laboratories for genetics, biochemistry, and haematology testing (onsite/external).
- Virtual clinics have proved to be useful and effective in recent times. There are currently no studies examining their use in RM care to demonstrate any benefits or harms. The GDG suggests that while virtual clinics may be offered, they should remain optional.

Information provision and plans:

- In advance of the first visit/appointment, providing written information for women/couples about what to expect can help to reduce anxiety and manage expectations. All women/couples should receive an information leaflet and the summary of sources of support at an early stage in the pathway. This will facilitate repeated discussion as appropriate.
- Each individual and/or couple should have a tailored investigation plan which is explained to them, including details about expected timeframes where known; and a tailored management plan should follow for any immediate treatment and future pregnancy.
- The first visit should allow time for the clinician to review the individual's history, to answer questions and to propose a plan for investigations and, perhaps, treatment.
- The first visit is the opportunity to provide general information about RM incidence, causes and investigations and to link it to the individual's history. Staff should be aware that many women/couples with RM will already have information from a variety of sources, and some explanation and updating may be needed. Information leaflets from professional and/or reputable societies or the clinic should be offered. In addition, clinics can organise information sessions for women/couples with RM.
- Where required, interpreter services should be provided, and information should be provided in languages other than English. Care should be sensitive to cultural/ethnic backgrounds [RE:CURRENT Research Advisory Group].

### Recommendations

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.**

# Section 3: Supportive Care

## Introduction

RM is associated with significant psychological distress which may lead to more significant long-term mental health conditions if appropriate psychological care and supports are not provided [22]. This distress can be amplified for women with co-existing infertility [36,37]. Male partners are also affected by miscarriage, with feelings of grief exacerbated by being excluded from supportive care [29,38,39]. It is therefore important to take a holistic and couple-centred approach to RM care to best meet their needs [27].

Preferred supportive care in subsequent pregnancies as chosen by women with RM included:

- Early and frequently repeated ultrasounds
- BHCG monitoring
- Practical advice concerning lifestyle and diet
- Emotional support in the form of counselling
- A clear management policy for the first trimester and any medications. [25]
- Continuity of care with a single doctor who listened to and understood their concerns, with knowledge of their history and RM care, exhibiting empathy and awareness of their emotional needs was also preferred. [24]

Supportive care should be offered following the first and subsequent miscarriages, according to the needs of the individual woman/couple.

## Clinical Question 2.3: **How should the psychological needs of women/couples with recurrent miscarriage be addressed?**

### Evidence Statement

The evidence to support this recommendation is largely derived from expert consensus within the ESHRE [10] and Public Health Agency NI [40] guidelines, subject to minor wording changes when adapting to the Irish context.

### Clinical Practice

- Women/couples' psychological states and needs will vary. Whilst no single model of care will suit every individual's need, the following elements will be appreciated and should be considered:
- Recognition of the woman as an individual; time for questions, information, repetition and discussion; good listening; respect: clear and sensitive language; honesty; shared planning; supportive care in the next pregnancy/ies; kindness [10].
- Women/couple's preferred type of support, experience of recurrent miscarriages/other pregnancy loss, additional fertility issues, financial, social and personal circumstances and emotional needs should be taken into account when considering support options [10].
- Psychological counselling and support should be offered to couples with RM; these may be formal therapies where appropriate or informal supportive resources.
- The following options of support should be highlighted: (i) bereavement services within the hospital, (ii) community and voluntary sector resources – these need to be credible/trustworthy [40].

### Recommendations

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

# Section 4: Investigation of RM

## Introduction

As mentioned in Section 2 the first visit should allow adequate time for a full medical and family history of both partners to be taken. The identification of individual epidemiological and medical risk factors should tailor diagnostic investigations.

## CLINICAL INVESTIGATIONS

The investigation of women and couples with RM includes anatomical, immunological, haematological, endocrine, infectious, genetic and male factor conditions. The section which follows clinical question 2.5 will lay out the recommended investigations in each category.

Investigations could be instigated by a woman's GP in the community, but some investigations such as parental karyotype and cytogenetics must be sent from a maternity unit.

## Clinical Question 2.4: **What epidemiological factors are relevant for women/couples presenting with RM?**

### Evidence Statement

The evidence to support this recommendation is largely derived from evidence underpinning the ESHRE updated 2022 guideline [41] RCOG updated guideline [35] and the Public Health agency of Northern Ireland guideline [40] in addition to an updated search of the relevant literature.

#### Maternal age

It is recognised that miscarriage risk increases with maternal age, in addition to infertility, ectopic pregnancy, second-trimester miscarriage, stillbirth, and maternal morbidity [42,43] The risk of miscarriage is approximately 12% for women aged 20-29 and rises to 65% at age 45.[9] This is directly related to an age-related increase in embryonic trisomy, particularly trisomies on chromosomes 13, 14, 15, 16, 18, 20, 21, and 22 [9]. The risk of trisomy 16, the most common cause of miscarriage, rises linearly from 20 to 40 years of age, whereas the risks of other trisomies rise after the age of 35 [9]. Chromosomal abnormalities are found to be the primary cause of sporadic miscarriage in up to 60% of cases [9].

As explained by Rai and Regan, RM is identifiable as a distinct entity, rather than sequential sporadic miscarriages, as it may occur with a normal fetal karyotype, (particularly in women aged under 36); it has a higher incidence rate than would be expected by chance alone (1% vs 0.34%) and is related to past obstetric history [44,45]. It must be acknowledged however, that the incidence of three sporadic miscarriages (i.e., RM occurring by chance) increases significantly with age, 0.13% at age 20-24 vs 13% at age 45, i.e., a 100-fold increase [46]. It follows that the incidence of two sporadic miscarriages by chance alone also increases with age, 1.21% at age 20 vs 26% at age 45 [35]. This must be sensitively explained during counselling and is of particular relevance to women over 35 with cytogenetics results demonstrating aneuploidy.

Maternal age is an important prognostic indicator for future obstetric complications and livebirth [47,48], alongside previous obstetric history [49]. Therefore, maternal age must be taken into account when counselling regarding prognosis for future pregnancy.

### Paternal age

A systematic review has shown an increased risk of spontaneous miscarriage with paternal age greater than 45 years [50]. A direct association with paternal age and RM has yet to be proven. However, a recent study has shown that when combined with other characteristics such as number of previous pregnancy losses, maternal age, maternal and paternal BMI, maternal smoking status, and mode of conception, the probability of an ongoing pregnancy after unexplained RM declined with increasing paternal age [51].

### Previous obstetric history

Previous miscarriages impact on future pregnancy success. The chance of livebirth decreases according to the number of preceding losses [49,52]. A recent systematic review has reported subsequent miscarriage rates of 11.3%, 17.0%, 28.0%, 39.6%, 47.2% and 63.9% for women with 0, 1, 2 or 3, 4, 5 and 6 or more previous miscarriages respectively [53].

Two studies have shown that previous livebirth does not protect against miscarriage in subsequent pregnancies [54,55]. A larger register-based study over 40 years showed the chance of a livebirth in a pregnancy is higher for those women with a history of livebirth or consecutive livebirths in the immediately preceding pregnancies compared to a first-trimester miscarriage, consecutive miscarriages, second-trimester loss or stillbirth [56]. A thorough obstetric history detailing the order of livebirths, miscarriages and other adverse pregnancy outcomes may assist in counselling women with RM regarding their prognosis for a future livebirth.

### Ethnicity

A retrospective cohort study of 196,040 women demonstrated that compared with white Europeans, the odds of a previous miscarriage were increased in black African (adjusted odds ratio [aOR] 1.20; 95% confidence interval [CI] 1.12-1.29) and black Caribbean women (aOR 1.31; 95% CI 1.21-1.41) [57].

### Smoking

A systematic review demonstrated that any active smoking was associated with increased risk of miscarriage (relative risk ratio (RRR) 1.23, 95% confidence interval (CI): 1.16, 1.30; n = 50 studies) [58]. The risk of miscarriage increased with the amount smoked (1% increase in relative risk per cigarette smoked per day) [58]. Second-hand smoke increased the risk of miscarriage by 11% [58]. Significant negative outcomes were detected in the female smokers compared with non-smokers undergoing artificial reproductive technology (ART) including decreases in live birth rate per cycle (OR = 0.52, 95% CI 0.37-0.74), in clinical pregnancy rate per cycle (odds ratio (OR) 0.59, 95% CI 0.51-0.68), in number of retrieved oocytes (mean difference (MD) = –0.87, 95% CI –1.39 to –0.25), and in average fertilization rate (MD = –4.80, 95% CI –8.49 to –2.02), as well as a significantly increased miscarriage rate per pregnancy (OR = 2.48, 95% CI 1.79-3.43) [59].

In a meta-analysis of eight studies, paternal smoking of >10 cigarettes per day in the preconception period was found to be associated with an increased risk of pregnancy loss, after adjustment for maternal smoking status (1-10 cigarettes per day) aOR 1.01; 95% confidence interval [CI], 0.97-1.06; 11-19 cigarettes per day, 1.12; 95% CI, 1.08-1.16; ≥20 cigarettes per day, 1.23; 95% CI, 1.17-1.29) [60].

Therefore, given the association between smoking and poor obstetric outcomes in addition to miscarriage, it is recommended that women are encouraged to stop smoking in advance of trying to conceive. Male partners should also be encouraged to quit smoking both to reduce the risk of miscarriage and to minimise second-hand smoke inhalation for their partner.

### Alcohol

Alcohol has a clear negative impact on pregnancy and neonatal outcomes, including the fetal alcohol spectrum disorders. Therefore, it is advisable that women avoid consumption of alcohol during pregnancy [41].

A large Chinese study of 4.5 million women demonstrated that preconception alcohol consumption was associated with higher odds of miscarriage, and an increasing risk was found with paternal and maternal alcohol consumption. Compared with non-drinkers, the aOR of miscarriage was 1.06 (95% CI 1.02 to 1.10) and 1.59 (95% CI 1.15 to 2.20) in maternal occasional drinkers and regular drinkers, respectively. Compared with couples in which neither the male nor the female consumed alcohol, the aOR for miscarriage among women was 1.09 (95% CI 1.07 to 1.10), 1.13 (95% CI 1.06 to 1.21) and 1.12 (95% CI 1.07 to 1.17) in the couples in which only the female drank alcohol, only the male drank alcohol, and both drank alcohol, respectively. Conversely, the aOR was 0.58 (95% CI 0.51 to 0.65) in women with alcohol abstinence compared with alcohol drinkers [61]. However, a separate systematic review did not find an association between RM and alcohol consumption [62].

Women and their partners should be advised to limit alcohol consumption if trying to conceive. Women who are concerned that previous consumption may have had a role in pregnancy loss should be reassured that there is no causal association [41].

### Caffeine

The evidence for an increased risk of RM with caffeine consumption has been conflicting, with observational studies reporting an increased risk of RM [63,64] and others reporting no association [65,66]. The risk of RM has been shown to increase with higher doses of caffeine intake with those consuming >300mg/day at highest risk [63,64].

This Guideline, in line with RCOG guidance, recommends that women aim to consume no more than 200mg caffeine per day [35].

### Body Mass Index (BMI)

Pregnant women with a BMI >30 are at greater risk of a variety of pregnancy-related complications compared with women with a BMI ≤30, including pre-eclampsia and gestational diabetes [67]. A systematic review and subsequent meta-analysis has shown that women with a BMI < 18.5 and women with a BMI ≥ 25 have higher odds of RM than the general population (OR 1.2, 95% CI 1.12– 1.28 and OR 1.21, 95% CI 1.06–1.38, respectively) [62]. In women with RPL, having BMI ≥ 30 and BMI ≥ 25 has increased odds of further miscarriages (OR 1.77, 95% CI 1.25–2.50 and OR 1.35, 95% CI 1.07–1.72, respectively) [62]. The quality of the evidence for these findings was low or very low. Women trying to conceive should be advised that a BMI ≥ 18.5 and <25 is associated with decreased risk of miscarriage.

### Stress

Women with RM have been shown to have higher levels of stress in addition to established mental health conditions such as post-traumatic stress, anxiety and depression [19,52]. Whether stress is in itself a cause of RM has yet to be definitively proven, with some studies showing an association [68,69] and others failing to show that stress is a factor in pregnancy loss [70,71].

The potential association between stress and miscarriage is of concern to women with RM (this may include other stresses such as work-related or significant life-event related stressors, other than the direct stress of RM) and thus women and their partners should be reassured that there is no evidence of a direct causal association and any specific concerns should be addressed [35].

Pre-existing mental health issues and any impact of RM or concerns should be addressed, and additional supports provided. Prescribed medications such as anti-depressants should be identified, and women should be advised that they should not be stopped abruptly in early pregnancy without discussion with their GP/mental health physician and that drugs such as SSRIs may be continued in pregnancy if deemed necessary.

## Clinical Practice

*The following are the adapted/adopted recommendations with approximate GRADE recommendation rating (see Appendix 6) with source guideline and strength of recommendation and evidence in square brackets. GPP = Good practice point, NS = not specified.*

- The first visit is an opportunity to obtain a detailed maternal medical history in addition to a thorough obstetric history, family history and social history. Details regarding past fertility treatment should also be noted. A full history should also be taken from a male partner to examine contributory medical, fertility, behavioural or weight-related factors. These histories should be used to tailor subsequent diagnostic investigations [41]. Best practice [ESHRE 2022; GPP]
- Women should be sensitively informed that the risk of pregnancy loss is lowest between the ages of 20 and 35, with a significant increase after the age of 40 [41]. 1B [ESHRE; Strong, 3]
- Maternal age and previous pregnancy history offer the best available prognostic information [41]. 1B [ESHRE; Strong, 3]
- Factors that infer increased future obstetric risk, such as preterm birth, in women with RM such as ethnicity, BMI and smoking should also be discussed and considered in any subsequent antenatal care plans [35]. 2C [RCOG; ethnicity (2+, D) smoking (2+D), BMI 2++, B)]
- Paternal age is also associated with miscarriage, as is sperm quality [72,73]. Therefore, male contributory factors should be examined. 2C [ESHRE; Conditional, 2]
- 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) [35,41]. 2C [RCOG;2D-]
- Where applicable, weight management supports/referrals should be provided in line with HSE Model of Care [74], as should smoking cessation supports,[75] with the informed consent of the woman. Best practice [GDG; GPP]
- Routine antenatal advice regarding folic acid and vitamin D supplementation should also be given [40]. Best practice [PHA NI; GPP]
- Information and explanation about RM should be provided, in particular; the challenge in identifying a cause, the lack of evidence-based treatments and the excellent prognosis for future pregnancy outcome without pharmacological intervention if offered supportive care alone in the setting of a dedicated early pregnancy assessment unit. Best practice [PHA NI; GPP]
- It is important to emphasise to women with unexplained RM that the chance for a future successful pregnancy can exceed 50%-60% depending on maternal age and parity [40]. Best practice [PHA NI; GPP]

### Recommendations

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.

## Clinical Question 2.5: **What are the recommended investigations for women/couples presenting with RM?**

Investigations are covered according to category. In appendix 5, a summary of suggested bloods to be taken prior to review at the RM clinic are listed. See algorithm for suggested investigations of RM.

## ANATOMICAL INVESTIGATIONS

### Evidence Statement

Uterine anomalies have been associated with RM. These can be congenital or acquired.

The recommendations in this section are derived from existing guideline recommendations [11,35,41,76] with updated literature searches where relevant, in addition to supporting literature for each association to illustrate clinical significance.

#### Congenital uterine anomalies

A systematic review and meta-analysis found the prevalence of uterine anomalies diagnosed 5.5% [95% CI, 3.5-8.5] in women with no history of RM or infertility, 8.0% (95% CI, 5.3-12) in infertile women, 13.3% (95% CI, 8.9-20.0) in those with a history of miscarriage and 24.5% (95% CI, 18.3-32.8) in those with miscarriage and infertility.[77] The most common anomaly in the unselected population was arcuate uterus, which was not more prevalent in women with miscarriage [77]. Canalisation defects, namely septate uterus, were significantly more common in women with a history of miscarriage (5.3%; 95% CI, 1.7-16.8,P=0.021) or miscarriage and infertility (15.4%; 95% CI, 12.5-19,P=0.001) [77]. Unification defects such as bicornuate, unicornuate or didelphic uteri were also more prevalent in women with miscarriage (2.1%; 95% CI, 1.4-3,P=0.001) or miscarriage and infertility (4.7%; 95% CI, 2.9-7.6,P=0.001) than in the unselected population (0.4%; 95% CI, 0.2-0.6) [77].

A systematic review and meta-analysis to determine the clinical implications of congenital uterine anomalies found that women with septate (RR 2.65, 95% CI 1.39-5.06) and bicornuate uterus (RR 2.32, 95% CI 1.05-5.13) had a significantly increased probability of first-trimester spontaneous miscarriage compared with their controls [78]. There were insufficient studies to examine specific anomalies and recurrent first-trimester miscarriage risk, but overall women with RM and congenital anomalies were at increased of first and/or second-trimester miscarriage compared to women with unexplained RM RR 1.13 (95% CI 1.06-1.22) [78].

### Acquired uterine anomalies

#### Fibroids

A large meta-analysis demonstrated no association between fibroids and miscarriage, however it did not examine for differences between submucosal, intra-mural or subserosal fibroids, which has been shown to be of relevance for fertility and spontaneous miscarriage [79,80]. Submucosal fibroids have been shown to have an association with second-trimester miscarriage, but further studies are needed to determine such an association with recurrent first-trimester miscarriage [81].

#### Adhesions

Intrauterine adhesions are more prevalent among women having two or more miscarriages, with surgical management of miscarriage a likely risk factor [82]. Women with identified and treated adhesions had fewer ongoing pregnancies and live births in addition to a prolonged time to a live birth [83].

#### Polyps

There is no evidence to link endometrial polyps and RM [41].

## Clinical Practice

- Although the role of uterine anomalies in first-trimester RM is debatable, assessment of uterine anatomy is widely recommended [11]. Best practice [ASRM, NS]
- The preferred technique to evaluate the uterus is transvaginal 3D ultrasound, which has a high sensitivity and specificity, and can distinguish between septate uterus and bicorporeal uterus with normal cervix (former American Fertility Society (AFS) bicornuate uterus) [41]. 2C [ESHRE; Conditional, 2]
- The RM clinic should have excellent ultrasound provision and offer 3D ultrasound or additional saline or gel infusion sonography if indicated. Best practice [GDG; GPP]
- Sonohysterography (SHG) is more accurate than hysterosalpingography (HSG) in diagnosing uterine malformations. It can be used to evaluate uterine morphology when a 3D Ultrasound is not available. 2C [ESHRE; Conditional, 2]
- 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 [41]. 2C [ESHRE; Conditional, 2]
- MRI results should be interpreted by Radiologists with experience in gynaecological imaging, in the context of relevant ultrasound imaging and a multi-disciplinary meeting should be undertaken prior to any surgical treatment of congenital uterine anomalies. Best practice [GDG; GPP]
- 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 [76]. Best practice [ASRM; B, NS]

- If a Müllerian uterine malformation is diagnosed, further investigation (including investigation of the kidneys and urinary tract) should be considered [41]. 2C [ESHRE; Conditional, 2]
- At a minimum, all women should have a 2D transvaginal ultrasound to exclude any contributory gynaecological [41]. 2C [ESHRE; Conditional, 2]

### Recommendations

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 INVESTIGATIONS

### Evidence Statement

There has been much interest in immunological factors such as human leukocyte antigens (HLA), cytokines and peripheral and uterine natural killer (NK) cells and their potential role in RM.

The recommendations here are derived from the RCOG and ESHRE guidelines in addition to updated relevant literature.

#### Human Leukocyte Antigens (HLA)

HLA alleles and HLA sharing were found to be associated with RM in one systematic review, however the included studies had a high degree of selection and inclusion bias, thus must be interpreted with caution [84]. There is a paucity of information on subsequent pregnancy outcomes in women with these findings and thus the significance of these associations is yet to be determined.

HLA-C antibodies have been shown to be raised in women with RM [85] and to be higher in women who have previous miscarriage compared to a previous livebirth [86], but their association with RM has not been definitively proven [87].

#### Cytokines

It has been theorised that pro-inflammatory conditions, such as an increased ratio of inflammatory Th1 cytokines (in particular TNF-α) to anti-inflammatory cytokines may contribute to RM [88]. A review of immunological testing in RM concluded that while some abnormal cytokine profiles are associated with RM, the intrinsic variations in cytokine levels makes reliable measurement and interpretation difficult [89]. Moreover, cytokine polymorphism studies have found that no corresponding cytokine gene polymorphism has been strongly associated with RM [90-92]. Therefore, greater study is required on the role of cytokines in RM.

### Natural Killer Cells (NK)

NK cells are part of the innate immune system and may be classified according to their degree of CD 56+ expression (bright or dim) and their location (peripheral or uterine), with uterine NK typically being predominantly CD56+ bright [93]. An updated systematic review and meta-analysis found that the CD56+ uterine NK level in women with RM was not elevated compared with controls, however in subgroup analysis of mid-luteal endometrial samples, women with RM had significantly higher levels of CD56+ uterine NK (standardised MD 0.49, CI 0.08, 0.90; P = 0.02; I2 88%; 1100 women) [94]. However, there was no difference in pregnancy outcome in women with RM stratified by uterine NK level, and no significant correlation between peripheral NK and uterine NK levels in women with RM [94]. Overall the findings indicated that measurements made on peripheral NK do not predict uterine NK level or activity [94]. There was also significant heterogeneity between the studies, with differences in collection technique and reference ranges. Combined with the complexity of NK cells interactions, it is not yet possible to conclude if raised uterine NK cells are an association or consequence of RM.

### Anti-Nuclear Antibodies (ANA)

Two meta-analyses have confirmed an association between RPL (defined as two miscarriages prior to viability) and ANA positivity [95,96]. ANA positivity was associated with increased RPL risk, particularly with higher ANA titres [96]. The significance of this association is not yet clear.

### Anti-HY antibodies

Anti-HY antibodies are antibodies directed against male-specific minor histocompatibility (HY) antigens expressed on most or all nucleated cells from males [41]. A single observational study implicated these antibodies in reduced livebirth after RM, but additional evidence has not been forthcoming [97]. Thus, measurement is not recommended in clinical practice.

## Clinical Practice

- Human leukocyte antigen determination in women with RM is not recommended in clinical practice [41]. 2C [ESHRE; Conditional, 2]
- Cytokine (including cytokine gene polymorphisms) testing should not be used in women with RM in clinical practice [41]. 2B [ESHRE; Conditional, 3]
- Measurement of anti-HY antibodies in women with RM is not recommended in clinical practice [41]. 2C [ESHRE; Conditional, 2]
- Antinuclear antibodies testing could be considered for explanatory purposes [41]. 2C [ESHRE; Conditional, 2]
- There is insufficient evidence to recommend natural killer (NK) cell testing of either peripheral blood or endometrial tissue in women with RM outside of clinical studies [41]. 1C [ESHRE; Strong 1]

### Recommendations

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

# INVESTIGATIONS FOR THROMBOPHILIA

## Evidence Statement

Thrombophilic disorders associated with RM can be acquired or inherited.

The recommendations in this section are taken from the ESHRE, British Society of Haematology guidelines and DGGG, OEGGG and SGGG guidelines with updated relevant literature [41,102,110].

### Acquired

Antiphospholipid syndrome is an acquired autoimmune condition defined as the association between antiphospholipid antibodies (lupus anticoagulant (LA), anticardiolipin antibodies (ACA, IgG and IgM), and β2 glycoprotein I antibodies (aβ2GPI, IgG and IgM)) and thrombosis (venous, arterial or microvascular) with pregnancy morbidity.

Pregnancy morbidity includes:

a. one or more deaths of a fetus (without any attributable congenital anomaly) after ten weeks' gestation

b. one or more preterm births of a neonate up to 34 weeks due to eclampsia/pre-eclampsia or placental insufficiency

c. three or more miscarriages less than ten weeks' gestation [98].

However, a later publication demonstrated no difference in diagnostic yield for antiphospholipid syndrome after three miscarriages compared to two miscarriages, thus the ESHRE GDG took the decision to implement antiphospholipid antibody testing after two miscarriages [99].

Overall, antiphospholipid antibodies have been shown to have an association with RM, although the association appears stronger with second-trimester loss [100,101]. Testing for antiphospholipid antibodies is in line with the British Haematology Society Guideline which states, "For women with recurrent or late pregnancy loss, screening for antiphospholipid antibodies can be considered as the results aid risk stratification and treatment decisions" (Evidence grade 2B)[102].

It is important to check with local laboratories prior to ordering antiphospholipid antibodies, as they may require written consent from the woman in advance.

### Inherited

There is conflicting evidence as to whether inherited thrombophilias such as factor V Leiden (FVL), prothrombin gene mutation, protein S, protein C, Anti-Thrombin or MTHFR mutations are associated with recurrent pregnancy loss (RPL), that is, first and second-trimester miscarriages.

An updated systematic review and meta-analysis has reviewed the associations between inherited thrombophilias and RPL, and whether the association varied according to first or second-trimester losses or two or three losses [103]. Analysis of pooled data from 81 studies indicated a significant association between FVL mutation and RPL (OR: 2.44, 95% CI: 1.96-3.03), for both heterozygous (OR 2.07, 95% CI 1.57,-2.72) and homozygous status (OR 2.76, 1.34-5.71)[103]. Compared to the reference group, the risk of early RPL (OR 1.69, 95% CI: 1.18-2.41) and late RPL (OR: 5.07, 95% CI:2.22-11.57) were significantly higher among pregnant women with the *FVL* mutation [103].

Analysis of pooled data from 64 studies indicated a significant association between the prothrombin gene mutation and RPL (OR: 2.08, 95% CI: 1.61-2.68) [35]. Nonetheless, there was no significant

difference in the risk of first or second-trimester losses with the prothrombin gene mutation. A more recent study of 1155 women with RM in the UK found that inherited thrombophilias (FVL, prothrombin gene, anti-thrombin, protein S and C deficiencies) were equally prevalent in a RM population compared to the general population [104].

Screening for FVL is initially done by checking for Activated Protein C resistance, 90% of APCR is caused by the presence of FVL gene mutation. The test for APCR is not a genetic test. APCR is tested by performing an APTT with and without activated protein C and a resultant reduced ratio between these two results would prompt formal clotting and molecular tests (usually PCR) for the FVL gene mutation [105]. Subsequently formal consent should be sought for the genetic test with adequate explanation of the ramifications of such testing for the individual and their family. However, it is important to check local laboratory policy regarding written consent for the APCR test and subsequent FVL test as it may be required in advance.

Meta-analysis from ten studies indicated a significant association between deficiency of PS and RPL (OR: 3.45, 95% CI: 1.15-10.35) [106]. However, considering the limited number of included studies and substantial between-study heterogeneity, the result should be interpreted with caution.

Analysis of pooled data from seven studies showed no significant association between anti-thrombin deficiency and RPL (OR: 0.83, 95% CI: 0.29-2.36) and analysis of pooled data from nine studies showed no significant association between Protein C deficiency and RPL (OR: 1.98, 95% CI: 0.97-4.04) [103]. The authors note that in addition to heterogeneity of studies, controlling of confounders was limited and thus these associations may be confounded by other risk factors for pregnancy loss.

The MTHFR C677T mutation has been shown to be associated with RM in one systematic review [107], but not in others [108,109].

Considering the association between FVL and miscarriage, particularly with second-trimester miscarriage, the GDG had considered FVL screening to be of relevance to future pregnancy management and identifying potential causative factors of RM. However, following consultation with the Coagulation Special Interest Group of the Irish Haematological Society, testing for FVL and other inherited thrombophilias are *not* recommended in the investigation of RM in line with the British Society for Haematology Guideline 2022 [102], and with the concerns that FVL screening would not fulfil the WHO criteria for a screening programme and may cause potential harms such as anxiety, unnecessary treatment, implications for other family members and cost. This is in keeping with the ESHRE RPL draft guideline which limits inherited thrombophilia testing to those with additional risk factors [41]. The RCOG draft guideline recommends limited inherited thrombophilia testing (FVL, Prothrombin gene and protein S deficiency) in second-trimester miscarriage, but with the caveat that there is limited evidence that treatment improves outcomes [35]. If women have a significant family or personal VTE history alongside a RM history or other adverse pregnancy outcome arising from thrombosis, testing and/or treatment could be discussed with local haematology services if uncertainty arises.

## Clinical Practice

- 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, 2B [ESHRE; Conditional, 3]

- Any screening undertaken for inherited thrombophilia should be accompanied with adequate counselling as to the implications of such screening (pregnancy risks, potential for affected family members etc.) and the lack of evidence that antithrombotic prophylaxis improves subsequent pregnancy outcomes. Best practice [GDG]
- Testing for non-criteria antiphospholipid syndrome based on clinical and laboratory parameters should be undertaken in women with RM, particularly if clinical manifestations are present (livedo reticularis, ulcerations, renal microangiopathies, neurological disorders and cardiac manifestations) [110]. Best practice [DGGG, OEGGG and SGGG; ++, expert]
- For women with RM (two or more miscarriages before ten weeks of gestation), we recommend screening for antiphospholipid antibodies [41]. 2C [ESHRE; Strong, 2]
- The recommended antibodies for testing are lupus anticoagulant, anticardiolipin antibodies (IgG and IgM), and β2 glycoprotein I antibodies (IgG and IgM) [41]. Best practice [ESHRE; adapted]
- Monitoring of plasma coagulation markers (D dimers, prothrombin fragments, etc.) during pregnancy is not recommended in women with RM. Determination of these markers must not be used as an indication to initiate therapy to prevent miscarriage [110]. Best practice [DGGG, OEGGG and SGGG; +++, expert]

### Recommendations

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 2B**
17. **For women with RM, we recommend screening for antiphospholipid antibodies.**
18. **The recommended antibodies for testing are lupus anticoagulant, anticardiolipin antibodies (IgG and IgM), and β2 glycoprotein I antibodies (IgG and IgM).**

## ENDOCRINE INVESTIGATIONS

### Evidence Statement

Recommendations in this section have been adapted from ESHRE and Public Health Agency for Northern Ireland guidelines with updated literature.

#### Thyroid disease

Due to the adverse outcomes linked with overt hyper- and hypothyroidism in pregnancy, and clear indications for treatment, the focus of research in thyroid disease and RM is whether RM is linked to sub-clinical hypothyroidism and the presence of thyroid antibodies.

Subclinical hypothyroidism is a biochemical diagnosis defined by raised levels of serum TSH, above the accepted laboratory reference range, accompanied by normal concentrations of circulating thyroid hormones (free thyroxine (FT4) and free triiodothyronine (FT3).[111] SCH is usually asymptomatic and may represent the earliest stages of thyroid dysfunction, which can progress to overt hypothyroidism (OH).[111] There is debate as to what constitutes a raised TSH level, 4.0mIU/l is generally accepted, but in certain populations (e.g., women with RM or infertility) this was reduced to 2.5mIU/l. These variations have

contributed to heterogeneity between studies, as well as in clinical practice. The RCOG have suggested that upper-normal TSH level is 2.5-4.0mIU/l and that mild-moderate subclinical hypothyroidism encompasses TSH values above 4.0mIU/l up to 10.0mIU/l [111]. A TSH value above 10.0mIU/l, even combined with normal free T4, is considered to represent OH [111].

A systematic review and meta-analysis estimated the prevalence of sub-clinical hypothyroidism to be 12.6% in RM populations [112]. Current evidence suggests no association between subclinical hypothyroidism and RPL when RPL is defined by non-consecutive pregnancy losses (five studies) [112]. Just one of these studies, by Triggianese *et al.*, suggests that there may be an association between subclinical hypothyroidism and consecutive RPL [113]. Within the systematic review, the definition of sub-clinical hypothyroidism also varied with cut-offs of 2.5 and 4.0mIU/l. A review by the RCOG concluded that mild-moderately raised levels of TSH (>4.0-10.0 mIU/l) during pregnancy are associated with sporadic miscarriage, but insufficient evidence of this association exists for upper normal TSH levels (2.5-4.0 mIU/l) or for RM [111].

Meta-analysis of the 17 studies that provided data comparing the prevalence of thyroid autoimmunity (that is having thyroid peroxidase antibodies (TPOab) or anti-thyroglobuin antibodies) in a cohort of women with RPL to those without RPL revealed a statistically significant association between thyroid autoimmunity and RPL (OR 1.94; 95% CI, 1.43-2.64) [112]. Additional sensitivity analysis that excluded studies that did not have an entirely euthyroid cohort demonstrated that the association between thyroid antibodies and RPL remained statistically significant [112].

### Polycystic Ovarian Syndrome (PCOS)

PCOS is characterised by oligo- or an-ovulation, hyperandrogenism, and antral follicular excess on ultrasound [114]. A recent study has estimated the prevalence of PCOS in a single RM cohort to be 9.5%, with pooled prevalence from three studies estimated at 14.3% [115].

Women with PCOS revealed significantly higher luteinising hormone, testosterone, and Anti-Mullerian Hormone (AMH) levels ($p < 0.05$) than the control group without PCOS, which had been noted in other studies [116,117]. While hyperandrogenaemia, obesity and hyperinsulinemia are postulated to be contributory to RM in this cohort, the role of raised luteinising hormone is unclear [116]. Women with PCOS were significantly more likely to experience a further miscarriage (71.4% versus 53.6%; $p = 0.031$). These findings are consistent with previous reports which showed that women with PCOS had a higher risk for first trimester miscarriages [118].

### Diabetes

Women with well-controlled diabetes are not at increased risk for RM. Poorly controlled diabetes and a high HbA1c is associated with fetal anomalies and RM [119]. However, in a RM cohort clinically significant glucose levels were only found in 0.3% of women [120]. Therefore, evaluation for diabetes is likely better reserved for high risk or symptomatic women.

### Prolactin

Hyperprolactinaemia has a low prevalence in RM populations, with a single study demonstrating high prolactin in 1.2% of women tested (6/465) [121]. There is insufficient evidence to suggest asymptomatic hyperprolactinaemia is associated with RM. There has been conflicting evidence as to whether high or low normal levels of prolactin contribute to miscarriage, which requires further study [122,123].

### Ovarian reserve testing

Given the associations between RM and aneuploidy and advanced maternal age, it is a reasonable hypothesis that diminished ovarian reserve and RM would also be associated [124]. To date, women with a history of aneuploid pregnancy have not been definitively proven to have diminished ovarian reserve or earlier menopause [125-127]. Women with diminished ovarian reserve have been shown to have higher rates of miscarriage [128]. In a systematic review, women with RPL (variably defined) were more likely to have diminished ovarian reserve (various markers of ovarian reserve were included such as AMH, antral follicle count follicle-stimulating hormone (FSH), luteinising hormone (LH), estradiol, and FSH:LH ratio) [129]. AMH levels have been shown to be lower in women with unexplained RPL and in younger women [130]. Nonetheless, a universal definition of diminished ovarian reserve and gold standard diagnostic test are required to confirm this association and determine the role of ovarian reserve testing for women with RM.

## Clinical Practice

- Thyroid stimulating hormone (TSH), thyroid peroxidase antibody (TPOAb) levels and Free thyroxine (FT4) levels should be tested routinely in women with RM (ESHRE, adapted by GDG)
- Prolactin testing is not recommended in women with RM in the absence of clinical symptoms of hyperprolactinemia (oligo/amenorrhea) [41]. 2C [ESHRE; Conditional, 2]
- Ovarian reserve testing is not routinely recommended in women with RM but may be considered in women with risk factors for sub-fertility or low ovarian reserve (e.g. women with family history) or women demonstrating signs of premature ovarian failure [41]. Best practice [ESHRE; adapted]
- A 'day 2-5' hormone profile [Follicle stimulating hormone (FSH), oestradiol, FSH/luteinising hormone (LH) ratio] may be considered based on individual assessment [40]. Best Practice [PHA NI; NS]
- Luteal phase insufficiency testing is not routinely recommended in women with RM [41]. 1C [ESHRE; Strong, 2]
- Androgen testing is not routinely recommended in women with RM [41]. 1C [ESHRE; Strong, 2]
- Assessment of PCOS, fasting insulin and fasting glucose is not recommended in women with RM to improve next pregnancy prognosis [41]. [ESHRE; Strong, 2] 1C
- Vitamin D measurement in women with RM is not recommended [41]. Best practice [ESHRE; adapted]

### Recommendations

19. **Thyroid stimulating hormone (TSH), thyroid peroxidase (TPO)-antibody 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, markers for 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.**

# INVESTIGATIONS FOR INFECTION

## Evidence Statement

Recommendations in this section have been adapted from the DGGG, OEGGG and SGGG guideline, with updated literature.

Systemic infections with malaria, brucellosis, cytomegalovirus and human immunodeficiency virus, dengue fever, influenza virus and of vaginal infection with bacterial vaginosis, are associated with increased risk of miscarriage [131]. The effects of Chlamydia trachomatis, Toxoplasma gondii, human papillomavirus, herpes simplex virus, parvovirus B19, Hepatitis B and polyomavirus BK infections remain controversial, as some studies indicate increased miscarriage risk and others show no increased risk [131]. There has been increased interest in the vaginal microbiome, with lactobacillus depletion linked to first-trimester miscarriage [132,133]. Infection is also linked to chronic endometritis, which has also been linked to RM [134]. Greater study is required to understand the role of infections and to determine what characteristics of the vaginal microbiome in women with RM may be significant.

## Clinical Practice

- It is important to consider potential contributory infections when taking a history from women with RM, which may offer an explanation for a very small number of women. Best practice [GDG]
- Infectious screening using vaginal swab specimens is not recommended in *asymptomatic* women with RM [110]. Best practice [DGGG, OEGGG and SGGG; +++, expert]

### Recommendations

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

# GENETIC INVESTIGATIONS

## Evidence Statement

Recommendations in this section come from the RCOG and ESHRE 2022 updated draft guidelines, in addition to updated literature and consultation with a Clinical Geneticist.

### Genetic factors and RM

#### Chromosomal analysis of pregnancy tissue

Fetal aneuploidy is the most commonly identified cause of sporadic and recurrent miscarriage, particularly in the first-trimester [135]. Chromosomal analysis offers an explanation for approximately 70% of women/couples with RM, although this figure may improve as newer techniques identify greater numbers of chromosomal anomalies [136,137].

As mentioned previously, fetal aneuploidy is associated with maternal age [138]. Chromosome anomalies in miscarriage specimens include trisomies, monosomies, polyploidies and structural anomalies. Trisomies are the most common numeric chromosome error, with trisomy 16 and 22 being the most frequent, while Monosomy X is the most frequent sex chromosome error [139]. Trisomies in particular are associated with maternal age >35 years [140,141], whereas unbalanced translocations are to be found more frequently in pregnancy tissue of younger women (aged <35) presenting with RM [141]. In a meta-analysis of RM cohorts, aneuploidy was less likely with successive miscarriages [142], but this trend was only evident in women aged under 35, with higher aneuploidy rates persisting in women aged over 35 [140,143,144].

While ESHRE has recommended array-CGH as the optimal test for cytogenetic testing, it must be borne in mind that their guideline encompasses first and second-trimester miscarriage, which may have very different aetiologies. Array CGH allows for high-resolution analysis of sequences mapped to specific regions and compared to test and control DNA [145]. Array CGH can be performed on fresh or paraffin-embedded tissue, allowing retrospective testing of miscarriage tissue saved from a prior dilation and curettage [145].

The ESHRE draft guideline suggests that array-CGH is superior as it has a reduced rate of maternal cell contamination (MCC) and does not require cell culture [41]. However, this fails to take into consideration steps taken by (some) laboratories such as sorting, dissecting and cleaning each sample and regular auditing of ratios of identified normal female to male karyotype to ensure MCC is minimal [146]. Culture failure due to fungal or bacterial contamination is an accepted risk in traditional karyotyping, however reflexive use of additional molecular technology using DNA can salvage genetic analysis, with reported success rates comparable to QF-PCR and assay regimens [147]. These molecular tests can detect common aneuploidies and nine microdeletion syndromes in addition to alterations in the p and q arm of all chromosomes [147]. Comparatively, a failed array may result in the complete loss of genetic material and repeat array is not always possible.

Another disadvantage is that array-CGH cannot detect balanced translocations, inversions, triploidy, tetraploidy, mosaicism or maternal cell contamination [145]. Single nucleotide polymorphisms (SNP) are locations within non-coding regions of the genome where one nucleotide is highly variable between individuals. Using a SNP microarray, these nucleotide polymorphisms of the pregnancy tissue can be characterised and then compared to a maternal sample [145]. This allows clinicians to identify maternal cell contamination, parental origin of aneuploidy and unbalanced chromosome segments and placental mosaicism. However, the SNP array is unable to detect balanced translocations, inversions or tetraploidy [145]. Arrays are an evolving technology and will produce significant numbers of results where interpretation remains difficult e.g. families with rare CNVs whose significance may be uncertain until further examples are reported [148].

There are also specific benefits to traditional karyotype in the investigation of first-trimester miscarriage. Half of first-trimester miscarriage is caused by large chromosomal abnormalities, such as trisomy, which would be detected by karyotype [138,149]. Karyotype analysis allows for cell-by-cell analysis which can identify abnormal male or female cell lines separate to that of a normal male/female allowing for the detection of mosaicism in addition to MCC [145]. Karyotyping is crucial in identifying Robertsonian unbalanced translocations and determining the recurrence risk [150]. Laboratories should perform QF-PCR prior to performing an array-CGH on pregnancy tissue in first-trimester miscarriage[148]. This allows for early identification of molar pregnancy and trisomies 13, 18 and 21, which allows for deferral to karyotype if T13 or T21 is detected [151]. Karyotype will detect an unbalanced Robertsonian translocation and importantly, the balanced carrier [150]. The recurrence risk can be 100% for 13;13 and 21;21 Robertsonian carriers, which would be missed if array-CGH alone was performed [150].

In the absence of a national genetics laboratory or a standardised operating procedure (SOP) for preparation of pregnancy tissue to ensure consistency, it is important that efforts are made to ensure the testing is performed in accredited laboratories with appropriate clinical governance. Clinical leads should liaise with laboratories to ensure that the SOP for first trimester cytogenetic testing provides the “best test” i.e., one that allows for comprehensive fetal karyotyping with due reference to maternal cell contamination while minimising the potential for inaccurate or “failed” results. It is hoped that these issues will be addressed in the National Genomics Strategy for Ireland. https://www.hse.ie/eng/about/who/strategic-programmes-office-overview/genetics-and-genomics/national-strategy-for-genetics-and-genomics-in-ireland.html

### Parental Karyotype

Parental chromosomal anomalies are also associated with RM. These can be classified into structural and numeric anomalies. Structural includes balanced reciprocal translocations, Robertsonian translocations, inversions, deletions and duplications, whereas numeric refers to anomalies such as trisomies or monosomies [152]. Of these, parental balanced translocations are the most commonly identified in RM cohorts.

The format of the parental testing will vary according to whether a translocation or other anomaly is detected in pregnancy tissue. The testing may be performed by karyotyping (full or targeted), fluorescent in situ hybridisation (FISH), quantitative PCR, quantitative fluorescent PCR, Multiplex Ligation-dependent Probe Amplification (MLPA), or rarely microarray.[153] More than one technique may be used.

The prevalence of structural chromosomal anomalies was 5.3% for couples with two miscarriages and 6.6% with three, in a systematic review, with more recent studies reporting 4.4% and 3.7%, respectively [152,154,155]. Chromosomal anomalies have been shown to be more common in the female partner and in younger couples [152]. However, although miscarriage rates have been reported to be higher among couples of with balanced translocations, livebirth rates are reassuring, with low reported rates of unbalanced chromosomal abnormalities [155-157].

It must be noted that for some parental structural rearrangements, there is a risk of miscarriage only. With other more high-risk re-arrangements, there can be a risk of an ongoing pregnancy with a risk of a fetus with an unbalanced form which may present postnatally only with significant disability. Referral to Clinical Genetics is required in a family with a structural re-arrangement to facilitate future pregnancy planning. This should be timely.

Parental karyotyping does not need to be undertaken when fetal karyotype demonstrates a trisomy that is reported to have arisen from non-disjunction.

NOTE: In the absence of routine parental karyotyping, there must be a reasonable level of chromosomal analysis on pregnancy tissue to detect potential translocations and to afford women/couples a possible explanation for their miscarriage. This should be considered in the management of a third or subsequent miscarriage, or the second or subsequent miscarriage in women under 35 with no prior livebirth, i.e., consideration should be given to surgical management or inpatient medical management to ensure pregnancy tissue is collected for cytogenetics. Staff caring for women experiencing spontaneous miscarriage in emergency room/wards/delivery suites should be educated in the preservation and processing of pregnancy tissue for cytogenetic analysis. Due diligence should also be paid to the processes for respectful treatment of fetal tissue.

## Clinical Practice

- Cytogenetic analysis should be performed on pregnancy tissue of the third or subsequent miscarriage(s) or on the second or subsequent miscarriage if aged <35 years and no prior livebirth [35]. 2C [RCOG 2-, D]
- 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. Best practice [Expert consensus; GDG]
- 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 after the second miscarriage if aged < 35 years and no prior livebirth (35,41).2C [RCOG; 3, D/ESHRE Conditional, 2]

- Parental peripheral blood karyotyping should be performed for couples in whom testing of pregnancy tissue reports an unbalanced structural chromosomal abnormality. 2C [RCOG;3, D]
- All individuals and couples with an abnormal parental karyotype result, and a proportion of those with an atypical fetal karyotype, should be offered genetic counselling (this decision must be made by a Consultant/senior level Clinician) and discussion of possible treatment options relevant to their individual situation considered [41]. Best practice [GDG; adapted from ESHRE]

### Recommendations

23. **Cytogenetic analysis should be performed on pregnancy tissue of the third or subsequent miscarriage(s) or on the second or subsequent miscarriage(s) if aged <35 and no prior livebirth.**
24. **Genetic analysis of the pregnancy tissue should be performed in an accredited laboratory and 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 after the second miscarriage if aged < 35 years and no prior livebirth.**
26. **All individuals and couples with an abnormal parental karyotype result, and a proportion of those with an atypical fetal karyotype, should be offered genetic counselling.**

## HISTOPATHOLOGICAL INVESTIGATIONS

### Evidence Statement

Routine histopathological examination of pregnancy tissue, where available, is recommended [158].

In addition to identifying hydatidiform moles, additional contributory pathology such as chronic histiocytic intervillositis (CHI) and massive perivillous fibrin deposition (MPFD) and impaired trophoblast invasion may be seen [159]. These features are more likely to be seen in the late first trimester. In particular, CHI and MPFD have a recurrence risk and would merit treatment with aspirin, LMWH or prednisolone and additional antenatal surveillance in a subsequent pregnancy due to associations with growth restriction and pregnancy loss [160,161].

Review of any previous histopathological results as part of RM clinic work-up is therefore important to ensure such diagnoses are not missed. If indicated, a repeat pathological review may be requested.

### Clinical Practice

- 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.

### Recommendations

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 IN RM

### Evidence Statement

The following recommendations have been adapted from the RCOG 2021 [35] draft guideline and the ESHRE 2022 [41] draft guideline update.

#### Male Factor

There is increasing recognition of the role of male factors beyond the parental karyotype in RM.

A recent review identified that male BMI and age contribute to unexplained RM [162]. There are several case-control studies and a recent meta-analysis which demonstrate the rate of sperm aneuploidy in male partners of women with RM is higher, even where other semen parameters are within range (or typical) [163,164]. Sperm DNA fragmentation are breaks in the genome of spermatazoa [165] which have also been shown to be present more frequently in male partners of women with RM [164,166-170]. However, this association has not been extensively examined with regards to pregnancy outcomes. One systematic review and meta-analysis demonstrated a lower pregnancy rate, and higher miscarriage rate, for couples where high levels of sperm DNA fragmentation existed in IVF and in intra-cytoplasmic sperm injection (ICSI) [171].

Semen quality and sperm DNA fragmentation may be affected by modifiable risk factors such as smoking, alcohol consumption, weight status and presence of a varicocoele, but the degree to which such interventions may improve sperm quality and reduce RM risk remains unclear [172].

While there is an increasing body of evidence to suggest an association between sperm DNA damage and RM, greater evidence that sperm aneuploidy or DNA fragmentation significantly affects pregnancy outcomes is required to recommend routine testing. Evidence to support any subsequent interventions or ART is also required. Moreover, considering current reproductive medicine services in Ireland, the andrology services required to offer this kind of analysis routinely would require a substantial input of resources.

### Clinical Practice

- In couples with RM, it is recommended to assess factors in the male partner which may contribute to sperm health (paternal age, smoking, alcohol consumption, exercise pattern and body weight) [41]. 2C [ESHRE; Conditional, 2]
- Evidence indicates that sperm DNA fragmentation testing is most beneficial in men with unexplained and idiopathic infertility, RM, varicocele, opting for ART and in those with lifestyle/environmental risk factors.[173] Best practice [Argawal, NS]
- Couples with RM should not be offered routine sperm DNA fragmentation screening out of the research context [35]. 2C RCOG; 4, D]

### Recommendations

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, exercise pattern and body weight).**
29. **Couples with RM should not be offered routine sperm DNA fragmentation screening out of the research context.**

# Section 5: Treatment of RM

## Introduction

Treatments should also be tailored from the medical history and investigative findings.

The risks and benefits of any treatment should be discussed with the woman/couple and written information given alongside the prescription/scheduled procedure.

Possible treatments for specific conditions are laid out below. Additional evidence which has become available in the published literature after the publication of the 2021/2022 RCOG and ESHRE updates is included for the currency of the guideline.

## Clinical Question 2.6: **What are the possible treatments for women/couples presenting with RM?**

## ANATOMICAL TREATMENTS

## Evidence Statement

The recommendations in this section stem from the ESHRE and RCOG guidelines, The Thessaloniki ESHRE/ESGE Consensus on diagnosis of female genital anomalies, the NICE guideline, "Hysteroscopic metroplasty of a uterine septum for primary infertility" as well as updated literature.

### Congenital uterine anomalies

#### Hysteroscopic uterine septum resection

This minimally-invasive technique has been studied in women with first and second-trimester miscarriage. A 2021 systematic review showed that hysteroscopic septum resection was associated with a lower rate of miscarriage (OR 0.25, 95% CI 0.07-0.88) compared with untreated women. No significant effect was seen on live birth, clinical pregnancy rate or preterm delivery [174].

More recently, Carrera *et al.* updated this evidence to include the findings of the long-awaited TRUST randomised control trial in their analyses [175]. The pooled OR for miscarriage was 0.45, (95% CI, 0.22–0.90). When the analysis was performed according to the type of septum, pooled OR in complete septum subgroup was 0.16 (95% CI, 0.03–0.78), 0.36 (95% CI, 0.19–0.71) in the partial septum subgroup and 0.58 (95% CI, 0.20–1.67) in those studies not differentiating between complete or partial septum. Again, no significant differences were found between the two groups in OR of clinical pregnancy, term live birth, or risk of caesarean delivery. There was a significant decrease in the frequency of preterm birth in patients who underwent partial septum resection (OR = 0.30, 95% CI, 0.11–0.79) [175].

The TRUST trial alone demonstrated no evidence of a difference in clinical pregnancy, ongoing pregnancy, pregnancy loss or preterm birth rates. but was limited by its small sample size, (n=80), and was not powered to evaluate any differential effect of septum resection in women with pregnancy loss compared with those presenting with subfertility, or according to the number of pregnancy losses [176].

Thus, while there is evidence that hysteroscopic uterine septum resection decreases miscarriage, there is no significant difference in livebirth rates. Additionally, there remains no consensus on clinically significant uterine septum depth. Therefore, surgery in this cohort should proceed with caution and ideally in the context of research [35].

#### Surgeries for other congenital uterine anomalies

Currently, abdominal or laparoscopic metroplasty for fusion or unification defects is generally not advisable owing to its potential association with significant intraoperative and postoperative complications and lack of evidence to support improved reproductive outcomes [177].

### Acquired uterine anomalies

#### Myomectomy for fibroids

There are no studies assessing myomectomy in women with RM and fibroids. Following a Cochrane review on surgical treatment of fibroids for subfertility, the authors concluded that it was uncertain if myomectomy improved clinical pregnancy rate for women with any type of fibroid (sub-mucosal, intra-mural or sub-serosal) [178]. It was also uncertain whether myomectomy for any of the described types of fibroids had any effect on the miscarriage rate [178]. The uncertainty stems from the very low-quality evidence, with the main limitations being due to serious imprecision, inconsistency and indirectness [178]. There is a need for high-quality studies to determine whether myomectomy is of benefit to women with RM and fibroids.

#### Intra-uterine adhesions

Hysteroscopy remains the gold standard for identification of intra-uterine adhesions and hysteroscopic resection the primary treatment, but has not been demonstrated to improve outcomes in RM populations [179]. The use of gels and hormonal treatments appear to improve outcomes, but these have also not been demonstrated in RM populations to date [180].

## Clinical Practice

- 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 [41].2C [ESHRE; Conditional 1]
- 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 [181]. [NICE; NS]
- 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 [41].1C [ESHRE; Strong, 1]
- Uterine reconstruction is not recommended for hemi-uterus (former American Fertility Society (AFS) unicornuate uterus) and RM [41]. 1C [ESHRE; Strong, 1]

- There is insufficient evidence of benefit for surgical removal of intrauterine adhesions for pregnancy outcome. After hysteroscopic removal of intrauterine adhesions in women with RM, precautions have to be taken to prevent recurrence of adhesions [41]. 2C [ESHRE; Conditional, 1]
- Myomectomy (laparoscopic or open) in women with RM is not recommended due to insufficient evidence that it reduces miscarriage rates [41]. 2C [ESHRE; Conditional, 1]
- There is insufficient evidence supporting hysteroscopic resection of submucosal fibroids or endometrial polyps in women with RM [41]. 2C [ESHRE; Conditional, 1]
- In light of the poor evidence available and heterogeneity of studies and patient selection, the GDG suggests consideration of surgical management of acquired uterine anomalies on an individual basis with respect to factors such as the size of the fibroid/polyp, cavity distortion and gynaecological symptoms. Best practice [GDG]

### Recommendations

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

There are many immunological medications and therapies in existence that have been suggested as treatments for RM.

### Evidence Statement

The recommendations in this section are based on EHSRE, RCOG, and DGGG, OEGGG and SGGG guidelines with updated evidence.

A Cochrane review found paternal cell immunisation, third-party donor leukocytes, trophoblast membranes, and intravenous immunoglobulin provide no significant beneficial effect over placebo in improving the live birth rate [182]. A recent review found no evidence for the use of lymphocyte immunotherapy [183]. Moreover, the controversies for the evidence of its effectiveness are present due to several factors: the methodological quality of studies, lack of consensus on laboratory controls, heterogeneity of the study populations, a lack of immune profiling or established parameters and the different treatment protocols [183].

Intralipid has only been suggested as a treatment for RM in women with elevated uterine natural killer cells, with a systematic review demonstrating that treatment of the target population (women with RPL or recurrent implantation failure) with intralipid led to an improvement in implantation rate, OR: 2.97, 2.05-4.29), pregnancy rate (OR: 1.64, 1.31-2.04), and livebirth rate (OR: 2.36, 1.75-3.17), with a reduction in miscarriage (OR: 0.2, 0.14-0.30) [184]. It must be noted however that although this data includes randomised control trials, these are small heterogenous studies and it is not established which women benefit from such treatment or how to optimally diagnose an abnormal endometrial immune profile [184].

One RCT of etanercept, a TNF-a inhibitor demonstrated increased livebirth rate and fewer miscarriages in the treatment group compared to placebo [185]. However, this small study is inadequate to recommend such treatment.

In addition to improving outcomes for women with antiphospholipid syndrome, hydroxychloroquine has been shown to be of benefit in patients with RM and lupus erythematosus [186,187], as well as some types of placental inflammation [188]. While it appears that hydroxychloroquine may be of benefit to women with RM with autoimmune disease [189], two randomised control trials are underway to determine if hydroxychloroquine improves pregnancy outcomes in women with RM without any autoimmune disease [190,191].

There are considerable costs associated with immunotherapy and the potential for serious side effects, including transfusion reaction, anaphylactic shock and hepatitis, also demands caution and consideration before prescribing in this cohort [35,182].

## Clinical Practice

- Corticosteroids (e.g., prednisolone) should not be administered outside clinical studies as prophylaxis to prevent miscarriage in women with RM but without pre-existing autoimmune disease. They do not improve pregnancy rates and may be associated with an increased risk of adverse pregnancy outcomes [110]. Best practice [DGGG, OEGGG and SGGG; ++, expert consensus]
- Intravenous immunoglobulin (IVIG) is not recommended as a treatment of RM [41]. 2C [ESHRE; Strong, 2]
- There is insufficient evidence to recommend intralipid therapy for improving live birth rate in women with unexplained RM [41].1C [ESHRE; Strong, 1]
- Lymphocyte immunisation therapy (i.e. paternal cell immunisation, third-party donor leucocytes) should not be used as treatment for unexplained RM as it has no significant effect and there may be serious adverse effects [41]. 2C [ESHRE; Strong, 2]
- There is insufficient evidence to recommended granulocyte colony-stimulating factor (G-CSF) in women with unexplained RM [41]. 2B [ESHRE; Strong, 3]
- Paternal cell immunisation, third-party donor leucocytes, trophoblast membranes and intravenous immunoglobulin in women with previous unexplained RM do not improve the live birth rate [35]. 1A [RCOG;A, 1++]
- Therapy with tumour necrosis factor (TNF)-β receptor blockers should not be given to women with RM outside clinical studies [110]. Best practice [DGGG, OEGGG and SGGG; ++, expert consensus]

### Recommendations

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.**

## TREATMENTS FOR THROMBOPHILIA

### Evidence Statement

These recommendations are adapted from the ESHRE, RCOG and British Society for Haematology guidelines, along with evidence from updated literature [35,41,102].

#### Inherited thrombophilia

Systematic reviews have failed to show any benefits from low-dose aspirin and low molecular weight heparin (LMWH) for RM in those with inherited thrombophilia or unexplained RM [32]. An updated systematic review of randomised control trials has shown that LMWH alone or in combination with low-dose aspirin have no influence on the miscarriage rate or occurrence of pre-eclampsia, and that LMWH alone has no influence on the livebirth rate [192]. However, it is noted in all reviews that the quality of studies and randomised control trials are variable, with significant heterogeneity and that there is a need for high-quality randomised control trials [32,192]. Preliminary results of the Alife2 Trial published in December 2022 found that live birth rates were 116/162 (71.6%) in the LMWH group and 112/158 (70.9%) in the standard surveillance group [adjusted OR 1.08 (95% CI 0.65 to 1.78) absolute difference 0.7% (95% CI -9.2% to 10.6%)]. Compared with standard surveillance, the use of LMWH did not result in higher live birth rates in women who had two or more pregnancy losses and confirmed inherited thrombophilia [193]. Thus, the guidance remains that routine use of LMWH in women with recurrent pregnancy loss and confirmed inherited thrombophilia is not recommended [102].

However, treatment decisions should be individualised and should involve a discussion with the woman, taking into consideration additional risk factors, such as maternal risk of thrombosis or evidence of previous placental thrombosis [35].

#### Acquired thrombophilia

Low dose aspirin and (LMWH) are widely used to reduce the risk of RM in women with APLS. The American College of Rheumatology and the European Alliance of Associations for Rheumatology (EULAR) agree that with a history of ≥ 3 recurrent spontaneous miscarriages < 10$^{th}$ week of gestation and in those with a history of fetal loss (≥ 10th week of gestation), combination treatment with aspirin and LMWH at prophylactic dosage during pregnancy is recommended [194,195]. An updated systematic has shown livebirth rates were higher with aspirin and LMWH compared to aspirin alone, but the evidence is of low-quality [196].

If aspirin and LMWH are unsuccessful there is little evidence to support the use of prednisolone or hydroxychloroquine [41,195], and the American College of Rheumatology does not recommend the use of prednisolone [194]. IVIG is not associated with increased livebirths and there is insufficient evidence to recommend its use [41,194].

Should a woman with a positive test for APLS become pregnant while awaiting repeat test results, a decision regarding aspirin and LMWH must be made on an individual basis by the relevant consultant with the best available information.

### Clinical Practice

- 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 [41]. 2C [ESHRE; Conditional, 2]
- For antiphospholipid syndrome – if laboratory and clinical criteria are fulfilled, referral to a local haematology service should be considered and potential for treatment with low dose aspirin and prophylactic dose LMWH in the next pregnancy discussed. Best practice [PHA NI; NS]
- Treatment with aspirin should commence before conception and LMWH must be initiated as soon as the pregnancy test is positive [41]. 2C [ESHRE; Conditional,1]
- Intravenous immunoglobulin therapy does not improve the live birth rate of women with RM associated with antiphospholipid antibodies compared with other treatment modalities; its use may provoke significant maternal and fetal morbidity [197].1A [RCOG 2011; A, 1++]

### Recommendations

**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 and prophylactic LMWH in next pregnancy discussed.**

**39. For APLS, treatment with aspirin should commence before conception and LMWH must be initiated as soon as the pregnancy test is positive.**

## TREATMENT FOR ENDOCRINE DISORDERS

### Evidence Statement

The recommendations in this section are adapted from the ESHRE guideline with updated evidence from the recent published literature.

#### Thyroid disease

The treatment of euthyroid women with TPOAb with levothyroxine has been debated. The Tablet Trial, which did not have sufficient power to analyse the RM subgroup alone, and T4life trials (which was specifically examining women with two or more miscarriages) found that compared with placebo, levothyroxine treatment did not result in higher live birth rates in euthyroid women who tested positive for TPOAb [198,199].

A further RCT has since been published which examined levothyroxine for the treatment of sub-clinical hypothyroidism or the presence of TPOAb [200]. With RPL (two or more pregnancy losses prior to viability) and sub-clinical hypothyroidism, the rate of live births was significantly higher in the treatment group than in the control group (70.2% vs. 47.1%, $p < .001$), while the rate of pregnancy loss was significantly lower in the treatment group than in control group (21.4% vs. 39.7%, $p < .001$). Similar behaviour was noted

for the RPL group that were pregnant and euthyroid with TPOAb, where the levothyroxine treatment group had a higher rate of live births and a lower rate of pregnancy loss than those without treatment (90.5% vs. 68.3%, $p = .022$ and 7.1% vs. 26.8%, $p = .006$ for treatment vs. control, respectively) [200]. Given the small numbers in these treatment/control groups (n=41 and 42), these results should be interpreted with caution.

It is important to note that within the three trials there were varying TSH cut-offs defining euthyroidism, which determined subsequent levothyroxine treatment.

Thus, although thyroid antibodies are associated with RM, treatment with levothyroxine for TPOAb or anti-thyroglobulin antibodies in euthyroid women is best done within the context of research at present.

A systematic review and meta-analysis found just three studies examining if levothyroxine treatment conferred any benefit to women with sub-clinical hypothyroidism and RM. They found a reduction in miscarriage (risk ratio (RR) 0·20 [0·05, 0·76]) and a small increase in livebirth (RR 1·20 [0·82, 1·75]). All 3 studies were of a low-methodological quality with TSH cut-offs of >4.0 and 4.5mIU/l however. Thus, treatment could be considered preconception or during pregnancy for women with RM and mild-moderate subclinical hypothyroidism (based on TSH levels above the pregnancy and population-specific laboratory-reference ranges, or above 4.0 mIU/l if unavailable)[111].

As the association with TSH levels >2.5m-4.0IU/l and RM is indeterminate, treatment should ideally be in the context of research and merits a discussion with the woman/couple regarding the risks and benefits of treatment in this instance [41].

### Progesterone supplementation

There has been a move towards recommending progesterone in women with a history of RM and bleeding in the first trimester.

Pair-wise analysis using data from the PROMISE and PRISM trials,[201,202] demonstrated that women with one or more previous miscarriages and early pregnancy bleeding, twice daily dosage of 400mcg vaginal micronised progesterone increases the live birth rate compared to placebo (RR 1.08, 95% CI 1.02 to 1.15, high-certainty evidence) [203]. This treatment has also been shown to be cost-effective, leading to the National Institute for Health and Care Excellence committee for the guideline 'Ectopic pregnancy and miscarriage: diagnosis and initial management (NG126)' updating their guidance to recommend the use of vaginal micronised progesterone to treat women with the dual risk factors of a history of one or more previous miscarriages and early pregnancy bleeding [204,205].

There remains uncertainty as to how long progesterone should be taken for, and whether this treatment is of greater benefit at earlier gestations [206]. A further double-blind placebo trial of vaginal micronised progesterone showed no benefit in women presenting with bleeding and a live intra-uterine fetus [207]. More research is needed in this area to determine the optimal timing, dosage and formulation of progesterone for use in RM.

### Sitagliptin

Sitagliptin is an oral antidiabetic drug, classed as a dipeptidyl-peptidase IV (DPP4) inhibitor. In the recent "SIMPLANT" randomised-control trial, this drug was shown to increase the endometrial mesenchymal stem-like progenitor cells counts in women with RM and reduce endometrial senescence [208]. In other words, it enhanced endometrial receptivity and plasticity. The trial was not powered to assess pregnancy outcomes, however. An adequately powered randomised control trial to evaluate sitagliptin in this cohort is warranted before this medication can be recommended for clinical use.

## Clinical Practice

- Overt hypothyroidism arising before conception or during early gestation should be treated with levothyroxine in women with RM [41]. 1C [ESHRE; Strong, 2]
- There is low-quality evidence that levothyroxine treatment of women with mild-moderate SCH (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 [111]. [Adapted; RCOG Scientific Impact Paper 70, GDG]
- If women with subclinical hypothyroidism and RM become pregnant again, TSH level should be checked in early gestation (7-9 weeks gestational age), and hypothyroidism should be treated with levothyroxine [41]. Best practice [ESHRE; GPP]
- If women with thyroid autoimmunity and RM are pregnant again, TSH level should be checked in early gestation (7-9 weeks gestational age), and hypothyroidism should be treated with levothyroxine [41]. Best practice [ESHRE; GPP]
- There is insufficient evidence to support treatment with levothyroxine in euthyroid women with thyroid antibodies and RM outside a clinical trial [41]. 2C [ESHRE; Conditional, 2]
- On the basis of insufficient evidence, human chorionic gonadotrophin supplementation in pregnancy is not recommended [41]. 2C [ESHRE; Conditional, 2]
- Bromocriptine treatment can be considered in women with RM and hyperprolactinemia to increase live birth rate [41]. 2C [ESHRE; Conditional, 1]
- There is insufficient evidence to evaluate the effect of metformin supplementation in pregnancy to prevent a miscarriage in women with RM [35]. 1C [RCOG; C, 1++]
- Vaginal progesterone may improve livebirth rate in women with one or more miscarriages and vaginal bleeding in a subsequent pregnancy [41].1B [NICE;NS, ESHRE; Strong, 3]

### Recommendations

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 LT4 treatment of women with mild-moderate SCH (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. **400mcg 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.**

# TREATMENT OF INFECTIONS

## Evidence Statement

A systematic review and meta-analysis of seven studies of women with chronic endometritis found no difference in implantation rate, clinical pregnancy rate, miscarriage rate or livebirth rate between those women treated with broad spectrum antibiotics (of varying regimens) and women who were untreated [209].

The following is adopted from the ASRM guideline and review of the current evidence by the Guideline Development Group.

## Clinical Practice

- There is no evidence to recommend endometrial biopsy or scratching in women with unexplained RM. [41] Best practice [ESHRE; GPP]
- Given the lack of a clear association between treating chronic endometritis and pregnancy outcomes, antibiotics are not recommended in the treatment of chronic endometritis [11]. Best practice [GDG consensus

### Recommendations

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

## Evidence Statement

### Preimplantation genetic testing for structural rearrangements

Women/couples identified as having balanced translocations should meet with a clinical geneticist to discuss the significance of their particular translocation and the management of future pregnancies. The options include continuing to try to conceive naturally or to undergo IVF with preimplantation genetic testing (PGT) for structural rearrangements [35].

PGT is an embryo-selection technique developed to assess the chromosomal or genetic status of an oocyte or embryo prior to embryo transfer. PGT-SR is differentiated from PGT-A in that it is used to detect cases of unbalanced hereditary chromosomal abnormalities, which are a result of one or both parents having a balanced chromosomal rearrangement (e.g., reciprocal translocations, Robertsonian translocations, and inversions) [210].

There is mixed evidence as to which option is more appropriate, with PGT-SR not demonstrating any significant increase in the livebirth rate between either group [210,211], however it appears to be of benefit to those with at least two pregnancy losses in sub-group analysis [212]. Conversely, a systematic review and meta-analysis of six studies, all of which used the older FISH technique, revealed that this method of PGT was associated with an increased successful pregnancy outcome of translocation carriers (OR = 8.58; 95%CI: 1.40-52.76) [213]. A study using next generation sequencing has shown higher rates of chromosomal abnormalities, including chromosomal unbalanced translocations and aneuploidy, in blastocysts from chromosomal rearrangement carriers, especially from the female carriers [214].

Overall, the evidence is low-quality and insufficient in RM groups to suggest any deviation from the RCOG or ESHRE guidelines. High-quality RCTs are required in order to establish a definite benefit for IVF with PGT-SR for couples with a balanced translocation.

### Pre-implantation genetic testing for aneuploidy for RM

Given the association between aneuploidy and RM, the selection of euploid embryos through PGT-A has been postulated as a way to reduce miscarriage rates and increase livebirth rates in women/couples with RM. However, the evidence for PGT-A in any IVF to date is conflicting and there is a paucity of high-quality, adequately powered retrospective trials. A Cochrane review found insufficient evidence of any difference between IVF and IVF with PGT-A and advised PGT-A with FISH is likely harmful [215].

Examining newer techniques, Sanders *et al.* conducted a large UK cohort study using the HFEA data (2464 PGT-A cycles), which demonstrated an increased livebirth rate with PGT-A compared to non-PGT-A across all age groups [216]. The STAR trial showed PGT-A did not improve overall pregnancy outcomes in all women, as analysed per embryo transfer or per intention to treat [217]. There was a significant increase in ongoing pregnancy rate per embryo transfer with the use of PGT-A in the subgroup of women aged 35-40 years but this was not significant when analysed by intention to treat [217].

In a large cohort study using clinical outcome reporting system data which examined over 12,000 IVF cycles including women with recurrent pregnancy loss, the use of PGT-A with FET was associated with increased rates of live birth in women with three or more miscarriage (48% vs 34%, $P < 0.001$) and rates of clinical pregnancy (59% vs 47%, $P < 0.001$) [218]. In addition, for women with RM use of PGT-A was associated with a significant decrease in the rate of spontaneous miscarriage (11 vs 13%, $P = 0.02$), and biochemical pregnancy (9.9% vs 11.5%, $P = 0.02$)[218] In women with RM aOR comparing IVF with PGT-A versus without PGT-A for live birth outcome was 1.31 (95% CI: 1.12, 1.52) for age <35 years, 1.45 (95% CI: 1.21, 1.75) for ages 35-37 years, 1.89 (95% CI: 1.56, 2.29) for ages 38-40, 2.62 (95% CI: 1.94-3.53) for ages 41-42, and 3.80 (95% CI: 2.52, 5.72) for ages >42 years, for miscarriage the OR was 0.95 (95% CI: 0.74, 1.21) for age <35 years, 0.85 (95% CI: 0.65, 1.11) for ages 35-37 years, 0.81 (95% CI: 0.60, 1.08) for ages 38-40, 0.86 (95% CI: 0.58, 1.27) for ages 41-42, and 0.58 (95% CI: 0.32, 1.07) for ages >42 years [218]. A smaller study examining PGT-A in a cohort of women with RM also observed a significant decrease of early pregnancy loss rates in the PGT-A group (18.1% vs 75%) and a significant increase in live birth rate per transfer (50% vs 12.5%) and live birth rate per patient (36% vs 12.5%) [219].

These results must be interpreted with caution, and women/couples with RM must be carefully counselled regarding the specific difficulties with PGT-A. There is much to be learned and perfected with regards to the technique, which is not standardised and there is much heterogeneity among studies and between laboratories [210,220]. There is a high rate of embryo loss, the potential for non-read or inconclusive results (with low chance of successful second biopsy), and the issue of mosaicism has not been definitively dealt with [210,220,221]. The Human Fertilisation and Fertility Authority which govern IVF in the UK designates PGT-A a “code-red” add-on, i.e. not recommended [222].

## Clinical Practice

- Options for couples with chromosomal rearrangements include attempting a further natural conception, preimplantation genetic testing for structural rearrangements (PGT-SR) or gamete donation [35]. 2C [RCOG; 2-, C]
- There are currently insufficient data to support the routine use of pre-implantation genetic testing for couples with unexplained recurrent miscarriage, while the treatment may carry a significant cost and potential risk [35]. 2C [RCOG; 2-, C]

### Recommendations

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

## Evidence Statement

A Cochrane review in 2019 found no evidence that sperm selection with hyaluronic acid had an effect on livebirth or clinical pregnancy, but may reduce miscarriage [223]. The HABSelect Trial demonstrated no difference in livebirth rate for those receiving intra-cytoplamsic sperm injection (ICSI) or physiological ICSI (PICSI) (where sperm are selected according to how they bind to hyaluronic acid) [224], but secondary analysis suggests it may be of benefit for older couples [225]. The HFEA have designated PICSI as a "code red" i.e., not recommended, add-on [226]. To date, no conclusive evidence exists to justify PICSI for RM.

International guidelines for sperm DNA fragmentation offer low grade evidence for anti-oxidants and addressing lifestyle factors, in addition to medium grade evidence for varicocele repair, for men with high levels of sperm DNA fragmentation [165]. Until a role for sperm DNA fragmentation testing is established in RM care, antioxidants and varicocele repair are not recommended solely to prevent RM.

## Clinical Practice

There is as yet no evidence to recommend treatments for male factors [35]. 2C [RCOG; 3, D]

Antioxidants for men are not recommended as they have not been shown to improve the chance of a live birth [41]. 2C [ESHRE; Conditional 1]

### Recommendations

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

.

# Clinical Question 2.7: **What are the possible treatments for women/ couples presenting with unexplained RM?**

## Evidence Statement

These recommendations stem from the RCOG Guideline [35] and relevant literature, in addition to GDG discussions.

### The impact of RM on subsequent pregnancy

Despite completing investigations, approximately 50% of women/couples will not receive an explanation for RM. Even so, women/couples can be reassured that their chances of achieving a livebirth are high, with livebirth rates of 74-86% in RM cohorts within the international literature [227,228]. However, a history of RM does confer increased risks for future pregnancy, which must be considered in regard to antenatal care and empiric treatments. The Lancet series recently outlined these particular intrinsic risks of RM following a systematic review of international data. [9] The risk of miscarriage itself increases with each miscarriage, as demonstrated in Table 2.

**Table 2: Adapted from "Miscarriage Matters: The Epidemiological, Physical, Psychological, and Economic Costs of Early Pregnancy Loss", Quenby *et al.*, The Lancet 2021.**

| No of miscarriages | Miscarriage risk (95% CI) |
|---|---|
| **0** | 11 (7.2, 17.6) |
| **1** | 20·4 (13·8, 30·3) |
| **2** | 28·3 (19·0, 42·1) |
| **≥3** | 42·1 (38·0, 46·7) |

Women with three miscarriages are over four times more likely than women without a history of miscarriage to have a further miscarriage, OR 4·46 [3·48, 5·72]. [229] Thus, it is vital that supportive aspects of care are in place for subsequent early pregnancy.

Quenby *et al.* in the Lancet series also outline that compared to women without a history of RM, specific obstetric risks apply to women with RM for a future pregnancy (Table 3).

**Table 3: Adapted from "Miscarriage Matters: The Epidemiological, Physical, Psychological, and Economic Costs of Early Pregnancy Loss", Quenby *et al.*, The Lancet 2021.**

| Demographic risks after 3 miscarriages | Adjusted Estimates; Odds ratio [95% CI] |
|---|---|
| Pre-eclampsia | 1.22 [0.86-1.73] |
| Placental abruption | 1.67 [1.21-2.30] |
| Placenta praevia | 2.81 [0.87-9.04] |
| Preterm Birth | 1.76 [1.39-2.22] |
| Low Birth Weight | 1.98 [1.09-3.58] |
| Stillbirth | 1.69 [1.17-2.45] |
| Cardiovascular complications | 1.42 [1.16-1.74] |
| Venous thromboembolism | 6.13 [2.48-15.16] |

Preterm birth risk increases with each miscarriage in a stepwise manner [229]. This is potentially linked to repeated surgical management of miscarriage, which may also contribute to abnormal placentation and the increased risk of placental dysfunction but has yet to be proven definitively [229].

The identified cardiovascular and thromboembolic risks extend beyond pregnancy and the reproductive years, demonstrating the significance of RM as a wider and significant women's health issue [229].

## Management of Unexplained RM

For women with unexplained RM, a number of treatments are suggested and prescribed, some of which are not included in current international clinical guidance [30,230].

### Aspirin and/or LMWH

There is conflicting evidence regarding aspirin, LMWH or a combination as a treatment for RM. Several systematic reviews and meta-analyses have found no difference in livebirth rates or miscarriage rates [231-233], of which two included aspirin and LMWH [234,235]. These are at odds with other systematic reviews of LMWH in unexplained RM that showed a reduction in miscarriages rates [236], a reduction in miscarriage rate and improvement in livebirth rate [237] or an improvement in ongoing pregnancies after 20 weeks [238]. These differences likely stem from the variations in LMWH used, differences in dosages and small sample sizes in the trials analysed. Large multi-centre trials are required to establish if LMWH is of any benefit in RM as well as the optimal formulation and dose.

The EAGeR trial, a randomised control trial examining aspirin in women with one or two miscarriages (n=1078) showed pre-conception initiated aspirin improved livebirth rates in those with raised C-Reactive protein [239]. Further per-protocol analysis demonstrated that adhering to low-dose aspirin at least four days per week improved pregnancy outcomes (pregnancy rate, livebirth rate and fewer miscarriages) compared to placebo [240]. A second randomised control trial demonstrated that low-dose aspirin did not improve livebirth rates in women with a history of RM (n=400) [241].

While aspirin has not been proven to reduce miscarriage risk, it does have a role in reducing future placental dysfunction, pre-eclampsia and fetal growth restriction risk, particularly in women over 35, smokers and those undergoing artificial reproductive technology [242-244]. In low-risk nulliparous women,

low-dose aspirin has been shown to improve fetal growth and reduced pre-term birth rates as well as pre-term preeclampsia [245,246], although there is no significant reduction in pre-eclampsia and gestational hypertension rates [246]. Routine low-dose aspirin in low-risk nulliparous women has been shown to have a greater health gain and is more cost-effective than "screen and treat" approaches [247].

In the absence of large multi-centre, randomised clinical trials of aspirin or LMWH in women with risk factors for placental dysfunction such as RM, the GDG has considered the benefits of aspirin as demonstrated above, in addition to the risks posed to women with a history of RM, to be sufficient to justify administration of low-dose (75mg) aspirin in a future pregnancy. Women with additional risk factors for pre-eclampsia may be prescribed 150mg aspirin as per national/international guidelines. LMWH should be reserved for those with additional risk factors for venous thrombo-embolism or pregnancy loss, previous adverse pregnancy outcomes or for higher-order miscarriage after other therapies have been unsuccessful.

Aspirin and LMWH have been subject to countless RCTs and there is no significant evidence to suggest maternal or fetal harm from use in pregnancy [248-250]. Nonetheless, a careful medical history should exclude any risks of bleeding or previous bleeds, particularly intracranial haemorrhage. Women should also be advised around the timing of these medications and when to hold doses, especially if they have concerns that they might be miscarrying or towards the end of pregnancy when spontaneous labour may occur.

**Prednisolone**

A recent systematic review and meta-analysis suggested oral immunosuppressants such as prednisolone or cyclosporine A may be of benefit to women with unexplained RM [251]. Oral administration of cyclosporine A or prednisolone increased live birth rate (OR = 3.6, 95% CI: 2.1-6.15, $p < 0.001$) and ongoing pregnancy rate (OR = 8.82, 95% CI: 2.91-26.75, $p = 0.0001$) and also reduced miscarriage rate (OR = 0.21, 95% CI: 0.08-0.52, $p = 0.0007$). However there was significant heterogeneity between studies, a moderate to severe risk of bias and dosing regimens were inconsistent [251].

Moreover, prednisolone has been suggested to be associated with adverse pregnancy outcomes such as oral cleft, fetal growth restriction, preeclampsia and gestational diabetes mellitus, and while a systematic review was failed to demonstrate conclusive evidence of any such association, corticosteroids should only be prescribed when there is a clear indication for use and evidence of benefit for treating an underlying maternal condition. [252]. Similarly, cyclosporine A use during pregnancy appears to be associated with premature delivery and low birthweight infants [253]. Comorbidities such as hypertension, pre-eclampsia and gestational diabetes mellitus are also reported at higher incidences than the general population [253]. Thus, there is a need for greater evidence before prednisolone or cyclosporin A can be recommended in women with unexplained RM.

**Progesterone**

Progesterone is one of the most widely used empiric treatments for recurrent miscarriage [230].

An updated systematic review and meta-analysis showed that following progesterone treatment, the miscarriage rate for women with recurrent miscarriage was reduced and livebirth rate was increased, but these results were not statistically significant [231]. The livebirth rate was higher for the subgroup of women with a history of three or more miscarriages than the subgroup of women with a history of two or more miscarriages. The authors suggest that micronised vaginal progesterone treatment can therefore be considered for asymptomatic women with recurrent miscarriage and is likely to be more effective in women with a high number of previous miscarriages, given that there are no safety concerns for the use of micronised progesterone or dydrogesterone [203,254].

### *Safety Note*

Sound-alike look-alike drug (SALAD) errors have occurred in maternity care with serious or extreme consequences. If a prostaglandin analogue e.g., misoprostol or dinoprostone, is used in error during pregnancy, serious patient harm including preterm delivery and fetal/neonatal death may occur.

The following mix-ups have occurred:

- Progesterone (CycloGEST®) and misoprostol (CytoTEC®)
- Progesterone and Prostin E2® (dinoprostone)

Such errors have been reported in Ireland and internationally in women receiving progesterone supplements to maintain a pregnancy in the context of RM or preterm birth [255]. Women should be informed at the time of prescribing what their prescribed medications are and why they are being prescribed and should be advised that they check prescriptions with their pharmacist or with any staff administering medication in hospital prior to taking any medication.

### Folic Acid

As discussed at length in the updated ESHRE guideline, folic acid has not been shown to reduce the risk of miscarriage in women with RM [41]. However in an Irish population, it must be borne in mind that food is not fortified with folic acid and Ireland has a higher incidence rate of babies born with neural tube defects than the rest of Europe, and thus folic acid supplementation in pregnancy is of particular importance [256]. High risk groups such as women with obesity, epilepsy, or diabetes mellitus are advised to take a 5mg dose of folic acid to reduce the risks of neural tube defects and in an Irish context, this may include women with RM [257,258].

The decision regarding empiric treatments should be after assessment of individual risk factors, particularly age of either parent, previous number of miscarriages, previous failed treatments, fertility history and ART use, as well as the wishes of the woman/couple. The uncertain effectiveness of these agents must be explained, and the potential risks associated with individual treatments should be outlined.

## Clinical Practice

- Women with unexplained RM have 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. 2B [RCOG; 2+]
- LMWH or low dose aspirin are not recommended for the sole intention of reducing miscarriage risk, as there is conflicting evidence that they do not improve live birth rate in women with unexplained RM [41]. 1C [ESHRE; Strong, 3]
- However, women with RM are at increased risk of placental dysfunction and for this purpose low-dose aspirin is recommended in a future pregnancy, with consideration of LMWH based on individual risk factors and history. Best practice [GDG]
- Corticosteroids/glucocorticoids should not be administered outside clinical studies as prophylaxis to prevent miscarriage in women with RM but without pre-existing autoimmune disease as they do not improve pregnancy rates and may be associated with adverse pregnancy outcomes. Best practice [DGGG, OEGGG and SGGG; ++, expert]

- In women with three or more consecutive miscarriages immediately preceding their current pregnancy, empiric progestogen administration of 400mg vaginally twice daily may be of some potential benefit [231]. Best practice [GDG]
- 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 [41].2C [ESHRE, Strong 2]
- 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. Best practice [GDG]

### Recommendations

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 prophylactic dose aspirin (75mg) is recommended in a future pregnancy, with consideration of prophylactic 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.**

# Section 6: Future Pregnancy Planning

## Evidence Statement

These recommendations stem from the RCOG, in addition to GDG discussions.

On completion of the visit to a RM clinic, it is important that clear plans are in place for future pregnancy for the woman/couple.

Qualitative work with couples experiencing RM has demonstrated that the first trimester of a subsequent pregnancy is a time of stress and anxiety, where women/couples experience a turmoil of emotions and hypervigilance [259]. While women/couples employ their own coping strategies and divide the difficult time period into personal milestones, they found that ultrasound was a valuable source of reassurance, albeit short-lived [259]. Regular ultrasounds in this period have been shown to be an important part of supportive care for RM cohorts [55,260], and they are desired by women/couples [24,259,261].

Couples also valued the environment of the EPC, away from busy emergency or antenatal areas [262]. Empathy and compassion from staff were highlighted as additional sources of support in the first-trimester, especially when the anxiety this period poses to those experiencing RM was acknowledged [259]. Staff knowledge and competence in RM care was particularly appreciated, as was continuity of care [261,262].

As discussed in 6.8, RM confers additional risks in a subsequent pregnancy and thus it is recommended that, at a minimum, women with a history of RM should book in a consultant led antenatal clinic to facilitate additional surveillance for associated obstetric complications. Ideally, this would be a "high-risk" clinic or perinatal medicine clinic.

## Clinical Practice

- As part of their visit to the RM Clinic, women/couples should receive
    - written information regarding their results of any investigations performed
    - written instructions regarding any treatments
    - prescriptions for any necessary medications
    - details on when to start or stop any medications in future pregnancy
    - instructions for support persons to contact if they become pregnant (of particular importance to those who may be conceiving via ART elsewhere)
    - details on how to arrange an early pregnancy unit appointment for reassurance scans and how many scans to expect as per local policy
    - details for the local maternity emergency room and early pregnancy assessment unit. Best practice [GDG]
- A personalised plan should also be in place for further pregnancy loss and necessary investigations, e.g., aware that cytogenetic testing may need to be done on pregnancy tissue and to request surgical management of a future miscarriage. It is vital that contact numbers for relevant support persons are available to facilitate these plans for investigations, as well as to provide psychological support [35]. Best Practice [GDG]
- Provisions should be made for women to receive appropriate supportive care in terms of communication with relevant healthcare professionals, ultrasound examinations and access to services in case of subsequent miscarriage(s) [35]. 2C [RCOG; 3, D]
- Women with RM who become pregnant again should also be booked into a consultant-led antenatal clinic at a minimum, ideally a "high-risk" or perinatal medicine clinic. [35]. 2C [RCOG; 3, D]

**GDG note:**

During the Guideline review process, it was queried if women should abstain from pregnancy while awaiting review and how to proceed in the scenario where a woman became pregnant while awaiting clinical review or repeat testing on tests such as ACLA.

Women/couples should consider their own personal circumstances, particularly concerning fertility, in delaying pregnancy to await investigative results, potential treatments and advice from the RM clinic. When the initial decision to refer to a RM service is made, women should be given contact details of the RM service (i.e., Bereavement Midwife Specialist) in their local hospital to seek advice and obtain supportive services such as early pregnancy scanning should they become pregnant prior to review.

## Recommendations

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 RM who become pregnant again should also be booked into a consultant-led antenatal clinic, 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.

# Chapter 3: Development of Clinical Practice Guideline

In developing a National Clinical Guideline for Ireland, the Guideline Development Group (GDG) decided to adapt existing guidelines and/or guideline recommendations using the ADAPTE process [6].

The ADAPTE process for guideline adaptation takes into consideration that guideline development utilises significant resources [6]. It "takes advantage of existing guidelines in order to enhance the efficient production and use of high-quality guidelines" [6]. Moreover, it allows for recommendations to address specific health questions in the context of particular health settings as well as considering relevant needs, priorities, legislation, policies and resources [5].

The ADAPTE process has three main phases:

1. **Set-up phase (steps 1-6)**

   The set-up phase is primarily the assembly of the team to be involved and planning for the resources and skills required.

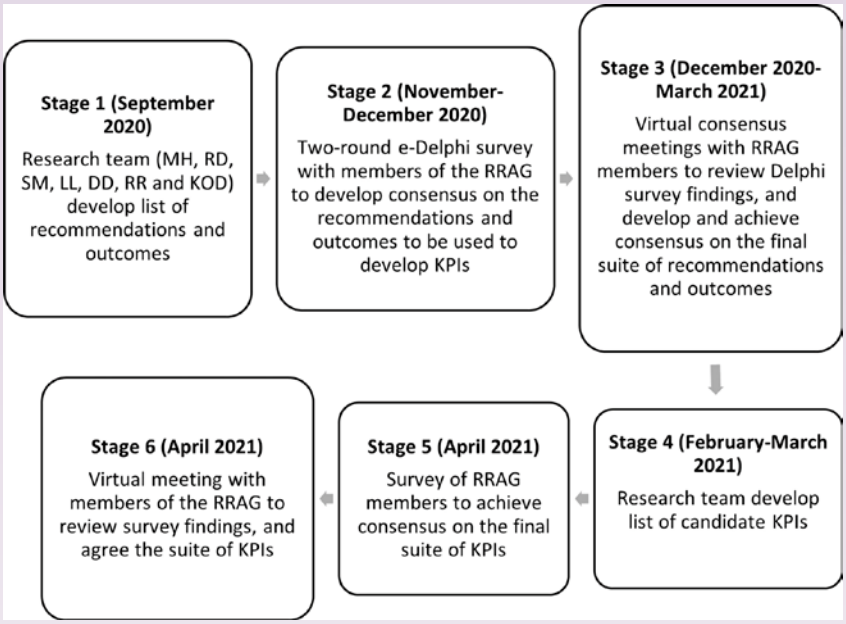
   This process over-lapped significantly with the initiation of the RE:CURRENT Project and establishment of its RAG.

2. **Adaption phase (steps 7-18)**

   The adaption phase is the longest part of the ADAPTE process. It involves a systematic review of guidelines, screening the selected guidelines using the AGREE II tool, narrowing down guidelines based on quality, currency, content, consistency and considering the acceptability and applicability of recommendations [5].

   As part of the RE:CURRENT Project, a systematic review of guidelines on RM was undertaken and the AGREE II tool was also used to assess guidelines [5,6]. This aligns with the 'Search and Screen and Assess' guidelines aspects of the ADPATE process [8-10]. Recommendations from these guidelines were extracted in order to facilitate the development of Key Performance Indicators (KPI) for RM care [6,263]. These recommendations were discussed with the RAG regarding their quality, currency and feasibility and voted on by the RAG for inclusion for KPI development [263]. This aligns very closely to steps 11-17 and is outlined in Fig. 1 [5, 7].

**Figure 1: KPI development process (RRAG; RE:CURRENT RAG)**




**3. Finalisation phase (steps 19-22)**

This phase relates to external review and acknowledgement, which is covered in later chapters of this Guideline.

We acknowledge that the RE:CURRENT RAG was not assembled for the purposes of guideline development and does not fully equate to a GDG. However, to essentially replicate this lengthy and complex process with a similar group of stakeholders to produce similar results and recommendations would not be economically prudent. Thus, the decision was made to proceed to guideline development (led by members of the RM GDG) with adoption or adaption (following an updated review of the literature, where necessary) of the recommendations identified and agreed by the RE:CURRENT RAG, subsequent to discussion by the GDG.

The GDG used the information gathered from the guidelines as well as at consensus meetings to generate recommendations from the evidence. This involved meetings for discussions about which recommendations from existing guidelines to adopt and/or adapt. The AGREE II scores had some bearings on which guidelines to include, but ultimately the currency and standing of the RCOG and ESHRE guidelines meant they were the best candidates for adaptation. Select recommendations on niche topics were retained from other guidelines also.

Good Practice Points were developed by the GDG to provide guidance on important aspects of RM management that had little existing evidence base but were agreed by GDG consensus.

## 3.1 Literature search strategy

A systematic review of international guidelines on RM from high-income countries was undertaken [5]. Subsequent to this, two professional bodies updated their guidance [35,41]. Any new recommendations within these were incorporated into the guideline development process.

A further review of the wider literature was undertaken by LL in May 2022 to ensure that the evidence was up to date. This was a topic-specific search of Google Scholar, PubMed and the Cochrane database focused on those studies published between 2020 up to end of May 2022, e.g. “miscarriage” AND “antiphospholipid syndrome”/RM AND “antiphospholipid syndrome”/“recurrent pregnancy loss” AND “antiphospholipid syndrome” with additional terms added as necessary, e.g. “recurrent miscarriage” AND “antiphospholipid syndrome” AND “aspirin” etc.

## 3.2 Appraisal of evidence

Guidelines were appraised as outlined in the systematic review described in 3.1 and following that systematic approach to searching, screening and appraisal, this review has identified a number of evidence-based recommendations for the management of RM, adapted to reflect care in the Irish healthcare setting.

## 3.3 AGREE II process

While being developed, the Guideline was assessed using the AGREE II checklist (Appendix 7) as recommended by the Department of Health in the ‘How to Develop a National Clinical Guideline: a manual for Guideline developers’, 2019.[8]

The purpose of AGREE II is to provide a framework to:

1. Assess the quality of guidelines;
2. Provide a methodological strategy for the development of guidelines; and
3. Inform what information and how information ought to be reported in guidelines

## 3.4 Literature review

Details of supportive evidence-based literature for this Guideline are reported in chapter two.

As mentioned previously, a systematic review of guidelines was undertaken and appraisal of the selected guidelines was done as part of the RE:CURRENT Project and detailed methods are described within the published paper [5].

Briefly, the review was conducted by MH with the RE:CURRENT Team and LL assisted in the AGREE II appraisal [5]. Data extraction and creation of matrices was completed by MH, with recommendations condensed through a review process with the other members of the RE:CURRENT Team and these recommendations were discussed, agreed and prioritised by the RAG in a modified e-Delphi study [263].

The secondary review of the literature was undertaken in May 2022 by LL. Evidence was appraised according to study design, study sample size, methodology, primary and secondary outcomes as well as applicability and relevance to the PICOH question. Individual study findings are outlined as relevant in Chapter 2. In the Guideline, the evidence to support the association of various factors with RM is provided. Updated evidence pertaining to individual investigations and treatments is presented in each section, alongside the adapted recommendations from the international guidance. However, to minimise overlap, not all original evidence supporting every recommendation for each investigation and treatment is presented here but is present within the guidelines of origin.

8 Department of Health (2019). How to develop a National Clinical Guideline. Available at: https://www.gov.ie/en/collection/cd41ac-clinical-effectiveness-resources-and-learning/

## 3.5 Grades of recommendation

A number of international guidelines were used in creating recommendations for this Guideline as previously outlined. These guidelines are supplemented by an updated review of the literature to maintain the currency of this Guideline. Additionally, supporting evidence for the association of various factors with RM is provided for background information and comprehensiveness.

Due to the number of international Guidelines used in this guideline and the variation in how the evidence and strength of recommendations were graded, it was decided by the GDG to retain the grading as per guidelines of origin. Primarily this was simply because to collate this evidence and to integrate the various grading systems from each individual guideline into updated recommendations according to GRADE would require resources beyond that of the GDG, but additionally, there was seldom sufficient high-quality evidence to warrant the adjustment of recommendations. Thus, evidence strengths from international guidelines were retained and approximately translated into GRADE as per Appendix 6. The GDG accepts that this translation may not be wholly accurate. Good practice points or consensus points are highlighted as such.

GRADE offers a transparent and structured process for developing and presenting evidence summaries and for carrying out the steps involved in developing recommendations [264]. While we acknowledge that for this particular work an extensive GRADE approach is not possible, we have used the suggested language set out in the GRADE table when making recommendations.[9]

## 3.6 Future research

An important outcome of the Guideline development process is in highlighting gaps in the evidence base. These are identified throughout the Guideline.

Some suggested topics in this broad area include:

- Establishing associations with RM, for example, hereditary thrombophilia, ovarian reserve, subclinical hypothyroidism, TPOAbs, sperm DNA fragmentation, acquired uterine anomalies
- There is a need for robust RCTs in RM populations to determine the efficacy of suggested treatments, in particular PGT-A, levothyroxine for subclinical hypothyroidism and/or TPOAbs, progesterone, sitagliptin
- The experiences and needs of gender diverse/LGBTQ+ people who have and/or are experiencing RM.

9 SMFM adopts GRADE (Grading of Recommendations Assessment, Development, and Evaluation) for clinical guidelines. Society for Maternal-Fetal Medicine (SMFM), Chauhan SP, Blackwell SC. Am J Obstet Gynecol. 2013 Sep;209(3):163-5. doi: 10.1016/j.ajog.2013.07.012. PMID: 23978245 https://pubmed.ncbi.nlm.nih.gov/23978245/

# Chapter 4: Governance and Approval

## 4.1 Formal governance arrangements

This Guideline was written by the Guideline Developers under the direction of the Guideline Programme Team. An Expert Advisory Group was formed to review the Guideline prior to submission for final approval with the National Women and Infants Health Programme. The roles and responsibilities of the members of each group and their process were clearly outlined and agreed.

## 4.2 Guideline development standards

This Guideline was developed by the Guideline Developer Group (GDG) within the overall template of the HSE National Framework[10] for developing Policies, Procedures, Protocols and Guidelines (2016) (Appendix 8) and under supervision of the Guideline Programme Team (GPT).

A review was conducted by a group of experts, specialists and advocates (the EAG) prior to approval by the Clinical Advisory Group (CAG) of the National Women and Infants Health Programme (NWIHP) with final sign off for publication by CAG Co-Chairs, the Clinical Director of NWIHP and the Chair of the IOG, see Appendix 3 for membership list.

10 Health Service Executive (2016). National Framework for developing Policies, Procedures, Protocols and Guidelines (PPPGs). Available from: https://www.hse.ie/eng/about/who/qid/use-of-improvement-methods/nationalframeworkdevelopingpolicies/

# Chapter 5: Communication and Dissemination

A communication and dissemination plan for this Guideline has been developed by the GPT and endorsed by NWIHP.

Effective ongoing clear communication is essential in explaining why the Guideline is necessary and securing continued buy-in. It provides an opportunity to instil motivation within staff, helps overcome resistance to change and gives an opportunity for feedback[11].

The Clinical Guideline will be circulated and disseminated through the Guideline Programme Team as well as through the professional networks who participated in developing and reviewing the document.

Senior management within the maternity units are responsible for the appropriate dissemination of new and updated guidelines. Local hospital groups including guideline committees will also be instrumental in the circulation of new and updated guidelines and promoting their use in the relevant clinical settings.

The HSE will make this Guideline available to all employees through standards networks as well as storing it in the online PPPG repository. Electronic versions available on the NWIHP https://www.hse.ie/eng/about/who/acute-hospitals-division/woman-infants/clinical-guidelines/ and RCPI websites (https://www.rcpi.ie/faculties/obstetricians-and-gynaecologists/national-clinical-guidelines-in-obstetrics-and-gynaecology/) and other communication means can be used to maximise distribution. The NWIHP website will also provide a training webinar introducing each guideline and where relevant a downloadable version of the recommended algorithm will be available.

In the case of this Guideline, a plain language summary should be made available for people experiencing RM given findings from the RE:CURRENT Project which highlighted the lack of RM information resources available. This would support informed decision-making, providing evidence-informed guidance and help prepare people attending appointments.

11 Department of Health (2018). NCEC Implementation Guide and Toolkit. Available at: https://health.gov.ie/national-patient-safety-office/ncec/

# Chapter 6: **Implementation**

## 6.1 Implementation plan

Implementation was considered at the beginning, and throughout the Guideline development process. The local multidisciplinary clinical team, senior executive and clinical management in each maternity and gynaecology unit are ultimately responsible for the appropriate structured adoption and implementation of the Guideline within their area of responsibility. They must ensure that all relevant personnel under their supervision have read and understood the Guideline and monitor both its effectiveness and adoption.

Within each site, local multidisciplinary teams are responsible for the clinical implementation of Guideline recommendations, and ensuring that their local clinical practices and processes reflect and are aligned with the Guideline recommendations.

The following have been put in place to help facilitate the implementation of this Guideline.

- Quick Summary Document (QSD) for clinical staff (includes key recommendations, auditable standards, algorithms and recommended reading)
- Clinical Guideline mobile application
- Plain language summary

## 6.2 Education plans required to implement the Guideline

It is acknowledged that this Guideline should be complemented by ongoing education, training and assessment where required.

This Guideline's education plan could include:

- Formal launch of the guideline
- Presentation at local levels
- Use of summary documents and algorithms
- Awareness campaign through relevant media including websites such as the NWIHP, RCPI and www.pregnancyandinfantloss.ie.

## 6.3 Barriers and facilitators

To ensure successful implementation of guidelines, it is first necessary to look at potential barriers and facilitators. Taking these into account when developing the implementation plan should improve levels of support from relevant users. (DOH 2018, 2019)

Barriers may be categorised as internal (specific to the Guideline itself) or external (specific to the clinical environment). The Guideline Development Group has aimed to address any internal barriers during the development of this Guideline.

Potential external barriers include:

- Structural factors (e.g. budget or service redesign)
- Organisational factors (e.g. lack of facilities or equipment)
- Individual factors (e.g. knowledge, skills, training)
- Patient perceptions

In the case of this Guideline, it will be necessary to examine possible barriers and consider implementation strategies to address them. By example, this may include discussion with relevant management groups with regards budgetary impact or providing training to the relevant staff.

Findings from the RE:CURRENT Project highlight variation in RM practices nationally, with maternity units/clinics using a range of international RM guidelines, with some having adapted/adopted their own RM guidelines locally. The need to support champions (locally/regionally/nationally), provide resources (suitably trained staff, facilities, access to laboratories, timely access to genetic counselling), and highlight the evidence to support practice changes were identified facilitators and should be addressed as part of Guideline implementation.

## 6.4 Resources necessary to implement recommendations

The implementation of this Guideline should be undertaken as part of the quality improvement of each hospital. Hospitals should review existing service provision against this Guideline, identifying necessary resources required to implement the recommendations in this Guideline.

In the case of this Guideline, funding is required to equip all maternity hospitals with 3D ultrasound and to provide staff training. Currently not all hospitals have access to consistent maternity mental health care services, with few having access to an on-site psychologist or counselling and psychotherapy services and this requires investment. Moreover, women with RM are currently outside the official remit of Perinatal Mental Health services.

Consideration may need to be given to improving the provision of hysteroscopic surgery nationally and the required upskilling of Gynaecologists. If male factors are to feature more prominently in investigations, there is an urgent need to develop andrology services nationally. Currently andrology services are predominantly within the remit of private fertility services and developing public services would require significant resources, including capital investment for laboratories and the recruitment of skilled staff. Consideration could be given to a national standard operating procedure for first-trimester cytogenetic studies, which would require liaison between laboratories and clinical leads for Obstetrics and Genetics.

Consideration must be given to provision of required genetic testing within this country and it follows that additional Clinical Geneticists must be recruited in order to provide the necessary genetics counselling, including for RM.

# Chapter 7: Audit and Evaluation

## 7.1 Introduction to audit

It is important that both implementation of the Guideline and its influence on outcomes are audited to ensure that this Guideline positively impacts on patient care. Institutions and health professionals are encouraged to develop and undertake regular audits of Guideline implementation. Personnel tasked with the job of conducting the audit should be identified on receipt of the most recent version of the Guideline.

## 7.2 Auditable standards

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

## 7.3 Evaluation

Evaluation is defined as a formal process to determine the extent to which the planned or desired outcomes of an intervention are achieved[12].

Implementation of this Guideline will be audited periodically at national level, with standards for this set by the NWIHP. Evaluation of the auditable standards should also be undertaken locally by senior hospital clinical management to support implementation.

12 Health Information Quality Authority (2012). National Standards for Safer Better Healthcare [Internet]. Available from: https://www.hiqa.ie/reports-and-publications/standard/national-standards-safer-better-healthcare

# Chapter 8: **Revision Plan**

## 8.1 Procedure for the update of the Guideline

It may be a requirement to amend, update or revise this Guideline as new evidence emerges. This Guideline will be reviewed at national level every three years, or earlier if circumstances require it, and updated accordingly.[13]

The Guideline Development Group will be asked to review the literature and recent evidence to determine if changes are to be made to the existing Guideline. If the Guideline Development Group are unavailable, the GPT along with the NWIHP senior management team will select a suitable expert to replace them.

If there are no amendments required to the Guideline following the revision date, the detail on the revision tracking box must still be updated which will be a new version number and date.

The recommendations set out in this Guideline remain valid until a review has been completed.

## 8.2 Method for amending the Guideline

As new evidence become available it is inevitable that Guideline recommendations will fall behind current evidence based clinical practice. It is essential that clinical guidelines are reviewed and updated with new evidence as it becomes available.

In order to request a review of this Guideline one of the following criteria must be met:

a. 3 years since the Guideline was published

b. 3 years since last review was conducted

c. Update required as a result of new evidence

Correspondence requesting a review of the Guideline should be submitted to the National Women and Infants Health Programme. Any such requests should be dealt with in a timely manner.

13 Health Service Executive (2016). National Framework for developing Policies, Procedures, Protocols and Guidelines (PPPGs). Available from: https://www.hse.ie/eng/about/who/qid/nationalframeworkdevelopingpolicies/

# Chapter 9: **References**


1. National Clinical Effectiveness Committee (NCEC) and Health Information and Quality Authority (HIQA) (2015) National quality assurance criteria for clinical guidelines. Version 2. Dublin: NCEC and HIQA. [Internet]. [cited 2022 Jul 29]. Available from: https://www.gov.ie/pdf/?file=https://assets.gov.ie/11533/2d070cb758a44fcb8b56f28784b10896.pdf#page=1
2. Moseson H, Zazanis N, Goldberg E, Fix L, Durden M, Stoeffler A, *et al.* The Imperative for Transgender and Gender Nonbinary Inclusion. Obstet Gynecol. 2020 May;135(5):1059-68.
3. Brotto LA, Galea LAM. Gender inclusivity in women's health research. BJOG: An International Journal of Obstetrics & Gynaecology [Internet]. [cited 2022 Jun 9];n/a(n/a). Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/1471-0528.17231
4. Gribble KD, Bewley S, Bartick MC, Mathisen R, Walker S, Gamble J, *et al.* Effective Communication About Pregnancy, Birth, Lactation, Breastfeeding and Newborn Care: The Importance of Sexed Language. Frontiers in Global Women's Health [Internet]. 2022 [cited 2022 Jun 9];3. Available from: https://www.frontiersin.org/article/10.3389/fgwh.2022.818856
5. Hennessy M, Dennehy R, Meaney S, Linehan L, Devane D, Rice R, *et al.* Clinical practice guidelines for recurrent miscarriage in high-income countries: a systematic review. Reproductive BioMedicine Online. 2021 Jun 1;42(6):1146-71.
6. The ADAPTE Collaboration. The ADAPTE Process: Resource Toolkit for Guideline Adaptation. Version 2.0. Berlin: Guideline International Network; 2010.
7. Pregnancy Loss Research Group. The RE:CURRENT study [Internet]. University College Cork. 2022 [cited 2022 Jun 9]. Available from: https://www.ucc.ie/en/obsgyn/plrg/plrgresearchactivity/therecurrentstudy/
8. Dennehy R, Hennessy M, Meaney S, Matvienko-Sikar K, O'Sullivan-Lago R, Uí Dhubhgain J, *et al.* How we define recurrent miscarriage matters: Views of those with professional and lived experience. Health Expectations. Under Review;
9. 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.
10. ESHRE Early Pregnancy Guideline Development Group. Guideline on the Management of Recurrent Pregnancy Loss. Version 2. Grimbergen, Belgium: European Society of Human Reproduction and Embryology; 2017.
11. Practice Committee of the American Society for Reproductive Medicine. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. Fertility and Sterility. 2012 Nov 1;98(5):1103-11.
12. Royal College of Obstetricians & Gynaecologists. Regan L, Rai R, Saravelos S. RCOG Consultation Document Oct – Nov 2021 2021;4:1-48.13. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 200: Early Pregnancy Loss. Obstetrics & Gynecology. 2018 Nov;132(5):e197.

14. McPherson E. Recurrence of stillbirth and second trimester pregnancy loss. American Journal of Medical Genetics Part A. 2016;170(5):1174-80.
15. Shields R, Hawkes A, Quenby S. Clinical approach to recurrent pregnancy loss. Obstetrics, Gynaecology and Reproductive Medicine. 2020 Nov 1;30(11):331-6.
16. Joyce CM, Coulter J, Kenneally C, McCarthy TV, O'Donoghue K. Experience of women on the Irish National Gestational Trophoblastic Disease Registry. European Journal of Obstetrics and Gynecology and Reproductive Biology. 2022 May 1;272:206-12.
17. Chen X, Cheung WC, Liu Y, Zhang T, Li TC. Subsequent pregnancy and perinatal outcome in women with a history of recurrent miscarriage: a systematic review and meta-analysis. The Lancet. 2018 Oct 1;392:S81.
18. Wu CQ, Nichols K, Carwana M, Cormier N, Maratta C. Preterm birth after recurrent pregnancy loss: a systematic review and meta-analysis. Fertility and Sterility. 2022 Apr 1;117(4):811-9.
19. Farren J, Mitchell-Jones N, Verbakel JY, Timmerman D, Jalmbrant M, Bourne T. The psychological impact of early pregnancy loss. Human Reproduction Update. 2018 Nov 1;24(6):731-49.
20. Kolte AM, Olsen LR, Mikkelsen EM, Christiansen OB, Nielsen HS. Depression and emotional stress is highly prevalent among women with recurrent pregnancy loss. Human Reproduction. 2015 Apr 1;30(4):777-82.
21. McCarthy FP, Moss-Morris R, Khashan AS, North RA, Baker PN, Dekker G, *et al.* Previous pregnancy loss has an adverse impact on distress and behaviour in subsequent pregnancy. BJOG: An International Journal of Obstetrics & Gynaecology. 2015;122(13):1757-64.
22. Farren J, Mitchell-Jones N, Verbakel JY, Timmerman D, Jalmbrant M, Bourne T. The psychological impact of early pregnancy loss. Human Reproduction Update. 2018 Nov 1;24(6):731-49.
23. Flannery C, Burke LA, Gillespie P, Dennehy R, Hennessy M, O'Donoghue K. The economic impact of recurrent miscarriage care in Ireland: the patient's perspective. In preparation;
24. Musters AM, Koot YEM, van den Boogaard NM, Kaaijk E, Macklon NS, van der Veen F, *et al.* Supportive care for women with recurrent miscarriage: a survey to quantify women's preferences. Human Reproduction. 2013 Feb 1;28(2):398-405.
25. Musters AM, Taminiau-Bloem EF, van den Boogaard E, van der Veen F, Goddijn M. Supportive care for women with unexplained recurrent miscarriage: patients' perspectives. Human Reproduction. 2011 Apr 1;26(4):873-7.
26. van den Berg MMJ, Dancet EAF, Erlikh T, van der Veen F, Goddijn M, Hajenius PJ. Patient-centered early pregnancy care: a systematic review of quantitative and qualitative studies on the perspectives of women and their partners. Human Reproduction Update. 2018 Jan 1;24(1):106-18.
27. Koert E, Malling GMH, Sylvest R, Krog MC, Kolte AM, Schmidt L, *et al.* Recurrent pregnancy loss: couples' perspectives on their need for treatment, support and follow up. Human Reproduction. 2019 Feb 1;34(2):291-6.
28. Flannery C, Hennessy M, Dennehy R, Matvienko-Sikar K, Lucey C, Uí Dhubhgain J, *et al.* Factors that shape recurrent miscarriage care experiences: Findings from a national survey. BJOG. Under review;
29. Hennessy M, Dennehy R, Meaney S, Matvienko-Sikar K, O'Sullivan-Lago R, Uí Dhubhgain J, *et al.* Stakeholder perspectives on recurrent miscarriage services and priorities for improvement: Qualitative findings from a national evaluation of recurrent miscarriage care. In preparation;

30. Hennessy M, Linehan L, Flannery C, O'Donoghue K. Recurrent miscarriage care in Ireland: Findings from a national service evaluation. Irish Medical Journal 2023; in press.;

31. van Dijk MM, Kolte AM, Limpens J, Kirk E, Quenby S, van Wely M, *et al.* Recurrent pregnancy loss: diagnostic workup after two or three pregnancy losses? A systematic review of the literature and meta-analysis. Human Reproduction Update. 2020 Apr 15;26(3):356-67.

32. 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.

33. van den Boogaard E, Kaandorp SP, Franssen MTM, Mol BWJ, Leschot NJ, Wouters CH, *et al.* Consecutive or non-consecutive recurrent miscarriage: is there any difference in carrier status? Human Reproduction. 2010 Jun 1;25(6):1411-4.

34. van den Boogaard E, Cohn DM, Korevaar JC, Dawood F, Vissenberg R, Middeldorp S, *et al.* Number and sequence of preceding miscarriages and maternal age for the prediction of antiphospholipid syndrome in women with recurrent miscarriage. Fertil Steril. 2013 Jan;99(1):188-92.

35. Regan L, Rai R, Saravelos S. RCOG Consultation Document Oct – Nov 2021. 2021;4(17):1-48.

36. Farren J, Jalmbrant M, Falconieri N, Mitchell-Jones N, Bobdiwala S, Al-Memar M, *et al.* Posttraumatic stress, anxiety and depression following miscarriage and ectopic pregnancy: a multicenter, prospective, cohort study. American Journal of Obstetrics and Gynecology. 2020 Apr 1;222(4):367.e1-367.e22.

37. Bhat A, Byatt N. Infertility and Perinatal Loss: When the Bough Breaks. Curr Psychiatry Rep. 2016 Mar;18(3):31.

38. Harty T, Trench M, Keegan O, O'Donoghue K, Nuzum D. The experiences of men following recurrent miscarriage in an Irish tertiary hospital: A qualitative analysis. Health Expect. 2022 Jun;25(3):1048-57.

39. Williams HM, Topping A, Coomarasamy A, Jones LL. Men and Miscarriage: A Systematic Review and Thematic Synthesis. Qual Health Res. 2020 Jan;30(1):133-45.

40. Northern Ireland Public Health Agency. Recurrent Pregnancy Loss Care Pathway for Northern Ireland. Befast: Northern Ireland Public Health Agency; 2020.

41. ESHRE Early Pregnancy Guideline Development Group E. Guideline Recurrent Pregnancy Loss Update 2022. 2022.

42. Nybo Andersen AM, Wohlfahrt J, Christens P, Olsen J, Melbye M. Maternal age and fetal loss: Population based register linkage study. British Medical Journal. 2000 Jun 24;320(7251):1708-12.

43. Sauer M V. Reproduction at an advanced maternal age and maternal health. Fertility and Sterility. 2015 May 1;103(5):1136-43.

44. Stephenson MD, Awartani KA, Robinson WP. Cytogenetic analysis of miscarriages from couples with recurrent miscarriage: a case-control study. Human reproduction (Oxford, England). 2002;17(2):446-51.

45. Rai R, Regan L. Recurrent miscarriage. Vol. 368, Lancet. Elsevier; 2006. p. 601-11.

46. Saravelos SH, Regan L. Unexplained Recurrent Pregnancy Loss. Obstetrics and Gynecology Clinics of North America. 2014 Mar 1;41(1):157-66.

47. Cauchi MN, Pepperell R, Kloss M, Lim D. Predictors of Pregnancy Success in Repeated Miscarriage. American Journal of Reproductive Immunology. 1991;26(2):72-5.

48. Bhattacharya S, Townend J, Bhattacharya S. Recurrent miscarriage: Are three miscarriages one too many? Analysis of a Scottish population-based database of 151,021 pregnancies. European journal of obstetrics, gynecology, and reproductive biology. 2010;150(1):24-7.

49. Lund M, Kamper-Jørgensen M, Nielsen HS, Lidegaard Ø, Andersen AMN, Christiansen OB. Prognosis for Live Birth in Women With Recurrent Miscarriage. Obstetrics & Gynecology. 2012 Jan;119(1):37-43.

50. du Fossé NA, van der Hoorn MLP, van Lith JMM, le Cessie S, Lashley EELO. Advanced paternal age is associated with an increased risk of spontaneous miscarriage: a systematic review and meta-analysis. Human Reproduction Update. 2020 May 2;1-20.

51. du Fossé NA, van der Hoorn MLP, de Koning R, Mulders AGMGJ, van Lith JMM, le Cessie S, *et al.* Toward more accurate prediction of future pregnancy outcome in couples with unexplained recurrent pregnancy loss: taking both partners into account. Fertility and Sterility. 2022 Jan 1;117(1):144-52.

52. Kolte AM, Olsen LR, Christiansen OB, Schmidt L, Nielsen HS. Pregnancy outcomes after recurrent pregnancy loss: a longitudinal cohort study on stress and depression. Reproductive BioMedicine Online. 2019 Apr 1;38(4):599-605.

53. Coomarasamy A, Devall AJ, Brosens JJ, Quenby S, Stephenson MD, Sierra S, *et al.* Micronized vaginal progesterone to prevent miscarriage: a critical evaluation of randomized evidence. Vol. 223, American Journal of Obstetrics and Gynecology. Mosby Inc.; 2020. p. 167-76.

54. Brigham SA, Conlon C, Farquharson RG. A longitudinal study of pregnancy outcome following idiopathic recurrent miscarriage. Human Reproduction. 1999;14(11):2868-71.

55. Clifford K, Rai R, Regan L. Future pregnancy outcome in unexplained recurrent first trimester miscarriage. Human Reproduction. 1997;12(2):387-9.

56. Kolte AM, Westergaard D, Lidegaard Ø, Brunak S, Nielsen HS. Chance of live birth: a nationwide, registry-based cohort study. Human Reproduction. 2021;36(4):1065-73.

57. Oliver-Williams CT, Steer PJ. Racial variation in the number of spontaneous abortions before a first successful pregnancy, and effects on subsequent pregnancies. International Journal of Gynaecology and Obstetrics. 2015 Jun 1;129(3):207.

58. Pineles BL, Park E, Samet JM. Systematic Review and Meta-Analysis of Miscarriage and Maternal Exposure to Tobacco Smoke During Pregnancy. American Journal of Epidemiology. 2014;179(7):807.

59. Zhang RP, Zhao WZ, Chai BB, Wang QY, Yu CH, Wang HY, *et al.* The effects of maternal cigarette smoking on pregnancy outcomes using assisted reproduction technologies: An updated meta-analysis. Journal of gynecology obstetrics and human reproduction. 2018 Nov 1;47(9):461-8.

60. du Fossé NA, van der Hoorn MLP, Buisman NH, van Lith JMM, le Cessie S, Lashley EELO. Paternal smoking is associated with an increased risk of pregnancy loss in a dose-dependent manner: a systematic review and meta-analysis. F&S Reviews. 2021 Jul 1;2(3):227-38.

61. Chai J, Guo T, Deng Y, Jiang L, Zhang J, Xu Q, *et al.* Preconception alcohol consumption and risk of miscarriage in over 4.5 million Chinese women aged 20-49 years. BMJ Sexual & Reproductive Health. 2022 Jan 1;48(e1):e53-9.

62. Ng KYB, Cherian G, Kermack AJ, Bailey S, Macklon N, Sunkara SK, *et al.* Systematic review and meta-analysis of female lifestyle factors and risk of recurrent pregnancy loss. Scientific Reports 2021 11:1. 2021 Mar 29;11(1):1-10.

63. George L, Granath F, Johansson ALV, Olander B, Cnattingius S. Risks of repeated miscarriage. Paediatric and Perinatal Epidemiology. 2006 Mar;20(2):119-26.

64. Stefanidou EM, Caramellino L, Patriarca A, Menato G. Maternal caffeine consumption and sine causa recurrent miscarriage. European Journal of Obstetrics and Gynecology and Reproductive Biology. 2011 Oct 1;158(2):220-4.

65. PARAZZINI F, BOCCIOLONE L, VECCHIA C LA, NEGI E, FEDELE L. Maternal and paternal moderate daily alcohol consumption and unexplained miscarriages. BJOG: An International Journal of Obstetrics & Gynaecology. 1990;97(7):618-22.

66. Zhang BY, Wei YS, Niu JM, Li Y, Miao ZL, Wang ZN. Risk factors for unexplained recurrent spontaneous abortion in a population from southern China. International Journal of Gynecology & Obstetrics. 2010 Feb 1;108(2):135-8.

67. Denison FC, Aedla NR, Keag O, Hor K, Reynolds RM, Milne A, *et al.* Care of Women with Obesity in Pregnancy: Green-top Guideline No. 72. BJOG: An International Journal of Obstetrics and Gynaecology. 2019;126(3):e62-106.

68. Nepomnaschy PA, Welch KB, McConnell DS, Low BS, Strassmann BI, England BG. Cortisol levels and very early pregnancy loss in humans. Proceedings of the National Academy of Sciences of the United States of America. 2006 Mar 7;103(10):3938.

69. Li W, Newell-Price J, Jones GL, Ledger WL, Li TC. Relationship between psychological stress and recurrent miscarriage. Reproductive BioMedicine Online. 2012 Aug 1;25(2):180-9.

70. Nelson DB, Grisso JA, Joffe MM, Brensinger C, Shaw L, Datner E. Does stress influence early pregnancy loss? Annals of epidemiology. 2003 Apr;13(4):223-9.

71. Plana-Ripoll O, Parner E, Olsen J, Li J. Severe stress following bereavement during pregnancy and risk of pregnancy loss: results from a population-based cohort study. J Epidemiol Community Health. 2016 May 1;70(5):424-9.

72. du Fossé NA, van der Hoorn MLP, van Lith JMM, le Cessie S, Lashley EELO. Advanced paternal age is associated with an increased risk of spontaneous miscarriage: a systematic review and meta-analysis. Human Reproduction Update. 2020 Sep 1;26(5):650-69.

73. Agarwal A, Farkouh A, Parekh N, Zini A, Arafa M, Kandil H, *et al.* Sperm DNA Fragmentation: A Critical Assessment of Clinical Practice Guidelines. World J Mens Health. 2022;40(1):30.

74. Obesity National Clinical Programme [Internet]. HSE.ie. [cited 2022 Jun 15]. Available from: https://www.hse.ie/eng/about/who/cspd/ncps/obesity/national-obesity-clinical-programme.html

75. Tobacco Cessation [Internet]. HSE.ie. [cited 2022 Jun 15]. Available from: https://www.hse.ie/eng/about/who/tobaccocontrol/cessation/nationalstandardortobaccocessationsupportprogramme.html

76. Pfeifer S, Butts S, Dumesic D, Gracia C, Vernon M, Fossum G, *et al.* Uterine septum: a guideline. Fertility and Sterility. 2016 Sep 1;106(3):530-40.

77. Chan YY, Jayaprakasan K, Zamora J, Thornton JG, Raine-Fenning N, Coomarasamy A. The prevalence of congenital uterine anomalies in unselected and high-risk populations: A systematic review. Human Reproduction Update. 2011;17(6):761-71.

78. Venetis CA, Papadopoulos SP, Campo R, Gordts S, Tarlatzis BC, Grimbizis GF. Clinical implications of congenital uterine anomalies: a meta-analysis of comparative studies. Reproductive BioMedicine Online. 2014;29:665-83.

79. Sundermann AC, Velez Edwards DR, Bray MJ, Jones SH, Latham SM, Hartmann KE. Leiomyomas in Pregnancy and Spontaneous Abortion: A Systematic Review and Meta-analysis. Obstet Gynecol. 2017 Nov;130(5):1065-72.

80. Pritts EA, Parker WH, Olive DL. Fibroids and infertility: an updated systematic review of the evidence. Fertility and Sterility. 2009 Apr;91(4):1215-23.

81. Saravelos SH, Yan J, Rehmani H, Li TC. The prevalence and impact of fibroids and their treatment on the outcome of pregnancy in women with recurrent miscarriage.

82. Hooker AB, Lemmers M, Thurkow AL, Heymans MW, Opmeer BC, Brö Lmann HAM, *et al.* Systematic review and meta-analysis of intrauterine adhesions after miscarriage: prevalence, risk factors and long-term reproductive outcome. Human Reproduction Update. 2014;20(2):262-78.

83. Hooker AB, De Leeuw RA, Twisk JWR, Brö Lmann HAM, Huirne JAF. Reproductive performance of women with and without intrauterine adhesions following recurrent dilatation and curettage for miscarriage: long-term follow-up of a randomized controlled trial. Human Reproduction. 2021;36(1):2020.

84. Meuleman T, Lashley LELO, Dekkers OM, van Lith JMM, Claas FHJ, Bloemenkamp KWM. HLA associations and HLA sharing in recurrent miscarriage: A systematic review and meta-analysis. Human Immunology. 2015 May 1;76(5):362-73.

85. Meuleman T, van Beelen E, Kaaja RJ, van Lith JMM, Claas FHJ, Bloemenkamp KWM. HLA-C antibodies in women with recurrent miscarriage suggests that antibody mediated rejection is one of the mechanisms leading to recurrent miscarriage. Journal of Reproductive Immunology. 2016 Aug 1;116:28-34.

86. Geneugelijk K, Hönger G, van Deutekom HWM, Hösli IM, Schaub S, Spierings E. A Previous Miscarriage and a Previous Successful Pregnancy Have a Different Impact on HLA Antibody Formation during a Subsequent Successful Pregnancy. Frontiers in Immunology [Internet]. 2016 [cited 2022 May 17];7. Available from: https://www.frontiersin.org/article/10.3389/fimmu.2016.00571

87. Lashley EELO, Meuleman T, Claas FHJ. Beneficial or Harmful Effect of Antipaternal Human Leukocyte Antibodies on Pregnancy Outcome? A Systematic Review and Meta-Analysis. American Journal of Reproductive Immunology. 2013;70(2):87-103.

88. Wegmann TG, Lin H, Guilbert L, Mosmann TR. Bidirectional cytokine interactions in the maternal-fetal relationship: is successful pregnancy a TH2 phenomenon? Immunology Today. 1993 Jul 1;14(7):353-6.

89. Wang NF, Kolte AM, Larsen EC, Nielsen HS, Christiansen OB. Immunologic abnormalities, treatments, and recurrent pregnancy loss: What is real and what is not? Clinical Obstetrics and Gynecology. 2016;59(3):509-23.

90. Bombell S, McGuire W. Cytokine polymorphisms in women with recurrent pregnancy loss: Meta-analysis. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2008 Apr 1;48(2):147-54.

91. Choi YK, Kwak-Kim J. REVIEW ARTICLE: Cytokine Gene Polymorphisms in Recurrent Spontaneous Abortions: A Comprehensive Review. American Journal of Reproductive Immunology. 2008 Aug 1;60(2):91-110.

92. Su D, Zhang Y, Wang Q, Wang J, Jiao B, Wang G, *et al.* Association of interleukin-10 gene promoter polymorphisms with recurrent miscarriage: a meta-analysis. American Journal of Reproductive Immunology. 2016 Aug 1;76(2):172-80.

93. Guerrero B, Hassouneh F, Delgado E, Casado JG, Tarazona R. Natural killer cells in recurrent miscarriage: An overview. Vol. 142, Journal of Reproductive Immunology. Elsevier Ireland Ltd; 2020. p. 103209.

94. Von Woon E, Greer O, Shah N, Nikolaou D, Johnson M, Male V. Number and function of uterine natural killer cells in recurrent miscarriage and implantation failure: a systematic review and meta-analysis. Human Reproduction Update. 2022 Mar 9;1-35.

95. Cavalcante MB, Cavalcante CT de MB, Sarno M, Silva ACB, Barini R. Antinuclear antibodies and recurrent miscarriage: Systematic review and meta-analysis. Am J Reprod Immunol [Internet]. 2020 Mar [cited 2022 May 17];83(3). Available from: https://onlinelibrary.wiley.com/doi/10.1111/aji.13215

96. Chen S, Yang G, Wu P, Sun Y, Dai F, He Y, *et al.* Antinuclear antibodies positivity is a risk factor of recurrent pregnancy loss: A meta-analysis. Semin Arthritis Rheum. 2020 Aug;50(4):534-43.

97. Nielsen HS, Wu F, Aghai Z, Steffensen R, van Halteren AG, Spierings E, *et al.* H-Y antibody titers are increased in unexplained secondary recurrent miscarriage patients and associated with low male : female ratio in subsequent live births. Hum Reprod. 2010 Nov;25(11):2745-52.

98. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, *et al.* International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). Journal of thrombosis and haemostasis : JTH. 2006 Feb;4(2):295-306.

99. Van Den Boogaard E, Cohn DM, Korevaar JC, Dawood F, Vissenberg R, Middeldorp S, *et al.* Number and sequence of preceding miscarriages and maternal age for the prediction of antiphospholipid syndrome in women with recurrent miscarriage. Fertility and sterility. 2013 Jan;99(1):188-92.

100. Opatrny L, David M, Kahn SR, Shrier I, Rey E. Association between antiphospholipid antibodies and recurrent fetal loss in women without autoimmune disease: a metaanalysis. The Journal of Rheumatology. 2006;33(11).

101. Santos T da S, Ieque AL, de Carvalho HC, Sell AM, Lonardoni MVC, Demarchi IG, *et al.* Antiphospholipid syndrome and recurrent miscarriage: A systematic review and meta-analysis. Journal of Reproductive Immunology. 2017 Sep 1;123:78-87.

102. Arachchillage DJ, Mackillop L, Chandratheva A, Motawani J, MacCallum P, Laffan M. Thrombophilia testing: A British Society for Haematology guideline. British Journal of Haematology. 2022;198(3):443-58.

103. Liu X, Chen Y, Ye C, Xing D, Wu R, Li F, *et al.* Hereditary thrombophilia and recurrent pregnancy loss: a systematic review and meta-analysis. Human Reproduction. 2021 Apr 20;36(5):1213-29.

104. Shehata H, Ali A, Silva-Edge M, Haroon S, Elfituri A, Viswanatha R, *et al.* Thrombophilia screening in women with recurrent first trimester miscarriage: is it time to stop testing? – a cohort study and systematic review of the literature. BMJ Open. 2022 Jul;12(7):e059519.

105. Kadauke S, Khor B, Van Cott EM. Activated protein C resistance testing for factor V Leiden. American Journal of Hematology. 2014;89(12):1147-50.

106. Liu XY, Fan Q, Wang J, Li R, Xu Y, Guo J, *et al.* Higher chromosomal abnormality rate in blastocysts from young patients with idiopathic recurrent pregnancy loss. Fertility and Sterility. 2020 Apr 1;113(4):853-64.

107. Chen H, Yang X, Lu M. Methylenetetrahydrofolate reductase gene polymorphisms and recurrent pregnancy loss in China: a systematic review and meta-analysis.

108. Rey E, Kahn SR, David M, Shrier I. Thrombophilic disorders and fetal loss: A meta-analysis. Lancet. 2003 Mar 15;361(9361):901-8.

109. Hickey SE, Curry CJ, Toriello H V. ACMG Practice Guideline: lack of evidence for MTHFR polymorphism testing. Genetics in Medicine 2013 15:2. 2013 Jan 3;15(2):153-6.

110. Toth B, Würfel W, Bohlmann M, Zschocke J, Rudnik-Schöneborn S, Nawroth F, *et al.* Recurrent Miscarriage: Diagnostic and Therapeutic Procedures. Guideline of the DGGG, OEGGG and SGGG (S2k-Level, AWMF Registry Number 015/050). Geburtshilfe Frauenheilkd. 2018 Apr;78(04):364-81.

111. Dhillon-Smith RK, Boelaert K, Jeve YB, Maheshwari A, Coomarasamy A, Royal College of Obstetricians and Gynaecologists. Subclinical hypothyroidism and antithyroid autoantibodies in women with subfertility or recurrent pregnancy loss. BJOG: An International Journal of Obstetrics & Gynaecology [Internet]. [cited 2022 Jul 23];n/a(n/a). Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/1471-0528.17187

112. Dong AC, Morgan J, Kane M, Stagnaro-Green A, Stephenson MD. Subclinical hypothyroidism and thyroid autoimmunity in recurrent pregnancy loss: a systematic review and meta-analysis.

113. Triggianese P, Perricone C, Conigliaro P, Chimenti MS, Perricone R, De Carolis C. Peripheral blood natural killer cells and mild thyroid abnormalities in women with reproductive failure. International Journal of Immunopathology and Pharmacology. 2016 Mar 1;29(1):65-75.

114. Fauser BCJM. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertility and Sterility. 2004;81(1):19-25.

115. Mayrhofer D, Hager M, Walch K, Ghobrial S, Rogenhofer N, Marculescu R, *et al.* The Prevalence and Impact of Polycystic Ovary Syndrome in Recurrent Miscarriage: A Retrospective Cohort Study and Meta-Analysis. Journal of Clinical Medicine. 2020 Aug 21;9(9):2700.

116. Cocksedge KA, Li TC, Saravelos SH, Metwally M. A reappraisal of the role of polycystic ovary syndrome in recurrent miscarriage. Vol. 17, Reproductive BioMedicine Online. Reproductive Healthcare Ltd; 2008. p. 151-60.

117. Tal R, Seifer DB, Khanimov M, Malter HE, Grazi R V., Leader B. Characterization of women with elevated antimüllerian hormone levels (AMH): Correlation of AMH with polycystic ovarian syndrome phenotypes and assisted reproductive technology outcomes. American Journal of Obstetrics and Gynecology. 2014;211(1):59.e1-59.e8.

118. Glueck CJ, Wang P, Goldenberg N, Sieve-Smith L. Pregnancy outcomes among women with polycystic ovary syndrome treated with metformin. Human Reproduction. 2002 Nov 1;17(11):2858-64.

119. Kaur R, Gupta K. Endocrine dysfunction and recurrent spontaneous abortion: An overview. Int J Appl Basic Med Res. 2016;6(2):79-83.

120. Jaslow CR, Carney JL, Kutteh WH. Diagnostic factors identified in 1020 women with two versus three or more recurrent pregnancy losses. Fertil Steril. 2010 Mar 1;93(4):1234-43.

121. Li W, Laird S, Li TC. The relationship between the plasma prolactin level and pregnancy outcome in women with recurrent spontaneous abortion. Archives of Disease in Childhood – Fetal and Neonatal Edition. 2010 Jun 1;95(Suppl 1):Fa106-Fa106.

122. Hirahara F, Andoh N, Sawai K, Hirabuki T, Uemura T, Minaguchi H. Hyperprolactinemic recurrent miscarriage and results of randomized bromocriptine treatment trials. Fertility and Sterility. 1998 Aug 1;70(2):246-52.

123. Li W, Ma N, Laird SM, Ledger WL, Li TC. The relationship between serum prolactin concentration and pregnancy outcome in women with unexplained recurrent miscarriage. Journal of Obstetrics and Gynaecology. 2013 Apr;33(3):285-8.

124. Dean DD, Agarwal S, Tripathi P. Connecting links between genetic factors defining ovarian reserve and recurrent miscarriages. J Assist Reprod Genet. 2018 Dec;35(12):2121-8.

125. Kline J, Kinney A, Reuss ML, Kelly A, Levin B, Ferin M, *et al.* Trisomic pregnancy and the oocyte pool. Human Reproduction. 2004 Jul 1;19(7):1633-43.

126. Kline JK, Kinney AM, Levin B, Kelly AC, Ferin M, Warburton D. Trisomic pregnancy and elevated FSH: implications for the oocyte pool hypothesis. Human Reproduction. 2011 Jun 1;26(6):1537-50.

127. Kline J, Kinney A, Levin B, Warburton D. Trisomic Pregnancy and Earlier Age at Menopause. Am J Hum Genet. 2000 Aug;67(2):395-404.

128. Lyttle Schumacher BM, Jukic AMZ, Steiner AZ. Anti-Müllerian hormone as a risk factor for miscarriage in naturally conceived pregnancies. Fertil Steril. 2018 Jun;109(6):1065-1071.e1.

129. Bunnewell SJ, Honess ER, Karia AM, Keay SD, Al Wattar BH, Quenby S. Diminished ovarian reserve in recurrent pregnancy loss: a systematic review and meta-analysis. Fertil Steril. 2020 Apr;113(4):818-827.e3.

130. Wald KA, Shahine LK, Lamb JD, Marshall LA, Hickok LR. High incidence of diminished ovarian reserve in young unexplained recurrent pregnancy loss patients. Gynecol Endocrinol. 2020 Dec;36(12):1079-81.

131. Giakoumelou S, Wheelhouse N, Cuschieri K, Entrican G, Howie SEM, Horne AW. The role of infection in miscarriage. Human Reproduction Update. 2016 Jan 1;22(1):116-33.

132. Al-Memar M, Bobdiwala S, Fourie H, Mannino R, Lee YS, Smith A, *et al.* The association between vaginal bacterial composition and miscarriage: a nested case-control study. BJOG: An International Journal of Obstetrics & Gynaecology. 2020 Jan 1;127(2):264-74.

133. Soyer Caliskan C, Yurtcu N, Celik S, Sezer O, Kilic SS, Cetin A. Derangements of vaginal and cervical canal microbiota determined with real-time PCR in women with recurrent miscarriages. Journal of Obstetrics and Gynaecology. 2022;

134. McQueen DB, Bernardi LA, Stephenson MD. Chronic endometritis in women with recurrent early pregnancy loss and/or fetal demise. Fertility and Sterility. 2014 Apr 1;101(4):1026-30.

135. Marquard K, Westphal LM, Milki AA, Lathi RB. Etiology of recurrent pregnancy loss in women over the age of 35 years. Fertility and Sterility. 2010 Sep;94(4):1473-7.

136. Sugiura-Ogasawara M, Ozaki Y, Katano K, Suzumori N, Kitaori T, Mizutani E. Abnormal embryonic karyotype is the most frequent cause of recurrent miscarriage. Human Reproduction. 2012;27(8):2297-303.

137. Popescu F, Jaslow CR, Kutteh WH. Recurrent pregnancy loss evaluation combined with 24-chromosome microarray of miscarriage tissue provides a probable or definite cause of pregnancy loss in over 90% of patients. Human Reproduction. 2018 Apr 1;33(4):579-87.

138. Hardy K, Hardy PJ. 1(st) trimester miscarriage: four decades of study. Translational Pediatrics. 2015;4(2):189-200.

139. Levy B, Sigurjonsson S, Pettersen B, Maisenbacher MK, Hall MP, Demko Z, *et al.* Genomic imbalance in products of conception: Single-nucleotide polymorphism chromosomal microarray analysis. Obstetrics and Gynecology. 2014;124(2 PART1):202-9.

140. Ozawa N, Ogawa K, Sasaki A, Mitsui M, Wada S, Sago H. Maternal age, history of miscarriage, and embryonic/fetal size are associated with cytogenetic results of spontaneous early miscarriages. Journal of Assisted Reproduction and Genetics. 2019 Apr 15;36(4):749-57.

141. Grande M, Borrell A, Garcia-Posada R, Borobio V, Muñoz M, Creus M, *et al.* The effect of maternal age on chromosomal anomaly rate and spectrum in recurrent miscarriage. Human reproduction (Oxford, England). 2012;27(10):3109-17.

142. Lei D, Zhang XY, Zheng PS. Recurrent pregnancy loss: fewer chromosomal abnormalities in products of conception? a meta-analysis. Journal of Assisted Reproduction and Genetics. 2022 Mar 1;39(3):559-72.

143. Sullivan AE, Silver RM, LaCoursiere DY, Porter TF, Branch DW. Recurrent fetal aneuploidy and recurrent miscarriage. Obstetrics and Gynecology. 2004 Oct;104(4):784-8.

144. Werner M, Reh A, Grifo J, Perle MA. Characteristics of chromosomal abnormalities diagnosed after spontaneous abortions in an infertile population. Journal of Assisted Reproduction and Genetics. 2012 Aug;29(8):817-20.

145. McQueen DB, Lathi RB. Miscarriage chromosome testing: Indications, benefits and methodologies. Seminars in Perinatology. 2019 Mar 1;43(2):101-4.

146. TDL Genetics Limited. TDL Patient Information Leaflet [Internet]. TDL; [cited 2022 Aug 31]. Available from: https://www.tdlpathology.com/media/Multisite8478/tap2227b_pocpatientinfoleaflet_v5.pdf

147. Onsod P, Jaranasaksakul W, Areesirisuk P, Parinayok R, Rerkamnuaychoke B, Chareonsirisuthigul T. Rapid Molecular Karyotyping for Products of Conception by BACs-on-beads Technology. International Journal of Infertility & Fetal Medicine. 2022 Jun 16;13(2):61-6.

148. Best Practice Guidelines [Internet]. The Association for Clinical Genomic Science. [cited 2022 Sep 30]. Available from: https://www.acgs.uk.com/quality/best-practice-guidelines/

149. Pylyp LY, Spynenko LO, Verhoglyad NV, Mishenko AO, Mykytenko DO, Zukin VD. Chromosomal abnormalities in products of conception of first-trimester miscarriages detected by conventional cytogenetic analysis: a review of 1000 cases. J Assist Reprod Genet. 2018 Feb;35(2):265-71.

150. Poot M, Hochstenbach R. Prevalence and Phenotypic Impact of Robertsonian Translocations. MSY. 2021;12(1):1-11.

151. Donaghue C, Davies N, Ahn JW, Thomas H, Ogilvie CM, Mann K. Efficient and cost-effective genetic analysis of products of conception and fetal tissues using a QF-PCR/array CGH strategy; five years of data. Mol Cytogenet. 2017 Apr 5;10:12.

152. Park SJ, Min JY, Kang JS, Yang BG, Hwang SY, Han SH. Chromosomal abnormalities of 19,000 couples with recurrent spontaneous abortions: a multicenter study. Fertility and Sterility. 2022 May 1;117(5):1015-25.

153. House B. Parental cytogenetic testing. :1.

154. Van Dijk MM, Kolte AM, Limpens J, Kirk E, Quenby S, Van Wely M, *et al.* Recurrent pregnancy loss: Diagnostic workup after two or three pregnancy losses? A systematic review of the literature and meta-analysis. Vol. 26, Human Reproduction Update. Oxford University Press; 2020. p. 356-67.

155. Li S, Chen M, Zheng PS. Analysis of parental abnormal chromosomal karyotype and subsequent live births in Chinese couples with recurrent pregnancy loss. Scientific Reports |. 123AD;11:20298.

156. Franssen MTM, Korevaar JC, Van Der Veen F, Leschot NJ, Bossuyt PMM, Goddijn M. Reproductive outcome after chromosome analysis in couples with two or more miscarriages: case-control study. BMJ. 2006 Mar 30;332(7544):759-63.

157. Flynn H, Yan J, Saravelos SH, Li TC. Comparison of reproductive outcome, including the pattern of loss, between couples with chromosomal abnormalities and those with unexplained repeated miscarriages. Journal of Obstetrics and Gynaecology Research. 2014 Jan 1;40(1):109-16.

158. Ohayi SR, Onyishi NT. Routine Histopathological Analysis of the Products of Conception: Is there a Value? Niger Med J. 2020;61(3):136-9.

159. Jindal P, Regan L, Fourkala EO, Rai R, Moore G, Goldin RD, *et al.* Placental pathology of recurrent spontaneous abortion: the role of histopathological examination of products of conception in routine clinical practice: a mini review. Human Reproduction. 2007 Feb 1;22(2):313-6.

160. Kim EN, Lee JY, Shim JY, Hwang D, Kim KC, Kim SR, *et al.* Clinicopathological characteristics of miscarriages featuring placental massive perivillous fibrin deposition. Placenta. 2019 Oct 1;86:45-51.

161. Moar L, Simela C, Nanda S, Marnerides A, Al-Adnani M, Nelson-Piercy C, *et al.* Chronic histiocytic intervillositis (CHI): current treatments and perinatal outcomes, a systematic review and a meta-analysis. Frontiers in Endocrinology [Internet]. 2022 [cited 2022 Sep 29];13. Available from: https://www.frontiersin.org/articles/10.3389/fendo.2022.945543

162. du Fossé NA, van der Hoorn MLP, de Koning R, Mulders AGMGJ, van Lith JMM, le Cessie S, *et al.* Toward more accurate prediction of future pregnancy outcome in couples with unexplained recurrent pregnancy loss: taking both partners into account. Fertility and Sterility. 2022 Jan 1;117(1):144-52.

163. Pu Y, Yang X, Guo Y, Zhu X, Yan L, Lu S. Sperm aneuploidy and recurrent pregnancy loss: A systematic review and meta-analysis. Zang T, editor. Cogent Biology. 2020 Jan 1;6(1):1759393.

164. Ramasamy R, Scovell JM, Kovac JR, Cook PJ, Lamb DJ, Lipshultz LI. Fluorescence in situ hybridization detects increased sperm aneuploidy in men with recurrent pregnancy loss. Fertility and Sterility. 2015;103(4):906-909.e1.

165. Agarwal A, Parekh N, Zini A, Arafa M, Kandil H, Tadros N, *et al.* Sperm DNA Fragmentation: A Critical Assessment of Clinical Practice Guidelines. World J Mens Health. 2022;(1):30-7.

166. Carrell DT, Liu L, Peterson CM, Jones KP, Hatasaka HH, Erickson L, *et al.* Sperm DNA fragmentation is increased in couples with unexplained recurrent pregnancy loss. Archives of Andrology. 2003 Jan;49(1):49-55.

167. Khadem N, Poorhoseyni A, Jalali M, Akbary A, Heydari ST. Sperm DNA fragmentation in couples with unexplained recurrent spontaneous abortions. Andrologia. 2014 Mar;46(2):126-30.

168. Leach M, Aitken RJ, Sacks G. Sperm DNA fragmentation abnormalities in men from couples with a history of recurrent miscarriage. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2015 Aug 1;55(4):379-83.

169. Esquerré-Lamare C, Walschaerts M, Chansel Debordeaux L, Moreau J, Bretelle F, Isus F, *et al.* Sperm aneuploidy and DNA fragmentation in unexplained recurrent pregnancy loss: A multicenter case-control study. Basic and Clinical Andrology. 2018 Apr 2;28(1):4.

170. McQueen DB, Zhang J, Robins JC. Sperm DNA fragmentation and recurrent pregnancy loss: a systematic review and meta-analysis. Fertility and Sterility. 2019 Jul 1;112(1):54-60.e3.

171. Zhao J, Zhang Q, Wang Y, Li Y. Whether sperm deoxyribonucleic acid fragmentation has an effect on pregnancy and miscarriage after in vitro fertilization/intracytoplasmic sperm injection: a systematic review and meta-analysis.

172. Ibrahim Y, Johnstone E. The male contribution to recurrent pregnancy loss. Vol. 7, Translational Andrology and Urology. AME Publishing Company; 2018. p. S317-27.

173. Agarwal A, Majzoub A, Baskaran S, Panner Selvam MK, Cho CL, Henkel R, *et al.* Sperm DNA Fragmentation: A New Guideline for Clinicians. World J Mens Health. 2020 Oct;38(4):412-71.

174. Krishnan M, Narice BF, Ola B, Metwally M. Does hysteroscopic resection of uterine septum improve reproductive outcomes: a systematic review and meta-analysis. Arch Gynecol Obstet. 2021 May;303(5):1131-42.

175. Carrera M, Pérez Millan F, Alcázar JL, Alonso L, Caballero M, Carugno J, *et al.* Effect of Hysteroscopic Metroplasty on Reproductive Outcomes in Women with Septate Uterus: Systematic Review and Meta-Analysis. J Minim Invasive Gynecol. 2022 Apr;29(4):465-75.

176. Rikken JFW, Kowalik CR, Emanuel MH, Bongers MY, Spinder T, Jansen FW, *et al.* Septum resection versus expectant management in women with a septate uterus: an international multicentre open-label randomized controlled trial. Human Reproduction. 2021 Apr 20;36(5):1260-7.

177. Akhtar M, Saravelos S, Li T, Jayaprakasan K, the Royal College of Obstetricians and Gynaecologists. Reproductive Implications and Management of Congenital Uterine Anomalies: Scientific Impact Paper No. 62 November 2019. BJOG: Int J Obstet Gy [Internet]. 2020 Apr [cited 2022 May 16];127(5). Available from: https://onlinelibrary.wiley.com/doi/10.1111/1471-0528.15968

178. Metwally M, Raybould G, Cheong YC, Horne AW. Surgical treatment of fibroids for subfertility. Cochrane Database of Systematic Reviews [Internet]. 2020 [cited 2022 May 16];(1). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD003857.pub4/full

179. Di Guardo F, Della Corte L, Vilos GA, Carugno J, Török P, Giampaolino P, *et al.* Evaluation and treatment of infertile women with Asherman syndrome: an updated review focusing on the role of hysteroscopy. Reprod Biomed Online. 2020 Jul;41(1):55-61.

180. Zheng F, Xin X, He F, Liu J, Cui Y. Meta-analysis on the use of hyaluronic acid gel to prevent intrauterine adhesion after intrauterine operations. Experimental and Therapeutic Medicine. 2020 Apr 1;19(4):2672-8.

181. Hysteroscopic metroplasty of a uterine septum for primary infertility. :7.

182. Wong LF, Porter TF, Scott JR. Immunotherapy for recurrent miscarriage. Cochrane Database of Systematic Reviews [Internet]. 2014 [cited 2022 May 13];(10). Available from: https://www.readcube.com/articles/10.1002%2F14651858.cd000112.pub3

183. Cavalcante MB, Sarno M, Barini R. Lymphocyte immunotherapy in recurrent miscarriage and recurrent implantation failure. Am J Reprod Immunol [Internet]. 2021 Apr [cited 2022 May 16];85(4). Available from: https://onlinelibrary.wiley.com/doi/10.1111/aji.13408

184. Kumar P, Marron K, Harrity C. Intralipid therapy and adverse reproductive outcome: is there any evidence? Reprod Fertil. 2021 Jul;2(3):173-86.

185. Fu J, Li L, Qi L, Zhao L. A randomized controlled trial of etanercept in the treatment of refractory recurrent spontaneous abortion with innate immune disorders. Taiwanese Journal of Obstetrics and Gynecology. 2019 Sep 1;58(5):621-5.

186. Tian Y, Xu J, Chen D, Yang C, Peng B. The additional use of hydroxychloroquine can improve the live birth rate in pregnant women with persistent positive antiphospholipid antibodies: A systematic review and meta-analysis. J Gynecol Obstet Hum Reprod. 2021 Oct;50(8):102121.

187. Dao KH, Bermas BL. Systemic Lupus Erythematosus Management in Pregnancy. Int J Womens Health. 2022 Feb 15;14:199-211.

188. Bouariu A, Gică N, Ciobanu AM, Scutelnicu AM, Popescu MR, Panaitescu AM. The Potential Benefit of Hydroxychloroquine in Chronic Placental Inflammation of Unknown Etiology Associated with Adverse Pregnancy Outcomes. Healthcare (Basel). 2022 Jan 17;10(1):168.

189. de Moreuil C, Alavi Z, Pasquier E. Hydroxychloroquine may be beneficial in preeclampsia and recurrent miscarriage. British Journal of Clinical Pharmacology. 2020;86(1):39-49.

190. Pasquier E, Saint-Martin L de, Marhic G, Chauleur C, Bohec C, Bretelle F, *et al.* Hydroxychloroquine for prevention of recurrent miscarriage: study protocol for a multicentre randomised placebo-controlled trial BBQ study. BMJ Open. 2019 Mar 1;9(3):e025649.

191. Yang S, Ni R, Lu Y, Wang S, Xie F, Zhang C, *et al.* A three-arm, multicenter, open-label randomized controlled trial of hydroxychloroquine and low-dose prednisone to treat recurrent pregnancy loss in women with undifferentiated connective tissue diseases: protocol for the Immunosuppressant regimens for LIving FEtuses (ILIFE) trial. Trials. 2020 Sep 9;21(1):771.

192. Yan X, Wang D, Yan P, Li H. Low molecular weight heparin or LMWH plus aspirin in the treatment of unexplained recurrent miscarriage with negative antiphospholipid antibodies: A meta-analysis of randomized controlled trial. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2022 Jan 1;268:22-30.

193. Quenby S, Booth K, Hiller L, Coomarasamy A, Hamulyák E, Scheres L, *et al.* Low-Molecular-Weight Heparin Versus Standard Pregnancy Care for Women with Recurrent Miscarriage and Inherited Thrombophilia (ALIFE2): An Open-Label, Phase III Randomized Controlled Trial. Blood. 2022 Dec 6;140(Supplement 2):LBA-5.

194. Sammaritano LR, Bermas BL, Chakravarty EE, Chambers C, Clowse MEB, Lockshin MD, *et al.* 2020 American College of Rheumatology Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases. Arthritis Rheumatol. 2020 Apr;72(4):529-56.

195. Tektonidou MG, Andreoli L, Limper M, Amoura Z, Cervera R, Costedoat-Chalumeau N, *et al.* EULAR recommendations for the management of antiphospholipid syndrome in adults. Annals of the Rheumatic Diseases. 2019 Oct 1;78(10):1296-304.

196. Hamulyák EN, Scheres LJJ, Goddijn M, Middeldorp S. Antithrombotic therapy to prevent recurrent pregnancy loss in antiphospholipid syndrome-What is the evidence? J Thromb Haemost. 2021 May;19(5):1174-85.

197. Royal College of Obstetricians and Gynaecologists. Green-top Guideline Number 17. The Investigation and Treatment of Couples with Recurrent First-trimester and Second-trimester Miscarriage. London: RCOG; 2011.

198. Dhillon-Smith RK, Middleton LJ, Sunner KK, Cheed V, Baker K, Farrell-Carver S, *et al.* Levothyroxine in Women with Thyroid Peroxidase Antibodies before Conception. New England Journal of Medicine. 2019 Apr 4;380(14):1316-25.

199. van Dijk MM, Vissenberg R, Fliers E, van der Post JAM, van der Hoorn MLP, de Weerd S, *et al.* Levothyroxine in euthyroid thyroid peroxidase antibody positive women with recurrent pregnancy loss (T4LIFE trial): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Diabetes Endocrinol. 2022 May;10(5):322-9.

200. Leng T, Li X, Zhang H. Levothyroxine treatment for subclinical hypothyroidism improves the rate of live births in pregnant women with recurrent pregnancy loss: a randomized clinical trial. Gynecological Endocrinology. 2022 Apr 15;0(0):1-7.

201. Coomarasamy A, Williams H, Truchanowicz E, Seed PT, Small R, Quenby S, *et al.* PROMISE: first-trimester progesterone therapy in women with a history of unexplained recurrent miscarriages – a randomised, double-blind, placebo-controlled, international multicentre trial and economic evaluation. Health Technol Assess. 2016 May;20(41):1-92.

202. Coomarasamy A, Devall AJ, Cheed V, Harb H, Middleton LJ, Gallos ID, *et al.* A Randomized Trial of Progesterone in Women with Bleeding in Early Pregnancy. New England Journal of Medicine. 2019 May 9;380(19):1815-24.

203. Devall AJ, Papadopoulou A, Podesek M, Haas DM, Price MJ, Coomarasamy A, *et al.* Progestogens for preventing miscarriage: a network meta-analysis. Cochrane Database of Systematic Reviews [Internet]. 2021 [cited 2022 May 27];(4). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013792.pub2/full

204. Devall AJ, Melo P, Coomarasamy A. Progesterone for the prevention of threatened miscarriage. Obstetrics, Gynaecology and Reproductive Medicine. 2022 Mar 1;32(3):44-7.

205. Ectopic pregnancy and miscarriage: diagnosis and initial management. 2021;35.

206. Duncan WC. Did the NICE guideline for progesterone treatment of threatened miscarriage get it right? Reproduction and Fertility. 2022 Apr 1;3(2):C4-6.

207. Abenhaim HA, Audibert F, Gagnon R, Girard I, Kellow Z, Klam S. Progesterone for Prevention of Miscarriage and Preterm Birth in Women With First-Trimester Bleeding: PREEMPT Trial [A260]. Obstetrics & Gynecology. 2022 May;139:75S.

208. Tewary S, Lucas ES, Fujihara R, Kimani PK, Polanco A, Brighton PJ, *et al.* Impact of sitagliptin on endometrial mesenchymal stem-like progenitor cells: A randomised, double-blind placebo-controlled feasibility trial. EBioMedicine. 2020 Jan;51:102597.

209. Kato H, Yamagishi Y, Hagihara M, Hirai J, Asai N, Shibata Y, *et al.* Systematic review and meta-analysis for impacts of oral antibiotic treatment on pregnancy outcomes in chronic endometritis patients. Journal of Infection and Chemotherapy. 2022 May 1;28(5):610-5.

210. Harris BS, Bishop KC, Kuller JA, Alkilany S, Price TM. Preimplantation genetic testing: a review of current modalities. F&S Reviews. 2021 Jan 1;2(1):43-56.

211. Li S, Chen M, Zheng PS. Analysis of parental abnormal chromosomal karyotype and subsequent live births in Chinese couples with recurrent pregnancy loss. Sci Rep. 2021 Dec;11(1):20298.

212. Huang C, Jiang W, Zhu Y, Li H, Lu J, Yan J, *et al.* Pregnancy outcomes of reciprocal translocation carriers with two or more unfavorable pregnancy histories: before and after preimplantation genetic testing. J Assist Reprod Genet. 2019 Nov 1;36(11):2325-31.

213. Mahdavi M, Sharafi SM, Daniali SS, Riahi R, Kheirollahi M. The Clinical Effectiveness of Preimplantation Genetic Diagnosis for Chromosomal Translocation Carriers: A Meta-analysis. Glob Med Genet. 2020 Jun;07(1):14-21.

214. Ma X, Xu X, Mao B, Liu H, Li H, Liu K, *et al.* Chromosomal analysis for embryos from balanced chromosomal rearrangement carriers using next generation sequencing. Molecular Reproduction and Development. 2021;88(5):362-70.

215. Cornelisse S, Zagers M, Kostova E, Fleischer K, Wely M van, Mastenbroek S. Preimplantation genetic testing for aneuploidies (abnormal number of chromosomes) in in vitro fertilisation. Cochrane Database of Systematic Reviews [Internet]. 2020 [cited 2022 May 31];(9). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD005291.pub3/full

216. Sanders KD, Silvestri G, Gordon T, Griffin DK. Analysis of IVF live birth outcomes with and without preimplantation genetic testing for aneuploidy (PGT-A): UK Human Fertilisation and Embryology Authority data collection 2016-2018. J Assist Reprod Genet. 2021 Dec 1;38(12):3277-85.

217. Munné S, Kaplan B, Frattarelli JL, Child T, Nakhuda G, Shamma FN, *et al.* Preimplantation genetic testing for aneuploidy versus morphology as selection criteria for single frozen-thawed embryo transfer in good-prognosis patients: a multicenter randomized clinical trial. Fertil Steril. 2019 Dec;112(6):1071-1079.e7.

218. Bhatt SJ, Marchetto NM, Roy J, Morelli SS, McGovern PG. Pregnancy outcomes following in vitro fertilization frozen embryo transfer (IVF-FET) with or without preimplantation genetic testing for aneuploidy (PGT-A) in women with recurrent pregnancy loss (RPL): a SART-CORS study. Hum Reprod. 2021 Jul 19;36(8):2339-44.

219. Pantou A, Mitrakos A, Kokkali G, Petroutsou K, Tounta G, Lazaros L, *et al.* The impact of preimplantation genetic testing for aneuploidies (PGT-A) on clinical outcomes in high risk patients. J Assist Reprod Genet. 2022 Mar 25;

220. Papas RS, Kutteh WH. Genetic Testing for Aneuploidy in Patients Who Have Had Multiple Miscarriages: A Review of Current Literature. Appl Clin Genet. 2021 Jul 23;14:321-9.

221. Orvieto R. The reproducibility of trophectoderm biopsies – The chaos behind preimplantation genetic testing for aneuploidy. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2020 Nov 1;254:57-8.

222. Pre-implantation genetic testing for aneuploidy (PGT-A) | HFEA [Internet]. [cited 2022 Jun 1]. Available from: https://www.hfea.gov.uk/treatments/treatment-add-ons/pre-implantation-genetic-testing-for-aneuploidy-pgt-a/

223. Lepine S, McDowell S, Searle LM, Kroon B, Glujovsky D, Yazdani A. Advanced sperm selection techniques for assisted reproduction. Cochrane Database of Systematic Reviews [Internet]. 2019 [cited 2022 May 31];(7). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD010461.pub3/full

224. Miller D, Pavitt S, Sharma V, Forbes G, Hooper R, Bhattacharya S, *et al.* Physiological, hyaluronan-selected intracytoplasmic sperm injection for infertility treatment (HABSelect): a parallel, two-group, randomised trial. Lancet. 2019 Feb 2;393(10170):416-22.

225. West R, Coomarasamy A, Frew L, Hutton R, Kirkman-Brown J, Lawlor M, *et al.* Sperm selection with hyaluronic acid improved live birth outcomes among older couples and was connected to sperm DNA quality, potentially affecting all treatment outcomes. Human Reproduction. 2022 Apr 23;deac058.

226. Physiological intracytoplasmic sperm injection (PICSI) | HFEA [Internet]. [cited 2022 Jun 1]. Available from: https://www.hfea.gov.uk/treatments/treatment-add-ons/physiological-intracytoplasmic-sperm-injection-picsi/

227. Dempsey MA, Flood K, Burke N, Fletcher P, Kirkham C, Geary MP, *et al.* Perinatal outcomes of women with a prior history of unexplained recurrent miscarriage. The Journal of Maternal-Fetal & Neonatal Medicine. 2015 Mar 24;28(5):522-5.

228. Ticconi C, Pietropolli A, Specchia M, Nicastri E, Chiaramonte C, Piccione E, *et al.* Pregnancy-Related Complications in Women with Recurrent Pregnancy Loss: A Prospective Cohort Study. Journal of Clinical Medicine. 2020 Sep;9(9):2833.

229. 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. The Lancet. 2021 May 1;397(10285):1658-67.

230. Manning R, Iyer J, Bulmer JN, Maheshwari A, Choudhary M. Are we managing women with Recurrent Miscarriage appropriately? A snapshot survey of clinical practice within the United Kingdom. Journal of Obstetrics and Gynaecology. 2021 Jul 4;41(5):807-14.

231. Coomarasamy A, Dhillon-Smith RK, Papadopoulou A, Al-Memar M, Brewin J, Abrahams VM, *et al.* Recurrent miscarriage: evidence to accelerate action. The Lancet. 2021 May;397(10285):1675-82.

232. Liu Y, Shan N, Yuan Y, Tan B, Che P, Qi H. The efficacy of enoxaparin for recurrent abortion: a meta-analysis of randomized controlled studies. The Journal of Maternal-Fetal & Neonatal Medicine. 2021 Feb 1;34(3):473-8.

233. Intzes S, Symeonidou M, Zagoridis K, Stamou M, Spanoudaki A, Spanoudakis E. Hold your needles in women with recurrent pregnancy losses with or without hereditary thrombophilia: Meta-analysis and review of the literature. Journal of Gynecology Obstetrics and Human Reproduction. 2021 Apr 1;50(4):101935.

234. Lin T, Chen Y, Cheng X, Li N, Sheng X. Enoxaparin (or plus aspirin) for the prevention of recurrent miscarriage: A meta-analysis of randomized controlled studies. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2019 Mar 1;234:53-7.

235. Rasmark Roepke E, Hellgren M, Hjertberg R, Blomqvist L, Matthiesen L, Henic E, *et al.* Treatment efficacy for idiopathic recurrent pregnancy loss – a systematic review and meta-analyses. Acta Obstetricia et Gynecologica Scandinavica. 2018;97(8):921-41.

236. Wang G, Zhang R, Li C, Chen A. Evaluation of the effect of low molecular weight heparin in unexplained recurrent pregnancy loss: a meta-analysis of randomized controlled trials. The Journal of Maternal-Fetal & Neonatal Medicine. 2021 Jul 26;0(0):1-8.

237. Jiang F, Hu X, Jiang K, Pi H, He Q, Chen X. The role of low molecular weight heparin on recurrent pregnancy loss: A systematic review and meta-analysis. Taiwanese Journal of Obstetrics and Gynecology. 2021 Jan 1;60(1):1-8.

238. Dias ATB, Modesto TB, de Oliveira SA. Effectiveness of the use of Low Molecular Heparin in patients with repetition abortion history: Systematic review and meta-analysis. JBRA Assist Reprod. 2021;25(1):10-27.

239. Levine LD, Holland TL, Kim K, Sjaarda LA, Mumford SL, Schisterman EF. The role of aspirin and inflammation on reproduction: the EAGeR trial. Can J Physiol Pharmacol. 2019 Mar;97(3):187-92.

240. Naimi AI, Perkins NJ, Sjaarda LA, Mumford SL, Platt RW, Silver RM, *et al.* The Effect of Preconception-Initiated Low-Dose Aspirin on Human Chorionic Gonadotropin-Detected Pregnancy, Pregnancy Loss, and Live Birth : Per Protocol Analysis of a Randomized Trial. Ann Intern Med. 2021 May;174(5):595-601.

241. Blomqvist L, Hellgren M, Strandell A. Acetylsalicylic acid does not prevent first-trimester unexplained recurrent pregnancy loss: A randomized controlled trial. Acta Obstet Gynecol Scand. 2018 Nov;97(11):1365-72.

242. van Oppenraaij RHF, Jauniaux E, Christiansen OB, Horcajadas JA, Farquharson RG, Exalto N, *et al.* Predicting adverse obstetric outcome after early pregnancy events and complications: a review. Human Reproduction Update. 2009 Jul 1;15(4):409-21.

243. Gunnarsdottir J, Stephansson O, Cnattingius S, Åkerud H, Wikström AK. Risk of placental dysfunction disorders after prior miscarriages: a population-based study. American Journal of Obstetrics and Gynecology. 2014 Jul 1;211(1):34.e1-34.e8.

244. Bartsch E, Medcalf KE, Park AL, Ray JG. Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. BMJ. 2016 Apr 19;353:i1753.

245. Roberge S, Bujold E, Nicolaides KH. Aspirin for the prevention of preterm and term preeclampsia: systematic review and metaanalysis. Am J Obstet Gynecol. 2018 Mar;218(3):287-293.e1.

246. Man R, Hodgetts Morton V, Devani P, Morris RK. Aspirin for preventing adverse outcomes in low risk nulliparous women with singleton pregnancies: A systematic review and meta-analysis. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2021 Jul 1;262:105-12.

247. Mone F, Mulcahy C, McParland P, Breathnach F, Downey P, McCormack D, *et al.* Trial of feasibility and acceptability of routine low-dose aspirin versus Early Screening Test indicated aspirin for pre-eclampsia prevention (TEST study): a multicentre randomised controlled trial. BMJ Open. 2018 Jul 28;8(7):e022056.

248. Jacobson B, Rambiritch V, Paek D, Sayre T, Naidoo P, Shan J, *et al.* Safety and Efficacy of Enoxaparin in Pregnancy: A Systematic Review and Meta-Analysis. Adv Ther. 2020 Jan 1;37(1):27-40.

249. Garza-Galvan ME, Ferrigno AS, Campos-Zamora M, Bain PA, Easter SR, Kim J, *et al.* Low-dose aspirin use in the first trimester of pregnancy and odds of congenital anomalies: A meta-analysis of randomized controlled trials. Int J Gynaecol Obstet. 2022 Jul 10;

250. Short VL, Hoffman M, Metgud M, Kavi A, Goudar SS, Okitawutshu J, *et al.* Safety of daily low-dose aspirin use during pregnancy in low-income and middle-income countries. AJOG Global Reports. 2021 Feb 1;1(1):100003.

251. Ma N, Qin R, Qin W, Liao M, Zhao Y, Hang F, *et al.* Oral immunosuppressants improve pregnancy outcomes in women with idiopathic recurrent miscarriage: A meta-analysis. J Clin Pharm Ther. 2022 Mar 6;

252. Bandoli G, Palmsten K, Forbess Smith CJ, Chambers CD. A review of systemic corticosteroid use in pregnancy and the risk of select pregnancy and birth outcomes. Rheum Dis Clin North Am. 2017 Aug;43(3):489-502.

253. Paziana K, Del Monaco M, Cardonick E, Moritz M, Keller M, Smith B, *et al.* Ciclosporin Use During Pregnancy. Drug Saf. 2013 May 1;36(5):279-94.

254. Katalinic A, Shulman LP, Strauss JF, Garcia-Velasco JA, Anker JN van den. A critical appraisal of safety data on dydrogesterone for the support of early pregnancy: a scoping review and meta-analysis. Reproductive BioMedicine Online [Internet]. 2022 Apr 10 [cited 2022 May 27]; Available from: https://www.sciencedirect.com/science/article/pii/S1472648322002309

255. IMSN. CycloGEST CytoTEC errors in pregnancy (Safety Alert) [Internet]. Irish Medication Safety Network. 2019 [cited 2022 Sep 30]. Available from: https://imsn.ie/cyclogest-cytotec-errors-in-pregnancy/

256. Friel KM, Murphy J. The fortification of folic acid to reduce the risk of neural tube defects: A systematic review of the evidence of practice for Ireland. :31.

257. Egan E, Kelly F, Sweeney MR. Voluntary folic acid fortification levels of food staples in Ireland continue to decline: further implications for passive folic acid intakes? Journal of Public Health. 2021 Jun 1;43(2):281-6.

258. Turner MJ. Neural Tube Defects and Folic Acid Food Fortification in Europe. Am J Public Health. 2018 May;108(5):601-2.

259. Bailey SL, Boivin J, Cheong YC, Kitson-Reynolds E, Bailey C, Macklon N. Hope for the best …but expect the worst: a qualitative study to explore how women with recurrent miscarriage experience the early waiting period of a new pregnancy. BMJ Open. 2019 May 1;9(5):e029354.

260. Saravelos SH, Regan L. The Importance of Preconception Counseling and Early Pregnancy Monitoring. Semin Reprod Med. 2011 Nov;29(6):557-68.

261. Gavrizi S, Pike J, Mak W. Understanding the Needs of Individuals Who Have Experienced Pregnancy Loss: A Retrospective Community-Based Survey. Journal of Women's Health [Internet]. 2021 Mar 1 [cited 2022 Jul 23]; Available from: https://www.liebertpub.com/doi/10.1089/jwh.2020.8747

262. Meaney S, Corcoran P, Spillane N, O'Donoghue K. Experience of miscarriage: an interpretative phenomenological analysis. BMJ Open. 2017 Mar 1;7(3):e011382.

263. Hennessy M, Linehan L, Dennehy R, Devane D, Rice R, Meaney S, *et al.* Developing guideline-based key performance indicators for recurrent miscarriage care: lessons from a multi-stage consensus process with a diverse stakeholder group. Research Involvement and Engagement. 2022 May 14;8(1):18.

264. GRADE guidelines: 1. Introduction – GRADE evidence profiles and summary of findings tables – ScienceDirect [Internet]. [cited 2022 Aug 10]. Available from: https://www.sciencedirect.com/science/article/pii/S0895435610003306?via%3Dihub

## Bibliography

Health Information Quality Authority (2012). National Standards for Safer Better Healthcare [Internet]. Available from: https://www.hiqa.ie/reports-and-publications/standard/national-standards-safer-better-healthcare

Scottish Intercollegiate Guidelines Network (SIGN). A guideline developer's handbook. Edinburgh: SIGN; 2019. (SIGN publication no. 50). [November 2019]. Available from URL: http://www.sign.ac.uk

Society of Maternal-Fetal Medicine. SMFM Clinical Practice Guidelines Development Process [Internet]. Available from: https://www.smfm.org/publications

Department of Health (2018). NCEC Implementation Guide and Toolkit. Available at: https://health.gov.ie/national-patient-safety-office/ncec/

Department of Health (2019). How to develop a National Clinical Guideline. Available at: https://www.gov.ie/en/collection/cd41ac-clinical-effectiveness-resources-and-learning/

Department of Health (2015). NCEC Standards for Clinical Practice Guidance. Available at: https://www.nmbi.ie/NMBI/media/NMBI/Forms/standards-for-clinical-practice-guidance-ncec.pdf

Health Service Executive (2016). National Framework for developing Policies, Procedures, Protocols and Guidelines (PPPGs). Available from: https://www.hse.ie/eng/about/who/qid/nationalframeworkdevelopingpolicies/

Health Service Executive (2019). National Review of Clinical Audit. Available from: https://www.hse.ie/eng/services/publications/national-review-of-clinical-audit-report-2019.pdf

National Clinical Effectiveness Committee (NCEC) and Health Information and Quality Authority (HIQA) (2015) National quality assurance criteria for clinical guidelines. Version 2. Dublin: NCEC and HIQA. https://www.hiqa.ie/sites/default/files/2017-01/National-Quality-Assurance-Criteria.pdf

Health Service Executive (2022), National Centre for Clinical Audit Nomenclature – Glossary of Terms, National Quality and Patient Safety Directorate. Available from: https://www.hse.ie/eng/about/who/nqpsd/ncca/

## Supporting Evidence

GRADE: http://www.gradeworkinggroup.org/

AGREE: http://www.agreetrust.org/agree-ii/

HSE: https://www.hse.ie/eng/about/who/qid/nationalframeworkdevelopingpolicies/

# Glossary
## (For The Purpose Of This Guideline)

**ACLA** Anticardiolipin Antibodies Test

**ACOG** American College of Obstetricians and Gynaecologists

**AFS** American Fertility Services

**AGREE** Appraisal of Guidelines for Research and Evaluation

**ART** Assisted Reproductive Technology

**ASRM** American Society for Reproductive Medicine

**BMI** Body Mass Index

**CAG** Clinical Advisory Group

**EAG** Expert Advisory Group

**ESHRE** European Society of Human Reproduction and Embryology

**FIGO** International Federation of Gynaecology and Obstetrics

**GDG** Guideline Development Group

**GPT** Guideline Programme Team

**GRADE** Grading of Recommendations, Assessments, Developments and Evaluations

**HIQA** Health Information and Quality Authority

**HSE** Health Service Executive

**ICSI** Intracytoplasmic Sperm Injection

**IOG** Institute of Obstetricians and Gynaecologists

**LMWH** Low Molecular Weight Heparin

**NCEC** National Clinical Effectiveness Committee

**NICE** The National Institute for Health and Care Excellence

**NWIHP** National Women and Infants Health Programme

**PCOS** Polycystic Ovary Syndrome

**PGT** Preimplantation Genetic Testing

**PICSI** Physiological Intracytoplasmic Sperm Injection

**PPPG** Policy, Procedures, Protocols and Guidelines

**RAG** Research Advisory Group

**RCOG** Royal College of Obstetricians and Gynaecologists

**RCPI** Royal College of Physicians of Ireland

**RM** Recurrent Miscarriage

**RPL** Recurrent Pregnancy Loss

# Appendix 1:
# Expert Advisory Group Members 2021-

| Name | Profession | Location (2021) |
|---|---|---|
| Dr Fergus McCarthy | Consultant Obstetrician, Gynaecologist, Senior Lecturer and Maternal-Fetal Medicine Sub-specialist | Cork University Maternity Hospital, University College Cork |
| Dr Mairead Butler | Consultant Obstetrician and Gynaecologist | University Hospital Waterford |
| Prof Declan Keane | Professor of Obstetrics and Gynaecology | National Maternity Hospital Dublin, Royal College of Surgeons in Ireland |
| Dr Katherine Astbury | Consultant Obstetrician and Gynaecologist Gynaecology Oncology Sub-specialist | University Hospital Galway |
| Dr Sarah Petch | Specialist Registrar, Obstetrics and Gynaecology | National Maternity Hospital Dublin |
| Dr Orla Donohoe | Specialist Registrar, Obstetrics and Gynaecology | Sligo University Hospital |
| Prof John Murphy | Consultant Neonatologist and Clinical Lead for the National Clinical Programme for Paediatrics and Neonatology | National Women and Infants Health Programme |
| Ms Siobhan Canny | Group Director of Midwifery | Saolta University Health Care Group |
| Ms Fiona Hanrahan | Director of Midwifery and Nursing | Rotunda Hospital Dublin |
| Ms Margaret Quigley | National Lead for Midwifery | Office of Nursing and Midwifery Services Director |
| Prof Valerie Smith | Professor of Midwifery | School of Nursing and Midwifery, Trinity College Dublin |
| Ms Triona Cowman | Director of the Centre for Midwifery Education | Centre for Midwifery Education, Coombe Women & Infants University Hospital |
| Ms Janet Murphy | Advanced Midwifery Practitioner | University Hospital Waterford |

| Attendee | Profession | Location (2021) |
|---|---|---|
| Dr Ciara McCarthy | General Practitioner and ICGP Women's Health Lead | Irish College of General Practitioners |
| Mr Fergal O' Shaughnessy<br>*And*<br>Dr Brian Cleary<br>*(Shared nomination)* | Senior Pharmacist, Honorary Lecturer<br>*And*<br>Chief Pharmacist, Honorary Clinical Associate Professor and Medications Lead, Maternal & Newborn Clinical Management System | Rotunda Hospital Dublin<br>Royal College of Surgeons in Ireland |
| Ms Marie Finn | Medical Social Work Counsellor | Saolta University Health Care Group |
| Ms Marie Culliton | Lab Manager/Chief Medical Scientist | National Maternity Hospital Dublin |
| Ms Marita Hennessy | Post-Doctoral Researcher | Pregnancy Loss Research Group, INFANT Centre, University College Cork |
| Ms Niamh Connolly-Coyne *And*<br>Ms Mandy Daly<br>*(Shared nomination)* | Board of Directors | Irish Neonatal Health Alliance |
| Ms Caroline Joyce | Principal Clinical Biochemist<br>PhD Candidate | Cork University Hospital<br>University College Cork |
| Dr Richard Duffy | Consultant Perinatal Psychiatrist | Rotunda Hospital Dublin |
| Ms Clare Farrell | Physiotherapy Manager | Coombe Women & Infants University Hospital |
| Ms Fiona Dunlevy<br>*And*<br>Ms Sinéad Curran<br>*(Shared nomination)* | Dietician Manager | Coombe Women & Infants University Hospital<br>National Maternity Hospital |
| Dr Nicholas Barrett | Lead for Obstetric Anaesthesiology services | Limerick University Hospital |
| Dr Brendan Fitzgerald | Consultant Perinatal Pathologist | Cork University Hospital |
| Dr Niamh Conlon | Consultant Histopathologist | Cork University Hospital |
| Ms Georgina Cruise | Service Manager | Patient Advocacy Ireland |

# Appendix 2: **Members of the RE:CURRENT Research Advisory Group 2020-2022**

| Name | Affiliation |
|---|---|
| Ms Úna Cahill | A/Assistant Director of Midwifery, Cork University Maternity Hospital |
| Ms Ríona Cotter | Programme Manager for the Implementation of the National Standards for Bereavement Care Following Pregnancy Loss and Perinatal Death, Cork University Maternity Hospital |
| Ms Mairie Cregan | Chairperson and Co-Founder, Féileacáin |
| Ms Carrie Dillon | Bereavement Clinical Midwife Specialist, University Hospital Kerry |
| Dr Linda Drummond | Project Lead, National Care Experience Programme, Health Information Quality Authority (HIQA) |
| Ms Angela Dunne | Director of Midwifery, National Women & Infants Health Programme |
| Dr Minna Geisler | Consultant in Reproductive Medicine, Waterstone Clinic & Consultant Obstetrician and Gynaecologist, Cork University Maternity Hospital |
| Dr Trish Horgan | General Practitioner, Broad Lane Family Practice, Cork |
| Dr Azy Khalid | Consultant Obstetrician and Gynaecologist, University Hospital Waterford |
| Mr Con Lucey | Parent Advocate |
| Ms Mary McAuliffe | Head of Clinical Services, Waterstone Clinic |
| Dr Moya McMenamin | Consultant Obstetrician and Gynaecologist, Cork University Maternity Hospital |
| Dr Yvonne O'Brien | Consultant Obstetrician and Gynaecologist, Galway University Hospital and Portiuncula Hospital Ballinasloe [01/09/2020] |
| Ms Orla O'Connell | Clinical Midwife Specialist in Bereavement & Loss, CUMH |
| Ms Anne O' Flynn | Clinical Nurse Specialist Perinatal Mental Health, Cork University Maternity Hospital |
| Ms Aideen Quigley | Risk & Quality Project Manager, National Women & Infants Health Programme |
| Ms Margaret Quigley | National Lead for Midwifery, Office of Nursing and Midwifery Services Director (ONMSD) |
| Ms Rachel Rice | Parent Advocate & School of Applied Social Studies, UCC |

| | |
|---|---|
| Dr Nóirín Russell | Consultant Obstetrician and Gynaecologist, Cork University Maternity Hospital |
| Ms Jennifer Uí Dhubhgain | Parent Advocate & Secretary, The Miscarriage Association of Ireland |
| Ms Anna Maria Verling | Midwife |
| Ms Jill Whelan | Clinical Midwife Specialist in Bereavement & Loss, University Hospital Waterford |

# Appendix 3: NWIHP/IOG CAG Membership (2022)

Dr Cliona Murphy (Chair). Consultant Obstetrician and Gynaecologist, Coombe Women and Infants University Hospital. Clinical Director, National Women and Infants Health Programme.

Dr Sam Coulter-Smith. Consultant Obstetrician and Gynaecologist, Rotunda Hospital. Chair, Institute of Obstetricians and Gynaecologists.

Angela Dunne. Director of Midwifery, National Women and Infants Health Programme.

Kilian McGrane. Director, National Women and Infants Health Programme.

Dr Peter McKenna. Clinical Lead, Obstetric Event Support Team, National Women and Infants Health Programme.

Prof John Murphy. Clinical Lead Neonatology, National Women and Infants Health Programme.

Prof Maeve Eogan. Consultant Obstetrician and Gynaecologist, Rotunda Hospital. Clinical Lead, Sexual Assault Treatment Units, National Women and Infants Health Programme.

Dr Aoife Mullaly. Consultant Obstetrician and Gynaecologist, Coombe Women and Infants University Hospital. Clinical Lead, Termination of Pregnancy Services, National Women and Infants Health Programme.

Prof Keelin O'Donoghue. Consultant Obstetrician and Gynaecologist, Cork University Maternity Hospital. Clinical Lead, National Guidelines, National Women and Infants Health Programme.

Prof Nóirín Russell. Consultant Obstetrician and Gynaecologist, Cork University Maternity Hospital. Clinical Director, Cervical Check.

Prof Richard Greene. Consultant Obstetrician and Gynaecologist, Cork University Maternity Hospital. Clinical Director, National Perinatal Epidemiology Centre, University College Cork.

Prof John Morrison. Consultant Obstetrician and Gynaecologist, University Hospital Galway. Clinical Director, Saolta Maternity Directorate.

Dr Suzanne O'Sullivan. Consultant Obstetrician and Gynaecologist, Cork University Maternity Hospital. Director of Education and Training, Obstetrics and Gynaecology, Institute of Obstetricians and Gynaecologists.

Prof Fergal Malone. Master, Consultant Obstetrician and Gynaecologist, Rotunda Hospital.

Prof John Higgins. Cork University Maternity Hospital, Consultant Obstetrician and Gynaecologist, Clinical Director, Ireland South Women and Infants Directorate.

Dr Mendinaro Imcha. Clinical Director, Consultant Obstetrician and Gynaecologist, University Maternity Hospital Limerick.

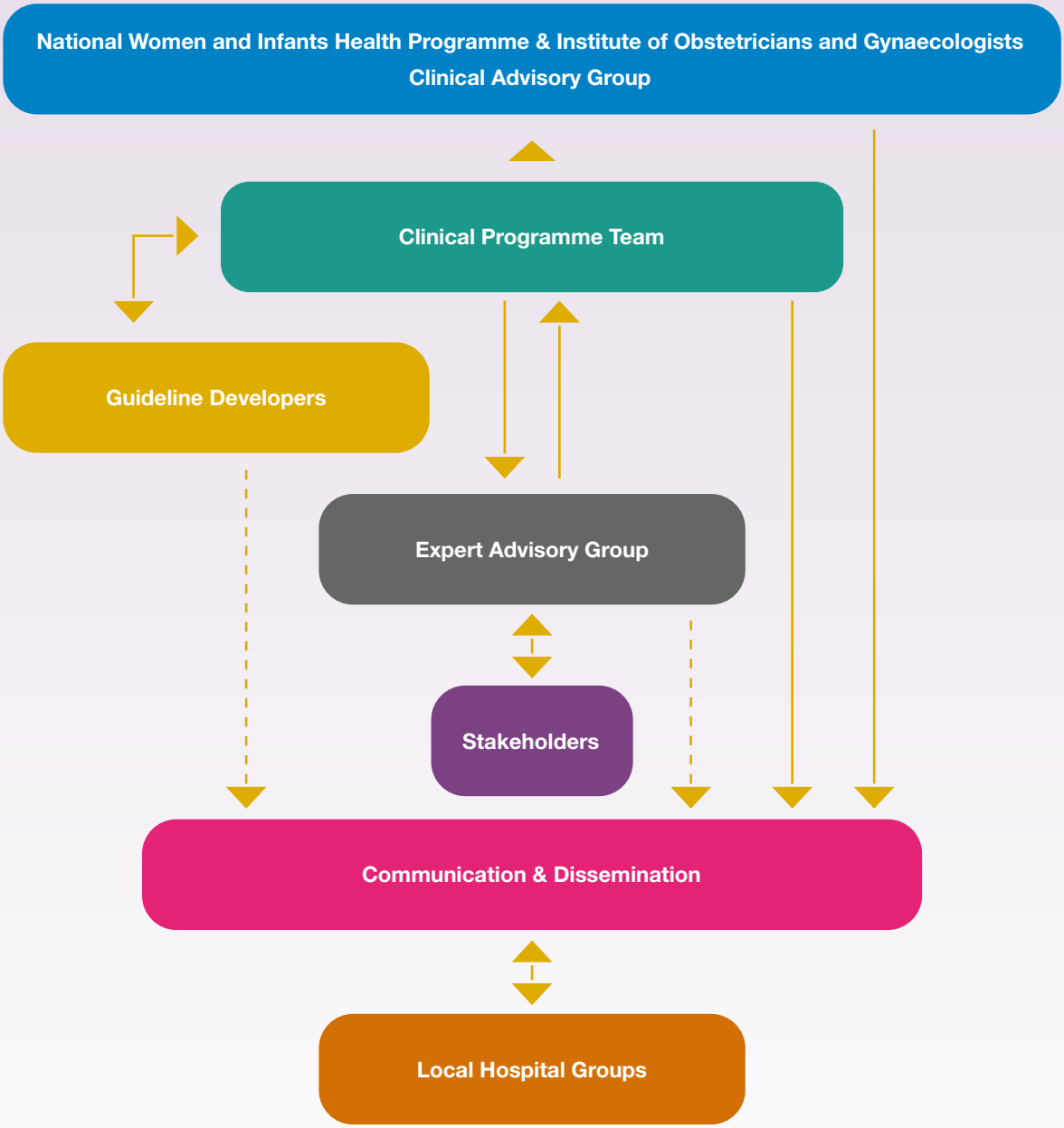
Prof Shane Higgins. Master, Consultant Obstetrician and Gynaecologist, National Maternity Hospital.

Prof Mike O'Connell. Master, Consultant Obstetrician and Gynaecologist, Coombe Women and Infants University Hospital.

Dr Brian Cleary. Chief Pharmacist, Rotunda Hospital. Medications Lead, Maternal and Newborn Clinical Management System Project.

# Appendix 4:
# Guideline Programme Process

## Guideline Programme Process



# Appendix 5:
# Blood Investigations Checklist

## Recurrent Miscarriage Clinic

Blood tests to investigate recurrent miscarriage

| Test | Department | Bottle ** |
|---|---|---|
| **Thyroid function test** | Biochemistry | Red |
| **Thyroid antibodies**:<br>• Thyroid peroxidase antibodies<br>• Thyroglobulin antibodies | Biochemistry | Red |
| **FBC** | Haematology | Purple |
| **Antinuclear antibodies** | Immunology | Red |
| **Thrombophilia**<br>Antiphospholipid syndrome<br>• Lupus anticoagulant<br>• Anticardiolipin antibodies (IgG and IgM)<br>• β2 glycoprotein I antibodies (IgG and IgM | Haematology | Red/Purple |
| **HBA1c**<br>**(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

# Appendix 6: **Grades of Recommendation** [14]

| Grade of recommendation | Clarity of risk/ benefit | Quality of supporting evidence | Implications | Suggested Language |
|---|---|---|---|---|
| **1 A.** Strong recommendation, high-quality evidence | Benefits clearly outweigh risk and burdens, or vice versa | Consistent evidence from well-performed randomised, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk | Strong recommendations can apply to most patients in most circumstances without reservation. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present | We strongly recommend…<br>We recommend that …should be performed/ administered…<br>We recommend that … is indicated/ beneficial/ effective… |
| **1 B.** Strong recommendation, moderate-quality evidence | Benefits clearly outweigh risk and burdens, or vice versa | Evidence from randomised, controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate | Strong recommendation and applies to most patients. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present | We recommend…<br>We recommend that … should be performed/ administered…<br>We recommend that … is (usually) indicated/ beneficial/ effective… |

14 SMFM adopts GRADE (Grading of Recommendations Assessment, Development, and Evaluation) for clinical guidelines. Society for Maternal-Fetal Medicine (SMFM), Chauhan SP, Blackwell SC. Am J Obstet Gynecol. 2013 Sep;209(3):163-5. doi: 10.1016/j.ajog.2013.07.012. PMID: 23978245

| Grade of recommendation | Clarity of risk/ benefit | Quality of supporting evidence | Implications | Suggested Language |
|---|---|---|---|---|
| **1 C.** Strong recommendation, low-quality evidence | Benefits appear to outweigh risk and burdens, or vice versa | Evidence from observational studies, unsystematic clinical experience, or from randomised, controlled trials with serious flaws. Any estimate of effect is uncertain | Strong recommendation that applies to most patients. Some of the evidence base supporting the recommendation is, however, of low quality | We recommend…<br>We recommend that … should be performed/ administered…<br>We recommend that … Is (maybe) indicated/ beneficial/ effective… |
| **2A.** Weak recommendation, high-quality evidence | Benefits closely balanced with risks and burdens | Consistent evidence from well-performed randomised, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk | Weak recommendation: best action may differ depending on circumstances or patients or societal values | We suggest…<br>We suggest that … may/might be reasonable… |
| **2B.** Weak recommendation, moderate-quality evidence | Benefits closely balanced with risks and burdens, some uncertainty in the estimates of benefits, risks and burdens | Evidence from randomised, controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate | Weak recommendation; alternative approaches likely to be better for some patients under some circumstances | We suggest…<br>We suggest that … may/might be reasonable… |

| Grade of recommendation | Clarity of risk/ benefit | Quality of supporting evidence | Implications | Suggested Language |
|---|---|---|---|---|
| **2C.** Weak recommendation, low-quality evidence | Uncertainty in the estimates of benefits, risks, and burdens; benefits may be closely balanced with risks and burdens | Evidence from observational studies, unsystematic clinical experience, or from randomised, controlled trials with serious flaws. Any estimate of effect is uncertain | Very weak recommendation: other alternatives may be equally reasonable. | We suggest… is an option<br>We suggest that … may/might be reasonable. |
| **Best practice** | A recommendation that is sufficiently obvious that the desirable effects outweigh undesirable effects, despite the absence of direct evidence, such that the grading of evidence is unnecessary | | | We recommend…<br>We recommend that … should be performed/ administered…<br>We recommend that … Is usually) indicated/ beneficial/effective |

# Appendix 7: **AGREE II checklist**[15]

## AGREE Reporting Checklist 2016

This checklist is intended to guide the reporting of clinical practice guidelines.

| CHECKLIST ITEM AND DESCRIPTION | REPORTING CRITERIA | Page # |
|---|---|---|
| **DOMAIN 1: SCOPE AND PURPOSE** | | |
| **1. OBJECTIVES**<br>*Report the overall objective(s) of the guideline. The expected health benefits from the guideline are to be specific to the clinical problem or health topic.* | ☐ Health intent(s) (i.e., prevention, screening, diagnosis, treatment, etc.)<br>☐ Expected benefit(s) or outcome(s)<br>☐ Target(s) (e.g., patient population, society) | |
| **2. QUESTIONS**<br>*Report the health question(s) covered by the guideline, particularly for the key recommendations.* | ☐ Target population<br>☐ Intervention(s) or exposure(s)<br>☐ Comparisons (if appropriate)<br>☐ Outcome(s)<br>☐ Health care setting or context | |
| **3. POPULATION**<br>*Describe the population (i.e., patients, public, etc.) to whom the guideline is meant to apply.* | ☐ Target population, sex and age<br>☐ Clinical condition (if relevant)<br>☐ Severity/stage of disease (if relevant)<br>☐ Comorbidities (if relevant)<br>☐ Excluded populations (if relevant) | |
| **DOMAIN 2: STAKEHOLDER INVOLVEMENT** | | |
| **4. GROUP MEMBERSHIP**<br>*Report all individuals who were involved in the development process. This may include members of the steering group, the research team involved in selecting and reviewing/ rating the evidence and individuals involved in formulating the final recommendations.* | ☐ Name of participant<br>☐ Discipline/content expertise (e.g., neurosurgeon, methodologist)<br>☐ Institution (e.g., St. Peter's hospital)<br>☐ Geographical location (e.g., Seattle, WA)<br>☐ A description of the member's role in the guideline development group | |

15 AGREE Reporting Checklist is available on the AGREE Enterprise website, a free and open access resource to support the practice guideline field (www. agreetrust.org)

| CHECKLIST ITEM AND DESCRIPTION | REPORTING CRITERIA | Page # |
|---|---|---|
| **5. TARGET POPULATION PREFERENCES AND VIEWS**<br>*Report how the views and preferences of the target population were sought/considered and what the resulting outcomes were.* | ☐ Statement of type of strategy used to capture patients'/publics' views and preferences (e.g., participation in the guideline development group, literature review of values and preferences)<br>☐ Methods by which preferences and views were sought (e.g., evidence from literature, surveys, focus groups)<br>☐ Outcomes/information gathered on patient/public information<br>☐ How the information gathered was used to inform the guideline development process and/or formation of the recommendations | |
| **6. TARGET USERS**<br>*Report the target (or intended) users of the guideline.* | ☐ The intended guideline audience (e.g. specialists, family physicians, patients, clinical or institutional leaders/administrators)<br>☐ How the guideline may be used by its target audience (e.g., to inform clinical decisions, to inform policy, to inform standards of care) | |
| **DOMAIN 3: RIGOUR OF DEVELOPMENT** | | |
| **7. SEARCH METHODS**<br>*Report details of the strategy used to search for evidence.* | ☐ Named electronic database(s) or evidence source(s) where the search was performed (e.g., MEDLINE, EMBASE, PsychINFO, CINAHL)<br>☐ Time periods searched (e.g., January 1, 2004 to March 31, 2008)<br>☐ Search terms used (e.g., text words, indexing terms, subheadings)<br>☐ Full search strategy included (e.g., possibly located in appendix) | |
| **8. EVIDENCE SELECTION CRITERIA**<br>*Report the criteria used to select (i.e., include and exclude) the evidence. Provide rationale, where appropriate.* | ☐ Target population (patient, public, etc.) characteristics<br>☐ Study design<br>☐ Comparisons (if relevant)<br>☐ Outcomes<br>☐ Language (if relevant)<br>☐ Context (if relevant) | |

| CHECKLIST ITEM AND DESCRIPTION | REPORTING CRITERIA | Page # |
|---|---|---|
| **9. STRENGTHS & LIMITATIONS OF THE EVIDENCE**<br>*Describe the strengths and limitations of the evidence. Consider from the perspective of the individual studies and the body of evidence aggregated across all the studies. Tools exist that can facilitate the reporting of this concept.* | ☐ Study design(s) included in body of evidence<br>☐ Study methodology limitations (sampling, blinding, allocation concealment, analytical methods)<br>☐ Appropriateness/relevance of primary and secondary outcomes considered<br>☐ Consistency of results across studies<br>☐ Direction of results across studies<br>☐ Magnitude of benefit versus magnitude of harm<br>☐ Applicability to practice context | |
| **10. FORMULATION OF RECOMMENDATIONS**<br>*Describe the methods used to formulate the recommendations and how final decisions were reached. Specify any areas of disagreement and the methods used to resolve them.* | ☐ Recommendation development process (e.g., steps used in modified Delphi technique, voting procedures that were considered)<br>☐ Outcomes of the recommendation development process (e.g., extent to which consensus was reached using modified Delphi technique, outcome of voting procedures)<br>☐ How the process influenced the recommendations (e.g., results of Delphi technique influence final recommendation, alignment with recommendations and the final vote) | |
| **11. CONSIDERATION OF BENEFITS AND HARMS**<br>*Report the health benefits, side effects, and risks that were considered when formulating the recommendations.* | ☐ Supporting data and report of benefits<br>☐ Supporting data and report of harms/side effects/risks<br>☐ Reporting of the balance/trade-off between benefits and harms/side effects/risks<br>☐ Recommendations reflect considerations of both benefits and harms/side effects/ risks | |
| **12. LINK BETWEEN RECOMMENDATIONS AND EVIDENCE**<br>*Describe the explicit link between the recommendations and the evidence on which they are based.* | ☐ How the guideline development group linked and used the evidence to inform recommendations<br>☐ Link between each recommendation and key evidence (text description and/or reference list)<br>☐ Link between recommendations and evidence summaries and/or evidence tables in the results section of the guideline | |

| CHECKLIST ITEM AND DESCRIPTION | REPORTING CRITERIA | Page # |
|---|---|---|
| **13. EXTERNAL REVIEW**<br>*Report the methodology used to conduct the external review.* | ☐ Purpose and intent of the external review (e.g., to improve quality, gather feedback on draft recommendations, assess applicability and feasibility, disseminate evidence)<br>☐ Methods taken to undertake the external review (e.g., rating scale, open-ended questions)<br>☐ Description of the external reviewers (e.g., number, type of reviewers, affiliations)<br>☐ Outcomes/information gathered from the external review (e.g., summary of key findings)<br>☐ How the information gathered was used to inform the guideline development process and/or formation of the recommendations (e.g., guideline panel considered results of review in forming final recommendations) | |
| **14. UPDATING PROCEDURE**<br>*Describe the procedure for updating the guideline.* | ☐ A statement that the guideline will be updated<br>☐ Explicit time interval or explicit criteria to guide decisions about when an update will occur<br>☐ Methodology for the updating procedure | |
| **DOMAIN 4: CLARITY OF PRESENTATION** | | |
| **15. SPECIFIC AND UNAMBIGUOUS RECOMMENDATIONS**<br>*Describe which options are appropriate in which situations and in which population groups, as informed by the body of evidence.* | ☐ A statement of the recommended action<br>☐ Intent or purpose of the recommended action (e.g., to improve quality of life, to decrease side effects)<br>☐ Relevant population (e.g., patients, public)<br>☐ Caveats or qualifying statements, if relevant (e.g., patients or conditions for whom the recommendations would not apply)<br>☐ If there is uncertainty about the best care option(s), the uncertainty should be stated in the guideline | |
| **16. MANAGEMENT OPTIONS**<br>*Describe the different options for managing the condition or health issue.* | ☐ Description of management options<br>☐ Population or clinical situation most appropriate to each option | |

| CHECKLIST ITEM AND DESCRIPTION | REPORTING CRITERIA | Page # |
|---|---|---|
| **17. IDENTIFIABLE KEY RECOMMENDATIONS**<br>*Present the key recommendations so that they are easy to identify.* | ☐ Recommendations in a summarized box, typed in bold, underlined, or presented as flow charts or algorithms<br>☐ Specific recommendations grouped together in one section | |
| **DOMAIN 5: APPLICABILITY** | | |
| **18. FACILITATORS AND BARRIERS TO APPLICATION**<br>*Describe the facilitators and barriers to the guideline's application.* | ☐ Types of facilitators and barriers that were considered<br>☐ Methods by which information regarding the facilitators and barriers to implementing recommendations were sought (e.g., feedback from key stakeholders, pilot testing of guidelines before widespread implementation)<br>☐ Information/description of the types of facilitators and barriers that emerged from the inquiry (e.g., practitioners have the skills to deliver the recommended care, sufficient equipment is not available to ensure all eligible members of the population receive mammography)<br>☐ How the information influenced the guideline development process and/or formation of the recommendations | |
| **19. IMPLEMENTATION ADVICE/TOOLS**<br>*Provide advice and/or tools on how the recommendations can be applied in practice.* | ☐ Additional materials to support the implementation of the guideline in practice.<br>For example:<br>• Guideline summary documents<br>• Links to check lists, algorithms<br>• Links to how-to manuals<br>• Solutions linked to barrier analysis (see Item 18)<br>• Tools to capitalize on guideline facilitators (see Item 18)<br>• Outcome of pilot test and lessons learned | |

| CHECKLIST ITEM AND DESCRIPTION | REPORTING CRITERIA | Page # |
|---|---|---|
| **20. RESOURCE IMPLICATIONS**<br>*Describe any potential resource implications of applying the recommendations.* | ☐ Types of cost information that were considered (e.g., economic evaluations, drug acquisition costs)<br>☐ Methods by which the cost information was sought (e.g., a health economist was part of the guideline development panel, use of health technology assessments for specific drugs, etc.)<br>☐ Information/description of the cost information that emerged from the inquiry (e.g., specific drug acquisition costs per treatment course)<br>☐ How the information gathered was used to inform the guideline development process and/or formation of the recommendations | |
| **21. MONITORING/ AUDITING CRITERIA**<br>*Provide monitoring and/or auditing criteria to measure the application of guideline recommendations.* | ☐ Criteria to assess guideline implementation or adherence to recommendations<br>☐ Criteria for assessing impact of implementing the recommendations<br>☐ Advice on the frequency and interval of measurement<br>☐ Operational definitions of how the criteria should be measured | |
| **DOMAIN 6: EDITORIAL INDEPENDENCE** | | |
| **22. FUNDING BODY**<br>*Report the funding body's influence on the content of the guideline.* | ☐ The name of the funding body or source of funding (or explicit statement of no funding)<br>☐ A statement that the funding body did not influence the content of the guideline | |
| **23. COMPETING INTERESTS**<br>*Provide an explicit statement that all group members have declared whether they have any competing interests.* | ☐ Types of competing interests considered<br>☐ Methods by which potential competing interests were sought<br>☐ A description of the competing interests<br>☐ How the competing interests influenced the guideline process and development of recommendations | |

From: Brouwers MC, Kerkvliet K, Spithoff K, on behalf of the AGREE Next Steps Consortium. The AGREE Reporting Checklist: a tool to improve reporting of clinical practice guidelines. BMJ 2016;352:i1152. doi: 10.1136/bmj.i1152.

For more information about the AGREE Reporting Checklist, please visit the AGREE Enterprise website at http://www.agreetrust.org.

# Appendix 8: **Policies, Procedures, Protocols and Guidelines Checklist**

The PPPG Checklists were developed to assist staff to meet standards when developing Clinical PPPGs.

| **Standards for developing clinical PPPG** | |
|---|---|
| **Stage 1 initiation** | **Checklist** |
| The decision making approach relating to the type of PPPG guidance required (policy, procedure, protocol, guideline), coverage of the PPPG (national, regional, local) and applicable settings are described. | ☐ |
| Synergies/co-operations are maximised across departments/organisations (Hospitals/ Hospital Groups/Community Healthcare Organisations (CHO)/National Ambulance Service (NAS)), to avoid duplication and to optimise value for money and use of staff time and expertise. | ☐ |
| The scope of the PPPG is clearly described, specifying what is included and what lies outside the scope of the PPPG. | ☐ |
| The target users and the population/patient group to whom the PPPG is meant to apply are specifically described. | ☐ |
| The views and preferences of the target population have been sought and taken into consideration (as required). | ☐ |
| The overall objective(s) of the PPPGs are specifically described. | ☐ |
| The potential for improved health is described (e.g. clinical effectiveness, patient safety, quality improvement, health outcomes, quality of life, quality of care). | ☐ |
| Stakeholder identification and involvement: The PPPG Development Group includes individuals from all relevant stakeholders, staff and professional groups. | ☐ |
| Conflict of interest statements from all members of the PPPG Development Group are documented, with a description of mitigating actions if relevant. | ☐ |
| The PPPG is informed by the identified needs and priorities of service users and stakeholders. | ☐ |
| There is service user/lay representation on PPPG Development Group (as required). | ☐ |
| Information and support is available for staff on the development of evidence-based clinical practice guidance. | ☐ |

| **Stage 2 development** | **Checklist** |
|---|---|
| The clinical question(s) covered by the PPPG are specifically described. | ☐ |
| Systematic methods used to search for evidence are documented (for PPPGs which are adapted/ adopted from international guidance, their methodology is appraised and documented). | ☐ |
| Critical appraisal/analysis of evidence using validated tools is documented (the strengths, limitations and methodological quality of the body of evidence are clearly described). | ☐ |
| The health benefits, side effects and risks have been considered and documented in formulating the PPPG. | ☐ |
| There is an explicit link between the PPPG and the supporting evidence. | ☐ |
| PPPG guidance/recommendations are specific and unambiguous. | ☐ |
| The potential resource implications of developing and implementing the PPPG are Identified e.g. equipment, education/training, staff time and research. | ☐ |
| There is collaboration across all stakeholders in the planning and implementation phases to optimise patient flow and integrated care. | ☐ |
| Budget impact is documented (resources required). | ☐ |
| Education and training is provided for staff on the development and implementation of evidence- based clinical practice guidance (as appropriate). | ☐ |
| Three additional standards are applicable for a small number of more complex PPPGs: | ☐ |
| Cost effectiveness analysis is documented. | ☐ |
| A systematic literature review has been undertaken. | ☐ |
| Health Technology Assessment (HTA) has been undertaken. | ☐ |
| **Stage 3 governance and approval** | **Checklist** |
| Formal governance arrangements for PPPGs at local, regional and national level are established and documented. | ☐ |
| The PPPG has been reviewed by independent experts prior to publication (as required). | ☐ |
| Copyright and permissions are sought and documented. | ☐ |
| **Stage 4 communication and dissemination** | **Checklist** |
| A communication plan is developed to ensure effective communication and collaboration with all stakeholders throughout all stages. | ☐ |
| Plan and procedure for dissemination of the PPPG is described. | ☐ |
| The PPPG is easily accessible by all users e.g. PPPG repository. | ☐ |

| **Stage 5 implementation** | **Checklist** |
|---|---|
| Written implementation plan is provided with timelines, identification of responsible persons/ units and integration into service planning process. | ☐ |
| Barriers and facilitators for implementation are identified, and aligned with implementation levers. | ☐ |
| Education and training is provided for staff on the development and implementation of evidence- based PPPG (as required). | ☐ |
| There is collaboration across all stakeholders in the planning and implementation phases to optimise patient flow and integrated care. | ☐ |
| **Stage 6 monitoring, audit, evaluation** | **Checklist** |
| Process for monitoring and continuous improvement is documented. | ☐ |
| Audit criteria and audit process/plan are specified. | ☐ |
| Process for evaluation of implementation and (clinical) effectiveness is specified. | ☐ |
| **Stage 7 revision/update** | **Checklist** |
| Documented process for revisions/updating and review, including timeframe is provided. | ☐ |
| Documented process for version control is provided. | ☐ |

To view in full refer to website: https://www.hse.ie/eng/about/who/qid/nationalframeworkdevelopingpolicies/