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REVIEW

Clinical practice guidelines for recurrent miscarriage in high-income countries: a systematic review

BIOGRAPHY

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KEY MESSAGE

Thirty-two clinical practice guidelines (CPG) for recurrent miscarriage were identified. Levels of consensus across the CPG varied, with some conflicting recommendations. Greater efforts are required to improve the quality of evidence underpinning CPG, the rigour of their development and the inclusion of multi-disciplinary perspectives, including those with lived experience of recurrent miscarriage.

ABSTRACT

Recurrent miscarriage affects 1–2% of women of reproductive age, depending on the definition used. A systematic review was conducted to identify, appraise and describe clinical practice guidelines (CPG) published since 2000 for the investigation, management, and/or follow-up of recurrent miscarriage within high-income countries. Six major databases, eight guideline repositories and the websites of 11 professional organizations were searched to identify potentially eligible studies. The quality of eligible CPG was assessed using the Appraisal of Guidelines for Research and Evaluation (AGREE II) Tool. A narrative synthesis was conducted to describe, compare and contrast the CPG and recommendations therein. Thirty-two CPG were included, from which 373 recommendations concerning first-trimester recurrent miscarriage were identified across four sub-categories: structure of care (42 recommendations, nine CPG), investigations (134 recommendations, 23 CPG), treatment (153 recommendations, 24 CPG), and counselling and supportive care (46 recommendations, nine CPG). Most CPG scored 'poor' on applicability (84%) and editorial independence (69%); and to a lesser extent stakeholder involvement (38%) and rigour of development (31%). Varying levels of consensus were found across CPG, with some conflicting recommendations. Greater efforts are required to improve the quality of evidence underpinning CPG, the rigour of their development and the inclusion of multi-disciplinary perspectives, including those with lived experience of recurrent miscarriage.

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KEYWORDS

AGREE II
Clinical guidelines
Early pregnancy loss
Miscarriage
Recurrent miscarriage
Systematic review

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1472-6483/
Declaration: KOD and RR were involved in the development of one of the clinical practice guidelines appraised in this paper (Health Service Executive, 2016); KOD is National Lead within Ireland for its implementation. Neither KOD nor RR were involved in the quality assessment of this CPG. The authors report no financial or commercial conflicts of interest.

INTRODUCTION

Recurrent miscarriage is estimated to affect 1–2% of women of reproductive age, depending on the definition used, and with the caveat that the actual prevalence is difficult to obtain owing to difficulty accessing data (*Hemminki and Forssas, 1999*; *Oliver-Williams and Steer, 2015*; *European Society of Human Reproduction and Embryology [ESHRE] Early Pregnancy Guideline Development Group, 2017*; *Rasmark Roepke et al., 2017*; *Woolner, et al., 2020*). The term used to describe the condition varies between countries and professional bodies (Youssef *et al*., 2020); for example, ESHRE uses the term 'recurrent pregnancy loss' (*ESHRE Early Pregnancy Guideline Development Group, 2017*), whereas the Royal College of Obstetricians and Gynaecologists (RCOG) in the UK uses the term 'recurrent miscarriage' (*RCOG, 2011*). For the purposes of reporting within this paper, the latter term is used throughout, and the focus is on recurrent first-trimester miscarriage given that this should be treated differently to second-trimester miscarriage (*McPherson, 2016*; *Shields et al., 2020*). Some professional bodies or organizations, such as ESHRE (*ESHRE Early Pregnancy Guideline Development Group, 2017*) and the American Society for Reproductive Medicine (ASRM) in the USA (*Practice Committee of the ASRM, 2012*) now define recurrent miscarriage as the loss of two or more consecutive pregnancies for investigations; however, the previous definition of three or more consecutive pregnancy losses remains in use by others, such as the *RCOG (2011)*, the Health Service Executive (HSE) in Ireland (*HSE, 2016*) and the French College of Gynaecologists and Obstetricians (*Huchon et al., 2016*). As the revised definition of recurrent miscarriage is used across more countries and regions, more women and/or couples will be accessing services for investigation and management.

Evidence-based, up-to-date clinical practice guidelines (CPG) are required to inform the effective management of recurrent miscarriage (*Van den Berg et al., 2014*; *Gibbins and Porter, 2016*). About 70% of women who have experienced two recurrent losses will conceive a subsequent pregnancy, with a 70% success rate (*Clifford et al., 1997*; *Brigham et al., 1999*; *Habayeb and Konje, 2004*). The risk of further miscarriage increases after each successive pregnancy loss, reaching about 40% after three consecutive pregnancy losses; a previous live birth does not prevent a woman experiencing recurrent miscarriage, and the prognosis worsens with increasing maternal age (*Clifford et al., 1997*; *Nybo Andersen et al., 2000*).

The suggested causes of recurrent miscarriage include uterine anomalies (inclusive of common acquired anomalies, such as fibroids, and more uncommon anatomical defects, such as uterine septae), endocrine disorders (such as thyroid disease), autoimmune diseases (such as lupus), acquired thrombophilia and genetic causes, in particular balanced translocations (*Toth et al., 2010*; *RCOG, 2011*; *El Hachem et al., 2017*; *van Dijk et al., 2020*). Others, such as chronic endometritis, infectious diseases, inherited thrombophilia, luteal phase deficiency, high sperm DNA fragmentation levels, polycystic ovary syndrome and high body mass index, have been proposed, but remain debated (*RCOG, 2011*; *El Hachem et al., 2017*; *ESHRE Early Pregnancy Guideline Development Group, 2017*; *Matjila et al., 2017*). Most investigations and treatments offered also remain controversial, with lack of consensus among professionals and/or groups (*Tzioras et al., 2009*; *Matthiesen et al., 2012*; *Branch and Silver, 2016*; *Scott, 2016*; *Bruno, et al., 2019*). Nevertheless, standard investigations for recurrent miscarriage continue to be important in evaluating potential factors responsible for pregnancy loss (*Clifford et al., 1994*).

It is also important that the provision of care meets the needs of those who experience recurrent miscarriage. The psychological wellbeing of women and men who experience recurrent miscarriage can be negatively affected in the medium- to long-term (*Klock et al., 1997*; *Lok and Neugebauer, 2007*; *Kolte et al., 2014*; *2015*; *McCarthy et al., 2015*; *Tavoli et al., 2018*). In addition, women and men report gaps in their perceived needs and their care experience after recurrent miscarriage, highlighting the need for more information, psychological support, the inclusion of partners in consultations, and follow-up care (*Musters et al., 2011*; *2013*; *van den Berg et al., 2017*; *Koert et al., 2018*).

Clinical practice guidelines synthesize the best available evidence to guide clinician and patient decision-making, with the aim of improving care quality and patient outcomes (*Lugtenberg et al., 2009*; *Graham et al., 2011*). They are 'statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options' (*Institute of Medicine, 2011*). The identification, appraisal and description of published CPG in high-income countries would be a valuable first step in informing efforts to promote the optimization and standardization of recurrent miscarriage care. Given the large discrepancies in pregnancy outcomes and care structures between high, low and middle-income countries (*Goldenberg et al., 2018*; *Gage et al., 2019*), this systematic review focuses on high-income countries, as defined by the *World Bank (2020)*. Some attempts have been made to do this already. *Youssef et al. (2019)* recently conducted a comparison and appraisal of the ESHRE, ASRM and RCOG recurrent miscarriage CPG using the Appraisal of Guidelines, Research and Evaluation version 2 (AGREE II) criteria, an accepted and validated tool for assessing the methodological quality of CPG (*Siering et al., 2013*). *Hong Li and Marren (2018)* also provide an overview of these three CPG, without any quality appraisal. *Khalife et al. (2019)* review and compare the ASRM and ESHRE CPG, noting the lack of consensus on standard evaluation of recurrent pregnancy loss. Each of these studies focused on a select group of CPG. Therefore, a more systematic approach to identifying CPG concerning recurrent miscarriage would add to the body of evidence.

The aim of the present systematic review was to identify, appraise and describe published CPG for the investigation, management, and/or follow-up of first-trimester recurrent miscarriage within high-income countries. The specific objectives were to identify published CPG for the investigation, management, and/or follow-up of recurrent miscarriage within high-income countries; appraise the quality of included CPG using the AGREE II instrument; and describe recommendations from the included CPG concerning first-trimester recurrent miscarriage.

MATERIALS AND METHODS

This systematic review is reported following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidance. The protocol for the review was published in advance (*Hennessy et al., 2020*) and pre-registered on PROSPERO, the International Prospective Register of Systematic Reviews (CRD42020173881; registered 28 April 2020).

Eligibility criteria

Inclusion and exclusion criteria were developed according to the 'PICAR' (population and clinical areas, interventions, comparators, attributes of CPG and recommendation characteristics) framework (TABLE 1). For this review, CPG were defined as 'systematically developed statements to assist practitioners about appropriate health care for specific clinical circumstances'; an adaptation of the

TABLE 1 ELIGIBILITY CRITERIA PERTAINING TO THE POPULATION AND CLINICAL AREAS, INTERVENTIONS, COMPARATORS, ATTRIBUTES OF CLINICAL PRACTICE GUIDELINES AND RECOMMENDATION CHARACTERISTICS (PICAR) STATEMENT

PICAR framework	Eligibility criteria
Population, clinical indication(s), and condition(s)	Study population • Women or couples experiencing recurrent miscarriage. • Humans only. Clinical indication • Investigation, management and/or follow-up of women and/or or couples with recurrent miscarriage, specifically first-trimester recurrent miscarriage. Clinical condition • Recurrent miscarriage is defined by the review team as the loss of two or more consecutive pregnancies (*ESHRE Early Pregnancy Guideline Development Group, 2017*), with a specific focus on first-trimester recurrent miscarriage. For the purposes of this review, all clinical practice guidelines (CPG) that focus on recurrent miscarriage, regardless of the definition used, will be included. The definition applied by each included CPG will be extracted and considered when synthesizing and interpreting the review findings.
Interventions	• Any intervention focusing on the investigation, management and/or follow-up of recurrent miscarriage.
Comparator(s), Comparison(s), and (key) Content	• Any comparator or comparison. • No 'key' CPG content is of interest, unless CPG are broader in scope; in such instances, content specific to recurrent miscarriage is only of interest.
Attributes of eligible CPGs	Language • Available in English. • CPG in which summaries are available in English, but full text is not, will be excluded. Year of publication • 2000 onwards. • In Ireland, the National Clinical Effectiveness Committee, requires a full guideline update within 3 years (*National Clinical Effectiveness Committee, 2019*); however, The Scottish Intercollegiate Guidelines Network also specifies 3 years, but also includes those over 3 years old and revalidated (*Scottish Intercollegiate Guidelines Network (SIGN), 2019*). The World Health Organization does not have a defined period for guideline updates (*World Health Organization, 2014*). To be comprehensive, CPG published within the last 20 years (January 2000 to date) will be eligible for inclusion given that international CPG concerning recurrent miscarriage can fall well outside the 3-year period (*American College of Obstetricians and Gynecologists, 2002*; *Association of Early Pregnancy Units, 2007*). A good-quality older guideline could be a good base on which to develop a new guideline (*The ADAPTE Collaboration, 2010*). Developing or publishing organization • Only CPG issued or endorsed by national or international scientific societies, professional colleges, charitable organizations and government organizations will be included. Country of publication • High-income countries, as defined by the World Bank (*World Bank, 2020*) as large discrepancies exist in pregnancy outcomes and care structures between high, low and middle-income countries (*Goldenberg et al., 2018*; *Gage et al., 2019*) Version • Latest version only. Development process • Evidence-based, consensus-based, or both. System of rating evidence • Use of a system to rate the level of evidence within CPG is not an eligibility criterion; however, such data will be extracted to inform synthesis and interpretation of findings. Quality of evidence • The eligibility of CPG will not be based on a specific minimum quality cut-off score based on the AGREE II criteria. • We are interested in all guidance generated regardless of quality, e.g. because CPG determined to be of 'high quality' may not necessarily report recommendations that are highly valid and implementable (Johnston *et al*., 2019); this will, however, be taken into consideration when synthesizing and interpreting the review findings. Scope • Must have a primary or secondary focus on the investigation and treatment of recurrent miscarriage. Must be national or international in scope. • Covers any aspect of recurrent miscarriage care and its organization, including the provision of dedicated pregnancy loss clinics, treatment and management of recurrent miscarriage, investigations carried out after recurrent miscarriage to inform prognosis of future pregnancy outcomes and counselling of parents after recurrent miscarriage. • Must be clearly identified as a CPG. • Must be published. Unpublished CPG, conference papers, discussion papers, drafts and opinions will be excluded.
Recommendations	Must have 'recommendations' concerning the identification, management and/or follow-up of recurrent miscarriage (either explicitly highlighted as such within the document or noted within the body of the document, but not explicitly identified as a recommendation). To be eligible, recommendations need not be accompanied by an explicit level of confidence (and quality assessment criteria system used specified); however, these data will be extracted (where available) and considered during the synthesis and interpretation of findings.

definitions used by the *National Clinical Effectiveness Committee (2019)* and *Scottish Intercollegiate Guidelines Network (SIGN) (2020)*.

Information sources and search strategy

The following databases were systematically searched to identify eligible CPG, published between January 2000 and March 2020: *CINAHL Plus* (EBSCOhost; 1994), *Embase*® (Elsevier; 1980), *MEDLINE* (Ovid®; 1946), *Open Grey* (INIST-CNRS; 2011), *Scopus* (Elsevier; 2004), and *Web of Science*™ (Thomson Reuters). Guideline repositories (n = 8) and the websites of professional organizations and associations from around the world (n = 11) were also searched. The search strategy was developed with the assistance of a specialist librarian. Key word searches, using combinations of key words and Medical Subject Headings (or equivalent), were used across two concepts using the AND Boolean operator: clinical guidelines; recurrent miscarriage. Within each of the categories, keywords were combined using the 'AND' or 'OR' Boolean operators. Information sources and search terms applied are detailed in Supplementary Table 1.

Study selection

Retrieved records were imported firstly into EndNote X9 and de-duplicated using the 'remove duplicates' function, as well as manually screening results for accuracy. They were then imported into Rayyan and screened again for duplicates. Two independent reviewers (MH and RD) subsequently screened titles and abstracts of retrieved records against the inclusion criteria; this process was repeated for full texts. Any disagreements were discussed and resolved via consensus, with the input of a third reviewer (SM/KOD), where necessary.

Data collection process

To ensure that the most up-to-date versions of CPG were included in the final results, MH conducted searches and contacted authors where necessary. Once the final set of included CPG was agreed, MH retrieved all documents related to the CPG (such as supplemental documents, methodology papers and others) before data extraction or quality assessment was undertaken. RD independently verified all documents collected to confirm the completeness and ensure that companion documents were matched appropriately.

Data extraction

Key features of CPG and the documented recommendations were extracted using a structured data extraction form in Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) (*Hennessy et al., 2020*), which was piloted in advance. Data were extracted by MH and verified for accuracy and completeness by RD. Discrepancies were resolved through consensus and, where agreement could not be reached, SM/KOD reviewed and made a final decision. To facilitate data synthesis, reviewers assigned categories and sub-categories to each recommendation during data extraction; some were pre-defined whereas others were generated iteratively. Details on the level of evidence (and strength, if provided) associated with each recommendation were also extracted.

Quality assessment

The quality of included CPG was assessed using the AGREE II criteria (*Brouwers et al., 2010*). The criteria encompass 23 items, over six domains, rated on a seven-point Likert scale: scope and purpose of the guideline; stakeholder involvement in the development of the guidelines; rigour of development and formulation of the recommendations within the guideline; clarity of presentation of the guideline; applicability of the guideline; and editorial independence in the formulation of recommendations within the guideline. As part of the overall assessment, two global ratings are included: a rating on the overall quality of the guideline; and whether the guideline would be recommended for use in practice. Three reviewers with methodological, clinical expertise, or both (MH, LL and SM), conducted an independent quality assessment of the CPG. Major discrepancies in the scores (where assigned scores differed by more than two points) were discussed and independently reassessed and consensus reached. Domain scores were calculated by summing up all the scores of the individual items in a domain and by scaling the total as a percentage of the maximum possible score for that domain, as per the AGREE II User Manual. To make the scores more relevant to readers and enable fair comparison, the AGREE II outcomes are reported categorically using the five-point Likert scale described by other reviews (*Eady et al., 2017*; *Daley et al., 2019*): excellent (>80%), good (>60–80%), average (>40–60%), fair (>20–40%) and poor (≤20%).

Data synthesis

A narrative synthesis is used to describe, compare and contrast CPG and the recommendations therein, taking account of quality appraisal (using the AGREE II tool) and recency of publication. The levels of evidence associated with the recommendations within each CPG is reported, and quality assessment rating system used; no attempt was made to standardize evidence ratings across CPG.

Patient and public involvement

The protocol for this systematic review was developed in conjunction with a pregnancy loss parent advocate (RR) and through consultations with Specialist Bereavement and Loss Midwives. This work is part of a broader project evaluating current services for recurrent miscarriage in the Republic of Ireland. The RE:CURRENT project Research Advisory Group includes representation from healthcare and allied health professionals, advocacy and support organizations, those involved in the administration, governance and management of maternity services, academics, and women and men who have experienced recurrent miscarriage. RR is a member of this group and was involved in discussions and decisions concerning the conduct, findings and outputs of the review.

RESULTS

Guideline selection

A total of 6065 records from the planned searches of databases (n = 5536), guideline repositories (n = 395) and websites of professional bodies and organizations (n = 134) were retrieved; the PRISMA flow chart is presented in FIGURE 1.

After removing duplicates, the titles and abstracts of 4108 records were screened and, subsequently, 170 full texts were assessed. Thirty-two CPG were included in the final synthesis (TABLE 2); the original data extraction file (containing CPG characteristics and recommendations) is available in an open access repository

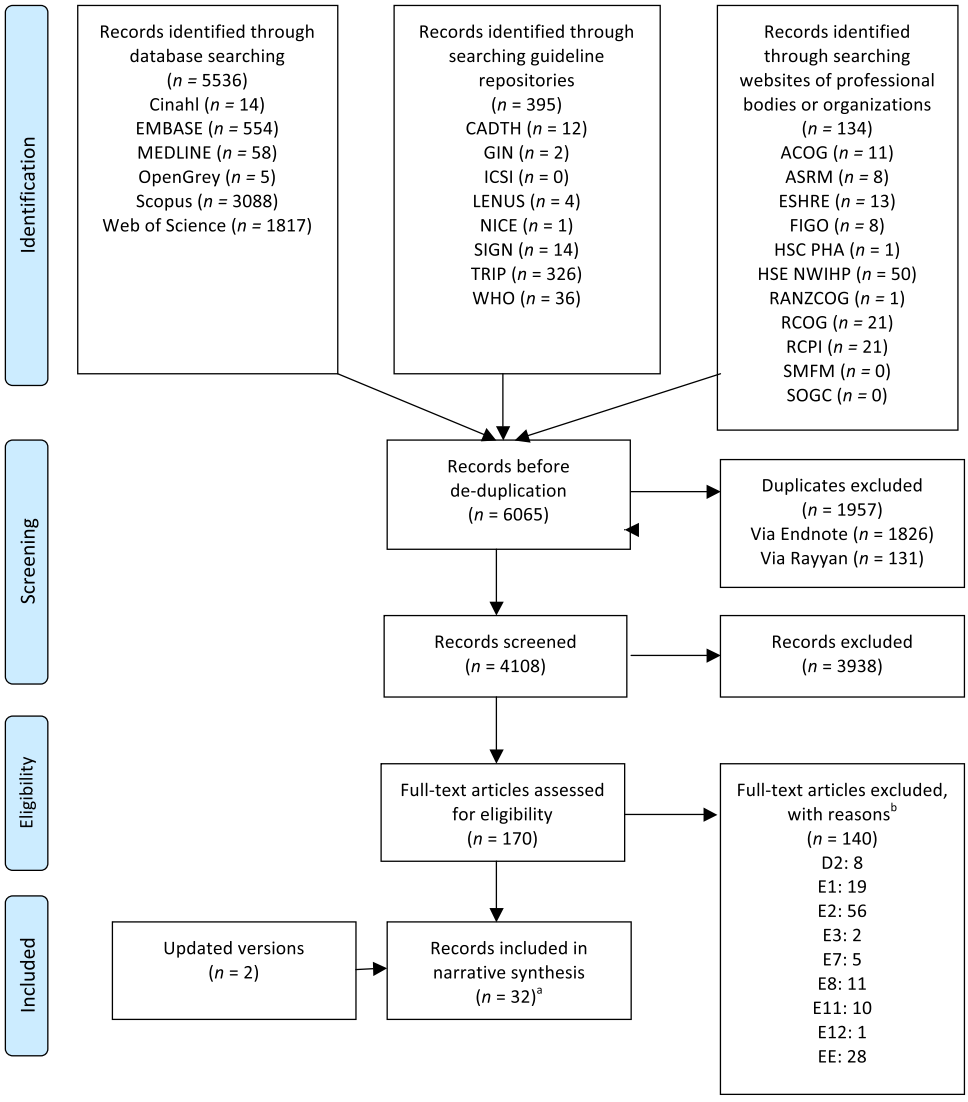

FIGURE 1 PRISMA flow diagram. [a]Plus two addenda (Arachchillage, 2020; Bashford, 2020). [b]D2, duplicate; E1, not a clinical practice guideline; E2, not focused (primary/secondary) on the investigation, management and/or follow-up of recurrent miscarriage; E3, not issued, endorsed, or both, by national or international scientific societies, professional colleges, charitable organizations and/or government organisations; E7, not published in English; E8, not latest version; E11, withdrawn or no longer available; E12, cannot access full text; EE, meets two or more exclusion criteria.

(*Hennessy et al., 2021*). Details of records excluded at the full-text review stage are presented in Supplementary Table 2.

Guideline characteristics

Most of the included CPG were described by their authors as guideline(s) (*n* = 9 [28%]), clinical practice guideline(s)/clinical guidelines (*n* = 9 [28%]), or practice guideline(s) (*n* = 3 [9%]) (TABLE 1). Seven (22%) CPG focused specifically on recurrent miscarriage, recurrent pregnancy loss (RPL), or both (including one focused on a specific procedure) (*RCOG, 2011*; *Practice Committee of the ASRM, 2012*; *National Institute for Health and Care Excellence [NICE], 2015*; *ESHRE Early Pregnancy Guideline Development Group, 2017*; *Toth et al., 2018*; *Arab et al., 2019*; *Northern Ireland Public Health Agency, 2020*), two (6%) focused on early pregnancy loss (*American College of Obstetrics and Gynaecology [ACOG], 2018*; *Queensland Clinical Guidelines, 2018*) and two (6%) on pregnancy loss, perinatal death, or both (*HSE, 2016*; *Huchon et al., 2016*). The remaining 21 (66%) CPG were broader in focus: uterine and/or genital anomalies (*American Association of Gynecologic Laparoscopists [AAGL], 2012*; *Grimbizis et al., 2016*; *Practice Committee of the ASRM, 2016; 2017*), infertility (*Practice Committee of the ASRM, 2015*; *Agarwal et al., 2017*; *Wall et al., 2020*), thyroid disease during pregnancy and the postpartum (*De Groot et al., 2012*; *Alexander et al., 2017*) and more generally (*Garber et al., 2012*), genetic testing and/or prenatal diagnosis (*Armour et al., 2018*; *Practice Committees of the ASRM and the Society for Assisted Reproductive Technology, 2018*; *Wilson, 2018*; ESHRE Preimplantation Genetic Testing [PGT] *Consortium Steering Committee et al., 2020*), venous thromboembolism, and thrombophilia and/or antiphospholipid syndrome (*Bates et al., 2012*; *Keeling et al., 2012*; *Hickey et al., 2013*; *Institute of Obstetricians and Gynaecologists Royal College of Physicians of Ireland [RCPI], HSE Clinical Care Programme in Obstetrics and*

TABLE 2 SUMMARY OF INCLUDED CLNICAL PRACTICE GUIDELINES

Title	Author, year	Developing or publishing organization, or authors	Country or countries of publication	Description provided by authors (e.g. guideline or algorithm)	Type of guideline (formulated, adapted, updated or revised)	Topic addressed (recurrent miscarriage, RPL or broader)	Number of recommendations specific to recurrent miscarriage	Development process (evidence-based, consensus-based, or both)	System of rating evidence or quality instrument used during guideline development (GRADE, Oxford, not mentioned, or other)	Funding
American Association of Gynecologic Laparoscopists (AAGL) practice report: practice guidelines for the diagnosis and management of submucous leiomyomas	AAGL, 2012	Practice Committee of the AAGL	Global	Practice guidelines	Not specified; formulated	Broader: submucous leiomyomas	3	Evidence-based; expert consensus-based	Modified method outlined by the US Preventive Services Task Force [USPSTF]; criteria described in the Report of the Canadian Task Force on the Periodic Health Examination	Not specified
American College of Obstetrics and Gynaecology (ACOG) practice bulletin number 200: early pregnancy loss	ACOG, 2018	ACOG	USA	Practice Bulletin/clinical management guidelines	Update	Broader: early pregnancy loss	2	Evidence-based; expert opinion	USPSTF	Not specified
The Society for Translational Medicine: clinical practice guidelines for sperm DNA fragmentation testing in male infertility	Agarwal, 2017	The Society for Translational Medicine	Global	Clinical practice guidelines	Not specified	Broader: male infertility	2	Not specified	Modified from Oxford Centre for Evidence-Based Medicine (http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/)	Not specified
Guidelines of the American Thyroid Association (ATA) for the diagnosis and management of thyroid disease during pregnancy and the postpartum	Alexander, 2017	ATA	USA	Guidelines	Revised	Broader: thyroid disease during pregnancy and the postpartum	2	Evidence-based; expert consensus-based	American College of Physicians Guideline Grading System	ATA without support from any commercial sources
Saudi guidelines for threatened and recurrent miscarriage management; the role of progestogens in threatened and idiopathic recurrent miscarriage	Arab, 2019	Saudi Society of Obstetrics and Gynecology	Saudi Arabia	Guidelines	Updated	Recurrent miscarriage	9	Evidence-based; expert consensus-based	Not mentioned	Abbott, Saudi Arabia provided funding for medical writing assistance, & sponsored the two consensus meetings
Practice guideline: Joint Society of Obstetricians and Gynaecologists of Canada (SOGC)-Canadian College of Medical Geneticists (CCMG) recommendations for the use of chromosomal microarray analysis for prenatal diagnosis and assessment of fetal loss in Canada	Armour, 2018	SOGC–CCMG	Canada	Practice guideline	Updated	Broader: use of chromosomal microarray analysis for prenatal diagnosis and assessment of fetal loss	1	Evidence-based	Modified criteria described in the Report of the Canadian Task Force on Preventive Healthcare	The Hospital for Sick Children Centre for Genetic Medicine and the University of Toronto McLaughlin Centre
Evaluation and treatment of recurrent pregnancy loss: a committee opinion	American Society for Reproductive Medicine (ASRM), 2012	ASRM	USA	Committee opinion	Not specified	Recurrent pregnancy loss	26	Not specified	None/not mentioned	Not specified

TABLE 2 *(continued)*

Title	Author, year	Developing or publishing organization, or authors	Country or countries of publication	Description provided by authors (e.g. guideline or algorithm)	Type of guideline (formulated, adapted, updated or revised)	Topic addressed (recurrent miscarriage, RPL or broader)	Number of recommendations specific to recurrent miscarriage	Development process (evidence-based, consensus-based, or both)	System of rating evidence or quality instrument used during guideline development (GRADE, Oxford, not mentioned, or other)	Funding
Subclinical hypothyroidism in the infertile female population: a guideline	ASRM, 2015	ASRM	USA	Guideline	Not specified; formulated	Broader: treating subclinical hypothyroidism in female patients with a history of infertility and miscarriage	3	Evidence-based; expert consensus-based	Described, but system name not mentioned	Not specified
Uterine septum: a guideline	ASRM, 2016	ASRM	USA	Guideline	Formulated	Broader: treatment of septate uterus	2	Evidence-based	Described, but system name not mentioned	Not specified
Removal of myomas in asymptomatic patients to improve fertility and/or reduce miscarriage rate: a guideline	ASRM, 2017	ASRM	USA	Clinical practice guideline	Formulated	Broader: removal of myomas in asymptomatic patients to improve fertility/ reduce miscarriage rate	2	Evidence-based	Described, but system name not mentioned	Not specified
The use of preimplantation genetic testing for aneuploidy (PGT-A): a committee opinion	ASRM, 2018	ASRM and the Society for Assisted Reproductive Technology (SART)	USA	Committee opinion	Formulated	Broader: use of preimplantation genetic testing for aneuploidy	1	Evidence-based	None/not mentioned	Not specified
Venous thromboembolism (VTE), thrombophilia, antithrombotic therapy, and pregnancy; antithrombotic therapy and prevention of thrombosis, 9th edn: American College of Chest Physicians evidence-based clinical practice guidelines	Bates, 2012	American College of Chest Physicians	USA	Clinical practice guidelines	Updated/ revised	Broader: VTE disease; this section is specifically on the management of VTE and thrombophilia as well as the use of antithrombotic agents during pregnancy	5	Evidence-based	GRADE	National Heart, Lung, and Blood Institute (R13 HL104758) and Bayer Schering Pharma AG. Educational grants provided by Bristol-Myers Squibb; Pfizer, Inc; Canyon Pharma-ceuticals; Sanofi -Aventis USA.
Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline	DeGroot, 2012	Endocrine Society. Co-Sponsoring Associations: Asia and Oceania Thyroid Association, European Thyroid Association, and Latin American Thyroid Society	Global	Clinical practice guideline	Update	Broader: management of thyroid dysfunction during pregnancy and postpartum	3	Evidence-based	GRADE and USPSTF	Co-Sponsoring Associations: Asia and Oceania Thyroid Association, European Thyroid Association, and Latin American Thyroid Society

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TABLE 2 *(continued)*

Title	Author, year	Developing or publishing organization, or authors	Country or countries of publication	Description provided by authors (e.g. guideline or algorithm)	Type of guideline (formulated, adapted, updated or revised)	Topic addressed (recurrent miscarriage, RPL or broader)	Number of recommendations specific to recurrent miscarriage	Development process (evidence-based, consensus-based, or both)	System of rating evidence or quality instrument used during guideline development (GRADE, Oxford, not mentioned, or other)	Funding
Recurrent pregnancy loss: guideline of the European Society of Human Reproduction and Embryology (ESHRE)	ESHRE, 2017	ESHRE	Europe	Guideline	Formulated, although previous version existed	Recurrent pregnancy loss	92	Evidence-based; expert consensus-based	GRADE	ESHRE
ESHRE PGT Consortium good practice recommendations for the organization of PGT	ESHRE, 2020	ESHRE	Europe	Good Practice Recommenda-tions	Updated	Broader: preimplantation genetic testing	3	Expert consensus-based	None	ESHRE
Clinical practice guidelines for hypothyroidism in adults	Garber, 2012	American Association of Clinical Endocrinologists (AACE) in association with ATA	USA	Clinical practice guidelines	Updated	Broader: clinical management of hypothyroidism in ambulatory patients	1	Evidence-based; expert consensus-based	Approach outlined in the AACE's Protocol for Standardized Production of Clinical Guidelines: 2010 update	Not specified
The Thessaloniki ESHRE/ESGE consensus on diagnosis of female genital anomalies	Grimbizis, 2016	ESHRE/European Society for Gynaecological Endoscopy (ESGE)	Europe	Consensus	Formulated	Broader: diagnosis of female genital anomalies	6	Evidence-based; expert consensus-based	None/not mentioned	ESHRE and ESGE
American College of Medical Genetics and Genomics (ACMG) practice guideline: lack of evidence for *MTHFR* polymorphism testing	Hickey, 2013 (Addendum: Bashford, 2020)	ACMG	USA	Clinical practice resource (practice guideline until 27 April 2020)	Unclear/not specified	Broader: *MTHFR* polymorphism testing	1	Not specified	Not mentioned	Not specified
Clinical practice guideline: venous thromboprophylaxis in pregnancy	Health Service Executive (HSE), 2013	Institute of Obstetricians and Gynaecologists, Royal College of Physicians of Ireland; HSE Clinical Care Programme in Obstetrics and Gynaecology	Ireland	Clinical practice guideline	Formulated	Broader: venous thromboprophylaxis in pregnancy	4	Consensus-based	None/not mentioned	Not specified
National standards for bereavement care following pregnancy loss and perinatal death	HSE, 2016	HSE	Ireland	Standards	Formulated	Broader: bereavement care following pregnancy loss and perinatal death	2	Evidence-based; expert consensus-based	None/not mentioned	Not specified
Pregnancy loss: French clinical practice guidelines	Huchon, 2016	College National des Gynecologues Obstetriciens Francais (CNGOF)	France	Clinical practice guidelines	Formulated	Broader: pregnancy loss	24	Evidence-based; expert consensus-based	Rating scheme developed by the Haute Autorite de Sante (French National Authority for Health)	Not specified

TABLE 2 *(continued)*

Title	Author, year	Developing or publishing organization, or authors	Country or countries of publication	Description provided by authors (e.g. guideline or algorithm)	Type of guideline (formulated, adapted, updated or revised)	Topic addressed (recurrent miscarriage, RPL or broader)	Number of recommendations specific to recurrent miscarriage	Development process (evidence-based, consensus-based, or both)	System of rating evidence or quality instrument used during guideline development (GRADE, Oxford, not mentioned, or other)	Funding
Guidelines on the investigation and management of antiphospholipid syndrome	Keeling, 2012 (Addendum: Arachchillage, 2020)	British Society for Haematology	UK	Guideline	Update	Broader: investigation and management of APS	6	Evidence-based; expert consensus-based	GRADE	Not specified
Hysteroscopic metroplasty of a uterine septum for recurrent miscarriage: Interventional procedures guidance	National Institute for Health and Care Excellence (NICE), 2015	NICE. Endorsed by: Healthcare Improvement Scotland	UK	Interventional procedures guidance	Formulated (note: updated before publication)	Recurrent miscarriage: hysteroscopic metroplasty of a uterine septum	3	Evidence-based; expert consensus-based	Not mentioned	Not specified
Recurrent pregnancy loss care pathway for Northern Ireland	Public Health Agency, 2020	Public Health Agency (Northern Ireland)	Northern Ireland	Care pathway	Formulated	Recurrent pregnancy loss	64	Evidence-based	None/not mentioned	Not specified
Maternity and neonatal clinical guideline: early pregnancy loss	Queensland Clinical Guidelines, 2018	Queensland Clinical Guidelines	Australia	Clinical Guideline	Update	Broader: early pregnancy loss	19	Evidence-based; expert consensus-based. Best described as 'evidence informed consensus guidelines'	National Health and Medical Research Council (NHMRC, 2009). Note: the 'consensus' definition is different from that proposed by the NHMRC. Instead, it relates to forms of evidence that are not identified by the NHMRC/that arise from the clinical experience of the guideline's clinical lead and working party	Healthcare Improvement Unit, Queensland Health
Green-top guideline number 17: the investigation and treatment of couples with recurrent first-trimester and second-trimester miscarriage	Royal College of Obstetrics and Gynaecology (RCOG), 2011	RCOG	UK	Guideline	Not specified (updated/revised)	Recurrent miscarriage	19	Evidence-based	Scottish Intercollegiate Guidelines Network (SIGN)	Not specified
The role of natural killer cells in human fertility: scientific impact paper number 53	RCOG, 2016	RCOG	UK	Scientific impact paper	Formulated	Broader: role of natural killer cells in human fertility	1	Not described	None/not mentioned	Not specified
SIGN 129: antithrombotics: indications and management	SIGN, 2013	SIGN	UK	Clinical guideline	Update	Broader: antithrombo-tics	5	Evidence-based	SIGN	NHS Quality Improvement Scotland

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TABLE 2 *(continued)*

Title	Author, year	Developing or publishing organization, or authors	Country or countries of publication	Description provided by authors (e.g. guideline or algorithm)	Type of guideline (formulated, adapted, updated or revised)	Topic addressed (recurrent miscarriage, RPL or broader)	Number of recommendations specific to recurrent miscarriage	Development process (evidence-based, consensus-based, or both)	System of rating evidence or quality instrument used during guideline development (GRADE, Oxford, not mentioned, or other)	Funding
Intravenous immunoglobulin G in women with reproductive failure: The Korean Society for Reproductive Immunology practice guidelines	Sung, 2017	Korean Society for Reproductive Immunology	Korea	Practice guidelines	Formulated	Broader: intravenous immuno-globulin G in women with reproductive failure	6	Evidence-based; expert consensus-based	System used by Fauser *et al.* (2012); available at https://www.fertstert.org/article/S0015-0282(11)02552-0/fulltext#appsec1	Partially supported by a grant from the Korean Health Technology R&D Project, Ministry of Health and Welfare, Republic of Korea
Recurrent miscarriage: diagnostic and therapeutic procedures. Guideline of the German Society of Gynecology and Obstetrics (DGGG), Austrian Society of Gynecology and Obstetrics (OEGGG) and the Swiss Society of Gynecology and Obstetrics (SGGG) (S2k-Level, AWMF Registry Number 015/050)	Toth, 2018	DGGG, ÖGGG and SGGG	Germany, Austria, Switzer-land	Guideline	Update	Recurrent miscarriage	45	Evidence-based (though no systematic search); expert consensus-based	Guideline does not discuss levels of evidence. The recommendations are graded according to their own instrument, described but name not mentioned	Not specified
American College of Radiology (ACR) appropriateness criteria infertility	Wall, 2020	ACR	USA	Guidelines	Revised	Broader: infertility	2	Evidence-based	RAND/UCLA Appropriateness Method and ACR's own criteria for Study Quality and Strength of Evidence, using concepts from GRADE (https://www.acr.org/-/media/ACR/Files/Appropriateness-Criteria/EvidenceTableDevelopment.pdf)	Not specified
Woman's pre-conception evaluation: genetic and fetal risk considerations for counselling and informed choice	Wilson, 2018	Genetics Committee of The SOGC	Canada	Consideration for Care Statement	Not specified (an update is implied however)	Broader: pre-conception evaluation	9	Evidence-based	GRADE	None

MTHFR, methylenetetrahydrofolate reductase; PGT, preimplantation genetic testing; Rand/UCLA, Rand Corporation and University of California at Los Angeles; RPL, recurrent pregnancy loss.

Gynaecology, and Irish Haematology Society, 2013), thrombosis (SIGN, 2013), immunology (Sung et al., 2017) and natural killer cells (RCOG, 2016).

The CPG were predominantly country-specific, with most originating in the USA (*n* = 11 [34%]), with others from Australia (*n* = 1 [3%]), Canada (*n* = 2 [6%]), France (*n* = 1 [3%]), Ireland (*n* = 2 [6%]), Korea (*n* = 1 [3%]), Northern Ireland (*n* = 1 [3%]), Saudi Arabia (*n* = 1 [3%]), and the UK (*n* = 5 [16%]). Seven CPG (22%) focused on more than one country, with one CPG from Germany, Austria and Switzerland (3%), three European (9%) and three global (9%) CPG. The CPG were published between 2011 and 2020: 2011 (*n* = 1 [3%]), 2012 (*n* = 6 [19%]), 2013 (*n* = 3 [9%]), 2015 (*n* = 2 [6%]), 2016 (*n* = 5 [16%]), 2017 (*n* = 5 [16%]), 2018 (*n* = 6 [19%]), 2019 (*n* = 1 [3%]) and 2020 (*n* = 3 [9%]). Seventeen (53%) CPG specifically mentioned a system of rating evidence and/or quality instrument used during CPG development, four (13%) described a system but did not specifically mention a name, whereas 11 (34%) did not report or use any. Of the 17 that specifically mentioned a system of rating the evidence, a variety were mentioned, with GRADE (Grading of Recommendations, Assessment, Development and Evaluations) being the most common, mentioned by five CPG (29%).

The terms used to describe recurrent miscarriage within the included CPG, as well as the definitions provided, are presented in TABLE 3. Most CPG used the term RPL (*n* = 15 [47%]), whereas others used recurrent miscarriage (*n* = 8 [25%]), a combination of terms such as RPL, recurrent miscarriage or other (*n* = 7 [22%]); two CPG (6%) did not specify a term. Definitions of these terms also varied. Of the 17 CPG that provided a description of recurrent miscarriage, RPL or other, nine referred to three or more losses (53%), seven referred to two or more losses (41%) and one referred to two consecutive spontaneous losses or three or more spontaneous losses (6%). Fifteen CPG did not provide a definition (47%); however, two of these referred to three losses within their texts.

Quality assessment findings (AGREE II evaluations)

The quality assessment scores for the 32 included CPG are presented in FIGURE 2 and TABLE 4; the original data file, with individual reviewer scores, is available in an open access repository (Hennessy et al., 2021). Only two of the CPG were recommended for use in their current form (6%) (Bates et al., 2012; ESHRE Early Pregnancy Guideline Development Group, 2017); most CPG were recommended for use with modification (*n* = 29 [91%]), whereas one (3%) was not recommended (Hickey et al., 2013). The overall quality of most included CPG was fair (*n* = 14 [44%]) or average (*n* = 11 [34%]); only one (3%) scored excellent (Bates et al., 2012). Applicability and editorial independence were the two domains in which CPG scored most poorly; 84% and 69% of CPG rated these domains as poor, respectively.

Synthesis of recommendations

Each included recommendation was assigned to one of the following categories: structure of care; investigations; treatment; and counselling and/or supportive care, with further sub-categories assigned. The number of recommendations by category and sub-category are presented in TABLE 5. Given the diversity of the CPG included, and the varying quality of CPG and evidence underpinning recommendations therein, the recommendations were not synthesized further. Instead, a narrative description is provided, comparing and contrasting the recommendations under each category and sub-category.

Structure of care

Forty-two recommendations from nine CPG were categorized under 'Structure of care' (Supplementary Table 3 and Supplementary Table 4). Two of these recommendations were categorized under two or more sub-categories. Forty recommendations within this category did not have associated strength of recommendation, quality of evidence ratings, or both, primarily because they were statements, good practice points, or both, within the relevant CPG. Ten recommendations from six CPG (RCOG, 2011; NICE, 2015; ESHRE Early Pregnancy Guideline Development Group, 2017; Queensland Clinical Guidelines, 2018; Toth et al., 2018; Northern Ireland Public Health Agency, 2020) related to 'clinician knowledge/skills/expertise' referring to individual clinicians and/or multi-disciplinary teams that should be involved in the care of those who experience recurrent miscarriage, either within specialist clinics, elsewhere, or both. A further 10 recommendations from three CPG (RCOG, 2011; ESHRE Early Pregnancy Guideline Development Group, 2017; Northern Ireland Public Health Agency, 2020) related to 'specialist clinic', specifically around how women who experience recurrent miscarriage should be referred to and/or seen in a specialist clinic, with two of the CPG including recommendations about the location of the clinic, and one CPG making recommendations around what should happen at the first visit, and the equipment and facilities needed.

Seven recommendations from two CPG (ESHRE Early Pregnancy Guideline Development Group, 2017; Northern Ireland Public Health Agency, 2020) related to 'counselling (psychological and/or emotional), recognizing the effect of recurrent miscarriage on those who experience recurrent miscarriage, as well as the provision of appropriate support services, referral to these services, or both. Five recommendations from two CPG (HSE, 2016; Northern Ireland Public Health Agency, 2020) related to 'referral'. One CPG contained one recommendation to ensure that those who experience recurrent miscarriage are referred to a pregnancy loss or gynaecological clinic (HSE, 2016). Another CPG included recommendations on referral criteria, information to be provided on referral and information about referrals outside of a particular jurisdiction (Northern Ireland Public Health Agency, 2020). Four recommendations from three CPG (Practice Committee of the ASRM, 2012; ACOG, 2018; Northern Ireland Public Health Agency, 2020) related to 'investigations'. Two of these recommendations related to proceeding with investigations for recurrent miscarriage after two consecutive clinical pregnancy losses (Practice Committee of the ASRM, 2012; ACOG, 2018), one recommendation concerned the tailoring of investigation plans, i.e. matching an intervention or components to previously measured characteristics of the participant (Northern Ireland Public Health Agency, 2020), whereas one related to experimental tests and how they should not take place outside of research settings (Northern Ireland Public Health Agency, 2020).

Four recommendations from two CPG (ESHRE Early Pregnancy Guideline Development Group, 2017; Northern Ireland Public Health Agency, 2020)

TABLE 3 DEFINITION OF RECURRENT MISCARRIAGE USED WITHIN CLINICAL PRACTICE GUIDELINES

Title	Author, year	Terminology used	Definition provided
AAGL practice report: practice guidelines for the diagnosis and management of submucous leiomyomas	AAGL, 2012	Recurrent pregnancy loss	None.
ACOG practice bulletin number 200: early pregnancy loss	ACOG, 2018	None	None; however, they refer to 'women who have experienced three prior pregnancy losses'. Early pregnancy loss is defined as loss of an intrauterine pregnancy in the first trimester.
The Society for Translational Medicine: clinical practice guidelines for sperm DNA fragmentation testing in male infertility	Agarwal, 2017	Recurrent pregnancy loss	Three consecutive pregnancy losses before 20-week gestation.
Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum	Alexander, 2017	Recurrent pregnancy loss	Two consecutive spontaneous losses or three or more spontaneous losses.
Saudi guidelines for threatened and recurrent miscarriage management; the role of progestogens in threatened and idiopathic recurrent miscarriage	Arab, 2019	Recurrent miscarriage	The loss of two or more pregnancies (biochemical/ultrasound confirmation). Note: drew on ESHRE guidelines
Practice guideline: joint CCMG-SOGC recommendations for the use of chromosomal microarray analysis for prenatal diagnosis and assessment of fetal loss in Canada	Armour, 2018	None	None. They refer to 'third pregnancy loss'
Evaluation and treatment of recurrent pregnancy loss: a committee opinion	ASRM, 2012	Recurrent pregnancy loss	Two or more failed clinical pregnancies; pregnancy is defined as a clinical pregnancy documented by ultrasonography or histopathological examination. Ideally, a threshold of three or more losses should be used for epidemiological studies while clinical evaluation may proceed following two first-trimester pregnancy losses.
Subclinical hypothyroidism in the infertile female population: a guideline	ASRM, 2015	Recurrent miscarriage; recurrent pregnancy loss	None.
Uterine septum: a guideline	ASRM, 2016	Recurrent pregnancy loss	None.
Removal of myomas in asymptomatic patients to improve fertility, reduce miscarriage rate. or both: a guideline	ASRM, 2017	Recurrent pregnancy Loss	None (note: one of the included studies defines as two or more miscarriages).
The use of PGT-A: a committee opinion	ASRM, 2018	Recurrent pregnancy loss	None.
VTE, thrombophilia, antithrombotic therapy, and pregnancy; antithrombotic therapy and prevention of thrombosis, 9th edn. American College of Chest Physicians evidence-based clinical practice guidelines	Bates 2012	Recurrent pregnancy loss; recurrent first trimester loss; recurrent early pregnancy loss	Recurrent early pregnancy loss: three or more miscarriages before 10 weeks of gestation. Note: In TABLE 1, defined as 'Preferred as defined by three early losses before 12 weeks; if not able to extract by this definition'.
Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline	DeGroot, 2012	Recurrent miscarriage; recurrent abortion; recurrent pregnancy loss	None.
Recurrent pregnancy loss: guideline of the European Society of Human Reproduction an Embryology	ESHRE, 2017	Recurrent pregnancy loss	The loss of two or more pregnancies. It excludes ectopic pregnancy and molar pregnancy. A pregnancy loss (miscarriage) is defined as the spontaneous demise of a pregnancy before the fetus reaches viability. The term, therefore, includes all pregnancy losses from the time of conception until 24 weeks of gestation. Primary RPL is described as RPL without a previous ongoing pregnancy (viable pregnancy) beyond 24 weeks' gestation, while secondary RPL is defined as an episode of RPL after one or more previous pregnancies progressing beyond 24 weeks' gestation. A pregnancy in the definition is confirmed at least by either serum or urine beta-HCG, i.e. including non-visualized pregnancy losses (biochemical pregnancy losses, resolved and treated pregnancies of unknown location, or both). Recurrent 'early' pregnancy loss is the loss of two or more pregnancies before 10 weeks of gestational age. Recommend the use of 'recurrent pregnancy loss' to describe repeated pregnancy demise and to reserve 'recurrent miscarriage' to describe cases where all pregnancy losses have been confirmed as intrauterine miscarriages.
ESHRE PGT Consortium good practice recommendations for the organisation of PGT	ESHRE, 2020	Recurrent miscarriage	Two or more pregnancy losses before 24 weeks of gestation (including chemical pregnancy).
Clinical practice guidelines for hypothyroidism in adults	Garber, 2012	Recurrent miscarriage	None.

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TABLE 3 *(continued)*

Title	Author, year	Terminology used	Definition provided
The Thessaloniki ESHRE/ESGE consensus on diagnosis of female genital anomalies	Grimbizis, 2016	Recurrent pregnancy loss	None.
ACMG practice guideline: lack of evidence for MTHFR polymorphism testing	Hickey, 2013	Recurrent pregnancy loss	None.
Clinical practice guideline: venous thromboprophylaxis in pregnancy	HSE, 2013	Recurrent miscarriage	None.
National standards for bereavement care following pregnancy loss and perinatal death	HSE, 2016	Recurrent miscarriage	The loss of three or more consecutive pregnancies before 24 weeks' gestation.
Pregnancy loss: French clinical practice guidelines	Huchon, 2016	Recurrent pregnancy loss (also known as repeated miscarriages)	The experience of three or more consecutive miscarriages before 14 weeks' gestation.
Guidelines on the investigation and management of antiphospholipid syndrome	Keeling, 2012	Recurrent pregnancy loss; recurrent fetal loss	Three or more pregnancy losses, before 10 weeks' gestation.
Hysteroscopic metroplasty of a uterine septum for recurrent miscarriage: interventional procedures guidance	NICE, 2015	Recurrent miscarriage	Usually defined as three or more miscarriages in a row
Recurrent pregnancy loss care pathway for Northern Ireland	Public Health Agency, 2020	Recurrent pregnancy loss	A diagnosis of RPL could be considered after the loss of two or more pregnancies (ESHRE). Pregnancy loss is defined as the spontaneous loss of a pregnancy before the fetus reaches viability. It therefore includes all pregnancy losses from the time of conception until 24 weeks of gestation.
Maternity and neonatal clinical guideline: early pregnancy loss	Queensland Clinical Guidelines, 2018	Recurrent miscarriage	Three or more consecutive miscarriages. There is no specific term for non-consecutive pregnancy losses. Note: scope of document is women experiencing pregnancy loss before 20 weeks' gestation.
Green-top guideline number 17: the investigation and treatment of couples with recurrent first-trimester and second-trimester miscarriage	RCOG, 2011	Recurrent first-trimester and second-trimester miscarriage	Three or more first-trimester miscarriages, or one or more second-trimester miscarriages. Includes all pregnancy losses from the time of conception until 24 weeks of gestation.
The role of natural killer cells in human fertility: scientific impact paper number 53	RCOG, 2016	Recurrent miscarriage; recurrent spontaneous pregnancy loss	None.
SIGN 129: antithrombotics: indications and management	SIGN, 2013	Recurrent pregnancy failure; recurrent miscarriage; recurrent pregnancy loss	None.
Intravenous immunoglobulin G in women with reproductive failure: The Korean Society for Reproductive Immunology practice guidelines	Sung, 2017	Recurrent pregnancy loss	State recurrent pregnancy loss traditionally defined as three or more consecutive miscarriages, but ASRM define as two or more failed pregnancies, based on the risk of recurrence and the prevalence of etiologies.
Recurrent miscarriage: diagnostic and therapeutic procedures. Guideline of the DGGG, OEGGG and SGGG (S2k-Level, AWMF Registry Number 015/050)	Toth, 2018	Recurrent miscarriage	Three or more consecutive recurrent miscarriages (WHO definition).
ACR appropriateness criteria infertility	Wall, 2020	Recurrent pregnancy loss	Two or more consecutive early pregnancy losses (ASRM definition).
Woman's pre-conception evaluation: genetic and fetal risk considerations for counselling and informed choice	Wilson, 2018	Recurrent pregnancy loss	None.

AAGL, American Association of Gynecologic Laparoscopists; ACMG, American College of Medical Genetics and Genomics; ACOG, American College of Obstetrics and Gynaecology; ACR, American College of Radiology; ASRM, American Society for Reproductive Medicine; CCMG, Canadian College of Medical Geneticists; DGGG, German Society of Gynecology and Obstetrics; ESGE, European Society for Gynaecological Endoscopy; ESHRE, European Society of Human Reproduction and Embryology; HSE, Health Service Executive; MTHFR, methylenetetrahydrofolate reductase; NICE, National Institute for Health and Care Excellence; OEGGG, Austrian Society of Gynecology and Obstetrics; PGT-A, preimplantation genetic testing for aneuploidy; RCOG, Royal College of Obstetrics and Gynaecology; RPL, recurrent pregnancy loss; SGGG, Swiss Society of Gynecology and Obstetrics; SIGN, Scottish Intercollegiate Guidelines Network; SOGC, Society of Obstetricians and Gynaecologists of Canada; VTE, Venous thromboembolism; WHO, World Health Organization.

related to 'treatment' and concerned tailored treatment plans, including plans for future pregnancies; one CPG referred to experimental treatments and how they should not take place outside of research settings (*Northern Ireland Public Health Agency, 2020*). Three recommendations from two CPG (*ESHRE Early Pregnancy Guideline Development Group, 2017*; *Northern Ireland Public Health Agency, 2020*) related to 'informational support' and concerned information (written, spoken, or both) that should be provided to those who experience recurrent miscarriage at

FIGURE 2 AGREE II Domain scores for the 32 guidelines, percentage (%). Excellent (>80%), good (>60–80%), average (>40–60%), fair (>20–40%) and poor (≤20%)

the outset, including information about what will happen, sources of support, or both. Two recommendations from one CPG (*Northern Ireland Public Health Agency, 2020*) related to 'research'; these related to experimental investigations and treatments mentioned earlier under those sub-categories, as well as travel funding requests for assessment of trial eligibility.

Investigations

One hundred and thirty-four recommendations from 23 CPG were categorized under 'Investigations' (Supplementary Table 5 and Supplementary Table 6). Nine of these recommendations were categorized under two or more sub-categories. Fifty-six recommendations did not have the strength of recommendation, quality of evidence ratings, or both, to accompany them, as they were statements, good practice points, or both, within the relevant CPG, or were not specified.

Thirty recommendations from nine CPG related to 'metabolic and endocrinologic factors'. No clear agreement was reached, with some conflicting recommendations. Thyroid-stimulating hormone (TSH) was recommended by three CPG (*Practice Committee of the ASRM, 2012*; *ESHRE Early Pregnancy Guideline Development Group, 2017*; *Toth et al., 2018*). Thyroid peroxidase antibody testing was recommended only in the event of abnormal TSH by two of the three CPG (*Practice Committee of the ASRM, 2012*; *Toth et al., 2018*), whereas they were recommended as standard tests by three CPG (*Huchon et al., 2016*; *ESHRE Early Pregnancy Guideline Development Group, 2017*; *Northern Ireland Public Health Agency, 2020*). Prolactin level testing was recommended as standard by two CPG (*Practice Committee of the ASRM, 2012*; *Huchon et al., 2016*). Two CPG (*Huchon et al., 2016*; and *ESHRE Early Pregnancy Guideline Development Group, 2017*) directly contradicted each other's recommendations in the investigations required. Three CPG recommended a screen for diabetes (*Practice Committee of the ASRM, 2012*; *Huchon et al., 2016*; *Queensland Clinical Guidelines, 2018*). *Wilson (2018)* recommended an overall endocrine assessment, but no evidence for any particular investigation or test.

Twenty-nine recommendations from 12 CPG related to 'thrombophilia screening'. Greater consensus was reached in this section with 10 CPG recommending antiphospholipid antibodies (APLA) after two or three miscarriages as standard (*RCOG, 2011*; *Bates et al., 2012*; *Keeling et al., 2012*; *Practice Committee of the ASRM, 2012*; *Institute of Obstetricians and Gynaecologists RCPI et al., 2013*; *Huchon et al., 2016*; *ESHRE Early Pregnancy Guideline Development Group, 2017*; *Queensland Clinical Guidelines, 2018*; *Toth et al., 2018*; *Northern Ireland Public Health Agency, 2020*), two of which had caveats (*Practice Committee of the ASRM, 2012*; *Toth et al., 2018*). Four specified repeating APLA after 12 weeks (*RCOG, 2011*; *Keeling et al., 2012*; *Institute of Obstetricians and Gynaecologists RCPI et al., 2013*; *Northern Ireland Public Health Agency, 2020*). The remaining CPG requested APLA testing on meeting certain conditions, i.e. not as standard after two or three miscarriages. Only the *Queensland Clinical Guidelines (2018)* recommended an inherited thrombophilia screen as standard. Only *Hickey et al. (2013)* suggested methylenetetrahydrofolate reductase (*MTHFR*) genetic screening and did not recommend it as standard.

Twenty-six recommendations from 12 CPG concerned 'anatomical investigations'. It was generally agreed that uterine anatomy should be assessed as part of the routine investigation of recurrent miscarriage. Opinions differed, however, on what the most appropriate investigation was, with little supporting evidence. Many CPG agreed that ultrasound is a suitable primary investigation for assessing pelvic anatomy (*RCOG, 2011*; *Grimbizis et al., 2016*; *Huchon et al., 2016*; *ESHRE Early Pregnancy Guideline Development Group, 2017*; *Queensland Clinical Guidelines, 2018*; *Wall et al., 2020*). No consensus, however, was reached on what second-line investigations were more appropriate, with saline infusion sonohysterogram, hysterosalpingography (HSG), hysterosalpingo-contrast-sonography, three-dimensional ultrasound and magnetic resonance imaging all suggested. Some CPG recommended the use of HSG (*Practice Committee of the ASRM, 2012*), others did not (*Huchon et al., 2016*; *ESHRE Early Pregnancy Guideline Development Group, 2017*); similarly, one recommended magnetic resonance imaging (*Wall et al., 2020*),

TABLE 4 AGREE II QUALITY ASSESSMENT RATINGS, BY DOMAIN (% CLINICAL PRACTICE GUIDELINES)

Title	Author, year	Domain 1: scope and purpose (%)	Domain 2: stakeholder involvement (%)	Domain 3: rigour of development (%)	Domain 4: clarity of presentation (%)	Domain 5: applicability (%)	Domain 6: editorial independence (%)	Overall quality of the guideline (%)	Recommend for use
AAGL practice report: practice guidelines for the diagnosis and management of submucous leiomyomas	AAGL, 2012	Average (43)	Poor (9)	Fair (35)	Good (67)	Poor (6)	Poor (17)	Average (56)	YWM
ACOG practice bulletin number 200: early pregnancy loss	ACOG, 2018	Average (57)	Fair (24)	Poor (20)	Good (63)	Poor (4)	Poor (8)	Average (50)	YWM
The Society for Translational Medicine: clinical practice guidelines for sperm DNA fragmentation testing in male infertility	Agarwal, 2017	Average (46)	Poor (17)	Poor (13)	Average (48)	Poor (0)	Poor (6)	Fair (33)	YWM
Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum	Alexander, 2017	Good (67)	Average (44)	Average (42)	Good (69)	Poor (7)	Good (67)	Good (67)	YWM
Saudi guidelines for threatened and recurrent miscarriage management; the role of progestogens in threatened and idiopathic recurrent miscarriage	Arab, 2019	Average (50)	Fair (37)	Fair (21)	Average (54)	Poor (0)	Poor (19)	Fair (39)	YWM
Practice guideline: joint CCMG-SOGC recommendations for the use of chromosomal microarray analysis for prenatal diagnosis and assessment of fetal loss in Canada	Armour, 2018	Average (54)	Average (48)	Fair (28)	Good (72)	Poor (15)	Poor (17)	Average (56)	YWM
Evaluation and treatment of recurrent pregnancy loss: a committee opinion	ASRM, 2012	Average (41)	Poor (9)	Poor (16)	Average (41)	Poor (3)	Fair (22)	Fair (39)	YWM
Subclinical hypothyroidism in the infertile female population: a guideline	ASRM, 2015	Average (50)	Poor (11)	Fair (27)	Average (56)	Poor (4)	Fair (22)	Average (44)	YWM
	Author, Year	Domain 1: scope and purpose	Domain 2: stakeholder involvement	Domain 3: rigour of development	Domain 4: clarity of presentation	Domain 5: applicability	Domain 6: editorial independence	Overall quality of the guideline	Recommend for use
Uterine septum: a guideline	ASRM, 2016	Average (44)	Poor (17)	Average (41)	Average (57)	Poor (0)	Poor (17)	Average (44)	YWM
Removal of myomas in asymptomatic patients to improve fertility and/or reduce miscarriage rate: a guideline	ASRM, 2017	Fair (31)	Poor (15)	Fair (34)	Average (54)	Poor (1)	Poor (19)	Fair (33)	YWM
The use of PGT-A: a committee opinion	ASRM, 2018	Fair (26)	Poor (15)	Fair (31)	Fair (37)	Poor (8)	Fair (22)	Fair (33)	YWM
VTE, thrombophilia, antithrombotic therapy, and pregnancy; Antithrombotic therapy and prevention of thrombosis, 9th edn: American College of Chest Physicians evidence-based clinical practice guidelines	Bates, 2012	Good (76)	Average (57)	Good (65)	Good (76)	Fair (22)	Good (72)	Excellent (83)	Yes
Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline	DeGroot, 2012	Average (57)	Fair (28)	Fair (38)	Good (74)	Poor (3)	Fair (22)	Average (56)	YWM
Recurrent pregnancy loss: guideline of the European Society of Human Reproduction and Embryology	ESHRE, 2017	Good (74)	Good (61)	Good (66)	Excellent (81)	Poor (19)	Average (50)	Good (72)	Yes
ESHRE PGT Consortium good practice recommendations for the organization of PGT	ESHRE, 2020	Average (46)	Average (41)	Poor (20)	Average (52)	Poor (7)	Poor (14)	Fair (33)	YWM
Clinical practice guidelines for hypothyroidism in adults	Garber, 2012	Good (61)	Fair (30)	Fair (37)	Good (70)	Poor (8)	Poor (14)	Average (50)	YWM
The Thessaloniki ESHRE/ESGE consensus on diagnosis of female genital anomalies	Grimbizis, 2016	Fair (39)	Fair (30)	Poor (20)	Average (48)	Poor (11)	Poor (14)	Fair (33)	YWM
ACMG practice guideline: lack of evidence for *MTHFR* polymorphism testing	Hickey, 2013	Poor (15)	Poor (13)	Poor (9)	Average (44)	Poor (0)	Poor (6)	Poor (11)	No

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TABLE 4 *(continued)*

Title	Author, year	Domain 1: scope and purpose (%)	Domain 2: stakeholder involvement (%)	Domain 3: rigour of development (%)	Domain 4: clarity of presentation (%)	Domain 5: applicability (%)	Domain 6: editorial independence (%)	Overall quality of the guideline (%)	Recommend for use
Clinical practice guideline: Venous thromboprophylaxis in pregnancy	HSE, 2013	Average (54)	Average (41)	Fair (26)	Good (72)	Poor (15)	Poor (0)	Average (44)	YWM
National standards for bereavement care following pregnancy loss and perinatal death	HSE, 2016	Average (50)	Good (65)	Poor (10)	Average (54)	Fair (22)	Poor (0)	Fair (33)	YWM
Pregnancy loss: French clinical practice guidelines	Huchon, 2016	Poor (17)	Fair (26)	Poor (16)	Average (48)	Poor (10)	Poor (0)	Fair (33)	YWM
Guidelines on the investigation and management of antiphospholipid syndrome	Keeling, 2012	Average (43)	Fair (28)	Fair (35)	Average (54)	Poor (0)	Poor (8)	Fair (50)	YWM
Hysteroscopic metroplasty of a uterine septum for recurrent miscarriage: interventional procedures guidance	NICE, 2015	Average (44)	Poor (13)	Average (58)	Good (70)	Poor (18)	Poor (14)	Average (50)	YWM
Recurrent pregnancy loss care pathway for Northern Ireland	Public Health Agency, 2020	Average (54)	Average (48)	Poor (7)	Average (56)	Fair (21)	Poor (0)	Fair (22)	YWM
Maternity and neonatal clinical guideline: early pregnancy loss	Queensland Clinical Guidelines, 2018	Good (63)	Average (48)	Fair (33)	Excellent (81)	Fair (40)	Fair (36)	Good (61)	YWM
Green-top guideline number 17: the investigation and treatment of couples with recurrent first-trimester and second-trimester miscarriage	RCOG, 2011	Average (57)	Fair (22)	Average (42)	Good (76)	Poor (8)	Poor (6)	Average (50)	YWM
The role of natural killer cells in human fertility: scientific impact paper number 53	RCOG, 2016	Fair (28)	Poor (20)	Poor (17)	Average (54)	Poor (0)	Poor (8)	Fair (22)	YWM
SIGN 129: antithrombotics: indications and management	SIGN, 2013	Average (54)	Good (70)	Average (56)	Good (72)	Fair (26)	Fair (25)	Good (61)	YWM
Intravenous immunoglobulin G in women with reproductive failure: The Korean Society for Reproductive Immunology practice guidelines	Sung, 2017	Fair (30)	Poor (13)	Fair (22)	Average (43)	Poor (0)	Poor (14)	Fair (33)	YWM
	Author, Year	Domain 1: Scope & purpose	Domain 2: Stakeholder involvement	Domain 3: Rigour of development	Domain 4: Clarity of presentation	Domain 5: Applicability	Domain 6: Editorial independence	Overall quality of the guideline	Recommend for use
Recurrent miscarriage: diagnostic and therapeutic procedures. Guideline of the DGGG, OEGGG 7 SGGG (S2k-level, AWMF registry number 015/050)	Toth, 2018	Fair (39)	Fair (35)	Fair (31)	Average (59)	Poor (7)	Poor (14)	Fair (33)	YWM
ACR appropriateness criteria infertility	Wall, 2020	Average (52)	Fair (31)	Average (56)	Good (67)	Poor (3)	Poor (6)	Average (50)	YWM
Woman's pre-conception evaluation: Genetic and fetal risk considerations for counselling and informed choice	Wilson, 2018	Average (44)	Poor (19)	Fair (24)	Average (54)	Poor (10)	Fair (22)	Poor (17)	YWM

Excellent (>80%), good (>60–80%), average (>40–60%), fair (>20–40%), poor (≤20%).

AAGL, American Association of Gynecologic Laparoscopists; ACMG, American College of Medical Genetics and Genomics; ACOG, American College of Obstetrics and Gynaecology; ACR, American College of Radiology; ASRM, American Society for Reproductive Medicine; CCMG, Canadian College of Medical Geneticists; DGGG, German Society of Gynecology and Obstetrics; ESGE, European Society for Gynaecological Endoscopy; ESHRE, European Society of Human Reproduction and Embryology; HSE, Health Service Executive; MTHFR, methylenetetrahydrofolate reductase; NICE, National Institute for Health and Care Excellence; OEGGG, Austrian Society of Gynecology and Obstetrics; PGT-A, preimplantation genetic testing for aneuploidy; RCOG, Royal College of Obstetrics and Gynaecology; SGGG, Swiss Society of Gynecology and Obstetrics; SIGN, Scottish Intercollegiate Guidelines Network; SOGC, Society of Obstetricians and Gynaecologists of Canada; VTE, Venous thromboembolism; YWM, yes with modifications.

TABLE 5 NUMBER OF RECOMMENDATIONS BY CATEGORY AND SUB-CATEGORY

Category	Sub-category	Number of recommendations[a]	Number of clinical practice guidelines[b]
Structure of care (*n* = 42)	Clinician knowledge/skills/expertise	10	6
	Counselling	7	2
	Informational support	3	2
	Investigations	4	3
	Referral	5	2
	Research	2	1
	Specialist clinic	10	3
	Treatment	4	2
	Sub-total	**45**	**9**
Investigations (*n* = 134)	Anatomical investigations	26	12
	Haematology	2	1
	Immunological screening	13	7
	Male factors	5	4
	Medical and family history	5	3
	Metabolic and endocrinologic factors	30	9
	Microbiological factors	4	3
	Risk factors[c]	4	4
	Screening for genetic factors	22	9
	Tailoring	4	3
	Thrombophilia screening	29	12
	Unexplained recurrent miscarriage	2	2
	Sub-total	**146**	**23**
Treatment (*n* = 153)	Antiphospholipid syndrome	18	10
	Assisted reproductive technology	1	1
	Genetic factors	11	6
	Immunotherapy	15	6
	Male factors	4	2
	Metabolic or endocrinologic factors	44	12
	Microbiological factors	2	2
	Prognosis	1	1
	Risk factors	1	1
	Tailoring	1	1
	Thrombophilia	12	7
	Unexplained recurrent miscarriage	21	6
	Uterine factors	22	10
	Vitamins	4	3
	Sub-total	**157**	**24**
Counselling and/or supportive care (*n* = 46)	Clinician knowledge/skills/expertise	1	1
	Genetic counselling	4	4
	Informational support	3	2
	Investigations	4	3
	Prognosis	6	5
	Psychological and/or emotional counselling	11	5
	Research	2	2
	Risk factors[3]	13	5
	Tailoring	2	1
	Treatment	1	1
	Sub-total	**47**	**9**
Total (*n* = 373)		**375**	**32**

[a] Sub-total of the number of recommendations may be higher than the number of recommendations highlighted under the category as some recommendations were categorized under more than one sub-category.

[b] Sub-total of the number of clinical practice guidelines (CPG) is not the sum of the number of CPG; it is the total number of CPG with recommendations within the particular category.

[c] Risk factors mentioned could include the following: age; successive pregnancy losses; anatomical, endocrine/metabolic and genetic factors; smoking; drug, alcohol use, or both; obesity or underweight; diet (including caffeine consumption); and physical inactivity.

whereas one did not recommend it as a first-line option (*ESHRE Early Pregnancy Guideline Development Group, 2017*). *Toth et al. (2018)* and the *Practice Committee of the ASRM (2016)* suggested hysteroscopy as more appropriate for uterine septae or adhesions. The *ESHRE Early Pregnancy Guideline Development Group (2017)* and *Huchon et al. (2016)* both stated that HSG is not an appropriate first-line investigation for uterine anomalies.

Twenty-two recommendations from nine CPG related to 'screening for genetic factors'. Five CPG recommended karyotyping of pregnancy tissue as standard (*Practice Committee of the ASRM, 2012*; *Huchon et al., 2016*; *Queensland Clinical Guidelines, 2018*; *Toth et al., 2018*; *Wilson, 2018*); two did not routinely recommend, but on an individual basis as an explanatory investigation (*ESHRE Early Pregnancy Guideline Development Group, 2017*; *Northern Ireland Public Health Agency, 2020*); a further one stated that, in cases of congenital anomalies, intrauterine growth restriction, or both, in any fetal loss before 20 weeks' gestation, if quantitative fluorescent polymerase chain reaction methodologies, other-directed diagnostic inquiries, or both, did not provide a diagnosis and further cytogenetic analysis is intended, karyotype should be replaced with chromosomal microarray analysis (*Armour et al., 2018*). Parental karyotyping was suggested as a standard investigation by three CPG if pregnancy tissue was not available (*Huchon et al., 2016*; *Queensland Clinical Guidelines, 2018*; *Toth et al., 2018*); two CPG suggested it if the pregnancy tissue testing reported an abnormality (*Practice Committee of the ASRM, 2012*; *Toth et al., 2018*). Two CPG mentioned other genetic tests on women and men (*Huchon et al., 2016*; *Toth et al., 2018*).

Thirteen recommendations from seven CPG related to 'immunological screening'. Five of these CPG made recommendations around natural killer cell testing: four did not recommend such testing (*Practice Committee of the ASRM, 2012*; *RCOG, 2016*; *ESHRE Early Pregnancy Guideline Development Group, 2017*; *Toth et al., 2018*), whereas one did (*Sung et al., 2017*). The consensus amongst CPG in relation to immunological screening was that human leukocyte antigen analysis, peripheral and uterine natural killer cell analysis, T helper type 1 and type 2 measurements were all experimental, with the exception of the guidelines from *Sung et al. (2017)*, which recommended them all as standard. The *ESHRE Early Pregnancy Guideline Development Group (2017)* cited an exception for one disorder in which women had miscarriages after one previous male child.

Five recommendations from four CPG related to 'male factors', with one of these relating to risk factors (mentioned later also). Four of the recommendations concerning male factors related to sperm testing: three recommended sperm testing, with two specifically recommending sperm DNA fragmentation (*Agarwal et al., 2017*; *ESHRE Early Pregnancy Guideline Development Group, 2017*), whereas one recommended against routine testing for spermploidy or sperm DNA fragmentation (*Practice Committee of the ASRM, 2012*); the strength of recommendation, quality of evidence, or both, was not assessed, i.e. they were statements, or was low for these. Five recommendations from three CPG related to 'medical and family history', i.e. the need to take such a history, and four of these related to tailoring investigations accordingly (mentioned later also) (*ESHRE Early Pregnancy Guideline Development Group, 2017*; *Queensland Clinical Guidelines, 2018*; *Northern Ireland Public Health Agency, 2020*). Four recommendations from three CPG related to 'microbiological factors'. Two of these CPG recommended against routinely screening for infections (*Practice Committee of the ASRM, 2012*; *Toth et al., 2018*), with one of these recommending that endometrial biopsy may be carried out to rule out chronic endometritis (*Toth et al., 2018*); another CPG recommended testing for Rubella immune status (*Northern Ireland Public Health Agency, 2020*); only two had the strength of recommendation, quality of evidence ratings (expert consensus), or both. Four recommendations from three CPG related to 'tailoring' investigations to each woman or couple (*ESHRE Early Pregnancy Guideline Development Group, 2017*; *Queensland Clinical Guidelines, 2018*; *Northern Ireland Public Health Agency, 2020*). Four recommendations from four CPG related to 'risk factors', e.g. alcohol, smoking, caffeine, weight status, physical activity, and the need to evaluate these (*Practice Committee of the ASRM, 2012*; *ESHRE Early Pregnancy Guideline Development Group, 2017*; *Wilson, 2018*; *Northern Ireland Public Health Agency, 2020*), with two of the CPG explicitly stating the inclusion of males or partners (*ESHRE Early Pregnancy Guideline Development Group, 2017*; *Northern Ireland Public Health Agency, 2020*). Two recommendations from one CPG related to 'haematology' and stated that full blood count and electrolytes and liver function tests should be standard investigations (*Queensland Clinical Guidelines, 2018*). Two recommendations from two CPG related to 'unexplained recurrent miscarriage' and how this diagnosis can be made when investigations have been conducted, and no cause of recurrent miscarriage found (*Toth et al., 2018*; *Arab et al., 2019*).

Treatment

One hundred and fifty-three recommendations from 24 CPG were categorized under 'Treatment' (Supplementary Table 7 and Supplementary Table 8). Three of these recommendations were categorized under two or more sub-categories. Sixty-two recommendations did not have the strength of recommendation, quality of evidence ratings, or both, to accompany them, as they were statements, good practice points, or both, within the relevant CPG, or were not specified.

Forty-four recommendations from 12 CPG related to 'metabolic or endocrinologic factors'. Three CPG recommended that overt hypothyroidism is treated in recurrent miscarriage (*Practice Committee of the ASRM, 2015*; *ESHRE Early Pregnancy Guideline Development Group, 2017*; *Toth et al., 2018*). Two CPG stated that subclinical hypothyroidism (TSH >4.0 mIU/l as per ASRM) should be treated in the presence of recurrent miscarriage (*Huchon et al., 2016*; *Toth et al., 2018*). Three CPG recommended that treatment of subclinical hypothyroidism in recurrent miscarriage should be considered as benefits may outweigh risks (*Alexander et al., 2017*; *ESHRE Early Pregnancy Guideline Development Group, 2017*; *Northern Ireland Public Health Agency, 2020*). The recommendations were less clear on treatment if women were euthyroid and had antibodies: *Huchon et al. (2016)* and *Toth et al. (2018)* recommended treatment; *De Groot et al. (2012)* recommended treatment if other autoimmune disease was present;

Alexander et al. (2017) stated that the benefits might outweigh the risks; and the *Northern Ireland Public Health Agency (2020)* did not recommend treatment. Two CPG stated that progesterone treatment had insufficient evidence demonstrating benefit (*RCOG, 2011*; *ESHRE Early Pregnancy Guideline Development Group, 2017*), whereas three suggested it may be of help (*Practice Committee of the ASRM, 2012*; *ACOG, 2018*; *Northern Ireland Public Health Agency, 2020*). Three CPG recommended bromocriptine for hyperprolactinaemia (*Huchon et al., 2016*; *ESHRE Early Pregnancy Guideline Development Group, 2017*; *Northern Ireland Public Health Agency, 2020*). According to two CPG, HCG, metformin and growth factors were not recommended (*ESHRE Early Pregnancy Guideline Development Group, 2017*; *Northern Ireland Public Health Agency, 2020*).

Twenty-two recommendations from 10 CPG related to 'uterine factors'. Three CPG stated that the evidence for any of the mentioned procedures in recurrent miscarriage was insufficient (*RCOG, 2011*; *ESHRE Early Pregnancy Guideline Development Group, 2017*; *Northern Ireland Public Health Agency, 2020*). Two CPG recommended surgical correction of any anomaly after three miscarriages (*Huchon et al., 2016*; *Toth et al., 2018*). *The American Association of Gynecologic Laparoscopists (AAGL) (2012)* recommended submucosal myomectomy. The *Practice Committee of the ASRM (2016)* suggested septal incision. The *Practice Committee of the ASRM (2017)* stated that myomectomy makes no difference to live birth rates after assisted reproductive technology but that it also does not reduce the miscarriage rate. *NICE (2015)* stated that some evidence suggested that uterine surgery may be of some efficacy but with rare serious side-effects. Overall, the evidence seems insufficient to merit advising procedures on anything but an individual basis.

Twenty-one recommendations from six CPG related to 'unexplained recurrent miscarriage'. Two CPG recommended reassurance of excellent prognosis for future pregnancy and supportive care (*RCOG, 2011*; *ESHRE Early Pregnancy Guideline Development Group, 2017*). One CPG recommended that early IVF or intracytoplasmic sperm injection as a potential alternative treatment (*Agarwal et al., 2017*). Three CPG recommended against intravenous immunoglobulin (IVIG) for unexplained recurrent miscarriage (*Huchon et al., 2016*; *ESHRE Early Pregnancy Guideline Development Group, 2017*; *Sung et al., 2017*); two recommended against aspirin (*Huchon et al., 2016*; *ESHRE Early Pregnancy Guideline Development Group, 2017*), low molecular weight heparin (*Huchon et al., 2016*; *ESHRE Early Pregnancy Guideline Development Group, 2017*), progesterone and natural micronized progesterone in the first trimester (*ESHRE Early Pregnancy Guideline Development Group, 2017*; *Toth et al., 2018*), and the administration of granulocyte-colony stimulating factor (*ESHRE Early Pregnancy Guideline Development Group, 2017*; *Toth et al., 2018*). One CPG recommended against acetylsalicylic acid with or without additional heparin (*Toth et al., 2018*); lymphocyte immunization therapy (*ESHRE Early Pregnancy Guideline Development Group, 2017*); this CPG also recommended against glucocorticoids in recurrent miscarriage with selected immunological biomarkers, folic acid for treatment of unexplained recurrent miscarriage, progesterone, intralipid therapy and endometrial scratching (*ESHRE Early Pregnancy Guideline Development Group, 2017*).

Eighteen recommendations from 10 CPG related to 'antiphospholipid syndrome'. The CPG consistently recommended that antiphospholipid syndrome requires treatment with aspirin and heparin (*RCOG, 2011*; *Bates et al., 2012*; *Keeling et al., 2012*; *Practice Committee of the American Society for Reproductive Medicine, 2012*; *Institute of Obstetricians and Gynaecologists RCPI et al., 2013*; *SIGN, 2013*; *Queensland Clinical Guidelines, 2018*; *Toth et al., 2018*; *Northern Ireland Public Health Agency, 2020*). Recommendations for dose of aspirin, and unfractionated heparin (*Bates et al., 2012*; *Practice Committee of the ASRM, 2012*) compared with low-molecular-weight heparin, and whether a prophylactic or intermediate dose was required, were inconsistent. Some also recommended treatment with the caveat that they fulfilled clinical and laboratory criteria for antiphospholipid syndrome (*Bates et al., 2012*; *Practice Committee of the ASRM, 2012*; *SIGN, 2013*; *Northern Ireland Public Health Agency, 2020*), whereas *Toth et al. (2018)* recommended treatment in all cases. *Huchon et al. (2016)* specified that antiphospholipid syndrome and recurrent miscarriage only warranted aspirin and heparin if there was a history of venous thromboembolism.

Fifteen recommendations from six CPG related to 'immunotherapy'. All CPG were in agreement that immunotherapies were not recommended outside of clinical trials or in specific autoimmune diseases (*RCOG, 2011*; *Practice Committee of the ASRM, 2012*; *Alexander et al., 2017*; *Toth et al., 2018*; *Northern Ireland Public Health Agency, 2020*), except for *Sung et al. (2017)*, which recommended IVIG for recurrent miscarriage and cellular immune abnormalities. One recommendation from one CPG related to 'non-conventional treatments' and how intralipid therapy should not be recommended (*Northern Ireland Public Health Agency, 2020*).

Twelve recommendations from seven CPG related to 'thrombophilia' (*RCOG, 2011*; *Bates et al., 2012*; *Institute of Obstetricians and Gynaecologists RCPI et al., 2013*; *ESHRE Early Pregnancy Guideline Development Group, 2017*; *Sung et al., 2017*; *Queensland Clinical Guidelines, 2018*; *Toth et al., 2018*). Most were in agreement that inherited thrombophilia and a history of recurrent miscarriage are insufficient to warrant aspirin and heparin prophylaxis in the absence of thrombotic events or risk factors. *Sung et al. (2017)* suggested IVIG as an alternative if heparin, aspirin, or both, were not tolerated. *Toth et al. (2018)* stated that aspirin should not be given for recurrent miscarriage.

Eleven recommendations from six CPG related to 'genetic factors'. Two CPG stated that PGT should not be undertaken routinely (*Practice Committee of the ASRM, 2012*; *Toth et al., 2018*). Preimplantation genetic diagnosis (PGD) and PGT are the terms used within the respective guidelines. For consistency in reporting, the term PGT is used; furthermore, PGT has replaced PGD and preimplantation genetic screening (PGS) after changes to terminology in infertility care (ESHRE PGT *Consortium Steering Committee et al., 2020*). One CPG stated that the value of PGT for aneuploidy (PGT-A) as a universal screening test for all IVF patients has yet to be determined (*Practice Committees of the ASRM and the Society for Assisted Reproductive Technology, 2018*). ESHRE PGT

Consortium Steering Committee et al. (2020) recommended against PGT-A for recurrent miscarriage without a genetic cause. The *RCOG (2011)* and *Practice Committee of the ASRM (2012)* also made a point of declaring that PGT and IVF do not lead to a higher live birth rate in women who experience recurrent miscarriage, whereas the *RCOG (2011)* and *ESHRE Early Pregnancy Guideline Development Group (2017)* clearly stated the natural live birth rate in this cohort is, in fact, higher than with PGT and IVF.

Four recommendations from two CPG related to 'male factors'. Two CPG recommended against sperm selection (*ESHRE Early Pregnancy Guideline Development Group, 2017*; *Northern Ireland Public Health Agency, 2020*), one recommended against antioxidants for men (*ESHRE Early Pregnancy Guideline Development Group, 2017*) and another recommended smoking cessation, normal body weight, limited alcohol consumption and a normal exercise pattern in couples who have experienced recurrent miscarriage (*ESHRE Early Pregnancy Guideline Development Group, 2017*); this recommendation was also categorized under 'risk factors' (the only recommendation in this sub-category).

Four recommendations from three CPG related to 'vitamins'. One CPG recommended pre-conceptual folic acid supplementation, and pre-conceptual vitamin B6 and vitamin B9 (and during pregnancy, if occurs), in women who had experienced recurrent miscarriage and a diagnosis of B9 deficiency, hyperhomocysteinaemia, or both (*Huchon et al., 2016*). Two CPG recommended advising on multi-vitamins that are safe during pregnancy, if asked (*ESHRE Early Pregnancy Guideline Development Group, 2017*; *Northern Ireland Public Health Agency, 2020*).

Two recommendations from two CPG related to 'microbiological factors': one consensus-based CPG recommended that antibiotics may be administered to women who had experienced recurrent miscarriage and chronic endometritis (*Toth et al., 2018*); however, another stated that any use of antibiotics was not supported by the evidence (*Practice Committee of the ASRM, 2012*).

One recommendation from one CPG related to 'prognosis', including basing prognosis on the number of preceding losses and female age (*ESHRE Early Pregnancy Guideline Development Group, 2017*). One recommendation from one CPG related to assisted reproductive technology and how oocyte donation could be discussed as an alternative treatment in women with low ovarian reserve who have experienced recurrent miscarriage (*Huchon et al., 2016*). One recommendation from one CPG related to 'tailoring' treatment to individual clinical circumstances (*Queensland Clinical Guidelines, 2018*).

Counselling and/or supportive care

Forty-six recommendations from nine CPG were categorized under 'Counselling/supportive care', which includes anything from general supportive care, informational support, to psychological counselling and genetic counselling (Supplementary Table 9 and Supplementary Table 10). Three of these recommendations were categorized under two sub-categories. Thirty-six recommendations did not have the strength of recommendation, quality of evidence ratings, or both, to accompany them, as they were statements, good practice points, or both, within the relevant CPG, or were not specified.

Thirteen recommendations in five CPG (*Practice Committee of the ASRM, 2012*; *ESHRE Early Pregnancy Guideline Development Group, 2017*; *Queensland Clinical Guidelines, 2018*; *Toth et al., 2018*; *Northern Ireland Public Health Agency, 2020*) related to 'risk factors' and providing information, discussing risk factors for recurrent miscarriage with patients, or both. Risk factors primarily included age, successive pregnancy losses and anatomical, endocrine or metabolic and genetic factors, as well as smoking, drug and/or alcohol use, obesity or underweight, diet (including caffeine consumption) and physical inactivity. Eleven recommendations in five CPG (*Practice Committee of the ASRM, 2012*; *HSE, 2016*; *Huchon et al., 2016*; *Toth et al., 2018*; *Northern Ireland Public Health Agency, 2020*) related to 'psychological and/or emotional counselling'. These included acknowledging the emotional effect of pregnancy loss; offering (or highlighting the availability of) counselling and support (psychological and/or emotional) to couples who had experienced recurrent miscarriage, including exploring which support might be best for the woman or couple; and offering access or referral to the Bereavement Specialist Teams and others. Recommendations in this sub-category also encompassed reassurance with repeated consultations with ultrasounds in women who had experienced recurrent miscarriage and the provision of 'tender loving care' for psychological support, despite its efficacy for recurrent miscarriage being unproven. Discussion to identify preferred language or terminology to be used in discussions, and offering additional emotional support if necessary in future pregnancies, were also recommended.

Six recommendations from five CPG (*Practice Committee of the ASRM, 2012*; *ESHRE Early Pregnancy Guideline Development Group, 2017*; *Queensland Clinical Guidelines, 2018*; *Wilson, 2018*; *Northern Ireland Public Health Agency, 2020*) related to 'prognosis' and covered potential for unexplained recurrent miscarriage; emphasising chance for a future successful pregnancy in unexplained recurrent miscarriage; lack of evidence-based treatments for recurrent miscarriage; and the use of prognostic tools to provide an estimate of the subsequent chance of live birth or prognostic information.

Four recommendations from three CPG (*ESHRE Early Pregnancy Guideline Development Group, 2017*; *Wilson, 2018*; *Northern Ireland Public Health Agency, 2020*) related to 'investigations': The *Northern Ireland Public Health Agency (2020)* recommended advising women to not become pregnant before a second blood sample at 12 weeks if a second antiphospholipid test is indicated, whereas *Wilson (2018)* advised cautioning women and couples about investigations (and treatments) that are not evidence-based. The *ESHRE Early Pregnancy Guideline Development Group (2017)* highlighted how it should be made clear from the beginning that investigations do not necessarily lead to treatment options, and that the wishes and views of those who experience recurrent miscarriage should be taken into consideration when discussing investigation options, as well as providing the timeframe for the results and discussion of the results.

Three recommendations from two CPG (*ESHRE Early Pregnancy Guideline Development Group, 2017*; *Northern Ireland Public Health Agency, 2020*) related to 'informational support' and

provision of a regional information leaflet; appropriate information on available support services; and information about benefits and disadvantages of conditions for which treatment is uncertain. Four recommendations from four CPG (*RCOG, 2011*; *Practice Committee of the ASRM, 2012*; *ESHRE Early Pregnancy Guideline Development Group, 2017*; *Northern Ireland Public Health Agency, 2020*) related to 'genetic counselling' and how it should be provided when a genetic factor is identified during investigations.

Two recommendations from two CPG (*ESHRE Early Pregnancy Guideline Development Group, 2017*; *Northern Ireland Public Health Agency, 2020*) related to 'research' and informing those who experience recurrent miscarriage about relevant clinical trials and research. Two recommendations from one CPG (*Northern Ireland Public Health Agency, 2020*) related to 'tailoring' and how supportive care and emotional support should be tailored to each individual or couple. One recommendation from one CPG (*Wilson, 2018*) related to 'treatment' and cautioned against non-evidence-based treatments (covered previously in this section under 'investigations'). One recommendation concerned 'clinician knowledge, skills and expertise' in caring for those who have experienced recurrent miscarriage. It stated the need for individual care, time for discussions, respect, clear and sensitive language, honesty, shared planning kindness and supportive care in the next pregnancy (*ESHRE Early Pregnancy Guideline Development Group, 2017*).

DISCUSSION

We identified 32 CPG for the management, investigation and/or follow-up of recurrent miscarriage within high-income countries, most of which were from the USA. Seven of the identified CPG focused specifically on recurrent miscarriage, recurrent pregnancy loss, or both (including one focused on a specific procedure). Seventeen CPG specifically mentioned a system of rating evidence or quality instrument, or both, used during CPG development, with various systems mentioned; four described a system but did not specifically mention a name. We extracted 373 recommendations, under four categories: structure of care (42), investigations (134), treatment (153), and counselling and/or supportive care (46); with two recommendations classified under two categories. There were varying levels of consensus across the CPG, with some conflicting recommendations, particularly relating to investigations and treatments. Conflicting recommendations across CPG has been noted elsewhere in maternity care (*Zheng et al., 2019*) and in recurrent miscarriage, specifically (*Khalife et al., 2019*).

Of the 17 CPG that defined recurrent miscarriage and/or RPL, nine referred to three or more losses, seven referred to two or more losses, and one referred to two consecutive spontaneous losses or three or more spontaneous losses. This is also reflected in the recent ESHRE CPG, which suggests a definition of two or more, but notes that consensus was not achieved on this within the CPG development group (*ESHRE Early Pregnancy Guideline Development Group, 2017*). The results of a recent systematic review of the current evidence on the prevalence of abnormal test results for recurrent miscarriage among patients with two versus three or more pregnancy losses, were supportive of investigations after two pregnancy losses in couples who had experienced recurrent miscarriage, but the authors stressed the need for additional studies on the prognostic value of test results used in the recurrent miscarriage population (*van Dijk et al., 2020*). The findings of our review also support such calls for more research to inform the development of consensus on both the definition of recurrent miscarriage, including when investigations should be conducted, and terminology used to describe the condition.

Only two of the CPG in our review were recommended for use in their current form (*Bates et al., 2012*; *ESHRE Early Pregnancy Guideline Development Group, 2017*); 29 were recommended for use with modification, whereas one was not recommended. The quality of CPG was quite poor overall, with applicability and editorial independence scoring most poorly. Other reviews, across different topics, have noted poor reporting within domain five (applicability), which addresses factors that may affect a CPG's implementation, the potential effect on resources, and strategies to improve uptake (*Lei et al., 2017*; *Johnston et al., 2018*; *Dans et al., 2020*). To enhance the translation of CPG into practice, more consideration needs to be given to these factors during the development process. Use of the validated ADAPTE framework (*The ADAPTE Collaboration, 2010*) could assist in this regard. Issues with inadequate reporting of conflicts of interest or editorial independence have been noted in many reviews of CPG, in general (*Dans et al., 2020*; *Elder et al., 2020*) as well as in areas such as the prevention and treatment of pregnancy-associated venous thromboembolism (*Zheng et al., 2019*).

Other AGREE II domains, such as stakeholder involvement and rigour of development, also scored quite poorly in our review. A recent review of the methodological quality of local CPG on the identification and management of gestational diabetes highlighted issues with the reporting of those who have undertaken development of the CPG, user involvement, an assessment of resource implications, a listing of conflicts of interests, and external review (*Daley et al., 2019*). In their review, *van de Bovenkamp and Zuiderent-Jerak (2015)* found that Dutch CPG generally scored low on patient participation. Follow-up interviews highlighted that, although some felt that patient participation was beneficial, many felt that it was difficult in practice to accommodate patient experiences within the traditional evidence-based medicine structure of CPG development; when patients became experienced in this area, it often resulted in them losing their credibility as patient representatives (*van de Bovenkamp and Zuiderent-Jerak, 2015*). Lack of patient involvement in CPG development, from a conduct and reporting perspective, potentially limits the relevance, use and beneficial impact of CPG (*Blackwood et al., 2020*). Similar to our review, in a review of CPG in the Philippines (*Dans et al., 2020*), the involvement of a range of relevant external stakeholders, and the incorporation of patient views and preferences was lacking or poorly documented. The involvement and incorporation of the perspectives of a multidisciplinary team in CPG development, and in the formulation of recommendations, will enhance their acceptability and applicability. More significant efforts should be made to incorporate multi-disciplinary perspectives, including the involvement of patients and/or experts by experience, in CPG development.

Other reviews have also highlighted issues concerning rigour of development, e.g. CPG for the management of pregnant women with obesity (*Simon et al., 2020*) and the prevention and treatment of pregnancy-associated venous thromboembolism (*Zheng et al., 2019*). There have been calls to improve the quality of evidence underpinning CPG and the rigour of CPG development, as well as efforts to enhance CPG implementation (*Heneghan et al., 2017*). Our review illustrates that there are clear gaps in the evidence base in relation to many aspects of recurrent miscarriage and emphasizes the need for more research in the area to better inform CPG development and, ultimately, practice. This has also been highlighted by *Vlaanderen (2014)* who argues that evidence underpinning recurrent miscarriage CPG is 'meagre or even absent' and should be addressed to inform better CPG, which in turn will influence their implementation and, ultimately, the care of women and men who experience recurrent miscarriage. Future research and CPG should also consider the needs of those who have multiple medical conditions, a topic that is often neglected within CPG (*Shekelle et al., 2012*). Furthermore, despite tools such as AGREE II to assist with the development process, concerns about quality and reporting of CPG persist. The consistent use of CPG development standards will improve the quality of CPG (*Simon et al., 2020*); these should be incorporated into the routine development and updating of CPG. Our findings are relevant to those involved in the development or updating of CPG, including professional organizations such as the RCOG, whose CPG for recurrent miscarriage was published in 2011. Our findings will also inform the development of a CPG for recurrent miscarriage in the Republic of Ireland, which will be undertaken by members of the research team.

Although CPG are promising and effective tools for improving the quality of care, many are not implemented fully in practice after dissemination; this is also the case for recurrent miscarriage (*Franssen et al., 2007*; *Poddar et al., 2011*; *Van den Boogaard et al., 2011*; *2013*; *Parry, 2018*; *Manning et al, 2020*) and pregnancy loss (*Le Gouic et al., 2017*; *Ijaz et al., 2019*) and reproductive CPG more broadly (*Gameiro et al., 2019*). Barriers to recurrent miscarriage CPG implementation occur at four levels: the CPG; professionals; patients; and organizations (*Van Den Boogaard et al., 2011*). Several barriers and facilitators to CPG implementation have been documented (*Francke et al., 2008*) across a variety of areas, including cancer treatment (*Bierbaum et al., 2020*) and recurrent miscarriage (*Van Den Boogaard et al., 2011*). Barriers can include concern over CPG content and currency, concern about the evidence underpinning CPG (*Gameiro et al., 2019*; *Bierbaum et al., 2020*) and perceptions that the CPG is too complicated for use in practice (*Gameiro et al., 2019*). Others include difficulties complying with patient wishes when they diverge with CPG recommendations (*Van Den Boogaard et al., 2011*); clinician uncertainty and negative perceptions of CPG (*Bierbaum et al., 2020*); organizational and environmental factors, including lack of peer or managerial support and insufficient time and resources (*Francke et al., 2008*; *Bierbaum et al., 2020*); and patient factors, such as cases of co-morbidity (*Francke et al., 2008*; *Bierbaum et al., 2020*). Facilitators of CPG implementation include CPG that are accessible, easy to understand and use and do not require specific resources (*Francke et al., 2008*; *Bierbaum et al., 2020*); endorsement and dissemination of CPG and adequate access to treatment facilities and resources (*Bierbaum et al., 2020*); awareness of CPG and belief in their relevance; belief that CPG support decision making, improve patient care, reduce clinical variation and reduce costs (*Bierbaum et al., 2020*). Effective CPG implementation strategies often have multiple components; the use of one single strategy, such as reminders only or an educational intervention, is less effective (*Francke et al., 2008*). In a recent review of the effectiveness of CPG dissemination and implementation strategies on the behaviour of healthcare professionals and patient outcomes in the context of cancer care, however, the number of strategies used per intervention was not associated with positive outcomes (*Tomasone et al., 2020*).

The present review has several strengths. We conducted a rigorous systematic review of CPG for the investigation treatment and/or follow-up of recurrent miscarriage. One of the strengths of is the rigorous and transparent search strategy used to ensure that all published and unpublished CPG concerning recurrent miscarriage were identified. We evaluated the quality of CPG using AGREE II, a validated international CPG quality assessment tool. Assessments were conducted by three independent reviewers, with methodological, clinical expertise, or both. Several limitations should be acknowledged. First, only CPG published in English were eligible for inclusion. Those written in other languages may exist, e.g. we excluded five full-texts as they were not published in English, which may have otherwise been relevant CPG. Second, the appraisal of CPG was merely based on the information reported by the authors in the CPG or any other material referenced alongside the CPG, e.g. manuals and patient booklets. Furthermore, we categorized guidelines as evidence-based, consensus-based, or both, depending on how the CPG developers described them. We recognize that such distinction is not advised given that both require interpretation of the evidence and consensus (*Djulbegovic and Guyatt, 2019*). Some items in AGREE II maybe have been assigned a low score as the authors did not report the necessary information in their CPG or related documentation to inform the scoring, even though they could have undertaken the required processes during CPG development. Third, AGREE II is a tool used to access the quality of the CPG development instead of the quality of the evidence. Recommendations from high-score CPG might be based on weak evidence and *vice versa*. The AGREE II focuses primarily on methodological quality and internal validity of CPG, with limited attention on the external validity of the recommendations (*Brouwers et al., 2020*). We did not assess the quality of CPG recommendations within this systematic review. *Brouwers et al. (2020)* recently developed the Appraisal of Guidelines Research and Evaluation–Recommendations Excellence (AGREE-REX) tool to appraise the quality of CPG; future work could apply this tool to the identified CPG.

In conclusion, we identified 32 CPG for recurrent miscarriage in high-income countries. There is a need to build the evidence base for recurrent miscarriage, develop consensus on the definition of recurrent miscarriage and terminology used to describe the condition, and to improve the quality

of evidence underpinning CPG and the rigour of their development. This will influence CPG implementation and, ultimately, the care of women and men who experience recurrent miscarriage. More significant efforts should also be made to incorporate multi-disciplinary perspectives, including the involvement of those who experience recurrent miscarriage, in CPG development.

DATA AVAILABILITY STATEMENT

In the protocol, we stated that we would search CINAHL Complete (EBSCOhost; 1994); we searched Cinahl Plus With Full Text, due to access issues. We also searched the websites of two additional professional bodies: HSC Public Health Agency and Health Service Executive National Women and Infants Health Programme.

The data underlying this article are available on Open Science Framework (*Hennessy et al., 2021*).

ACKNOWLEDGEMENTS

This work was funded by the Health Research Board (HRB) Ireland (ILP-HSR-2019-011). The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript. We wish to thank Donna Ó Doibhlin, Medicine and Health Sciences Liaison Librarian at University College Cork for her assistance when developing the search strategy for this review. We would also like to thank the RE:CURRENT Project Research Advisory Group for their strategic direction, advice and guidance concerning this research.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.rbmo.2021.02.014.

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Received 17 November 2020; received in revised form 22 February 2021; accepted 23 February 2021.