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SYSTEMATIC REVIEW

The definition of unexplained infertility: A systematic review

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Abstract

Background: There is no consensus on tests required to either diagnose unexplained infertility or use for research inclusion criteria. This leads to heterogeneity and bias affecting meta-analysis and best practice advice.

Objectives: This systematic review analyses the variability of inclusion criteria applied to couples with unexplained infertility. We propose standardised criteria for use both in future research studies and clinical diagnosis.

Search strategy: CINAHL and MEDLINE online databases were searched up to November 2022 for all published studies recruiting couples with unexplained infertility, available in full text in the English language.

Data collection and analysis: Data were collected in an Excel spreadsheet. Results were analysed per category and methodology or reference range.

Main results: Of 375 relevant studies, only 258 defined their inclusion criteria. The most commonly applied inclusion criteria were semen analysis, tubal patency and assessment of ovulation in 220 (85%), 232 (90%), 205 (79.5%) respectively. Only 87/220 (39.5%) studies reporting semen analysis used the World Health Organization (WHO) limits. Tubal patency was accepted if bilateral in 145/232 (62.5%) and if unilateral in 24/232 (10.3%). Ovulation was assessed using mid-luteal serum progesterone in 115/205 (56.1%) and by a history of regular cycles in 87/205 (42.4%). Other criteria, including uterine cavity assessment and hormone profile, were applied in less than 50% of included studies.

Conclusions: This review highlights the heterogeneity among studied populations with unexplained infertility. Development and application of internationally accepted criteria will improve the quality of research and future clinical care.

KEYWORDS
definition, heterogeneity, inclusion criteria, unexplained infertility

1 | INTRODUCTION

Infertility is defined as the inability to conceive a pregnancy, usually for a time period of at least 12 months although some absolute diagnoses negate the need for a time period of trying to conceive. Unexplained infertility (sometimes referred to as subfertility) is a diagnosis of exclusion for couples who fail to conceive despite regular unprotected intercourse and who do not fit the criteria for diagnosis of male factor infertility, oligo/anovulatory infertility or anatomical concerns such as blocked fallopian tubes, endometriosis, uterine cavity defects or cervical/vaginal obstruction. It is a diagnosis applied to up to one-third of heterosexual couples attending tertiary fertility units.[1] The inability to apply a specific infertility diagnosis is clearly related to the depth of testing applied to couples and rather than unexplained infertility being a true

diagnosis it can be seen as an exclusion of proven pathology and an acknowledgement that generic rather than specific treatment strategies should be applied. Unexplained infertility can be either primary or secondary and it is possible that the underlying contributory factors may differ between these two. There is little evidence on how the aetiology differs and therefore they have been included together for the purposes of this paper, as they are in most research.

The biggest debate in the treatment of unexplained infertility is the decision between expectant management, stimulated intrauterine insemination or in vitro fertilisation as a first-line treatment option.[2]

The most recent systematic review and meta-analysis stated that 'the wide field of definitions of unexplained infertility poses significant challenges in conducting research in this field'.[3]

1.1 | Existing definitions

The existing guidelines vary hugely in their criteria and in the specificity of how they confirm positive and negative findings, as detailed in Table 1.

1.2 | Diagnostic tests

When applying a chosen definition, the availability or selection of diagnostic tests by individual centres may further contribute to the variability of diagnosis. Individual clinics and healthcare systems will have differing panels of standard tests offered to couples and different 'normal' laboratory standards to compare results to. More detailed testing will probably uncover subtle pathologies that lead to alternative diagnoses. The reported prevalence of unexplained infertility is therefore subjective and highly variable, as it is dependent on the testing criteria and testing methodologies used.[1,4–6]

Adhering to a stricter set of diagnostic criteria may lead to more invasive and expensive testing for affected couples and is likely to lower the reported prevalence of unexplained infertility.

1.3 | Rationale

The lack of a universal definition for unexplained infertility is a barrier to the development of a best-practice diagnosis and treatment plan for the condition. Heterogeneity of inclusion criteria leads to heterogeneous study populations. This in turn reduces the quality of the research on this topic through the introduction of significant bias. This has implications for research and the clinical diagnosis and treatment of affected couples.

1.4 | Objectives

This systematic review aims to analyse the inclusion criteria used for recruiting couples with unexplained infertility into

TABLE 1 Current definitions of unexplained infertility.

Definition source	Proof of ovulation	Semen analysis	Tubal patency	Other tests	Additional information
ICMART (International Committee for Monitoring Assisted Reproductive Technologies)	'Apparently normal ovarian function' (no testing specified)	'Apparently normal testicular function, genitourinary anatomy and a normal ejaculate' (No testing or laboratory ranges specified)	'Apparently normal… fallopian tubes' (No testing specified)	'Apparently normal… uterus, cervix, and pelvis with adequate coital frequency'	'The potential for this diagnosis is dependent upon the methodologies used and/or those methodologies available'[7]
NICE (National Institute for Health and Care Excellence)	Ovulation as indicated by regular menses and by measuring luteal serum progesterone	Semen analysis should be measured according to WHO standards. One normal result is accepted but an abnormal result should be repeated	Tubal patency testing with HSG or HyCoSy is recommended unless pelvic pathology is likely, in which case laparoscopy may be superior	Prolactin measurement is not recommended in women with regular ovulatory cycles and thyroid function testing is reserved for symptomatic women only	Unexplained infertility is a diagnosis for couples where 'no reason has been found for your fertility problems'[8]
ACOG (American College of Obstetrics and Gynecology)	'Should have evidence of ovulation' (no testing specified)	A normal semen analysis (no laboratory ranges specified)	'Should have evidence of tubal patency' (no testing specified)		
ESHRE (European Society of Human Reproduction and Embryology)	Investigations should include assessment of ovulation (no testing specified)	Semen analyses (no laboratory ranges specified)	Assessment of… normal tubal patency (no testing specified)		Multiple other factors play a role for unexplained infertility

Abbreviations: HSG, hysterosalpingogram; HyCoSy, hysterosalpingo-contrast-sonography.

clinical studies. These inclusion criteria will be compared, and the results will used to illustrate the level of heterogeneity between study populations.

2 | METHODS

A systematic review was performed and reported in accordance with updated PRISMA guidance 2020.[7] A clear review protocol was developed and submitted to PROSPERO (see Appendix S1). However, the study did not meet the criteria for registration on PROSPERO because no true data were extracted. The review is registered in the Open Science Forum at https://osf.io/registries.

2.1 | Eligibility criteria

Any primary research (observational or interventional trials or studies) recruiting heterosexual couples with unexplained infertility was eligible. Included studies were available in full text and published in English. Studies were excluded that studied male idiopathic infertility, or that were secondary analyses of trials, case reports or literature reviews and opinion pieces.

2.2 | Information sources

Online databases MEDLINE in-Process and other non-indexed citations and Cumulative Index to Nursing and Allied Health Literature (CINAHL) were searched from inception to 24 November 2022.

2.3 | Search strategy

Both databases were searched using the Boolean search terms 'unexplained infertility' OR 'idiopathic infertility'. The search terms were broad to ensure that all relevant studies were identified. Results were filtered to include only papers published in English.

2.4 | Selection process

Two authors (CR and JD) manually screened all titles for relevance. Abstracts were then screened for the same criteria and to ensure that full papers were accessible. Full papers were obtained and screened thoroughly through assessment of their materials and methods sections, inclusion/exclusion criteria and results. Disagreements between authors were settled through discussion and where necessary, a third author (PB) was consulted. Three authors (CR, JD, DQ) screened all papers at the full-text stage, checking for suitability and documenting the inclusion criteria described within the articles. The search protocol is attached as Appendix S1.

2.5 | Data collection process

A list of included papers was then recorded in rows in an Excel spreadsheet and papers were accessed to obtain the list of inclusion criteria used for their unexplained infertility group. The exact wording for the inclusion criteria was copied from the materials and methods section of each paper. This was then interrogated and the broad categories, specific testing methodologies and laboratory reference ranges mentioned were individually recorded in the appropriate columns of the spreadsheet.

2.6 | Data synthesis

Each column was assessed to investigate the number of papers that included the distinct category of testing, individual testing methodologies and or accepted reference ranges. Simple numbers and percentages were recorded because no statistical analysis was appropriate. A Venn diagram and heatmaps were created to display the results visually and to compare the frequency of different categories tested simultaneously.

There was no patient or public involvement in the development or execution of this study.

3 | RESULTS

3.1 | Study selection

The database search identified 751 papers. Of these, 85 duplicate papers were excluded, leaving 666 papers. After title and abstract review, 132 papers were deemed not to be relevant to unexplained infertility. A further 105 papers were excluded because their full text was not available. Three investigators then searched the full texts of the remaining papers, of which a further 54 papers were excluded as they were either deemed not relevant to unexplained infertility or were not primary research. Of the remaining 375 papers, 117 did not classify a definition of unexplained infertility. As a result, a total of 258 primary research papers with full text available were included.[8–265] These results have been documented in a PRISMA flowchart (Figure 1).

3.2 | Included studies

The types of included studies were observational studies, randomised controlled trials and cohort studies investigating many different aspects of infertility including treatment options, aetiological factors, impact of the condition and long-term outcomes.

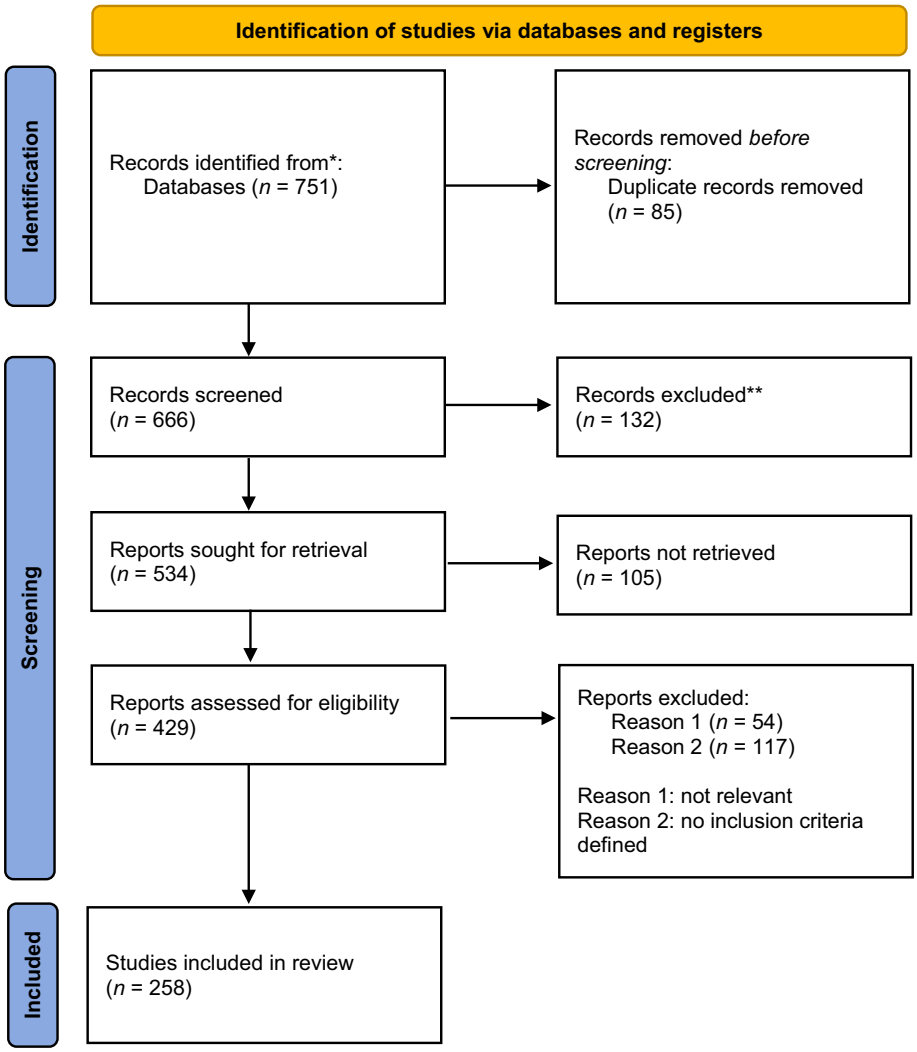

FIGURE 1 PRISMA search results flowchart.

3.3 | Results of syntheses

3.3.1 | Semen analysis

Semen analysis was included in the criteria in 220/258 (85.3%) papers. Of these, 87/220 (39.5%) described using WHO criteria to assess the results (different versions of these criteria were used depending on the age of the paper), 68/220 (30.9%) mentioned applying different reference ranges but many did not specify these and the other 65/220 (29.5%) did not specify how semen analysis was graded.

3.3.2 | Tubal patency

Patent fallopian tubes were required by 232/258 (89.9%) studies as an inclusion criterion. Of these, 145/232 (62.5%) specified bilateral patency as a requirement. Unilateral patency was accepted in 24/232 (10.3%) and 63/232 (27.2%) did not specify. Methods for demonstrating patency included hysterosalpingogram (HSG) (36/232, 15.5%), laparoscopy (40/232, 17.2%), a combination of either (68/232, 29.3%) or both (53/232, 22.8%) of these or hysterosalpingo-contrast-sonography (HyCoSy) (2/232, 0.8%). Thirty-three of the 232 (14.2%) papers did not specify an imaging modality.

3.3.3 | Ovulatory function

Evidence of regular ovulation was required by 205/258 (79.5%) of the included papers. Of these, 33/205 (16.1%) did not specify a method of assessment, 84/205 (40.9%) accepted one method to assess this and 91/205 (44.4%) accepted more than one method of assessment.

Of the papers testing ovulatory function, mid-luteal serum progesterone levels were accepted by 115/205 (56.1%), 87/205 (42.4%) required regular cycles (patient-reported) and 34/205 (16.6%) used basal body temperature pattern assessment. Other methods mentioned by a minority of papers included endometrial biopsy (33/205, 16.1%) and ultrasound follicular tracking (22/205, 10.7%). Serum or urinary luteinising hormone (LH) levels were accepted as methods of ovulation detection in 4/205 (2%) papers; however, a further

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50/205 (2.4%) papers measured LH without specifying that this was used for detection of ovulation.

3.3.4 | Hormone profile

'Normal' endocrine profiles were specified as required for inclusion in 114/258 (44.2%) studies. of which 103/114 (90.4%) specified which hormones were evaluated. FSH and prolactin were measured in 74/114 (64.9%), follicle-stimulating hormone, 24/114 (21.1%) measured estradiol and 56/114 (49.1%) measured thyroid function. Anti-müllerian hormone was measured in 7/114 (6%) studies, inhibin B in 1/114 (0.8%), testosterone in 17/114 (14.9%), dehydroepiandrosterone in 10/114 (8.7%) and sex-hormone binding globulin in 4/114 (3.5%).

3.3.5 | Uterine cavity assessment

Assessment of the uterine cavity was only mentioned in 121/258 (46.9%) of the included studies, 62.8% (76/121) of these using HSG to assess the cavity, other methods mentioned include ultrasound (31/121, 25.6%) or hysteroscopy (18/121, 14.8%).

3.3.6 | Additional tests

A small proportion of studies required results from less common tests with 54/258 (20.9%) performing a post-coital test, 1 study assessed DNA fragmentation (0.4%) and 6/258 (2.3%) studies assessed anti-sperm antibody levels.

Only 16/258 (6.2%) papers required either exclusion of or evidence of only minimal endometriosis. Six of 258 papers excluded women with a history of sexually transmitted infection or pelvic inflammatory disease and 7/258 excluded those specifically with a history of chlamydia.

The heatmaps (Figures 2 and 3) demonstrate visually the frequency with which different categories were tested simultaneously, expressed as percentages of the total 258 papers and number of papers. The most common combinations of tests were tubal patency and semen analysis, semen analysis and ovulation, and tubal patency and ovulation. The low incidence of uterine cavity and hormone profile assessment among the included studies is clearly illustrated.

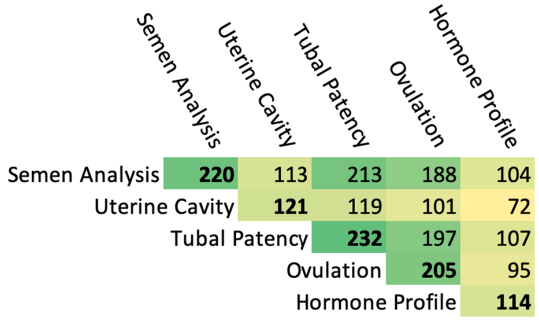

FIGURE 2 Heatmaps displaying frequency of test combinations (*n*). Key: S: semen analysis, C: uterine cavity, T: tubal patency, O: ovulation, H: hormone profile.

3.4 | Additional criteria

Age and body mass index (BMI) are both factors that are known to affect fertility, especially in women. Neither of these contribute to the diagnosis of unexplained infertility, but they are often applied as inclusion criteria for clinical trials, as is the length of time trying to conceive; these factors help to define the populations studied.

3.4.1 | Time to conceive

Only 35.7% (92/258) of papers specified duration of infertility. Timescales varied from 1 year (46/92, 50%), 2 years (34/92, 37.1%) or 3 years (12/92, 13%).

3.4.2 | Age

Of the 258 papers, 83 (32.2%) applied a limit for female age as an inclusion criterion. An upper age limit was applied in 82/83 (98.8%) (Table 2) and 39/83 (47.6%) specified a lower age limit (Table 3).

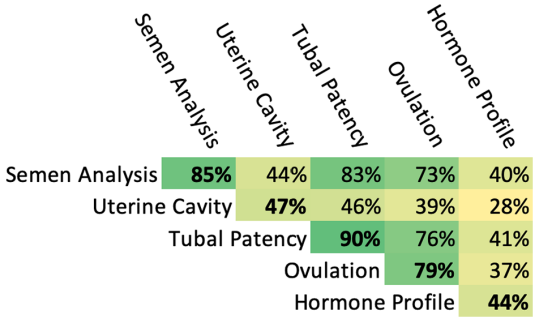

FIGURE 3 Heatmaps displaying frequency of test combinations (%). Key: S: semen analysis, C: uterine cavity, T: tubal patency, O: ovulation, H: hormone profile.

TABLE 2 Applied upper age limits of unexplained infertility.

Female upper age limit (years)	No. of studies applying this limit
30	2
35	17
36	3
37	7
38	12
39	8
40	28
42	5

TABLE 3 Lower age limits of unexplained infertility.

Female lower age limit (years)	No. of studies applying this limit
17	1
18	23
20	11
25	4

TABLE 4 Body mass index (BMI) upper limits of unexplained infertility.

Upper limit for female BMI (kg/m^2)	No. of studies applying this limit
25	2
26	1
28	2
29	1
30	16
32	1
35	6

TABLE 5 Body mass index (BMI) lower limits of unexplained infertility.

Lower limit for female BMI (kg/m^2)	No. of studies applying this limit
18	5
19	5
20	1
25	1

3.4.3 | Body Mass Index

Body mass index limits were applied in the inclusion criteria of 30/258 (11.6%) studies (Table 4). Of these, 29 applied an upper limit (11.3%) (Table 4), 12 applied a lower limit (4.7%) (Table 5) and one did not specify what BMI limits were used to assess eligibility for recruitment (0.4%).

3.4.4 | Combined Results

When combining the results to assess the frequency in which different categories were tested simultaneously, the pairing of categories are displayed in heatmaps (Figures 2 and 3) both as absolute numbers and as percentages of the total number of studies. A venn diagram (Figure 4) displays the combinations of the most common 4 testing categories and the frequencies with which these were tested in the same studies.

4 | DISCUSSION

4.1 | Main findings

This review demonstrates substantial heterogeneity in the diagnostic criteria used to define unexplained infertility and methods of assessment for each criterion used. In 117/375 (31.2%) papers that were assessed as full texts, no definition of unexplained infertility was described. Of note, only 35.7% (92/258) of studies required all four of semen analysis, tubal patency, ovulation and uterine cavity assessment to be assessed as a minimum standard for inclusion or diagnosis with unexplained infertility (Figure 4).

The demonstrated heterogeneity reduces the impact of any meta-analyses comparing treatment efficacies for this diagnosis by introducing significant 'misclassification bias'.[266,267] This is defined as 'sampling bias which occurs when a disease of interest is poorly defined, when there is no gold standard for diagnosis of the disease'.[266] This bias is acknowledged by the authors of many published meta-analyses on unexplained infertility, which state heterogeneity as a major limitation of their findings.[268,269]

4.2 | Interpretation of results

4.2.1 | Semen analysis

Semen analysis should be reported according to an international set of laboratory standards. Semen analyses in the included studies were either assessed against the current WHO criteria (39.5%) or local criteria (29.5% of papers did not specify criteria). The WHO criteria (and the associated laboratory manual to ensure standardisation of practice) are the most widely used and only available international criteria. A paper published by Gelbaya et al. analysing the evidence behind different diagnostic tests for unexplained infertility suggested that semen analysis should be performed at least twice to reduce the rate of false positives in diagnosing male factor infertility, as supported by Opsahl et al.[270,271]

4.2.2 | Tubal patency testing

For tubal patency testing, there is some disagreement regarding the need for unilateral or bilateral patency before unexplained infertility can be diagnosed. Bilateral tubal patency was a criterion in 62.5% of studies that mentioned tubal patency, 10.3% accepted unilateral and the remainder did not specify. Many of the common causes of unilateral tubal blockage, damage or malposition, including endometriosis, infection (chlamydia/gonorrhoea) or iatrogenic adhesions (damage during pelvic surgery), could also affect the contralateral tube. This means anyone with previous unilateral damage may still be affected by tubal factor infertility despite apparent patency on imaging.

The methodologies for assessing tubal patency varied between studies. Laparoscopic chromo-pertubation and HSG are the most used modalities in the included studies (84.9%). Although HyCoSy has been a recognised technique with good diagnostic sensitivity and specificity[271–274] since the early 1990s,[275] its uptake in clinical practice has grown

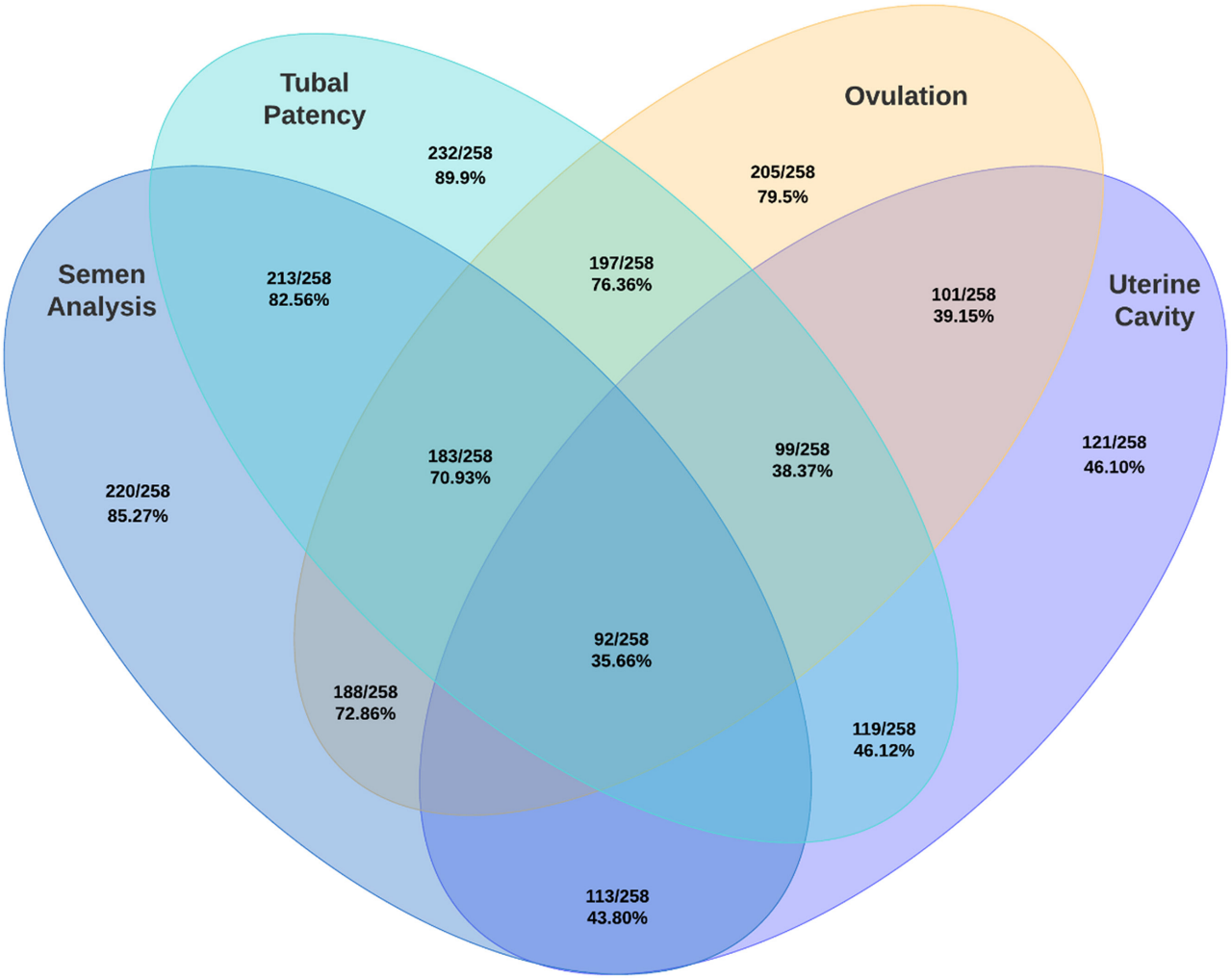

FIGURE 4 Venn diagram demonstrating the frequency with which the four major categories were assessed individually and in combination with each other.

in the last decade. Only 0.8% of the included studies used HyCoSy; this was probably related to the age of many of the included papers. Three-dimensional HyCoSy has a diagnostic accuracy for detecting tubal patency of up to 90%[276] and can also be used for assessing the uterine cavity and for the detection of endometrial polyps, leiomyomas and intrauterine adhesions.[272] Gelbaya et al.'s paper[271] suggested that tubal patency testing with HSG or HyCoSy may miss between 21% and 68% of abnormalities subsequently seen at laparoscopy—usually related to undiagnosed endometriosis.[277–279] Meta-analysis has shown that HyCoSy is comparable to laparoscopy and superior to HSG for diagnosing tubal blockage.[280]

The time to conceive after tubal patency test was not described in any of the inclusion criteria. There is some evidence that tubal patency testing, especially HSG, may improve the chances of conception,[281–283] but this is not conclusive and further research is required. It is beyond the scope of this paper to assess whether time trying to conceive after tubal patency test is a factor required in the definition of unexplained infertility.

4.2.3 | Ovulation assessment

Research regarding the efficacy of the various methods of ovulation confirmation is lacking and many studies supporting the various methods come from small and often uncontrolled studies.[284]

In 56.1% of the studies requiring proof of ovulation, mid-luteal serum progesterone levels were used for this purpose. Regular menses was proof of ovulation in 42.4% and 16.6% used basal body temperature testing. The European Society of Human Reproduction and Embryology (ESHRE) guidance on unexplained infertility supported the use of urinary LH monitoring with an accuracy and agreement with ultrasound findings of 97%–100%.[285–289] In contrast they reported the accuracy of basal body temperature monitoring

and mid-luteal serum progesterone to be between 70% and 80%. A systematic review published in 2017 had conflicting findings and reported mid-luteal serum progesterone testing (89.6% comparative accuracy), urinary LH either with simple test strips (97%) or digital interpretation kits (95.8%–97%) or urinary pregnanediol-3-glucuronide testing (92.2%).[284]

The evidence supports the use of transvaginal ultrasound tracking as the reference standard[285]. The evidence for using regular menses is mixed[290–292] and basal body temperature testing is outdated and has been shown to be inaccurate.[293–295] However, despite this, the ESHRE guidance suggests that testing for ovulation detection in women with regular menstrual cycles is not necessary and if testing is required, ultrasound follicular tracking, urinary LH measurement or mid-luteal serum progesterone testing are suggested. They do not support the use of basal body temperature.

4.2.4 | Hormone profile

Hormone profiling is mentioned by 44.2% of studies; however, the panel of hormones evaluated varied hugely and the evidence for the impact of abnormal results on female fertility in the presence of ovulation is limited. Abnormal thyroid hormones and prolactin can certainly impact on ovulatory function but in the presence of ovulatory cycles assessed by the methods mentioned above, the relevance of these tests is questionable. Increased prolactin levels have been implicated in endometriosis-related infertility, but there is little evidence that hyperprolactinaemia in the presence of ovulatory cycles affects fertility.[296,297]

4.2.5 | Uterine cavity assessment

Uterine cavity assessment was required in 46.9% of included studies. As tubal patency testing is likely to be performed using HSG or HyCoSy, imaging of the uterine cavity is performed concurrently. Standard fertility investigations commonly include tubal patency and pelvic ultrasound, both of which should be possible opportunities to assess the cavity without extra risk or financial cost. The evidence for the impact of endometrial polyps, septae and unusual cavity shapes on fertility is mixed. However, submucosal fibroids are associated with reduced fecundity[298,299] and should be excluded.

4.2.6 | Category combinations

To visually display the frequency of combinations of different categories of testing, we have displayed the results in both heatmaps (Figures 2 and 3) which display how likely two different categories were to both be tested, and a Venn diagram (Figure 4) to display the frequency of simultaneous testing of the most common 3 or 4 categories.

4.2.7 | Non-diagnostic inclusion criteria

Time to conceive

Time to conceive is important to consider in any diagnosis of infertility because it is acknowledged that conception in humans is inefficient and even in the absence of any problems it will take many couples some time to become pregnant. Including a specified minimum time that couples have been trying to conceive is therefore appropriate before applying a diagnosis of infertility.

Time limits for trying to conceive were specified in 35.7% of studies included in this review. Of these, 50% specified 1 year and 37.1% specified 2 years.

Over 84% of couples with no obvious pathology will conceive within 12 months[300–303] with several studies quoting rates of more than 80% in only 6 months.[303,304] It can be concluded therefore that the remaining 10%–15% have a degree of subfertility.[305] WHO,[306] the International Committee Monitoring Assisted Reproductive Technologies[307] and the American Society of Reproductive Medicine[308] all define infertility after a minimum of 1 year trying to conceive. Of the studies that referred to time to conceive in their inclusion criteria, 46.5% also adhered to a minimum of 1 year.

Age and ovarian reserve

There is huge variation in the age at which ovarian function and reserve decline in women, and a relationship between ovarian reserve and oocyte quality.[309,310] There is no evidence that reducing the ovarian reserve impacts the likelihood of spontaneous conception, but oocyte quality will undoubtedly play a role because of the likelihood of associated aneuploidy. Discriminating between age-related infertility and unexplained infertility is complex.[5] The incidence of infertility overall rises with age, and it is not possible to determine whether this is solely due to increasing rates of aneuploidy in the population of couples with no other diagnosed cause for infertility.

This is reflected in the fact that only 83/258 papers included in this systematic review included age limits as inclusion criteria. The most applied upper age limit was 40 years. Ovarian reserve testing is usually reserved for women undergoing fertility treatment to manage expectations and plan ovarian stimulation regimens.

Age limits may be appropriate for the inclusion criteria for clinical trials as age affects fertility overall and therefore populations studied should be comparable.

Body mass index

The upper limit specified in 52% of the studies that set an upper BMI limit was 30 kg/m^2. The evidence that supports BMI directly impacting fertility is not of high enough quality to support the use of BMI as a diagnostic criterion, but it is useful as an inclusion criterion for research studies, as with female age, to ensure that population demographics are comparable.

TABLE 6 Recommended inclusion criteria for future studies.

Category	Accepted methodologies or reference ranges
Semen analysis	Graded according to current WHO criteria
Tubal patency	Bilateral patency as assessed by HSG, HyCoSy or laparoscopy
Ovulatory status	Positive, confirmed by ultrasound follicular tracking, urinary LH testing, regular cycles, mid-luteal serum progesterone or PDG testing
Uterine cavity assessment	Normal cavity seen on two-/three-dimensional ultrasound or HSG/HyCoSy

Abbreviations: HSG, hysterosalpingogram; HyCoSy, hysterosalpingo-contrast-sonography; LH, luteinising hormone; PDG, pregnanediol-3-glucuronide.

4.3 | Strengths and limitations

The strengths of this study are that no comparable study has ever been published before and the broad search terms allowed inclusion of a large number of studies.

The major limitation of the study was that we were not able to contact the authors of every paper to confirm details where they had not specified inclusion criteria or testing methodologies, although it is possible that explicit inclusion criteria were applied to these studies. We also excluded papers not published in the English language, which may have led to a bias as it may not completely represent the full spectrum of international research. However, the authors feel that the search was comprehensive and further exhaustive searches would not substantially change the findings. We did not assess the quality of each included study. This however would not impact the objective outcomes studied or the quality of the review because the review did not aim to assess the intervention for which the study was primarily conducted.

4.4 | Implications of results

A defined set of criteria would benefit future clinical trials to define unexplained infertility and act as a benchmark to standardise populations, thereby improving the quality of research. This would benefit affected couples too with higher certainty of diagnosis and appropriate treatment options with a stronger evidence base.

We recommend that further research is undertaken to develop a set of international standards agreed for diagnosing this condition in future.

As an interim measure to guide research until an international definition is agreed, the results of this study suggest the following inclusion/diagnostic criteria, which support the current National Institute for Health and Care Excellence guidance with the addition of uterine cavity assessment and also support the suggestions made in the recent draft ESHRE guidance on the definition of unexplained infertility (due to be published in 2023) (Table 6).

To ensure homogeneity of research study populations and estimate the true effect of the intervention studied, age/BMI limits may be applied, or their effect taken into consideration in data analysis. The following limits were the most commonly used in the included studies:

Upper age limit of 40 years.
Upper BMI limit of 30 kg/m^2.
Trying to conceive for at least 1 year of regular penetrative intercourse.

5 | CONCLUSION

There is no single universally accepted definition of unexplained infertility. Primary research studies that recruit couples with unexplained infertility use widely variable inclusion criteria and often do not define their criteria at all. The heterogeneity between populations studied, which this paper illustrates, detracts from the utility of the research and the ability for meaningful meta-analysis, which is an obstacle in developing a best-practice plan for treating affected couples. It is important in future for all studies to publish their inclusion and eligibility criteria as per CONSORT[311] for randomised controlled trials and other equator network guidance for other study types.[312] Applying one universal diagnostic set of criteria for unexplained infertility will allow future research to be more powerful and for meta-analysis of relevant trials to be more meaningful. This will benefit both the clinical community with regards to validating the results of research trials and the affected couples, who will feel they have been adequately and appropriately investigated and diagnosed.

AUTHOR CONTRIBUTIONS
The idea for the project was conceived by CR and discussed with PB, RH, KSK, and EC. The protocol and plan were made by CR, PB and RH. Literature searches were performed by CR and JD. Data extraction was performed by DQ, JD and CR. Data analysis was performed by DQ, ER and CR. The manuscript was drafted by CR with editing and input from AB, EC, RH, KSK and PB.

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No-one other than the named authors were involved with this project.

FUNDING INFORMATION
No funding was received for this review.

CONFLICT OF INTEREST STATEMENT
None declared.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

ETHICS APPROVAL

No ethical approval was required for this study.

REGISTRATION

This systematic review was not eligible for PROSPERO registration as no true data were being extracted. It is registered at https://osf.io/registries.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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