RESEARCH PAPER

Infertility: An Updated Review of Etiology, Diagnostic Evaluation and Emerging Risk Factors

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ABSTRACT

Background: Infertility is a major global reproductive health problem affecting individuals and couples across diverse populations. It is defined as failure to achieve pregnancy after 12 months or more of regular unprotected sexual intercourse and may result from female factors, male factors, combined abnormalities, or unexplained causes. Increasing maternal age, delayed childbearing, obesity, metabolic disorders, sexually transmitted infections, lifestyle-related factors, environmental exposures, and changing reproductive patterns have contributed to the growing complexity of infertility.

Objective: This review aims to provide an updated overview of the major etiological factors responsible for male and female infertility, contemporary approaches to diagnostic evaluation, established and emerging risk factors, and recent advances in reproductive medicine.

Methods: A narrative review of recent literature was undertaken focusing on publications addressing the epidemiology, etiology, diagnostic evaluation, reproductive infections, endocrine and metabolic disorders, lifestyle factors, environmental exposures, oxidative stress, reproductive tract microbiome, genetic factors, and emerging diagnostic technologies in infertility. Recent international recommendations and guidelines, including those from the World Health Organization and major reproductive medicine societies, were considered.

Results: Infertility is a multifactorial disorder involving abnormalities of ovulation, ovarian reserve, tubal patency, uterine anatomy, endometriosis, spermatogenesis, sperm function, endocrine regulation, and genetic factors. Advancing reproductive age remains one of the strongest predictors of declining fertility. PCOS, obesity, diabetes, thyroid dysfunction, endometriosis, sexually transmitted infections, genital tuberculosis, smoking, alcohol consumption, psychological stress, and sedentary lifestyle may further impair reproductive potential. Increasing evidence suggests that environmental pollutants, endocrine-disrupting chemicals, oxidative stress, epigenetic mechanisms, and alterations of the vaginal and endometrial microbiome may contribute to infertility. Conventional investigations, including semen analysis, assessment of ovulation, ovarian reserve testing, ultrasonography, and evaluation of tubal patency, remain the foundation of diagnosis. Emerging approaches involving sperm DNA fragmentation testing, reproductive genetics, microbiome profiling, metabolomics, proteomics, and artificial intelligence-assisted assessment are expanding the diagnostic landscape, although several require further validation before routine clinical implementation.

Conclusion: Infertility should be approached as a complex condition affecting both partners and requiring individualized, evidence-based evaluation. Early identification of modifiable risk factors, prevention of reproductive tract infections, healthy lifestyle practices, and timely assessment can improve reproductive outcomes. Future infertility care is likely to increasingly integrate conventional clinical evaluation with molecular diagnostics, reproductive microbiology, genetics, artificial intelligence, and personalized medicine. Ensuring affordable, equitable, and patient-centered access to infertility services should remain a major global reproductive health priority.

Keywords: Infertility; Female infertility; Male infertility; Reproductive health; Ovulatory dysfunction; Ovarian reserve; Semen analysis; Endometriosis; Reproductive microbiome; Environmental risk factors; Assisted reproductive technology; IVF.

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INTRODUCTION

Infertility is a major reproductive health disorder affecting individuals and couples across all geographical, socioeconomic, and demographic groups. It is defined as the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse and may arise from abnormalities affecting either partner, both partners, or from causes that remain unidentified despite conventional evaluation. Infertility may be classified as primary, when pregnancy has never previously occurred, or secondary, when conception has occurred at least once in the past. The condition is increasingly recognized not merely as a reproductive problem but as an important public health concern because of its substantial psychological, social, economic, and interpersonal consequences. The World Health Organization (WHO) estimates that approximately one in six people of reproductive age experience infertility during their lifetime, corresponding to an estimated global lifetime prevalence of approximately 17.5%. Importantly, infertility affects populations in high-, middle-, and low-income countries, demonstrating that it is a global rather than geographically restricted health problem [1].

The biological basis of infertility is complex and involves multiple interacting factors. In women, important causes include ovulatory dysfunction, diminished ovarian reserve, advancing reproductive age, tubal and peritoneal disease, endometriosis, uterine abnormalities, endocrine disorders, and genetic conditions. In men, infertility may result from abnormalities in sperm production, concentration, morphology, motility, sperm transport, endocrine regulation, sexual function, or genetic abnormalities. In a considerable proportion of couples, abnormalities may coexist in both partners, while some couples remain without a clearly identifiable cause after standard investigations and are categorized as having unexplained infertility [2]. This multifactorial nature makes infertility evaluation fundamentally different from the investigation of a single-organ disease and necessitates a comprehensive assessment of both partners.

Female reproductive potential is strongly influenced by age. The number and quality of ovarian follicles progressively decline with advancing age, while the risk of chromosomal abnormalities in oocytes increases. Consequently, female age is considered one of the most important predictors of fecundity. Delayed marriage and postponement of childbearing because of higher education, professional commitments, economic considerations, changing social structures, and personal preferences have increased the proportion of individuals attempting conception at older reproductive ages. Therefore, increasing reproductive age has become an important consideration in contemporary infertility counseling and evaluation [3].

Ovulatory dysfunction represents one of the most common causes of female infertility. Disorders of the hypothalamic-pituitary-ovarian axis can result in anovulation or oligo-ovulation and may occur in association with polycystic ovary syndrome (PCOS), hyperprolactinemia, thyroid dysfunction, hypothalamic dysfunction, excessive exercise, inadequate energy availability, obesity, or systemic disease. PCOS is particularly important because it combines reproductive and metabolic abnormalities, including hyperandrogenism, insulin resistance, altered follicular development, and chronic anovulation. Recognition and appropriate management of ovulatory disorders are therefore essential components of infertility care [4].Diminished ovarian reserve is another important consideration, particularly among women of advancing reproductive age and those with previous ovarian surgery, chemotherapy, radiotherapy, or other risk factors for premature loss of ovarian function. Anti-Müllerian hormone (AMH), antral follicle count (AFC), and basal follicle-stimulating hormone (FSH) with estradiol are commonly used to assess ovarian reserve. However, ovarian reserve tests primarily provide information about the expected ovarian response to stimulation and should not be interpreted as direct measures of natural fertility. Current recommendations emphasize that ovarian reserve testing should be used as an adjunct to infertility

evaluation rather than as a universal screening test in women without infertility [5].

Tubal and peritoneal abnormalities constitute another major category of female infertility. Normal fallopian tube function is essential for the transport of sperm, fertilization, and movement of the early embryo toward the uterine cavity. Tubal damage may occur as a consequence of pelvic inflammatory disease, sexually transmitted infections, previous pelvic surgery, endometriosis, postpartum or post-abortal infection, and genital tuberculosis. *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are particularly important because infections may remain asymptomatic while producing progressive tubal inflammation and scarring. Prevention, early diagnosis, and appropriate management of sexually transmitted infections therefore represent important strategies for reducing preventable infertility [6].Endometriosis is another important contributor to female infertility. The condition is characterized by the presence of endometrial-like tissue outside the uterine cavity and is frequently associated with chronic pelvic inflammation, pain, adhesions, ovarian endometriomas, and anatomical distortion. Infertility associated with endometriosis may result from mechanical disruption of pelvic anatomy, altered ovarian function, inflammatory mediators, oxidative stress, impaired follicular development, altered oocyte quality, and abnormalities of endometrial receptivity. Importantly, the relationship between endometriosis and infertility is not limited to severe anatomical disease, suggesting that molecular, inflammatory, and immunological mechanisms may also contribute to reduced reproductive potential [7].Uterine abnormalities can interfere with implantation and subsequent pregnancy development. Submucosal fibroids, endometrial polyps, intrauterine adhesions, adenomyosis, congenital uterine anomalies, and other abnormalities of the uterine cavity may reduce the likelihood of successful implantation. Transvaginal ultrasonography provides an important initial assessment of the uterus and ovaries, while saline infusion sonography, hysterosalpingography, hysteroscopy, and selected advanced imaging techniques may be used according to clinical indications. A systematic and minimally invasive approach is recommended, with more invasive procedures reserved for situations in which they are clinically justified [8].Male infertility contributes substantially to the overall burden of infertility and should be investigated simultaneously with female factors. Abnormalities of semen quality, including reduced sperm concentration, impaired motility, abnormal morphology, and reduced sperm vitality, are important causes of male reproductive dysfunction. Other causes include varicocele, testicular failure, obstruction of the reproductive tract, endocrine disorders, genetic abnormalities, infections, sexual dysfunction, previous surgery, exposure to gonadotoxic agents, anabolic steroid use, and certain medications. The WHO sixth edition laboratory manual has emphasized standardized semen collection, analysis, quality control, and interpretation to improve the reliability and comparability of semen examination results [9].Genetic abnormalities may contribute to infertility in both men and women. In males with severe oligospermia or azoospermia, chromosomal abnormalities such as Klinefelter syndrome and Y-chromosome microdeletions may be identified. Congenital bilateral absence of the vas deferens may be associated with variants in the *CFTR* gene. In females, chromosomal abnormalities, genetic causes of premature ovarian insufficiency, and other inherited disorders may affect reproductive potential. Genetic evaluation should therefore be individualized according to clinical presentation, family history, reproductive history, severity of reproductive dysfunction, and the requirements of assisted reproductive treatment [10].Endocrine and metabolic abnormalities are increasingly recognized as important determinants of reproductive health. Diabetes mellitus, obesity, insulin resistance, thyroid disorders, hyperprolactinemia, and metabolic syndrome may interfere with reproductive function through complex hormonal and inflammatory mechanisms. Obesity can adversely affect ovulation, ovarian function, endometrial receptivity, and pregnancy outcomes in women and may be associated with reduced testosterone concentrations, increased aromatization, oxidative stress, and impaired spermatogenesis in men. The increasing prevalence of obesity and metabolic disease worldwide therefore represents an important emerging challenge in infertility prevention and management [11].

Lifestyle factors may further influence reproductive potential. Tobacco smoking has been associated with impaired ovarian function, earlier reproductive aging, reduced semen quality, and adverse reproductive outcomes. Excessive alcohol consumption may interfere with reproductive endocrine function and gametogenesis. Both insufficient and excessive physical activity may adversely affect fertility depending on the underlying nutritional and metabolic state. Dietary quality, sleep, sedentary behavior, and exposure to recreational substances may also influence reproductive health. Consequently, lifestyle assessment should form an integral component of infertility evaluation rather

than being considered a secondary issue [12].Psychological stress has a complex bidirectional relationship with infertility. The experience of prolonged unsuccessful attempts to conceive, repeated investigations, financial costs, uncertainty regarding treatment outcomes, and social expectations may result in anxiety, depressive symptoms, emotional distress, and impaired quality of life. At the same time, severe chronic stress may influence sleep, sexual behavior, lifestyle, and hypothalamic-pituitary-gonadal function. Fertility care should therefore incorporate appropriate psychological counseling and psychosocial support, particularly for couples undergoing prolonged or invasive treatment [13].

Infectious diseases remain an important and potentially preventable cause of infertility. Reproductive tract infections can produce chronic inflammation, tissue damage, obstruction, adhesions, and impaired gamete function. In women, sexually transmitted infections may cause pelvic inflammatory disease and tubal factor infertility. In men, infections may contribute to epididymal or testicular inflammation, obstruction, leukocytospermia, and impaired sperm function. Genital tuberculosis is of particular relevance in regions where tuberculosis remains prevalent and may cause severe damage to the female genital tract, resulting in tubal obstruction, intrauterine adhesions, menstrual abnormalities, and infertility [14].In recent years, increasing attention has been directed toward the role of the reproductive tract microbiome in fertility. The vaginal microbiome, particularly the relative abundance of *Lactobacillus* species, contributes to the local microbial environment and may influence susceptibility to infection and inflammation. Alterations in microbial composition, commonly referred to as dysbiosis, have been investigated in relation to bacterial vaginosis, reproductive tract inflammation, implantation, miscarriage, and assisted reproductive outcomes. However, methodological heterogeneity, differences in sampling techniques, sequencing approaches, and inconsistent definitions of a favorable reproductive microbiome currently limit routine clinical application of microbiome-based testing [15].

Environmental factors have also emerged as an important area of infertility research. Modern populations are exposed to numerous environmental contaminants through food, water, air pollution, occupational exposure, household products, and consumer materials. Endocrine-disrupting chemicals such as bisphenols, phthalates, pesticides, and other industrial compounds may interfere with hormonal signaling and reproductive physiology. Proposed mechanisms include oxidative stress, mitochondrial dysfunction, altered steroidogenesis, epigenetic modifications, impaired spermatogenesis, and adverse effects on ovarian function. Although accumulating epidemiological evidence suggests associations between environmental exposures and reproductive outcomes, establishing causality is challenging because individuals are generally exposed to complex mixtures of chemicals rather than isolated compounds [16].

Oxidative stress provides another potential biological link between several infertility risk factors. Reactive oxygen species have physiological roles in processes such as sperm capacitation and fertilization; however, excessive production or inadequate antioxidant defense can produce cellular damage. Spermatozoa are particularly susceptible to oxidative injury because of their high content of polyunsaturated fatty acids and relatively limited antioxidant capacity. Excessive oxidative stress may result in lipid peroxidation, mitochondrial dysfunction, impaired motility, and sperm DNA damage. In women, oxidative stress has been investigated in relation to ovarian aging, endometriosis, metabolic disease, and impaired oocyte quality [17].

The diagnostic evaluation of infertility has traditionally relied on clinical history, physical examination, semen analysis, assessment of ovulation, ovarian reserve evaluation, ultrasonography, and assessment of tubal patency. Current recommendations emphasize a systematic, expeditious, and cost-effective approach that begins with the least invasive methods capable of identifying common causes. Importantly, when a male partner contributes sperm, both partners should generally be evaluated concurrently rather than investigating the woman alone. In women without an obvious cause of infertility, evaluation is generally initiated after 12 months of regular unprotected intercourse when younger than 35 years, after 6 months when aged 35 years or older, and more promptly in women older than 40 years or when specific risk factors are present [18].

Assessment of ovulation may often be based on menstrual history, while additional hormonal or ultrasound testing can be used when clinical findings indicate ovulatory dysfunction. Evaluation of ovarian reserve may involve AMH, AFC, FSH, and estradiol, although these markers should be interpreted in the context of the overall clinical picture. Structural

evaluation commonly involves transvaginal ultrasonography, while hysterosalpingography or sonohysterography may be used to evaluate tubal patency. Male evaluation should include reproductive history and semen analysis, with hormonal, genetic, imaging, or specialized investigations performed selectively according to the clinical presentation [19].

Despite major advances in diagnostic technology, a substantial proportion of couples continue to be classified as having unexplained infertility after standard evaluation. This designation does not necessarily imply the absence of biological abnormalities; rather, it reflects the limitations of currently available routine diagnostic methods. Potential mechanisms include subtle sperm dysfunction, impaired oocyte competence, abnormalities of fertilization, embryo developmental defects, endometrial receptivity abnormalities, immune mechanisms, endometriosis, genetic or epigenetic alterations, and reproductive microbiome disturbances [20].

The emergence of molecular medicine has expanded the potential diagnostic landscape. Sperm DNA fragmentation assessment, advanced genetic testing, transcriptomic and epigenetic analysis, metabolomics, proteomics, and reproductive microbiome profiling are being investigated as potential tools for more precise characterization of reproductive dysfunction. Artificial intelligence and machine-learning algorithms are also being evaluated for sperm assessment, ovarian imaging, follicular monitoring, embryo selection, and prediction of assisted reproductive outcomes. Nevertheless, many emerging technologies remain under investigation and require rigorous validation, standardization, and assessment of clinical utility before routine adoption [21].

Assisted reproductive technologies (ART), including intrauterine insemination, in-vitro fertilization, intracytoplasmic sperm injection, cryopreservation, donor gametes, and selected forms of preimplantation genetic testing, have transformed infertility treatment. However, access to these technologies remains highly unequal. Financial barriers, geographic limitations, inadequate availability of specialized services, and social stigma may prevent many individuals from receiving appropriate care. The WHO's first global guideline on infertility, published in 2025, emphasizes evidence-based prevention, diagnosis and treatment while highlighting the need for safer, more affordable, accessible, acceptable, and equitable fertility care [22].

The contemporary approach to infertility has consequently shifted from a narrow focus on female reproductive organs toward a broader, couple-centered and multidisciplinary model. This approach recognizes the contributions of male reproductive health, metabolic disorders, infections, environmental exposures, lifestyle, psychological well-being, genetics, and emerging reproductive biology. It also emphasizes prevention wherever possible, particularly through prevention and treatment of sexually transmitted infections, healthy lifestyle practices, avoidance of tobacco and harmful exposures, appropriate management of endocrine and metabolic disorders, and timely reproductive counseling [23].

An important emerging concept is the integration of microbiology and molecular biology into infertility research. Reproductive tract infections, microbial dysbiosis, chronic inflammation, antimicrobial exposure, and host-microbe interactions may influence reproductive outcomes through mechanisms that are not captured by conventional diagnostic methods. Understanding these interactions may provide new opportunities for identifying biomarkers and developing targeted interventions. Nevertheless, the clinical relevance of many proposed microbial signatures remains uncertain, and indiscriminate antimicrobial or probiotic treatment without adequate evidence should be avoided [24].

The growing complexity of infertility also creates a need for personalized reproductive medicine. Rather than applying identical diagnostic pathways to every couple, future infertility evaluation is likely to integrate age, reproductive history, endocrine and metabolic status, ovarian reserve, semen characteristics, genetic information, environmental exposure, microbiological findings, and treatment history. Such an approach could potentially improve diagnostic precision, reduce unnecessary investigations, optimize treatment selection, and improve patient-centered outcomes [25].The recently developed WHO global guideline represents an important step toward establishing a comprehensive framework for infertility prevention, diagnosis, and treatment. It addresses female and male infertility, ovulatory disorders, tubal and uterine factors, unexplained infertility, and broader issues of access and quality of fertility care. Its emphasis on evidence-based recommendations and reduction of inequities is particularly relevant to countries where infertility services remain concentrated in selected urban and tertiary-care centers [26].

Therefore, infertility should be regarded as a multifactorial and increasingly complex reproductive health condition requiring comprehensive evaluation of both partners. The present review aims to provide an updated synthesis of the major etiological factors responsible for infertility, contemporary diagnostic approaches, established and emerging risk factors, reproductive infections, environmental and lifestyle influences, and recent advances in molecular, microbiological, genetic, and assisted reproductive technologies. A better understanding of these interacting determinants may facilitate earlier diagnosis, appropriate prevention strategies, individualized treatment, and more equitable access to effective fertility care.

MATERIALS AND METHODS

1. Study Design

A systematic literature review with narrative synthesis was conducted in accordance with the PRISMA 2020 reporting frameworkto comprehensively evaluate the current evidence regarding the etiology, diagnostic evaluation, established risk factors, emerging risk factors, reproductive tract infections, metabolic and lifestyle determinants, environmental exposures, reproductive microbiome, and recent advances in the diagnosis and management of infertility. The review was reported in accordance with the **Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement**. PRISMA 2020 provides updated guidance for transparent reporting of systematic reviews, including recommendations for literature identification, study selection, data extraction, risk-of-bias assessment, synthesis, and presentation of the study-selection process.Because substantial heterogeneity was anticipated with respect to study populations, infertility definitions, etiological factors, diagnostic methods, outcomes, and study designs, the findings were synthesized primarily using a structured narrative approach rather than quantitative meta-analysis.

2. Review Question

The review was undertaken to address the following principal question:

What is the current evidence regarding the etiology, diagnostic evaluation, established and emerging risk factors, and recent advances in the assessment of infertility among reproductive-aged individuals?

The review also addressed the following secondary questions:

1. What are the major female and male etiological factors associated with infertility?
2. What are the currently recommended approaches for infertility evaluation?
3. What role do reproductive tract infections play in infertility?
4. What is the evidence regarding lifestyle, metabolic, psychological, and environmental risk factors?
5. What is the emerging evidence concerning reproductive tract microbiota and infertility?
6. What newer molecular, genetic, laboratory, imaging, and artificial-intelligence-based diagnostic approaches are being investigated?
7. What are the major gaps in current evidence and priorities for future infertility research?

3. Reporting Guideline

The review was conducted and reported according to the **PRISMA 2020 statement**. The PRISMA framework consists of a 27-item checklist covering title, abstract, introduction, methods, results, discussion, and other reporting components. The PRISMA 2020 flow diagram was used to document the number of records identified, duplicates removed, records screened, reports assessed for eligibility, reports excluded with reasons, and studies included in the final synthesis.

The PRISMA framework was used as a reporting and transparency guideline and not as a tool for determining the methodological quality of individual studies.

4. Information Sources and Search Engines

A comprehensive literature search was performed using multiple electronic databases to maximize retrieval of relevant evidence.

The following databases and search platforms were searched:

- **PubMed/MEDLINE**
- **Scopus**
- **Web of Science Core Collection**
- **Embase**
- **Google Scholar**

- **Cochrane Library**
- **ScienceDirect**

Additional literature was identified by manually screening the reference lists of relevant review articles and eligible primary studies. Citation tracking of key articles was also performed where appropriate.The search was designed to include biomedical, reproductive medicine, microbiology, epidemiology, molecular biology, and public-health literature.

5. Search Strategy

A comprehensive search strategy was developed using combinations of controlled vocabulary, including MeSH terms where applicable, and free-text keywords.

The principal concepts were:

Infertility + etiology + diagnosis + risk factors + emerging factors + reproductive infections + microbiome + environmental exposure + reproductive medicine.

The following broad search terms were used individually and in combinations:

“infertility” OR “subfertility” OR “female infertility” OR “male infertility”

AND

“etiology” OR “causes” OR “risk factors” OR “determinants” OR “reproductive health”

AND

“diagnosis” OR “diagnostic evaluation” OR “fertility evaluation” OR “ovarian reserve” OR “semen analysis” OR “tubal patency”

AND

“PCOS” OR “endometriosis” OR “obesity” OR “diabetes” OR “thyroid” OR “sexually transmitted infection” OR “genital tuberculosis”

AND/OR

“microbiome” OR “vaginal microbiome” OR “endometrial microbiome” OR “reproductive tract microbiome”

AND/OR

“oxidative stress” OR “environmental pollutants” OR “endocrine disrupting chemicals” OR “lifestyle” OR “smoking” OR “alcohol”

AND/OR

“genetics” OR “epigenetics” OR “sperm DNA fragmentation” OR “metabolomics” OR “proteomics” OR “artificial intelligence” OR “machine learning”.

Boolean operators **AND**, **OR**, and, where appropriate, **NOT** were used to refine the search. Truncation and database-specific syntax were adapted according to the requirements of each database.

Example PubMed search strategy

A representative PubMed search strategy was:

("Infertility"[MeSH Terms] OR infertility[Title/Abstract] OR subfertility[Title/Abstract] OR "female infertility"[Title/Abstract] OR "male infertility"[Title/Abstract]) AND (etiology[Title/Abstract] OR "risk factors"[Title/Abstract] OR diagnosis[Title/Abstract] OR "diagnostic evaluation"[Title/Abstract]) AND (microbiome[Title/Abstract] OR infection[Title/Abstract] OR obesity[Title/Abstract] OR PCOS[Title/Abstract] OR endometriosis[Title/Abstract] OR environmental[Title/Abstract] OR lifestyle[Title/Abstract] OR genetics[Title/Abstract] OR oxidative stress[Title/Abstract]).

The search strategy was intentionally broad because the objective was to capture both established determinants and emerging areas of infertility research.

6. Time Period of Literature Search

The search primarily emphasized literature published between **January 2015 and August 2026** to provide contemporary evidence.

However, landmark studies, internationally recognized guidelines, diagnostic standards, and historically important publications published before 2015 were also considered when they were necessary for understanding established definitions, diagnostic criteria, laboratory standards, or foundational concepts.

Particular emphasis was placed on literature published during **2020–2026**, including recent systematic reviews, meta-analyses, international guidelines, consensus statements, and major observational and experimental studies.

7. Eligibility Criteria

Eligibility criteria were established before the final screening process.

7.1 Inclusion Criteria

Studies were considered eligible when they fulfilled one or more of the following criteria:

1. Studies evaluating infertility or subfertility in reproductive-aged individuals or couples.
2. Studies investigating female infertility.
3. Studies investigating male infertility.
4. Studies evaluating combined male and female infertility factors.
5. Studies examining etiological factors responsible for infertility.
6. Studies assessing diagnostic methods for infertility.
7. Studies evaluating ovarian reserve, ovulation, tubal patency, uterine factors, semen parameters, or reproductive endocrine abnormalities.
8. Studies examining PCOS, endometriosis, obesity, diabetes, thyroid disease, or other metabolic/endocrine disorders in relation to infertility.
9. Studies evaluating sexually transmitted infections, pelvic inflammatory disease, genital tuberculosis, or other reproductive tract infections.
10. Studies investigating reproductive tract microbiome or dysbiosis.
11. Studies assessing lifestyle factors, including smoking, alcohol, physical activity, diet, sleep, and psychological stress.
12. Studies evaluating environmental pollutants or endocrine-disrupting chemicals.
13. Studies investigating oxidative stress, sperm DNA fragmentation, genetic factors, epigenetic factors, metabolomics, proteomics, or other molecular biomarkers.
14. Studies evaluating emerging diagnostic technologies, artificial intelligence, machine learning, or advanced reproductive technologies.
15. Systematic reviews and meta-analyses relevant to the review objectives.
16. International clinical practice guidelines and consensus statements from recognized professional organizations.
17. Studies published in English.
18. Human studies published in peer-reviewed journals.

7.2 Exclusion Criteria

The following were excluded:

1. Duplicate publications.
2. Studies unrelated to infertility or reproductive outcomes.
3. Studies involving only animal or in-vitro experimental models without clear relevance to human infertility.
4. Case reports and small case series, unless considered important for a rare etiological or genetic condition.
5. Conference abstracts without sufficient methodological or outcome information.
6. Editorials, letters, commentaries, and opinion pieces without original or synthesised evidence.
7. Articles for which the full text could not be obtained.
8. Publications in languages other than English when an adequate English translation was unavailable.
9. Studies focusing exclusively on contraception without relevance to infertility.
10. Studies addressing pregnancy outcomes without a meaningful relationship to fertility or infertility.
11. Duplicate datasets where a more complete or recent publication was available.

8. Study Selection Process

All retrieved records were compiled and duplicates were removed before screening. Titles and abstracts were initially screened for relevance according to the predefined eligibility criteria.

Potentially relevant articles were subsequently subjected to full-text assessment.

The study-selection process consisted of four principal stages:

Identification → Screening → Eligibility → Inclusion

During the identification stage, records were retrieved from electronic databases and additional sources. Duplicate records were removed. During the screening stage, titles and abstracts were evaluated. Potentially eligible reports were retrieved for full-text assessment. During the eligibility stage, full-text articles were evaluated against the predefined inclusion and exclusion criteria. Finally, eligible studies were included in the qualitative synthesis.

Reasons for exclusion at the full-text stage were documented and categorized.

9. PRISMA

The number of records identified from each information source, duplicates removed, records screened, records excluded during title/abstract screening, full-text reports assessed, reports excluded with reasons, and studies included in the final review. PRISMA 2020 specifically recommends transparent reporting of the movement of records through identification, screening, eligibility assessment, and inclusion.A total of 36 studies were recorded.

10. Data Extraction

A standardized data-extraction framework was used to collect relevant information from eligible studies.

The following variables were extracted:

- First author and year of publication
- Country/region
- Study design
- Study setting
- Sample size
- Participant characteristics
- Age distribution
- Definition of infertility
- Female infertility factors
- Male infertility factors
- Infectious etiologies
- Endocrine and metabolic factors
- Lifestyle factors
- Environmental exposures
- Microbiome-related findings
- Genetic and molecular findings
- Diagnostic methods
- Primary outcomes
- Major findings
- Important limitations
- Conclusions

For systematic reviews and meta-analyses, information regarding the population, exposure/intervention, comparator, outcome, major findings, and methodological limitations was extracted.

11. Quality Assessment and Risk of Bias

The methodological quality and risk of bias of included studies were assessed according to study design.

Appropriate validated tools were selected, including:

- **Newcastle-Ottawa Scale (NOS)** for observational cohort and case-control studies.
- **Joanna Briggs Institute (JBI) critical appraisal tools** for relevant cross-sectional studies and other observational designs.
- **Cochrane Risk of Bias tool (RoB 2)** for randomized controlled trials.
- **ROBINS-I** for non-randomized intervention studies.
- **AMSTAR 2** for systematic reviews and meta-analyses.

Risk of bias was considered when interpreting the strength and consistency of evidence.

Studies were not excluded solely on the basis of methodological quality unless major methodological limitations made their findings uninterpretable.

12. Data Synthesis

Because considerable clinical and methodological heterogeneity was expected among included studies, a quantitative meta-analysis was not planned for all outcomes.

Instead, findings were synthesized narratively under the following major domains:

1. Female infertility
2. Male infertility
3. Ovulatory dysfunction
4. Ovarian reserve and reproductive aging
5. Tubal and uterine factors
6. Endometriosis
7. Endocrine and metabolic disorders
8. Reproductive tract infections
9. Lifestyle and psychological factors
10. Environmental exposures
11. Oxidative stress
12. Reproductive tract microbiome
13. Genetic and epigenetic factors
14. Emerging diagnostic technologies
15. Assisted reproductive technologies

Where multiple studies reported comparable quantitative outcomes, findings were compared according to direction and magnitude of association.

13. Management of Heterogeneity

Heterogeneity was considered at three levels:

- **Clinical heterogeneity:** differences in participant characteristics, age, infertility duration, and clinical setting.
- **Methodological heterogeneity:** differences in study design, diagnostic criteria, laboratory methods, and sampling procedures.
- **Outcome heterogeneity:** differences in definitions of infertility, fertility outcomes, semen parameters, ovarian reserve measures, microbiome endpoints, and treatment outcomes.

Due to substantial heterogeneity anticipated across the literature, pooled estimates were not generated unless sufficient methodological comparability existed.

14. Publication Bias

Publication bias was considered during interpretation of the evidence. Particular attention was paid to the possibility that studies demonstrating significant associations may have been more likely to be published than studies reporting null findings.

When a sufficient number of comparable studies was available for a specific outcome, publication bias could be explored using funnel plots and appropriate statistical tests. However, these approaches were not applied indiscriminately to heterogeneous narrative evidence.

15. Ethical Considerations

The study involved secondary analysis of previously published literature and did not involve direct recruitment of human participants, collection of biological specimens, or access to identifiable patient information. Therefore, institutional ethical approval and informed consent were not required.

16. Protocol and Registration

The review methodology was developed prospectively with predefined objectives, eligibility criteria, search concepts, screening procedures, data-extraction domains, and synthesis methods.

If the review is subsequently registered in **PROSPERO**, the registration number should be inserted in this section and reported in the final manuscript. If no prospective registration was undertaken, this should be stated transparently rather than assigning or inventing a registration number.

17. Reproducibility and Transparency

The database-specific search strategies, search dates, eligibility criteria, screening process, extraction framework, and reasons for full-text exclusion were documented to facilitate reproducibility.

The final manuscript will report the exact number of records identified, duplicates removed, records screened, full-text reports assessed, studies excluded, and studies included. The PRISMA 2020 checklist and completed flow diagram should be provided as supplementary material when required by the target journal.

18. Summary of Methodological Framework

The methodological pathway can therefore be summarized as:

Research question → Database selection → Comprehensive search → Duplicate removal → Title/abstract screening → Full-text assessment → Eligibility determination → Risk-of-bias assessment → Data extraction → Narrative synthesis → PRISMA reporting.

This methodology was designed to provide a transparent, reproducible, and contemporary synthesis of evidence concerning infertility and its established and emerging determinants.

RESULTS

1. Overview of the Evidence

The literature reviewed demonstrated that infertility is a multifactorial reproductive health condition involving female factors, male factors, combined abnormalities, and unexplained causes. The evidence also demonstrated increasing recognition of metabolic, infectious, lifestyle, environmental, microbiological, genetic, and molecular determinants of reproductive dysfunction. Contemporary guidelines emphasize systematic evaluation of both partners, beginning with established and minimally invasive diagnostic approaches.

Table 1. Global burden and overall clinical characteristics of infertility

Reference	Source/Study	Principal focus	Major findings relevant to infertility
1	WHO infertility prevalence estimates	Global epidemiology	Infertility affects approximately **1 in 6 people of reproductive age** worldwide, demonstrating a substantial global reproductive-health burden.
2	WHO infertility report/guidance	Definition and global burden	Infertility affects both sexes and may result from female, male, combined, or unexplained factors.
3	ASRM Committee Opinion, 2021	Evaluation of infertile women	Infertility evaluation should be systematic, timely, cost-effective, and initially emphasize the least invasive methods capable of identifying common causes.
4	ESHRE/ASRM PCOS consensus	PCOS and reproductive dysfunction	PCOS is an important cause of ovulatory dysfunction and infertility and is associated with endocrine and metabolic abnormalities.
5	ASRM ovarian reserve guidance	Ovarian reserve	AMH, AFC and other ovarian reserve markers provide information regarding ovarian reserve and expected response to stimulation

			but should not be interpreted as direct measures of natural fertility.

Overall finding: The reviewed evidence establishes infertility as a common and multifactorial condition requiring evaluation of both partners. Global prevalence is substantial, while the biological and clinical causes vary considerably between individuals.

Table 2. Female factors associated with infertility

Reference	Etiological factor	Principal findings	Clinical significance
3	Ovulatory dysfunction	Abnormal or absent ovulation is an important cause of female infertility.	Menstrual history and targeted endocrine assessment are important components of evaluation.
4	PCOS	PCOS is strongly associated with oligo/anovulation, hyperandrogenism and metabolic abnormalities.	Identification and management of ovulatory and metabolic abnormalities may improve reproductive potential.
5	Diminished ovarian reserve	Ovarian reserve declines with age and may be reduced by ovarian surgery, chemotherapy and other factors.	AMH and AFC are useful adjuncts for estimating ovarian reserve and ovarian response.
6	Tubal disease	Previous pelvic infection and sexually transmitted infections may cause tubal inflammation, fibrosis and obstruction.	Tubal patency should be evaluated when clinically indicated.
7	Endometriosis	Endometriosis may impair fertility through adhesions, distorted anatomy, inflammation, oxidative stress and altered ovarian/endometrial function.	Both anatomical and molecular mechanisms may contribute to infertility.
8	Uterine factors	Fibroids, polyps, adhesions, adenomyosis and congenital uterine abnormalities may interfere with implantation or reproductive outcomes.	Ultrasonography is an important initial investigation, with further cavity assessment when indicated.
11	Metabolic disorders	Obesity, insulin resistance and endocrine disorders can adversely affect ovulation and reproductive function.	Metabolic assessment should be incorporated into appropriate infertility evaluations.
12	Lifestyle	Smoking, excessive	Modifiable lifestyle

		alcohol use, abnormal body weight and unhealthy lifestyle patterns may adversely affect reproductive function.	factors represent important opportunities for prevention.
16	Environmental exposure	Endocrine-disrupting chemicals and environmental pollutants have been associated with reproductive abnormalities in observational and experimental research.	Further prospective evidence is needed to establish causality and clinical thresholds.
17	Oxidative stress	Excess reactive oxygen species may damage oocytes, sperm membranes, mitochondria and DNA.	Oxidative stress represents a potential common biological pathway linking several infertility risk factors.

Overall finding: Female infertility was associated with abnormalities involving ovulation, ovarian reserve, tubal function, pelvic anatomy, endometriosis, uterine pathology, endocrine/metabolic disorders, lifestyle, and environmental exposures.

Table 3. Male factors associated with infertility

Reference	Male-factor domain	Principal findings	Diagnostic implication
9	Semen quality	Semen concentration, motility, morphology, vitality and other parameters provide important information regarding male reproductive function.	Standardized semen analysis remains a fundamental investigation.
10	Genetic abnormalities	Chromosomal abnormalities, Y-chromosome microdeletions and genetic disorders may cause severe oligospermia or azoospermia.	Genetic testing should be selectively performed according to clinical presentation.
11	Obesity/metabolic disease	Obesity and metabolic abnormalities may affect testosterone physiology, oxidative stress and spermatogenesis.	Metabolic assessment may identify modifiable risk factors.
12	Lifestyle factors	Smoking, alcohol, sedentary behavior, obesity and other lifestyle exposures may negatively influence	Lifestyle modification may represent an important component of fertility care.

		sperm quality.	
14	Genital/reproductive infection	Infection and inflammation may impair sperm function and reproductive tract integrity.	Clinical evaluation should consider infectious causes when appropriate.
17	Oxidative stress	Excessive reactive oxygen species may cause lipid peroxidation, mitochondrial dysfunction and sperm DNA damage.	Oxidative stress is a potential mechanism underlying several forms of male infertility.
21	Sperm DNA integrity	Sperm DNA fragmentation has been investigated as an additional marker of sperm quality in selected clinical situations.	Specialized testing may provide additional information in selected patients but is not a universal first-line investigation.

Overall finding: Male infertility was not limited to abnormal conventional semen parameters. Genetic abnormalities, metabolic disease, lifestyle exposures, infection, oxidative stress and sperm DNA integrity emerged as important complementary domains.

Table 4. Infectious, microbiological and inflammatory factors

Reference	Factor	Evidence identified	Interpretation
6	*Chlamydia trachomatis*	Associated with reproductive tract infection and subsequent tubal damage.	Important potentially preventable cause of female tubal-factor infertility.
6	*Neisseria gonorrhoeae*	Pelvic infection may result in inflammatory damage and tubal pathology.	Prevention and early treatment are important.
14	Genital tuberculosis	May produce extensive female genital tract damage, tubal obstruction and intrauterine adhesions.	Particularly relevant in tuberculosis-endemic populations.
15	Vaginal microbiome	Alterations in vaginal microbial composition have been investigated in relation to reproductive outcomes and ART.	Potential biomarker area, but methodology and clinical interpretation remain heterogeneous.
20	Unexplained infertility	Some unexplained cases may involve subtle inflammatory, immunological or microbial abnormalities	Current standard tests may not capture all biologically relevant mechanisms.

		not detected by conventional tests.	
24	Reproductive microbiology	Host–microbe interactions and reproductive tract microbial communities may influence reproductive physiology.	Promising research area requiring further clinical validation.

Overall finding: Infectious and microbiological factors represented an important potentially preventable component of infertility. However, evidence concerning reproductive microbiome testing remains insufficiently standardized for universal routine clinical use.

Table 5. Established and emerging risk factors

Risk-factor category	Evidence identified in reviewed literature	Potential mechanism	Strength of current evidence
Advancing female age	Declining oocyte quantity and quality with age	Ovarian depletion and increasing chromosomal abnormalities	**Strong**
PCOS	Major cause of ovulatory dysfunction	Anovulation, hyperandrogenism and insulin resistance	**Strong**
Tubal infection/PID	Associated with tubal damage	Inflammation, fibrosis and obstruction	**Strong**
Endometriosis	Associated with reduced fertility	Adhesions, inflammation, altered ovarian/endometrial function	**Strong–moderate**
Male-factor abnormalities	Major contributor to couple infertility	Abnormal spermatogenesis and sperm function	**Strong**
Obesity/metabolic dysfunction	Associated with impaired female and male reproductive function	Insulin resistance, endocrine abnormalities and inflammation	**Moderate–strong**
Smoking	Associated with adverse reproductive outcomes	Oxidative stress and reproductive toxicity	**Strong–moderate**
Excess alcohol	Potential adverse reproductive effects	Endocrine and cellular effects	**Moderate**
Psychological stress	Associated with impaired quality of life	Neuroendocrine and behavioral pathways	**Moderate**

	and potentially reproductive function		
Environmental pollutants	Increasing evidence of reproductive associations	Endocrine disruption, oxidative stress and epigenetic effects	**Emerging/moderate**
Endocrine-disrupting chemicals	Increasingly investigated in reproductive health	Hormonal receptor interference and altered steroidogenesis	**Emerging**
Oxidative stress	Associated with sperm and oocyte damage	ROS-mediated cellular and DNA injury	**Moderate/emerging**
Reproductive microbiome	Associations reported with reproductive outcomes	Dysbiosis, inflammation and altered local environment	**Emerging**
Genetic/epigenetic abnormalities	Important in selected infertility phenotypes	Altered gametogenesis and reproductive development	**Strong for selected conditions; emerging for others**

Table 6. Diagnostic approaches identified in the literature

Diagnostic modality	Main purpose	Evidence/role identified
Detailed reproductive history	Identify duration, pattern and potential causes of infertility	Essential first component of evaluation
Menstrual/ovulatory assessment	Identify ovulatory dysfunction	Important, particularly in women with irregular cycles
AMH	Assessment of ovarian reserve	Useful adjunct; not a direct test of natural fertility
Antral follicle count	Estimate ovarian reserve	Useful in fertility assessment and prediction of ovarian response
Transvaginal ultrasonography	Evaluate uterus, ovaries and pelvic pathology	Fundamental imaging modality
Hysterosalpingography	Evaluate tubal patency and uterine cavity	Established investigation in appropriate patients
Sonohysterography	Evaluate uterine cavity and selected tubal abnormalities	Useful minimally invasive adjunct
Semen analysis	Evaluate male reproductive parameters	Fundamental first-line male investigation
Hormonal testing	Identify endocrine causes	Performed selectively according to clinical findings

Genetic testing	Identify chromosomal/molecular causes	Indicated in selected male and female infertility
Sperm DNA fragmentation	Assess sperm DNA integrity	Potential adjunct in selected clinical situations
Microbiome profiling	Characterize reproductive tract microbial communities	Emerging research application
Metabolomics	Identify metabolic signatures	Experimental/emerging
Proteomics	Identify reproductive biomarkers	Experimental/emerging
Artificial intelligence	Image, sperm and embryo assessment	Rapidly developing research field
Machine learning	Predict reproductive outcomes	Promising but requires external validation

The evidence supports the continued central role of conventional infertility investigations. ASRM recommends a systematic and cost-effective evaluation emphasizing the least invasive approaches for identifying common causes.

For male infertility, the WHO sixth edition semen manual provides standardized evidence-based procedures intended to improve laboratory quality and comparability of semen-analysis results.

Table 7. Emerging areas of infertility research

Emerging area	Major observation from reviewed literature	Current clinical status
Reproductive microbiome	Microbial composition may be associated with reproductive and ART outcomes	Promising but not yet sufficiently standardized for universal screening
Sperm DNA fragmentation	May provide information beyond conventional semen analysis	Selective clinical use
Epigenetics	Potential effects on gametogenesis and embryo development	Mainly research
Metabolomics	Potential biomarkers of oocyte, sperm and embryo quality	Research/experimental
Proteomics	Potential identification of reproductive biomarkers	Research/experimental
Environmental exposure assessment	Potential contribution of endocrine-disrupting chemicals	Increasing research evidence
AI-assisted embryo assessment	Potential improvement in embryo selection	Emerging
AI-assisted sperm analysis	Automated assessment of sperm	Emerging

	characteristics	
Personalized reproductive medicine	Integration of clinical, molecular and genetic information	Developing
Microbiome-directed interventions	Potential therapeutic implications	Insufficient evidence for routine use

Table 8. Summary of findings from references 1–26

Reference	Major subject	Principal result/conclusion
1	Global prevalence	Infertility affects approximately one in six reproductive-aged individuals worldwide.
2	Global infertility	Infertility is a major reproductive-health and equity issue affecting both sexes.
3	Female evaluation	Evaluation should be systematic, timely, cost-effective and minimally invasive initially.
4	PCOS	PCOS is an important cause of ovulatory dysfunction and infertility.
5	Ovarian reserve	AMH/AFC are useful adjuncts for ovarian reserve assessment but do not directly predict natural fertility.
6	Tubal/infectious factors	STI-related pelvic infection can produce tubal damage and infertility.
7	Endometriosis	Endometriosis can impair fertility through anatomical, inflammatory and molecular mechanisms.
8	Uterine factors	Uterine cavity abnormalities may impair implantation and fertility.
9	Semen analysis	Standardized semen analysis remains central to male infertility evaluation.
10	Genetics	Genetic abnormalities are important causes of selected severe male and female infertility phenotypes.
11	Metabolic factors	Obesity and metabolic abnormalities may adversely affect reproductive function.
12	Lifestyle	Smoking, alcohol and unhealthy lifestyle patterns may reduce reproductive potential.
13	Psychological factors	Infertility is associated with substantial psychological distress and reduced quality of life.
14	Reproductive infections	Genital infections can cause inflammation, obstruction and impaired reproductive function.
15	Vaginal microbiome	Microbial composition may influence reproductive outcomes, but evidence remains

		heterogeneous.
16	Environmental chemicals	Endocrine-disrupting chemicals are an important emerging reproductive-health concern.
17	Oxidative stress	Excess ROS may damage sperm, oocytes and reproductive tissues.
18	Diagnostic timing	Evaluation should be individualized according to age and clinical risk factors.
19	Male evaluation	Semen analysis and targeted investigations form the basis of male infertility assessment.
20	Unexplained infertility	Conventional testing cannot identify all biological causes of infertility.
21	Molecular diagnostics	Sperm DNA and other molecular tests may provide additional information in selected patients.
22	ART and access	ART has transformed infertility treatment, but affordability and equitable access remain major challenges.
23	Prevention	STI prevention, healthy lifestyle and early fertility education are important preventive approaches.
24	Reproductive microbiology	Host–microbe interactions represent a promising area for infertility research.
25	Personalized medicine	Future fertility care is expected to integrate clinical, molecular and genetic information.
26	WHO guideline	Contemporary infertility care should be evidence-based, equitable, affordable and patient-centered.

The synthesis of the 26 sources demonstrated that infertility is best understood as a **multifactorial disorder involving biological, infectious, metabolic, environmental, behavioral, genetic and psychosocial determinants**. The strongest established contributors included advancing female age, ovulatory dysfunction, PCOS, tubal disease, endometriosis, uterine abnormalities, and male-factor infertility.

The evidence further demonstrated that infertility cannot be adequately assessed by evaluating the female partner alone. Standard semen analysis remains an essential component of male evaluation, while selected patients require endocrine, genetic, imaging, or specialized sperm investigations. The WHO sixth edition semen manual provides standardized procedures intended to improve the quality and comparability of semen testing.

A second major finding was the increasing recognition of **modifiable risk factors**. Obesity, metabolic dysfunction, smoking, excessive alcohol use, sedentary lifestyle, sexually transmitted infections, and certain environmental exposures may adversely influence reproductive health. The WHO's 2025 global infertility guideline emphasizes prevention, early diagnosis, evidence-based treatment, healthy lifestyle practices, and equitable access to fertility care.

A third important finding concerned **emerging reproductive determinants**. Reproductive tract microbiome alterations, oxidative stress, endocrine-disrupting chemicals, epigenetic mechanisms, sperm DNA integrity, metabolomics, proteomics, and artificial intelligence are increasingly investigated as potential contributors or diagnostic tools. However, the evidence for several emerging technologies remains heterogeneous and insufficiently standardized for universal clinical

implementation.Finally, the reviewed literature demonstrated a clear movement toward **personalized and couple-centered infertility care**, in which conventional clinical assessment is integrated with molecular, genetic, microbiological, metabolic and environmental information. Current ASRM guidance similarly emphasizes systematic, expeditious and cost-effective infertility evaluation using the least invasive methods capable of identifying common causes.

DISCUSSION

Infertility is increasingly recognized as a complex reproductive health disorder involving biological, genetic, endocrine, metabolic, infectious, environmental, behavioral, psychological, and social determinants. The present review synthesizes evidence addressing these interacting factors and highlights the transition from conventional infertility assessment toward a more comprehensive, couple-centered and increasingly personalized approach. The reviewed literature demonstrates that infertility cannot be adequately explained by a single mechanism in many individuals and that evaluation should encompass both partners while considering potentially modifiable risk factors and emerging biological pathways [1-3].

Global burden and changing concept of infertility

The global burden of infertility is substantial. WHO estimates indicate that approximately one in six reproductive-aged individuals experience infertility during their lifetime, emphasizing that infertility is a major public-health issue rather than an uncommon clinical problem [1,2]. The high prevalence is observed across high-, middle-, and low-income settings, although the causes, availability of diagnostic services, and access to treatment vary considerably between populations. The 2025 WHO guideline further emphasizes that fertility care should include prevention, diagnosis, and treatment and should be integrated into broader reproductive healthcare systems [26].

The increasing recognition of infertility as a disease affecting either the male or female reproductive system represents an important conceptual development. Historically, infertility was frequently considered predominantly a female problem, resulting in disproportionate investigation and social blame directed toward women. Contemporary evidence demonstrates that male factors make a substantial contribution and that both partners should be evaluated concurrently [2,3,9]. This couple-centered model is particularly important because abnormalities may coexist in both partners, while in some couples no definite cause is identified using conventional investigations.

The burden of infertility extends beyond failure to conceive. Couples may experience anxiety, depression, social stigma, relationship difficulties, reduced quality of life, and significant financial consequences. WHO has specifically emphasized the inequitable distribution of fertility services, with high costs and limited availability representing major barriers, particularly in low- and middle-income countries [2,22,26]. Thus, the clinical challenge is not only to improve diagnostic accuracy but also to ensure that effective fertility care is accessible and affordable.

Female age and reproductive aging

Advancing female age remains one of the most important determinants of reproductive potential. The decline in fertility with age reflects both quantitative and qualitative changes in the ovarian follicular pool. Although ovarian reserve decreases progressively, the age-related decline in oocyte competence and increasing chromosomal abnormalities are particularly important contributors to reduced fecundity [3,5].

The increasing tendency to postpone childbearing has made reproductive aging increasingly relevant in contemporary fertility medicine. Higher education, career development, economic considerations, delayed marriage, and changing family structures have contributed to later attempts at conception. Although assisted reproductive technologies can provide important opportunities for individuals with age-related infertility, ART cannot completely overcome the biological effects of advancing maternal age. Consequently, fertility counseling should incorporate age-related reproductive decline in an individualized and non-directive manner [3].

Ovarian reserve testing has improved the ability to characterize reproductive potential, particularly in women undergoing fertility treatment. AMH and AFC are useful indicators of ovarian reserve and are valuable for anticipating ovarian response to stimulation. However, their clinical interpretation requires caution. As emphasized by ASRM, ovarian reserve tests should not be interpreted as direct measures of natural fertility and should not be used as screening tests in women who do not meet criteria for

infertility [5]. This distinction is important because an abnormal ovarian reserve marker may create unnecessary anxiety if interpreted as equivalent to imminent infertility.

Ovulatory dysfunction and PCOS

Ovulatory dysfunction is one of the most established causes of female infertility. PCOS represents a particularly important cause because of the coexistence of anovulation, hyperandrogenism, insulin resistance, and metabolic abnormalities [4]. The reproductive consequences of PCOS are heterogeneous, ranging from occasional ovulatory disturbances to persistent anovulation.

The relationship between PCOS and infertility also illustrates the importance of considering metabolic health within reproductive medicine. Obesity and insulin resistance can aggravate hyperandrogenism and ovulatory dysfunction, while lifestyle factors may modify the severity of reproductive manifestations. Consequently, infertility management in women with PCOS should not focus exclusively on ovulation induction but should also address metabolic risk, body weight, lifestyle, and long-term health.

The contemporary approach therefore favors individualized evaluation rather than assuming that all women with PCOS have the same degree of infertility. Menstrual pattern, evidence of ovulation, age, ovarian reserve, duration of infertility, partner factors, and metabolic characteristics should be considered collectively.

Tubal disease and reproductive tract infections

Tubal disease remains an important and potentially preventable cause of female infertility [6,14]. Sexually transmitted infections, particularly infections capable of causing pelvic inflammatory disease, may produce tubal inflammation followed by fibrosis, adhesions, and obstruction. A major clinical difficulty is that some reproductive tract infections remain asymptomatic, meaning that substantial tubal damage may develop before the individual seeks medical attention.

The prevention and early treatment of sexually transmitted infections therefore represent important infertility-prevention strategies. WHO specifically identifies untreated STIs as an important preventable contributor to infertility [26]. This reinforces the need to integrate sexual-health services, STI screening where appropriate, partner management, and reproductive-health education into infertility prevention.

Genital tuberculosis represents an additional consideration in regions with a high tuberculosis burden. Female genital tuberculosis can affect the fallopian tubes, endometrium, and other reproductive structures and may produce tubal obstruction, intrauterine adhesions, menstrual abnormalities, and infertility [14]. In endemic regions, the possibility of genital tuberculosis should therefore be considered in women with otherwise unexplained tubal-factor infertility, particularly when supported by epidemiological and clinical features.

Endometriosis and infertility

Endometriosis represents an important and complex cause of infertility. The relationship between endometriosis and reduced fertility cannot be explained solely by mechanical pelvic distortion. In addition to adhesions and anatomical disruption, inflammation, oxidative stress, altered follicular development, impaired oocyte competence, altered endometrial receptivity, and immune dysregulation have all been proposed as contributing mechanisms [7,20].

Recent literature reinforces the complexity of this relationship. Contemporary reviews suggest that endometriosis may affect reproductive outcomes through alterations in gametes, embryos, endometrial function, and implantation biology [27]. A recent systematic review and meta-analysis also evaluated the effect of endometriosis on IVF outcomes, emphasizing that the effect may vary according to disease characteristics and treatment context [28].

An important clinical issue is the balance between surgical treatment and preservation of ovarian reserve. Although surgery can be beneficial in selected patients, particularly when there is significant anatomical disease or specific symptoms, ovarian surgery may reduce ovarian reserve in some circumstances. Recent literature therefore supports a more individualized approach rather than automatically recommending surgery before fertility treatment [27,28]. This is particularly important in younger women with endometriomas and diminished ovarian reserve.

Uterine factors and implantation

Uterine and endometrial abnormalities may impair implantation and fertility. Fibroids, endometrial polyps, adhesions, adenomyosis, and congenital uterine abnormalities may alter the uterine environment or distort the endometrial cavity [8]. However, not every structural abnormality has the same reproductive significance. The location and relationship of the lesion to the uterine cavity are important when determining clinical relevance.

Transvaginal ultrasonography remains an important first-line investigation, while hysterosalpingography and sonohysterography may be used according to the clinical question [3]. This supports the broader principle that infertility evaluation should proceed systematically and should prioritize investigations with established diagnostic value rather than indiscriminate testing.

Male infertility and semen quality

Male infertility represents a major component of overall couple infertility and should not be considered a secondary aspect of fertility assessment. Semen analysis remains the cornerstone of initial male evaluation [9]. The WHO sixth edition laboratory manual provides standardized procedures for semen collection, examination, processing, quality control, and interpretation and was specifically developed to improve laboratory quality and comparability between laboratories.

Importantly, semen parameters should not be interpreted as an absolute binary classification of fertile versus infertile men. WHO emphasizes that semen examination provides information about male reproductive function, while fertility is ultimately a characteristic of the couple rather than an isolated laboratory value.

Male reproductive dysfunction may result from abnormalities of sperm production, transport, endocrine regulation, sexual function, testicular pathology, infection, genetic abnormalities, obesity, lifestyle exposures, and environmental factors. This multifactorial model supports the need for a detailed reproductive and medical history rather than reliance on semen analysis alone.

Genetic contribution to infertility

Genetic abnormalities are particularly important in selected severe infertility phenotypes. Chromosomal abnormalities, Y-chromosome microdeletions, and genetic causes of congenital absence of the vas deferens may explain severe male-factor infertility [10]. In females, genetic and chromosomal abnormalities may contribute to premature ovarian insufficiency, gonadal dysfunction, recurrent reproductive failure, and other infertility phenotypes.

The increasing availability of molecular genetic testing is expanding the diagnostic possibilities. However, genetic investigations should remain clinically targeted. Unrestricted testing may generate variants of uncertain significance, incidental findings, and additional costs without necessarily improving clinical management. Genetic counseling and appropriate interpretation are therefore essential components of reproductive genetic evaluation.

Obesity, metabolic dysfunction and infertility

Obesity has emerged as an important reproductive-health concern. Its effects on fertility are mediated through endocrine, metabolic, inflammatory, and oxidative pathways. In women, obesity may contribute to anovulation, insulin resistance, hyperandrogenism, altered follicular development, and impaired endometrial function. In men, obesity may be associated with altered testosterone physiology, increased aromatase activity, oxidative stress, and impaired spermatogenesis [11,12].

Recent evidence has further explored whether weight reduction before ART improves reproductive outcomes. A 2024 systematic review and meta-analysis evaluated weight-loss interventions before IVF in women with overweight or obesity and infertility, highlighting the importance of distinguishing improvements in metabolic health and intermediate reproductive measures from definitive outcomes such as live birth [29].

This distinction is clinically important. Weight management should be promoted primarily as part of overall health and reproductive optimization, but clinicians should avoid presenting weight loss as a guaranteed treatment for infertility. Management should be individualized according to age, ovarian reserve, infertility duration, metabolic health, and treatment urgency.

Lifestyle factors

Smoking, alcohol exposure, recreational drugs, sedentary behavior, inadequate physical activity, nutritional imbalance, and abnormal body weight can influence reproductive health [12]. Tobacco exposure is particularly important because of its associations with reproductive aging, ovarian dysfunction, oxidative stress, and adverse sperm characteristics.

Lifestyle modification is therefore a potentially accessible component of infertility prevention. Unlike many emerging diagnostic technologies, lifestyle interventions can also provide broader cardiovascular, metabolic, and psychological health benefits. The WHO 2025 guideline specifically emphasizes prevention and identifies tobacco use and untreated STIs among important modifiable risk factors [26].

However, infertility counseling should avoid stigmatizing individuals based on lifestyle or body weight. Infertility is rarely attributable to one behavioral factor, and lifestyle modification should complement rather than replace appropriate medical investigation.

Psychological stress and mental health

Infertility can generate substantial psychological distress. The repeated cycle of unsuccessful conception attempts, diagnostic procedures, uncertainty, financial expenditure, and treatment failure may contribute to anxiety, depression, relationship difficulties, and reduced quality of life [13].

Recent evidence reinforces the importance of psychosocial care. A systematic review and meta-analysis examining psychological factors in women undergoing IVF/ICSI reported associations between higher anxiety and depression and lower treatment success, although interpretation of such associations requires caution because psychological distress may itself be influenced by infertility severity, previous treatment failures, and socioeconomic factors [30].

Importantly, psychological support should not be framed as implying that infertility is caused by stress. Rather, counseling and psychosocial support are important because infertility itself can generate substantial emotional burden. WHO's current guidance similarly emphasizes people-centered care and the psychosocial consequences of infertility [26].

Oxidative stress and cellular mechanisms

Oxidative stress provides a potential mechanistic link between several established and emerging infertility risk factors. Reactive oxygen species have physiological functions in reproductive biology, but excessive oxidative stress can damage lipids, proteins, mitochondria, and DNA [17].

Spermatozoa are particularly susceptible because of their high polyunsaturated fatty-acid content and limited antioxidant defenses. Oxidative injury can impair sperm motility and membrane function and may contribute to sperm DNA damage. Similar mechanisms have been investigated in relation to ovarian aging, endometriosis, obesity, metabolic disease, infection, and environmental exposure.

Nevertheless, the clinical application of oxidative-stress biomarkers remains limited by differences in laboratory methods and lack of universally standardized thresholds. Therefore, oxidative stress is currently better regarded as an important biological mechanism and research target than as a universal routine diagnostic test.

Sperm DNA fragmentation as an emerging diagnostic marker

Conventional semen analysis does not fully characterize sperm genomic integrity. Sperm DNA fragmentation has therefore attracted considerable interest as a complementary measure of sperm quality. Recent reviews have summarized potential causes, laboratory approaches, and clinical applications of sperm DNA fragmentation testing [31,32].

Factors associated with increased sperm DNA damage may include oxidative stress, advanced paternal age, smoking, infection, varicocele, obesity, and environmental exposures. However, considerable methodological heterogeneity exists between DNA-fragmentation assays, and thresholds are not uniform across platforms.

Consequently, sperm DNA fragmentation should not replace conventional semen analysis. Rather, it may provide additional information in selected clinical circumstances, particularly when conventional semen parameters do not adequately explain reproductive outcomes.

Reproductive tract microbiome

The reproductive tract microbiome represents one of the most rapidly developing areas of infertility research. The vaginal microbial environment is often characterized by a predominance of Lactobacillus species, and alterations in microbial composition have been investigated in relation to bacterial vaginosis, inflammation, implantation, and ART outcomes [15,24].

The proposed mechanisms are biologically plausible. Microbial dysbiosis may influence local pH, inflammatory signaling, epithelial integrity, immune responses, and susceptibility to ascending infection. The endometrial microbiome has also generated considerable interest, although its characterization remains technically challenging.

Importantly, the presence of an association does not establish that microbiome modification improves fertility. Recent systematic evidence has continued to examine associations between vaginal microbiome profiles and assisted reproduction outcomes [33].

The major limitations include differences in sampling sites, sequencing techniques, definitions of dysbiosis, timing of sampling, antibiotic exposure, and patient populations. Therefore, microbiome profiling remains promising but should not currently replace established infertility investigations.

Environmental exposures and endocrine-disrupting chemicals

Environmental exposure is an increasingly important emerging determinant of reproductive health. Individuals may be exposed to mixtures of endocrine-disrupting chemicals through food packaging, consumer products, occupational environments, pesticides, household materials, and air pollution [16].

Potential mechanisms include disruption of hormone receptors, altered steroidogenesis, oxidative stress, mitochondrial dysfunction, epigenetic changes, and impairment of gametogenesis. Evidence concerning bisphenols, phthalates, pesticides, and other chemical classes has generated increasing concern about potential reproductive effects.

However, environmental epidemiology presents major methodological challenges. Exposure levels fluctuate over time, individuals are exposed to mixtures rather than single chemicals, and reproductive outcomes are influenced by age, lifestyle, socioeconomic factors, and underlying disease. Consequently, associations reported in observational studies should not automatically be interpreted as definitive causal relationships.

The growing evidence nonetheless supports greater attention to environmental reproductive health and the development of strategies to reduce unnecessary exposure, particularly in occupationally exposed populations.

Unexplained infertility

Unexplained infertility remains an important clinical category. It is diagnosed when standard assessment does not reveal abnormalities of ovulation, tubal patency, uterine anatomy, or semen parameters [20]. The term should not be interpreted as meaning that the couple has no biological abnormality. Instead, it reflects limitations in the sensitivity of currently available routine diagnostic tools.

Potential mechanisms include subtle sperm dysfunction, impaired oocyte competence, fertilization abnormalities, embryo developmental abnormalities, altered endometrial receptivity, endometriosis, immune mechanisms, genetic abnormalities, epigenetic changes, and microbiome disturbances.

The current evidence therefore supports caution regarding the widespread adoption of expensive commercial tests marketed as solutions for unexplained infertility. A diagnostic test should demonstrate analytical validity, clinical validity, and—most importantly—clinical utility before routine adoption.

Diagnostic evaluation: toward a rational and individualized approach

The reviewed evidence supports a structured approach to infertility evaluation. ASRM recommends systematic, expeditious, and cost-effective evaluation, beginning with the least invasive methods capable of identifying common causes [3]. The evaluation should include assessment of ovulatory status, female reproductive anatomy and tubal patency, and semen analysis of the male partner.

The timing of evaluation should also be individualized. In women younger than 35 years without concerning clinical features, evaluation is generally initiated after 12 months of unsuccessful attempts; evaluation is recommended after 6 months in women aged 35 years or older, while more immediate assessment may be warranted after age 40 or when known infertility risk factors are present [3].

This age-based framework is clinically useful because it balances avoidance of unnecessary investigation in low-risk younger individuals with the need to minimize treatment delay in women with declining reproductive potential.

Emerging molecular diagnostics

The diagnostic landscape is rapidly expanding beyond conventional clinical and laboratory methods. Molecular approaches such as metabolomics, proteomics, transcriptomics, epigenetic profiling, and advanced genetic testing may eventually help identify biological subgroups currently classified as having unexplained infertility [21,25].

These technologies could potentially permit more precise characterization of oocyte quality, sperm function, embryo competence, endometrial receptivity, and reproductive tract microbial environments. However, the translation from research biomarker to clinically useful diagnostic test remains challenging.

A clinically useful biomarker should demonstrate reproducibility, standardized methodology, validated thresholds, incremental diagnostic value over existing tests, and evidence that its use changes management and improves meaningful reproductive outcomes.

Artificial intelligence and assisted reproductive technology

Artificial intelligence has emerged as another major area of innovation in reproductive medicine. AI models are being evaluated for embryo selection, sperm analysis, follicular assessment, prediction of implantation, and prediction of IVF outcomes.

A systematic review of AI-assisted embryo selection found promising performance compared with conventional embryologist assessment, although the included studies were heterogeneous and many lacked prospective external validation [34].

More recent evidence has continued to support the potential of AI while emphasizing the need for robust validation. A 2025 systematic review and diagnostic meta-analysis of AI-based embryo assessment reported promising predictive performance for implantation outcomes but also highlighted the need for larger and more diverse datasets [35].

An important limitation is that AI performance may deteriorate when algorithms are transferred from one fertility center to another because patient characteristics, laboratory protocols, imaging systems, and embryo culture conditions differ. Recent evidence has also raised concerns regarding model instability and inconsistent embryo ranking across datasets [36].

Therefore, AI should currently be viewed as a decision-support technology rather than a replacement for trained embryologists and reproductive specialists. Future studies should prioritize external validation, transparency, fairness, reproducibility, calibration, and clinically meaningful outcomes such as cumulative live birth rather than surrogate measures alone.

Assisted reproductive technologies and equity

ART has transformed infertility care and has enabled millions of individuals and couples to achieve parenthood. However, access remains highly unequal. Treatment costs, availability of trained personnel, laboratory infrastructure, geographic location, regulatory frameworks, and health insurance coverage substantially influence access [22,26].

WHO's 2025 guideline places particular emphasis on reducing inequities and promoting cost-effective care across the continuum from prevention and diagnosis to treatment [26].

This is particularly relevant in low- and middle-income countries, where advanced ART may be available predominantly in private urban centers while basic infertility evaluation may itself remain inaccessible. A public-health approach should therefore strengthen primary reproductive healthcare, STI prevention, basic diagnostic laboratory services, appropriate referral systems, and affordable treatment pathways before focusing exclusively on high-technology interventions.

Prevention and public-health implications

One of the most important implications of the current evidence is that a proportion of infertility is potentially preventable. STI prevention and treatment, smoking cessation, healthy weight management, management of metabolic disorders, avoidance of unnecessary gonadotoxic exposures, and reproductive-health education can contribute to preservation of reproductive potential [6,12,23,26].

Fertility awareness is particularly relevant because delayed childbearing is increasingly common. Appropriate counseling should provide accurate information about the age-related decline in female fertility without creating unnecessary fear or pressure.

Prevention should also address male reproductive health. Men should be included in reproductive-health education and should receive appropriate counseling regarding tobacco, alcohol, anabolic steroid use, obesity, occupational exposures, infections, and other potentially modifiable factors.

Personalized and couple-centered fertility medicine

The collective evidence supports a transition from a conventional organ-specific model toward personalized reproductive medicine. The traditional approach often divides infertility into female and male categories; however, reproductive outcomes are determined by interactions between gametes, reproductive tract anatomy, endocrine function, metabolic health, environmental factors, and embryo development.

Personalized fertility care could integrate age, ovarian reserve, ovulatory function, tubal status, endometriosis, semen characteristics, genetic information, metabolic status, infection history, environmental exposures, and previous treatment response [25].

Such integration may reduce unnecessary investigations and enable more rational treatment selection. Nevertheless, personalized medicine should remain evidence-based. The availability of large quantities of biological data does not automatically guarantee better clinical decisions.

Strengths of the current evidence

The principal strength of the literature is its multidisciplinary nature. Infertility research now encompasses reproductive endocrinology, gynecology, urology, microbiology, genetics, molecular biology, epidemiology, environmental health, psychology, and artificial intelligence.

Another strength is the increasing availability of international evidence-based guidance. The WHO 2025 guideline provides a comprehensive global framework covering prevention, diagnosis, and treatment and explicitly addresses inequities in fertility care [26].

The WHO semen manual also provides standardized laboratory procedures that improve the reliability of semen analysis and facilitate comparison across laboratories [9].

Limitations of the current evidence

Despite substantial progress, important limitations remain. First, infertility studies use heterogeneous definitions, populations, diagnostic criteria, and outcomes. Second, many emerging biomarkers are supported predominantly by observational or exploratory studies. Third, microbiome studies vary considerably in sampling and sequencing methods. Fourth, environmental exposure studies frequently involve complex mixtures and cannot easily establish causality.

Similarly, AI studies often rely on retrospective datasets generated within individual centers. Differences in laboratory practice, imaging equipment, patient demographics, embryo culture conditions, and outcome definitions may limit generalizability. Recent evidence of model instability further emphasizes the importance of independent external validation [36].

Another important limitation is the underrepresentation of low-resource populations in advanced infertility research. Technologies developed in high-resource settings may not necessarily be feasible or cost-effective elsewhere.

Future research priorities

Future infertility research should move toward large, prospective, multicenter studies incorporating standardized definitions and clinically meaningful

outcomes. Particular priorities include validation of reproductive microbiome biomarkers, development of standardized environmental exposure assessments, evaluation of molecular sperm and oocyte biomarkers, and prospective validation of AI-based diagnostic systems.

Research should also prioritize outcomes that matter to patients, particularly healthy live birth, cumulative live birth, treatment safety, quality of life, and cost-effectiveness. Surrogate outcomes such as embryo morphology, biochemical pregnancy, or changes in individual biomarkers should not automatically be considered evidence of improved fertility.

The WHO's current framework provides an important foundation for this direction by emphasizing evidence-based, equitable, affordable, and people-centered infertility care [26]. The future of infertility medicine will likely depend not on a single diagnostic test or technology but on integration of multiple validated information sources into a coherent clinical decision-making framework.

Overall interpretation

Taken together, references 1–26 establish the major conventional causes and diagnostic principles of infertility, while the newer evidence represented by references 27–36 demonstrates rapid expansion into microbiome science, sperm DNA integrity, environmental reproductive health, AI-assisted ART, and personalized reproductive medicine.The evidence supports a hierarchy of clinical importance. Established causes such as advancing reproductive age, ovulatory dysfunction, tubal disease, endometriosis, uterine pathology, and male-factor infertility should remain the foundation of clinical evaluation. Modifiable factors such as smoking, obesity, metabolic disease, and reproductive tract infections should receive greater attention because prevention and early intervention may reduce infertility burden. Emerging areas such as microbiome profiling, sperm DNA fragmentation, environmental biomarkers, metabolomics, proteomics, and AI should be considered promising but should not displace validated diagnostic approaches until sufficient evidence of clinical utility becomes available.

Ultimately, infertility should be approached as a **couple-centered, multifactorial and personalized reproductive-health disorder**. The integration of conventional reproductive medicine with microbiology, genetics, molecular diagnostics, environmental health, and artificial intelligence has the potential to improve diagnostic precision and treatment selection. However, technological advancement must remain accompanied by rigorous validation, affordability, ethical oversight, and equitable access to care.

CONCLUSION

Infertility is a complex and multifactorial reproductive health disorder that affects both men and women and has substantial medical, psychological, social, and economic consequences. The evidence reviewed in the present article demonstrates that infertility results from an interaction of established reproductive abnormalities and increasingly recognized metabolic, infectious, lifestyle, environmental, genetic, molecular, and psychosocial factors.

Female infertility is predominantly associated with advancing reproductive age, ovulatory dysfunction, PCOS, diminished ovarian reserve, tubal disease, endometriosis, and uterine abnormalities, whereas male infertility is frequently associated with abnormal semen parameters, impaired spermatogenesis, endocrine and metabolic disorders, genetic abnormalities, infections, and lifestyle-related factors. Importantly, both partners should be evaluated concurrently because male and female factors may coexist.

Reproductive tract infections, particularly sexually transmitted infections and genital tuberculosis in endemic settings, remain important potentially preventable causes of infertility. Similarly, obesity, smoking, unhealthy lifestyle patterns, metabolic disorders, and certain environmental exposures represent potentially modifiable determinants of reproductive health. Increasing evidence regarding oxidative stress, endocrine-disrupting chemicals, sperm DNA fragmentation, and reproductive tract microbiome alterations suggests that several biological mechanisms remain incompletely characterized.

Conventional diagnostic approaches—including detailed reproductive history, assessment of ovulation, ovarian reserve evaluation, pelvic ultrasonography, assessment of tubal patency, and standardized semen analysis—remain the foundation of infertility evaluation. Emerging technologies such as genetic testing, sperm DNA fragmentation analysis, reproductive microbiome profiling, metabolomics, proteomics, and artificial intelligence-

assisted embryo and sperm assessment offer promising opportunities for more precise and personalized diagnosis. However, these technologies require further standardization, external validation, and demonstration of clinical utility before widespread routine implementation.

Future infertility care should therefore move toward a **personalized, evidence-based and couple-centered model** integrating reproductive endocrinology, gynecology, andrology, microbiology, genetics, environmental health, and molecular medicine. Prevention and early recognition of modifiable risk factors should be emphasized alongside timely investigation and appropriate treatment. At the same time, access to fertility services must become more affordable, equitable, and patient-centered, particularly in resource-limited settings.

Overall, advances in infertility research are shifting the field from conventional diagnosis toward an integrated understanding of reproductive health. Continued high-quality prospective and multicenter research is required to validate emerging biomarkers, clarify the role of the reproductive microbiome and environmental exposures, improve artificial-intelligence-based technologies, and translate molecular discoveries into clinically meaningful improvements in fertility and live-birth outcomes. The ultimate goal should be not only to improve conception rates but also to provide safe, accessible, scientifically robust, and individualized fertility care for all individuals and couples affected by infertility.

Limitations

1. Considerable heterogeneity existed among the included studies.
2. Many emerging risk factors were supported mainly by observational evidence.
3. Diagnostic and laboratory methods varied between studies.
4. Evidence regarding the reproductive microbiome and molecular biomarkers remains limited.
5. Environmental exposures are difficult to measure accurately and establish causality for.
6. Studies from low-resource settings were relatively limited.
7. Publication and selection bias cannot be completely excluded.
8. Emerging technologies such as AI require further prospective validation.
9. Long-term clinical outcomes were not consistently reported.
10. Further large, multicenter prospective studies are required to confirm current findings.

FUTURE PROSPECTS

1. **Personalized fertility care:** Integration of clinical, hormonal, genetic, metabolic, microbiological, and environmental information may enable individualized diagnosis and treatment.
2. **Reproductive microbiome:** Further research may establish the role of vaginal and endometrial microbiota as diagnostic or prognostic biomarkers.
3. **Molecular diagnostics:** Genomics, epigenetics, metabolomics, proteomics, and sperm DNA testing may improve identification of currently unexplained infertility.
4. **Artificial intelligence:** AI-based analysis of sperm, oocytes, embryos, and reproductive imaging may improve diagnostic accuracy and treatment selection.
5. **Environmental reproductive health:** Prospective studies are needed to clarify the effects of endocrine-disrupting chemicals, air pollution, and other environmental exposures.
6. **Preventive strategies:** Greater emphasis should be placed on STI prevention, healthy lifestyle, metabolic health, fertility awareness, and preservation of reproductive potential.
7. **Improved male infertility evaluation:** Greater integration of genetic, molecular, hormonal, and sperm-function testing may improve diagnosis of male-factor infertility.
8. **Affordable fertility care:** Development of cost-effective diagnostic and treatment pathways is essential, particularly in low- and middle-income countries.
9. **Better clinical validation:** Emerging biomarkers and technologies should undergo large, multicenter prospective studies before routine clinical implementation.
10. **Patient-centered outcomes:** Future research should prioritize cumulative live birth, treatment safety, quality of life, affordability, and long-term maternal and neonatal outcomes rather than surrogate biomarkers alone.

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