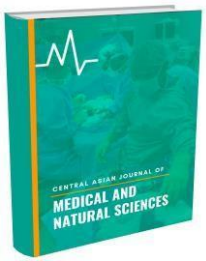

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Article

Optimizing Clinical Evaluation of the Infertile Male: Current Guidelines, Gaps, and Future Directions

Dr Iyama Anslem Chester[1]

1. Department of Surgery (Urology Unit), Rivers State University, Port Harcourt, Rivers State, Nigeria
* Correspondence: anslemiyama@gmail.com

Abstract: Male infertility contributes substantially to the global burden of infertility and is implicated in approximately half of infertile partnerships. Contemporary evaluation has expanded beyond conventional semen analysis to include endocrine, genetic, and targeted imaging assessments, reflecting a broader understanding of male reproductive dysfunction as both a fertility disorder and a potential marker of systemic disease. Still unable to identify specific diagnostic gaps, and make an overview of future directions which are likely to provide advances in precision diagnostics and clinical decision-making. Objective: To summarize and discuss contemporary recommendations among the American Urological Association and American Society for Reproductive Medicine, the European Association of Urology and the World Health Organization jointly, as well as the latest peer-reviewed research on epidemiology, genetics, sperm DNA integrity and advanced diagnostics as related to male infertility. Modem recommendations advocate an evaluated approach that includes thorough reproductive history, medical history and physical examination, a minimum of one well-executed semen analysis, directed endocrine assessment, judicious genetic investigation and imaging in narrowly defined clinical contexts. There are still large diagnostic gaps, particularly for men classified as either idiopathic infertility or severe spermatogenic failure. The present approaches for assessment are clinically valid but not comprehensive. Integration of validated molecular diagnostics, broader genomic testing in selected patients, and outcome-focused research may improve diagnostic yield and support more individualized management strategies.

Keywords: Male Infertility, Semen Analysis, Azoospermia, Reproductive Genetics, Sperm DNA Fragmentation, Infertility Evaluation

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1. Introduction

Male infertility affects clinical practice across urology, andrology, and reproductive medicine because male factors contribute to about 40-50% of infertility cases worldwide. Contemporary diagnostic frameworks no longer view male infertility as a problem defined solely by semen parameters; instead, they approach it as a heterogeneous syndrome involving testicular, endocrine, genetic, obstructive, and environmental contributors [1][2][3][4][5].

The key international standards that shape current practice include the revised AUA/ASRM male infertility guideline for 2024, the EAU Sexual and Reproductive Health guideline for 2025 and the sixth edition WHO laboratory manual for the examination of human semen [1][2][3]. These documents coalesce around four key principles: that the male partner be evaluated as soon as possible, that the couple be evaluated in tandem, that

semen analysis be subject to established laboratory standards, and that any further testing be phenotype-driven as opposed to universal [1][2][3].

Background

Infertility affects a substantial number of couples globally and represents a major component of reproductive health care. Estimates suggest that approximately one in seven couples experience difficulty achieving conception, with male reproductive factors contributing to roughly half of these cases. The underlying causes of male infertility include abnormalities in spermatogenesis, hormonal regulation, genetic factors, anatomical obstruction, and environmental influences.

Diagnostic evaluation of the infertile male has traditionally been mainly based on semen analysis, examining sperm concentration, motility and morphology. Despite this investigation being a fairly simple one, it doesn't shed much light on the underlying biological mechanisms involved in defective fertility.

For decades, improvements in terms of reproductive endocrinology, genetics, and molecular biology have helped clinicians better comprehend precisely what causes male infertility. These developments have prompted the introduction of more comprehensive diagnostic approaches. Professional bodies including the American Urological Association (AUA), American Society for Reproductive Medicine (ASRM), and European Association of Urology (EAU) have developed clinical guidelines outlining recommended evaluation pathways.

Despite these efforts, a substantial proportion of infertile men continue to receive a diagnosis of unexplained or idiopathic infertility. This limitation highlights the need for continued research into the underlying mechanisms of impaired male fertility and improved diagnostic methodologies.

2. Materials and Methods

This study conducts a narrative review of current approaches to the clinical assessment of the male partner; in cases of couple infertility. Methods A structured synthesis of current clinical guidelines, peer-reviewed literature, and other authoritative medical references relevant to MA pathology in the setting of male infertility diagnostics. The current standards and recommendation of diagnostics were primarily assessed against three major international guideline documents — the American Urological Association and American Society for Reproductive Medicine 2019 guidelines, the European Association of Urology 2020 guidelines, and the World Health Organization 2021 laboratory manual for the examination of human semen. A more thorough understanding of the current clinical practice and its limitations was derived from structured literature review of relevant publications that targeted epidemiology, reproductive endocrinology, genetic testing, sperm DNA integrity, and novel diagnostic approaches. The analysis consisted of defining the main elements of guideline-based assessment, namely, a detailed medical and reproductive history, focused physical examination, a laboratory semen analysis performed according to established laboratory protocols, endocrine testing, genetic testing when indicated and imaging when clinically indicated. In addition to summarising relevant established diagnostic pathways, the review also provided an appraisal of cases in which existing assessment methods are limited, particularly regarding those considered as idiopathic infertility and severe spermatogenic disorders. To expand the discussion of emerging diagnostic methods such as expanded genetic testing, sperm DNA fragmentation testing, and multi-omics technologies we also reviewed evidence from recent molecular and genomic studies. This methodological approach of combining guideline recommendations with newer science provides a current snapshot of clinical assessment practices while identifying diagnostic deficiencies and future diagnostics opportunities to accurately assess and manage male infertility.

3. Results and Discussion

Epidemiology and Clinical Significance

Infertility affects an estimated 10-15% of couples, with male factors identified in roughly half of cases [4][6][7]. That pang of guilt goes beyond just reproduction because there is now considerable evidence that substandard or aberrant semen quality and sterility is a long-term health risk factor for a spectrum of diseases, most notably cancer and metabolic or cardiovascular disease [4],[5],[8].

Moreover, systematic reviews indicating that sperm counts are decreasing in many parts of the world have further highlighted population-level worry. Put simply, whereas causal attribution is difficult, the trend has fuelled interest in environmental exposures, obesity, smoking, alcohol, endocrine disruptors and occupational risk factors as causative agents in poor male reproductive health [6],[7].

Current Guideline-Based Evaluation

The initial clinical evaluation should begin with a detailed reproductive, sexual, medical, surgical, family, and social history. Current guidance emphasizes prior paternity, duration of infertility, intercourse frequency and timing, pubertal development, cryptorchidism, sexually transmitted infections, scrotal or inguinal surgery, medication exposure, testosterone or anabolic steroid use, and relevant systemic illness [2],[3],[5],[7].

Focused physical examination remains central. Examination should assess body habitus and androgenization, penile anatomy, testicular size and consistency, epididymal fullness, presence or absence of the vas deferens, and varicocele. Varicocele remains the commonest surgically correctable lesion identified in infertile men, but guideline documents continue to stress clinical correlation rather than reflex imaging in all patients [2],[3],[5].

Semen analysis remains the cornerstone laboratory investigation. The WHO sixth edition manual provides updated standardized procedures for collection, processing, and reporting, and both AUA/ASRM and EAU guidance recognize that semen results must be interpreted in context rather than as definitive proof of fertility or infertility [1][2][3],[9]. Because of biologic variability, repeat semen analysis is advisable when the initial study is abnormal [1],[3].

When clinical findings or abnormal semen parameters suggest hypothalamic-pituitary-gonadal dysfunction, endocrine evaluation is indicated. First-line studies usually consist of serum follicle-stimulating hormone and testosterone and sometimes luteinizing hormone, prolactin, and estradiol. A high follicle-stimulating hormone usually favors impaired spermatogenesis, while low testosterone suggests hypogonadism or secondary endocrine pathology [2],[3],[5].

Genetic assessment is most pertinent in those phenotypes at high risk of selection. Karyotype analysis and Y-chromosome microdeletion testing should be performed in men with non-obstructive azoospermia or severe oligozoospermia, whereas CFTR testing is pivotal in congenital bilateral absence of vas deferens [2],[3],[5],[8],[10],[11][12]. Imaging is generally targeted (scrotal ultrasonography or transrectal ultrasonography) based on testicular findings (uncertain testicular findings), obstructive pathology (suspected obstructive pathology), or equivocal physical examination.

Evidence gaps in current practice

The principal limitation of current evaluation remains the modest predictive value of conventional semen analysis. Although indispensable, semen parameters do not map directly onto natural fecundity at the individual level. Men with apparently normal semen analyses may still experience infertility, while some men with abnormal values may achieve spontaneous conception.1,9

A second persistent limitation is the large proportion of men categorized as having idiopathic infertility. Even after standard clinical, endocrine, and genetic work-up, many

patients cannot be assigned a specific etiologic diagnosis. This reflects the incomplete reach of conventional testing and the biological complexity of spermatogenic failure [5],[11],[12].

Genetic underdiagnosis remains especially important. Traditional karyotype, Y-microdeletion, and CFTR testing explain only a subset of severe male infertility, whereas recent systematic reviews and genomic studies indicate a much broader monogenic basis for male reproductive failure than previously appreciated [5],[10][11][12].

Advanced sperm function tests also remain incompletely integrated into routine care. Sperm DNA fragmentation has been associated with poorer reproductive outcomes in some settings, but heterogeneity in assays and thresholds has limited universal adoption. Consequently, many guidelines reserve such tests for selected clinical scenarios rather than routine use in all infertile men [3],[12][13][14][15].

Future Directions

Future progress in male infertility evaluation is likely to depend on more precise phenotyping integrated with broader molecular diagnostics. Whole-exome sequencing and, in selected research or refractory settings, whole-genome approaches may increase diagnostic yield in severe spermatogenic disorders [3],[11],[12].

Multi-omics strategies involving transcriptomic, proteomic, and epigenetic assessment may eventually refine classification of men currently labeled as idiopathic. At the same time, artificial intelligence tools may improve interpretation of semen images, morphology patterns, and integrated clinical data, although validation in real-world practice remains necessary [4],[11],[12].

An additional future direction is the full integration of reproductive evaluation with men's health assessment. Because infertility may coexist with endocrine, oncologic, or cardiometabolic risk, a modern infertile male work-up should not be narrowly reproductive in scope [4],[5],[8].

4. Conclusion

The assessment of the infertile male has become more organized, evidence-based, and clinically relevant. Step 3: The clinical models of care that support early and simultaneous couple assessment, cautious application of semen analysis, phenotype-directed endocrine and genetic testing, and selective imaging were consistently endorsed as optimal practice and numerous revisions were made at the local and global level to provide clarity and precision.

However, there are significant gaps, most notably the weak discriminatory ability of semen analysis, a high rate of idiopathic infertility, and incomplete identification of genetic disease. Male infertility classification by its qualitative or quantitative descriptors lends itself to molecular diagnostics but will ultimately necessitate further refinement of molecular diagnostics and stronger consensus based prospective outcome based evidence to elevate from description toward true individualized reproductive medicine.

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