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REVIEW

Sperm morphology: Evaluating its clinical relevance in contemporary fertility practice

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Abstract

Background: The World Health Organization (WHO) recommends reporting sperm morphology in a standard semen analysis. However, the clinical utility and prognostic value of morphology is often debated.

Methods: We reviewed and summarized studies that assessed both the benefits and limitations of sperm morphology in the context of natural fertility, assisted reproductive technologies, and recurrent pregnancy loss. We additionally describe possible environmental and anatomical etiologies of teratozoospermia.

Results: Sperm morphology evaluation has continuously evolved since the release of the first WHO manual in 1980. Initially, several large studies reported significant inverse associations between fertility outcomes and teratozoospermia. Most recent studies, however, fail to show an association between sperm morphology and natural or assisted fertility outcomes.

Conclusion: Sperm morphology analysis may have limited diagnostic and prognostic value. Providers should be aware of these limitations when counseling or managing infertile patients.

KEYWORDS
andrology, assisted reproductive technology, sperm physiology

1 | BACKGROUND

Infertility affects approximately 15% of couples, and a male factor is a contributor in about 50% of these couples.[1–3] The evaluation of male factor infertility initially consists of two or more semen analyses which are used to guide potential medical and/or surgical therapies.[4] Morphologic differences in sperm were first identified by van Leeuwenhoek in 1677[5] but specific morphologic abnormalities and their potential for subfertility were not described until the 1950s.[6,7] In the 1980s, a series of papers by Kruger et al. found significantly diminished oocyte fertilization rates when sperm morphology (using the "strict" criteria) dropped below 14%,[8,9] calling more attention to the role of sperm morphology in male fertility. While examination of sperm morphology has been recommended since the 1st edition of the World Health Organization (WHO) manual released in 1980, the criteria for defining spermatozoa as "abnormal" has drastically changed over the past 40 years. Consequently, the most recent 6th edition manual contains the most detailed focus on the systematic assessment of sperm morphology to date.[10,11] Despite several iterations of the WHO criteria and widespread adoption of morphology as an integral component of a semen analysis, there has been a lack of unanimous support for this test among clinicians due, in part, to its poor analytical reliability and inconclusive prognostic value.[12,13]

With numerous conflicting studies in the scientific literature, it is critical that clinicians are aware of the limitations and advantages of sperm morphology assessment. The purpose of this review is to describe the factors that impact sperm morphology, report both natural and assisted fertility outcomes in the context of abnormal morphology, and outline future considerations that may improve the usefulness of morphology in the clinical setting.

2 | METHODS

We conducted a literature search using both PubMed/MEDLINE and Google Scholar databases. The search strategy included relevant key terms and phrases, including "sperm morphology", "male infertility", "natural pregnancy", "spontaneous pregnancy", "assisted reproductive technology", "intrauterine insemination", "in vitro fertilization". Several Boolean searches with various combinations of these terms was performed. Articles were included if they were written in English and if titles or abstracts appeared relevant to this review.

3 | KEY FINDINGS

3.1 | Factors impacting sperm morphology

Sperm morphology criteria have evolved since the introduction of the first WHO manual in 1980. In the 1st and 2nd editions of the WHO handbook, sperm labeled as "morphologically abnormal" needed to have at least one obvious, well-defined abnormality as defined by Macleod and Gold.[7,12,14] In these manuals, the cutoff for normal forms was 50–80%. The 3rd edition (1992) introduced the Kruger (Tygerberg) strict criteria, which characterized sperm with borderline abnormalities as "morphologically abnormal." Still, in this edition the reference value for normal forms was empirically reported as >30%. The 4th edition (1999) also used the strict criteria, although no precise reference value was reported; rather, a note suggested that a value <15% may be associated with lower IVF rates. The 5th and 6th edition (2010 and 2021, respectively) precisely defined and standardized reporting of morphologic abnormalities, while also decreasing the reference value to 4%.

The 6th edition handbook contains several notable recommendations and criteria. First, assessments of sperm morphology should be performed by trained personnel familiar with all criteria used to designate spermatozoa as abnormal. Frequent internal and external quality assessments should be utilized to minimize variability in results. Importantly, a major change in the 6th edition is an increased emphasis on characterizing specific defects in each region of the sperm—head, neck/midpiece, tail, and cytoplasm—rather than grouping all defects into a single "abnormal" category. (Table 1) The head should be evaluated for size, shape, and contour; the midpiece for shape, width, length, and alignment; the tail for width and smoothness; and the cytoplasm for size relative to the head.[11] Some examples of common morphologic abnormalities are illustrated in Figure 1. After completing the morphologic assessment, the percentage of abnormal forms are tabulated and reported.

3.1.1 | Environmental factors

Sperm morphology may be negatively affected by toxins or environmental/workplace exposures, although most studies examining the magnitude of this impact are retrospective and of lower quality.

TABLE 1 WHO 6th edition guidelines: classification of sperm morphology.

Location	Normal appearance	Abnormal
Head	• Smooth, regular contour • Oval • Acrosomal region 40%–70% of total area • No large vacuoles, no more than two small vacuoles	• Acrosome <40% or >70% of head area • Length-to-width ratio less than 1.5 or larger than 2 • Amorphous, asymmetrical, or non-oval • Double heads • Vacuoles >1/5th head area
Midpiece	• Slender • About the same length as sperm head • Major axis of midpiece aligned with major axis of head	• Irregular shape • Irregular thickness • Asymmetrical, angled, or bent
Tail	• Uniform caliber • ~10 times length of head • No sharp angulations	• Sharply angulated • Hairpin bends or coiled • Short • Irregular width • Multiple tails
Cytoplasmic residue	• Acceptable for cytoplasmic droplets less than 1/3 normal head size	• Residual cytoplasm >1/3 normal head size

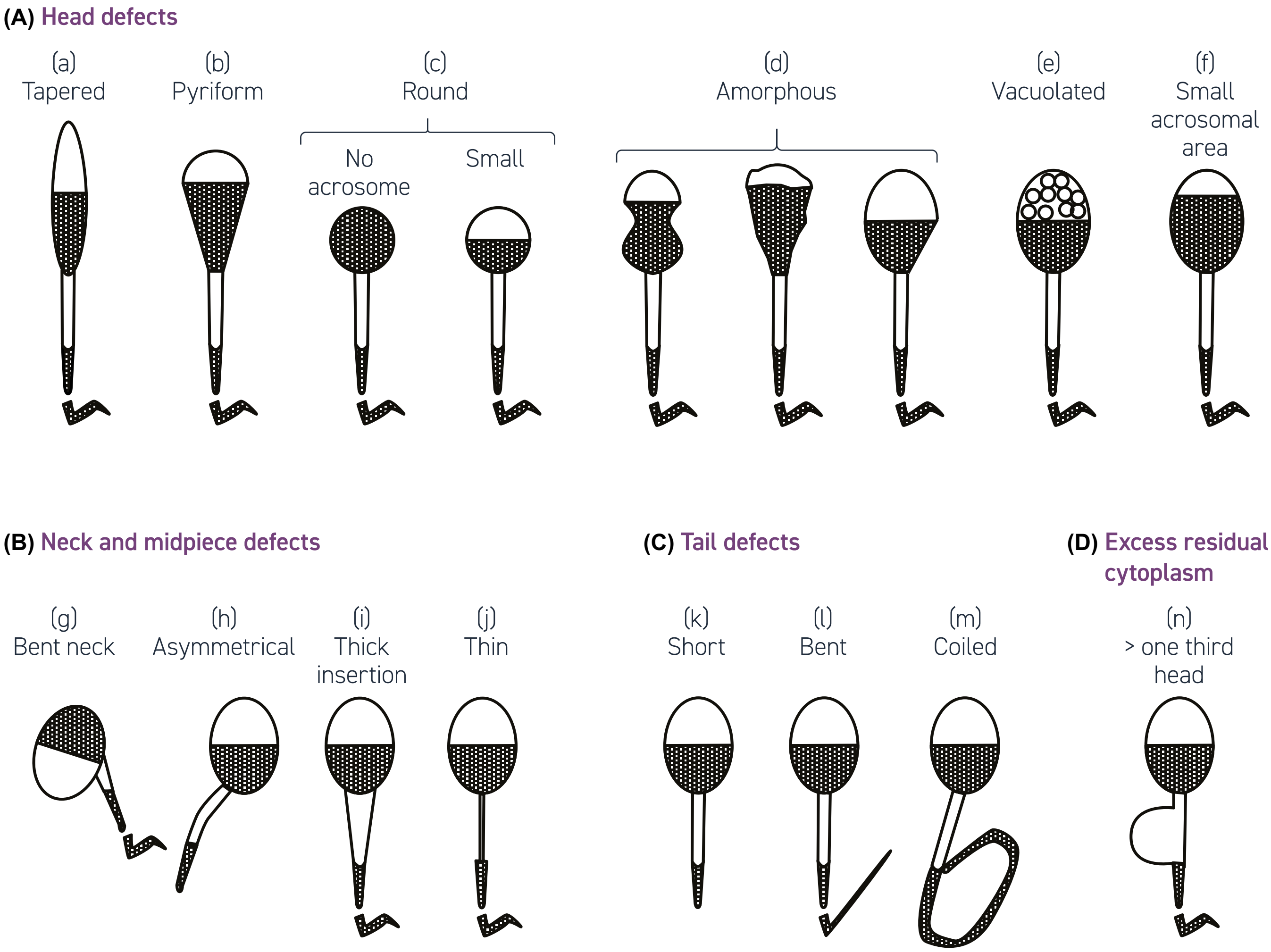

FIGURE 1 WHO 6th edition illustrations of abnormal sperm morphology. Adapted from *WHO laboratory manual for the examination and processing of human semen, sixth edition*. Geneva: World Health Organization, 2021. License: CC BY-NC-SA 3.0 IGO.

In a meta-analysis of 20 studies with 5865 patients examining the effects of smoking on semen parameters, smokers had a −1.37% difference in normal forms, suggesting a negative association between cigarette smoking and sperm morphology.[15] However, the mean difference for the subgroup analyzed with WHO 1999 criteria was −1.88% (i.e., negative effect on morphology) and with WHO 2010 criteria was 1.36% (i.e., positive effect on morphology). The authors were unable to draw a definitive conclusion due to the confounding factor of semen analysis method. Few studies have addressed the effects of cannabis on sperm morphology. Three larger studies, each with over 200 subjects, had conflicting results with one study demonstrating a negative effect and two showing no association.[16–18] Ultimately, a meta-analysis of these three studies found no association between cannabis usage and teratozoospermia.[19] A more recent prospective single-center study found that cannabis users were two times more likely to have teratozoospermia (strict criteria, normal forms <4%).[20] Alcohol use was associated with poor morphology in a meta-analysis of 11 studies and appeared to have a dose-dependent effect, with daily alcohol users having a lower percentage of normal sperm compared with occasional or never users.[21]

Several other environmental exposures have been studied for their effects on sperm morphology. Occupational pesticide exposure showed inadequate evidence of toxicity toward sperm morphology, although decreases in DNA integrity and sperm motility were observed.[22] Exposure to air pollution was significantly associated with teratozoospermia in addition to increased rates of DNA fragmentation and asthenozoospermia.[23] Lastly, other groups have studied the effects of cell phone usage on sperm morphology (and other semen parameters). Radiation and heat generated by cell phones, particularly those kept in front pockets, may worsen semen quality, but results thus far have been conflicting.[24,25]

3.1.2 | Anatomic and health-related factors

Many hereditary and acquired illnesses may interfere with normal sperm development, resulting in teratozoospermia. A recent systematic review and meta-analysis of several prospective studies and 1357 patients assessed the outcomes of varicocele repair versus observation in men with any-grade varicocele.[26] In the treatment arm, sperm morphology improved by a mean difference in 6.1% after repair, although results were inconsistent among the included studies. Viral and bacterial infections may also induce morphologic changes, both through direct testicular involvement and febrile events (via disruption of testicular thermoregulation). In 1951, Macleod studied three medical students with pneumonia or chickenpox and found reductions in sperm concentration, motility, and morphology in the weeks following infection.[27] Other groups have reported similar findings following various febrile illnesses.[28] More recently, two small meta-analyses found a minimal, if any, impact of COVID-19 on sperm morphology.[29,30] The study of the semen microbiome is still in its infancy, but some recent studies have suggested that certain bacteria such as *Ureaplasma urealyticum* or *Mycoplasma hominis* have a detrimental effect on morphology.[31,32]

Because of the inherent complexities of spermatogenesis, it is challenging to accurately determine the degree to which these exposures affect sperm morphology. Future studies corroborating the existing literature will be needed to more definitively establish causal relationships for each of these factors.

3.2 | Effect of sperm morphology on natural fertilization outcomes

There is sparse data assessing the prognostic value of sperm morphology on natural conception. In the LIFE study of 501 couples who recently discontinued contraception, percent abnormal morphology by both strict and traditional criteria was associated with a small but statistically significant increase in time to pregnancy.[33] However, after controlling for other semen parameters such as sperm count or concentration, this association was not retained, suggesting that sperm morphology is not an independent predictor of fecundity. In a retrospective analysis of 24 patients with 0% normal forms, 29% of patients were able to conceive without assisted reproductive technologies (ART) compared with 56% of controls.[34] In addition, all men with 0% normal forms who conceived naturally went on to have another child also via natural conception. The authors concluded that morphology alone should not be used to predict fertilization, pregnancy, or live birth potential.

3.3 | Effect of sperm morphology on assisted reproductive technology outcomes

The association between ART outcomes and sperm morphology have been rigorously studied, although evolution of sperm morphology assessment over time and advances in ART have confounded direct comparison between studies of various eras. Sperm morphology has been considered in both the context of intrauterine insemination (IUI) and in vitro fertilization (IVF) with or without intracytoplasmic sperm injection (ICSI).

3.3.1 | Intrauterine insemination

While it is commonly accepted that total motile sperm counts $>10\times10^6$ correlate positively with IUI success,[35] similar conclusions cannot be drawn for sperm morphology. In theory, morphologically abnormal sperm may result in poor capacity to bind to the zona pellucida, ineffective or absent acrosome reactions, or impaired intracellular calcium regulation.[36] We identified 21 studies from 1995 to 2023 which examined the relationship between sperm morphology and IUI outcomes, including clinical pregnancy rates and live birth rates.

Earlier studies from the mid-late 1990s and early 2000s were highly variable in both their assessments of morphology and outcomes. While few studies reported no association between teratozoospermia and IUI outcomes,[37–39] most studies from this time period demonstrated a significant decrease in IUI success when teratozoospermia was present.[40–46] In studies that showed an association, the clinical pregnancy rates for couples with normal morphology were three to 40 times those of couples with poor morphology. However, it should be noted that the definition of abnormal morphology was inconsistent and ranged from <4% to <14% normal forms. Given the significant decrease in success, some authors advocated forgoing IUI in favor of IVF +/− ICSI if morphology <4% was seen.[43,44]

More recent studies, particularly those which came after the release of the 5th Edition WHO manual in 2010, have largely been consistent in finding no association between sperm morphology and IUI outcomes. Of the 10 studies we identified which were published after 2005, eight found no association[47–54] while two reported differences in outcomes for couples with abnormal morphology.[55,56] In a study of 984 IUI procedures, Patel et al. additionally examined rates of birth abnormalities or spontaneous abortions and found no relationship to teratozoospermia.[52]

Kohn et al. conducted a large systematic review and meta-analysis in 2018 comparing results from 20 observational studies and 21 018 IUI cycles.[57] No significant difference in ultrasound-verified pregnancy rates was found when using either 4% or 1% normal forms threshold. Pregnancy rates per cycle were 14.2% versus 12.1% in the ≥4% and <4% morphology groups and 14.0% versus 13.9% in the ≥1% and <1% morphology groups, respectively. Interestingly, after stratifying by WHO manual era (3rd edition, pre-1999; 4th edition, 2000–2010; 5th edition, 2011–2018), a significant difference in pregnancy rate was observed for studies in the 3rd edition era (13.1% vs. 7.3%) but not for later eras.

In conclusion, an analysis of the entire body of literature assessing the effects of morphology on IUI outcomes is difficult due to the varied results from many studies over the last 30 years. It is impossible to determine whether the recent shift is purely due to changes in our assessment of sperm morphology or improvement in IUI techniques and/or patient selection. Ultimately, the most recent data, including a large meta-analysis, do not show any correlation between teratozoospermia and pregnancy rates after IUI.

3.3.2 | In vitro fertilization

The prognostic value of sperm morphology for IVF±ICSI outcomes has also evolved over the past 4 decades. The seminal study by Kruger et al. from 1986 reported decreased fertilization success for patients with <14% versus >14% normal forms, and a follow-up study reported lower fertilization rates for patients with <4% versus 4–14% normal forms.[8,9] Subsequent work in 1994 by Ombelet et al. echoed these findings, albeit with different thresholds of 5% and 9%.[58] In this study, no couple with "severe" teratozoospermia (<5% normal forms) achieved a successful pregnancy, while fertilization rates were similar between control and "good prognosis" teratozoospermia patients (5%–8%). However, pregnancy rate per transfer, baby take-home rate, pregnancy rate per cycle, and pregnancy rate per embryo were all significantly decreased in men with normal forms <9% compared with control. A large, structured review of 18 studies written in 1998 echoed these findings.[59] In this review analyzing more than 25 000 cycles, fertilization rates were 59.3% versus 77.6% for men with ≤4% and >4% normal forms, respectively. When using a 14% threshold, fertilization rates were 72.7% versus 83.6% for ≤14% and >14% normal forms, respectively.

Starting in the mid-1990s, the results of these landmark papers were challenged as newer methodologies for morphology analysis began to increase in popularity. Nagy et al.[60] reported in 1995 that neither total sperm count, sperm motility, nor sperm morphology were predictive of ICSI outcome. Similarly, in a series of 354 consecutive ICSI cycles, Svalander et al.[61] found no difference in fertilization, pregnancy, or implantation rates in men with morphology >14%, 4%–14%, and <4%. Even in men with complete teratozoospermia (i.e., 0% normal forms), pregnancy rates of 39% per cycle have been reported, leading the authors to conclude that use of donor sperm should not be recommended as the sole fertility option in this population.[62] Similar findings were reported in a small series of 75 fresh TESE IVF+ICSI cycles, of which 17 cycles used no morphologically normal sperm. Of these, a 70% fertilization rate and 65% pregnancy rate was observed, similar to rates seen in the normal morphology group.[63]

Overall, there is no clear consensus for whether sperm morphology is a valuable prognostic indicator for IVF±ICSI cycle success. Like the literature regarding IUI success, studies exploring the relationship of morphology and IVF are plagued by inconsistent results and continuously evolving assessments of morphology over the past 30 years. However, most recent studies have robustly and reproducibly shown that using morphologically abnormal sperm leads to similar pregnancy outcomes in couples undergoing IVF.

3.4 | Effect of sperm morphology on recurrent pregnancy loss

Few studies examine the role of sperm morphology in couples with recurrent pregnancy loss (defined as either ≥2 or ≥3 recurrent abortions before the 20th week of gestation, depending on society guidelines). Much of this literature has focused on genetic abnormalities within sperm (i.e. DNA fragmentation or chromosomal aneuploidies) as a primary outcome; the importance of these abnormalities remains poorly understood and is beyond the scope of this review. However, many of these studies reported morphologic assessment in their results or as a secondary outcome even though they were not designed to analyze morphology directly.

The causal relationship between DFI and teratozoospermia is unclear and, thus, it is important to understand that DFI may be a confounding factor if we look at morphology in isolation.[64,65] Sperm with high DNA fragmentation may have normal morphology and sperm with abnormal morphology may have low rates of DNA fragmentation. A review and meta-analysis of 15 studies which examined DFI and RPL found that eight of the 15 studies reported lower morphology in men with RPL compared to control, but these results were not expounded upon.[66] Three recent studies reported significant increases in morphologic abnormalities for men with RPL versus controls,[67–69] although none of these used the 5th or 6th edition WHO morphology criteria. Moderately large studies by Busnelli et al.[70,71] and Eisenberg et al. demonstrated no difference in sperm morphology between RPL couples and control despite significant differences in DFI.

3.5 | Known morphologic abnormalities that affect fertility

Most studies that investigate sperm morphology tend to report abnormal forms as one all-encompassing variable (usually a percentage), with few specifying the predominant location or character of the abnormality. For many abnormal forms, the cause—whether genetic environmental, anatomic, etc—is unknown. However, it is well established that some genetic conditions produce characteristic morphologic defects and, in turn, require specific counseling and management.[72]

First described in 1971, globozoospermia is a rare condition associated with round-headed spermatozoa which lack an acrosome. It typically occurs in families and leads to infertility due to inability of the spermatozoa to bind or penetrate the zona pellucida.[73] For this reason, patients with globozoospermia should be counseled about the very low likelihood of success with natural pregnancy, IUI, or IVF without ICSI. Accordingly, ICSI with or without artificial oocyte activation should be recommended as a treatment option for these patients.

Macrozoospermia, also known as large-headed multiflagellar spermatozoa, causes sperm with irregular-appearing, oversized heads and often multiple flagella.[72,74] In most cases, this is due to a deletion within the Aurora kinase C (*AURKC*) gene. Interestingly, patients with this mutation have a 100% (or near 100%) chance of having only aneuploid sperm present, resulting in no chance of a successful term pregnancy. In these cases, IVF+ICSI should not be attempted, as even successful fertilization would produce an aneuploid embryo.

Patients with macrozoospermia who do not have the *AURKC* mutation can produce offspring, although pregnancies should be closely followed for aneuploidy. Consequently, genetic testing should be performed in all patients with macrozoospermia in order to appropriately counsel patients about reproductive options.[74]

These two examples illustrate the importance of associating specific morphologies to respective pathologies within the male reproductive tract to assist with counseling and ART patient selection. Focusing solely on the percentage of abnormal sperm (and not the abnormalities themselves) may limit our ability to optimally manage patients with these genetic conditions.

4 | CONCLUSIONS

The value of sperm morphology assessment has often been debated since the release of the WHO manual's 1st edition in 1980. The role of morphology in clinical practice remains largely controversial, even despite 4 decades of study. Unfortunately, due to advancements in ART techniques and changes in morphology criteria, it is nearly impossible to directly compare studies from different eras. Even in contemporary studies, semen analyses are still routinely performed by humans, not machines, and consequently are subject to inter- and intra-laboratory variability. In addition, most modern studies have not associated teratozoospermia to inferior pregnancy rates or outcomes.

In conclusion, based on the most recent literature which includes several large meta-analyses, it seems that morphology may have a limited impact on fertility potential than previously stated. Clinicians, researchers, and laboratory staff should be aware of these limitations, particularly as they relate to management and counseling.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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