THERAPEUTIC ADVANCES in
Reproductive Health

Review

Sperm morphology value in assisted reproduction: dismantling an enigma and key takeaways for the busy clinician

Ther Adv Reprod Health

2024, Vol. 18: 1–11

DOI: 10.1177/26334941241303888

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***Abstract*:** The ideal morphology of the sperm cell was initially described based on the characteristics of sperm able to migrate through the endocervical canal assuming these had the best fertilization potential. Sperm morphology assessment has moved over the years toward stricter criteria based on the findings from studies that underline its value in successful reproductive outcomes. While treatment options are clear for some conditions related to abnormal sperm morphology, the value of sperm morphology in assisted reproduction requires further investigation. The objective of this review is to offer care providers updated guidance for choosing appropriate treatment strategies based on sperm morphology assessment and morphological deviations. Issues to be considered for a reliable determination and interpretation of sperm morphology using the current thresholds and criteria are discussed. In addition, key knowledge on morphological abnormalities relevant to the clinical care of infertile patients, distinguishing between monomorphic and polymorphic forms as well as the isolated or non-isolated occurrence of teratozoospermia in semen is presented. Furthermore, the impact of impaired morphology on assisted reproductive technique outcomes is summarized in light of the latest research.

Keywords: assisted reproductive technique (ART), ICSI, IUI, IVF, sperm morphology, teratozoospermia

Received: 19 March 2024; revised manuscript accepted: 14 November 2024.

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Introduction

Correlations between sperm morphology and male fertility have been explored and established over the last few decades. The shape of the ideal sperm was historically determined based on sperm observed to cross the endocervical mucus assuming its fertilization potential.[1] Soon after the establishment of the strict sperm morphology criteria, which remain the gold standard in the latest 2021 (Sixth Edition) WHO manual,[2] associations with the fertilization outcome in conventional in vitro fertilization (cIVF) were reported.[3] In addition, abnormal sperm morphology has been correlated with an increased possibility of genetic structural or functional defects, including aneuploidies[4] and with gene mutations such as homozygous mutations of aurora kinase C (AURKC), spermatogenesis-associated 16 (SPATA16), and dpy-19-like2 (DPY19L2).[5] Strong correlations between DNA methylation profiles responsible for modification of gene expression levels involved in spermatogenesis regulatory mechanisms and sperm morphology[6] have also been identified.

However, the exact impact of sperm abnormalities on the fertility potential is not completely understood. This is illustrated by the possibility of spontaneous conception even when sperm morphology is poor.[7] Implications on male fertility are also different if all or almost all sperm present with the same morphological abnormality, the so-called monomorphic form, or if various abnormal morphological features are present on different sperm cells, also named polymorphic forms. While the clinical implications of polymorphic anomalies and the usefulness of

describing each of these anomalies to calculate indices of multiple anomalies are still unclear, identifying a single category of abnormalities, for example, large sperm heads or the absence of acrosomes often serves as a powerful prognostic tool for decisions on the treatment strategy and its clinical outcomes.

In this review, the requirements for proper sperm morphology assessment will be presented before highlighting relevant data on the value of sperm morphology in assisted reproductive technology (ART; cIVF and intracytoplasmic sperm injection (ICSI)) and intrauterine insemination (IUI) that may help the reproductive specialist decide on treatment strategies. The implications of sperm morphology on natural conception and the impact of other interventions, for example, varicocele repair on sperm morphology are not in the scope of this review.

How should sperm morphology be assessed?

A morphologically normal spermatozoon possesses a smooth and oval-shaped head, an acrosome covering 40%–70% of its head, the absence of large and multiple small vacuoles, a slender midpiece with an equal length to the head without cytoplasmic residues axially attached to the head, and a lengthy tail lacking any sharp bends.

Classifications and reference values for sperm morphology under a brightfield microscope have changed over the years[8] toward the current threshold value following the strict criteria of $\geq$4% corresponding to the fifth percentile of a large population of ethnically diverse men who were able to conceive within a 1-year period.[2]

According to the WHO Sixth Edition manual,[2] precise technical aspects of how to handle, stain, and read the sample are crucial for proper evaluation. The recommended Papanicolaou staining gives the best overall visibility of all regions of the spermatozoon but other staining methods such as rapid Diff-Quick and Shorr can be used if properly validated with the standard technique. Each clinician should therefore ensure that their reference laboratory is in line with this manual's recommendations. Trained laboratory personnel participating in continuous internal and external quality control is also required to reduce the wide intra- and inter-laboratory variations.[9]

Does sperm morphology affect ART or IUI outcomes?

The influence of teratozoospermia on ART and IUI outcomes has been investigated as an isolated condition or as part of other semen impairments, as well as based on the proportion of specific abnormalities among the sperm population, that is, polymorphic versus monomorphic teratozoospermia. While some controversy exists and a simple dichotomous classification of normal versus abnormal sperm could be considered useless, the evidence of the impact of teratozoospermia is only clear in cases of some monomorphic abnormalities, as described in more detail in the relevant next sections.

Polymorphic teratozoospermia associated with other abnormal sperm parameters

Impact on IUI. It has been reported that sperm morphology is of little prognostic value in predicting the success of IUI.[8] To exclude some confounders linked to female factors, a systematic review was conducted including IUI cycles in couples with male infertility that assessed both the threshold levels of sperm morphology above which pregnancy outcome is significantly improved and the discriminative performance of cutoff values.[10] In 11 out of 16 studies, >4% morphologically normal sperm was reported as the most efficient cutoff value to predict IUI outcome. The systematic review further highlighted sperm morphology as a valuable predictive marker for IUI success if the inseminated motile count (IMC) is below one million (area under the curve (AUC) of the receiver operating characteristic (ROC) = 77.6%). In this case, when normal sperm morphology was >4%, the cumulative live birth rate after three cycles (21.9%) was comparable to that achieved with an IMC greater than one million (24%).

A more recent meta-analysis reported the effect of sperm morphology in a subgroup of patients with a total motile sperm count (TMSC) above 10 million and female partners with an age range between 25 and 40 years.[11] When morphology was assessed according to the Fourth and Fifth Editions of the WHO semen analysis manual with a cutoff of 4%, no difference was observed in clinical pregnancy rates (14.2%, 12.1%, and 13.9%) between three subgroups of patients with normal sperm forms of >4%, $\leq$4%, and <1%, respectively. Of note, most studies included in the

aforementioned meta-analysis are limited by their retrospective nature and variation in male infertility etiology, ovulation stimulation and induction regimens, sperm preparation methods, and additives such as antioxidants or platelet-activating factors. In addition, the duration of infertility, female age, and female factors are most often overlooked despite their well-known impact on reproductive outcomes. To illustrate the importance of these factors, two of the studies included in the meta-analysis are worth mentioning.[12,13] Interestingly, when adjusting for female infertility factors, the probability of pregnancy following the first IUI cycle was highest in couples with ⩽4% morphologically normal sperm (OR = 1.58; 95% CI = 1.13–2.22).[12] With regards to the impact of female age, no differences in pregnancy rates were found for different levels of morphologically normal sperm in couples where the woman was under 35 years of age, while no pregnancy was achieved through IUI for women older than 35 years when normal sperm morphology was below 5%.[13]

There is also some discussion around the fact that percentages of morphologically normal sperm can be different in the processed sample compared to the raw unprocessed sample, suggesting that this may explain discrepant findings. Trying to address a question related to the potential impact of sperm processing, a retrospective cohort study comprising 234 IUI cycles found that the percentage of normal sperm morphology (>4%, <4%, and <1%) in the processed sample was not predictive of IUI success after adjusting for female age, female anti-mullerian hormone, and TMSC.[14] The question of differences in sperm morphology between a sample provided prior to or on the day of the insemination was also raised. Looking at the sperm morphology of 1059 pre-washed samples on the day of the insemination, clinical pregnancy rates were not different among the various morphology categories (⩾4%, 2%–3%, and ⩽1%), regardless of the pre-wash TMSC when the cutoff was set <9 or >9 million.[15] This study further highlighted that only the post-wash TMSC was predictive of the clinical pregnancy rate.

Overall, in cases of teratozoospermia with other abnormalities in conventional sperm parameters, the prognosis of IUI depends on the inseminated motile sperm count, with one million reported as the lowest threshold for success. Normal sperm morphology below 5% may predict poor outcomes for women older than 35 years.

Impact on cIVF. Generally, studies assessing the impact of sperm morphology on cIVF tend to agree on a poor predictive value of sperm morphology for pregnancy rates as observed in a large retrospective study including 3922 cIVF cycles.[16] This is in contrast with another large observational study including 2323 cycles where pregnancy rates appeared to be reduced with decreases in percentages of normal forms,[17] although the ROC analysis showed an AUC of only 54%. However, fertilization rates may be affected by a lower probability of oocyte fertilization for a lower percentage of morphologically normal sperm.[16,17] In a matched case–control study of 2202 IVF cycles comparing patients with teratozoospermia and patients with normozoospermia, with female partners diagnosed with tubal infertility without any other infertility factor present, a significantly lower rate of high-quality embryos was observed for teratozoospermia, although with no significant impact on implantation, pregnancy, and abortion rates.[18] The absence of the impact of sperm morphology on pregnancy rates in cIVF cycles was further confirmed in a large retrospective cohort study including 5819 cycles. It is of note that in this study the fertilization rates were directly correlated with sperm morphology.[19]

However, sperm counts may play a role in cIVF outcomes in cases of teratozoospermia. In this regard, fertilization rates were not compromised by reduced sperm morphology >2% to <4%, as compared to semen samples with normal morphology (85.9% vs 85.8%, respectively) when cIVF was performed with TMSCs >10 million.[20]

Overall, while fertilization rates and rates of high-quality embryos could, in some cases, be negatively impacted by polymorphic teratozoospermia in cIVF, pregnancy rates are not compromised.

Impact on ICSI. The prognostic value of sperm morphology for pregnancy rates remains poor in ICSI.[17,21] Because we may assume that the physician's choice to assign a patient either to cIVF or to ICSI introduces a bias in studies, it is interesting to consider the study of French et al. where the center performed ICSI in all cycles but those where patients specifically requested cIVF. After subgrouping 1074 ICSI cycles by each percentage

of morphology assessed with strict criteria from 0% to >7%, sperm morphology did not appear to be predictive of outcomes including clinical pregnancy rates in women under the age of 37 years, and none of the studied reproductive outcomes were reduced in the subgroup with 0% normal forms.[22]

In a retrospective matched case–control cohort of over 2500 ICSI cycles, there was no significant impact of teratozoospermia on the development of high-quality embryos, fertilization, implantation, and pregnancy rates.[18] It is of note that female factors were well considered (only tubal infertility in the absence of any other pathological condition, age under 35 years, and at least four oocytes retrieved) and that sperm concentration was lower for the teratozoospermia group (4.48 ± 8.35 vs 14.44 ± 8.65).

By contrast, a retrospective analysis of 16,194 ICSI cycles including all couples attending the fertility clinic for ICSI defined a correlation between fertilization rates and sperm morphology, and logistic regression analysis demonstrated sperm morphology to be predictive of pregnancy and live birth rates following ICSI.[19] In the latter study, the ROC analysis defined a cutoff value of 5.5% to successfully predict clinical pregnancy (AUC = 0.811, SE = 0.009, $p < 0.001$) with a sensitivity of 72% and specificity of 71%, whereas no predictive cutoff value could be detected for live birth rates. Such controversial results between studies could be partly explained by study inclusion criteria, for example, female reproductive characteristics that may impact the outcomes and promote notable differences when disseminating results according to sperm morphology.

Studies using sibling oocytes may help resolve the impact of many important confounding factors by allowing comparable groups as half of the oocytes of a patient are assigned to cIVF and the other half to ICSI. In 31 patients with sperm morphology <5% according to strict criteria, fertilization rates of 59% and 67% were found, respectively, for ICSI and cIVF although with more patients with total fertilization failure for cIVF (5 vs 3 patients). No significant differences were observed for cleavage rates, embryo quality, implantation, and pregnancy rates.[23] However, caution is still needed in the interpretation of these results. An important point for consideration is that the manual selection of morphologically competent spermatozoa by the embryologist during ICSI produces results that are not representative of the total sperm population in terms of morphology.

Overall, studies on the impact of polymorphic teratozoospermia on pregnancy rates after ICSI are controversial. The predictive value of sperm morphology is likely poor and study outcomes may be influenced by the role of the embryologist in selecting the right sperm cell and other potential confounding factors, notably those related to the female side. No lower morphology threshold for refuting ICSI was reported, regardless of the sperm count.

Isolated polymorphic teratozoospermia

In this section, the question of whether sperm morphology is a key parameter for IUI and ART results when other basic parameters are normal will be explored.

It has been demonstrated that pregnancies have been achieved through IUI in cases of isolated teratozoospermia, even with very low percentages of normal morphology (0%–1%)[24] suggesting IUI be a reasonable first option when all other reproductive conditions permit this. This is further supported by a very recent study showing no difference in clinical pregnancy rates between patients with isolated teratozoospermia (using a lower threshold for pre-wash TMSC at 12 million) and patients without teratozoospermia, irrespective of the severity of teratozoospermia.[15]

According to a meta-analysis of studies reporting the impact of isolated teratozoospermia on cIVF and ICSI, no association was found with pregnancy rates, regardless of the ART method used.[25] However, in a retrospective study considering various female factors (collection of >5 oocytes, <35 years, and no factors impairing oocyte quality and endometrial receptivity), lower fertilization rates and a higher risk of total fertilization failure were observed in cIVF for isolated teratozoospermia compared to normal semen profiles.[26]

Considering the outcomes of cIVF and ICSI on sibling oocytes, results were contradictory between two small studies. In a study including 20 ART cycles, fertilization rates were significantly higher with ICSI,[27] while in a slightly larger study including 183 ART cycles, no differences

were noted between the two approaches in terms of fertilization.[28] In the latter study, no differences in implantation, pregnancy, miscarriage rates, and embryo quality at day 3 were observed.[28] Controversial conclusions may arise from sperm selection procedures during ICSI, where morphological and motional competency is sought by the individual embryologist, with varying experience and background.

By considering the conclusions surfacing from the conducted studies, it appears that isolated teratozoospermia does not significantly affect the efficiency of IUI in obtaining a positive reproductive outcome. Men with polymorphic teratozoospermia without any other sperm impairment can thus be advised to opt for IUI provided that the female age and infertility work-up allow it. When ART is considered, ICSI allows sperm selection according to some morphological criteria, which by extension, can avoid compromised fertilization rates and total fertilization failure.

Monomorphic teratozoospermia

Four main forms of sperm monomorphic abnormalities require specific attention with regard to infertility management and genetic counseling, irrespective of their association with abnormalities established in other semen parameters.

Globozoospermia. Globozoospermia is characterized by a high percentage of round-headed spermatozoa present within a sperm sample, with an absent acrosomal cap, an aberrant nuclear membrane, and midpiece defects, that occur in less than 0.1% of infertile patients worldwide.[29] Genetic defects and deregulation of proteins potentially involved in the condition have recently been reviewed[29] along with evidence on gene panels to be evaluated.[30] Acrosome anomalies are usually responsible for the inability to penetrate and interact with the oocyte and induce oocyte activation (OA), due to the lack of phospholipase C zeta, eventually hampering the fertilization process.[31]

Fertilization rates with ICSI are low for cases with globozoospermia, although the induction of OA through the incubation of the oocytes with a calcium ionophore has been shown to significantly improve pregnancy rates.[30,32]

Spermatozoa from patients with globozoospermia carry chromosomal aneuploidies and present an increased percentage of sperm DNA fragmentation (SDF), although at rates similar to polymorphic teratozoospermia.[4] In a systematic review on globozoospermia, including insight on outcomes of ICSI, the clinical pregnancy rate was 31.3% with OA (vs 19.5% without OA).[30] Among a total of 86 live births, one cardiofaciocutaneous malformation was found in a patient with complete globozoospermia and ZPBP mutation but further information on offspring health was not available.[30] However, concerns have been expressed regarding the possible epigenetic effects when "forcing" the fertilization cascade of events with calcium ionophores.[33]

Macrocephaly or SMS. This condition is associated with a very high percentage of spermatozoa with enlarged irregular heads and multiple tails.[34] A sperm aneuploidy rate of ~98% has been reported in sperm macrocephaly syndrome (SMS), compared to 1.3% in fertile control patients and ~8% in polymorphic teratozoospermia,[4] as well as increased SDF values.[35] Sperm macrocephaly syndrome is usually related to homozygous mutations of the *AURKC* gene, a gene that plays a key role in the control of mitosis and meiosis. A particularly high prevalence of the c.144delC deletion in a heterozygous state (1.84%) was reported in the Moroccan population.[36] In cases with SMS, ICSI as the only option to conceive with genetically own sperm, appeared mainly ineffective or led invariably to recurrent miscarriages.[37] The delivery of a healthy baby was however reported after ICSI with extremely rare almost morphologically normal sperm that were found in the ejaculated sample (5 sperm among 1521 observed cells corresponding to 0.33% of the sperm population) of a patient presenting with macrocephalic and multiple-tailed sperm but the genetic analysis was not provided in the description.[38]

Due to high genetic risk and poor outcomes, patients should at least benefit from genetic counseling and sperm donation can be proposed. Notably, some cases of macrocephaly are also reported in patients treated with sulfasalazine for ulcerative colitis or Crohn's disease. Discontinuation of the medication may reverse the condition in these cases.[39]

Decapitated sperm syndrome or acephalic spermatozoa syndrome. Headless spermatozoa may be sporadically observed in fertile men while their

percentage reaches 10%–20% in infertile patients, and in some rare cases even 100% of the total sperm population. The condition results from a failure of the interaction of the centrioles with the spermatid nucleus, which subsequently causes the independent development of head and tail, with heads usually phagocytosed by Sertoli cells or along the epididymis.[40] Various gene mutations appeared to be involved in this pathogenesis, including the primarily identified targeted mutation in the *SUN5* gene.[41] Some live births have been historically reported through ICSI, although in cases with partial acephalic spermatozoa syndrome (ASS).[42] ICSI was performed using sperm having head and tail including sperm with abnormal head–tail junctions that are observed in 0.9%–4.4% of the sperm population.[37] Live births were reported for some gene variants of *SUN5*, *PMFBP1*, *HOOK1*, and *TGA10* genes[43,44] while other variants such as the mutated *BRDT* gene will likely result in ICSI failure due to a dysfunctional centrosome[44] but more research is needed. In these cases, appropriate counseling should be based on the percentage of normal forms present in the sample, if any, while information should be provided on the possibility of the inheritance of these genetic traits and the fertility state of the male offspring.

Dysplasia of the fibrous sheath. Dysplasia of the fibrous sheath is a genetic sperm defect characterized by structural abnormalities of the sperm tail appearing short, thick, and irregular. Geographical clustering has been reported in North Africa and South America and pedigree analysis suggests an autosomal recessive mode of inheritance.[40] The condition includes a heterogeneous array of ultrastructural defects of the tail causing almost complete immotility while the nucleus and acrosome are generally preserved.

Few data are available on reproductive outcomes but fertilization after ICSI, clinical pregnancy, and miscarriage rates seem comparable to rates generally achieved with ICSI. There was no increase in birth abnormalities among 13 singletons.[45] However, reported cases question the possibility that specific axonemal structural defects, especially if related to centrosomal or pericentrosomal protein defects, could be responsible for reduced kinetics of early embryo cleavage and implantation rate.[5]

Overall, monomorphic sperm abnormalities have been treated with ICSI with various success rates. As causal gene mutations are associated, patients should be informed about specific genetic risks and the limited data on reproduction and offspring health.

Discussion

The potential role of sperm morphology in IUI and ART outcomes has been investigated with different observations reported on its impact on treatment cycles. Debates around the predictive value of sperm morphology for IUI and ART outcomes are fed by challenging interpretations of study results, especially for polymorphic forms, because of the changing criteria for sperm morphology assessment over the years, the lack of controlling for many confounders influencing infertility care outcomes including female factors and sperm preparation methods, as well as the retrospective nature of available studies. It becomes an even bigger challenge when some laboratories adopt their sperm morphology criteria and thresholds.

The use of a proper methodology for sperm determination according to the latest edition of the WHO manual is a prerequisite to rely on study outcomes. However, even when properly performed by skilled laboratory technicians, the manual nature of the evaluation and the human subjectivity are of concern and need mitigation measures. Maintaining staff competence over time by monitoring average values on their samples, continuous training, and external quality control may help. Indeed, in a Belgian external quality control program, a median coefficient of variation as high as 79.4% among an average of 120 laboratories over a 10-year period was observed, and thanks to the participation of laboratory technicians in training courses, this variability decreased over the years.[46]

Artificial intelligence has also been proposed as an option to reduce the innate subjectivity of the manual evaluation of semen and allow single-sperm morphology assessment in a standardized manner.[47] While this approach is in its early stages, it also presents the prospect of further advancements by including machine training algorithms linking sperm morphology with DNA

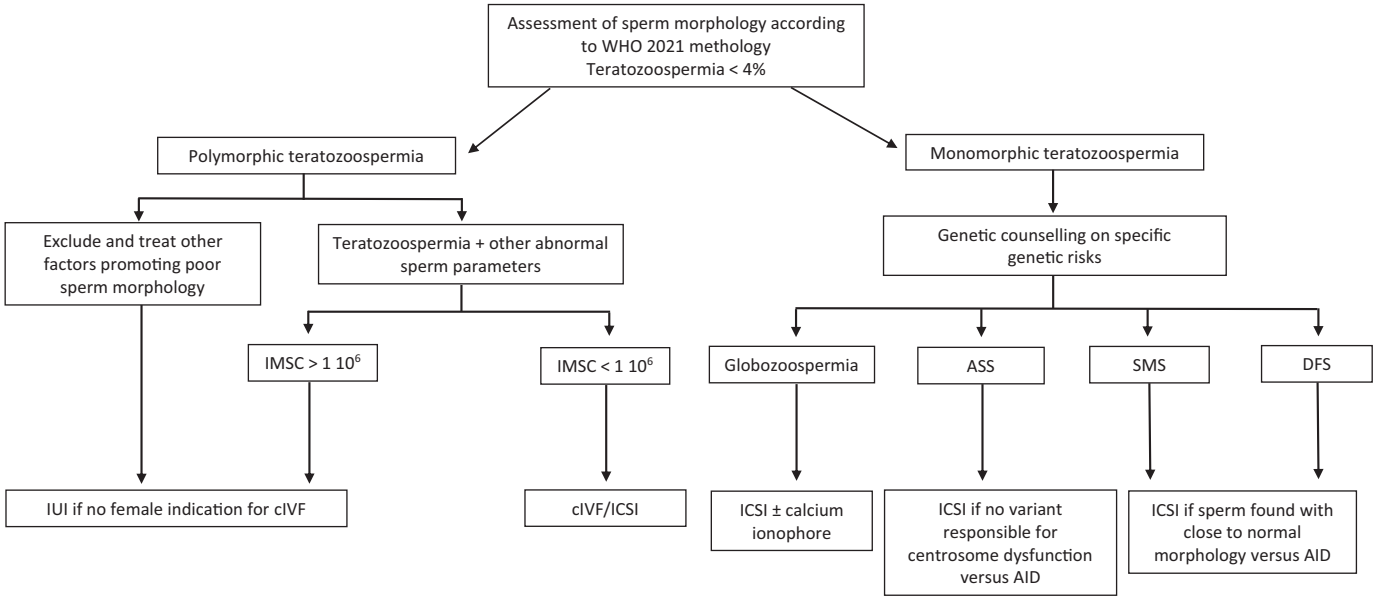

Figure 1. Decision tree on clinical care based on sperm morphology.
AID, artificial insemination with donor sperm; ASS, acephalic spermatozoa syndrome; DFS, dysplasia of the fibrous health; IMSC, inseminated motile sperm count; SMS, sperm macrocephaly syndrome.

content or protein expression to allow optimal sperm selection toward improved ART outcomes.[48] In addition, AI image analysis has been shown to identify spermatozoa significantly faster than an embryologist when integrated into an ICSI microscope[49] giving the technique the prospect to be applied to other sperm samples. However, besides such promising goals, the validity of the AI algorithms for the general population remains questionable and there is so far no demonstration of a true association between the use of AI technologies for sperm selection and increased pregnancy rates after ART and IUI.[50]

In addition, several factors that may promote variations from the normal morphology of the spermatozoon, including environmental and lifestyle factors, varicocele, malignancy, scrotal temperature elevation, infection, and inflammation are overlooked in studies. Some of these factors are modifiable and hence, an accurate clinical assessment is paramount to identify reversible causes of morphological anomalies and apply adapted care prior to any referral to ART or IUI.

The main components guiding the choice between IUI, cIVF, and ICSI based on available literature on the value of sperm morphology are depicted in a summarizing decisional tree (Figure 1).

Identifying the monomorphic versus polymorphic nature of poor sperm morphology is undoubtedly the most important distinction due to implications on treatment choices and outcomes while differentiating between isolated and non-isolated teratozoospermia could be considered of less importance. However, the implications of poor sperm morphology when other conventional sperm parameters are abnormal cannot be neglected as it was shown that the inseminated motile sperm count is predictive of IUI and cIVF outcomes.

Next efforts can be directed toward the use of artificial intelligence to reduce the subjectivity of the test. It is likely that future studies based on high-throughput analysis combined with artificial intelligence tools could elucidate and standardize further the connection between sperm morphology and reproductive outcomes and thus enhance the medical management of the infertile patient.

Clinical case scenarios

Case 1. Description: A 27-year-old female patient with primary infertility of 3-year duration. No remarkable abnormalities were detected during the gynecological examination. The sperm sample of the male partner had normal sperm parameters

with a concentration of 22 million/ml, 32% progressive motility, and a total volume of 1.5 ml. Assessment of morphology revealed polymorphic teratozoospermia with only 1% morphologically typical forms by strict criteria according to the Sixth Edition of the WHO manual of human semen analysis.[2]

Management: This is a case of isolated teratozoospermia with polymorphic sperm abnormalities. This couple can be offered IUI. Pregnancies have been achieved through IUI in cases of isolated teratozoospermia, even with very low percentages of normal morphology (0%–1%) suggesting IUI to be a reasonable option when all other reproductive conditions permit this. The decision to proceed with IUI was taken and the patient delivered a healthy baby after the third attempt with the development of a single dominant follicle and an inseminated progressive motile sperm count of 4.1 million.

Case 2. Description: A 35-year-old female patient with a history of primary infertility of 4 years. The husband's semen analysis revealed normal sperm count and motility and teratozoospermia at 0% after examination of 200 sperm cells according to the Sixth WHO manual. All sperm showed small round heads without acrosomes. Genetic testing showed a homozygous deletion of the DPI19-L2 gene on chromosome 12. Reproductive hormones and karyotype were normal. SDF following terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick-end labeling (TUNEL) was at 25% (below 20%: normal; 20%–30%: increased without significant impact on fertility; superior to 30%: abnormal).

Management: This is a case of globozoospermia. The couple should be offered ICSI. Pregnancies have been reported with the same condition with the use of ICSI although with low success rates.[51,52] Oocyte activation using calcium ionophore may help enhance the success of ICSI.

Key points

- The clinical utility of sperm morphology is still under scrutiny due to the lack of standardization of sperm morphology assessment in many previous studies, and the evolution of criteria becoming more stringent over time.
- The evidence on the value of sperm morphology in the context of IUI and ART is limited due to many confounders such as etiological factors, female age, sperm handling, and assessment methods including the innate subjectivity of the manual evaluation.
- It is essential to distinguish between monomorphic and polymorphic forms to guide the treatment option.
- Determination of sperm morphology remains an essential initial diagnostic tool to identify monomorphic abnormalities that may carry genetic disorders.
- Data on the impact of sperm morphology are so far insufficient to robustly orient the choice of infertility care but show that IUI and cIVF cannot be denied solely on sperm morphology except for the monomorphic abnormalities that require ICSI.

Conclusion

Based on the available evidence on the impact of sperm morphology on outcomes of IUI and ART, there is a clear need for reliable standardized morphology determination and every laboratory should internally and externally monitor assessments. It is expected that new standardized classifications for polymorphic teratozoospermia rather than the current dichotomous assessment as normal versus abnormal will be able to further guide infertility care.

So far, except for monomorphic forms, IUI can lead to pregnancies regardless of the sperm morphology percentage, and success rates will mainly depend on female factors and inseminated motile sperm counts. As for ART, studies are limited by numerous confounders that were not considered. The challenge of linking sperm morphology to ART outcomes is likely the highest for ICSI as the morphology of the sperm selected for ICSI exclusively relies on the expertise of the embryologist to select the sperm in unstained preparations. Therefore, well-designed studies are warranted to understand the real value of sperm morphology.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication
Not applicable.

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Christine Wyns: Conceptualization; Methodology; Writing – original draft; Writing – review & editing.

Paraskevi Vogiatzi: Formal analysis; Writing – review & editing.

Ramadan Saleh: Formal analysis; Writing – review & editing.

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Acknowledgements
The authors thank Dr. Damayanthi Durairajanayagam (Physiologist, Malaysia) for help with the scientific editing and review of this manuscript. The authors are thankful to the Global Andrology Forum (part of the Global Andrology Foundation) for its support of this project.

Funding
The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
Not applicable.

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Appendix

Glossary

Artificial insemination with donor sperm (AID): The process of placing sperm obtained after processing semen into the reproductive tract of a woman to obtain a pregnancy.

Assisted reproductive technology (ART): All interventions that include the in vitro handling of both human oocytes and sperm, or embryos for reproduction. This does not include intrauterine insemination.

Conventional in vitro fertilization (cIVF): A laboratory procedure that involves all steps for achieving ex vivo fertilization of gametes by bringing together oocytes and sperm in a culture dish.

Intracytoplasmic sperm injection (ICSI): A laboratory procedure in which a single sperm cell is injected into the oocyte cytoplasm.

Intrauterine insemination (IUI): The process of placing sperm after semen processing in the uterus of a woman to obtain a pregnancy.

Sibling oocytes: Oocytes obtained from a woman following a single ovarian stimulation.

Terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick-end labeling (TUNEL): Assay used to detect apoptotic DNA fragmentation.

Receiver operating characteristic (ROC): Graphical plot used to define the performance of a test/assay which shows the true-positive rate (sensitivity) against the false-positive rate (1-specificity).