Review Article

Isolated teratozoospermia: revisiting its relevance in male infertility: a narrative review

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Background and Objective: Basic semen analysis is the first step in the evaluation of male infertility. It includes an assessment of sperm morphology which is believed to reflect on overall spermatogenesis and sperm function. Teratozoospermia, defined as abnormal sperm morphology, is frequently present in association with severe oligoasthenozoospermia, but isolated teratozoospermia (in the presence of normal counts and motility) is a poorly understood clinical entity with conflicting implications in terms of fertility potential and treatment strategies. The following paper aims to: (I) discuss the classification of sperm morphology, causes, and molecular mechanism of teratozoospermia; (II) analyze the clinical significance and potential treatment options of isolated teratozoospermia as a cause of male infertility and a predictor of fertility outcome; and (III) provide a SWOT (strengths, weaknesses, opportunities, and threats) analysis based on the existing literature on this topic.

Methods: A comprehensive search from database inception to 25 April 2023 was conducted in PubMed for relevant papers relating to isolated teratozoospermia in male infertility. Finally, seven systematic reviews/reviews/meta-analyses and 81 original articles were synthesized into the current narrative review.

Key Content and Findings: Classification of sperm morphology has evolved significantly since the first edition of the World Health Organization (WHO) Manual of Human Semen Analysis. Kruger's strict criteria are the most used classification and have been shown to correlate with fertility outcomes. There are many causes of teratozoospermia including genetic and environmental factors and physical conditions like varicocele. Teratozoospermia correlates with sperm DNA damage, elevated oxidative stress, low antioxidant function, and apoptotic alterations, which can result in impaired spermatozoa function and lower pregnancy rates. However, the clinical correlation between teratozoospermia and assisted reproductive technology (ART) outcome shows conflicting data with recent meta-analyses suggesting that isolated teratozoospermia was not associated with poor fertility outcomes from ART and that intrauterine insemination (IUI) can be an effective option even in the presence of teratozoospermia. There is very limited data on effective therapeutic options to treat idiopathic isolated teratozoospermia. The opportunity for future research is huge to fill the gap in the medical literature on this topic.

Conclusions: Contemporary literature on isolated teratozoospermia shows conflicting results in terms of its actual clinical implication in male infertility and the utility of available treatment options. Further research is warranted on this clinical entity to improve sperm function and future paternity.

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Introduction

Couples who are unable to achieve a clinical pregnancy despite regular and unprotected sexual intercourse after 12 months are considered to be infertile (1). It is estimated that around 15% of couples worldwide are infertile (2). Between 30% and 70% of cases are due to a male factor, and the global rate of male infertility is estimated between 2.5% and 12%, with the highest rate of male infertility reported in Africa and Central/Eastern Europe (3). Initial evaluation of the male fertility potential involves a medical and reproductive history, physical examination, and semen analysis (4).

The recent sixth edition of the World Health Organization (WHO) Manual for human semen analysis categorizes the evaluation of semen into three levels—basic, extended, and advanced (5). Basic semen analysis is useful in the initial stage before proceeding with other assessments. One of the parameters in the basic semen analysis is sperm morphology, which can be classified as normal, borderline, or abnormal morphology (5). The manual provides dedicated descriptions and micrographs for anomalies in the head, mid-piece, and tail of the sperm, and of other abnormalities, such as abnormal cytoplasmic residues.

Teratoazoospermia is defined as the presence of spermatozoa with normal morphology with a proportion below the lower reference limit (6). Isolated teratozoospermia refers to a condition where teratozoospermia is the only abnormality found in semen analysis (7). Nevertheless, the concept, criteria, and reference limits for normally shaped spermatozoa have constantly changed since the first to the sixth edition of the WHO Manual (5,6,8-11). To further complicate matters, morphological assessment can be highly subjective, with high intra- and inter-laboratory variations resulting in questionable reliability and high heterogeneity of the available evidence (12).

Some studies have shown a correlation between sperm morphological defects and nuclear genetic defects, apoptotic alterations, and reactive oxidative stress, which may negatively impact fertility potential (13-15). Hence, assisted reproductive technology (ART), particularly intracytoplasmic sperm injection (ICSI), are often recommended in men with severe teratozoospermia (16,17). However, existing literature shows the inconsistent impact of teratozoospermia on pregnancy outcomes and ART success (7,18,19), and one study found that isolated teratozoospermia was more common in fertile than infertile males (20).

At present, there are no guidelines available for the treatment of isolated teratozoospermia. Despite the huge increase in the literature on male infertility, a very limited number of review articles specifically address isolated teratozoospermia (17,21). The present narrative review aims to discuss the clinical significance and potential treatment options of isolated teratozoospermia as a cause of male infertility and a predictor of fertility outcome. Additionally, the classification of sperm morphology, causes, and molecular mechanism of teratozoospermia will be discussed, though an in-depth discussion on laboratory assessment of sperm morphology or specific sperm morphological abnormalities is outside the scope of this narrative review. A critical SWOT (strengths, weaknesses, opportunities, and threats) analysis has been undertaken to evaluate the current evidence on isolated teratozoospermia. This article is presented following the Narrative Review reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-23-397/rc).

Methods

A broad and comprehensive literature search on PubMed was performed by two independent authors (W.A., M.S.) using all iterations of the relevant search terms to identify articles from database inception to 25 April 2023. From the initial articles retrieved during our search using PubMed, the title and abstract were screened, followed by a full-text review of selected abstracts. A subsequent manual search was conducted for additional articles. All the studies that discussed isolated teratozoospermia in the context of male infertility were considered. From a total of 145 articles reviewed, we included all the studies in English that

Table 1 The search strategy summary

Items	Specification
Data of search	2 April 2023–25 April 2023
Databases	PubMed
Search term used	((“Teratozoospermia” [Mesh]) OR ((“Isolated” [All Fields]) AND ((“Teratozoospermia” [All Fields]) OR ((“Abnormal” [All Fields]) AND (“Sperm Morphology” [All Fields]))))) AND ((“Infertility, Male” [Mesh]) OR (((“Male” [All Fields]) OR (“Men” [All Fields])) AND ((“Infertil*” [All Fields]) OR (“Subfertil*” [All Fields]))))) AND (“Assisted Reproductive Technology” [All Fields] OR “Etiology” [All Fields] OR “Mechanism” [All Fields] OR “Pathophysiology” [All Fields] OR “Classification” [All Fields] OR “Management” [All Fields]) and their combination for the hand searching
Timeframe	Database inception until April 2023
Inclusion and exclusion criteria	Included studies: all relevant articles (trials, observational studies, review, case series or report, and meta-analysis) in English Excluded studies: editorials, author’s reply, and non-English articles
Selection process	Two authors conducted an independent search to select the articles related to teratozoospermia’s pathogenesis and molecular mechanism, classification and testing method of sperm morphology, clinical relevance, and treatment of isolated teratozoospermia for male infertility

provided strong evidence or were most relevant to the topic of interest. A complete search strategy for article selection can be found in *Table 1*. No prior registration protocol or ethical approval is required for the present review.

A total of 88 publications were included in this analysis, of which 55 of them were published in the last ten years. The included articles cover seven systematic reviews/reviews/meta-analyses and 81 original articles. *Figure 1* summarizes the selection process for the present review. Information contained in these publications was extracted and synthesized to create a comprehensive narrative review of isolated teratozoospermia and its implication for male infertility.

Evidence synthesis

Normal sperm morphology criteria

Spermatozoa are shaped as polarized cells with a head, a connecting midpiece, and a tail or flagellum (22). The primary structure of the sperm head is the acrosome and the nuclear envelope. The acrosome is separated into a posterior and anterior region; the latter participates in the acrosomal reaction (23). The tail of sperm consists of a midpiece, a principal piece with a ciliary structure, and lastly, an endpiece that is hardly seen with a light microscope (5,24). The integrity of each part of the sperm is essential for the normal functioning of the spermatozoa (25).

Initially, the depiction of sperm morphology was mainly based on observation from veterinary medicine and *in vitro* research through a microscope (5). It was gradually refined over the years, as reflected by the updates in each edition of the WHO manuals. In the first two editions (1980 and 1987), all spermatozoa without obvious defects were classified as normal morphology (8,9). Based on this approach, the threshold of normal spermatozoa reached as high as 80.5% in the first edition of the WHO manual (8), and it was not surprising that this approach was found to have a poor correlation to pregnancy outcomes (26).

Menkveld *et al.*, in later years, proposed a Tygerberg strict criteria based on detailed observation of spermatozoa, particularly from the postcoital cervical mucus (27). This approach was based on the observation that the morphology of spermatozoa in the cervical mucus was better than those from the semen sample and similar to the morphology required for binding to zona pellucida (28,29). These criteria consider a slight or borderline abnormality as abnormal, which results in a significantly lower threshold of normally shaped sperm compared to the liberal approach (30). It also emphasized the importance of optimal preparation and evaluation procedure of sperm morphology (27).

The third edition of the WHO Manual in 1992 was the first to apply strict criteria for sperm morphology using a cut-off of 30% for normal morphology, which was continually decreased in the later editions (10). The fourth [1999] and fifth [2010] editions of the WHO manual adopted 14% and 4% as the cut-off of normal

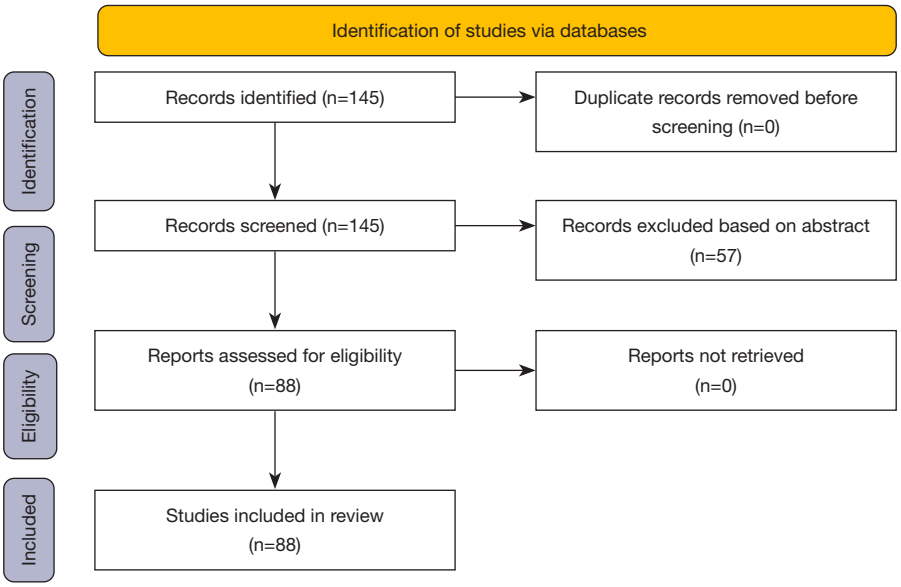

Figure 1 Flowchart of the study selection process.

sperm morphology, respectively (6,11). Notably, in the fourth edition, the cut-off was used with a statement that multicenter investigations were ongoing and that the data suggested a decrease in *in vitro* fertilization (IVF) when the proportion of normal morphology was under 15% (11).

Compared to the third edition, the fifth edition has a better definition of normal spermatozoa and sperm abnormalities (6). Although some research found a good correlation between the strict classification of sperm morphology and pregnancy outcome, the cut-off of 4% in the fifth edition was criticized as being too low, resulting in poor prediction of ART outcomes (31). Moreover, there is still the possibility of other contributing male infertility factors in patients with 5–14% normal sperm morphology. Therefore, the low cut-off points may have missed a proper infertility evaluation (32).

In 2021, the WHO released the latest edition of the manual for semen analysis which no longer gives any cut-off of normal sperm parameters either for concentration, morphology, or motility (5). The ideal or typical appearance of sperm is described as a smooth and oval with a regular contour of a well-defined acrosomal region that takes up 40–70% of the sperm head area. In the acrosomal area, there should not be any giant vacuoles and only two or fewer tiny vacuoles. These vacuoles should only take up a maximum of one-fifth of the sperm head (5). On the other hand, there should not be any vacuoles at all in the post-acrosomal region. The sperm should have a regular and narrow midpiece. The sperm head and the midpiece's axis should be around the same length. The caliber should be uniform on the tail, with a length approximately 10 times the head length. No sharp angulation is allowed on the tail. For the cytoplasmic droplets, only those smaller than one-third of normal sperm heads are considered normal. Several high-quality photographs were also made available in the manual to depict normal and abnormal sperm morphology (5).

Aside from the classification used by the WHO, other sperm morphology classifications also exist. However, they are not accepted globally but are used in certain countries only (33,34). Differences in classification and method of morphological assessment can have a significant impact on diagnostic interpretation (30). Therefore, for every study or article, a detailed method of sperm morphological assessment and the criteria used should be considered and cannot be directly compared to the findings of another study.

Classification of sperm morphology characterizes sperm with a better fertilization potential. Specific structural defects such as globozoospermia, pin head defects, tapered sperm head, macro- or microcephalic sperm, multiple tail defects, or large residual cytoplasmic sperm droplets should be correctly reported as they significantly affect the prognosis. Nevertheless, a systematic detailing of abnormalities is unnecessary and not recommended in the WHO manual (11).

A detailed evaluation based on multiple sperm defect indices has also been proposed to give a better evaluation of sperm damage; these include teratozoospermia index (TZI), multiple anomalies index (MAI), and sperm deformity index (SDI). Even though these indices have been correlated to both *in vivo* and IVF outcomes, there is still an overlap between fertile and sub-fertile men, and they cannot be used as a strict assessment to define men's sperm potential (5). There needs to be more evidence of their clinical value (30). Moreover, even sperm with normal morphology can still exhibit other problems in function (22).

Sperm morphological assessment should be conducted using a systematic approach as clearly described by the WHO manual of human semen analysis (5). However, the assessment of sperm morphology continues to be one of the most challenging assessments due to its very subjective nature which results in difficulties in standardization and achieving consistent and reproducible findings (12). Therefore, proper evaluation, training, and standardization of laboratory technicians, as well as quality assurance in all steps of preparation and interpretation are critical to ensure the accuracy and reliability of morphology assessment.

Causes and risk factors of teratozoospermia

Genetic causes

Advances in the genetics of male infertility have shown a significant contribution of genetics towards abnormal sperm morphology (35), especially in cases of severe or specific sperm morphological defects (36).

The abnormalities of sperm morphology can be on the head, midpiece, tail, or in the form of excess residual cytoplasm (5). It can also be in multiple or monomorphic forms (37). The sperm defect is defined as monomorphic when all the spermatozoa show a unique and uniform abnormality. Among all sperm morphological defects, head abnormalities are found to be the most severe form (38). The earlier protocol of the WHO manual also recommended prioritizing reporting head defects compared to the other defects of sperm morphology (11). Interestingly, two of the most commonly found monomorphic teratozoospermic defects are macrocephalic head syndrome (macrozoospermia) and total globozoospermia syndrome (39).

In macrozoospermia, the spermatozoa have a large head, a length >4.7 µm and a width >3.2 µm, and multiple flagella (6). This abnormality has been reported to result in a high rate of aneuploid and polyploid spermatozoa (40). It also correlates with high sperm DNA fragmentation (SDF) and results in primary infertility. Several observational studies of a small number of infertile men with macrozoospermia found that the most common genetic causes of this abnormality are the mutations of the *AURKC* gene, which is a member of the serine/threonine Aurora kinase family and is responsible for the regulation of meiosis and mitosis during spermatogenesis (41,42).

The other abnormality is globozoospermia, the round-headed sperm without acrosome, with an aberrant nuclear membrane, and a defect on the midpiece of sperm (43). Like macrozoospermia, it is also associated with aneuploid spermatozoa and SDF (44). In some cases of globozoospermia with certain genetic mutations, sperm cannot initiate oocyte activation even after the use of ICSI (45). A cohort study in Italy of 18 unrelated men found several genes to be responsible for globozoospermia including mutations or deletions of DPY19L2, PICK1, and SPATA16 (46). A multicenter study in China also found DPY19L2 variants in more than 55% of Chinese globozoospermic men (47). Additionally, a study in China on a young man with globozoospermic primary infertility found that a loss-of-function variant of the *SSFA2* gene contributed to infertility due to globozoospermia and failure of oocyte activation (45). Other genetic causes of sperm morphological abnormalities include mutations of the SUN5, SPATA20, ACTL7A, and *CCIN* genes which result in pinhead spermatozoa and acephalic spermatozoa syndrome, bubble-shaped acrosome and severe head malformations, respectively (37,48,49,50). However, the majority of the findings come from case reports or case series.

Aside from the defect mentioned above, sperm tail defects were also found to correlate with several genetic defects. Tail defects are critical and can result in asthenozoospermia or abnormal motility. Several observational studies reported that mutations on DNAH1, SPEF2, and SEPT12 were correlated with sperm tail anomalies (51-53). Patients who harbor a pathogenic variant of ZMYND15 are also found to have abnormalities in sperm morphology based on sequencing analysis of 227 infertile men in China (54).

Clinical and environmental risk factors for teratozoospermia

In addition to genetic causes, several clinical conditions, lifestyle habits, and exposure to a certain substance have been shown to be associated with teratozoospermia. There are conflicting findings on the association between smoking and sperm morphology. Some studies showed that heavy

smoking is correlated with lower sperm quality, including teratozoospermia, and incidence of cytoplasmic droplets in sperm (55-57). On the contrary, a multicenter study by Pacey *et al.* in 2014 showed a non-significant association between smoking, alcohol consumption, type of underwear, and even body mass index to sperm morphology. Instead, they found that sample production in summer and Cannabis use in the 3 months before semen collection are associated with teratozoospermia in men aged thirty or less (58). Another survey of 409 infertile men found that the use of marijuana resulted in abnormal sperm parameters, especially semen volume and sperm morphology (59). Some other chemicals that correlate with abnormal sperm morphology include exposure to polychlorinated biphenyls, dibenzofurans, and sulfasalazine (60,61). The effect of the latter can be temporary and semen may return to normal after cessation of use (61).

Exposure to infection or bacteria also showed contradictory results. Mehta *et al.* found that the rate of teratozoospermia was found to be significantly higher in men with S. *faecalis* compared to semen that contained micrococci, *alpha-hemolytic streptococci* or those that did not contain bacteria at all (62). Sperm samples with *Ureaplasma urealityicum* also showed a lower normal-shaped sperm than those without any (63). An *in vitro* study of semen contaminated with *Ureaplasma urealityicum* found that colonies of bacteria were attached to the head and mid-piece of sperm with abnormal morphology (64). These findings were in contrast with another study that found that the presence of asymptomatic bacteriospermia does not correlate with abnormal semen parameters (65).

Patients with Kartegener syndrome have immotile cilia syndrome, due to abnormal morphology and function of the sperm tail (66). Varicocele, which is an important cause of male infertility, also results in an increased rate of abnormal sperm morphology (67). Some abnormalities that are related to varicocele include elongated sperm head and abnormal retention of cytoplasmic droplets (68,69). Febrile illness and testicular cancer have also been shown to affect sperm morphology due to defective spermatogenesis (70,71).

Molecular pathway of teratozoospermia

A defect in sperm morphology significantly correlates with global spermatogenic damage (72). While some morphological defects are associated with specific functional deficiencies, such as those with tail defects that result in abnormal motility, abnormal sperm morphology, in general, has shown a correlation with changes in genetic materials, increased rate of apoptosis, overproduction of oxidative stress as well as a decrease in antioxidant activities (13-15). At the metabolomic level, there are significant differences in teratozoospermic men compared to those with normozoospermia. There is a dysregulation of metabolites in the tricarboxylic acid cycle antioxidant system, cytoskeleton assembly and organization of membrane phospholipids, which results in fertility impairment in teratozoospermic men.

Men with isolated teratozoospermia have higher rates of SDF, chromosomal aneuploidy, and chromosome 13 disomy. These factors are primarily associated with aberrant sperm with round heads, amorphous heads, and tail defects (73).

Causes for increased oxidative stress in teratozoospermic men include the increase of MDA (malondialdehyde), lipid peroxidation, iron, and NADPH (nicotinamide adenine dinucleotide phosphate), which is positively correlated with the damage to sperm DNA (74,75). Oxidative stress results in lower protamination and disulfide bond formation, leading to DNA breaks and increased free radicals (13). Reactive oxygen species (ROS) production is also found to be higher among immature spermatozoa with abnormal morphology which may indicate abnormal regulation of spermatogenesis (76). During sperm migration to the epididymis, the ROS from immature spermatozoa will cause oxidative and DNA damage to the mature spermatozoa (77). A real-world study also showed that infertile men with isolated teratozoospermia have a higher SDF rate than those without abnormalities (20). However, other studies reported no correlation, or a very weak correlation, between abnormal sperm morphology and SDF (78-80).

One study found that patients with teratozoospermia had a higher proportion of spermatozoa with late-stage apoptosis, and there was a substantial correlation between the frequencies of atypical sperm forms and apoptotic biomarkers (81). A diminished seminal antioxidant capacity was also considered a vital component of the mechanism in sperm cell death-mediated DNA breaks among teratozoospermic semen (82).

Clinical significance of isolated teratozoospermia

Currently available data shows conflicting results on the value of isolated teratozoospermia in predicting pregnancy outcomes for natural pregnancy or ART.

Kovac *et al.* (82) found that up to 30% of couples

with men with absolute teratozoospermia (0% normal forms) could still conceive spontaneously, and hence they contended that sperm morphology assessment may not be a reliable indicator of fertility potential. Isolated teratozoospermia contributed to 20% of all isolated sperm abnormality cases, accounting for more than 5% of infertile men cases based on a study of almost five thousand infertile men (83). In further analysis of 1,084 men with isolated sperm defects the authors found that sperm DNA damage was more correlated with isolated asthenozoospermia as compared to isolated teratozoospermia (83). Interestingly, a recent study of 1,824 infertile men found that while 11.9% of infertile males had isolated teratozoospermia, the prevalence was higher in 103 fertile controls at 35.9% (20).

In a study on the impact of impaired morphology on intrauterine insemination (IUI) outcomes Lee *et al.*, found significantly different pregnancy outcomes after IUI between couples with <4% and >9% normal forms (84). Further, another study also showed that the cumulative live birth rate after four IUI attempts from 1,641 IUI cycles was significantly lower in the teratozoospermia groups (30.32% *vs.* 53.22%, P<0.001) (85). Hence, they, and other researchers, advised that couples with less than 4% normal sperm should undergo IVF or ICSI instead of IUI (86,87). However, a retrospective study by Lockwood *et al.* found no statistically significant difference between the IUI pregnancy rates in the group with very low strict morphology compared to those with normal morphology, and suggested that IUI should be considered even in those with a very low percentage of sperm with normal shape (88). Another study by Patel *et al.* also found no impact of abnormal sperm morphology on pregnancy or live birth rate after IUI (89).

The predictive value of morphological assessment by strict criteria during IVF was first highlighted by Kruger *et al.* who reported that men with less than 4% sperm with normal morphology had a fertilization rate of 7.6% while those with normal morphology between 4% and 14% had a fertilization rate of 63.9% (90). However, a later meta-analysis of four studies on outcomes after IVF, with or without ICSI, in couples with isolated teratozoospermia found no significant decrease in the likelihood of pregnancy (7).

Pisarska *et al.* compared IVF and ICSI outcomes in men with isolated teratozoospermia and found that ICSI produced insignificantly higher rates of oocytes fertilized than conventional IVF (100% *vs.* 90%) (91). A study by Knez *et al.* (92) reported a higher clinical pregnancy rate with IMSI (intracytoplasmic morphologically selected sperm injection) compared to ICSI for those with teratozoospermia. This study also found that the number of morphologically normal zygotes, blastocyst rate, and fraction of arrested embryos were better when using spermatozoa without head vacuoles than when using spermatozoa with vacuoles and other head problems. Along similar lines, sperm selection with density gradient centrifugation followed by magnetic-activated cell sorting recovered a higher percentage of mature, viable sperm with intact chromatin among patients with isolated teratozoospermia (93). A study by Demir *et al.* on couples undergoing ICSI found that morphology did not predict fertilization, embryo quality, and clinical pregnancy in ICSI cycles (19). However, Keegan *et al.* in a study of 495 couples assessed by the Kruger/Tyberberg strict criteria found no difference in IVF pregnancy rates between couples with isolated teratozoospermia (<5% normal) versus those with normal parameters and concluded that in men with isolated teratozoospermia IVF is sufficient and there is no need for ICSI just because of isolated teratozoospermia (94). Similar findings were reported by Fan *et al.* who showed that the outcomes of IVF were not influenced by isolated teratozoospermia (95).

Management of isolated teratozoospermia

There are some instances where aberrant sperm morphology requires clinical intervention for fertilization and conception to be possible. These abnormalities include total globozoospermic syndrome and sperm macrocephalic syndrome (5). However, there is no absolute recommendation available for isolated teratozoospermia. Some authors also consider that referral to a urologist can be deferred in men with isolated teratozoospermia (96). However, given the strong evidence linking abnormal sperm shape, oxidative stress, and the integrity of sperm DNA and chromatin, there is a role for therapy to try and increase the percentage of normal sperm morphology.

Several studies have evaluated the role of varicocelectomy and antioxidants in improving sperm morphology, particularly for immature sperm and those with head and tail defects based on Kruger's classification (97-104). A study on men with isolated teratozoospermia and clinically palpable varicocele reported an increase in all sperm parameters (concentration, motility, and morphology), lower SDF, and a higher rate of natural pregnancy at 30.5% in the varicocelectomy groups compared to 16.7%

pregnancy rate in the control group that only received an antioxidant (L-carnitine, vitamin C, and vitamin E) (97). Studies also found that around one-sixth to one-third of subjects with isolated teratozoospermia achieve spontaneous pregnancy after varicocelectomy (98,99). Furthermore, Ilktac *et al.* observed that subjects who attained natural conception after varicocelectomy had a higher rate of sperm with normal morphology and a lower rate of sperm with head anomalies compared to those who failed to achieve pregnancy or those who should undergo ART (99). However, other studies have reported no significant improvement in sperm morphology after varicocelectomy in men with clinical varicocele and pre-operative normal sperm density (100,101). Another retrospective study on 80 patients found that only 20% of operated patients had significant benefits after varicocelectomy, with their mean morphology improving from 1.3% to 9.1% (102).

Thus, the evidence recommending varicocelectomy for isolated teratozoospermia is weak. Despite the fact that the majority of respondents to a global varicocele survey (103), that included 574 clinicians from 59 countries, said they would routinely (41.1%) or in special cases (30.3%) advise varicocele surgery for isolated teratozoospermia, the benefits of varicocelectomy are not supported by strong data.

Antioxidants have also been investigated for the treatment of teratozoospermia. Fathi *et al.* showed that the use of antioxidants (L-carnitine, vitamin C, and vitamin E) could significantly improve sperm morphology (0.9% *vs.* 1.5%, P=0.04) and SDF rates (33% *vs.* 29%, P=0.03) after 6 months of treatment (97) among men with isolated teratozoospermia and clinical varicocele. This finding was in line with a meta-analysis that showed that L-carnitine is the best antioxidant to improve sperm morphology among idiopathic male infertility cases (104). Unfortunately, there are no controlled trials on the role of antioxidants in men with isolated teratozoospermia without varicocele. Further studies are needed before antioxidants can be recommended for these patients.

Other areas for future research include studies on SDF in patients with isolated teratozoospermia, and studies on the clinical efficacy and risk-benefit analysis of ART in the context of isolated teratozoospermia.

A SWOT analysis and summary of clinical recommendations on isolated teratozoospermia

We analyzed the present state of evidence among isolated teratozoospermia among infertile men using the SWOT analysis framework. The result of the analysis is presented in *Figure 2*.

The clinical significance of isolated teratozoospermia is still unclear and treatment for this condition should be done cautiously due to the lack of recommendations from professional societies and controversies in contemporary literature. Finding specific sperm abnormalities, such as complete globozoospermia, can direct the patient to a specific treatment. However, it is yet to be seen if empiric therapy with antioxidants can improve the outcome in isolated teratozoospermia. In the case of isolated teratozoospermia with clinically palpable varicocele, although some studies showed some benefit after varicocelectomy, the evidence is still inadequate to make routine recommendations. The need for, and role of, ART for isolated teratozoospermia is also controversial, and other factors—female fertility status, comorbidities, duration of infertility, etc.—should be considered when deciding whether IUI or ART (IVF/ICSI) is required in a couple with isolated teratozoospermia as the only male factor.

Conclusions

The sixth edition of the WHO manual on human semen examination recommends morphological assessment by strict criteria. However, there is considerable controversy about the diagnostic utility and predictive value of such a morphological assessment. There is no clear evidence whether severe or moderate teratozoospermia compromises chances of natural pregnancy, or whether it is a contra-indication for IUI or IVF. While several genetic causes of monomorphic defects have been identified, the etiology of the majority of cases is unclear and no specific therapy has been recommended. Given the low quality of available evidence, further studies are necessary to make detailed recommendations for assessing and managing isolated teratozoospermia.

Figure 2 A SWOT analysis of the present evidence on isolated teratozoospermia in the context of male infertility. ART, assisted reproductive technology; IUI, intrauterine insemination; WHO, World Health Organization; SWOT, strengths, weaknesses, opportunities, and threats.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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