High rate of isolated teratospermia in a population of fertile men and the questionable clinical utility of sperm morphology

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Objective: To better understand the impact of sperm morphology on fertility by assessing sperm morphology in a population of known fertile men.
Design: A prospective cohort study.
Setting: Fertility center associated with the university.
Patient(s): Healthy men >18 years of age were recruited to provide one semen sample before a vasectomy appointment scheduled between March 2020 and November 2022. Patients were included in the study when they had at least one biologic child and no history of difficulty achieving pregnancy or fertility procedures.
Intervention(s): None.
Main Outcome Measure(s): Sperm morphology.
Result(s): A total of 68 patients (mean age 36.7 years) were included. Thirty-eight (55.9%) patients had 3% or lower normal sperm morphology, including two patients who had 0 normal morphology. The most common morphologic abnormalities were head-shaped defects (n = 59, 84.3%), followed by coiled tails (n = 14, 20.3%). Count, concentration, motility, and progressive motility were normal in >90% of patients.
Conclusion(s): More than half (55.9%) of fertile male patients had lower than normal sperm morphology in our study. The results of our study further question the clinical relevance of sperm morphology on fertility outcomes and when the current approach in assessing morphology is too strict. (Fertil Steril Rep® 2024;5:140–4. ©2024 by American Society for Reproductive Medicine.)
Key Words: Sperm morphology, fertility, isolated teratospermia

Over the last several decades, sperm morphology has represented a standard component of semen analysis (SA) (1). First defined and strictly classified in 1992 by the 3rd edition of the World Health Organization (WHO) Manual for Human Semen Analysis, sperm morphology assessment has undergone several classification iterations (2–4). As of the most recently published 6th edition of the WHO manual, sperm morphology guidelines characterize abnormal vs. normal spermatozoa by the appearance of the head, midpiece, tail, and cytoplasmic residue (5).

Despite efforts to address critiques of SA with each subsequent WHO manual edition, the clinical value of the increasingly strict WHO morphology guidelines remains elusive. Issues with intralaboratory and interlaboratory technical variability, in addition to the subjective nature of the morphology assessment, have called into question the accurate repeatability of SA and have been thoroughly discussed in existing literature (6–10). Furthermore, current literature has highlighted the low predictive value of sperm morphology abnormalities in assisted reproductive technology (ART) treatment and natural pregnancy outcomes (11). Although sperm morphology was traditionally considered a strong success predictor for in vitro fertilization therapy, recent data have not demonstrated a similar consistent correlation (12, 13). Similarly, the rate of successful intrauterine insemination and intracytoplasmic sperm injection has not been consistently demonstrated

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to statistically significantly differ between men with normal and abnormal sperm morphology (14).

As of 2020, the joint American Urological Association and American Society for Reproductive Medicine (AUA and ASRM) guidelines have noted that morphology alone is neither highly predictive nor diagnostic of infertility (15). However, past survey studies have demonstrated the pervasive belief among physicians of the value of sperm morphology, potentially leading to counseling patients toward more expensive ART therapies (16). These concerns call into question the emphasis placed on sperm morphology assessment and its value in the clinical setting. To better understand the impact of sperm morphology on fertility, we assessed sperm morphology in a population of known fertile men.

MATERIALS AND METHODS

Study Design

We conducted a prospective cohort study. Healthy men >18 years of age were recruited to provide one semen sample before a vasectomy appointment scheduled between March 2020 and November 2022 at the University of Pittsburgh Medical Center. Patients were included in the study when they met the following criteria: have at least one biologic child under the age of 5 years old; have no history of difficulty achieving pregnancy; and have undergone no prior fertility procedures.

Study data were collected and managed using tools hosted by the University of Pittsburgh. The study protocol was approved by the Institutional Review Board of the University of Pittsburgh (IRB 20010192).

Study Variables

Patient demographic data were collected from patients' electronic health records. Variables of interest included age, body mass index (BMI), smoking history, the number of biologic children, and the age of biologic children.

Sperm morphology was analyzed using Papanicolaou stain with Kruger strict criteria by two technicians in an Andrology specialty laboratory per the WHO 5th Edition manual. The technicians were blinded by the fact that they were reading study samples. Thus, they did not both review each of the samples in this study to assess concordance, as this is not standard laboratory practice and would have resulted in unblinding. Variables of interest included mean sperm concentration, motility, progressive motility, morphology, and details about morphologic abnormalities.

Statistical Analysis

Chi-square test, Fisher's exact test, and univariate Welch's *t*-test were used to analyze the significance of characteristic differences between men with 4% or greater normal sperm morphology compared with men with <3% normal sperm morphology. Statistical results with a P value <.05 were considered statistically significant. All analysis was performed with Stata SE Software (Version 17.0, College Station, Texas).

RESULTS

A total of 83 patients participated, 68 (81.9%) of whom had a complete sperm morphology assessment available. The average age of participants was 36.7 years, and the mean BMI was 28.0 (22.8, 33.2) kg/m^2. Patients had an average of three children, with a mean youngest child age of 11.5 months old. Of the 61 patients with a smoking history, 38 (62.3%) were nonsmokers, 7 (11.5%) were former smokers, and 16 (26.2%) were current smokers. Meanwhile, 59 patients had an alcohol usage history available; 49 (83.1%) consumed alcohol infrequently, 9 (15.3%) abstained from alcohol, and 1 (1.69%) used alcohol frequently (Table 1).

Regarding SA, the mean sperm concentration was 54.2 mil/mL, the mean motility was 61.4%, and the mean progressive motility was 70.9%. The median normal morphology was 3%. There were 38 (55.9%) patients with 3% or lower normal sperm morphology, including two patients who had 0 normal morphology (Table 2). The most common morphologic abnormalities were head-shaped defects (n = 59, 84.3%), followed by coiled tails (n = 14, 20.3%). Men with 3% or lower normal sperm morphology were four times as likely to have both head and tail abnormalities than men with 4% or greater normal sperm morphology (n = 8 vs. n = 2, respectively); half of these men also had lower than normal motility, whereas none of the men with 4% or greater normal sperm morphology had lower than normal motility (Fig. 1).

Further analysis was performed to evaluate the association between modifiable factors and sperm morphology abnormalities. There was no significant association found between patients' current or past smoking status and an increased percentage of abnormal morphology (P=.763), nor was there a significant association found between patients' BMI and an increased percentage of abnormal morphology (P=.23). After subcategorizing patients by BMI

TABLE 1

Demographic characteristics of participants.

Characteristic	No.
Total participants	68
Age (y), mean (±SD)	36.7 (4.4)
Body mass index (kg/m^2), mean (±SD)	28.0 (5.2)
<18.5	1 (1.47%)
18.5–<25	12 (17.6%)
25–<30	34 (50.0%)
30–<35	16 (23.5%)
35+	5 (7.35%)
Smoking history	
Never	38 (62.3%)
Former	7 (11.5%)
Current	16 (26.2%)
Alcohol usage	
Frequent	1 (1.69%)
Infrequent	49 (83.1%)
None	9 (15.3%)
Total children, median	2 (IQR: 2, 3)
Age of youngest child (mo), mean (±SD)	11.5 (14.3)

IQR = interquartile range.

Cheng. Isolated teratospermia rate among fertile men. Fertil Steril Rep 2024.

TABLE 2

Breakdown of morphological abnormality type by percentage of normal sperm morphology.

	No. (%)	Median (IQR)
Total	68	
Normal semen analysis findings		
Volume >1.5 mL	55 (80.9%)	2.5 (1.6, 4)
Concentration 15 (10^6/mL)	66 (97.1%)	45.5 (37, 69)
Count >39 (10^6)	62 (91.2%)	112.8 (67.8, 229.1)
Motility >40%	64 (94.1%)	60 (50, 74)
Progressive motility >32%	66 (97.1%)	73 (61, 83.5)
Morphology ≥ 4%	38 (55.9%)	3 (2, 4)
Morphologic abnormality type		
Head only	59 (86.8%)	
Head + tail	10 (14.7%)	
Head + tail + neck	3 (4.4%)	
Head + acrosome	1 (1.5%)	
Tail only	1 (1.5%)	
Head + body	2 (2.0%)	
Head + neck	1 (1.5%)	

IQR = interquartile range.

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into normal (BMI < 25 kg/m^2), overweight (25 < BMI < 30 kg/m^2), obese (30 < BMI < 35 kg/m^2), and morbidly obese (BMI > 35 kg/m^2), we found no significant association between the BMI category and abnormal morphology (P=.685).

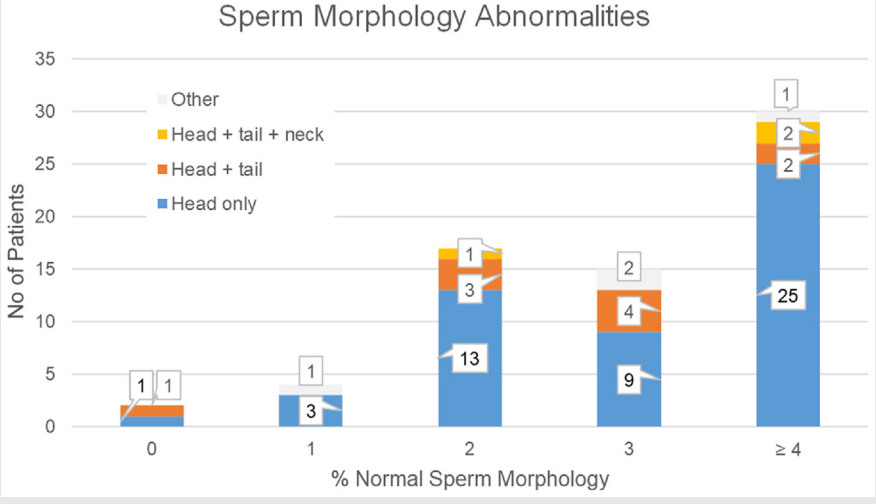
DISCUSSION

To our knowledge, our study is among the first to assess sperm morphology in a population of known fertile men. It is unique in that we prospectively enrolled patients, who then provided samples immediately before vasectomy. All of the men in our cohort had recently achieved successful natural conception with their partners within the preceding 5 years, yet a significant number of these fertile men have isolated teratospermia.

This study is important, in part, because of the anxiety that isolated teratospermia can induce for both clinicians and patients. Morphology was one of the original SA parameters thought to predict fertility (17); however, contemporary evidence has proven this to be far from the case (12, 13). Additionally, several historical studies have shown that isolated teratospermia can lead to worse outcomes for ART therapy (18–20). As a result, the use of intracytoplasmic sperm injection in cases of isolated severe teratospermia has been suggested (21). However, contemporary studies show that there is no difference in outcomes for patients with lower-than-normal morphology in terms of the probability of pregnancy with ART therapy (22). These findings are supported by two systematic reviews and meta-analyses, which found that isolated teratospermia is not associated with a decreased probability of pregnancy with ART therapy (16, 23). Furthermore, our study agrees with previous studies that have retrospectively shown that even in men with 0 normal morphology, the majority were able to conceive without assisted reproductive techniques (12). Thus, the presence of isolated severe teratospermia should not be the sole reason for progressing to ART therapy.

Although modifiable risk factors have been theorized to impact sperm morphology (24), existing literature has demonstrated little causal relationship between modifiable risk factors and abnormal sperm (25–27). Our cohort supports these established trends, as all patients had no difficulty achieving pregnancy, yet many had various modifiable risk factors involving tobacco usage or high BMI associated with their abnormal sperm morphology. Of patients with tobacco use data available, 41.8% were either

FIGURE 1



Most common sperm morphology abnormalities in men with 0, 1%, 2%, 3%, and 4+% normal sperm.

Cheng. Isolated teratospermia rate among fertile men. Fertil Steril Rep 2024.

former or current smokers. Meanwhile, 84.9% had a BMI that fell beyond a healthy weight range (>25), with 30.1% of patients falling within the obesity range (BMI > 30 kg/m^2). Our analysis found no statistically significant association between tobacco use or BMI and increased types of abnormal sperm morphologies. Isolated teratospermia has not been shown to be improved by varicocelectomy (28).

Morphology is a subjective and inaccurate measure. As mentioned previously, issues with intralaboratory and interlaboratory technical variability and subsequent lack of reproducibility call into question the practical applicability of semen morphology to clinical decision-making (6–10). A recent study similarly called into question the reproducibility and subsequent applicability of sperm morphology testing and demonstrated the poor reproducibility of sperm morphology in MOXI trial patients (29). Additionally, on the basis of existing literature on morphology, morphology is not an accurate direct measure of sperm activity and is, at best, a surrogate for other aspects of sperm function. This is reflected in the AUA and ASRM guidelines, which state that an individual sperm parameter such as morphology is not highly predictive of fertility nor does it diagnose infertility (15).

Although the assessment of sperm morphology is useful to rule out the condition of globozoospermia, the current level of morphology detail may not be beneficial in many cases as it causes undue patient anxiety with the potential to alter treatment courses unnecessarily. On the basis of contemporary evidence of the proven observation bias and poor reproducibility between technicians, perhaps one option for further consideration is changing the reporting to simply "sperm with normal morphology present or absent" in such cases.

There are several limitations to this study. We did not account for the period of abstinence before the semen sample, although participants were counseled to have 2–3 days of abstinence. Additionally, morphology was evaluated by two separate laboratory technicians; thus, there is potential for interobserver bias. We also obtained only one SA per patient and cannot account for possible variability between potential specimens. Finally, although our study was prospective insofar as patients were enrolled and provided samples before vasectomy, we were unable to collect samples from patients before their attempted conception. Semen parameters are inherently variable, and morphology reporting is subjective; thus, we cannot account for our patients' semen parameters at the moment of conception.

CONCLUSION

More than half (55.9%) of fertile male patients had lower than normal sperm morphology in our study. Although the assessment of sperm morphology as part of the SA is useful to rule out globozoospermia, isolated teratospermia is common even in known fertile men. Thus, current reporting of normal sperm percentages should be revisited, as they may cause undue anxiety for patients and clinicians. Future directions include the need for prospective assessment of semen parameters and sperm morphology before natural conception.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Lucille G. Cheng: Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Data curation. **David Miller:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Daniel Pelzman:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Anna Wecht:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Investigation, Data curation. **Kathleen Hwang:** Writing – review & editing, Validation, Supervision, Resources, Methodology, Investigation, Conceptualization.

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