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Global Practice Patterns in the Evaluation of Non-Obstructive Azoospermia: Results of a World-Wide Survey and Expert Recommendations

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Purpose: Non-obstructive azoospermia (NOA) represents the persistent absence of sperm in ejaculate without obstruction, stemming from diverse disease processes. This survey explores global practices in NOA diagnosis, comparing them with guidelines and offering expert recommendations.

Materials and Methods: A 56-item questionnaire survey on NOA diagnosis and management was conducted globally from July to September 2022. This paper focuses on part 1, evaluating NOA diagnosis. Data from 367 participants across 49 countries were analyzed descriptively, with a Delphi process used for expert recommendations.

Results: Of 336 eligible responses, most participants were experienced attending physicians (70.93%). To diagnose azoospermia definitively, 81.7% requested two semen samples. Commonly ordered hormone tests included serum follicle-stimulating hormone (FSH) (97.0%), total testosterone (92.9%), and luteinizing hormone (86.9%). Genetic testing was requested by 66.6%, with karyotype analysis (86.2%) and Y chromosome microdeletions (88.3%) prevalent. Diagnostic testicular biopsy, distinguishing obstructive azoospermia (OA) from NOA, was not performed by 45.1%, while 34.6% did it selectively. Differentiation relied on physical examination (76.1%), serum hormone profiles (69.6%), and semen tests (68.1%). Expectations of finding sperm surgically were higher in men with normal FSH, larger testes, and a history of sperm in ejaculate.

Conclusions: This expert survey, encompassing 367 participants from 49 countries, unveils congruence with recommended guidelines in NOA diagnosis. However, noteworthy disparities in practices suggest a need for evidence-based, international consensus guidelines to standardize NOA evaluation, addressing existing gaps in professional recommendations.

Key words: Azoospermia; Diagnosis; Guideline; Infertility, male; Surveys and questionnaires

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INTRODUCTION

Azoospermia is defined as the absence of spermatozoa in the ejaculate following centrifugation and subsequent microscopy of the specimen on 2 separate semen analyses [1,2]. Although it only affects 1%–2% of all men, the rate increases to 5%–15% among those seeking fertility evaluation or treatment [3,4]. Azoospermia can be broadly classified as obstructive azoospermia (OA) and non-obstructive azoospermia (NOA) and each of them has different causes and management [5]. NOA results from impairment of testicular sperm production and constitutes around two-thirds of azoospermia cases [3].

NOA may result from a variety of causes ranging from genetic defects to acquired damage and is frequently unexplained [6]. Therefore, an adequate and appropriate workup for the patient with azoospermia is important as it determines further management [7].

The basic evaluation includes history, physical examination, and serum hormone analysis but the clinical interpretation of these can be controversial. Thus, a widely cited study [8] asserts that a serum follicle-stimulating hormones (FSHs) level greater than 7.6 IU/L combined with a testicular long axis of 4.6 cm or less suggests that the azoospermia is due to spermatogenic dysfunction, consistent with NOA. However, another study [9] presents a subgroup of men with NOA due to uniform maturation arrest who had serum FSH less than 7.6 IU/L and normal testicular size. Similarly, the correct utility of other diagnostic modalities like genetic testing, imaging, or testicular biopsy remains a matter of debate.

Professional and academic society guidelines for the evaluation of NOA are limited and there are many controversies in the literature. Hence, considerable di-

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versity in the diagnostic approaches and management of azoospermia across the globe is to be expected.

The current study aims to assess contemporary global practices related to the diagnosis and evaluation of NOA among experts and to compare them with the current international practice guidelines and the available evidence in the literature. Expert recommendations derived through a Delphi consensus are also provided.

MATERIALS AND METHODS

The global survey was approved by the Global Andrology Forum (GAF) Internal Review Board (IR-02-23-110). The checklist for Reporting Results of the Internet E-Survey (CHERRIES) was used to guide the construction, dissemination, and analysis of the questionnaire [10]. The checklist is provided in Supplement File 1.

1. Target population

The survey targeted physicians who treat NOA patients in their daily practice. This group included urologists, andrologists, and reproductive endocrinologists. Clinicians not dealing with these patients were excluded.

2. Questionnaire creation and structure

Members of the GAF [11], which is an online collaboration of clinicians, embryologists, and researchers interested in andrology, were invited to submit multiple-choice questions on relevant clinical aspects of the evaluation and management of NOA. These suggestions were extensively reviewed and refined, by a group of ten experienced clinicians, to reflect the different options and practices available in the diagnosis and management of patients with NOA. The option "not applicable" was added when respondents did not encounter a particular situation in their clinical practice. The final survey had 56 questions accompanied by an invitation letter that mentioned the aims of the survey and recorded the respondent's consent to participation (Supplement File 2). While completing the survey, respondents were able to scan, review, and edit their responses before the final submission. This paper discusses the first part of the survey covering section 1 on demographic data (Q1–8) and section 2 on diagnosis and evaluation (Q9–21).

3. Questionnaire dissemination

The questionnaire was created using Google Forms and was available online from July 21st, 2022, to September 9th, 2022. The survey was published on the website of the GAF and all members were invited to complete the survey if they fit the inclusion criteria. On the final page, the respondents were able to recommend other experts who met the inclusion criteria. The survey questionnaire was also distributed to the members of the different organizations listed under the Acknowledgment.

4. Data collection and analysis

The survey data were extracted as a CSV file from the survey platform. Blank and duplicate responses were excluded. Partial responses were accepted if they included some questions beyond demographics. MedCalc® (MedCalc Software Ltd) was used to calculate responses and generate tables and graphs. When a question allowed more than one response, the total number of responses was used for calculations. Some respondents skipped some questions and hence the total number of responses per question varied.

5. Society guidelines

The male infertility guidelines of the American Urological Association/American Society for Reproductive Medicine (AUA/ASRM) [12], the European Association of Urology (EAU) [13] and the European Academy of Andrology (EAA) [14,15] were reviewed for their recommendations on the evaluation and diagnosis of NOA.

6. GAF expert recommendations

GAF expert recommendations were formulated using a Delphi process. Two senior authors (RS, AR) formulated the statements based on the survey results, available professional society guidelines, and the latest literature on the subject (Supplement File 3). These were then forwarded to 43 GAF clinicians with at least 15 years of experience in treating NOA. They rated the recommendations on a scale from 1 to 10, 1 being "completely disagree" and 10 "completely agree." When they disagreed with the statement, they were asked to provide a new changed recommendation. The final recommendation was accepted once 70% of the respondents scored 7 or above.

RESULTS AND DISCUSSION

In the current paper, we present the results of the first 21 questions dealing with the demographics of the survey and the approach to the evaluation of NOA.

The results of the survey have been grouped based on the question topics. For each group of questions, the survey results are discussed in the context of the guideline recommendations from major male infertility societies (AUA/ASRM, EAU, and EAA) and an extensive literature review of relevant contemporary publications. Finally, these are summarized as expert recommendations based on the Delphi process described above. All recommendations were accepted in the first round of the Delphi process (Table 1).

1. Demographics

A total of 367 participants from 49 countries submitted their answers. Of these, 31 responses were excluded, either due to incomplete data (n=6) or submission by

Table 1. Comparison of the different guidelines on NOA

	AUA/ASRM	EAU	EAA
Incidence of NOA	Not mentioned	Obstructive azoospermia is less common than NOA and occurs in 20%–40% of men with azoospermia	Not mentioned
Presence of varicocele in NOA	Not mentioned	10.9% of men with azoospermia have varicocele	Not mentioned
Number of semen samples before the diagnosis	2	2	Not mentioned
Optimal time interval to repeat semen analysis	1–2 weeks	No specific recommendation	Not mentioned
Initial hormonal evaluation	Total testosterone and FSH	Total testosterone and FSH/LH	No specific recommendation
Genetic testing	Karyotype and YCMD for men with azoospermia	Karyotype analysis and YCMD Gene coding for *CFTR* to exclude concomitant mutations	Karyotype analysis for detecting KS and YCMD
Genetic counselling	No specific recommendation	Mandatory in couples with genetic abnormalities prior to any ART protocols For all men with azoospermia For all couples with a genetic abnormality found on clinical or genetic investigation and in patients who carry a (potential) inheritable disease	Mandatory for all men with YCMD
Modalities to differentiate OA and NOA	History, physical examination (small volume testes), semen volume, and hormonal status (FSH, LH, testosterone)	No specific recommendation	No specific recommendation
Diagnostic testicular biopsy	Should not be routinely performed to differentiate between OA and NOA May be considered in infertile men with normal semen volume, normal testicular volume, and FSH<7.6 and no signs of epididymal engorgement	Performing a diagnostic biopsy before surgery (any type) unless dedicated to ART protocols is currently considered inappropriate	No specific recommendation
Predictors of successful surgical sperm retrieval	No specific recommendation	No preoperative biochemical and clinical variables may be considered sufficient and reliable predictors of positive sperm retrieval at surgery in patients with NOA	No specific recommendation

AUA: American Urological Association, ASRM: American Society for Reproductive Medicine, EAU: European Association of Urology, EAA: European Academy of Andrology, NOA: non-obstructive azoospermia, FSH: follicle-stimulating hormone, LH: luteinizing hormone, KS: Klinefelter syndrome, YCMD: Y chromosome microdeletion, OA: obstructive azoospermia, ART: assisted reproductive technology, CFTR: cystic fibrosis transmembrane conductance regulator.

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an ineligible respondent (n=25). Thus, a total of 336 participants were included in the study. The highest responses were received from respondents from Italy (n=36, 10.7%), Turkey (n=35, 10.4%), and India (n=35, 10.4%). Respondents and countries are presented in Fig. 1.

The majority of respondents were attending physicians, with training in general urology or andrology, and were equally divided between academic and private practice (Table 2). Almost half of the survey participants had 11 or more years of experience (Fig. 2) with more than 30% evaluating 11–20 new infertile men per week (Fig. 3).

2. Diagnosis and evaluation of NOA

1) Incidence of NOA in men presenting with infertility

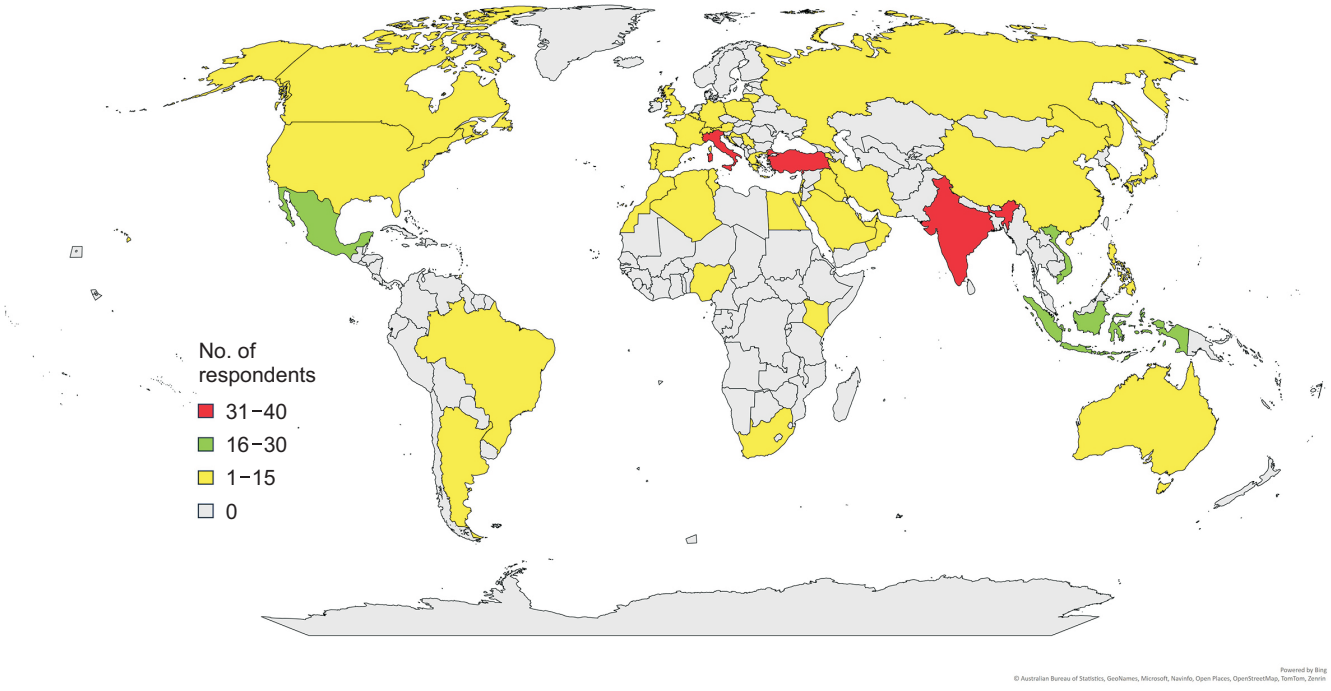
(1) Survey results

NOA appears to be a common problem in male infertility clinics with 39.6% of respondents reporting that 10%–25% of the infertile men they see present with NOA, and 19.94% reporting that >25% of their infertile men had NOA (Fig. 4).

Almost two-thirds (62.4%) of the respondents reported that at least 10% or more of their patients with NOA had a clinically significant varicocele (Fig. 5).

(2) Guidelines

Neither ASRM/ASRM nor EAA guidelines men-



1. Algeria	n=2	11. China	n=4	21. Israel	n=1	31. Philippines	n=1	41. Spain	n=3
2. Argentina	n=1	12. Croatia	n=1	22. Italy	n=36	32. Poland	n=1	42. Switzerland	n=2
3. Armenia	n=3	13. Egypt	n=14	23. Japan	n=5	33. Portugal	n=1	43. Trinidad and Tobago	n=1
4. Australia	n=4	14. France	n=5	24. Kenya	n=1	34. Qatar	n=5	44. Tunisia	n=2
5. Austria	n=13	15. Germany	n=1	25. Lebanon	n=2	35. Russia	n=1	45. Türkiye	n=35
6. Bahrain	n=1	16. Greece	n=7	26. Lithuania	n=1	36. Saudi Arabia	n=11	46. UAE	n=9
7. Barbados	n=1	17. India	n=35	27. Mexico	n=23	37. Serbia	n=5	47. UK	n=3
8. Belgium	n=1	18. Indonesia	n=27	28. Morocco	n=3	38. Singapore	n=6	48. USA	n=7
9. Brazil	n=9	19. Iran	n=11	29. Nigeria	n=1	39. South Africa	n=1	49. Vietnam	n=23
10. Canada	n=1	20. Iraq	n=3	30. Oman	n=1	40. South Korea	n=1		

Fig. 1. Geographical distribution of respondents. The number of respondents is shown in brackets after the name of each country, while the numbers on the map indicate the ranking of the countries according to the number of respondents. The map is also color-coded according to the number of respondents in each country.

Table 2. Demographic characteristics of the respondents

	Number (%)
Q4: What is the nature of your employment?	
Physician, attending or fellow	281 (83.63)
Physician, resident	37 (11.01)
Advanced practice provider (Physician Assistant, Nurse Practitioner)	7 (2.08)
Others	11 (3.27)
Q5: What is your area of specialization (as it relates to male infertility)?	
Fellowship-trained reproductive urology	99 (29.46)
General urology	115 (34.22)
Reproductive Endocrinology/ART specialist	67 (19.94)
Endocrinology	11 (3.27)
Other (specify)	44 (13.09)
Q6: What is your practice setting?	
Academic	85 (25.29)
Public	39 (11.60)
Private	102 (30.35)
Multiple	108 (32.14)
Other (specify)	2 (5.95)

ART: assisted reproductive technology.

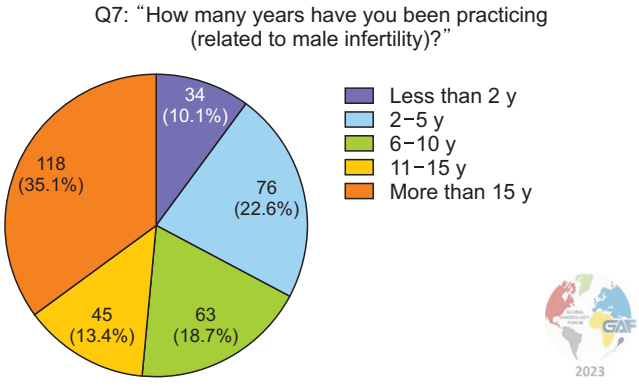


Fig. 2. The number of years the respondents have been practicing.

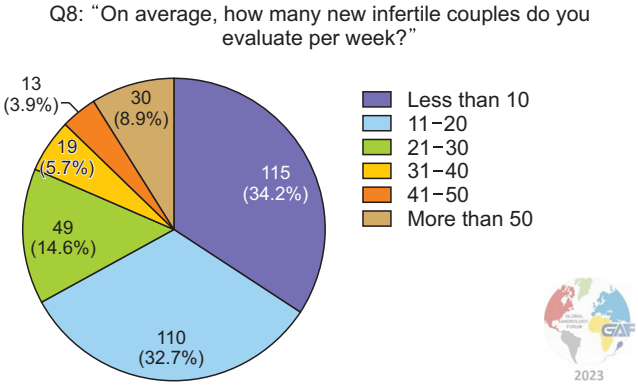


Fig. 3. The average number of new infertile couples evaluated per week by the respondents.

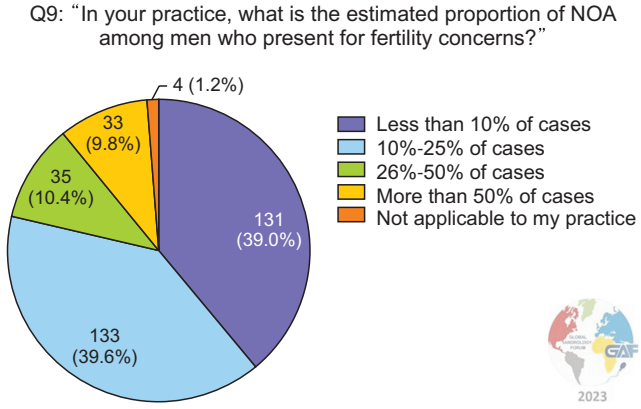


Fig. 4. Estimated proportion of NOA in men presenting with infertility. NOA: non-obstructive azoospermia.

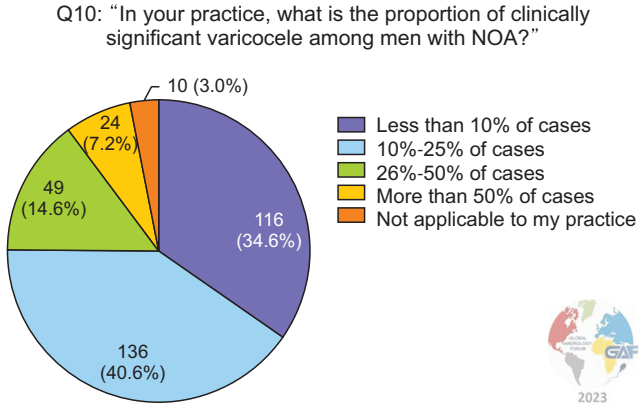


Fig. 5. Proportion of clinically significant varicocele among men with NOA. NOA: non-obstructive azoospermia.

tion the estimated prevalence of NOA among infertile men. In the EAU guidelines, the estimated proportion of azoospermia among men who present for fertility evaluations is 11.2% [13]. Although there is no explicit proportion of NOA in the EAU guidelines, it is stated that the prevalence of OA is less frequent compared to NOA at one-fifth to two-fifths of men with azoospermia. Therefore, the proportion of NOA is around 60% to 80% of men with azoospermia. EAU guidelines mentioned that the proportion of varicocele among men with azoospermia is 10.9%, however, no specific proportion is stated for NOA. On the other hand, both AUA/ASRM and EAA guidelines do not mention any specific proportion for this group [12,14,15].

(3) Discussion

This survey shows that NOA is commonly encountered in specialized infertility clinics around the globe. The majority of cases of NOA are due to primary hypogonadism (hypergonadotropic hypogonadism or testicular failure), while NOA due to secondary hypogonadism (hypogonadotropic hypogonadism) is uncommon [7]. There is a wide range of congenital, environmental, iatrogenic, and acquired conditions that can cause testicular failure leading to NOA [16].

While varicocele is commonly associated with oligoasthenozoospermia with an estimated prevalence of 35% [17], it is uncommon for it to be the primary cause of azoospermia. However, 5% to 10% of men with NOA have been reported to have an associated clinical varicocele [18], although in the current survey a higher incidence is suggested.

(4) Expert recommendation

The majority of cases of azoospermia are non-obstructive and are due to primary testicular failure. The clinical relevance of a varicocele associated with NOA is unclear.

2) Number of semen samples to confirm the diagnosis of NOA

(1) Survey result

Of 334 respondents, more than 80% requested two semen analyses before diagnosing NOA. Forty-six participants (13.8%) chose the "3 or more" option, whereas only 11 participants (3.3%) requested just one semen sample to diagnose NOA (Fig. 6).

(2) Guidelines

Although there is no specific mention in the EAA guidelines, both the AUA (statement 11) and EAU (11.6.1.2.3) guidelines state that a second semen sample is mandatory if the initial semen analysis shows azoospermia [12,13].

(3) Discussion

The practice of the majority of the respondents is in line with the guidelines' recommendation of requesting a second semen sample if the initial examination showed an absence of sperm in the ejaculate. However, about 14% of the participants recommend 3 or more tests to arrive at the definitive diagnosis, possibly reflecting the finding that some men with NOA do occasionally have sperm in the ejaculate which may be detected only on repeated testing [19,20]. Thus, Schlegel et al [21,22] recommended a semen analysis on the day before the planned sperm retrieval procedure.

The method of examination of the semen sample can also impact the diagnosis of azoospermia. Centrifugation of the semen sample at 3,000 g for 15 minutes and examination of the pellet at 200× magnification (EUA guideline 11.3.2) or at 400× magnification (EUA guideline 11.6.1.2.3) [13] is recommended to confirm the diagnosis of azoospermia. The whole pellet should be thoroughly examined; a study using an extended sperm preparation found sperm in 35% of men who were initially diagnosed with NOA, thus preventing them from undergoing unnecessary sperm retrieval [23]. In another study, the use of nuclear fast picroindigocarmine (NF-PIC) staining in combination with Cytospin cen-

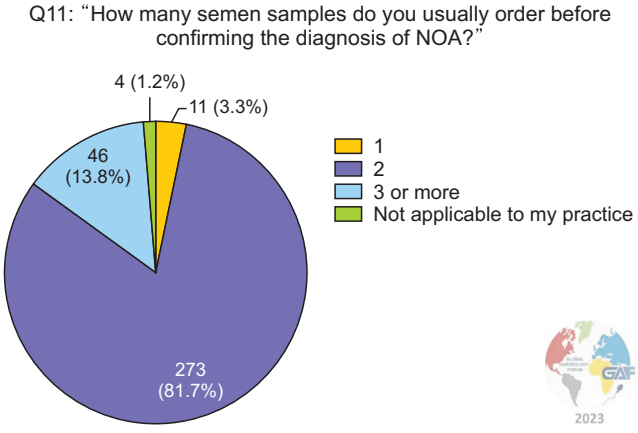


Fig. 6. Number of semen samples usually ordered prior to confirming a diagnoses of NOA. NOA: non-obstructive azoospermia.

trifugation found sperm in 23.9% of samples deemed azoospermic by conventional examination [24].

(4) Expert recommendation

Due to possible fluctuations, one semen sample might not be enough to diagnose azoospermia. At least two separate semen samples should be examined, after centrifugation to create a pellet, to establish a diagnosis of azoospermia.

3) Optimal time interval to repeat semen analysis in diagnosing NOA

(1) Survey result

Half the respondents (49.4%) do the second semen test within two to four weeks of the first test, while one-fourth (22.9%) prefer to wait for 3 months (Fig. 7). However, 10.1% of respondents highlighted that the interval between tests is best optimized as per the individual case.

(2) Guidelines

According to the AUA/ASRM guidelines, in cases of azoospermia a confirmatory semen analysis should be obtained at least one to two weeks later (AUA guideline statement 11) [12]. There is no specific recommendation in terms of the optimal time to repeat semen testing in EAA or EAU guidelines [13-15].

(3) Discussion

There is currently no study that definitively identifies the ideal time interval between two semen analyses for diagnosing NOA since azoospermia is typically used as an exclusion criterion in research that examines the ideal time for semen analysis [25,26]. Thus, while the AUA/ASRM guidelines recommend repeating the semen analysis after a couple of weeks, it is important to bear in mind that after exposure to reversible causes of azoospermia like high fever, infection, major medical illness, exposure to toxins, chemotherapy or radiotherapy, or some medications, the reappearance of sperm in ejaculate may take several weeks to months [27-33].

While the majority of participants of the survey cited a period of 14 to 29 days as ideal for the interval between two semen analyses, 22.9% cited a period of three months. The adoption of a three-month timeframe seems reasonable conceptually as it represents a full cycle of spermatogenesis [34]. Only 9.2% of participants routinely repeat the semen analysis in less than 14 days. However, individual considerations like the couple's age, urgency for planning the next step, and the logistics for repeating the semen test may also influence the timing of the next test.

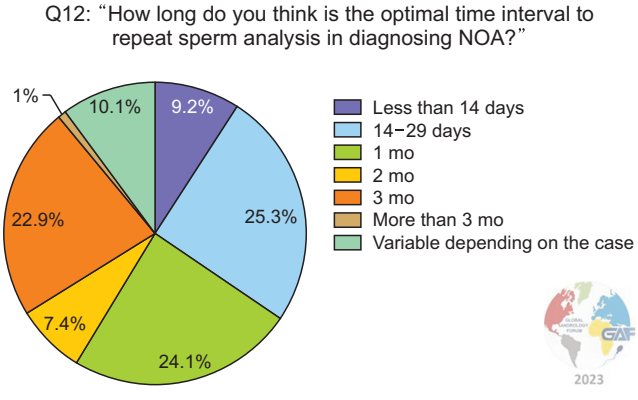


Fig. 7. Optimal time to repeat sperm analysis in diagnosing NOA. NOA: non-obstructive azoospermia.

(4) Expert recommendation

Generally, at least a month's interval is preferable between two semen reports in an azoospermic man, but the physician's clinical judgment should be used to determine the duration between the two tests, depending on individual circumstances and history of any recent medical illness that could have affected spermatogenesis.

4) Hormonal evaluation

(1) Survey result

The majority of respondents routinely perform serum FSH, luteinizing hormone (LH), and total testosterone tests in patients with NOA, and around half of the respondents also check for serum prolactin and estradiol levels. Only 15.5% consider inhibin-B levels to be of value (Fig. 8).

(2) Guidelines

The AUA/ASRM guidelines recommend an initial assessment of serum total testosterone and FSH levels; if the testosterone level is <300 ng/dL then they recommend repeating the total testosterone assay together with the measurement of free or bioavailable testosterone, serum LH, prolactin and estradiol (Statement 10). EAU guidelines recommend the measurement of serum total testosterone with FSH and LH (Guideline 11.3.4) [12,13]. The AUA guidelines do not discuss inhibin-B

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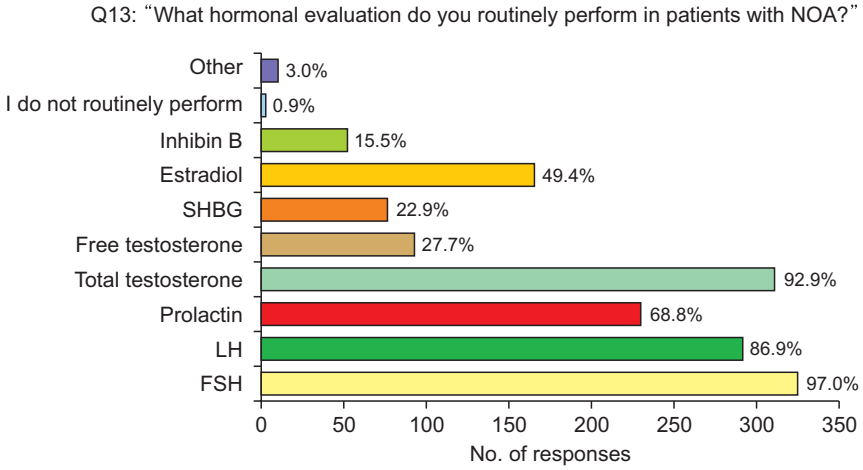

Fig. 8. Hormonal evaluation routinely performed for patients with NOA. NOA: non-obstructive azoospermia, SHBG: sex-hormone binding globulin.

while the EAU guidelines state that though inhibin-B is a useful indicator of Sertoli cell function, its diagnostic utility is not superior to FSH and hence is not widely used (Guideline 11.6.1.2.4). The EAA guidelines do not provide specific recommendations for hormonal evaluation for men with NOA [14,15].

(3) Discussion

The hypothalamic-pituitary-gonadal axis is essential for spermatogenesis. Rapid pulses of gonadotropin releasing hormone (GnRH) stimulate the release of FSH and LH from the anterior pituitary gland. FSH acts on the testes to promote spermatogenesis via Sertoli cells, whereas LH stimulates the Leydig cells to produce testosterone [35]. Studies have shown that serum FSH, LH, and testosterone levels are significantly different among men with NOA compared to those with OA [36,37].

The value of serum total testosterone level may not represent the functional testosterone available due to the changes in serum sex-hormone binding globulin (SHBG) levels which may be altered due to metabolic syndrome, hypo/hyperthyroidism, pituitary disease, chronic liver disease, prostate cancer, nephrotic syndrome, estrogen use, as well as drugs such as some anticonvulsants and steroids [38,39]. Therefore, the calculation of free testosterone may be useful in borderline cases [38].

Sertoli cells produce inhibin-B to give negative feedback. Estradiol is the predominant form of estrogen that mediates the negative feedback to the hypothalamus thus impacting GnRH release and consequently regulating spermatogenesis. Serum estradiol levels in infertile men with NOA may vary but the majority (up to 71.1%) have normal levels [40]. Thus, estradiol should be assessed for selected patients such as those with obesity, those working in a polluted workplace, or before trying hormonal therapy [40].

An elevated level of prolactin can also result in negative feedback to pituitary gonadotrophin secretion by directly influencing the prolactin reception in the testis, which then results in detrimental effects on spermatogenesis [35,41]. A study by Gonzales et al [42] reported a significantly higher prolactin level among the azoospermic group compared to the normozoospermic group while another study found that up to one-fourth of men with azoospermia have hyperprolactinemia [43]. However, there is no established causation or clinical relevance of raised prolactin to azoospermia. In a study of 204 men attending infertility clinics, there was no significant difference in pregnancy rates between men with high (greater than 5 ng/mL) and low (less than or equal to 5 ng/mL) prolactin [44]. Therefore, it is suggested that the investigation for prolactin in an azoospermic male is done only for those with hypogonadotropic hypogonadism, or with concomitant complaints of sexual dysfunction (especially decreased libido), or if there are clinical symptoms of hyperprolactinemia or pituitary disease [45].

The result of the survey showed that serum FSH, LH, and total testosterone were the most common initial hormones evaluated in patients with NOA. This

corresponds with the guidelines' recommendations.

(4) Expert recommendation

The initial evaluation of a patient with suspected NOA should include serum total testosterone level, FSH, and LH, as these hormones are the primary regulator for spermatogenesis. When the serum total testosterone level does not match the clinical symptoms or if there is any condition that could dramatically alter the SHBG level, then the calculation of free testosterone (after SHBG assay) is recommended. Serum estradiol should be measured in obese men. Serum prolactin should be assayed if there is an associated decreased sexual desire and erectile dysfunction.

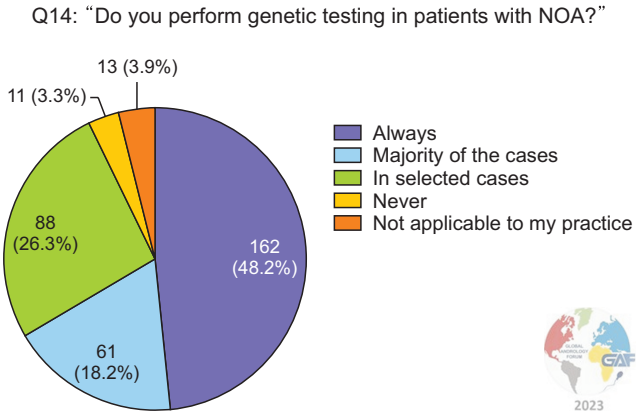

Fig. 9. Proportion of respondents who perform genetic testing in patients with NOA. NOA: non-obstructive azoospermia.

5) Genetic testing

(1) Survey result

Out of 335 respondents, two-thirds ask for genetic testing in men with NOA in all or the majority of the cases, while 26.3% of them would offer it in selected cases. A small minority (3.3%) of the participants chose the "never" option (Fig. 9).

For the genetic tests that are routinely performed, the majority of respondents order karyotype analysis and Y chromosome microdeletion, while one-fifth of respondents also test for the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene in patients with NOA. Only a few of the respondents (2.7%) ask for *Kal1* gene test (Fig. 10). For genetic counseling, half of the respondents refer their patients to a genetic counselor, while 22.1% feel that they could counsel adequately by themselves (Fig. 11).

(2) Guidelines

All guidelines agree on the need for karyotype and Yq deletion screening in all men with NOA [12-15]. The EUA guidelines also recommend testing for concomitant CFTR mutations (Guideline 11.6.2.1) [13].

The EAU guidelines recommend offering genetic counseling to men with azoospermia and oligozoospermia (spermatozoa <10 million/mL), especially for those who have a potential for inheritable disease and before any assisted reproductive technique (ART) procedure. In congruence, the EAA guidelines recommend offering genetic counseling for men with Y chromosome microdeletion and selected cases of men with Klinefelter Syndrome [14,15].

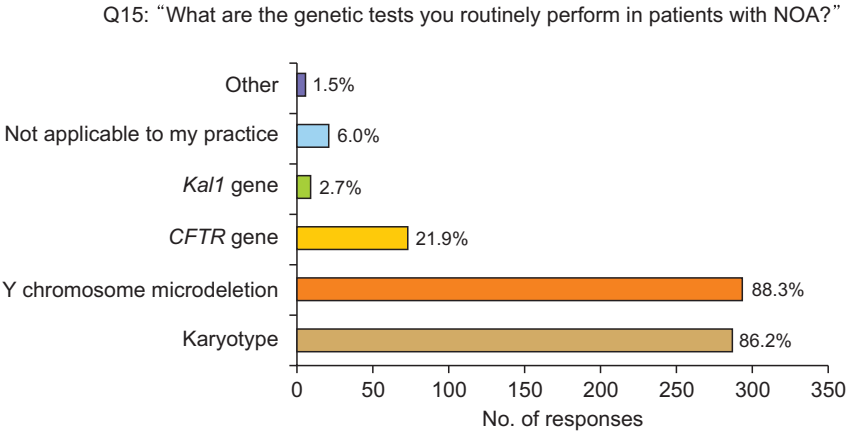

Fig. 10. Routinely performed genetic tests in patients with NOA. NOA: non-obstructive azoospermia, CFTR: cystic fibrosis transmembrane conductance regulator.

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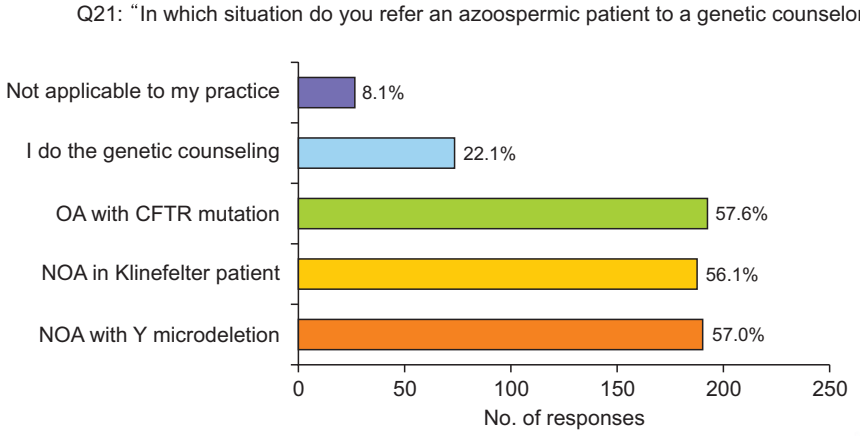

Fig. 11. Conditions in which the respondents refer an azoospermic patient to a genetic counselor. NOA: non-obstructive azoospermia, OA: obstructive azoospermia, CFTR: cystic fibrosis transmembrane conductance regulator.

(3) Discussion

A male patient with azoospermia or severe oligospermia has a higher likelihood of having genetic abnormalities. A study of 291 men attending infertility clinics reported that chromosomal abnormalities were significantly higher among azoospermic men (35.0%) compared to patients with normozoospermia (1.1%) [46]. Another study of 1,663 infertile men with azoospermia showed that the rate of chromosomal abnormalities was around 14.4% [47]. Among these abnormalities, Klinefelter syndrome was detected in 64% to 73% of patients [46,47], followed by autosomal abnormalities, terminal deletion of chromosomal Y, and XYY karyotypes [46]. Another study of 765 infertile men with NOA, showed that 13.99% had Y chromosome microdeletions [48].

These studies highlight the need for karyotyping and Y chromosome microdeletion testing in patients with NOA, which is consistent with the guidelines and practices of the majority of our respondents.

On the other hand, 2.7% of respondents would order *Kal1* gene testing. *Kal1* is the first gene discovered in X-linked Kallman Syndrome patients [49] and is the most common cause of congenital hypogonadotropic hypogonadism especially when associated with anosmia or severe hyposmia [5]. The test of Kal1 should be reserved for those with clinical suspicion of Kallman Syndrome.

There are many other genes as well as mutations of genes that are proposed to be responsible for NOA [50], but several of them have not yet been confirmed or are so rare in the community that routine screening would not be cost-effective [51].

Interestingly, 21.9% of participants stated that they routinely perform *CFTR* gene mutation testing in patients with NOA although *CFTR* gene mutation does not cause NOA, and testing for CFTR mutations is causally indicated in OA with congenital seminal tract anomalies. A reason to do this test could be linked to the high prevalence of CFTR mutations in some geographical areas and in these populations, both partners of a couple undergoing ART for NOA may coincidentally also be carriers of CFTR mutations. If that is found to be the case, then preimplantation genetic testing would be required to avoid cystic fibrosis in the offspring.

A causative role of CFTR mutations in NOA is unlikely. A case-controlled study of 100 men with NOA found that certain polyvariant mutations of the *CFTR* gene (T5 allele and TG12-T5-V470 genotypes) were associated with a higher risk of NOA, though the common F508del and R117H mutations were not found [52]. A study of 100 Iranian infertile men with NOA also showed that neither ΔI507 nor ΔF508 *CFTR* gene mutations played a role [53].

Genetic counseling is an important aspect of the management of azoospermia [54]. It includes a discussion of the risk and clinical consequences of vertical transmission to the offspring, and whether preimplantation genetic testing is advisable [55]. Our survey shows that a significant proportion of clinicians offer counseling themselves and do not refer the couple to a genetic counselor. This finding highlights the need for

providing training in genetic counseling to clinicians.

(4) Expert recommendation

Karyotype and Y microdeletion tests should be recommended for NOA patients, while *CFTR* gene mutation tests should be done only in cases of vas aplasia or congenital obstruction, or in regions with a high prevalence of carriers for CFTR mutations. Currently, other genetic tests like full exome or genome screening are not recommended as routine tests.

6) Preferred modalities to differentiate OA and NOA

(1) Survey result

Almost half (45.1%) of the respondents do not perform diagnostic testicular biopsy to differentiate between OA and NOA, while one-third (34.6%) perform it in selected cases. However, 14.1% of respondents reported that they routinely perform either unilateral or bilateral diagnostic testicular biopsies (Fig. 12).

In order to differentiate between NOA and OA, most respondents rely on clinical examination (76.1%), serum levels of reproductive hormones (69.6%), and basic and extended semen tests (68.1%). Only a minority of clinicians (29.0%) consider scrotal ultrasonography as being helpful in distinguishing between OA and NOA (Fig. 13).

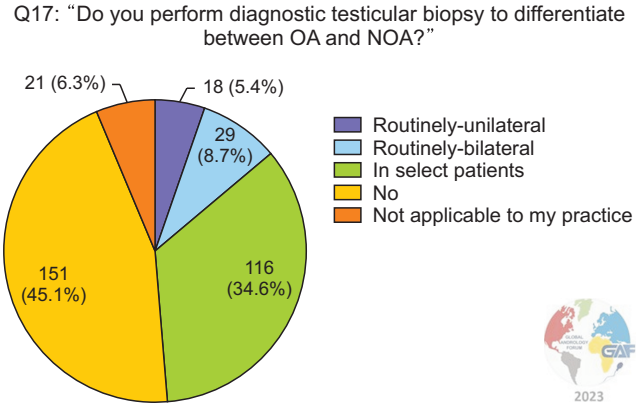

Fig. 12. Most helpful modality to differentiate between OA and NOA. NOA: non-obstructive azoospermia, OA: obstructive azoospermia.

(2) Guidelines

The EAU guidelines state that testicular histopathology from a diagnostic testicular biopsy is an important predictor of spermatogenesis and sperm retrieval, but it should not be performed in isolation and should, instead, always be combined with therapeutic sperm retrieval (Guideline 11.6.1.2.6). Further, the EAU guidelines state that diagnostic fine needle aspiration should not be performed in isolation without simultaneous therapeutic testicular sperm extraction (TESE) [13].

Likewise, the AUA/ASRM states that in the majority of cases, clinical and laboratory results are sufficient to differentiate NOA or OA without the need for an invasive diagnostic biopsy procedure (Guideline statement 11). Azoospermic men with small testicular volume, elevated serum FSH, and normal semen volume typically belong to the NOA group, while those with normal testis volume (length >4.6 cm) and serum FSH level <7.6 IU/mL will most likely have OA. The diagnosis of OA is more convincing if there is engorgement of proximal epididymis or clinical absence of

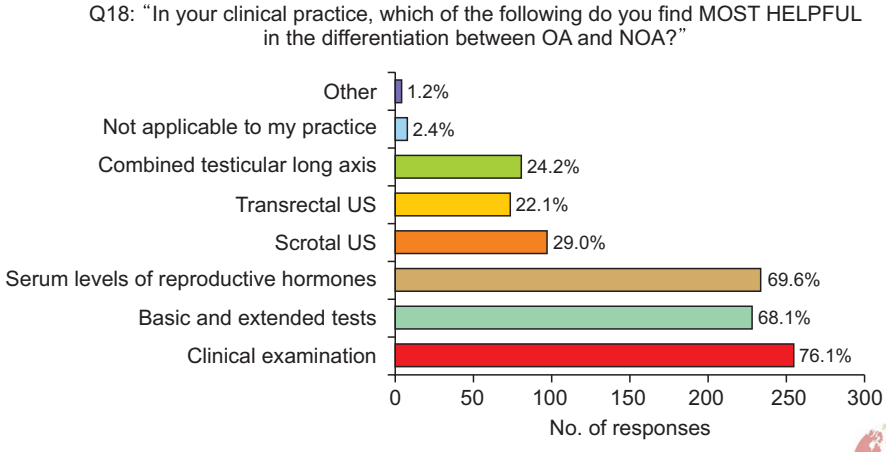

Fig. 13. Diagnostic testicular biopsy to differentiate between OA and NOA. NOA: non-obstructive azoospermia, OA: obstructive azoospermia.

vasa deferentia. A diagnostic testicular biopsy may be infrequently indicated in case of "intermediate values" and should be combined with sperm cryopreservation (Guideline statement 20) [12].

The EAU guidelines do not make any recommendation for an US in the evaluation of NOA, but an earlier section (11.3.6.1) discusses that an US may help in identifying testicular dysgenesis or testicular tumors, and in assessing testicular volume [13]. Both the AUA (Guideline statement 22) and EAU (11.3.6.2) suggest that trans-rectal sonography should be limited to cases where there is suspicion of distal obstruction at the level of the ejaculatory ducts, and need not be done routinely in all cases [12,13]. There is no specific mention in the EAA guidelines regarding modalities to differentiate between OA and NOA [14,15].

(3) Discussion

Categorization of azoospermia into OA or NOA is critical as the management strategies for the two are very different. While testicular biopsy is the "gold standard" to discriminate OA from NOA, it is an invasive procedure and should be reserved for inconclusive cases such as patients with normal FSH, normal testicular size, and no sign of obstruction [56]. In the majority of cases, differentiation can be made through clinical, biochemical, genetic and imaging assessment [56].

In our survey, almost half (45.1%, n=151) of the participants do not perform diagnostic testicular biopsy to differentiate between OA and NOA, while 34.6% of them would perform it in selected cases. This finding is consistent with the literature as well as the guidelines.

The AUA guidelines differentiate between OA and NOA based on FSH and testicular size (long axis). These are derived from a study by Schoor et al [8] which showed the serum FSH level was 7.6 mIU/mL or less and the testicular long axis was 4.6 cm or greater in 96% of males with OA. On the other hand, serum FSH levels higher than 7.6 mIU/mL and a testicular long axis less than 4.6 cm were present in 89% of males with NOA. While this is a useful finding for differentiating between OA and NOA, it has many limitations. In the study, 21.6% of men with OA had a long axis <4.6 cm and 22.2% of men with NOA had a long axis >4.6 cm. Similarly, 9.3% of men with OA had FSH >7.6 mIU/mL while 24.1% of men with NOA had FSH <7.6 mIU/mL. Hence, it is not uncommon to have men with large testes and normal FSH who have NOA. Thus, a 2007 study from Schlegel's group found that 32 men from a study group of 150 had maturation arrest but normal FSH and normal testicular size [9]. Hence, in addition to the testes size and FSH level, the turgidity of the epididymis on clinical examination should be considered [12]. This is in line with the survey finding where "clinical examination" was reported as "most helpful" in differentiating between OA and NOA.

We also need to consider that the range of normal FSH values vary widely from laboratory to laboratory [12]. In the study by Schoor et al [8], the upper limit of normal FSH was 15 mIU/mL. Thus, the value of 7.6 mIU/mL lies in the lower half of the normal range, and hence the cut-off value for FSH may be better defined as a value in the lower half of the range for that laboratory rather than as an absolute value.

Other studies have suggested different parameters to distinguish between OA and NOA. A study by Shamohammadi et al [37] proposed a cut-off of serum FSH >8.9 mIU/mL and testicular long axis <39 mm; their positive predictive value for NOA was 97.02% and for OA was 78.8%. Differences in cut-off point may also result from ethnic differences with Asian males reported to have higher serum FSH and smaller testes compared to Caucasian men [57,58].

Ultrasonography has a limited role in differentiating between OA and NOA and may be more relevant for ruling out a testicular tumor before therapeutic TESE.

(4) Expert recommendation

In most cases clinical and laboratory results are sufficient to diagnose NOA or OA.

Diagnostic testicular biopsy before definitive TESE is not recommended for use in routine clinical practice. Only in some cases, where the serum FSH and LH, and the testicular volumes are normal, a testicular biopsy may be indicated to provide a definitive diagnosis, and should always be combined with therapeutic TESE.

7) Predictive factors of sperm retrieval by cTESE/mTESE

(1) Survey result

The majority of respondents (66.4%) stated that normal serum FSH predicts a higher chance of sperm retrieval by cTESE (conventional TESE) or by mTESE (microdissection TESE). Normal testicular volume (63.1%) and a history of sperm (60.4%) in the ejaculate

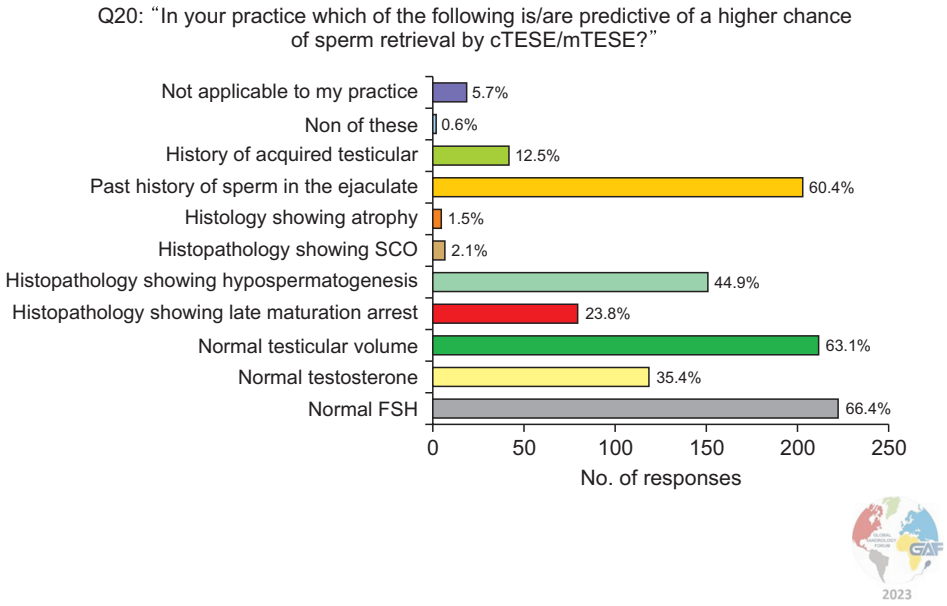

Fig. 14. Predictive factors of a higher success rate of sperm retrieval by cTESE/mTESE. cTESE: conventional therapeutic testicular sperm extraction, mTESE: microdissection therapeutic testicular sperm extraction, FSH: follicle-stimulating hormone, SCO: Sertoli cell only.

were the other popular answers (Fig. 14).

(2) Guidelines

The EAU guidelines state that testicular histology is a good predictor of successful surgical sperm retrieval but do not recommend routinely doing a biopsy for this purpose. They further state that serum hormone levels of FSH, LH, Inhibin, and anti-Mullerian hormone (AMH) have variably correlated with sperm retrieval in various studies and, given the conflicting results, none may be considered a reliable predictor of sperm presence in NOA (Guideline 11.6.2.3) [13].

The AUA/ASRM and EAA guidelines do not mention any specific factors for predicting sperm retrieval in NOA [12,14,15].

(3) Discussion

Predictors of successful TESE in patients with NOA have been widely studied but without consensus. Assessing the role of FSH, a single-center retrospective study of 108 patients with NOA showed that lower serum FSH and higher patient age (mean age of 40.04±12.22 years *versus* 33.98±6.18 years) were independent predictors of successful sperm retrieval in mTESE [59]. Other studies reported that testicular volume, FSH, and inhibin level were correlated with cTESE outcome [60]. Similarly, a new systematic review also showed that FSH has an inverse relationship to sperm retrieval for mTESE and cTESE and can be the sole predictor of cTESE success [61]. A recent meta-analysis reported that in men with Klinefelter's syndrome, younger age and higher testosterone were favorable indicators for successful sperm retrieval by mTESE, but found that no factor could predict recovery in men with AZFc microdeletions [62]. However, on the other hand, in a study on 329 Japanese men with NOA, Enatsu et al [63] did not find a significant correlation between testicular volume, FSH, LH, or testosterone and sperm retrieval by mTESE. Instead, older age and non-idiopathic etiology were significant in predicting sperm retrieval. Also validating the predictive value of the etiology of NOA, a systematic review and meta-analysis of 13 retrospective cohort studies comparing men with idiopathic NOA and those with surgically treated cryptorchidism, found that the sperm retrieval rates (SRR) were significantly higher in men with cryptorchidism who underwent orchiopexy than in men with idiopathic NOA (71.2% *vs.* 38.4%, relative risk [RR]=1.90; 95% confidence interval [CI]: 1.40–2.58; p<0.0001) [64]. Moreover, the SRR was significantly higher in men who underwent orchiopexy before the age of 10 years than in those who had surgery at an older age (RR=1.25, 95% CI: 1.06–1.47).

Several studies have found testicular histology to be the most accurate single factor in predicting TESE success [65,66]. A recent multi-center study has suggested that serum AMH levels <4 ng/mL was associated with a higher chance of finding sperm in men with NOA [67].

However, there is no single factor that can precisely predict the success of TESE [68] and some authors have

tried to build a predictive model for successful sperm retrieval in both cTESE and mTESE using multiple parameters [60,69,70].

(4) Expert recommendation

There are no preoperative biochemical or clinical variables that definitively predict positive sperm retrieval at surgery in patients with NOA. However, normal FSH, normal testicular volume, a history of sperm in the ejaculate, and histopathology with hypospermatogenesis predict higher chances of sperm retrieval.

CONCLUSIONS

The current survey has several limitations. First, the sample population was mainly drawn from a pre-existing group of clinicians with a special interest in male infertility (GAF). This may have caused some selection bias and the sample may not be representative of male infertility clinicians in general. Second, there is a predomination of responses from some countries (Italy, Turkey, India), while there is noticeable underrepresentation from many other countries (Russia, China, Canada). Third, the total response rate of the survey could not be determined due to the multiple ways of questionnaire dissemination, including emails, direct communication, and professional society websites which resulted in an unknown total number of invitations. Fourth, subgroup analysis of results based on specialization, practice setting, or years of practice was also limited due to small numbers in each subgroup.

However, despite these limitations, we believe that the 336 responses received from 49 countries provide a valid and comprehensive perspective of global practices. As the first global survey on clinical practices related to NOA, the present survey provides important information on real-life practices. A SWOT (Strength, Weakness, Opportunities, Threats) analysis listing the strengths and limitations of this survey, together with opportunities for further research are summarized in Fig. 15.

Our survey on global clinical practices in the evaluation of azoospermia has shown that there is a congruity between global clinical practices, evidence in the literature, and professional society recommendations, though there are also several areas where guidelines are not available. Further, the survey shows that there is a significant proportion of clinicians whose clinical practices differ from the recommendations, which suggests the need for further training and knowledge dissemination.

In summary, most clinicians rely on at least two semen reports, done a month apart, to diagnose azoospermia. The commonly requested hormone tests for diagnosis are FSH, LH, and testosterone. Differential diagnosis between OA and NOA is based on a combination of history, physical findings, and hormone profile, though these may be misleading in men with matura-

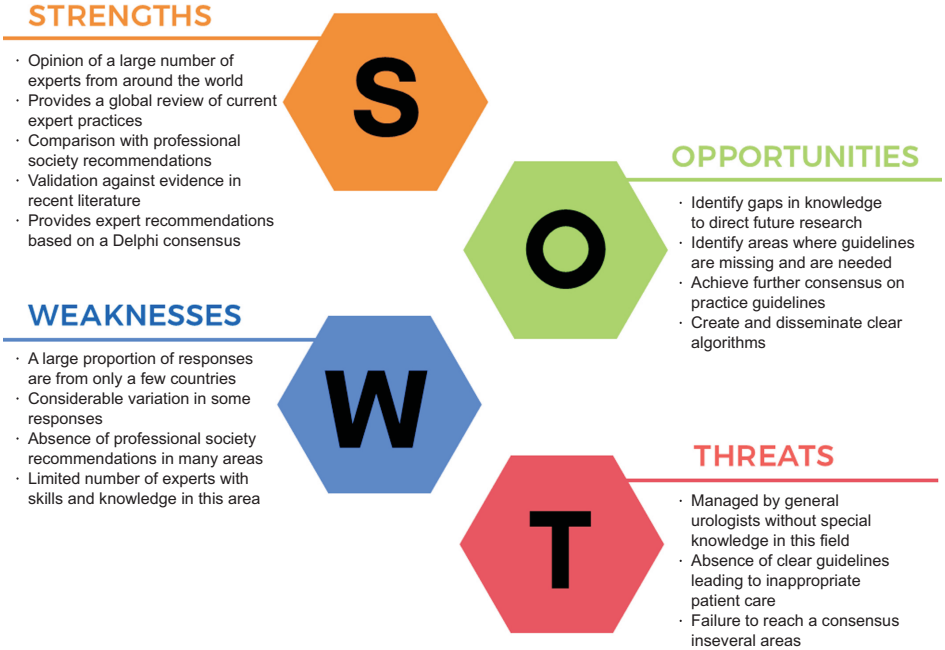

Fig. 15. Strength, Weakness, Opportunities, Threats (SWOT) analysis of the survey.

tion arrest who could present with normal testicular size and normal hormone levels. Diagnostic testicular biopsy is not routinely required to differentiate between OA and NOA, and if performed in selected cases it should be combined with therapeutic TESE. Imaging does not have a major diagnostic role. Karyotype and Yq microdeletion studies are still the only genetic tests performed by the majority. There is no single test that can predict successful sperm retrieval but a combination of assessments involving FSH, testosterone, testicular size, and histology (when available) can provide a reasonable probability of outcome.

Conflict of Interest

The authors have nothing to disclose.

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Author Contribution

Conceptualization: RS, AR. Data curation: GMS, MG, AM.H. Methodology, Project administration: AA, DD. Writing – original draft: RS, AR, WA, MM, IZ, PK, NT, NHVP, PK, AH, GS, MG, TH, TT, PB, EK, MA, RAG, VSK, RS, GIR, GMP, EC, GM.C, WZ, EP, HJP, SF, AT, CRC. Writing – review & editing: All authors.

Supplementary Materials

Supplementary materials can be found via https://doi.org/10.5534/wjmh.230333.

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