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Global Practice Patterns and Variations in the Medical and Surgical Management of Non-Obstructive Azoospermia: Results of a World-Wide Survey, Guidelines and Expert Recommendations

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Purpose: Non-obstructive azoospermia (NOA) is a common, but complex problem, with multiple therapeutic options and a lack of clear guidelines. Hence, there is considerable controversy and marked variation in the management of NOA. This survey evaluates contemporary global practices related to medical and surgical management for patients with NOA.

Materials and Methods: A 56-question online survey covering various aspects of the evaluation and management of NOA was sent to specialists around the globe. This paper analyzes the results of the second half of the survey dealing with the management of NOA. Results have been compared to current guidelines, and expert recommendations have been provided using a Delphi process.

Results: Participants from 49 countries submitted 336 valid responses. Hormonal therapy for 3 to 6 months was suggested before surgical sperm retrieval (SSR) by 29.6% and 23.6% of participants for normogonadotropic hypogonadism and hypergonadotropic hypogonadism respectively. The SSR rate was reported as 50.0% by 26.0% to 50.0% of participants. Interestingly, 46.0% reported successful SSR in <10% of men with Klinefelter syndrome and 41.3% routinely recommended preimplantation genetic testing. Varicocele repair prior to SSR is recommended by 57.7%. Half of the respondents (57.4%) reported using ultrasound to identify the most vascularized areas in the testis for SSR. One-third proceed directly to microdissection testicular sperm extraction (mTESE) in every case of NOA while others use a staged approach. After a failed conventional TESE, 23.8% wait for 3 months, while 33.1% wait for 6 months before proceeding to mTESE. The cut-off of follicle-stimulating hormone for positive SSR was reported to be 12–19 IU/mL by 22.5% of participants and 20–40 IU/mL by 27.8%, while 31.8% reported no upper limit.

Conclusions: This is the largest survey to date on the real-world medical and surgical management of NOA by reproductive experts. It demonstrates a diverse practice pattern and highlights the need for evidence-based international consensus guidelines.

Keywords: Azoospermia; Hypogonadism; Infertility, male; Semen; Sperm retrieval

INTRODUCTION

Azoospermia refers to the complete absence of sperm in the semen and the centrifuged pellets. Approximately 1% of the general male population and 5%–10% of infertile men are azoospermic [1,2]. Azoospermia can be classified as obstructive (OA) or non-obstructive azoospermia (NOA) and each has different etiologies and management [3]. NOA is due to impairment in testicular sperm production and constitutes 60% of azoospermia cases [4]. Currently, there is a lack of society guidelines, especially for the management of NOA. There is still controversy on the role of hormonal therapy, antioxidants, and varicocele repair (VR) prior to sperm retrieval. Moreover, there are questions about the best approach to surgical sperm retrieval (SSR), though microdissection testicular sperm extraction (mTESE) appears to be the most appropriate with the best chances of sperm retrieval. Further, it remains unclear whether it is better to perform mTESE simultaneously with oocyte retrieval or whether mTESE with cryopreservation followed by intracytoplasmic sperm injection (ICSI) at a later date gives equal results when considering different clinical scenarios. Additionally, factors such as cost, and accessibility also need to be considered.

The current study aims to assess contemporary expert global practices related to the medical and surgical management of NOA and to compare it with the avail-

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able international practice guidelines. Also, an "expert recommendation" is provided to clarify the current best practices of NOA management based on global practices, society guidelines, and available evidence from the literature.

MATERIALS AND METHODS

The global survey was approved by the Internal Review Board (IR-02-23-110). The checklist for Reporting Results of Internet E-Survey (CHERRIES) was used to guide the construction, dissemination, and analysis of the questionnaire [5]. The checklist is provided in the Supplement File 1.

1. Target population

The survey was conducted among physicians who treat NOA patients in their daily practice. The group included andrologists, urologists, and reproductive specialists. Clinicians with no experience in dealing with these patients were excluded.

2. Questionnaire creation and structure

Members of the Global Andrology Forum (GAF) were invited to submit multiple-choice questions (MCQs) on various aspects of NOA evaluation and treatment [6]. These MCQs were reviewed and integrated into a questionnaire by a group of ten experts who were experienced reproductive urologists actively engaged in treating patients with NOA. The option "not applicable" was added for any respondents who do not encounter the scenario in clinical practice. The final questionnaire comprised 56 questions divided into 4 sections: demographic data (Q1–8), medical management (Q9–15), surgical therapy (Q16–40), and future horizons (Q41–43) with the invitation letter on the first page including the aims of the survey and consent to participate (Supplement File 2). While completing the survey, respondents were able to scan, review, and edit answers before final submission.

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 who fit the inclusion criteria were invited to complete the survey. 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 Acknowledgements.

4. Data collection and analysis

The survey data were extracted from the Google Sheet associated with the Google Form. A total of 367 responses were submitted. Three hundred thirty-six responses were analyzed after the exclusion of invalid responses. Responses were excluded if respondents were clinicians not treating NOA (25 responses) or if respondents only completed the demographics section of the survey and no other sections (6 responses). Some questions allowed more than one response which increased the number of responses analyzed for that particular question. The question responses were calculated based on the number and percentage of each answer. For questions with the option (select all that apply), the analysis was based on the total number of responses. We determined percentages for each answer selection and graphically presented the data.

5. Society guidelines

There are limited available guidelines on the evaluation and management of men with NOA. Different societies such as the American Urological Association/American Society for Reproductive Medicine (AUA/ASRM), European Association of Urology (EAU), and European Academy of Andrology (EAA) have released guidelines pertaining to male infertility.

6. GAF expert recommendations

GAF expert recommendations were formulated using a Delphi process (Supplement File 3). Two senior authors (RS, AR) formulated the statements based on the survey results, available professional society guidelines, and the latest literature on the subject. 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 of 1 to 10, 1 being "completely disagree" and 10 being "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

We grouped the results of our survey by question topic. For each group of questions, we discuss guideline recommendations from the major male infertility guidelines (AUA/ASRM, EAU, EAA) (Table 1) and provide GAF expert recommendations based on the Delphi process (all recommendations were accepted in the first round).

1. Demographics

A total of 367 participants submitted their responses. Of these, 31 responses were excluded due to incomplete data (n=6) or submission by an ineligible respondent (n=25). A total of 336 participants were included in the study. Highest responses were from Italy (n=36, 10.7%), India (n=35, 10.4%), and Türkiye (n=35, 10.4%). Respondents and countries are presented in Fig. 1.

1) Respondent demographics

Most respondents were attending physicians, with training in general urology or completed andrology fellowships, which were equally divided between academic and private practice (Table 2). Almost half of them (48.5%) had 11 or more years of experience (Fig. 2) with more than 30% of them evaluating 11–20 new infertile men per week (Fig. 3).

2. Medical management of NOA

1) Hormonal therapy in men with NOA

(1) Survey results

Hormonal therapy was suggested prior to sperm retrieval for NOA patients with hypogonadotropic hypogonadism, normogonadotropic hypogonadism, and hypergonadotropic hypogonadism by 74.6%, 29.6%, and 23.6% of participants respectively (Fig. 4). Almost 24.6% of participants offer hormonal therapy for NOA pa-

Table 1. Comparison of the different guidelines on the medical and surgical management of NOA

	AUA/ASRM	EAU	EAA
Hormonal therapy before cTESE/mTESE	Limited data to support hormonal therapy prior to SSR (Schlegel et al., 2021 [8])	No routine therapy recommended (Salonia et al., 2022 [7])	No recommendation
NOA due to exogenous testosterone	No recommendation	Withdrawal of testosterone for 6 to 12 months, if no sperm in semen, hCG with or without FSH or clomiphene can be prescribed	No recommendation
Exogenous testosterone for patients with NOA and low testosterone	Testosterone therapy should not be prescribed as a clinical principle (Schlegel et al, 2021 [8])	Avoid testosterone therapy for male infertility (Salonia et al, 2022 [7])	No recommendation
Sperm retrieval in Klinefelter syndrome	Spermatogenesis found upon mTESE in up to 50%–60% of patients	Spermatogenesis found upon mTESE in up to 50% of patients	No recommendation
Microsurgical varicocelectomy for clinical varicocele and NOA	Couples should be informed of the absence of definitive evidence supporting VR prior to SSR for NOA (Schlegel et al, 2021 [8])	VR in NOA can result in the appearance of sperm in the ejaculate (Minhas et al, 2021 [37]). Evidence is not robust as it is based on observational studies	No recommendation
Microsurgical varicocelectomy for subclinical varicocele and NOA	Recommend against repair of subclinical varicocele	Recommend against repair of subclinical varicocele	No recommendation
FNA before mTESE	mTESE has a two times more likely successful outcome	No recommendation in view of the limited evidence	No recommendation
Predictors of successful SSR	No recommendation	No preoperative biochemical and clinical variables clinical variables may be considered sufficient and reliable predictors of positive sperm retrieval at surgery in patients with NOA	No recommendation

AUA: American Urological Association, ASRM: American Society for Reproductive Medicine, EAU: European Association of Urology, EAA: European Academy of Andrology, mTESE: microdissection testicular sperm extraction, cTESE: conventional testicular sperm extraction, SSR: surgical sperm retrieval, FSH: follicle-stimulating hormone, hCG: human chorionic gonadotrophin, VR: varicocele repair. NOA: non-obstructive azoospermia, FNA: fine-needle aspiration.

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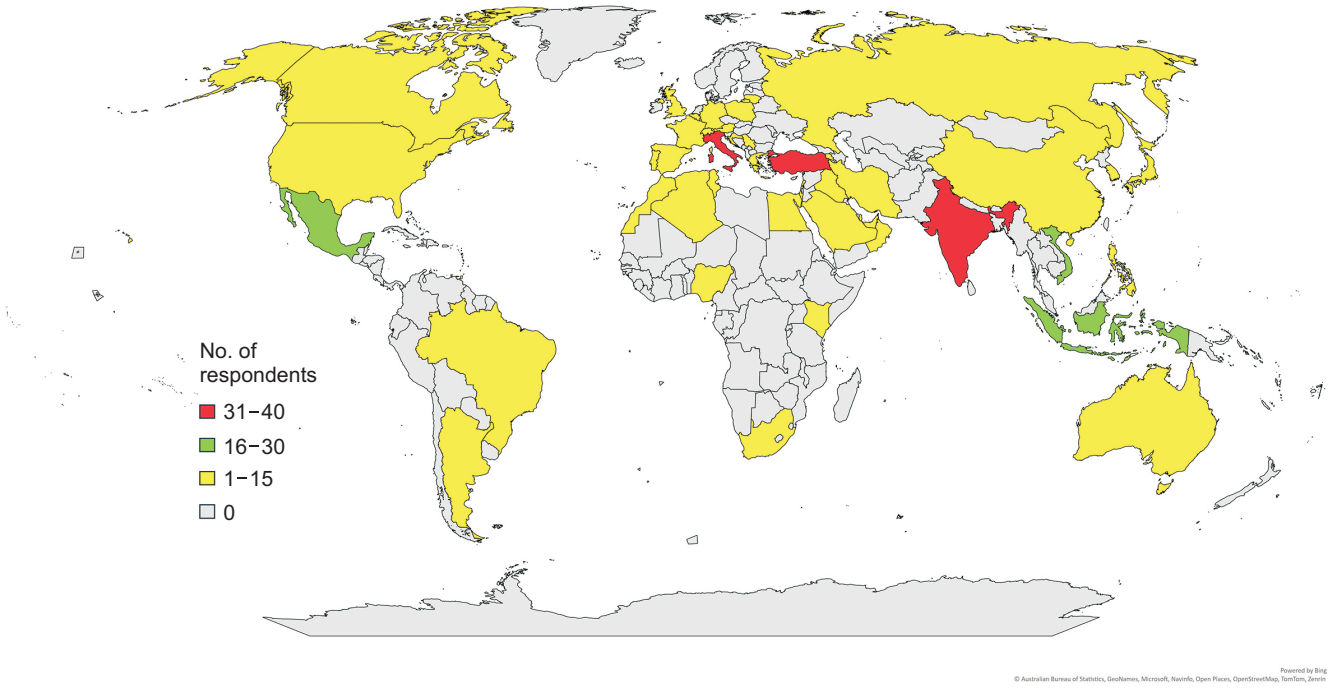

1. Algeria	n=2	11. China	n=4	21. Israel	n=1	31. Philippines	n=1	41. Spain	n=3
2. Argentina	n=1	12. Croatia	n=1	22. Italy	n=36	32. Poland	n=1	42. Switzerland	n=2
3. Armenia	n=3	13. Egypt	n=14	23. Japan	n=5	33. Portugal	n=1	43. Trinidad and Tobago	n=1
4. Australia	n=4	14. France	n=5	24. Kenya	n=1	34. Qatar	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. The map is color-coded according to the number of respondents in each country.

tients after the first failure of sperm retrieval while 9.9% offer it in all NOA patients undergoing an initial attempt at SSR.

When hormone therapy was recommended before sperm retrieval in NOA patients (excluding hypogonadotropic hypogonadism), 30.6% of respondents recommended it for a period for 6 months or less (Fig. 5).

The effect of hormonal therapy before sperm retrieval was evaluated by testosterone to estradiol ratio (T/E2), testosterone (T), follicle-stimulating hormone (FSH), luteinizing hormone (LH) levels, by 41.5%, 52.5%, 56.9%, and 34.3% of participants, respectively (Fig. 6).

Regarding the choice of hormone therapy prior to sperm retrieval in hypergonadotropic NOA, a marked diversity of choices was seen ranging from various oral and injectable drugs, singly or in combination (Fig. 7). A similar diversity of choices, with a preference for clomiphene or aromatase inhibitors, were reported for men with NOA and normal gonadotropins (Fig. 8).

(2) Guidelines

The EAU guidelines conclude that routine hormonal therapy should not be recommended before cTESE/mTESE [7]. The AUA/ASRM guidelines recommend that patients with NOA should be advised that there is limited data to support hormone therapy prior to SSR [8].

(3) Discussion

The heterogeneity of answers in the survey with over 70% of respondents using hormonal therapy (Fig. 4–6) even when the guidelines don't support its use may be explained by the lack of robust evidence with regard to the effectiveness of hormonal therapy in patients with NOA. A recent meta-analysis failed to

Table 2. Demographic characteristics of the respondents

	Number (%)
Q4: What is the nature of your employment?	n=344
Physician, attending	244 (70.93%)
Physician, fellow	26 (7.56%)
Physician, resident	37 (10.76%)
Advanced practice provider (Physician Assistant, Nurse Practitioner)	7 (2.03%)
Others	30 (8.72%)
Q5: What is your area of specialization (As it relates to male infertility)?	n=339
Fellowship-trained reproductive urology	99 (29.20%)
General urology	135 (39.82%)
Reproductive Endocrinology/ART specialist	75 (22.12%)
Endocrinology	16 (4.72%)
Other (specify)	14 (4.13%)
Q6: What is your practice setting?	n=428
Academic	148 (34.58%)
Public	85 (19.86%)
Private	151 (35.28%)
Multiple	42 (9.81%)
Other (specify)	2 (0.47%)

n: number of respondents.

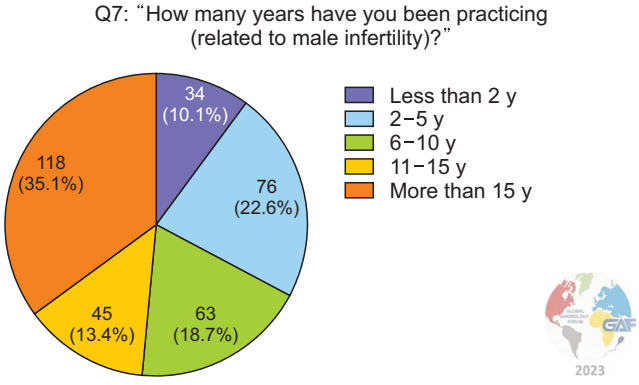

Fig. 2. Years of practice of the respondents.

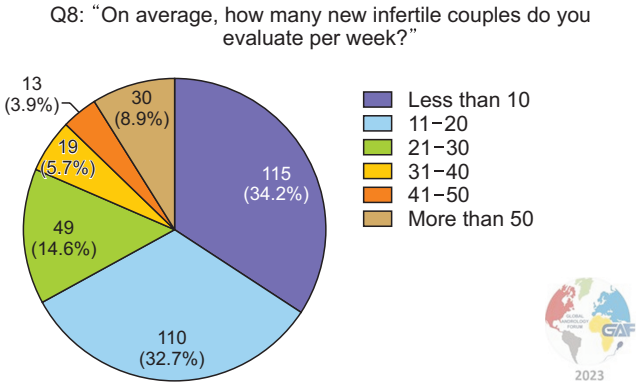

Fig. 3. The number of new couples evaluated per week by the respondents.

demonstrate an improvement in SSR rate after pretreatment with hormonal therapy in men with NOA and hypergonadotropic hypogonadism, while some improvement in SSR rates was demonstrated in eugonadal men with NOA, but the authors stated that the literature had a moderate to severe risk of bias [9]. A prospective study reported that pure FSH treatment improved the success of TESE for eugonadal NOA patients with normal FSH levels and the best outcome was when the histopathological analysis revealed focal spermatogenesis or hypospermatogenesis [10]. Foresta et al [11] reported similar findings with improvement in patients with hypospermatogenesis.

(4) Expert recommendation

The quality of evidence supporting hormonal therapy before SSR in NOA patients is low. However, it may improve the SSR rates in some NOA patients. Given the limited and poor-quality evidence, it is not routinely recommended but may be considered after adequate counseling.

2) Exogenous testosterone and NOA

(1) Survey results

With regard to the management of NOA due to exogenous testosterone, there was considerable variation

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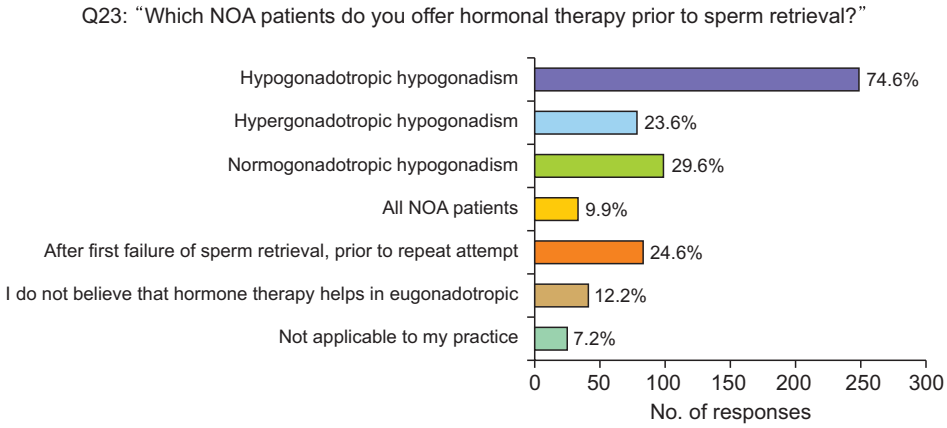

Fig. 4. Characteristics of NOA patients who are offered hormonal therapy. NOA: non-obstructive azoospermia.

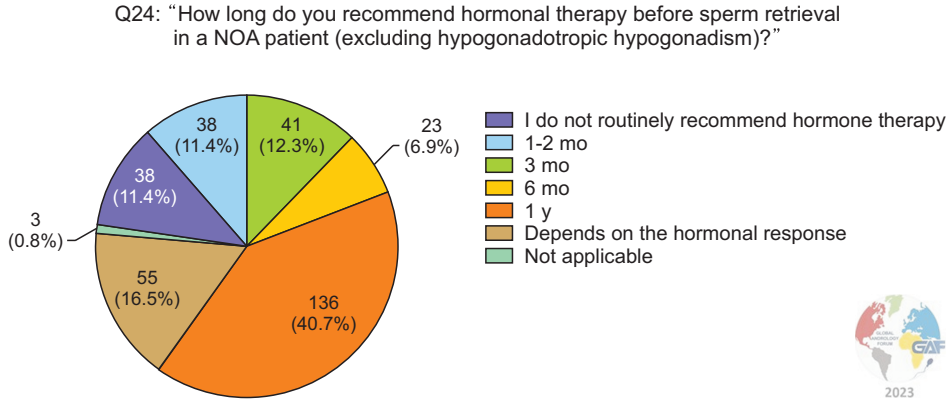

Fig. 5. Duration of hormonal therapy before sperm retrieval in NOA patient. NOA: non-obstructive azoospermia.

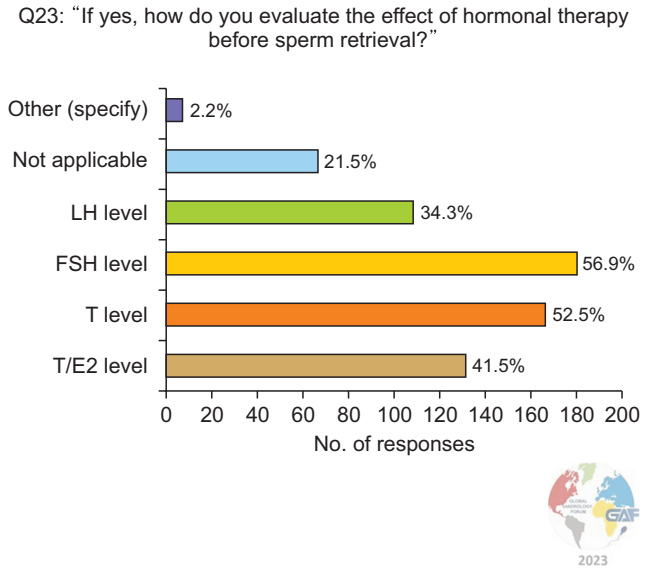

Fig. 6. Evaluation of the effect of hormonal therapy before sperm retrieval. LH: luteinizing hormone, FSH: follicle-stimulating hormone, T: testosterone, T/E2: testosterone to estradiol ratio.

in the treatment strategies reported by the respondents with about one-third (32.5%) opting to discontinue exogenous testosterone and allow natural recovery, while the rest choosing to discontinue testosterone, concomitantly starting stimulation with either clomiphene or human chorionic gonadotropin (hCG) or clomiphene citrate plus hCG or hCG and HMG/FSH (Fig. 9).

When asked about the use of exogenous testosterone in men with NOA and hypogonadism before undergoing TESE, surprisingly, 4.8% of respondents would still prescribe exogenous testosterone and another 9.6% would prescribe it sometimes. The majority of respondents (72.2%) would prescribe hCG/LH, selective estrogen receptor modulators (SERMs), or aromatase inhibitors (Fig. 10).

(2) Guidelines

Neither the EAA nor the AUA/ASRM guidelines make recommendations for the management of men with NOA induced by exogenous testosterone. How-

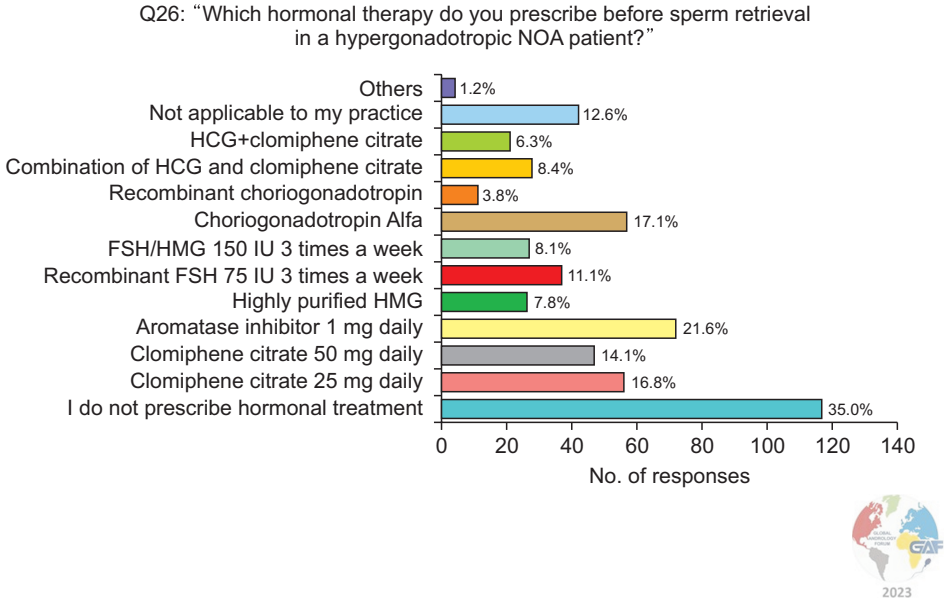

Fig. 7. Hormonal therapy before sperm retrieval in hypergonadotropic NOA patient. NOA: non-obstructive azoospermia, HCG: human chorionic gonadotropin, FSH: follicle-stimulating hormone, HMG: human menopausal gonadotropin.

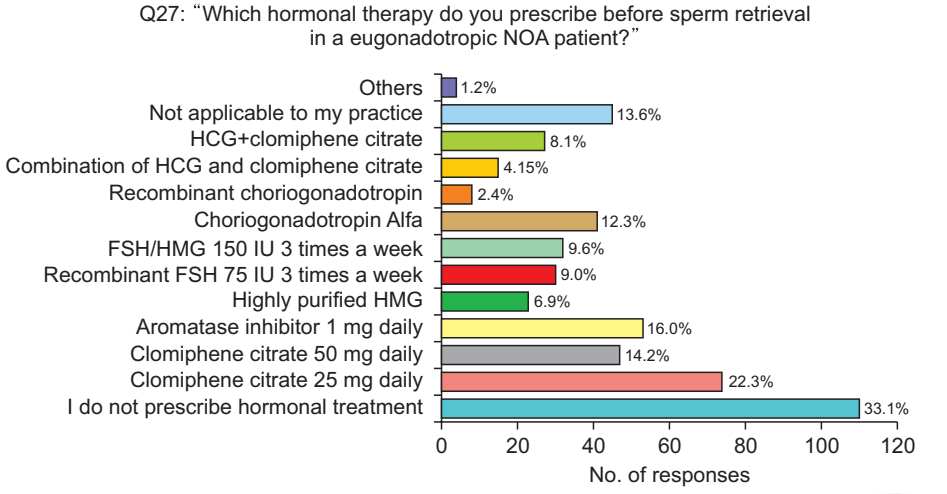

Fig. 8. Hormonal therapy before sperm retrieval in eugonadotropic NOA patient. NOA: non-obstructive azoospermia, HCG: human chorionic gonadotropin, FSH: follicle-stimulating hormone, HMG: human menopausal gonadotropin.

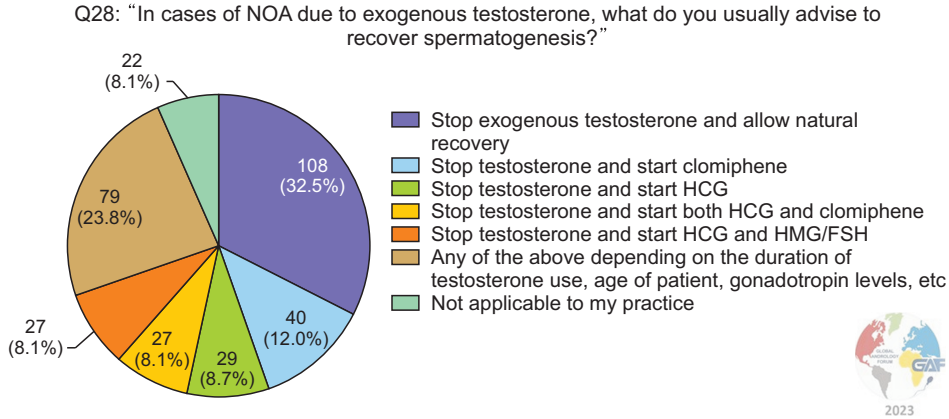

Fig. 9. Advice for patient with NOA due to exogenous testosterone. NOA: non-obstructive azoospermia, HCG: human chorionic gonadotropin, FSH: follicle-stimulating hormone, HMG: human menopausal gonadotropin.

ever, the EAU guidelines recommend withdrawal of exogenous testosterone as the initial treatment [7]. If there are no sperm in the semen by 6 to 12 months then hCG alone or in combination with FSH or clomiphene citrate can be prescribed [12].

However, there is poor quality of data supporting treatment algorithms in this scenario. The EAU guidelines recommend avoiding testosterone therapy for male infertility (strong level of recommendation) [7]. Similarly, a clinical principal recommendation from the AUA/ASRM guidelines states that "For the male interested in current or future fertility, testosterone monotherapy should not be prescribed." [8].

(3) Discussion

Exogenous testosterone has been increasingly used worldwide, especially in the form of anabolic steroid use with approximately 3 million users in the USA alone and with estimates as high as 25% of young men who work out in gyms [13,14]. Exogenous testosterone results in negative feedback on the hypothalamic-pituitary-gonadal axis leading to suppression of FSH and LH secretion resulting in a decrease in intratesticular androgen levels, thereby inhibiting spermatogenesis and resulting in NOA [15]. This negative effect on testicular function is expected to recover within 6 months of exogenous testosterone cessation. However, not all men will respond similarly. Only one-third of the patients will return to their baseline pre-treatment sperm density [16] and there remains a theoretical risk of permanent azoospermia in some men especially if they had poor pre-treatment spermatogenesis at baseline. There is no international consensus on the treatment regimen for NOA cases secondary to exogenous testosterone therapy. This is evident by the lack of recommendations from international societies. This is also reflected by the results of our survey, where there is no overwhelming agreement on one type of therapy. For infertile men with NOA who are planning to undergo SSR, exogenous testosterone therapy is contraindicated due to the pathophysiological effect of such treatment. Surprisingly, in our survey up to 15% of respondents would still use exogenous testosterone therapy in infertile men with NOA. A similar result was also reported by an earlier study surveying 387 urologists, where 25% of the respondents reported that they would treat infertile males with exogenous testosterone therapy while the couple actively pursues pregnancy [17].

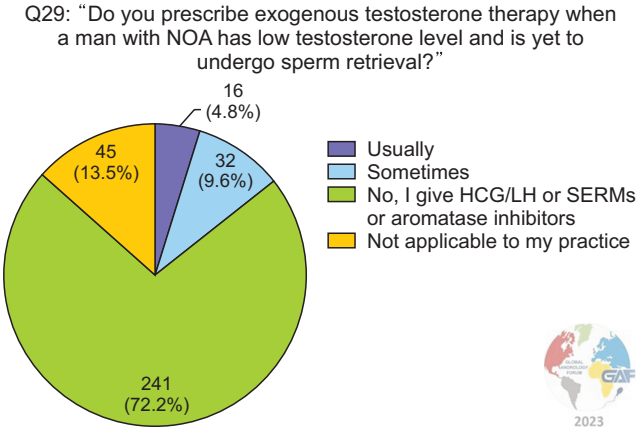

Fig. 10. Proportion of respondents who prescribe exogenous testosterone therapy when a man with NOA has a low testosterone level and is yet to undergo sperm retrieval. NOA: non-obstructive azoospermia, HCG: human chorionic gonadotropin, LH: luteinizing hormone, SERM: selective estrogen receptor modulators

(4) Expert recommendation

Exogenous testosterone should not be used for men with NOA who are still interested in testicular sperm retrieval and future fertility. Instead, SERMs, aromatase inhibitors, or hCG can be used to raise testosterone without compromising spermatogenesis.

3. Surgical management

1) Surgical therapy related to mTESE

(1) Survey result

Out of the 332 respondents, 14.5% indicated that they perform mTESE in <10% of NOA cases while 14.8% perform mTESE in 75% to 100% of cases (Fig. 11). The average SSR rate in men with NOA was reported to be 50.0% by 26%–50% of participants while 19% of the participants reported successful SSR in <10% of cases (Fig. 12). Approximately 2/3 of the respondents (68.1%) reported that most couples opted for mTESE to obtain their sperm, while 9% of the couples chose to have both options of own and donor sperm in the same cycle (Fig. 13).

(2) Discussion

The proportion of surgeons performing mTESE is relatively low. Approximately one third of the respondents performed mTESE in <50% of their patients; however, a few surgeons perform mTESE in the majority of their patients with NOA. The average SSR rates are around 50% but some reported it to be as low

as <10%. The wide range of SSR rates reported by the survey participants are probably due to the heterogenous nature of patients with NOA (age, location, testicular size, hormonal levels, etiology), and variations in surgeon experience and technique. The SSR rates will also be affected by the experience of the embryologists involved in finding sperm in mTESE specimens. Results of this survey also indicate that while most couples prefer to have their own biological children, some are open to donor sperm.

(3) Expert recommendation

mTESE is the most efficient procedure for sperm retrieval in men with NOA who wish to have biological children. The experience of the surgeon and the time spent by the embryologists can impact the success of mTESE.

2) Sperm retrieval in Klinefelter syndrome (KS) patients

(1) Survey result

Out of the 326 participants, 46.0% reported successful SSR in <10% of KS cases and another 30.4% reported success in only 10%–25% of cases, while 4.0% reported that they had successful SSR in >50% of these cases (Fig. 14).

(2) Guidelines

Sperm production is variable in patients with KS

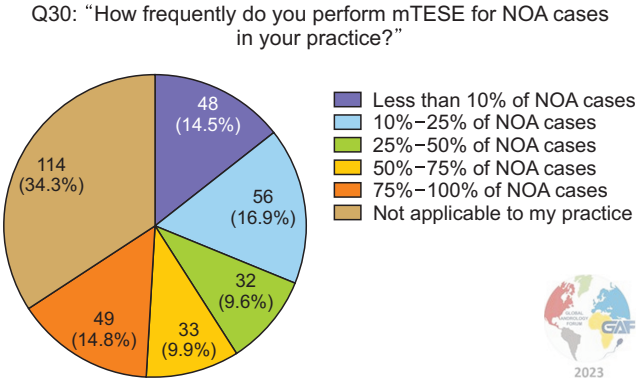

Fig. 11. Frequency performing mTESE for NOA cases. mTESE: microdissection testicular sperm extraction, NOA: non-obstructive azoospermia.

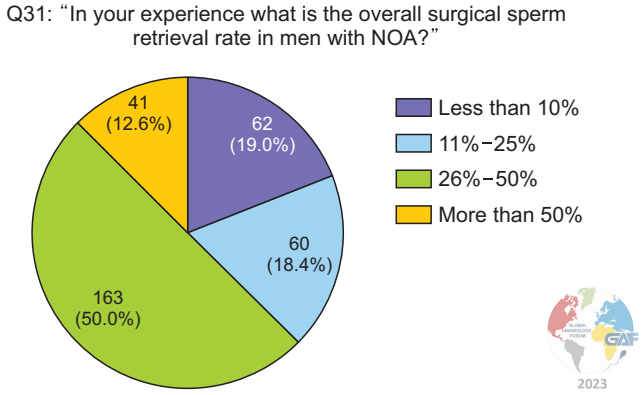

Fig. 13. General acceptability of mTESE in your practice. mTESE: microdissection testicular sperm extraction, OA: obstructive azoospermia, NOA: non-obstructive azoospermia

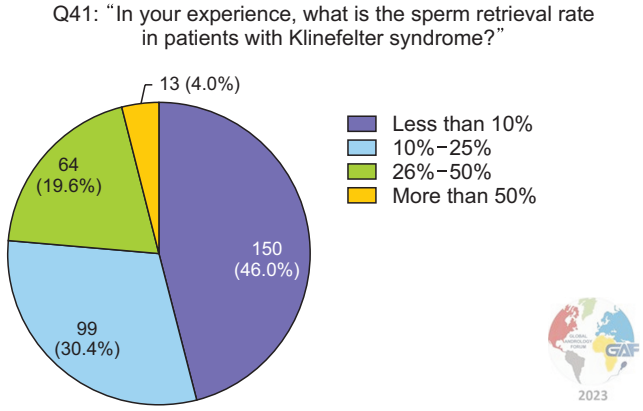

Fig. 14. Sperm retrieval rate in patients with Klinefelter syndrome.

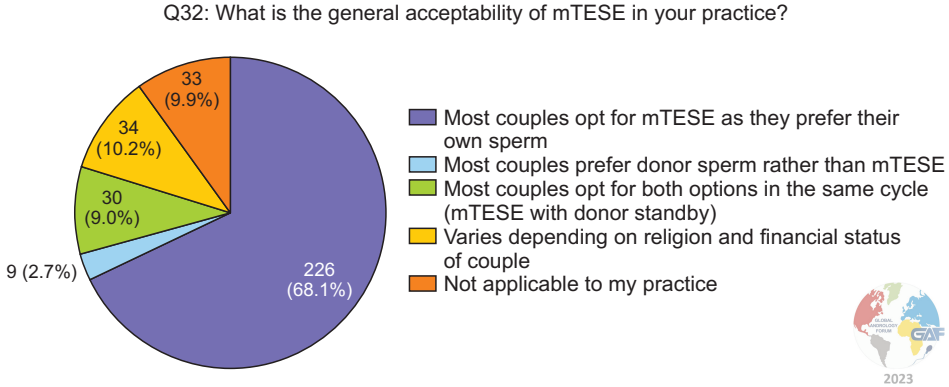

Fig. 12. Overall surgical sperm retrieval rate in men with NOA. mTESE: microdissection testicular sperm extraction, NOA: non-obstructive azoospermia.

and in those who are azoopsermic. TESE or mTESE can help recover sperm in up to 50% of cases [7,8]. The EAA male infertility guideline does not specifically discuss sperm retrieval in patients with KS.

(3) Discussion

While the guidelines and published studies claim SSR rates of 40%–60% in men with KS, the majority of respondents (76.4%) reported SSR rates of less than 25%, with the majority (46.0%) claiming that they found sperm in <10% of their KS patients. Though it is tempting to attribute the higher success reported in published papers to superior technique and experience, the results of such a large number of respondents cannot be ignored. Perhaps, there are unrecognized geographical differences in testicular histopathology of KS. A comparison of results between centers of the same region, and between different regions, may throw light on this significant discrepancy and allow for better and more realistic patient counseling. The 2020 AUA/ASRM and EAU guidelines report that the rate of spermatozoa found upon mTESE in up to 50%–60% of 47, XXY men [7,8] while other studies have reported SSR in 20%–60% of men with KS [18]. A study comparing rates of sperm retrieval between KS patients and other NOA patients with normal karyotype using skewed regression analysis showed a success rate of 28.4% for the KS group compared to 22.0% for the NOA with normal karyotype group. A statistically significant difference existed with higher testosterone levels in the successful SSR group [19]. The retrieval rates in KS patients are variable and testosterone levels could be an indicator for predicting success. Further studies are needed to provide more comprehensive data on this subject.

(4) Expert recommendation

The SSR rates reported in the literature in patients with KS undergoing mTESE range between 20%–60%. mTESE in patients with KS can be performed after explaining realistic success rates to patients. High volume mTESE centers may have better success in SSR in patients with KS.

3) Sperm retrieval: special considerations

(1) Survey result

The majority (80.2%) of the respondents have their laboratory team working in the operating room (37.7%) or in a nearby room in the same facility (42.5%) (Fig. 15). Only 32.9% of the respondents stated that their embryologist spent at least one hour looking for sperm before declaring the absence of sperm in the retrieved samples while the others reported that the time spent was less than 30 minutes (29.8%) or between 30 and 60 minutes (22.6%) (Fig. 16). In 59.8% of the centers performing mTESE, fresh sperm is preferred over cryopreserved sperm (Fig. 17).

(2) Discussion

There is no consensus guideline on this topic. Most centers have their laboratory team near the operating room or inside the same facility to identify sperm in the retrieved samples. The standard time for searching for sperm is around 60 minutes and may last up to 120 minutes before declaring it negative for sperm [8]. The results of this survey indicate that fresh sperm are preferred over cryopreserved sperm in most centers [20].

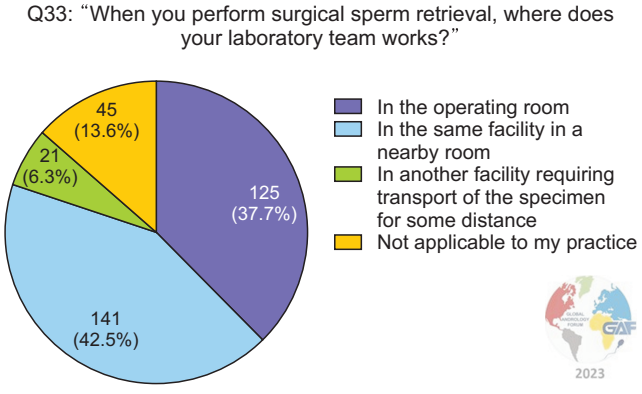

Fig. 15. Working place of laboratory team during surgical sperm retrieval.

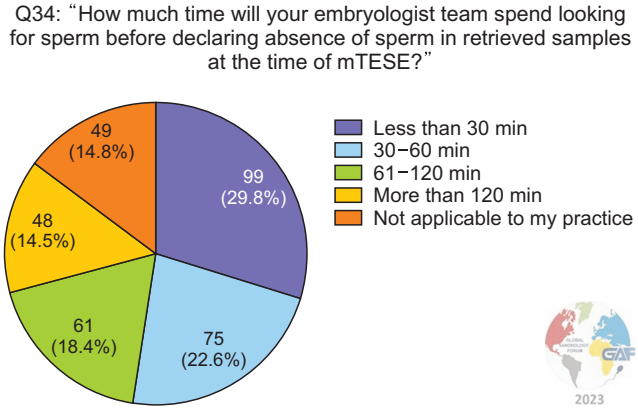

Fig. 16. Time needed by embryologist to look for sperm before declaring absence of sperm in retrieved samples at the time of mTESE. mTESE: microdissection testicular sperm extraction.

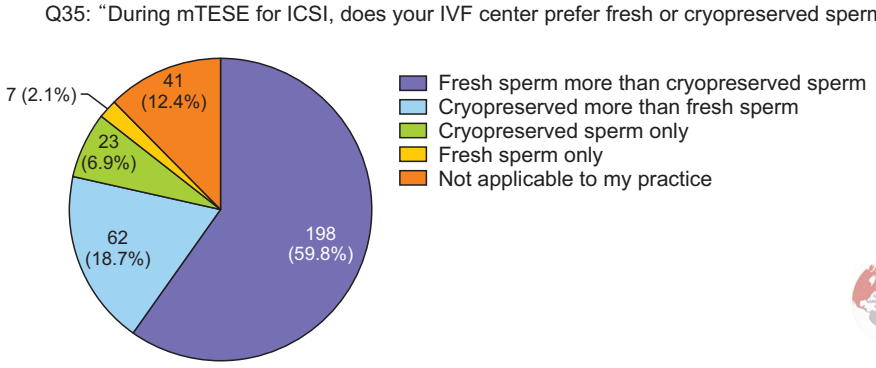

Fig. 17. Preference of sperm during mTESE for ICSI. mTESE: microdissection testicular sperm extraction, ICSI: intracytoplasmic sperm injection, IVF: *in vitro* fertilization.

(3) Expert recommendation

It is preferable for the laboratory team to be in reasonable proximity to the operating theater to facilitate the transfer of mTESE specimens. The samples should be subject to meticulous scrutiny and examination by the embryologist for at least 60 minutes in an attempt to identify sperm. Both fresh and cryopreserved sperm can be used depending upon the expertise of the center and the embryologist.

4) Testicular biopsy for histopathology during surgical sperm retrieval

(1) Survey result

Nearly 40% of the 335 respondents would routinely perform a bilateral testicular biopsy for histopathology at the time of SSR, while 17.9% of the participants would perform it unilaterally routinely. A quarter of the participants (25.4%) would perform it in selected patients, and 10.7% of the clinicians would not perform a testicular biopsy for histopathology at the time of SSR under any circumstance (Fig. 18).

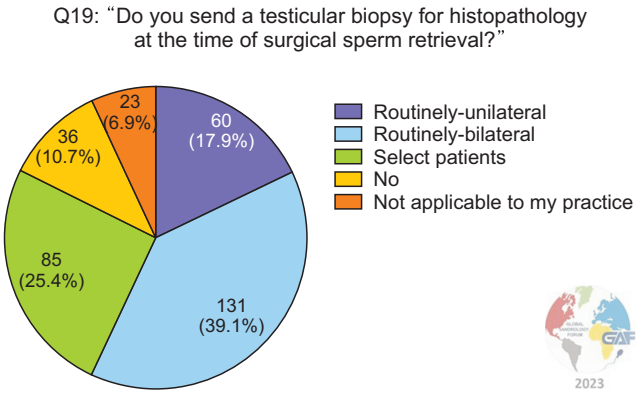

Fig. 18. Testicular biopsy for histopathology at the time of surgical sperm retrieval.

(2) Guidelines

Formal diagnostic biopsy is not recommended in this clinical setting by the EAU guidelines because patients with spermatogenic failure (*e.g.*, Sertoli cell-only syndrome [SCOS]) may harbor focal areas of spermatogenesis. Neither the EAA, AUA/ASRM guidelines mention any specific role of testicular histopathology in defining the prognosis and success of sperm retrieval rates of TESE in NOA patients.

(3) Discussion

Sperm retrieval in patients with NOA is successful in 29.5% to 90.0% of cases. There is some evidence that shows a positive correlation between the histology found at testicular biopsy and the likelihood of finding mature sperm cells during testicular sperm retrieval. Historically, the presence of hypospermatogenesis at testicular biopsy showed a positive correlation in predicting successful sperm retrieval up to 93.3% after either single or multiple conventional TESEs or mTESE compared with early maturation arrest (13.3%), late maturation arrest pattern (66.7%) or SCOS (18.1%) [21]. However, it is impractical to obtain a testicular biopsy prior to the sperm retrieval procedure.

Biopsy is best done during the SSR procedure to look for the histopathological findings. This approach is considered to be more cost-effective, and the histopathological finding can help guide the clinician in a scenario when repeat testicular sperm retrieval is necessary [22]. In our survey, most of the respondents perform testicular biopsy for histopathology at the time of SSR. Although most guidelines do not recommend taking a biopsy to determine prognosis before the procedure, they do not offer any recommendation regarding taking a biopsy during the procedure. In this regard, sending a testicular biopsy for histopathology during SSR

may be reasonable to determine the subsequent prognosis if no sperm is identified in the sample. Additionally, testicular biopsy for histopathological testing was also performed in men with risk factors for testicular malignancy such as cryptorchidism or intratesticular microlithiasis when no sperm are identified [23]. It is important to detect intratubular germ cell neoplasia *in situ* (GCNIS) which represents a high risk of development of testicular cancer [23]. There is a high percentage of testicular nodules and malignancies among azoospermic males with complete SCOS [24]. Vice versa, bilateral testicular tumor, testicular hypotrophy, higher tumor stage, GCNIS, smaller testes, SCOS, and history of undescended testicles can impact the spermatogenesis process and result in azoospermia [25].

(4) Expert recommendation

Sending a testicular biopsy during SSR may be considered as it can establish a histological diagnosis and prognosis for a subsequent sperm retrieval (if required) and may identify GCNIS. However, patients should be informed of the small added risk of a diagnostic testicular biopsy and the chance that this biopsy will contain spermatozoa despite a negative SSR.

5) Surgical therapy in men with genetic abnormalities

(1) Survey result

Y chromosome azoospermia factor c (AZFc) microdeletion (70.5%) and 47, XXY karyotype (67.3%) were the most chosen answers to indicate the need for SSR in patients with NOA. A significant percentage of respondents would offer SSR for men with AZFa (19.9%) and AZFb (23.2%) microdeletion, while only 8.3% of the participants would directly recommend donor sperm or adoption in the cases of genetic disorders (Fig. 19).

(2) Guidelines

In the EAU guidelines, it is recommended that TESE, regardless of technique, should not be attempted in patients with complete deletions that include the AZFa and AZFb regions, since they indicate a very poor chance of successful sperm retrieval. Although nonspecific recommendations are made, the AUA/ASRM guidelines also acknowledge that sperm have not been retrieved by TESE in men with complete AZFa and/or AZFb microdeletions, so surgical intervention is not indicated. Similarly, EAA guidelines also recommend against attempting sperm retrieval in cases of complete deletion of AZFa region, whereas in azoospermic carriers of deletions in AZFbc regions with proximal breakpoint in the P4 palindrome, a mTESE may be attempted. EAA guidelines also state that either standard or mTESE can be done in patients with KS.

(3) Discussion

Approximately 27.3% to 35.0% of men with NOA have genetic abnormalities [26,27]. According to a recent study by Gao et al [28] in 2022, men with certain NOA etiologies such as KS, Y chromosome microdeletion, cryptorchidism, and mumps orchitis have a higher or lower rate of successful SSR than idiopathic NOA [28]. A clinical factor that has been associated with a better prognosis in azoospermic men (higher probabil-

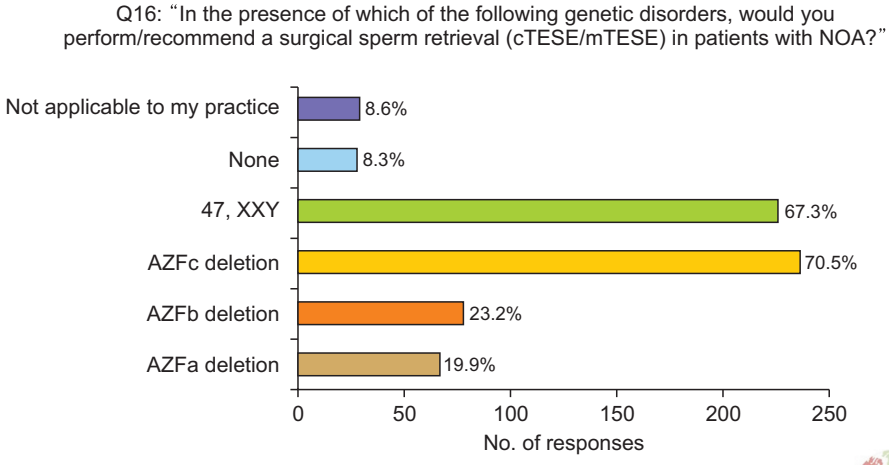

Fig. 19. Genetic conditions to perform surgical sperm retrieval in patients with NOA. mTESE: microdissection testicular sperm extraction, cTESE: conventional testicular sperm extraction, NOA: nonobstructive azoospermia, AZF: azoospermia factor.

ity of successful sperm retrieval) is a history of cryptorchidism with prior orchidopexy. One study revealed a SSR rate of 21.4% to 71.4% for men with KS [28,29]. For men with a Y chromosome microdeletion, sperm retrieval rates vary drastically depending on the site of the microdeletion.

Based on a systematic review of 32 studies, ranges as wide as 13% to 100% have been reported as the sperm retrieval rate among patients with AZFc microdeletion, with a mean of 47% [30]. Some men with AZFc microdeletions may even have low sperm counts in their ejaculate [30,31]. On contrary, there have been no instances of sperm retrieval from men with complete AZFa or AZFb microdeletions [31]. Rare sperm retrieval in men with AZFb microdeletion has been reported if partial deletion is present [32]. Standard tests for these microdeletions may not specify if a partial or complete deletion is present. Another study showed unfavorable sperm retrieval rates, despite the use of mTESE, in NOA patients with chromosomal anomalies excluding those patients with KS [33]. The result of the survey showed that 70.5% and 67.3% of respondents recommend SSR in patients with NOA with an AZFc microdeletion and KS (47, XXY) respectively, which is consistent with the literature that reports a better sperm retrieval rate for patients in these categories. Interestingly, 19.9% and 23.2% of participants still perform sperm retrieval attempts in AZFa and AZFb microdeletion patients despite the current literature revealing only rare cases of successful sperm retrieval in men with deletions of these regions of the Y chromosome.

Several studies described the possibility of sperm cells identified in patients with partial deletion of AZFa and AZFb [34,35]. Two cases of a non-classical, aberrant pattern of AZFb microdeletion, detected using extra Sequence-Tagged Sites markers in or around the AZFb region with some residual sperm production, have been reported [32]. In a study of 1,030 infertile men in Japan, the SSR rate of patients with gr/gr deletion (18.7%) was lower than those without gr/gr deletion, although not statistically significant. Further studies are needed to elucidate the effect of gr/gr deletion on SSR [36].

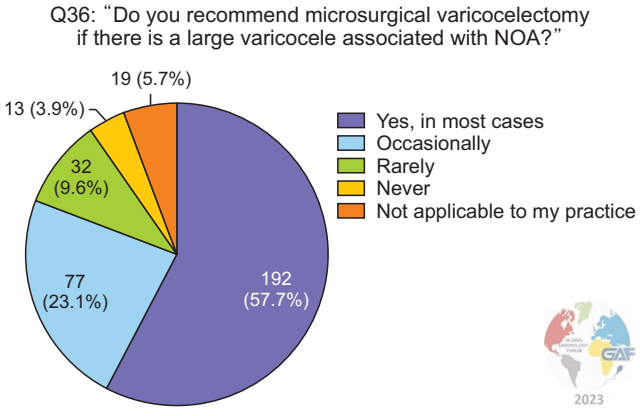

Fig. 20. Microsurgical varicocelectomy in case of large varicocele associated with NOA. NOA: non-obstructive azoospermia.

(4) Expert recommendation

The genetic status of a male has a significant impact on the success rate of SSR. There is a reasonable chance of finding sperm in men with KS and Y chromosome AZFc microdeletion. A complete deletion of AZFa and AZFb correlates with severe spermatogenesis impairment and sperm retrieval is not advised in these conditions. Sperm retrieval may be rarely successful in incomplete, aberrant, or non- classical AZFa and AZFb microdeletions. It is essential to offer proper counseling regarding the likelihood of sperm retrieval, the transmission of the AZF deletion to the male offspring, and the option for alternatives such as donor sperm and adoption.

6) Varicocele and NOA

(1) Survey result

In men with NOA and a large varicocele, 57.7% of the surgeons stated that they recommend microsurgical VR in most cases (Fig. 20). Factors favoring VR were smaller ipsilateral testis (35.1%), younger partners (34.2%), and FSH levels <10 IU/L (29.1%) (Fig. 21). In the presence of a genetic abnormality (such as AZFc deletion or 47, XXY), 36.8% of surgeons chose VR followed by sperm retrieval while an equal number (36.8%) of respondents chose to perform sperm retrieval only and would not do VR (Fig. 22). Most respondents chose to recommend VR (81.5%) for subclinical varicocele with NOA (Fig. 23). The proportion of sperm recovery in the ejaculate after VR was reported to be <10% by 38.1% and 10%–25% by 25.8% of respondents (Fig. 24).

(2) Guidelines

The AUA/ASRM guideline (statement 27) states, "couples should be informed of the absence of defini-

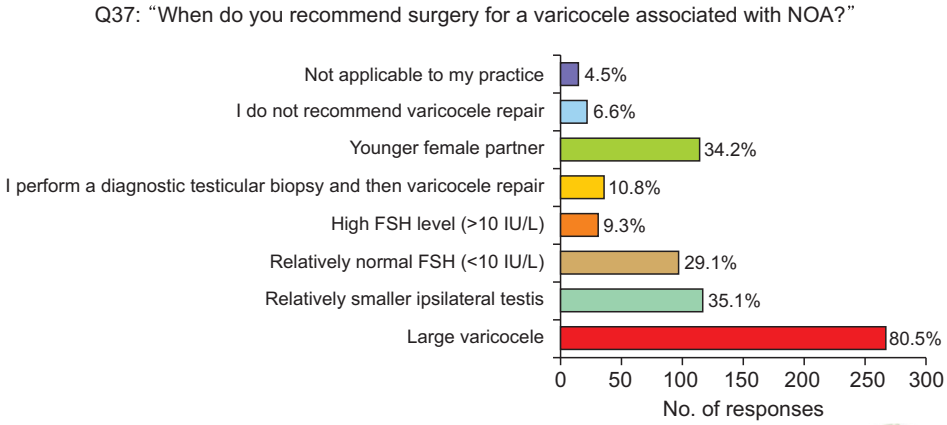

Fig. 21. Conditions to recommend surgery for a varicocele associated with NOA. NOA: non-obstructive azoospermia, FSH: follicle-stimulating hormone.

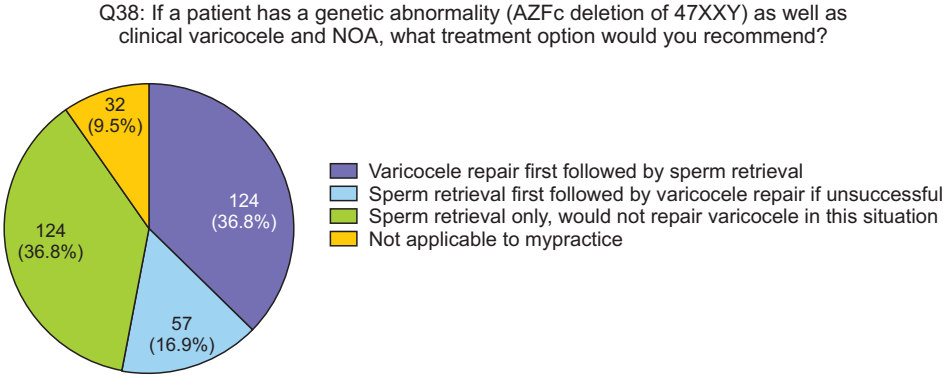

Fig. 22. Treatment option for patient with genetic abnormality as well as clinical varicocele and NOA. AZF: azoospermia factor, NOA: non-obstructive azoospermia.

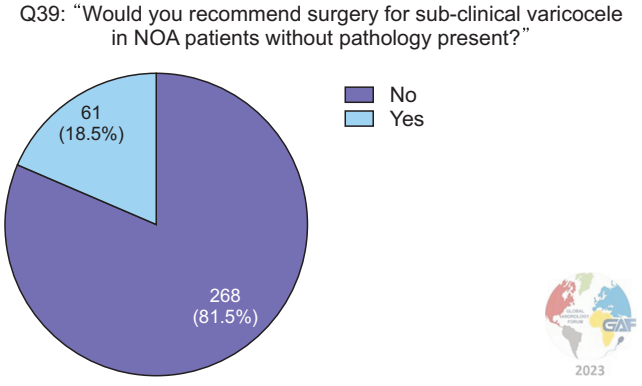

Fig. 23. Surgery for subclinical varicocele in NOA patient without other pathology present. NOA: non-obstructive azoospermia.

tive evidence supporting VR prior to ART" [8]. The EAU guideline (10.4.3.3.3) states that VR in men with NOA can result in the appearance of sperm in the ejaculate (20.8% to 55.0%) and results in improved SSR (odd ratio: 2.65; 95% confidence interval: 1.69–4.14) [37]. However, it cautions that the evidence is based on observational studies and advises that "the risks and benefits of VR must be discussed fully with the patient with NOA and a clinically significant varicocele". The current AUA/ASRM guidelines (statement 26) and EAU (10.4.3.3.2) guidelines are unequivocal in recommending against the repair of a subclinical varicocele [8,37].

(3) Discussion

The management of varicocele in men with NOA is controversial which is reflected in the divergent practice patterns reported by the survey respondents in this study. A high proportion (57.7%) of the survey participants stated that they recommend microsurgical VR in infertile men presenting with NOA and a clini-

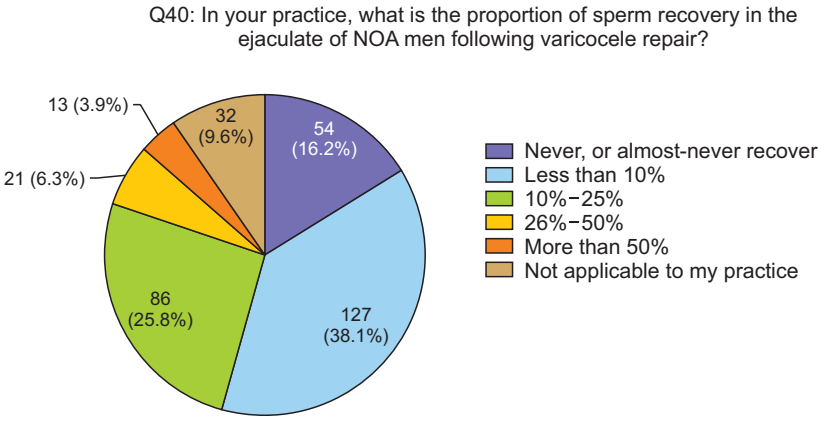

Fig. 24. Proportion of sperm recovery in the ejaculate of NOA men following varicocele repair. NOA: non-obstructive azoospermia.

cally palpable varicocele. Smaller size of the ipsilateral testis, normal FSH levels in serum, and younger age of female partners were considered by the surgeons as factors that favor the decision of VR in these patients. In a contemporary study beginning four months after VR surgery, 12/28 men (42.9%) had sperm in their ejaculates, with a mean sperm concentration of $1.2\pm3.6\times10^6$/mL at 24 months of follow-up. They reported two pregnancies following assisted reproductive technology (ART) treatment; however, there were no spontaneous pregnancies [38]. A recent prospective noncontrolled study, reported the recovery of motile sperm in the ejaculate of 10 of 31 (32.3%) men with NOA and clinically palpable varicoceles following subinguinal microsurgical varicocelectomy [39]. In the same study, there were greater chances of sperm recovery in cases of azoospermia with hypospermatogenesis and late spermatocyte arrest. Kim [38] further demonstrated the recovery of motile sperm in 43% of 28 men with NOA after microsurgical inguinal VR. In their series, 55% of men with hypospermatogenesis and 50% with late maturation arrest at the spermatid stage achieved recovery of sperm in ejaculate, whereas none of the patients with SCOS or early maturation arrest at the spermatocyte stage showed sperm recovery. Likewise, Esteves and Glina reported recovery of sperm in the ejaculate of 47% of men after VR [40]. Only men with hypospermatogenesis or maturation arrest patterns demonstrated improvement after surgery while all patients with SCOS continued to be azoospermic. Some studies have shown higher sperm retrieval during mTESE following prior correction of varicocele [41,42]. Additionally, the results of a meta-analysis indicated a strong trend towards increased live birth rates following VR prior to ICSI (odd ratio=2.208, p=0.052) [43]. However, the quality of evidence on the outcome of VR in men with clinical varicocele and NOA is still poor, and a clinician should consider correcting a clinically significant varicocele only after optimal patient counselling that the quality of evidence is poor, and the outcome of varicocele correction may be the appearance of a few sperm in the ejaculate which may take up to 12 months and would still need ICSI. Surprisingly, the majority of respondents (81.5%) stated that they would perform VR in men with subclinical varicocele and NOA, though this is completely contrary to the guidelines and evidence in the literature, perhaps as an attempt to grasp any possibility in a desperate situation.

(4) Expert recommendation

Evidence supporting VR in men with NOA is limited. The decision to perform VR in cases of NOA is a shared decision between the physician and the couple after a detailed discussion of the risks and benefits. The decision may be guided by parameters such as testicular volume, FSH level, female partner's age, testicular histology if available, and overall fertility status. VR for subclinical varicoceles is not recommended.

7) Techniques to optimize sperm retrieval.

(1) Survey result

Only a minority of the participants (5.4%) use ultrasound to locate the most vascularized areas of the testicular parenchyma for testicular biopsy in cases of NOA (Fig. 25). Additionally, most respondents (88.1%) reported not utilizing any innovative techniques dur-

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ing mTESE (Fig. 26).

Only about 5% routinely used fine needle aspiration (FNA) mapping prior to sperm retrieval, and 52.5% of respondents felt that it was not useful, with 20.4% of these stating that it may even be harmful in case of subsequent sperm retrieval (Fig. 27).

(2) Guidelines

According to the AUA/ASRM guidelines, mTESE has a success rate that is twice as high as other techniques, including FNA.

(3) Discussion

Currently, there is no evidence to support the use of imaging during testicular biopsy nor the use of in-

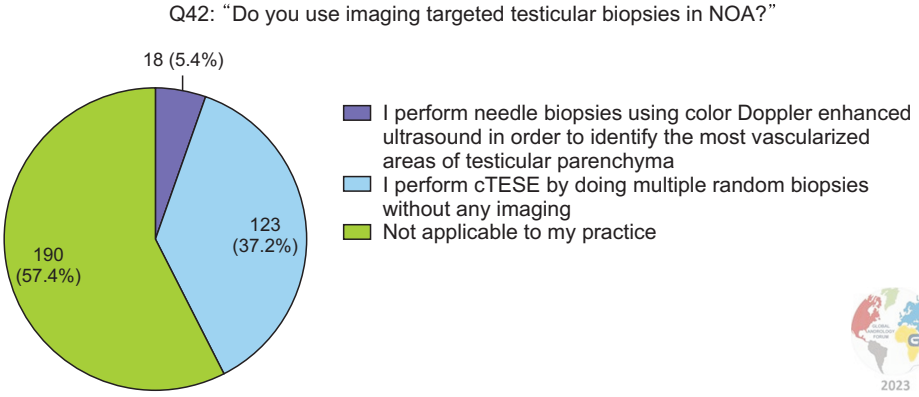

Fig. 25. Imaging targeted testicular biopsies in NOA. NOA: non-obstructive azoospermia.

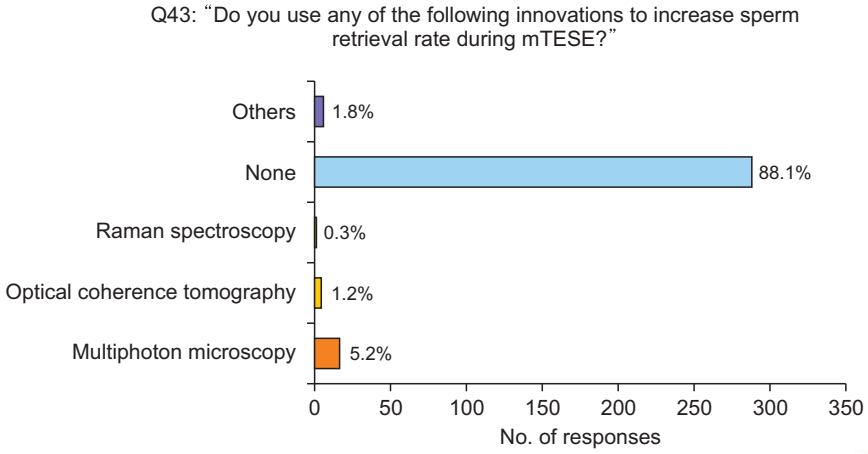

Fig. 26. Innovations to increase sperm retrieval rate during mTESE. mTESE: microdissection testicular sperm extraction.

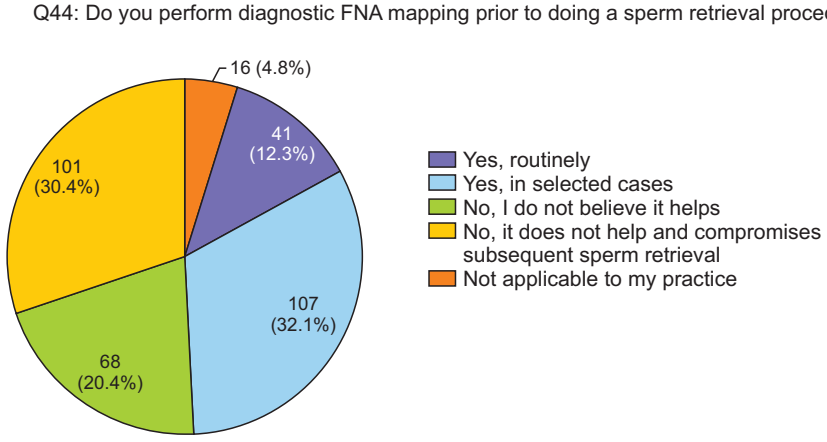

Fig. 27. Fine needle aspiration (FNA) mapping prior to sperm retrieval procedure.

novative techniques during mTESE to improve success rates [7]. However, the authors specified that shared decision-making between the physician and patient should determine which procedure to choose.

(4) GAF Expert recommendation

The evidence supporting the utility of diagnostic testicular FNA mapping prior to SSR is limited and the procedure may cause testicular damage. Hence, it is not routinely recommended. There is currently no evidence supporting the use of imaging techniques to improve the success of sperm retrieval.

8) Comparison of sperm retrieval techniques (TESA *vs* cTESE *vs* mTESE)

(1) Survey result

Of the 330 participants who answered a question regarding the use of cTESE *versus* mTESE for sperm retrieval in infertile men with NOA, 36 (10.9%) reported routinely beginning with a testicular sperm aspiration (TESA) in men with NOA. If the initial TESA failed to identify any usable sperm, then the participants perform cTESE or mTESE at a second session. Thirty-eight (11.5%) reported routinely performing cTESE first, followed by mTESE at the same session if the cTESE attempt fails to find sperm. One third of respondents (107, 32.4%) stated that they always proceed directly to mTESE (Fig. 28). A small testicular volume was an indication to directly perform mTESE for almost half the respondents (48.3%) (Fig. 29). Other conditions that led to primary mTESE included patients with very high FSH levels (38.5%), history of testicular insult or injury (19.0%), and KS (38.8%) (Fig. 29).

(2) Guidelines

Most guidelines and expert opinions recommend mTESE as the initial choice when available, as it has been found to be superior to both cTESE [44] and TESA [45]. The AUA/ASRM guidelines support this recommendation, stating that mTESE should be initially considered for men with NOA undergoing sperm retrieval.

(3) Discussion

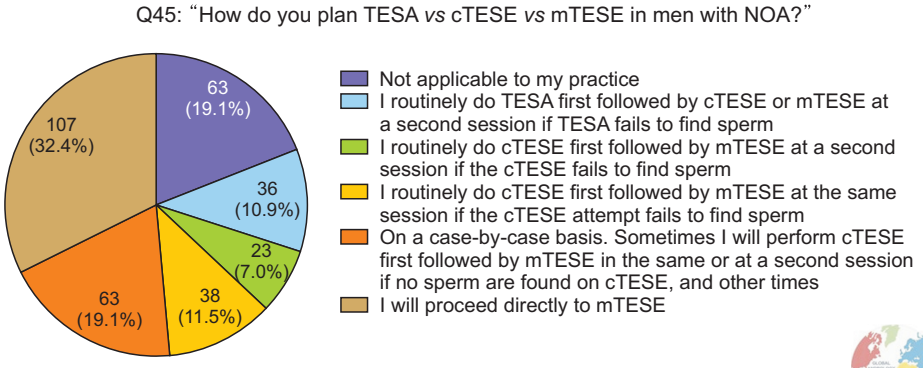

Fig. 28. Planning TESA *vs* cTESE *vs* mTESE in men with NOA. TESA: testicular sperm aspiration, cTESE: conventional testicular sperm extraction, mTESE: microdissection testicular sperm extraction, NOA: non-obstructive azoospermia.

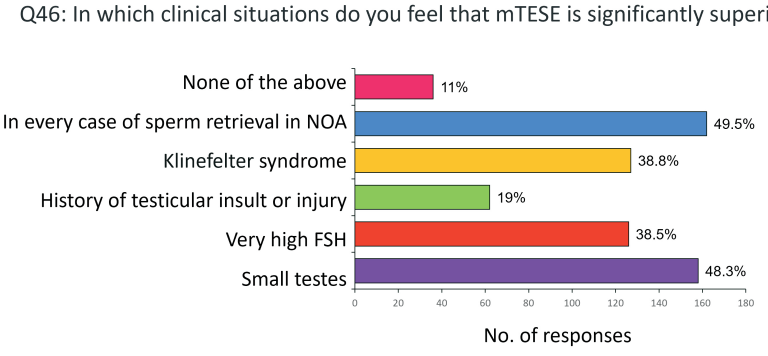

Fig. 29. Clinical situations where mTESE is significantly superior to cTESE. mTESE: microdissection testicular sperm extraction, cTESE: conventional testicular sperm extraction, NOA: non-obstructive azoospermia, FSH: follicle-stimulating hormone.

Surgical techniques such as TESA, cTESE, and mTESE are used to extract sperm in patients with NOA for ICSI purposes [44,46]. The order of these techniques may vary depending on practice, providers, and settings. Multiple studies have shown that mTESE has a higher success rate compared to cTESE, which in turn has a higher success rate than TESA [46]. However, there is lack of evidence if a less invasive TESA should be attempted before cTESE or mTESE. FSH and testicular volume were suggested as predictive factors for successful TESE and TESA [47].

(4) GAF expert recommendation

mTESE is considered the preferred method for sperm extraction due to its overall higher SSR rate compared to other procedures such as TESA and cTESE. For some testicular histological patterns, cTESE and TESA may have acceptable sperm retrieval rates. Hence, it may be acceptable, in some cases, to perform a cTESE as the first step of a mTESE.

9) Timing of repeat surgical sperm retrieval

(1) Survey results

Out of 332 respondents, 79 (23.8%) reported waiting for 3 months and 110 (33.1%) reported waiting for 6 months before proceeding to mTESE after a failed cTESE in men with NOA. Waiting for longer periods was less common (19 respondents; 5.7%) (Fig. 30). In patients with successful mTESE, approximately one-third (119, 35.7%) waited for 6 months before repeating a second mTESE, while 18.9% waited for 3 months (Fig. 31). For patients with a failed initial mTESE, 44 (13.2%) reported repeating mTESE in 3 months, and 90 (27.7%) reported repeating it in 6 months. Interestingly, 85 respondents (25.5%) stated that they do not repeat mTESE following a failed first attempt (Fig. 32).

(2) Guidelines

AUA/ASRM, EAU, and EAA guidelines do not address an optimal timing for repeat TESE.

(3) Discussion

There is currently insufficient evidence to determine the ideal time for repeating a TESE, regardless of whether the initial yield is positive or negative. However, several studies have reported that the time interval between the first and second biopsies can significantly impact the success rate of the second sperm extraction procedure [48-50]. The literature commonly recommends waiting for a duration of 6 months be-

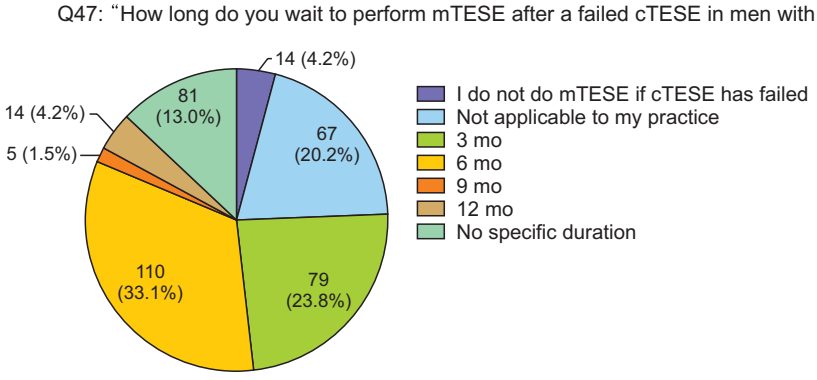

Fig. 30. Waiting period to perform mTESE after a failed cTESE in men with NOA. mTESE: microdissection testicular sperm extraction, cTESE: conventional testicular sperm extraction, NOA: non-obstructive azoospermia.

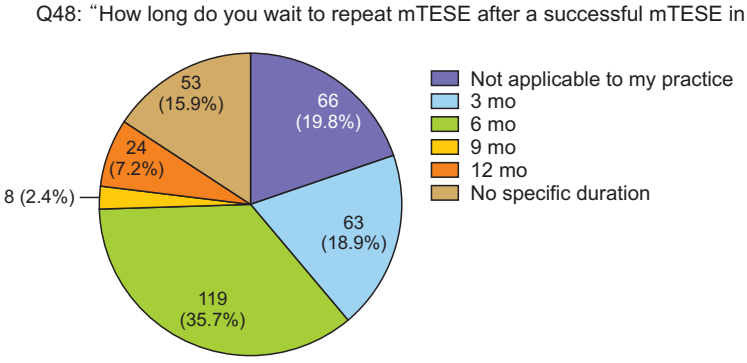

Fig. 31. Period of waiting to perform mTESE after successful mTESE in men with NOA. mTESE: microdissection testicular sperm extraction, NOA: non-obstructive azoospermia.

tween the initial and subsequent TESE procedures [51].

(4) GAF expert recommendation

A repeat mTESE can still be successful regardless of the outcome of the initial sperm retrieval procedure, although the chance of successful SSR during a repeat operation is higher if the original surgery found sperm. The recommended duration between the two procedures is 6 months. Waiting for 6 months after the first procedure may allow for the testicles to recover their function from the previous surgery.

10) mTESE miscellaneous questions

(1) Survey results

In men with symmetrical testes, approximately two-thirds (69.6%) of respondents would proceed with the contralateral testis with a 5% to 20% of finding sperm, while 8.1% had >20% expectation to find sperm in the opposite testis (Fig. 33). The cut off FSH value for positive sperm retrieval following mTESE was reported to be 12–19 IU/mL by 22.5% of participants, and 20–40 IU/mL by 27.8%, while 31.8% of respondents declared that there were no upper limits (Fig. 34). In men with KS (47, XXY) undergoing *in vitro* fertilization (IVF)/ICSI, 41.3% recommended preimplantation genetic testing (PGT) of embryos while 21.7% reported that it was not a routine practice (Fig. 35).

(2) Guidelines

The AUA/ASRM, EAU, and EAA guidelines do not offer definitive statements regarding proceeding with TESE in the contralateral testes with an initial negative result and PGT for KS patients. The guidelines do suggest that there is no cut-off value for FSH to proceed with mTESE.

(3) Discussion

In men with NOA with bilateral symmetrical testes, most surgeons prefer to perform mTESE on the second side if the initial search of one testis is negative [52]. Though there is no strict cut-off for FSH, most often the participants stated that mTESE could be success-

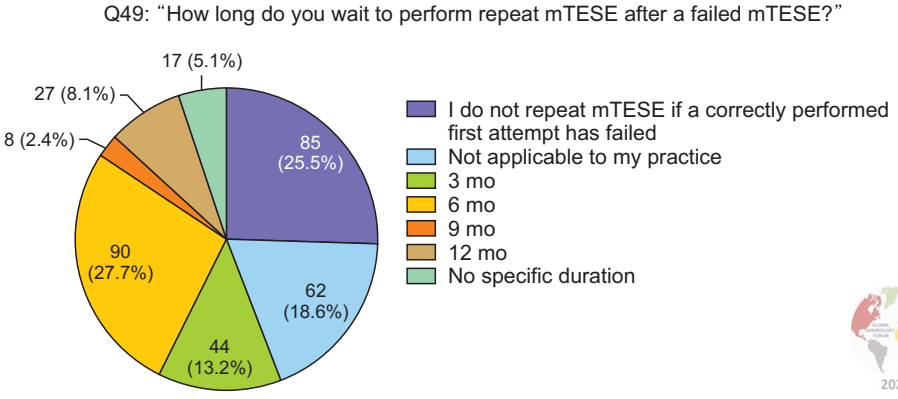

Fig. 32. Period of waiting to perform mTESE after failed mTESE. mTESE: microdissection testicular sperm extraction.

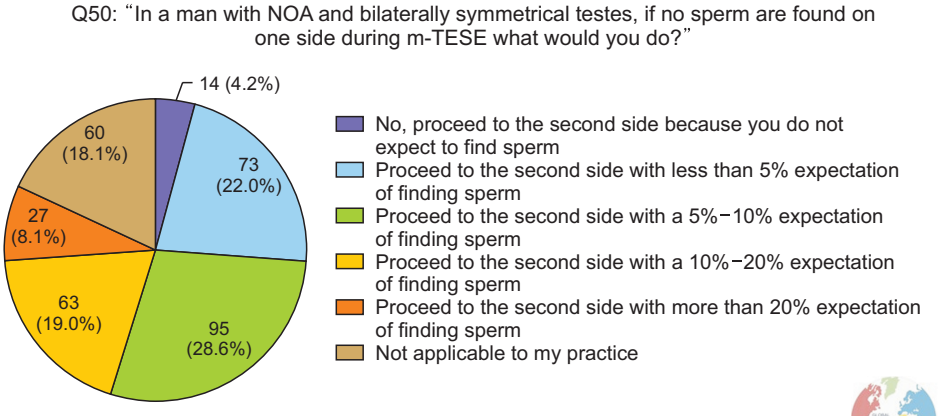

Fig. 33. Procedure for man with NOA and bilaterally symmetrical testes if no sperm found on one side during mTESE. NOA: non-obstructive azoospermia, mTESE: microdissection testicular sperm extraction.

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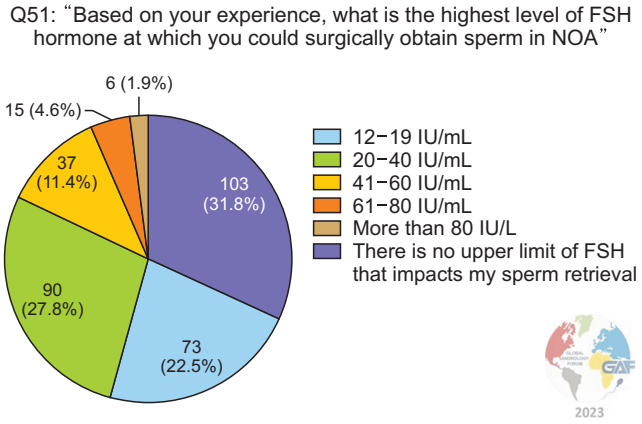

Fig. 34. The highest FSH level to surgically obtain sperm in NOA. FSH: follicle-stimulating hormone, NOA: non-obstructive azoospermia.

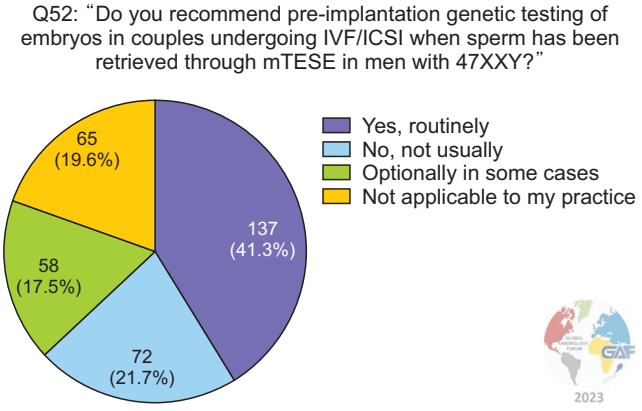

Fig. 35. Preimplantation genetic testing of embryos in couples doing IVF/ICSI when sperm have been retrieved with mTESE in men with 47XXY. IVF: *in vitro* fertilization, ICSI: intracytoplasmic sperm injection, mTESE: microdissection testicular sperm extraction.

ful when serum levels of FSH are less than 40 IU/mL [7,46,53]. While research has suggested that the risk of genetic abnormalities in the offspring of KS men is lower than previously believed [54], many fertility practitioners still consider PGT as a precautionary measure for safety reasons. Whenever feasible, it is advisable to undergo PGT to decrease the likelihood of transmitting the 47, XXY chromosome abnormality to offspring [55].

(4) GAF expert recommendation

With a negative mTESE on one side, mTESE can be attempted on the opposite side in bilateral symmetrical testes with a 10% chance of finding sperm on the second side. Though there is no defined cut-off value for FSH, higher success rates have been reported with FSH <40 IU/mL. In embryos formed from 47, XXY men, PGT can be offered whenever feasible, however, studies suggest that the majority of embryos from men with KS have no chromosomal abnormalities.

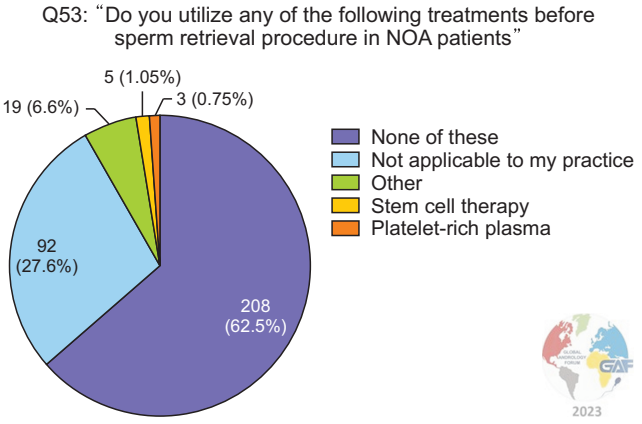

Fig. 36. Treatment before sperm retrieval procedure in NOA patients. NOA: non-obstructive azoospermia.

4. Future horizons

1) Treatment before sperm retrieval procedures

(1) Survey results

Stem cell therapy and platelet-rich plasma (PRP) are used by 5 (1.05%) and 3 (0.75%) responders, respectively. Most of the respondents (208, 62.5%) do not utilize any of the proposed techniques. The remaining respondents stated, "not applicable to my practice" (92, 27.6%) or "other" (19, 6.6%), the latter including acupuncture, antioxidants, and hormone therapy (Fig. 36).

(2) Guidelines

AUA/ASRM, EAU, and EAA guidelines include stem cells and PRP as experimental therapies. The EAA guideline does not discuss these.

(3) Discussion

The use of spermatogonial stem cell (SSC)-based therapy for fertility preservation is gaining attention as a promising alternative to overcome infertility caused by gonadotoxic treatments [56]. Cryopreserving SSC from pre-pubertal testicular tissue obtained after surgery is essential, although alternative adult tissue can be used provided that spermatogonial function is not compromised. There may also be a possibility for genome editing prior to transplantation in the future. Testicular (xeno) grafting has been shown to lead to successful spermatogenesis in testicular tissues of many mam-

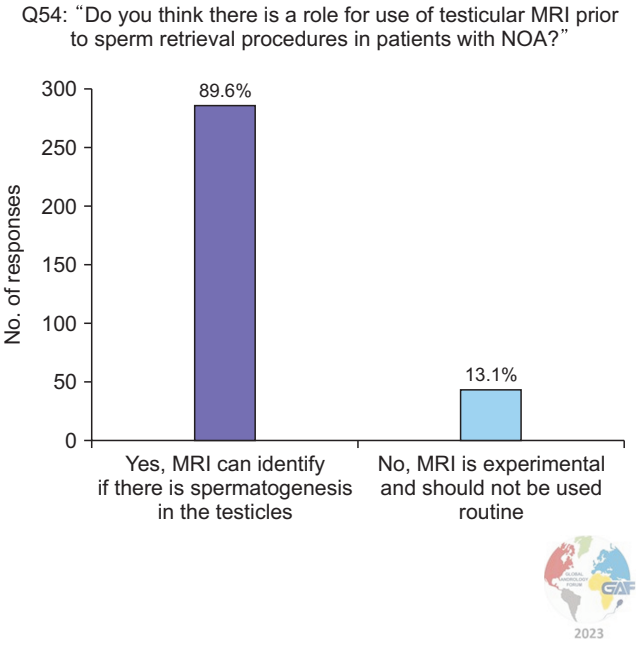

Fig. 37. Use of testicular MRI prior to sperm retrieval procedures in patients with the majority of the respondents (285, 86.9%) consider MRI useful in clinical practice, whereas 43 (13.1%) consider it as an experimental instrument. MRI: magnetic resonance imaging, NOA: non-obstructive azoospermia.

malian species, including mice, pigs, and monkeys [57-59], with reported success rate of live offspring as 87% by the use of ICSI [57,58,60]. Despite the promising but challenging results, current international guidelines do not support such treatment and thus we are far from specific recommendations. The literature regarding the application of PRP for azoospermia is scarce. An experimental study from Khadivi et al [61] conducted on different two-dimensional (2D) and three-dimensional (3D) culture systems of SSCs demonstrated the occurrence of proliferating SSCs. The number and diameter of colonies in the PRP-2D group showed a considerable increase ($p<0.01$) as compared to the control group. In the PRP-scaffold group, a significant increase ($p<0.01$) was seen only in the number of colonies related to the control group.

(4) GAF expert recommendation

Currently, there is not enough evidence to recommend the routine use of stem cells and PRP in the treatment of NOA. These are evolving and promising therapies but currently their use should be restricted to experimental settings.

2) Use of testicular MRI prior to sperm retrieval

(1) Survey result

The majority of the respondents (285, 89.6%) consider MRI useful in clinical practice, whereas 43 (13.1%) consider it as an experimental instrument (Fig. 37).

(2) Guidelines

AUA/ASRM, EAU, and EAA guidelines do not address this.

(3) Discussion

Previous preliminary studies have shown that diffusion-weighted imaging can be useful in evaluating patients with NOA [62,63]. Additionally, an increased apparent diffusion coefficient (ADC) has been observed in patients with histological patterns of maturation arrest and SCOS [64]. Tsili et al [65] reported that NOA with hypospermatogenesis had a lower 25th percentile of ADC compared to NOA with severe hypospermatogenesis and that the median ADC was the most significant metric ($p=0.007$) for predicting the presence of sperm.

(4) GAF expert recommendation

More evidence is needed before its use can be routinely recommended for identifying areas of spermatogenesis or potentially favorable patients for SSR.

3) Advancements over the next 10 years

(1) Survey result

We also provided a question on what the respondents thought the biggest advancement in the treatment of NOA over the next 10 years would be. Among the possibilities for future advancements, most of the participants answered gene therapy (189, 57.3%) or stem cells (223, 67.6%). Other advancements were PRP (48, 14.5%), advances in imaging studies (110, 33.3%), artificial sperm (62, 18.8%), 3D printing of testes or sperm (48, 14.5%), and artificial intelligence (88, 26.7%). A total of 11 subjects answered "other", including whole exome sequencing, *in vitro* spermatogenesis, and genetic testing (Fig. 38).

(2) Guidelines

AUA/ASRM and EAU guidelines include stem cells and PRP as experimental therapies. The EAA guideline does not discuss future therapies.

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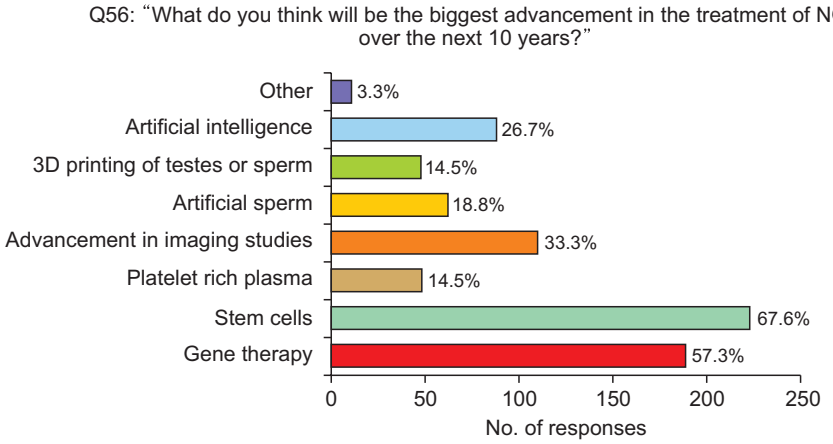

Fig. 38. The biggest advancement in the treatment of NOA over the next 10 years. NOA: non-obstructive azoospermia.

(3) Discussion

Gene therapy represents the most innovative technology able to change clinical practice in the near future in patients with NOA. In particular, CRISPR/Cas9 is a technology for RNA-directed modification of target sequences by Cas proteins, consisting mainly of CRISPR clusters, leading sequences (leaders), repeating sequence regions (tracers), and a set of conserved CRISPR-associated genes (Cas genes) [66,67]. In this context, gene therapy can be used to treat male infertility caused by genetic defects.

(4) GAF recommendation

Gene therapy with CRISPR/Cas9 may be able to cure NOA in selected patients. This is possible in theory, but future studies are needed to demonstrate its applicability.

5. Limitations

There are several limitations to the current survey. Firstly, the survey was distributed through a global group of experts with significant experience in NOA management, rather than to all male infertility or reproductive specialists, which may limit the generalizability of the findings. Furthermore, it was not possible to determine the total response rate due to the various ways in which the questionnaire was disseminated, including emails, direct communication, and professional society websites. As a result, the total number of invitations is unknown. In terms of demographics, there is a preponderance of responses from certain countries such as Italy, Turkey, and India, while other large countries such as Russia and Canada are noticeably under-represented. Finally, subgroup analysis based on specialization, practice setting, or years of practice was also limited due to the high heterogeneity of variables. The highlights of our global survey are summarized in a SWOT (strengths, weaknesses, opportunities, and threats). Using the SWOT method, the main advantages and limitations of our study are concisely displayed. We also provided opportunities for improvement in the future to treat men with NOA and posed threats which can limit advancements in NOA (Fig. 39).

CONCLUSIONS

This global survey provides a valuable and comprehensive perspective on global practices related to the medical and surgical management of NOA. It represents the first global survey for NOA and addresses important issues for clinicians. The results demonstrate a diverse range of practices in the medical and surgical management of NOA and underscore the need for evidence-based international consensus guidelines to ensure the highest standard of care for all patients.

The management of NOA is complex and success is defined by the ability to achieve the appearance of few sperms in the ejaculate via medical or surgical management or via successful SSR. The present guidelines are not very clear in many aspects about the management of NOA. This survey underlines the heterogeneity in the current worldwide practices among clinicians treating NOA. Some of the practices are clearly not in line with society recommendations. There is great

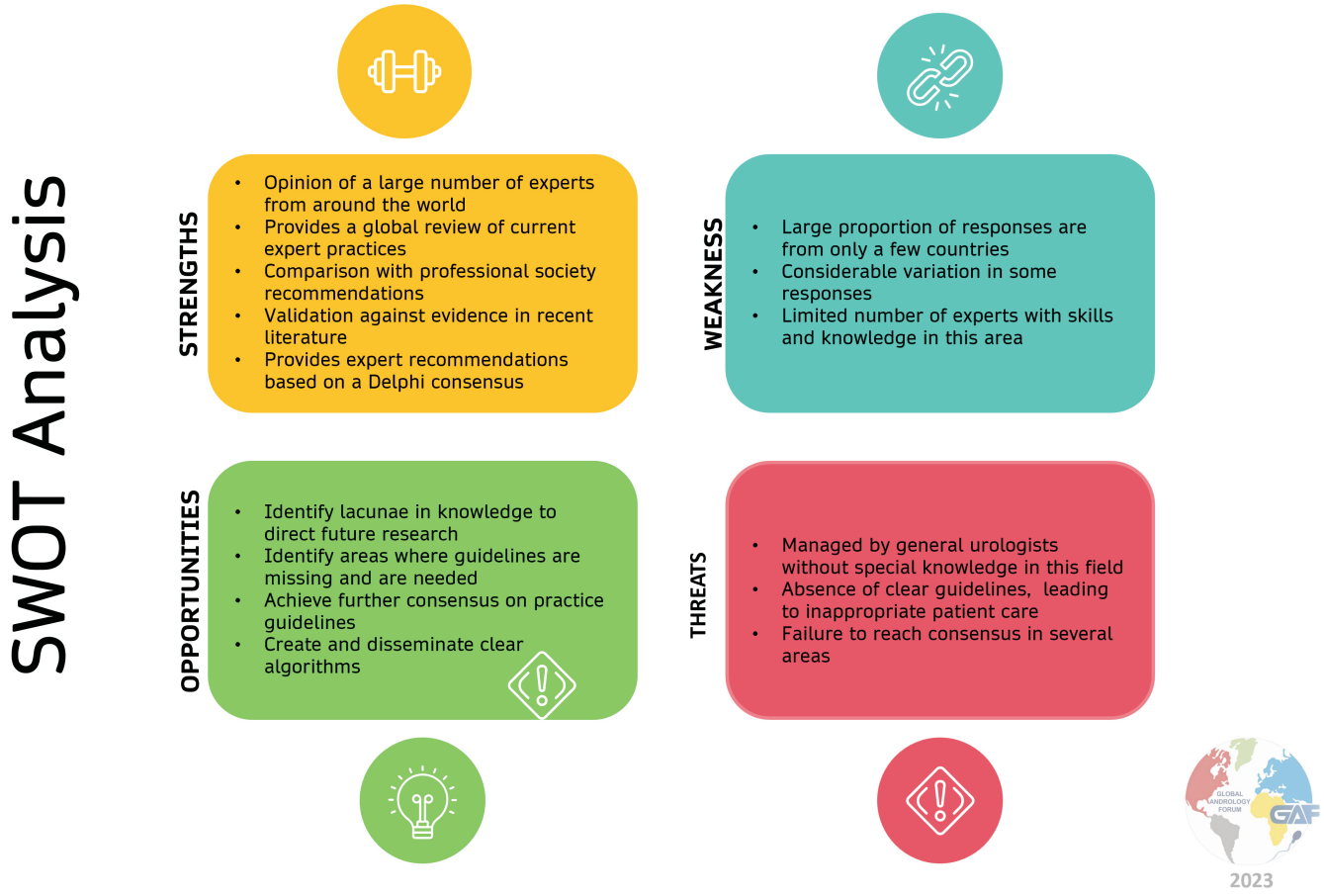

Fig. 39. The strength weakness, opportunities, and threat (SWOT) analysis.

variation in the results of various SSR techniques among the respondents which needs to be evaluated critically to find out whether a bias is responsible for these variations or there is a geographical impact on the SSRs. There is an urgent need for evidence-based international consensus guidelines for treatment as well as reporting. Well-planned meetings and research would be a step in the right direction.

Conflict of Interest

The authors have nothing to disclose.

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Author Contribution

Conceptualization: AA, RS. Statistical analysis: AH. Supervision: AS, RS. Writing – original draft: RS, AS, WA, MM, IZ, PK, NT, NHVO, PV, AH, GS, MG, TH, TT, PB, EK, MA, RAG, VSK, RS, GIR, GMP, EC. Writing – review & editing: all authors. All authors have read and agreed to the published version of the manuscript.

Supplementary Materials

Supplementary materials can be found via https://doi.org/10.5534/wjmh.230339.

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