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REVIEW ARTICLE

European Academy of Andrology guideline Management of oligo-astheno-teratozoospermia

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SUMMARY

Background: Oligo-astheno-teratozoospermia is frequently reported in men from infertile couples. Its etiology remains, in the majority of cases, unknown with a variety of factors to contribute to its pathogenesis. The aim of this European Academy of Andrology guideline was to provide an overview of these factors and to discuss available management options.

Materials and Methods: PubMed was searched for papers in English for articles with search terms: male infertility and oligo-astheno-teratozoospermia. For evidence-based recommendations, the GRADE system was applied. Issues related to urogenital infections/inflammations have not been included in this document as they will be covered by separate guidelines.

Results: For men with oligo-astheno-teratozoospermia, the European Academy of Andrology recommends:

- A general physical examination to assess signs of hypogonadism.
- A scrotal physical examination to assess (i) the testes and epididymes for volume and consistency, (ii) deferent ducts for total or partial absence, and (iii) occurrence of varicocoele.
- Performing two semen analyses, according to World Health Organization guidelines to define an oligo-astheno-teratozoospermia.
- An endocrine evaluation.
- A scrotal ultrasound as part of routine investigation.
- Karyotype analysis and assessment of Yq microdeletions in infertile men with a sperm concentration $\leq 5 \times 10^6$/mL.
- Cystic fibrosis transmembrane conductance regulator gene evaluation in case of suspicion for incomplete congenital obstruction of the genital tract.
- Against quitting physical activity to improve the chance of achieving pregnancy.
- Against androgen replacement therapy to improve the chance of achieving pregnancy.
- Assisted reproduction techniques to improve the chance of achieving pregnancy, in case other treatment options are not available or not efficient.
- Androgen replacement therapy in patients with biochemical/clinical signs of hypogonadism, after completion of the fertility treatment.

Conclusion: These guidelines can be applied in clinical work and indicate future research needs.

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SUMMARY OF RECOMMENDATIONS

1 We recommend a general physical examination to assess signs of hypogonadism. We also recommend scrotal physical examination in all cases of oligo-astheno-teratospermia (OAT) to assess the testes and epididymes for volume and consistency, deferent ducts for total or partial absence and occurrence of varicocoele (1 ØØØO).

2 We recommend scrotal ultrasound (US) as part of routine investigation of men with OAT (1 ØØOO). In case of testicular microlithiasis (TM), testicular biopsy should be considered although this is still a controversial issue (2 ØØOO).

3 We recommend an endocrine evaluation in all men with OAT. Determination of prolactin (PRL) should be added if a hypogonadotropic hypogonadism is suspected (1 ØØØØ).

4 We recommend that OAT patients with biochemical and clinical signs of hypoandrogenism should first complete fertility treatment and only after that androgen replacement therapy can be offered according to the existing guidelines (1 ØØØØ).

5 We recommend karyotype analysis of infertile men with a sperm concentration $\leq 5 \times 10^6$/mL to assess the risk for an unbalanced karyotype of embryos (1 ØØØO). We recommend assessment of Yq microdeletions of infertile men with a sperm concentration $\leq 5 \times 10^6$/mL, which will be inherited to male offspring (1 ØØØO). We recommend cystic fibrosis transmembrane conductance regulator (*CFTR*) gene evaluation in case of suspicion for incomplete congenital obstruction of the genital tract (1 ØØØO).

6 We recommend performing two (2) semen analyses, according to World Health Organization (WHO) guidelines to define an OAT (1 ØØØØ).

7 Sperm DNA integrity [e.g. Sperm Chromatin Structure Assay (SCSA); Alkaline COMET assay; TUNEL] could be applied in addition to standard semen analysis in following cases (1 ØØOO):

- **a** When it is considered whether the couple should be referred for assisted reproduction or given additional time for trying achieving spontaneous pregnancy;
- **b** When intrauterine insemination with partner's spermatozoa (AIH) is considered;
- **c** When standard *in vitro* fertilization (IVF) or intra-cytoplasmic sperm injection (ICSI) is considered.

8 Treatment with FSH can be suggested with low evidence in selected men from infertile couples (normogonadotropic men with idiopathic oligozoospermia or OAT) in attempt to improve quantitative and qualitative sperm parameters and pregnancy rate (2ØOOO).

9 According to the current evidence, we cannot recommend either for or against antioxidants and for antiestrogens (tamoxifen or clomiphene) or aromatase inhibitors (2ØOOO).

10 We recommend against therapy with androgens (1 ØØØØ).

11 Varicocoele treatment in infertile couples reporting OAT associated with palpable varicocoele can be discussed with the couple (2ØOOO)

12 We suggest only monitoring cases with subclinical varicocoele (2 ØØOO).

13 We suggest treatment for varicocoele in young males with progressive testicular failure and/or seminal deterioration (2 ØØOO).

14 We suggest to investigate by transrectal US (TRUS) patients with OAT, low semen volume (unrelated to hypogonadism or obvious agenesia of deferent ducts), and/or significant semen parameters fluctuations, acidic pH, and low fructose, because they might be affected by a distal seminal tract emptying disorder (2 ØOOO).

15 Because of the missing solid evidence from randomized studies, we currently do not suggest to perform as routine TESE in OAT patients with high DNA fragmentation or patients with cryptozoospermia. However, in cases of several (2 or more) ICSI failures after the use of ejaculated spermatozoa (with uncorrectable high DFI), the option of TESE and use of testicular spermatozoa for ICSI can be considered and discussed with the couple, which should be informed that this approach is based on low-quality evidence (2 ØOOO).

16 We suggest that subfertile men with OAT should quit cigarette smoking to improve the chance of the couple to achieve the desired pregnancy (2 ØØOO).

17 We suggest that subfertile obese men with OAT should reduce weight to improve the chance of the couple to achieve the desired pregnancy (2 ØØOO).

18 We suggest that subfertile men with OAT should reduce alcohol consumption (if excessive) to improve the chance of the couple to achieve the desired pregnancy (2 ØØOO).

19 We do not recommend asking men with OAT to quit physical activity to improve the chance of the couple to achieve the desired pregnancy (1 ØØOO).

20 We do not recommend scrotal cooling and changes in clothing or working conditions leading to decrease scrotal heating as measures toward increasing male fertility (1 ØØOO).

21 In case other treatment options are not available or not efficient, we recommend men with OAT and their partner assisted reproduction to improve their chance of achieving pregnancy (1 ØØØØ).

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INTRODUCTION

Oligo-astheno-teratozoospermia (OAT) is frequently reported in men from infertile couples. The etiology behind the OAT is in most cases unknown, and a variety of contributing factors can give rise to the syndrome. The aim of this document was to provide an overview of different mechanisms that may contribute and also to discuss available management options. PubMed was searched for papers in English for articles with search terms: male infertility and oligo-astheno-teratozoospermia. Issues related to urogenital infections/inflammations have not been included in this document as they will be covered by separate EAA Guidelines.

For evidence-based recommendations, the GRADE system used by numerous organizations as the Endocrine Society, World Health Organization (WHO), and the Cochrane Collaboration was applied. See below for details.

WHO CRITERIA FOR SEMEN ANALYSIS

According to the definition given by the WHO in the 'WHO laboratory manual for the examination and processing of human semen' (fifth edition, 2010), OAT means semen sample with:

- Presence of the spermatozoa in the ejaculate but the total number below the lower reference limit,
- Percentage of progressively motile (PR) spermatozoa below the lower reference limit, and
- Percentage of morphologically normal spermatozoa below the lower reference limit.

An overview of the etiology/pathogenesis behind OAT can be found in the supplement. The same is true for considerations regarding absolute asthenozoospermia and necrozoospermia.

For recommendations given in these guidelines, we will focus on papers in which the definition of OAT was based on abnormality of all three criteria in two consecutive semen samples. A shortcoming of our approach is the fact that the WHO criteria for normal sperm count, motility, and morphology have changed through the 30 years, between the first and the most recent edition of the WHO manual (Table 1).

The latest revision resulted in lower cutoff level for volume, concentration, motility, and morphology (percentage of normally formed spermatozoa) for semen characteristics of fertile men.

Thus, it should be kept in mind that the methodology for performing semen analysis and the definition of OAT in the papers being included in these guidelines have changed over time due to changes in the threshold values of the WHO manual.

In our recommendations, we have used the principles defined by the GRADE system of the Endocrine Society (Swiglo *et al.*, 2008). According to the GRADE, the terms 'we recommend' are applied to denote strong recommendations, whereas weak recommendations use the less definitive wording 'we suggest'. Furthermore, a strong recommendation receives a grade 1 classification, and a weak recommendation receives a grade 2 classification. The symbols used for the four levels of quality of evidence are ØOOO (very low); ØØOO (low); ØØØO (moderate); and ØØØØ (high) quality.

RECOMMENDED INVESTIGATION PROGRAM FOR PATIENTS WITH OAT

History and physical examination

History and physical examination should identify the risk factors for a reduced fertility.

1 We recommend a general physical examination to assess signs of hypogonadism. We also recommend scrotal physical

Table 1 Recommendations and levels of evidence for medical and surgical treatment of oligo-astheno-teratozoospermia

Intervention	Recommendation*	Level of evidence	Comments
Antioxidants	2	ØOOO	According to the current evidence, we cannot recommend either for or against antioxidants.
FSH	2	ØOOO	Treatment with FSH can be suggested with low evidence in selected men from infertile couples (normogonadotropic men with idiopathic oligozoospermia or OAT) in an attempt to improve quantitative and qualitative spermatozoa parameters and pregnancy rate
Antiestrogens	2	ØOOO	According to the current evidence, we cannot recommend for antiestrogens or aromatase inhibitors.
Androgens	1	ØØØØ	Contraindicated
No varicocelectomy/varicocelectomy in patients with palpable varicocoele, infertility, female age < 35 years	2	ØOOO	There is contradicting evidence that allows no reliable EAA recommendation for or against varicocelectomy. Varicocelectomy in infertile men with OAT and palpable varicocoele should be discussed individually with the couple
Varicocelectomy in patients with palpable varicocoele with progressive impairment of testicular function	2	ØØOO	Indication to correction
No varicocelectomy in patients with subclinical varicocoele	2	ØØOO	Monitoring
Surgery for cyst in seminal tract	2	ØOOO	The technique dependent on ± connection with the seminal tract. Patients should be referred to tertiary uro-andrological centers.
TESE	2	ØOOO	Not recommended as a routine in patients with OAT and high DNA fragmentation or in patients with cryptozoospermia. In cases of several (2 or more) ICSI failures after the use of ejaculated spermatozoa (with uncorrectable high DFI), the option of TESE and use of testicular spermatozoa for ICSI can be considered and discussed with the couple, which should be informed that this approach is based on low-quality evidence
Assisted reproduction	1	ØØØØ	Symptomatic therapy, after having excluded other therapeutical options

*(1) Corresponds to 'we recommend'; (2) Corresponds to 'we suggest'. TESE, Testicular sperm extraction; OAT, Oligo-astheno-teratozoospermia.

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examination in all cases of OAT to assess the testes and epididymes for volume and consistency, deferent ducts for total or partial absence and occurrence of varicocoele (1 ØØØO).

Evidence

Testicular volume assessed by Prader orchidometer (PO) is correlated with ultrasound (US) measures and both correlate with testicular function in infertile men (Behre *et al.*, 1989). The PO overestimates testicular volume of 2–3 mL, approximately, compared with the testicular US. An enlarged epididymis might indicate a partial or a total obstruction of the seminal tract. An absent vas deferens at palpation may be indicative for an obstruction of the seminal tract. Varicocoele is assessed by visualizing or palpating dilated testicular veins within the spermatic cord, manually, while standing or using Doppler US (Lotti & Maggi, 2015). OAT has been positively associated with cryptorchidism, and varicocoele, and negatively with testicular size and body mass index (BMI). Men with OAT have an increased risk for an overt testicular cancer (Hanson *et al.*, 2018).

Values

We place a relatively high value to the recommendations but the evidence for the association of testicular volume and semen quality is limited. We place a high value to the recommendations to assess varicocoele by physical examination although it cannot detect the presence of a subclinical varicocoele. Actually, the benefit to repair a subclinical condition is however not demonstrated yet. We place a high value to the recommendations to assess a mass indicative for a testicular cancer.

Remarks

We put a great relevance to physical examination to address attention to a possible hypogonadism associated with OAT. Scrotal examination is the first line method to assess a varicocoele, to discover a testicular cancer, and to suspect proximal seminal tract subocclusion/occlusion or primary/secondary hypogonadism.

Ultrasound

US evaluation includes the testis for testicular volume and texture, the epididymis for cysts and size, and the spermatic cord for varicocoele. Prostate and seminal vesicles are assessed by transrectal US (TRUS) (see recommendation 14).

2 We recommend scrotal US as part of routine investigation of men with OAT (1 ØØOO). In case of testicular microlithiasis (TM), testicular biopsy should be considered although this is still a controversial issue (2 ØØOO).

Evidence

The association of OAT and risk for testicular cancer (Hanson *et al.*, 2016) underlines the relevant role of scrotal US in men with OAT. TM may indicate a germ cell neoplasia *in situ* (GCNIS) (Elzinga-Tinke *et al.*, 2010). Epididymal cysts are not associated with altered testicular volume or sperm quality (Hart *et al.*, 2015). Caput epididymis is often enlarged in obstructive azoospermia, but its US size is not different in OAT and in normozoospermic men (Pezzella *et al.*, 2013). US confirms varicocoele when physical findings are equivocal. Consensus on method analysis and relevance of Doppler examination in varicocoele are undefined yet (Lotti & Maggi, 2015). TRUS of prostate and seminal vesicles is reserved to a suspected distal obstruction (Lotti & Maggi, 2015).

Values

We place a high value to the recommendations regarding US: (A) to exclude a testicular cancer or TM also when a physical examination did not show any abnormality, (B) to confirm a varicocoele suspected at physical evaluation, (C) when a genital tract obstruction is suspected.

Remarks

We are aware of the still limited value of US in the evaluation of OAT; however, it should be part of routine examination of OAT patients to recognize a testicular cancer or TM.

Hormones

Serum testosterone (T), luteinizing hormone (LH), and follicular-stimulating hormone (FSH) are determined in a morning sample. Serum sex hormone-binding globulin (SHBG) is added to calculate free T (fT), especially when borderline levels of total T are present and a diagnosis of hypogonadism is suspected.

3 We recommend an endocrine evaluation in all men with OAT. Determination of prolactin (PRL) should be added if a hypogonadotropic hypogonadism is suspected (1 ØØØØ).

4 We recommend that OAT patients with biochemical and clinical signs of hypoandrogenism should first complete fertility treatment and only after that androgen replacement therapy can be offered according to the existing guidelines (1 ØØØØ).

Evidence

Elevated levels of FSH are indicative for a primary hypogonadism and a level of FSH > 10 IU/L has a predictive power of 85.7% to detect a sperm count $<20 \times 10^6$/mL (Jensen *et al.*, 1997). Inadequate low/normal FSH and LH associated with low total T level are indicative for a secondary hypogonadism. Normal FSH might be indicative for an incomplete genital tract obstruction, but it is also observed in OAT due to partial spermatogenic arrest. Assessment of inhibin-B level does not increase the ability of FSH alone to predict a low sperm count (Meeker *et al.*, 2007). Evaluation of thyroid function is not routinely recommended as thyroid dysfunction in OAT is not frequently reported. Men with impaired semen quality are at increased risk of hypogonadism. Bearing in mind the potentially serious long-term consequences of undiagnosed androgen deficiency, men with OAT should routinely be offered endocrine evaluation for diagnosis of hypogonadism.

Values

We place an important value on broadening the traditional concept of managing men with fertility problems, not focusing on their semen quality only, but also including investigation for possible underlying conditions, such as impaired testosterone production.

Remarks

Due to the negative effect of exogenous testosterone on androgen production and on spermatogenesis, replacement therapy should be postponed and not to be initiated before fertility treatment has been completed. Existing guidelines for androgen replacement therapy should be followed (Bhasin *et al.*, 2010),

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and the diagnosis of hypogonadism should be based on biochemical and clinical symptoms.

Genetic tests

Genetic tests include karyotype analysis on blood lymphocytes and assessment of microdeletions in the long arm of chromosome Y (Yq), also called azoospermia factor (*AZF*) deletions.

5 We recommend karyotype analysis of infertile men with a sperm concentration $\leq 5 \times 10^6$/mL to assess the risk for an unbalanced karyotype of embryos (1 ØØØO). We recommend assessment of Yq microdeletions of infertile men with a sperm concentration $\leq 5 \times 10^6$/mL, which will be inherited to male offspring (1 ØØØO). We recommend cystic fibrosis transmembrane conductance regulator (*CFTR*) gene evaluation in case of suspicion for incomplete congenital obstruction of the genital tract (1 ØØØO).

Evidence

A recent large prospective study of infertile men reported genetic causes in 2.5% of patients with total sperm number between 1 and 10×10^6/ejaculate and in 10.8% of men with $<1 \times 10^6$/ejaculate (Punab *et al.*, 2017). Autosomal Robertsonian and reciprocal translocations predominate and may result in an early spontaneous abortion or more rarely in a chromosomally abnormal child. Yq microdeletions are associated with spermatogenic failure, and they are transmitted to the male embryo. Their prevalence is higher in men with azoospermia compared to those with severe oligozoospermia ($<2 \times 10^6$/mL), and the defect is very rarely seen in men with sperm concentration of $2–5 \times 10^6$/mL (Krausz *et al.*, 2014). Yq microdeletions were reported in 8.5% of men with $<1 \times 10^6$ sperm/ejaculate and in 0.3% of men with a number of spermatozoa ranging between 1 and 10×10^6/ejaculate (Punab *et al.*, 2017).

Values

We place a high value to the recommendations regarding karyotype analysis due to the association of OAT with autosome translocations that potentially increase the risk for an unbalanced karyotype in embryos. We place a high value to the recommendations regarding the assessment of Yq microdeletions as it identifies the cause of a severe OAT and provides information on the risk of conceiving a son with impaired spermatogenesis.

Remarks

Although genetic testing in severe OAT is expected to recognize defects in a very small number of cases, their identification allows the determination of potential genetic risk before undergoing ART (Punab *et al.*, 2017).

Semen analysis

6 We recommend performing two (2) semen analyses, according to WHO guidelines to define an OAT (1 ØØØØ).

Evidence

Semen analysis should be assessed at least twice, due to the intra-individual variability of semen parameters in healthy donors (Alvarez *et al.*, 2003) and in subfertile men (Francavilla *et al.*, 2007). Reliability of results is influenced by collection and transport, duration of abstinence, fever, and medical treatment interfering with spermatogenesis in the last 2–3 months (Carlsen *et al.*, 2004). The combination of the three parameters lower than the defined thresholds to define OAT sharply increases the odds of subfertility (Guzick *et al.*, 2001). In case of azoospermia, analysis of the pellet after centrifugation should distinguish an azoospermia from cryptozoospermia, the latter allowing for ICSI with ejaculated spermatozoa. Undefined is the relevance of detecting semen white blood cells (WBCs), as the relationship between WBCs concentration and semen quality is questioned in men asymptomatic for a genital tract infection (Aitken *et al.*, 1994). The presence of a high number of WBCs and a reduced ejaculated volume might indicate an accessory gland infection and it is suggested to be associated with altered sperm parameters (Calogero *et al.*, 2017).

Values

We place a high value to the recommendations although the large intra-individual variability of semen parameters and the intra-technician variability in assessing sperm motility and sperm morphology should be taken into consideration when evaluating variation in semen quality.

Remarks

Quality control and continuous training are essential.

Sperm DNA integrity testing

7 Sperm DNA integrity [e.g. Sperm Chromatin Structure Assay (SCSA); Alkaline COMET assay; TUNEL) could be applied in addition to standard semen analysis in following cases (1 ØØOO):

- **a** When it is considered whether the couple should be referred for assisted reproduction or given additional time for trying achieving spontaneous pregnancy;
- **b** When intrauterine insemination with partner's spermatozoa (artificial insemination by husband—AIH) is considered;
- **c** When standard *in vitro* fertilization (IVF) or intra-cytoplasmic sperm injection (ICSI) is considered.

Evidence

The biological background linking impairment of sperm DNA integrity to the fertilization process *in vivo* and *in vitro* as well to the early embryo development is not completely elucidated. There is a growing body of evidence showing a link between a high degree of impairment of sperm DNA integrity and low chance of spontaneous pregnancy as well as of successful results of intrauterine insemination (Spano *et al.*, 2000; Bungum *et al.*, 2007). High degree of sperm DNA impairment does also associate with poorer outcome of IVF or ICSI treatment (Oleszczuk *et al.*, 2016; Simon *et al.*, 2017).

Thus, high level of sperm DNA damage in patients with OAT may have clinical implications.

Even younger couple may be recommended to undergo immediate assisted reproduction as the chance of spontaneous pregnancy is low. ICSI should be considered as first choice although the conditions for intrauterine insemination or standard IVF are fulfilled according to the conventional parameters.

So far, clinically applicable levels for high degree of impairment of sperm DNA integrity have been defined for SCSA and for alkaline COMET assay.

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Values

Including sperm DNA integrity testing may add to strengthening the value of andrological investigation in management of infertility. We suggest the addition to standard semen analysis of a sperm DNA integrity testing (if the test is available and the laboratory has significant experience) to get further information on the couple's chance of spontaneous pregnancy and in selection of method of assisted reproduction.

Remarks

Improvement of sperm DNA integrity may indicate beneficial effects of antioxidant treatment (see below).

MEDICAL TREATMENT OF OAT

8 Treatment with FSH can be suggested with low evidence in selected men from infertile couples (normogonadotropic men with idiopathic oligozoospermia or OAT) in an attempt to improve quantitative and qualitative sperm parameters and pregnancy rate (2ØOOO).

9 According to the current evidence, we cannot recommend either for or against antioxidants and for antiestrogens (tamoxifen or clomiphene) or aromatase inhibitors (2ØOOO). It should be noted that most of the above drugs/substances are not licensed for this indication in various countries.

10 We recommend against therapy with androgens (1 ØØØØ).

Evidence

Antiestrogens

The antiestrogens tamoxifen and clomiphene have been widely used for treatment of idiopathic male infertility for decades. However, previous reviews revealed only insignificant higher pregnancy outcomes among antiestrogens-treated groups (Vandekerckhove *et al.*, 1996; Kamischke & Nieschlag, 1999). Therefore, treatment with antiestrogens has not been recommended (Jungwirth *et al.*, 2012). In contrast, in a recent new meta-analysis that included 11 randomized trials on men with idiopathic oligo- and/or asthenozoospermia up to March 2013, antiestrogens have been found to be associated with a statistically significant increased pregnancy rate compared with controls. In addition, a significant rise in sperm concentration and motility has been identified. No significant adverse effects were recorded. Treatment was performed with clomiphene 25 or 50 mg and tamoxifen 20–30 mg. The beneficial effects have not been observed in patients treated with clomiphene 25 mg. Therefore, the authors suggested the use of clomiphene 50 mg or tamoxifen 20–30 mg daily for 3–6 months and to proceed with assisted reproduction techniques (ART), if no pregnancy has been achieved (Chua *et al.*, 2013).

Antioxidants

In about half of infertile men, an imbalance between oxidative stress and antioxidant capacity in the seminal plasma is found (Tremellen, 2008). Reactive oxygen species (ROS) cause damage of spermatozoal membranes by lipid peroxidation which affects sperm motility and acrosome reaction. In addition, they lead to increased DNA fragmentation (Tremellen, 2008).

In a previous Cochrane Data Base Systemic Review (Showell *et al.*, 2011) that included 34 randomized controlled studies in total 2876 couples using various antioxidant compounds, a positive impact on live birth and pregnancy rate in subfertile couples undergoing ART cycles has been shown (Showell *et al.*, 2011). In the recent update of this review (Showell *et al.*, 2014), 48 randomized clinical trials were enrolled that compared single and combined antioxidants with placebo, no treatment, or another antioxidant in 4179 subfertile men. A wide variety of antioxidants was used comprising zinc, folic acid, N-acetylcysteine, Coenzyme Q10, vitamins E and C, selenium, carnitines, and pentoxifylline. Only a part of the studies reported on pregnancy rates while others were restricted to sperm parameters. In this review, it was concluded 'that there is low-quality evidence from only four small randomized controlled trials suggesting that antioxidant supplementation in subfertile males may improve live birth rates for couples attending fertility clinics'. Low-quality evidence suggests that clinical pregnancy rates may increase (Showell *et al.*, 2014).

FSH

While recombinant (recFSH) or human purified (hpFSH) FSH can be successfully used for treatment for hypogonadotropic hypogonadism (further guidelines on this topic are planned), its application to idiopathic male infertility is more controversial. Several studies in the past yielded completely different results regarding sperm parameters and pregnancy rates (reviewed in (Foresta *et al.*, 2009)). Later on, it has been shown that the response to FSH treatment in oligozoospermia may depend on polymorphisms of the FSH receptor gene (Ferlin *et al.*, 2011; Selice *et al.*, 2011; Attia *et al.*, 2013; Simoni *et al.*, 2016; Casamonti *et al.*, 2017).

A recent update of the Cochrane Database Systemic Review 2007 on 'Gonadotrophins for idiopathic male factor subfertility' that included six randomized controlled trials with 456 participants and variable treatment and follow-up periods reported on a beneficial effect of gonadotrophin (FSH) treatment on live birth and pregnancy rate. However, no significant improvement in pregnancy rates after IUI and ICSI-cycles could be encountered (Attia *et al.*, 2013).

In a most recent meta-analysis including 15 trials on 614 men treated with FSH and 661 with placebo or untreated, the authors concluded an improvement of pregnancy rates following FSH treatment regarding both spontaneous pregnancies and pregnancies after assisted reproductive techniques (ART), the effects of recFSH and highly purified FSH not being different (Santi *et al.*, 2015).

Androgens

Treatment regimens with androgens cannot be recommended, as several meta-analyses have failed to demonstrate any improvement in pregnancy rates or sperm parameters in men with idiopathic infertility (Jung & Seo, 2014).

Aromatase inhibitors

Aromatase inhibitors have been recommended for men with impaired sperm parameters and a low testosterone/estrogen ratio. Several small studies using letrozole or anastrozole revealed a significant increase in sperm parameters. Although these results are very promising, this kind of treatment can currently not be recommended in general due to the limited number of studies and size of study populations (Jung & Seo, 2014).

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Combined treatment regimens

Combined treatments with tamoxifen and testosterone-undecanoate, and clomiphene with vitamin E have shown beneficial effects on sperm parameters and pregnancy rates (Adamopoulos *et al.*, 2003; Ghanem *et al.*, 2010). Although these are rational approaches, these studies were rather small and have not been confirmed by others. Therefore, these treatments cannot be recommended.

Values

As indicated above, the precise selection criteria and evidence for the efficacy of medical treatment of OAT are still lacking. However, considering that many patients would prefer drug treatment instead of immediate application of ART, and most of the treatment options are not very expensive and usually well tolerated, in selected cases, some value can be given to empirically based therapy.

Remarks

We are aware of the fact that in many of the meta-analyses available, further studies based on more precise selection criteria were suggested. However, before these will be available, consideration of the recommendations discussed here can be helpful for a considerable number of couples.

SURGICAL TREATMENT OF OAT

In OAT, surgery may help to remove a cause of spermatogenic impairment (like varicocoele), to correct distal seminal tract emptying disorders (due to intraprostatic cyst or ejaculatory duct stenosis), to improve ICSI outcomes.

Varicocoele

11 Varicocoele treatment in infertile couples reporting OAT associated with palpable varicocoele can be discussed with the couple (2ØOOO)

12 We suggest only monitoring cases with subclinical varicocoele (2 ØØOO).

13 We suggest treatment for varicocoele in young males with progressive testicular failure and/or seminal deterioration (2 ØØOO).

Evidence

Correlation between varicocoele (uni- or bilateral) and OAT is controversial, due to its presence both in adult men with normal semen analysis and men with OAT (World Health Organization, 1992). Recent meta-analyses show semen quality improvement following palpable varicocoele repair (Marmar *et al.*, 2007), possibly with a higher conception rate after surgery vs. no-surgery (Agarwal *et al.*, 2007; Marmar *et al.*, 2007; Abdel-Meguid *et al.*, 2011; Baazeem *et al.*, 2011; Kroese *et al.*, 2012), and sperm DNA damage decrease (Abdelbaki *et al.*, 2017). In addition, varicocelectomy may increase total testosterone level in hypogonadal men with subfertility (Chen *et al.*, 2017).

On the contrary, no significant post-operative fertility improvement was shown in cases of OAT associated with subclinical varicocoele (Kim *et al.*, 2015).

Value

We place a high value to recommendation of avoiding treatment of subclinical varicocoele.

We place a relatively high value to the suggestion regarding varicocoele repair in case of progressive failure of testicular function documented by serial clinical examination, including semen analysis.

Remarks

The results from the RCTs available, at least before 2006, are conflicting and methodologically of poor quality, with difficulties of enrollment mainly of patients to be randomized in no treatment group. While waiting more appropriate randomized controlled trials (RCTs), the more recent meta-analyses (Abdel-Meguid *et al.*, 2011; Kroese *et al.*, 2012) support varicocoele correction in subfertile couples carefully selected according to the above-mentioned criteria. This a more correct approach than immediate application of IVF, which is more expensive and not completely risk-free for the female and the offspring. It has been discussed that the different fertility outcomes of varicocoele repair might be explained by the different degrees of testis damage correlated with the three anatomical types of varicocoele described by Coolsaet (Coolsaet, 1980).

Distal seminal tract emptying disorders

14 We suggest to investigate by transrectal US (TRUS) patients with OAT, low semen volume (unrelated to hypogonadism or obvious agenesia of deferent ducts), and/or significant semen parameters fluctuations, acidic pH, and low fructose, because they might be affected by a distal seminal tract emptying disorder (2 ØOOO).

Evidence

OAT may be sporadically associated with or caused by an intraprostatic cyst, either Wolffian (communicating with one ejaculatory duct and maybe compressing the contralateral one), or Müllerian (non-communicating, but compressing both ejaculatory ducts): it can cause a distal seminal tract voiding disorder during ejaculation. Such a voiding disorder may be also due to ejaculatory ducts stenosis, and other rarer functional anomalies.

Diagnosis is based on TRUS (comparing sonographic images after vs. before ejaculation) (Lotti *et al.*, 2012), showing seminal vesicle dilation, anechoic area inside the prostate, and/or prostatic fibrotic areas or calcifications in the presumptive site of the ejaculatory ducts (Jarow, 1996).

Transurethral endoscopic unroofing of Wolffian cyst or transurethral resection of ejaculatory ducts (TURED) may result into an improved semen quality (Schroeder-Printzen *et al.*, 2000; Netto & Epstein, 2008). Transperineal or transrectal voiding puncture and sclerosation of Müllerian cyst under sonographic control can result into OAT correction and has been shown as a safe procedure.

However, no meta-analyses or randomized prospective studies, but only retrospective studies or case reports, are available in the literature about this topic, with different views about it among androurologists.

Values

We place a relatively high value to the recommendation of studying an OAT patient with the above-mentioned semen characteristics by TRUS, to assess his distal seminal tract status.

We consider valuable the suggestion to treat non-communicating cysts by puncture and sclerosation, due to the procedure

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safety and high success rate, able to avoid subsequent recourse to ICSI.

Remarks

OAT patients with a suspected distal seminal tract emptying disorder should be referred to tertiary uro/andrological centres with adequate diagnostic and therapeutic expertise. Transurethral unroofing of communicating cysts and TURED in cases of ejaculatory duct subobstruction are procedures not completely free from complications (e.g. urinary reflux into the distal seminal ducts, and others): therefore, patients must be informed carefully about this. This is why, in the latest years, the success rates of TESE coupled with ICSI in very severe OAT cases due to partial distal seminal tract obstruction have caused largely decreased indications to all these endo-urologic procedures.

Testicular sperm extraction in selected cases of cryptozoospermia or OAT

15 Because of the missing solid evidence from randomized studies, we currently do not suggest to perform as routine TESE in OAT patients with high DNA fragmentation or patients with cryptozoospermia. However, in cases of several (2 or more) ICSI failures after the use of ejaculated spermatozoa (with uncorrectable high DFI), the option of TESE and use of testicular spermatozoa for ICSI can be considered and discussed with the couple, which should be informed that this approach is based on low-quality evidence (2 ØOOO).

Evidence

In some cases of OAT managed unsuccessfully with ICSI, an increased DNA damage was found in the spermatozoa from ejaculate. Data are emerging about a lower percentage of spermatozoa with DNA fragmentation recovered from testis by TESE or TESA compared with spermatozoa from ejaculate in these populations (Greco *et al.*, 2005; Arafa *et al.*, 2017). However, good evidence from randomized studies on clinical pregnancy rates and live birth rates is still missing (Esteves *et al.*, 2017).

In case of cryptozoospermia, based on experience showing reduced ICSI success rates when using spermatozoa from the ejaculate (Strassburger *et al.*, 2000), use of spermatozoa from TESE was reported in a retrospective study to result in higher clinical pregnancy and live birth rates (Ben-Ami *et al.*, 2013). A recent meta-analysis was not able to find any difference (Abhyankar *et al.*, 2016). EAA does not, generally, suggest to use testicular spermatozoa in preference over ejaculated spermatozoa of men with cryptozoospermia for ICSI.

Value

We place moderate value to the suggestion currently not to perform TESE in OAT patients with high DNA fragmentation or patients with cryptozoospermia.

Remarks

Randomized studies to compare ICSI outcomes in terms of clinical pregnancy and live birth rates using spermatozoa from ejaculate vs. from TESE in case of OAT with high DNA fragmentation or cryptozoospermia are still needed.

LIFESTYLE CHANGES

So far, there is insufficient evidence from real interventional studies that lifestyle changes improve male fertility. Nevertheless, the authors suggest that andrologists should counsel patients with OAT to improve their lifestyle, which will have additional health benefits.

16 We suggest that subfertile men with OAT should quit cigarette smoking to improve the chance of the couple to achieve the desired pregnancy (2 ØØOO).

17 We suggest that subfertile obese men with OAT should reduce weight to improve the chance of the couple to achieve the desired pregnancy (2 ØØOO).

18 We suggest that subfertile men with OAT should reduce alcohol consumption (if excessive) to improve the chance of the couple to achieve the desired pregnancy (2 ØØOO).

19 We do not recommend asking men with OAT to quit physical activity to improve the chance of the couple to achieve the desired pregnancy (1 ØØOO).

20 We do not recommend scrotal cooling and changes in clothing or working conditions leading to decrease scrotal heating as measures toward increasing male fertility (1 ØØOO).

Evidence

Cigarette smoking in men is associated with impairment of semen quality (Vine, 1996) and was also shown to have a negative impact on the outcome of ART (Fuentes *et al.*, 2010).

Table 2 Recommendations and levels of evidence for lifestyle changes in management of oligo-astheno-teratozoospermia

Intervention	Recommendation*	Level of evidence	Comments
Cessation of smoking	2	ØOOO	Association between smoking and impairment of semen quality is established but no evidence for improvement of semen quality after quitting smoking. Suggestion is based on other positive health effects
Weight reduction	2	ØOOO	Evidence for association between overweight/obesity and impairment of semen quality is contradicting and evidence for improvement of semen quality after weight reduction is lacking. Suggestion is based on other positive health effects and positive effect on reproductive hormone levels
Reduced alcohol intake	2	ØOOO	Evidence for association between low/moderate alcohol consumption and impairment of semen quality is debatable and evidence for improvement of semen quality after cessation is lacking. Suggestion is based on positive effect in females and for social reasons
Continuing physical activity	1	ØOOO	Continuing physical activity may have a positive impact on body weight (see above)
Scrotal cooling/changes in clothing and/or working conditions	1	ØOOO	The recommendation considers no measures for active scrotal cooling or changes in working place or clothing habits

*(1) Corresponds to 'we recommend'; (2) Corresponds to 'we suggest'.

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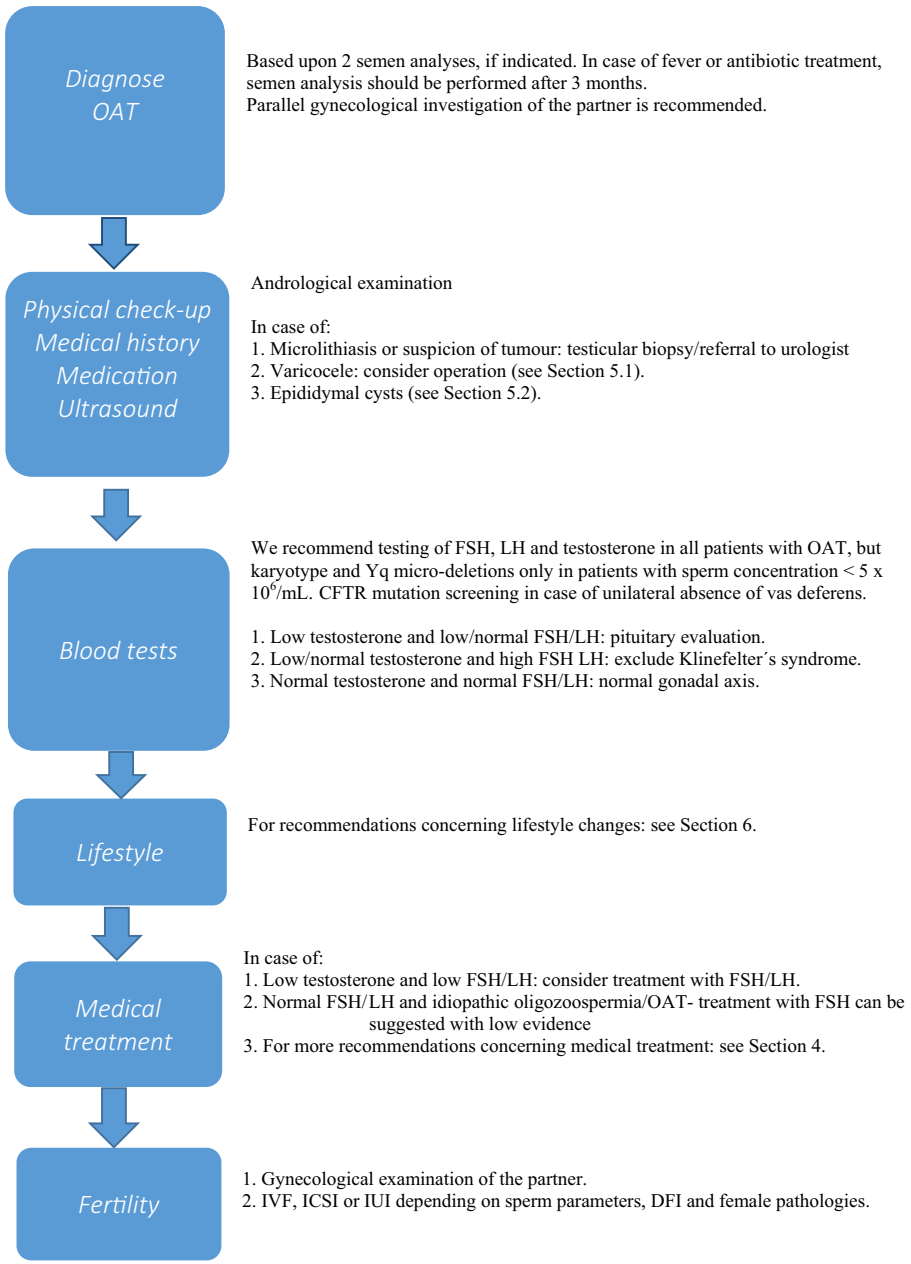
Figure 1 Flowchart for investigation and treatment for patients with oligo-astheno-teratozoospermia.



Impairment of semen quality has been reported in sons of smoking fathers (Axelsson *et al.*, 2013). However, there are no randomized studies showing that semen parameters or chance of pregnancy improves if the male partner quits smoking which has been shown for the female part. There is one case report indicating slight improvement in sperm concentration and motility in an OAT patient following 3-month smoking cessation (Santos *et al.*, 2011). Bearing in mind that cessation of smoking in one partner may facilitate similar action in the other, together with other positive health effects of being non-smoker, we think that there is sufficient evidence for recommending smoking OAT patients to quit this habit when they wish to become fathers.

The evidence regarding association between overweight and impairment of semen quality is contradicting (Sermondade *et al.*, 2013; Bandel *et al.*, 2015). There is only one, non-randomized study, indicating that weight reduction leads to improvement of semen parameters (Hakonsen *et al.*, 2011). Participants for this study were not selected due to OAT but based on their BMI and those men were severely obese (BMI > 33 kg/m^2), why nothing can be said about possible effect in less extreme cases. Recommendation of weight reduction to male partner may also have positive implications on the female—in case she also has an increased BMI. This can have an additional positive effect on the cumulative fertility of the couple. Additionally, weight loss may also improve the reproductive hormone balance (Corona *et al.*, 2013). Thus, we believe that such measure should be discussed with overweight/obese OAT men seeking for fertility problems.

The association between moderate to heavy alcohol consumption and impairment of semen parameters or fertility is

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debatable (Li *et al.*, 2011; La Vignera *et al.*, 2013; Jensen *et al.*, 2014). No randomized studies evaluating the impact of cessation or reduction of alcohol consumption and improvement of semen parameters or fertility in OAT patients or in other groups of men have been published. However, it is well known that heavy alcohol consumption may have a negative impact on male sexual performance. Due to that and for social reasons, we suggest that the issue of reduction of alcohol consumption is considered in OAT patients. It may also have a positive impact on concomitant over-consumption in the female partner, this possibly having more pronounced impact on the chance of couple of achieving pregnancy.

Association between lack of physical activity and poor semen quality has been documented (Gaskins *et al.*, 2014, 2015). It is unclear whether this is direct effect of inactivity or, perhaps, both effects are related to low testosterone levels. It has also been suggested that physical activity may lead to impairment of semen quality (Wise *et al.*, 2011), which might prompt some physicians to recommend men with fertility problems to quit/reduce physical activity. However, the available data are not consistent (Minguez-Alarcon *et al.*, 2014). Physical activity may also have a positive impact on body weight (see above). Thus, we recommend that physicians are not advising OAT patients to quit physical activity.

There are some epidemiological studies indicating an association between increased scrotal temperature due to clothing or working conditions and impairment of semen quality. However, there is not enough evidence to prove that active scrotal cooling (e.g. during night time) and/or changes in working place leading to decreased heat exposure imply improvement of semen quality and/or fertility.

Values

We place a relatively high value to recommendations which may improve the general health status of one or both partners. On the other side, we do not recommend measures which may have profound implications on the life situation of the patient and for which the evidence for positive effects is lacking.

Remarks

Unfavorable lifestyle habits (e.g. drinking and smoking) are often coincident, the reason why we recommend a holistic view when counseling the OAT patients. Additionally, it should be kept in mind that changes in lifestyle may not only have impact on semen quality and/or fertility but could also be beneficial in relation to testosterone production.

ASSISTED REPRODUCTION TECHNIQUES

21 In case other treatment options are not available or not efficient, we recommend men with OAT and their partner assisted reproduction to improve their chance of achieving pregnancy (1 ØØØØ).

Evidence

As evident from these guidelines, our possibilities to efficiently treat OAT are still rather limited. Thus, in many cases, the methods of ART will be the only efficient way of helping the couple to achieve pregnancy (Al-Inany *et al.*, 2016). This is a purely symptomatic measure not curable in relation to the underlying cause of the infertility problem.

Value

We place a significant value on investigation of both partners in the infertile couple. The age of the female partner is an important factor in decision-making. If the woman is below the age of 35 years and there are no obvious signs of non-curable serious impairment of fertility, there may be indications and time for testing some of the treatment options mentioned in these guidelines, before ART is offered to the couple. However, if the female partner is of a higher age, ART treatment should not be postponed.

Remarks

As the chance of achieving spontaneous pregnancy is dependent on the fertility of both partners, improving of the fertility of the female partner may help the couple to become pregnant even if no curable treatment can be offered to the male.

The recommendations and levels of evidence for different options of managing OAT are summarized in Table 2, as well as in Fig. 1.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Appendix S1. Supplementary material.

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