Guidelines on
Male Infertility

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Table 4: Lower reference limits (5th centiles and their 95% CIs) for semen characteristics

Parameter	Lower reference limit (range)
Semen volume (mL)	1.5 (1.4-1.7)
Total sperm number (10^6/ejaculate)	39 (33-46)
Sperm concentration (10^6/mL)	15 (12-16)
Total motility (PR + NP)	40 (38-42)
Progressive motility (PR, %)	32 (31-34)
Vitality (live spermatozoa, %)	58 (55-63)
Sperm morphology (normal forms, %)	4 (3.0-4.0)
Other consensus threshold values	
pH	> 7.2
Peroxidase-positive leukocytes (10^6/mL)	< 1.0
Optional investigations	
MAR test (motile spermatozoa with bound particles, %)	*< 50*
Immunobead test (motile spermatozoa with bound beads, %)	*< 50*
Seminal zinc (µmol/ejaculate)	*≥ 2.4*
Seminal fructose (µmol/ejaculate)	*≥ 13*
Seminal neutral glucosidase (mU/ejaculate)	*≤ 20*

CIs = confidence intervals; MAR = mixed antiglobulin reaction NP = non-progressive; PR = progressive.

2.1.1 Frequency of semen analysis

If the results of semen analysis are normal according to WHO criteria, one test is sufficient. If the results are abnormal in at least two tests, further andrological investigation is indicated. It is important to differentiate between the following:

- oligozoospermia: spermatozoa < 15 million/mL;
- asthenozoospermia: < 32% motile spermatozoa;
- teratozoospermia: < 4% normal forms.

Often, all three anomalies occur simultaneously, which is defined as OAT syndrome. As in azoospermia, in extreme cases of oligozoospermia (spermatozoa < 1 million/mL), there is an increased incidence of obstruction of the male genital tract and genetic abnormalities.

2.2 Recommendations for investigations in male infertility

Recommendations	GR
According to WHO criteria, andrological investigations are indicated if semen analysis is abnormal in at least two tests.	A
Assessment of andrological status must consider the suggestions made by WHO for the standardised investigation, diagnosis, and management of the infertile couple; this will result in implementation of evidence-based medicine in this interdisciplinary field of reproductive medicine (2).	C
Semen analysis must follow the guidelines of the WHO Laboratory Manual for the Examination and Processing of Human Semen (5th edn.) (1).	A*

**Upgraded following panel consensus*

3.5 Conclusions and recommendations for testicular deficiency

Conclusions	LE
Impaired spermatogenesis is often associated with elevated FSH concentration.	3
Spermatozoa are found in about 50% of patients with NOA.	2a
Pregnancies and live births are eventually obtained in 30-50% of couples with NOA, when spermatozoa have been found in the testicular biopsy.	3

Recommendations	GR
Men who are candidates for sperm retrieval must receive appropriate genetic counselling.	A
Testicular biopsy is the best procedure to define the histological diagnosis and possibility of finding sperm. Spermatozoa should be cryopreserved for use in ICSI.	A
For patients with NOA who have spermatozoa in their testicular biopsy, ICSI with fresh or cryopreserved spermatozoa is the only therapeutic option.	A
Men with NOA can be offered TESE with cryopreservation of the spermatozoa to be used for ICSI (28).	A
To increase the chances of positive sperm retrieval in men with NOA, TESE (single, multiple or microsurgical) should be used rather than PESA.	B

4.4.2.4 Conclusions and recommendations on clinical implications of Y microdeletions

Conclusions	**LE**
gr/gr deletion has been confirmed as a significant risk factor for impaired sperm production, whereas further evidence of the prognostic significance of gr/gr and development of a testicular germ cell tumour is needed.	2b
A son who inherits a complete AZF deletion will have abnormal spermatogenesis because these deletions have not been reported in normozoospermic men.	2a

Recommendations	**GR**
Testing for microdeletions is not necessary in men with OA (with normal FSH) when ICSI is used because spermatogenesis should be normal.	A
Men with severely damaged spermatogenesis (spermatozoa < 5 million/mL) should be advised to undergo Yq microdeletion testing for both diagnostic and prognostic purposes. Yq microdeletion also has important implications for genetic counselling (see below).	A
If complete AZFa or AZFb microdeletions are detected, micro-TESE is not necessary because it is extremely unlikely that any sperm will be found.	A
If a man with Yq microdeletion and his partner wish to proceed with ICSI, they should be advised that microdeletions will be passed to sons, but not to daughters.	A

4.10 Conclusions and recommendations for genetic disorders in male infertility

Conclusions	LE
New insights into the genetic basis of infertility and the advent of ICSI require a good understanding of genetics by clinicians and the general public.	3
Diagnostic advances will allow us to identify the genetic basis of more disorders and diagnose known disorders at a lower cost. For some of these disorders, gene therapy might be practical in the future.	2a

Recommendations	GR
Standard karyotype analysis should be offered to all men with damaged spermatogenesis (spermatozoa < 10 million/mL) who are seeking fertility treatment by IVF.	B
Genetic counselling is mandatory in couples with a genetic abnormality found in clinical or genetic investigation and in patients who carry a (potential) inheritable disease.	A
All men with Klinefelter's syndrome need long-term endocrine follow-up and may require androgen replacement therapy.	A
For men with severely damaged spermatogenesis (spermatozoa < 5 million/mL), testing for Yq microdeletions is strongly advised.	A
When a man has structural abnormalities of the vas deferens (unilateral or bilateral absence), he and his partner should be tested for CF gene mutations.	A

9. IDIOPATHIC MALE INFERTILITY

9.1 Introduction

No demonstrable cause of infertility is found in at least 44% of infertile men (1).

9.2 Empirical treatments

A wide variety of empirical drug treatments of idiopathic male infertility have been used; however, there is little scientific evidence for an empirical approach (2). Androgens, hCG/HMG, bromocriptine, alpha-blockers, systemic corticosteroids and magnesium supplementation are not effective in the treatment of OAT syndrome. Follicle-stimulating hormone (3) might be beneficial in a selection of patients (3). A Cochrane analysis showed that men taking oral antioxidants had an associated significant increase in live birth rate (pooled OR = 4.85; 95% CI: 1.92-12.24; P = 0.0008; I(2) = 0%) when compared with men taking the control treatment. No studies have reported harmful side effects from antioxidant therapy. The evidence suggests that antioxidant supplementation in subfertile men may improve the outcomes of live birth and pregnancy rate for subfertile couples undergoing assisted reproduction technique (ART) cycles. Further head-to-head comparisons are necessary to identify the superiority of one antioxidant over another (4).

Recommendation	GR
Medical treatment of male infertility is recommended only for cases of hypogonadotrophic hypogonadism.	A