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Author(s)	Lee, VCY; Ng, EHY; Ho, PC
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1 Point

Male Infertility

VCY Lee, MRCOG, FHKAM(OG); EHY Ng, MD, FRCOG; PC Ho, MD, FRCOG

EPIDEMIOLOGY

Infertility generally affects one in seven couples and is a growing problem worldwide.[1,2] This is illustrated by the increase in the number of assisted reproductive technology (ART) treatment cycles worldwide in 2009–2010, ranging from an increase of 5.9% to over 100%.[3–5] Male subfertility is one of the major causes, as a sole factor accounting for 29.7% and as a contributor for another 10.3–29.7% in the United Kingdom and Hong Kong.[3,5] There is some evidence suggesting that there might be a decline in semen concentration of men born in the 1930's to 1980's.[6–8]

DEFINITION

In the investigation of an infertile couple, semen analysis has all along been performed for the assessment of the fertility status of the male partner. The World Health Organization manual for examination and processing of human semen has been recognized as the global standard for semen analysis. The most recent World Health Organization manual for semen analysis was published in 2010 and set the lower 'reference' limits of semen parameters according to the fifth centile of men, whose partners had a time-to-pregnancy of 12 months or less, worldwide (Tables 1 and 2).[9] Therefore, men with semen parameters below the lower reference limits (other than those with azoospermia) are not necessarily infertile. It is recommended that semen samples should be collected by masturbation after 2–7 days of sexual abstinence without the use of lubricants. The process of analysis should be carried out within 1 hour of collection, and two or more samples are required especially for abnormal results.

AETIOLOGY

The aetiology of male infertility can be classified as pre-testicular, testicular, and post-testicular (Table 3).[10,11] The management of male infertility should be based on the aetiology if it is known. However, the exact aetiology is often not known.

Pre-testicular causes include hypogonadotrophic hypogonadism due to Kallmann syndrome (with anosmia), brain tumours, radiotherapy for brain tumours, gene mutations (such as luteinizing hormone receptor mutation), and idiopathic hypogonadotrophic hypogonadism. Post-testicular causes are mostly obstructive, which include iatrogenic obstruction (vasectomy), congenital bilateral absence of the vas deferens (CBAVD), and post-inflammation or infection. Testicular causes include genetic causes, infection, systemic diseases, and trauma. Coital dysfunction in the form of erectile and ejaculatory dysfunction is another possible cause of infertility. Retrograde ejaculation can be due to anatomical causes including bladder neck surgery and posterior urethral valves, neurogenic causes including diabetes mellitus and spinal cord injury, and drug-induced like alpha-receptor blockers and antipsychotics.[12]

The exact aetiology of male infertility is often not known.

CLINICAL WORKUPS

History and Physical Examinations

When infertile couples first attend the

infertility clinic, semen analysis reports should preferably be available for review. A detailed clinical history and clinical examination of the men should be conducted, and further investigations would be dependent on the severity of abnormal parameters. Clinical history includes history of torsion, trauma and infection/inflammation of the testicles (which may damage the testis), drug history like chemotherapy/radiotherapy, surgical history such as orchidopexy for cryptorchidism, and social history especially smoking history, sauna habit and occupation. Physical examination should include the size and consistency of the testes (which are indicators for testicular function), any distension of the epididymis (which may indicate obstructive causes), and the absence of vas deferens (which is indicative of CBAVD).

Table 1. Semen parameters according to the World Health Organization (2010)

Parameter	Lower reference limits (95% confidence interval)
Semen volume, mL	1.5 (1.4–1.7)
Total sperm number, × 10^6 per ejaculate	39 (33–46)
Sperm concentration, × 10^6/mL)	15 (12–16)
PR, %	32 (31–34)
Total motility (PR + NP), %	40 (38–42)
Sperm morphology (normal forms), %	4 (3.0–4.0)
Vitality (live spermatozoa), %	58 (55–63)

NP = non-progressive motility; PR = progressive motility.

Table 2. Nomenclatures of abnormal semen parameters according to the World Health Organization (2010)

Oligozoospermia	Sperm concentration < 15 × 10^6/mL or total sperm count < 39 × 10^6/mL
Asthenozoospermia	< 32% progressive motility or < 40% total motility
Teratozoospermia	Normal sperm morphology < 4%
Azoospermia	No spermatozoa found in ejaculate
Cryptozoospermia	Spermatozoa absent from fresh preparations but observed in a centrifuged pellet
Aspermia	Absence of ejaculate (either no ejaculate or retrograde ejaculation)

Any combinations of oligozoospermia, asthenozoospermia and teratooospermia mean the combination of abnormal parameters shown in semen analysis.

Genetic Tests

Genetic tests, including karyotype and Y chromosome microdeletion test, should be arranged if there is severe oligozoospermia or azoospermia. Karyotype abnormality and Y microdeletion account for about 15–21% and 8.5–10% of non-obstructive azoospermia (NOA), respectively.[10,13] Klinefelter syndrome (KS), including 80% non-mosaic type and 20% mosaic type, is the major cause of karyotype abnormality.[14] Most Y chromosome microdeletions occur on the long arm (q) and are subdivided into three azoospermia factor (AZF) regions: AZFa, AZFb, and AZFc.[15] There is evidence that the prevalence of karyotype anomalies and AZF deletions increases with decrease in semen concentrations. The prevalence of karyotype anomalies in oligozoospermic men with semen concentration below 5 million/mL is 8%, which increases to 15% in azoospermic men, while the prevalence of AZF deletion also increases from 5% to 10%.[10] Based on the prevalence of abnormalities of karyotype and Y microdeletion in 295 oligozoospermic or azoospermic men from Hong Kong with different sperm concentrations,[13] we recommend performing a karyotype and Y microdeletion test only if the semen concentration is below 2 million/mL.

Screening for cystic fibrosis genetic mutation should be done in men with CBAVD. The prevalence of cystic fibrosis transmembrane conductance regulator (CFTR) gene in Caucasian men with CBAVD is high, ranging from 71% to 87% in different Western countries,[16,17] and it warrants proper testing followed by screening of the female partner if a mutation is present. However, the prevalence of cystic fibrosis and the carrier rate of *CFTR* gene mutation in the Chinese population are very low. As

the main aim of genetic testing is to avoid full-blown cystic fibrosis in the offspring by prenatal diagnosis or preimplantation genetic diagnosis if the partner is also a carrier of the mutation, the tests for the mutation would not be necessary in the Chinese.

Hormonal Tests

Hormonal tests, including those for follicle-stimulating hormone (FSH) and testosterone, should be considered in azoospermic men. High gonadotrophin and normal/low testosterone levels (hypergonadotrophic hypogonadism) indicate gonadal failure, and low gonadotrophin and low testosterone levels indicate hypogonadotrophic hypogonadism. Hormonal tests are likely to be normal in azoospermia of obstructive aetiology. The treatment would be completely different. However, there is controversy over the use of hormonal levels and other factors like inhibin B and anti-mullerian hormone to predict the success in surgical retrieval of sperm in men with gonadal failure, and there is no consensus on the cut-off value of these tests in the prediction.[18–21] The association of hyperprolactinaemia with or without pituitary adenoma and male infertility is not clearly defined, yet hypogonadism caused by hyperprolactinaemia (resulting in erectile dysfunction) may be a contributing factor.[22] Dopamine agonists, such as bromocriptine, can normalize the prolactin level. However, they would not improve the infertility problem in terms of hormonal profiles, semen parameters and pregnancy outcome in hyperprolactinaemic patients or idiopathic infertile men.[22,23]

Table 3. Aetiology of male infertility

Pre-testicular causes

- Idiopathic (~50%) (idiopathic hypogonadotrophic hypogonadism)
- Hypothalamic-pituitary-gonadal axis problems (Kallmann syndrome; gene mutations, eg, luteinizing hormone receptor mutation; brain abnormality, eg, pituitary tumour)

Testicular causes

- Congenital including anorchia and cryptorchidism
- Genetic diseases (chromosomal including Klinefelter syndrome and balanced translocation; Y microdeletion)
- Infection/inflammation (eg, tuberculosis, prostatitis)
- Systemic diseases or medical therapy including chemotherapy and radiotherapy
- Trauma to testicles or torsion
- Varicocele

Post-testicular causes

- Congenital bilateral absence of the vas deferens (with or without cystic fibrosis mutation)
- Iatrogenic (post-vasectomy)
- Post-inflammation (epididymitis)

Coital dysfunction

- Erectile or ejaculatory problem
- Retrograde ejaculation (anatomical causes, eg, surgery to prostate and bladder neck, and posterior urethral valves; neurogenic causes, eg, diabetes mellitus and spinal cord injury; drug-induced, eg, alpha receptor blockers for benign prostate hyperplasia and antipsychotics)

Miscellaneous

Transrectal ultrasound scanning is used to confirm the diagnosis of obstructive causes and also to delineate the extent of obstruction to see if reconstructive surgery is feasible.[24]

Tests on sperm DNA integrity and fragmentation are some of the most controversial investigations in male infertility. It has been shown that fertilization and subsequent embryo development depend in part on the inherent integrity of the sperm DNA, and there seems to be a threshold of sperm DNA damage in terms of DNA fragmentation, abnormal chromatin packaging and protamine deficiency

resulting in impaired embryo development.[25,26] The American Society for Reproductive Medicine recommends that there is no proven role for routine DNA integrity testing as the results do not predict pregnancy outcomes in spontaneous conception and ART treatment cycles and there is no effective treatment available for abnormal DNA integrity.[27] Therefore, tests for DNA fragmentation should not be used routinely for infertility investigations.

TREATMENT

Treatment would depend on the aetiology of the male factor, the severity of abnormalities in semen parameters, and the presence of female factors such tubal status and woman's age. In men with mildly abnormal semen parameters to severe oligoasthenoteratozoospermia, intrauterine insemination (IUI) and *in vitro* fertilization (IVF) with or without intracytoplasmic sperm injection (ICSI) can improve the pregnancy rate. In men with azoospermia, treatment would be dependent on the underlying reasons. The algorithm is shown in Figure 1.

Azoospermia

Azoospermia can be classified as NOA and obstructive azoospermia (OA). NOA can further be classified as due to gonadal failure or hypogonadotrophic hypogonadism. Surgical retrieval of sperm is the treatment for OA and gonadal failure. There are different techniques including percutaneous epididymal sperm aspiration (PESA), microsurgical epididymal sperm aspiration (MESA), testicular sperm aspiration (TESA)/testicular sperm extraction (TESE), and microscopic or microdissection testicular sperm extraction (mTESE).

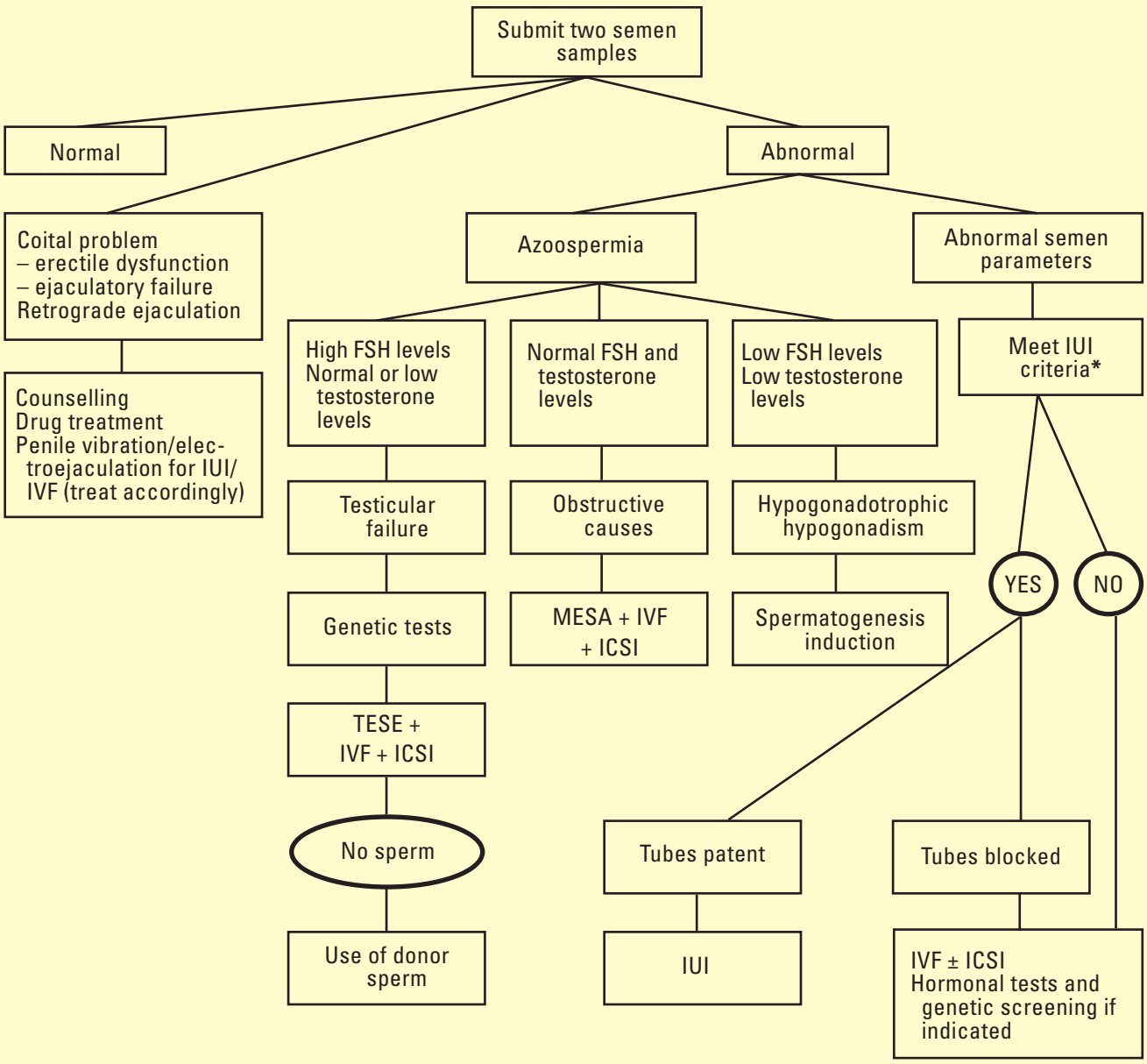
Obstructive azoospermia. PESA and MESA are used in OA to retrieve epididymal sperm from distended tubules in the epididymis. PESA can be done under local anaesthesia. It involves percutaneous puncture of the scrotal skin into the epididymis using a fine needle (eg, 26-gauge), and aspiration can be repeated in multiple sites.[28] MESA involves an open operation under an operating microscopy and is able to retrieve greater number of sperm and minimize contamination of the sample with blood. Some urologists advocate MESA over PESA in patients with OA who would consider more than one IVF cycle, as MESA typically results in sperm with adequate motility for effective cryopreservation for multiple treatment cycles.[29] There is so far no direct comparison between MESA and PESA. A Cochrane review commented that there is only scarce evidence on the choice of surgical technique in sperm retrieval.[30] So, the choice of surgical technique would mainly depend on personal preference and surgical expertise. If no sperm is obtained from the epididymis, direct retrieval of sperm from the testicles can be performed in the same setting.[28] MESA can be combined with reconstructive surgery in selected cases.[31]

NOA – gonadal failure. Surgical retrieval of testicular sperm is the mainstay of treatment for hypergonadotrophic hypogonadism. TESE/TESA involves retrieval of sperm directly from the testicles using different techniques. mTESE requires an operation under microscopy and helps in visualization of the larger, more opaque, whitish tubules, presumably containing more intratubular germ cells with active spermatogenesis. A higher retrieval rate was reported with mTESE than with conventional TESE.[32,33] The successful retrieval rate in NOA patients is typically quoted as less than 50%, although a higher retrieval rate may be possible with mTESE.

The use of TESE or mTESE, together with ICSI in IVF treatment cycles, is the only option for KS men to bear their own genetically linked children, and the success rate of surgical retrieval of sperm was reported to be similar with other NOA men with no karyotype abnormality.[34,35] One group reported a higher retrieval rate of 68% and 72% in KS men using mTESE or conventional TESE, respectively.[36,37] Not only is karyotype abnormality a predictor of the success of retrieval, the presence of AZF microdeletions on the Y chromosome is also a good predictor. Men with AZFc microdeletions alone have a similar success rate of surgical sperm retrieval on TESE, while those with AZFa or AZFb microdeletions will almost definitely have no sperm retrieved for ICSI.[15,38] Therefore, genetic tests would be extremely useful in counselling before the surgical retrieval of sperm and for examining the inheritance of the mutation in the next generation.

NOA – hypogonadotrophic hypogonadism. Induction of spermatogenesis with pulsatile gonadotrophin-releasing hormone (GnRH) or gonadotrophins, ie, human chorionic gonadotrophin (hCG) or FSH, is the treatment of choice for men with hypogonadotrophic hypogonadism.[39] Both treatments have been shown to in-

Figure 1. Algorithm



FSH = follicle-stimulating hormone; ICSI = intracytoplasmic sperm injection; IUI = intrauterine insemination; IVF = *in vitro* fertilization; MESA = microsurgical epididymal sperm aspiration; TESE = testicular sperm extraction.

duce spermatogenesis successfully.[39–41] Although some investigators showed that the use of pulsatile GnRH was related to a greater testicular growth and faster induction of spermatogenesis, the 'take-off' for this kind of treatment is limited by the high cost of the drug and the difficulty in handling the pump system. The high success rate of gonadotrophins, ranging from 53% to 78%, implies that it is the treatment of choice in some localities.[42,43] The usual recommended treatment consists of twice weekly injection of hCG 1,500 IU to 2,000 IU, with further dosage increment after review of the hormonal levels in 4 to 6 weeks' time. In men suffering from hypogonadotrophic hypogonadism after puberty, hCG alone is usually sufficient

for induction of spermatogenesis, with the median sperm count of 8 million/mL, when their partners get pregnant.[43] Whereas in men suffering prepubertal hypogonadism, the treatment usually requires FSH together with hCG injection in order to induce spermatogenesis.[42,43] Prior androgen administration was shown to be related to a slower induction of spermatogenesis. The average treatment duration may be up to 25 to 30 months before the men can impregnate their partners.[43]

Abnormal Semen Parameters

The treatment would be dependent on the severity of abnormal semen parameters, after taking into consideration the woman's age and tubal status. IUI and IVF can be offered.

Artificial insemination using husband's semen may be performed with intravaginal insemination, intracervical insemination, or IUI. IUI is currently the most commonly performed method in the management of male infertility. It is used in men with 2–5 million total motile spermatozoa after processing. The criteria differ in various clinics, with the lowest threshold of 1 million total motile spermatozoa in the inseminate.[44] Sperm morphology (strict criteria) seems to be predictive of the success rate of IUI, with a significantly higher pregnancy rate when the morphology is ≥ 4%.[45] However, different centres should have their own criteria for recruitment for IUI. There is contradicting evidence on the protocol of IUI. It was suggested that IUI has no significant benefit over timed intercourse and ovarian stimulation does not improve the outcome.[46] However, it was shown that gonadotrophin for ovarian stimulation offers a significantly better pregnancy outcome than does anti-oestrogen, while there was no difference between anti-oestrogen and aromatase inhibitor. There was also no benefit in using either GnRH agonist or antagonist in IUI in terms of pregnancy rate. Low-dose gonadotrophin was suggested, as doubling the dose would only increase the complication rate, namely multiple pregnancy rate and ovarian hyperstimulation syndrome, but not the pregnancy rate.[47] As there is no robust evidence, further properly designed trials are needed to confirm the present suggestions.

***In vitro* fertilization** consists of follicular development with various ovarian stimulation protocols, oocyte retrieval, fertilization inside laboratory environment, and transfer of embryos to the uterine cavity. Since the first report of the use of ICSI in human that resulted in a pregnancy, ICSI has become the routine practice for severe male infertility.[48] ICSI is the procedure of injecting a single sperm directly into an oocyte. Although sperm morphology was reported to be more relevant to fertilization failure,[49] the prediction of fertilization failure by morphology or other parameters is still poor[50] and so different centres have their own set of criteria for using ICSI. The development after fertilization including the blastulation rate was shown to be not affected by sperm morphology.[51] A study showed that the use of ICSI in non-male infertility was associated with a lower implantation rate when compared with conventional insemination[52]; thus, ICSI should be reserved for severe male factor infertility. As shown by a recent review, there is a slight increase in *de novo* chromosomal abnormalities and the major congenital malformation rate is similar for IVF and ICSI (~3–4%).[53]

Miscellaneous therapies. ***(a) Antioxidant.*** There is evidence suggesting that reactive oxygen species (ROS)-mediated damage to sperm is a significant contributing pathology in 30–80% of male factor infertility. There are two principal mechanisms of ROS-related infertility. Firstly, ROS damage the sperm membrane, impairing the sperm's motility and ability to fuse with the oocyte. Secondly, ROS causes sperm DNA damage, compromising the paternal genomic contribution to the embryo.[54] Raised ROS levels are usually associated with smoking, genital tract or systemic infections, and varicocele.[55,56] It has been shown that embryos formed from fertilization with sperm having high DNA damage are of poorer quality and have a decreased cleavage rate.[57]

As antioxidants (namely vitamins C and E, folate, zinc, selenium, carnitine, and carotenoids) are scavengers of ROS, they have been studied in male factor infertility. A Cochrane review indicated that the use of antioxidants, such as vitamin C and zinc, may improve the pregnancy outcome in ART cycles based on evidence from small randomized trials, and larger trials are needed to confirm the results.[58] There is also evidence of improvement of sperm parameters and spontaneous conceptions. However, the trials were all small and had significant methodological and clinical heterogeneity. Drawing a conclusion from these trials may not be appropriate,[59] and so antioxidants should not be recommended routinely.

(b) Treatment of varicocele. There is a hot controversy on the effectiveness of varicocele treatment (including surgical and radiological methods) on semen parameters and pregnancy outcomes. Some investigators reported no improvement[60,61] while others showed significant improvement in spontaneous conceptions.[62–64] According to the recommendation of the American Society for Reproductive Medicine, treatment of varicocele should be considered if all of the following conditions are met: (1) the varicocele is palpable on physical examination of the scrotum; (2) the couple has known infertility; (3) the female partner has normal fertility or a potentially treatable cause of infertility; and (4) the male partner has abnormal semen parameters or abnormal results from sperm function tests. Moreover, it explicitly expressed that varicocele treatment for infertility is not indicated in patients with normal semen qualities and a subclinical varicocele.[65] As some trials included men with subclinical varicocele, the outcome in men with clinical varicocele would be difficult to interpret. Nevertheless, the evidences come from the comparison between expectant management and varicocele treatment in spontaneous conception while there is no evidence of the effectiveness in ART cycles including IUI and IVF cycles. Different surgical approaches were compared in one randomized trial, which revealed that subinguinal microsurgical varicocelectomy had better outcomes than open inguinal and laparoscopic varicocelectomy.[66]

(c) Lifestyle modification. Tobacco smoking is associated with male factor infertility, probably related to the increase in ROS and DNA damage. There are many studies showing poorer semen quality in smokers compared with non-smoking counterparts.[67,68] However, there is no evidence showing that quitting smoking may improve semen parameters.[67] Nonetheless, smoking has been shown to reduce significantly the pregnancy rate in IVF treatment cycles.[69] It would be sensible to advise both partners to quit smoking before commencement of treatment cycles, not only for the ART cycles but also for their general health.

Coital Dysfunction

Psychosexual counselling is the mainstay of treatment for coital dysfunction. The use of phosphodiesterase inhibitors, such as sildenafil and vardenafil, should be considered in men with erectile dysfunction after excluding contraindications.[70] If these first-line treatment methods fail, intra-penile injections, vacuum constriction devices and implantation of a penile prosthesis for the treatment of their erectile dysfunction can be considered.[71] If the couple fails to conceive naturally after these measures or if the semen quality is not good, ART like IUI or IVF may also help.

For retrograde ejaculation, treatment of the underlying causes is needed. Drug treatment is the first-line treatment, including alpha agonistic drugs and parasympathomimetics. If the drug therapy fails, penile electrovibration stimulation and sperm retrieval from the urine with oral sodium bicarbonate a few hours before collection of urine can be offered.[12]

Other Options

In men who have NOA and no sperm retrieved from surgery, or men with AZFa or AZFb deletion, use of donor sperm should be counselled. Couples should be fully counselled on the implications of the use of donor gametes. The couple also needs to understand the regulation of the law and the code of practice in different countries and regions, like the Human Fertilisation and Embryology Authority in the United Kingdom and the Council on Human Reproductive Technology in Hong Kong. Adoption and childlessness are the other two options.

CONCLUSION

Semen analysis is the most common method for assessment of fertility status of the male partner, although its prognostic value is limited except in the case of azoospermia. The management of male infertility should be based on the aetiology if it is known. For male infertility with unknown cause, empirical treatment methods such as IUI, IVF and ICSI can be offered. The development of these methods offers hope for couples suffering from male infertility, even for those with severe sperm problems or azoospermia.

About the Authors

Dr Lee is Associate Consultant, Dr Ng is Clinical Associate Professor, and Dr Ho is Professor and Chair of Obstetrics and Gynaecology, in the Department of Obstetrics and Gynaecology, Queen Mary Hospital, The University of Hong Kong, Hong Kong SAR.

A complete list of references can be obtained upon request to the editor.

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CME Article 1 Point

Male Infertility

Answer True or False to the questions below.

	True	False
1. Male factor infertility accounts for 10% of subfertility problems.	○	○
2. Klinefelter syndrome is a major chromosomal abnormality found in patients with non-obstructive azoospermia.	○	○
3. Tests for *CFTR* gene mutation should not be offered to men with congenital bilateral absence of the vas deferens in various Caucasian populations.	○	○
4. Tests for Y chromosome microdeletion in the AZF region have prognostic value in the success of surgical retrieval of sperm.	○	○
5. Bromocriptine can improve semen parameters and pregnancy outcomes in men with hyperprolactinaemia.	○	○
6. Tests for DNA fragmentation should not be used routinely in the investigation of infertility.	○	○
7. Non-obstructive azoospermia can be classified as due to gonadal failure or hypogonadotrophic hypogonadism.	○	○
8. Induction of spermatogenesis with pulsatile gonadotrophin-releasing hormone (GnRH) or gonadotrophins is the treatment of choice for men with hypogonadotrophic hypogonadism.	○	○
9. The use of GnRH antagonists in intrauterine insemination cycles can improve the pregnancy rate.	○	○
10. Antioxidant treatment can clearly improve the sperm parameters.	○	○

Name in BLOCK CAPITALS: _____

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Answers

1	2	3	4	5	6	7	8	9	10
T	F	T	F	F	F	T	F	F	F