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# Andrology

## Reproductive years and beyond

### Background

In recent years, significant advances have been made in our knowledge of the role of testosterone in male fertility and sexual function. In addition, new microsurgical techniques have improved outcomes in testicular biopsy for sperm retrieval, varicocele treatment and vasectomy reversal.

### Objective

This article provides an update on the assessment and treatment of male infertility, and the role of testosterone replacement therapy and erectile dysfunction.

### Discussion

The evaluation of male infertility requires comprehensive history taking and a focused examination. Investigations that help form the basis for important treatment decisions include semen analysis and hormone testing. Further specialist assessment may be required to determine the need for genetic testing.

There is increased evidence for the role of microsurgery in sperm retrieval, varicolectomy and vasectomy reversal in men seeking paternity.

Testosterone plays a role in both spermatogenesis and sexual functioning in a man. While testosterone replacement therapy can restore erections in androgen deficient men and treat other conditions related to hypogonadism, it can also result in male infertility.

### Keywords

infertility/male; physical examination; diagnostic techniques



Patients affected by infertility frequently present to a range of medical and surgical specialties including general practice, urology, gynaecology and reproductive endocrinology.

In recent years, significant advances in our knowledge of the role of testosterone in male infertility and sexual function have been made. This article provides a timely review of male infertility treatments, the role of testosterone replacement and erectile dysfunction.

### Prevalence

Approximately 15% of couples are unable to conceive after 1 year of unprotected intercourse. A male factor is solely responsible for about 20% of these and contributory in another 30–40%.<sup>1,2</sup> Male infertility can result from a range of conditions (*Table 1*), but in 30–40% of cases no causative factor can be found (idiopathic male infertility).

### Evaluation of male infertility

While it is acceptable to allow at least 1 year for a couple to try to conceive naturally, the evaluation of male infertility should be performed earlier if male infertility risk factors exist (eg. a history of bilateral cryptorchidism) or if concerns are raised by the couple about the man's fertility.<sup>2</sup> The evaluation of male infertility should begin with a thorough history of:

- previous fertility
- sexual history (sexual desire, erection and/or ejaculation dysfunction, intercourse)
- developmental history
- risk factors for testicular dysfunction
  - family history of cryptorchidism
  - previous surgery (genitourinary or pelvic)
  - genitourinary infection
  - gonadal toxin exposure (eg. pesticides, illicit drug use and chemotherapy).

### Physical evaluation

Physical examination should focus on:

- evaluation of secondary male sexual characteristics including hair distribution and the presence of breast enlargement
- presence of surgical scars (abdominal, inguinal or genital)
- penile examination, including the location of the urethral meatus
- testicular examination – size based on orchidometer, shape and



consistency, presence of vasa and epidymides, presence of a varicocele.

Digital rectal examination for cystic dilatation of seminal vesicles or prostatic cyst is required in some cases and may be best performed by a specialist in the area of infertility.

## Investigations

Basic investigations in a suspected infertile man should include two semen analysis samples, endocrine and, in some cases, genetic testing (*Table 2*).<sup>2-4</sup> New World Health Organization semen analysis parameters are described in *Table 3*.<sup>3</sup>

The analysis of sperm DNA damage, as an indicator of sperm quality, remains experimental and controversial.<sup>4</sup>

Based on testicular examination and semen analysis, the azoospermic individual can be classified as having obstructive (usually absent/low volume) or nonobstructive (usually normal volume) azoospermia. Nonobstructive azoospermia is characterised by abnormal testicular histology. The presence of normal semen volume, fructose in semen and an alkaline pH indicates that seminal vesicles are present and localises the obstruction to a site proximal to the junction of the vas deferens and seminal vesicles. The presence of any mature sperm in the semen excludes the possibility of complete absence of spermatogenesis.

The initial endocrine evaluation should include serum testosterone, follicle stimulating hormone (FSH) and luteinising hormone (LH) levels. An FSH >7.6 IU/L and testicular length <4.5 cm predicts the presence of nonobstructive azoospermia (NOA), with greater than 89% probability in azoospermic men.<sup>5</sup> Genetic screening for male infertility such as chromosomal karyotyping, Y chromosome microdeletion and cystic fibrosis transmembrane regulator (CFTR) gene mutation is indicated in specific cases only and should be organised by an in vitro fertilisation (IVF) specialist. Scrotal ultrasonography is indicated when physical examination of the scrotum is difficult or inadequate, or when a testicular mass is suspected. Urinary tract ultrasound should be offered to any man with unilateral or bilateral vasal agenesis to exclude coexisting renal anomalies. Transrectal ultrasound can diagnose ejaculatory duct obstruction or an obstructing Müllerian or ejaculatory cyst.

## The role of microsurgery in male infertility

Since the introduction of intra-cytoplasmic sperm injection (ICSI), testicular biopsy is performed for therapeutic and diagnostic purposes. Results of a single random biopsy of one testis may not be indicative of the spermatogenic process in the remainder of that testis or the contralateral testis.<sup>6</sup> Microdissection testicular exploration and sperm extraction (TESE) is a microscopic surgical sperm retrieval technique that allows for more testicular tissue preservation and has a higher rate of sperm retrieval than conventional testicular biopsy. This technique should be considered the gold standard for sperm retrieval irrespective of previous histology or previous unsuccessful surgery.<sup>7</sup> Unfortunately, microdissection TESE is highly specialised,

**Table 1. Reasons for male infertility**

- Congenital factors – cryptorchism and testicular dysgenesis, congenital absence of vas deferens
- Acquired urogenital abnormalities – obstruction, testicular torsion, testicular tumour
- Urogenital infections, including sexually transmissible infections
- Varicocele
- Endocrine disturbances
- Genetic abnormalities (eg. Klinefelter syndrome, cystic fibrosis)
- Systemic diseases
- Gonadal toxins, including medications, toxins, radiation, lifestyle factors
- Idiopathic (30–40% of men)

**Table 2. Investigations in male infertility**

### Semen analysis

- Minimum two samples
- Perform at least 1 month apart
- Abstain from sexual activity for 2–3 days before collection
- Semen can be collected by masturbation or intercourse using a special sterile semen collection condom (nonspermicidal) or jar
- If sperm collection takes place outside of the laboratory, the specimen should be kept at room or body temperature during transport to the laboratory
- Sample examination within 1 hour of collection

### Blood tests

- Follicle stimulating hormone and testosterone levels
- Chromosomal karyotyping, Y chromosome microdeletion and CFTR gene mutation in selected cases

### Ultrasound

- Scrotal ultrasound if suspect varicocele
- Renal tract ultrasound to exclude renal anomalies if congenital bilateral absence of vas deferens suspected
- Transrectal ultrasound if ejaculatory duct obstruction is suspected

time consuming and requires the presence of a laboratory scientist for sperm preparation following sperm retrieval.

Varicocele – defined as abnormally dilated scrotal veins – is the commonest reversible male infertility factor.<sup>8</sup> Significant evidence suggests that clinical varicocele has a harmful effect on the testis and that varicocelectomy can not only prevent progressive decline in testicular function but also reverse the damage. Recent meta-analysis concluded that microsurgical varicocelectomy is associated with significant improvement in all semen parameters (concentration, motility and morphology) and has the highest spontaneous pregnancy



**Table 3. WHO lower reference limits (5th centiles and their 95% confidence intervals) for semen characteristics<sup>3</sup>**

Parameter	Lower reference limit
Semen volume (mL)	1.5 (1.4–1.7)
Total sperm number (10 <sup>6</sup> /ejaculate)	39 (33–46)
Sperm concentration (10 <sup>6</sup> /mL)	15 (12–16)
Total motility (PR+NR [nonprogressive motility], %)	40 (38–42)
Progressive motility (PR, %)	32 (31–34)
Vitality (live spermatozoa, %)	58 (55–63)
Sperm morphology (normal forms, %)	4 (3–4)
<b>Other consensus threshold values</b>	
pH	≥7.2
Peroxidase positive leukocytes (10 <sup>6</sup> /mL)	<1.0
Mixed antiglobulin reaction (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 (µmol/ejaculate)	≥20

rates and lowest complication rates when compared to other modalities of varicocele treatment.<sup>9</sup> Cost effectiveness analysis showed that primary treatment with varicocelectomy was more cost effective than sperm retrieval/ICSI.<sup>10</sup> Even though spontaneous pregnancy remains the ultimate standard for evaluating the success of varicocele treatment, the improvements in semen parameters may allow for some couples to proceed with intrauterine insemination (IUI) before more advanced assisted reproductive technologies.<sup>11</sup>

Microsurgical vasectomy reversal is a cost effective, reliable and effective means of restoring fertility, and has been shown to have higher spontaneous pregnancy rates than ICSI/IVF when there are no other male or female infertility factors.<sup>12,13</sup> Unfortunately, the current data comparing vasectomy reversal and sperm retrieval/ICSI/IVF are neither randomised nor homogenous<sup>12,13</sup> and presently there is increased use of ICSI as opposed to microsurgical vasectomy reversal among many men seeking paternity. This could be due to a number of factors including lack of microsurgery expertise in some areas, misperception and reluctance for referral by some IVF gynaecologists, differential Medicare rebates for microsurgery, reluctance of men to undergo the surgery, increasing female age and the perceived urgency for conception using IVF.

### Testosterone, male fertility and contraception

Testosterone is essential to maintain spermatogenesis and male fertility. However, exogenous testosterone suppresses the secretion of the pituitary gonadotropins, decreases endogenous testosterone secretion from the testis and deprives developing sperm of the signals required for normal maturation. This can result in a decline

in sperm production and male infertility. Whether or not endogenous testosterone levels and/or spermatogenesis recover if exogenous testosterone use is ceased, remains uncertain.

Various male contraceptive regimens, either testosterone alone or in combination with a progestin, have been developed<sup>14</sup> and studies show that after 2–3 months of treatment, low levels of pituitary gonadotropins lead to markedly decreased sperm counts and effective contraception in the majority of men.<sup>15</sup> While these novel contraceptive methods for men show promise, there are currently no commercially available male hormonal contraceptives due to variable efficacy and poor side effect profiles.

### Erectile dysfunction and male hypogonadism

Erectile dysfunction (ED), low testosterone levels and metabolic and cardiovascular disease are recognised as being closely linked<sup>16</sup> and a clear negative relationship exists between the presence of risk factors for metabolic syndrome and levels of circulating testosterone in patients with ED.<sup>16,17</sup> The current literature indicates that testosterone controls (either directly or indirectly) several mechanisms that lead to penile erection. These include promoting the commitment of penile stem cells to a smooth muscle phenotype and regulation of the formation of nitric oxide and expression of phosphodiesterase type 5.<sup>17</sup>

Male hypogonadism is defined as the failure to maintain adequate testosterone levels and/or sperm production. The diagnosis of primary and secondary hypogonadism is based on the levels of gonadotropins (LH and FSH), testosterone and/or sperm levels. Studies have shown that hypogonadal men restored to the eugonadal state with testosterone replacement therapy (TRT) may experience a general improvement in



sexual function (particularly ejaculation, orgasm and penile sensations) improved erections and restored or enhanced responsiveness to PDE5 inhibitors.<sup>18</sup> The last is an important indication for TRT, especially in men with type 2 diabetes, where the response to PDE5 inhibitors alone may be little more than 50%.<sup>19</sup> When choosing which TRT to prescribe, the physician must exercise good clinical judgement together with adequate knowledge of the advantages and drawbacks of TRT and consider the bioavailability, safety, tolerability and efficacy of each TRT product as well as any contraindications to TRT. Regular patient follow up is important following TRT initiation. Adverse events during therapy, such as an elevated hematocrit or prostate specific antigen (PSA), require rapid discontinuation of TRT and, as such, short acting preparations are preferred over long acting depot preparations in the initial treatment of hypogonadal men. Primary care physicians may wish to refer these patients to a specialist experienced in the area.

At present, the use of gonadotrophic hormones such as human chorionic gonadotropin and selective oestrogen receptor modulators (eg. clomiphene citrate) is not recommended in male hypogonadism except when fertility is an issue.<sup>20,21</sup>

## Conclusion

The evaluation of male infertility requires semen analysis, endocrine testing and in some cases, genetic testing. There is increased evidence for the role of microsurgery in both sperm retrieval and varicocelectomy.

While testosterone replacement therapy restores erection in androgen deficient men and treats other hypogonadism related conditions, it can result in male infertility.

## Key points

- The evaluation of male infertility requires comprehensive history taking, focused examination, semen analysis and hormone testing.
- Genetic testing for male infertility such as chromosomal karyotyping, Y chromosome microdeletion and CFTR gene mutation should be organised by an IVF specialist.
- Microsurgical sperm retrieval and varicocelectomy are state-of-the-art care for the infertile male.
- Microsurgical vasectomy reversal is more cost effective than ICSI/IVF.
- Exercise caution in the use of testosterone replacement therapy in younger men due to the risk of infertility.

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