The first Australian evidence-based guidelines on male infertility

Darren J Katz[1,2,3], Liza O'Donnell[4,5], Robert I McLachlan[4,6,7,8], Tim J Moss[6,7], Clare V Boothroyd[9], Veena Jayadev[10], Sarah R Catford[4,7,11,12]

Infertility, defined as the inability to achieve a spontaneous pregnancy despite at least 12 months of regular intercourse without contraception, affects about one in six couples.[1] In Australia, one in three assisted reproductive technology (ART) cycles are used because of male factor infertility,[2] and male factors solely explain 20–30% of cases and contribute to 50% cases of couple infertility overall.[3]

Male infertility is characterised by quantitative and/or qualitative defects in spermatogenesis arising from primary spermatogenic failure in most cases, genital tract obstruction, sexual dysfunction, or rarely hypogonadotrophic hypogonadism (HH). Despite thorough investigation, a specific cause is unknown in 77% of cases.[1] Male infertility is also a biomarker for overall health and its assessment presents an opportunity for remedial and/or preventative health interventions.[4] The male contribution to couple infertility has been recognised by international clinical practice guidelines for more than two decades but, until recently, Australian-based guidelines did not exist.

In Australia, male infertility is managed by a variety of medical specialists, including general practitioners, urologists, endocrinologists, and particularly obstetricians and gynaecologists through the use of ART. Therefore, there is a need for a unifying set of guidelines which are endorsed by key stakeholder organisations, relevant to the Australian context, to support clinical practice.

The terms male, men and man are used throughout this article to refer to individuals with a biological sex of male (cis males). The aim of the guidelines that we describe in this article is to inform and support Australian clinicians in the management of all major aspects of male infertility.

Methods

A modified version of the ADAPTE process[5] was used to develop Australian guidelines on male infertility. The target audience for the guidelines is broad, encompassing general practitioners, gynaecologists who frequently provide services to men with infertility and who sometimes lack formal andrology training, and endocrinologists and urologists who provide care to men before or during fertility intent.

A multidisciplinary panel of experts was formed by one of us (RIM, the named recipient of grant funding for the production of the guidelines) to include representatives from various professional organisations, including a urologist with a special interest in male infertility, reproductive endocrinologists with expertise in andrology, and a reproductive endocrinologist and gynaecologist with expertise in ART. Consumer representation was from Healthy Male, a not-for-profit organisation that provides male health information, education and advocacy. Conflicts of interest were disclosed and a timeframe was agreed.

Abstract

Introduction: Infertility affects about one in six couples and a male factor may contribute to 50% of cases. Until recently, no Australian-based clinical guidelines for the management of male infertility had been published. A panel of experts was assembled to formulate the first Australian evidence-based guidelines on male infertility.

Main recommendations:

- The initial evaluation of male fertility should include a reproductive and medical history, physical (including scrotal) examination and semen analysis, and simultaneous evaluation of the female partner.
- Further evaluation of men with suspected infertility should be guided by an expert in male reproduction and include hormonal evaluation and an estimate of testicular volume. Extra tests according to clinical indication are sperm DNA testing, somatic genetic testing and imaging.
- Varicocele treatment should be considered in men with infertility who have a clinical varicocele(s) and associated clinical indications.
- Men with azoospermia should be evaluated to differentiate between obstructive and non-obstructive azoospermia.
- Micro testicular sperm extraction is the preferred method of sperm retrieval in men with non-obstructive azoospermia and prior diagnostic biopsy or fine needle aspiration is not required.
- The management of male infertility should include counselling men regarding potentially modifiable risk factors, associated health conditions, and implications for their future health and offspring.
- Surgical management of infertility includes retrieval of sperm for use in assisted reproductive technology and treatment of varicocele, and non-surgical management includes management of hormonal disorders.
- Specific guidelines are included for men with cryptorchidism, varicoceles and Klinefelter syndrome and cancer and male infertility.

Changes in management as a result of the guidelines: These first Australian evidence-based guidelines will serve as a long overdue clinical aid to the large number of practitioners who provide services to men with infertility. The broad and comprehensive nature of the guidelines will facilitate evidence-based care for the most common areas of male infertility. The formulation of these guidelines by experts representing key stakeholder organisations should enhance the promotion of the guideline statements and help raise awareness of this common condition.

The goal of developing the first comprehensive guidelines on male infertility applicable to the Australian setting was established. The panel of experts recognised the existence of two recently published, well established and refined evidence-based guidelines on male infertility from the European Association of Urology and from the American Urological Association and

[1] Men's Health Melbourne, Melbourne, VIC. [2] Western Health, Melbourne, VIC. [3] The University of Melbourne, Melbourne, VIC. [4] Centre for Endocrinology and Reproductive Health, Hudson Institute of Medical Research, Melbourne, VIC. [5] Griffith University, Brisbane, QLD. [6] Healthy Male, Melbourne, VIC. [7] Monash University, Melbourne, VIC. [8] Monash IVF Group, Melbourne, VIC. [9] Care Fertility, Brisbane, QLD. [10] Concord Repatriation General Hospital, Sydney, NSW. [11] The Royal Women's Hospital, Melbourne, VIC. [12] Alfred Health, Melbourne, VIC.
dkatz@menshealthmelbourne.com.au • doi: 10.5694/mja2.70080

American Society for Reproductive Medicine.[6-8] Both guidelines are comprehensive, with much overlap, but nuanced for their different populations, cultures and health systems. The European guidelines used the strength rating from accepted methods which were modified from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[9] The American guidelines were similarly designated grading strengths with assistance from the Emergency Care Research Institute's Evidence-based Practice Center team.

Each statement within each guideline from the European and American guidelines was examined and discussed over a series of meetings from July 2022 to November 2024. Where concordance was found, the panel of experts discussed whether the statement was applicable to the Australian setting with considerations such as regional disparities in access to care, approved funding through Medicare, and different ethnicities of the Australian population including Indigenous people. Statements were modified by all members of the group stating agreement or dissent, providing caveats and making comments. Following group discussion, consensus was reached with the establishment of 80 revised guideline statements (hereafter referred to as GS1 to GS80) tailored to the Australian context. Wherever possible, pragmatic considerations relevant to Australian clinical practice were valued and, where applicable, references to studies of the Australian population were incorporated into the narrative.

Each of the guideline statements were rated as mandatory, recommended or suggested, based on level of evidence and the panel of experts' perceived importance of adhering to the recommendation. The panel of experts further stratified each guideline statement according to the level of evidence, using the GRADE evidence rating system (high, moderate or low–very low).[9] For all statements, each member wrote their opinion or comments for the group to consider. At the time of meeting, each comment was discussed and a decision was reached by consensus.

Following development of the draft guidelines, relevant Australian professional organisations were contacted to formally review the guidelines, and feedback was integrated. The finalised guidelines have been endorsed by Healthy Male, the Urological Society of Australia and New Zealand, the Endocrine Society of Australia and the Fertility Society of Australia and New Zealand.

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Recommendations

The guidelines are freely available at https://healthymale.org.au/projects/male-infertility-guidelines[10] and the guideline statements are provided in Box 1, arranged into categories to facilitate ease of use. In this summary article, we highlight key guideline statements within each category and subcategory. There is overlap between certain subcategories because some recommendations are pertinent to more than one.

Initial evaluation

The goals of the evaluation of infertile men include: identifying a reversible cause which, if treated, may improve a man's fertility potential; identifying an irreversible cause which may be overcome with ART; and diagnosing associated health conditions that may affect the man and/or their offspring.

An overview of the initial evaluation of male fertility, together with other information used for discriminating male infertility subtypes, is provided in Box 2. The first guideline statement (GS1) (Box 1) instructs clinicians to offer an assessment of male fertility to concerned men and/or couples experiencing infertility, which includes taking general and reproductive history, conducting a physical examination and performing a semen analysis. A detailed history with a focus on identifying risk factors and potential causes of infertility is crucial. A physical examination to identify signs of systemic disease and androgen deficiency, testicular volume and scrotal pathology is considered mandatory. Importantly, some causes of male infertility may be detected by clinical examination — for example, a varicocele or a testicular mass requiring immediate evaluation. A routine scrotal ultrasound is not recommended in the initial evaluation of male infertility (GS8). An ultrasound may be required for measurement of testicular volume if physical examination is not possible or suboptimal (eg, owing to assessment via telehealth or limitations due to body habitus) (GS12). Testicular volume assessed with a Prader orchidometer or by ultrasound correlates with testicular function in infertile men,[12] and men with testicular volumes of less than 12 mL (as assessed by ultrasound) have poorer semen parameters.[13]

Semen analysis is the most important laboratory investigation for male partners in infertile couples. A standard semen analysis provides total sperm count, assesses sperm concentration, motility and morphology, and evaluates parameters such as semen volume, pH and viscosity. A sample is ideally provided after masturbation on site to avoid delays in processing and extreme temperatures that may interfere with results, but otherwise delivery of the sample to the laboratory within 1 hour of collection is acceptable.[11] Abstinence from ejaculation for 2 to 7 days before sample collection is recommended. If the results of an initial semen analysis are abnormal, a second analysis should be performed about 6 weeks afterwards (GS4).[11] The World Health Organization has published reference values for human semen parameters that are commonly used as defining thresholds for male infertility,[11] but they require interpretation alongside a clinical assessment and other investigations. These reference values have changed over time and were most recently updated in 2021 (Box 2).[11] Although a confirmed abnormal result from a semen analysis may provide evidence of male contribution to a couple's infertility, it does not identify an underlying cause and further evaluation is required.

Routine use of antisperm antibody and sperm DNA fragmentation testing is not recommended in the initial evaluation (GS6, GS17). Antisperm antibody testing very rarely helps in the management of infertility; sperm DNA fragmentation testing can be considered as part of further evaluation.[14]

The initial evaluation should be performed in parallel with evaluation of the female partner's fertility to avoid delays in accessing appropriate and timely fertility care (GS2). Simultaneous assessment of partners may also obviate the need for unnecessary tests if a cause has been found and possibly treated in either partner.

Given that male infertility is often diagnosed by a primary health care practitioner, it is recommended that once male infertility is identified, the patient should be further evaluated by a specialist in male reproduction (GS5).

1 Guideline statements for evaluation of male infertility[10]

Number	Guideline statement	Strength of recommendation*	Quality of evidence†
Initial evaluation			
1	Offer an initial evaluation of male fertility to the concerned man and/or couple experiencing infertility. The evaluation should include a reproductive history, physical (including scrotal) examination and semen analysis.	Mandatory	High
2	For initial infertility evaluation, both male and female partners should undergo concurrent assessment.	Mandatory	High
3	The female partner should undergo a parallel assessment of her fertility status, including ovarian reserve, since this might influence clinical decision making regarding the timing and type of intervention (eg, ART versus surgical intervention).	Recommended	High
4	Offer semen analysis according to current WHO laboratory manual for the examination and processing of human semen. If the first semen analysis is abnormal, perform a second semen analysis approximately 6 weeks afterwards, or longer if clinically indicated.	Mandatory	High
5	Men with one or more abnormal semen parameters or those with suspected male factor infertility should be further evaluated by a specialist in male reproduction where available.	Recommended	Moderate
6	Do not perform antisperm antibody testing in the initial evaluation of male infertility.	Recommended	Moderate
7	Advise all men to undertake monthly testicular self-examination until the age of 55.	Recommended	Low–very low
8	Do not routinely perform scrotal ultrasound in the initial evaluation of male infertility.	Recommended	High
Further evaluation			
General			
9	Advise couples considering intrauterine insemination (IUI) that a low total motile sperm count, confirmed by repeated semen analyses, may reduce IUI success rates and ART (IVF/ICSI) should be considered as it is likely to be more effective.	Recommended	Moderate
10	Offer re-evaluation of the male in couples with: multiple failed ART cycles (failed fertilisation, impaired embryo development or no pregnancy after three transfers of high quality embryos in well conducted cycles), or recurrent pregnancy loss (RPL).‡	Recommended	Low–very low
11	Perform hormonal evaluation, including morning (preferably fasting) total testosterone, sex hormone binding globulin (SHBG), follicle stimulating hormone (FSH) and luteinising hormone (LH) for men with: any abnormal semen parameters, atrophic testes, and/or symptoms and/or signs of testosterone deficiency (eg, low libido, sexual dysfunction, lack of secondary sexual characteristics).	Mandatory	Low–very low
12	Testicular volume should be measured by physical examination, or a Prader orchidometer. Ultrasound can be used if physical examination is not possible or suboptimal.	Mandatory	Low–very low
Azoospermia			
13	Clinically evaluate men with azoospermia to differentiate genital tract obstruction (OA) from impaired sperm production (NOA) initially based on semen volume and pH, scrotal examination and serum FSH.	Mandatory	Low–very low
14	Diagnostic testicular biopsy should not be used routinely to differentiate between OA and NOA.	Mandatory	Low–very low
15	Perform a comprehensive assessment of men with NOA, including a detailed medical history, physical examination, hormonal profile and genetic tests to identify the underlying aetiology and associated comorbidities.	Recommended	Low–very low
16	Consider further imaging with MRI or transrectal ultrasound in men with azoospermia in whom a partial or complete distal obstruction (eg, ejaculatory duct obstruction) is suspected.	Recommended	Low–very low
Sperm DNA fragmentation testing			
17	Consider sperm DNA fragmentation (SDF) testing (where available) in the assessment of couples with unexplained infertility, RPL from natural or ART conception including failure in embryonic development, and/or where the man has a clinical varicocele.	Recommended	Moderate
Genetic testing			
18	Offer karyotype cytogenetic (standard) analysis in men in the assessment of couples with recurrent pregnancy loss (RPL) from natural or ART conception, including failure in embryonic development.	Recommended	High
19	Offer karyotype cytogenetic (standard) analysis to men with unexplained azoospermia and moderate oligozoospermia (sperm concentration < 10 million/mL).	Recommended	High
20	Offer testing for Y-chromosome microdeletions to men with unexplained severe oligozoospermia. Men with sperm concentrations < 5 million/mL can be offered testing, but testing should be mandatory in men with sperm concentrations < 1 million/mL.	Recommended	High

Continues

1 Continued

Number	Guideline statement	Strength of recommendation*	Quality of evidence†
21	Do not routinely offer a karyotype or Y-chromosome microdeletion screen in men with obstructive azoospermia, as spermatogenesis should be normal.	Recommended	High
22	Recommend cystic fibrosis transmembrane conductance regulator (CFTR) gene testing in men with structural abnormalities of the vas deferens (unilateral or bilateral absence) or idiopathic obstructive azoospermia.	Mandatory	High
23	For men with a clinical phenotype of congenital bilateral absence of the vas deferens (CBAVD) whose initial gene panel sequencing was negative, or who carry the CFTR gene variant, refer the couple to a genetic counsellor and/or clinical geneticist to discuss extended CFTR testing, including of the female partner, and implications for family planning.	Recommended	High
Imaging			
24	Recommend imaging for renal abnormalities in men with structural abnormalities of the vas deferens.	Mandatory	High
25	Consider scrotal ultrasound when: clinical examination is suboptimal (for example due to body habitus or position of testes), clinical examination reveals an abnormality which requires further delineation (such as epididymal abnormalities, thickened scrotal skin, inguinal testis, large hydrocele or testicular mass), history of cryptorchidism, and/or family or past history of contralateral testicular cancer.	Recommended	High
26	Consider scrotal ultrasound in men with abnormal semen parameters.§	Recommended	High
27	Consider specialist referral for imaging of the genitourinary tract (pelvic MRI or transrectal US) in men with clinical features of: (i) ejaculatory duct obstruction (acidic low volume azoospermia with normal gonadotrophins and testicular volumes, and palpable vas deferens), and (ii) obstructive azoospermia of unknown cause.	Recommended	High
Infection			
28	Consider further evaluation of men with pyospermia for the presence of infection.	Recommended	Low–very low
29	Refer sexual partners of men with a genitourinary tract infection due to a known or suspected sexually transmitted infection for evaluation and treatment.	Recommended	High
30	Do not routinely use antibiotics and antioxidants in men with infertility and pyospermia for improving live birth rates.	Recommended	Low–very low
31	Treatment of genitourinary tract infection is required and may improve sperm quality, but it does not necessarily improve pregnancy and live birth rates.	Recommended	Low–very low
Cryptorchidism			
32	Refer men with unilateral or bilateral cryptorchidism to a urologist for consideration of either an orchidopexy or orchidectomy.	Recommended	High
33	Do not use hormonal interventions to aid testicular descent in post-pubertal men with cryptorchidism.	Mandatory	High
Management and therapeutic considerations			
Counselling			
34	Offer genetic counselling and/or review by a clinical geneticist to all couples with an identified genetic abnormality and to men with a known inheritable disease, especially in men considering ART.	Mandatory	High
35	Inform men with a Y-chromosome microdeletion and their partners who wish to proceed with ICSI that microdeletions will be passed on to any sons, who therefore carry a high risk of spermatogenic impairment in adulthood.	Mandatory	High
36	Advise men with infertility that lifestyle changes, including maintaining a healthy weight, regular physical activity, smoking cessation and a reduction in alcohol intake, may improve sperm quality and the chances of conception.	Recommended	Low–very low
37	Inform men with abnormal semen parameters of associated health conditions that may require regular review.	Recommended	Low–very low
38	Inform couples with paternal age > 40 years of an increased risk of adverse health outcomes in offspring.	Recommended	High
Varicocele			
39	Do not routinely perform abdominal imaging solely for an isolated small or moderate right varicocele.	Recommended	Low–very low
40	Perform a scrotal examination, including with Valsalva manoeuvre, to identify a potentially clinically significant (ie, palpable) varicocele.	Mandatory	Moderate

Continues

1 Continued

Number	Guideline statement	Strength of recommendation*	Quality of evidence†
41	Consider varicocele treatment in men with infertility who have a clinical varicocele(s) and any of the following: (i) abnormal semen parameters (but not azoospermia), (ii) unexplained couple infertility, (iii) raised sperm DNA fragmentation, (iv) in couples who have experienced failed ART, including RPL or poor embryo development.	Recommended	High
42	Inform men with a clinical varicocele and non-obstructive azoospermia (NOA) of the lack of definitive evidence demonstrating that varicocele repair prior to ART improves pregnancy rate and live birth rate.	Recommended	Low–very low
43	Consider surgical varicocelectomy in adolescents with a clinical varicocele who have: (i) reduced volume of the ipsilateral testis, or (ii) progressive testicular dysfunction.	Recommended	Low–very low
44	Do not consider varicocelectomy in adolescents or men who have sub-clinical varicoceles.	Recommended	Low–very low
Surgical management — sperm retrieval			
45	Options for sperm retrieval in men with azoospermia due to anejaculation include: inducing ejaculation with sympathomimetics, penile vibratory stimulation or electroejaculation, and surgical testicular sperm retrieval.	Recommended	Moderate
46	Options for sperm retrieval in men with retrograde ejaculation include: (i) inducing anterograde ejaculation with sympathomimetics, (ii) urinary sperm retrieval after alkalinisation, and (iii) surgical testicular sperm retrieval.	Recommended	Moderate
47	In obstructive azoospermia, perform surgical sperm retrieval (such as microsurgical epididymal sperm aspiration, testicular sperm extraction and percutaneous techniques) in the following circumstances: (i) as an adjunct to reconstructive surgery, (ii) if the condition is not amenable to surgical repair, or (iii) patient preference.	Recommended	Low–very low
48	Diagnostic testicular biopsy is not required prior to surgical sperm retrieval, as it may compromise future sperm retrieval via micro testicular sperm extraction (TESE).	Suggested	Low–very low
49	Use of surgically retrieved sperm may be considered in non-azoospermic males with high sperm DNA fragmentation in ejaculated sperm or cryptozoospermia, especially in couples with previous ICSI failure using ejaculated sperm.	Suggested	Low–very low
Surgical management — obstructive azoospermia			
50	For men seeking conception after vasectomy, consider surgical reconstruction, surgical sperm retrieval or both reconstruction and simultaneous surgical sperm retrieval.	Recommended	Moderate
51	For men seeking natural conception after vasectomy, and those with vasal or epididymal obstructive azoospermia from other causes, surgical reconstruction with vasovasostomy or vasoepididymostomy should be discussed.	Recommended	Moderate
52	In cases of obstructive azoospermia, couples should be counselled about surgical reconstruction and surgical sperm retrieval and referral for ART. Counselling should consider factors, such as the female partner's age, ovarian reserve, tubal status, number of desired children, future contraception requirements and any other relevant factors.	Recommended	Low–very low
53	Testicular or epididymal sperm may be retrieved in men with obstructive azoospermia in whom surgical repair is either not possible or not chosen.	Recommended	Moderate
54	After successful reconstructive surgery, consider cryopreserving ejaculated sperm in case of delayed fibrosis and re-obstruction of the anastomoses.	Recommended	Low–very low
55	Consider transurethral resection of ejaculatory ducts (TURED) or surgical sperm retrieval in men with obstructive azoospermia due to ejaculatory duct obstruction (EDO).	Recommended	Low–very low
Surgical management — non-obstructive azoospermia			
56	Micro-TESE is the preferred method of sperm retrieval in men with NOA. If not available, conventional TESE can be used. Either fresh or cryopreserved sperm may then be used for ICSI.	Recommended	Moderate
57	Diagnostic testicular biopsy is not required prior to surgical sperm retrieval in men with NOA.	Suggested	Low–very low
58	There are no reliable endocrine and clinical predictors of successful sperm retrieval in men with NOA.	Suggested	Low–very low
59	Fine needle aspiration (FNA)/testicular sperm aspiration (TESA) are not recommended for surgical sperm retrieval in NOA.¶	Recommended	Moderate
60	Selective use of medical therapies (eg, FSH, human chorionic gonadotrophin (hCG), aromatase inhibitors or selective oestrogen receptor modulators (SERMs)) may be considered in men with NOA before surgical sperm retrieval, however there is insufficient evidence to recommend their routine use.	Recommended	Low–very low
61	Do not perform surgical sperm retrieval in men with complete *AZFa* and *AZFb* microdeletions.	Mandatory	High

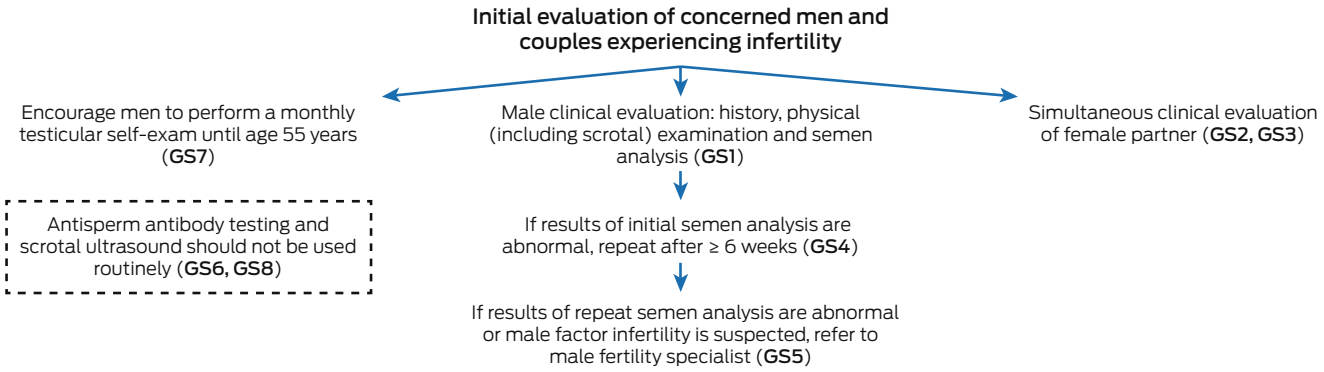
Continues

1 Continued

Number	Guideline statement	Strength of recommendation*	Quality of evidence†
Non-surgical management — hypogonadotrophic hypogonadism			
62	For men with hypogonadotrophic hypogonadism (HH), determine whether it is congenital or acquired. Evaluation should include a clinical and endocrine assessment, imaging and, if appropriate and available, genetic screening.	Recommended	High
63	For men with HH (either congenital or acquired), induce spermatogenesis with hCG and FSH, as needed.	Recommended	High
Non-surgical management — hormone treatments			
64	Do not prescribe testosterone for men with current or imminent reproductive intent.	Mandatory	High
65	For men with idiopathic infertility, the routine use of aromatase inhibitors (AIs), hCG or SERMs is not indicated to improve semen parameters, pregnancy rates and live birth rates.	Suggested	Low–very low
66	FSH therapy may be considered for men with idiopathic oligozoospermia in whom gonadotrophins are normal.	Suggested	Low–very low
67	Do not routinely offer FSH to men with non-obstructive azoospermia prior to surgical testicular sperm retrieval.	Suggested	Low–very low
Non-surgical management — hyperprolactinaemia			
68	Thoroughly evaluate infertile men with HH for hyperprolactinaemia and then identify the underlying cause and treat accordingly.	Recommended	High
69	There is limited evidence that dopamine agonists improve sperm output in men with mild idiopathic hyperprolactinaemia in whom serum gonadotrophins and testosterone levels are normal.	Recommended	Low–very low
Non-surgical management — supplements			
70	Advise men that there is some evidence that the use of supplements, such as antioxidants and vitamins, may improve semen parameters, but specific recommendations on their routine use cannot be made.	Recommended	Low–very low
Klinefelter syndrome			
71	Recommend semen analysis and sperm cryopreservation (where possible) in adult men with Klinefelter syndrome who desire paternity.	Mandatory	High
72	Recommend that adult men with Klinefelter syndrome and confirmed azoospermia who may desire paternity in the future have an informed discussion about the timing of micro-TESE (or conventional TESE if micro-TESE not available) and androgen replacement.	Recommended	High
73	After fertility issues have been addressed, men with Klinefelter syndrome require long-term follow-up for androgen replacement and management of associated comorbidities.	Mandatory	High
Cancer and male infertility			
74	Consider a multidisciplinary team discussion for men with ultrasound-detected indeterminate testicular lesions, especially if additional risk factors for malignancy are present, when contemplating surgery or surveillance.	Recommended	Low–very low
75	Offer sperm cryopreservation (ideally in multiple vials or straws) to men before an elective orchidectomy, noting that semen parameters are often abnormal in men with testicular cancer.	Mandatory	Low–very low
76	Consider offering oncotesticular sperm extraction at the time of radical orchidectomy for men with testicular cancer and azoospermia or severe semen abnormalities.	Recommended	Low–very low
77	Offer sperm cryopreservation (ideally in multiple vials or straws) to boys from mid-puberty onwards and men prior to commencement of gonadotoxic therapy or other cancer treatment that may affect male fertility.	Recommended	High
78	Advise men desiring paternity after gonadotoxic therapy that the interval between treatment cessation and attempted conception depends on the individual's treatment and multiple factors.	Recommended	Moderate
79	For men seeking fertility after gonadotoxic treatments, a semen analysis is recommended after treatment completion, noting that the time for return of ejaculatory sperm depends on the type, dose and duration of gonadotoxic therapy. Further assessment of fertility should include measurement of serum gonadotrophins and testosterone.	Recommended	High
80	Inform men seeking paternity who remain azoospermic after gonadotoxic therapies that surgical sperm retrieval is an option. Where possible micro-TESE is preferred, otherwise conventional TESE can be used.	Mandatory	High

AI = aromatase inhibitor; ART = assisted reproductive technology; CBAVD = congenital bilateral absence of the vas deferens; CFTR = cystic fibrosis transmembrane conductance regulator; EDO = ejaculatory duct obstruction; FNA = fine needle aspiration; FSH = follicle stimulating hormone; GRADE = Grading of Recommendations Assessment, Development and Evaluation; hCG = human chorionic gonadotrophin; HH = hypogonadotrophic hypogonadism; ICSI = intracytoplasmic sperm injection; IUI = intrauterine insemination; IVF = in vitro fertilisation; LH = luteinising hormone; MRI = magnetic resonance imaging; NOA = non-obstructive azoospermia; OA = obstructive azoospermia; RPL = recurrent pregnancy loss; SDF = sperm DNA fragmentation; SERM = selective oestrogen receptor modulator; SHBG = sex hormone binding globulin; TESA = testicular sperm aspiration; TESE = testicular sperm extraction; TURED = transurethral resection of ejaculatory ducts; US = ultrasound; WHO = World Health Organization. * Strength of recommendation (rated as mandatory, recommended or suggested) was based on level of evidence and the panel of experts' perceived importance of adhering to the recommendation. † Quality of evidence (rated as high, moderate or low–very low) was determined according to the level of evidence, using the GRADE evidence rating system.[9] ‡ RPL refers to two or more pregnancy losses. § Because men with abnormal semen parameters have a higher risk of testicular cancer. ¶ Because retrieval rates for FNA/TESA are much lower than retrieval rates for micro-TESE. ◆

2 Overview of the initial evaluation of male fertility and information used for discriminating male infertility subtypes



Nomenclature used to describe abnormal semen parameters[11]

Term	Reference cut-off
Oligozoospermia	Sperm concentration < 16 million/mL or total count < 39 million
Asthenozoospermia	< 42% motile sperm or < 30% progressively motile sperm
Teratozoospermia	< 4% morphologically normal sperm
Oligoasthenoteratozoospermia	Defects in all three parameters
Azoospermia	No sperm in the ejaculate

Reference values for semen parameters[11]

Semen parameter	Reference cut-off
Semen volume	≥1.4 mL
Sperm concentration	≥ 16 million/mL
Total sperm count	≥ 39 mL
Total motility	≥ 42%
Progressive motility	≥ 30%
Morphology (% normal forms)	≥ 4%

Typical clinical characteristics of obstructive and non-obstructive azoospermia

	Obstructive azoospermia	Non-obstructive azoospermia		
Measurement		Primary spermatogenic failure	Primary testicular failure	Hypogonadotropic hypogonadism
Seminal volume	Low or normal	Normal	Normal	Normal or low
Seminal pH	Low or normal	Normal	Normal	Normal
Testicular volume	Normal	Low	Low	Low
Follicle stimulating hormone level	Normal	High	High	Normal or Low
Luteinising hormone level	Normal	Normal	High	Normal or low
Testosterone level	Normal	Normal	Low or normal	Low

Further evaluation

General

In general, recommendations for further evaluation relate to management of patients requiring detailed evaluation by specialists in male reproduction (GS9-GS33). GS9–GS12 describe more general recommendations in this context. GS10 highlights the need for the man to be thoroughly reassessed in cases in which there are multiple failed ART cycles or recurrent pregnancy losses. Diagnoses such as a clinically significant varicocele or a high rate of sperm DNA fragmentation may be important to address before commencing further ART cycles.[15,16]

Hormonal evaluation is recommended if there is suspicion of male factor infertility and/or androgen deficiency based on abnormal semen parameters or clinical findings (GS11). Serum testosterone levels peak in the early morning and glucose consumption suppresses testosterone production, so blood for measurement of hormonal profiles should be collected before 10:00 am and ideally under fasting conditions.[17] Isolated elevation of serum follicle stimulating hormone (FSH) level suggests primary spermatogenic failure, whereas elevated serum FSH and luteinising hormone (LH) levels associated with a low testosterone level is consistent with primary testicular failure (the most useful FSH value for the upper limit of normal in a young man is 8.4 IU/L[18]). Low or inappropriately normal FSH and LH levels together with a low testosterone level is consistent with HH.

Azoospermia

Azoospermia is the most severe form of infertility, accounting for about 10–15% of male infertility.[19] It is crucial to differentiate between obstructive azoospermia (OA) and non-obstructive

azoospermia (NOA), as this guides further investigations and management. Application of a standardised assessment framework should permit differentiation in most circumstances (GS13) (Box 2). Features suggestive of OA include a low volume ejaculate with normal testicular volumes and a normal serum FSH level. Obstruction distal to the seminal vesicles, such as ejaculatory duct obstruction or bilateral absence of the vas deferens (usually associated with hypoplastic or absent seminal vesicles), characteristically causes an acidic ejaculate owing to impaired passage of alkaline seminal vesicle fluid. Conversely, men with NOA typically have normal volume and normal pH seminal fluid with reduced testicular volumes and either an elevated serum FSH level (in primary testicular failure) or a normal or low FSH level (in HH).

Routine diagnostic testicular biopsy is not recommended because it may compromise future sperm retrieval, especially in cases of NOA (GS14).[20] It is important to perform a comprehensive assessment of men with NOA to identify the underlying cause and associated comorbidities (GS15). Similarly, additional imaging (eg, magnetic resonance imaging) in cases of OA may be indicated to identify the nature and location of obstruction (GS16).[21]

Sperm DNA fragmentation testing

Sperm DNA fragmentation testing is only recommended in specific circumstances for which it may guide management, such as to determine whether varicoceles should be treated or decide whether testicular sperm should be used for ART (GS17).[16,22]

Genetic testing

The availability of genetic testing varies between health services. Genetic testing can be costly for the health care system and may generate significant out-of-pocket costs for patients. Therefore GS18–GS23 offer evidence-based approaches to genetic testing in a cost-effective and targeted manner,[23] noting that some results (eg, karyotypic anomalies and cystic fibrosis transmembrane conductance regulator gene mutation) may have serious implications for offspring.

Y-chromosome microdeletions are present in 5% and 10% of men with severe oligozoospermia (sperm concentration less than 5 million/mL) and NOA, respectively.[24] The frequency of Y-chromosome microdeletions in men with a sperm concentration of between 1 million/mL and 5 million/mL is very low (about 0.8%).[25-27] As such, it is recommended that screening for Y-chromosome microdeletions be offered to men with a sperm concentration of less than 5 million/mL but it should be mandatory for those with a sperm concentration of less than 1 million/mL (GS20).

Imaging

The guideline statements on imaging include detailed recommendations regarding the indications for scrotal ultrasound (GS25, GS26). Importantly, GS26 addresses advice from the European guidelines, which state that testicular cancer likely arises from testicular dysgenesis and that male infertility is a risk factor for testicular cancer.[6]

Infection

While pyospermia may be caused by infection, hence necessitating further assessment (GS28), there are other causes. Routine use of antibiotics (and antioxidants) is not recommended, as this does not improve live birth rates (GS30).[28]

Cryptorchidism

Patients with untreated cryptorchidism need to be referred to a urologist (GS32) because they may benefit from surgery, both from a fertility perspective and to permit self-surveillance owing to the increased risk of testicular malignancy.[29] Some patients with cryptorchidism may need an orchidectomy.

Management and therapeutic considerations

Counselling

The guideline statements on counselling focus on general advice and genetic counselling for infertile men. Some medical practitioners managing infertility may not be skilled in genetic counselling, so professional genetic counselling must be offered when abnormalities are found (GS34).

Medical practitioners will be aware that patients should be counselled about optimisation of potentially modifiable factors to improve fertility potential (GS36).[30] The association of male factor infertility with non-gonadal health conditions is likely less well known, thus necessitating a distinct guideline statement (GS37). Comorbidities of male infertility include cancer, cardiovascular disease, metabolic disease and premature mortality.[7,31] As such, it is advisable that clinicians perform a cardiometabolic assessment to identify comorbidities such as obesity, obstructive sleep apnoea, hypertension, and undiagnosed or poorly controlled diabetes. In obesity, sustained weight loss improves sperm count, and regular physical activity and a diet rich in nutrients improve sperm quality. It is important to appreciate that sperm quality deteriorates with age, with increased risks of autism spectrum disorder and some autosomal dominant diseases in offspring (GS38).[32]

Varicocele

Varicoceles are present in one-third of infertile men and in 10–15% of men in the general population, but their causative role in male infertility is contentious.[33] Varicoceles that are palpable on examination (not exclusively ultrasound detected) are considered clinically significant (GS40).[34]

Clinically significant varicoceles can cause or contribute to abnormal semen parameters, sperm DNA fragmentation, recurrent pregnancy loss and poor ART outcomes (GS41) and, as such, are important to identify.[15,35,36] Treatment for a varicocele should be considered in these contexts. A microsurgical varicocelectomy may improve pregnancy rates compared with other surgical treatments, and has the lowest complication rate, but other interventions (surgery or embolisation) may need to be considered in the context of availability.[37,38] The evidence supporting a varicocelectomy before micro testicular sperm extraction (TESE) in NOA is mixed, therefore it is not recommended and should only be considered in select cases (GS42).[39]

Surgical management

Sperm retrieval: The potential role for surgically retrieved sperm extends beyond the classic context of azoospermia. After addressing any reversible factors, clinicians may consider using surgically retrieved sperm in non-azoospermic men who have high sperm DNA fragmentation in ejaculated sperm or cryptozoospermia, particularly those in couples who have experienced previous failure of intracytoplasmic sperm injection using ejaculated sperm (GS49). Current evidence suggests that using surgically retrieved sperm for intracytoplasmic sperm injection in the such situations may improve pregnancy and

live birth rates, but high quality data are lacking.[40-43] The optimal method of surgical sperm retrieval will depend on spermatogenic function; fine needle aspiration or testicular sperm aspiration may be appropriate in those with high sperm DNA fragmentation and normal sperm concentration or mild oligozoospermia, while TESE (possibly with microsurgical assistance if needed) is recommended in men with cryptozoospermia.

Obstructive azoospermia: The most common cause of OA is a vasectomy, with about 25% of Australian men older than 40 years having undergone the procedure.[44] About 3–6% of men consider having another child after a vasectomy.[45] There are two options in this situation: a vasectomy reversal to restore natural fertility, or extraction of sperm for use in ART. Practitioners should discuss both options with patients, and highlight factors to consider in reaching a decision (GS51, GS52). If reconstructive surgery has been successful after vasectomy, then cryopreservation of ejaculated sperm should be considered given the risk of delayed anastomotic fibrosis, which can occur in about 10% of men who initially have sperm return to the ejaculate (GS54).[46] A rare cause of OA is ejaculatory duct obstruction, for which transurethral resection of ejaculatory ducts may restore fertility (GS55).[47]

Non-obstructive azoospermia: The gold standard for sperm retrieval in NOA is micro-TESE because it has higher sperm retrieval rates than other techniques (GS56).[48] A diagnostic biopsy is not necessary because every potential histology finding in NOA may still be associated with sperm production owing to heterogeneity between tubules (GS57).[49] Furthermore, there is a risk of compromising future sperm retrieval.[49] There are no known clinical or endocrine markers which can reliably predict sperm retrieval rates (GS58).[50]

In Australia, micro-TESE can be performed with results comparable to those from overseas.[51] If micro-TESE is not available, a conventional random open TESE can be used. Fine needle aspiration should not be used as the definitive technique in NOA (GS59).

Routine use of medical therapy such as human chorionic gonadotrophin (hCG), FSH, antioestrogens or aromatase inhibitors before TESE in NOA due to primary spermatogenic failure is not supported by current evidence but may be considered in select cases (GS60).[52] If a patient has complete *AZFa* or *AZFb* deletions, then any attempt at sperm retrieval is futile and should not be undertaken (GS61).[53]

Non-surgical management

Hypogonadotrophic hypogonadism and hyperprolactinaemia: HH is a rare cause of male infertility, but diagnosis is critical because natural fertility may be restored and the underlying cause could have serious health implications. It is essential to evaluate remaining pituitary function, including prolactin level, and to consider magnetic resonance imaging of the pituitary gland. If clinically significant hyperprolactinaemia is identified, then a thorough assessment for the cause must ensue to target treatment (GS68). Dopamine agonists are unlikely to be helpful in cases of mild idiopathic hyperprolactinaemia with normal serum gonadotrophin and testosterone levels (GS69).

It is important to determine whether HH is congenital or acquired, as this will guide further investigations, management and expectations around fertility potential (GS62). The genetic basis of congenital HH is complex, with variability in inheritance, penetrance and expressivity; more than 60 genes underlie congenital HH,[54] so genetic testing is appropriate in these cases. Congenital and acquired HH due to irreversible hypothalamic–pituitary disease may be treated with hCG, as an LH substitute, thereby restoring intratesticular testosterone levels and promoting spermatogenesis. This may be sufficient in many cases of HH with post-pubertal onset (GS63).[55] In congenital or pre-pubertal onset cases, optimal sperm output will typically require the addition of FSH. While simultaneous hCG and FSH therapy, or sequential therapy with unopposed FSH followed by hCG, have been suggested in severe cases of congenital HH, such as absence of spontaneous puberty (testicular volume < 4 mL) and/or cryptorchidism, the optimal approach to spermatogenesis induction is yet to be established.

Hormone treatments and supplements for idiopathic infertility: While frequently used in Australia,[56] the routine use of hCG, antioestrogens and aromatase inhibitors in men with idiopathic infertility is not strongly supported by available evidence (GS65) and they are not approved for this indication. Weak evidence indicates that clomiphene may be beneficial to sperm output and motility in normogonadotrophic and hypogonadal men with idiopathic oligozoospermia,[57] but improved fertility outcomes are unproven. Current evidence for aromatase inhibitor use in idiopathic male infertility is weak and there are concerns about adverse effects.[58] Some evidence suggests that semen parameters and pregnancy rates improve after FSH therapy in normogonadotrophic idiopathic male infertility (GS66).[59,60] A recent meta-analysis demonstrated improved sperm concentration, total sperm count and progressive sperm motility after FSH therapy compared with placebo or no treatment in men with idiopathic oligozoospermia and normal gonadotrophin levels; however, due to the heterogeneity of the data, further studies are needed.[59] Exogenous testosterone suppresses the hypothalamic–pituitary–gonadal axis and is contraindicated in men seeking fertility (GS64).[61]

Data from prospective controlled studies of the use of antioxidants in male infertility are poor, owing to the use of different antioxidants in different combinations and dosages for varying durations.[62] An additional challenge in this area of research is the lack of consensus regarding methods of detecting oxidative stress and subsequent difficulty in identifying patients most likely to benefit from antioxidant treatment.[63] Without results from well designed randomised controlled trials, specific recommendations on routine use of antioxidants cannot be made (GS70).

Klinefelter syndrome

For men diagnosed with Klinefelter syndrome (KS), it is necessary to assess their desire for paternity and its timing. For men with KS who are seeking imminent paternity and have NOA, a micro-TESE (where available) is recommended (GS72). If paternity is considered some time into the future, a detailed, personalised and informed discussion about micro-TESE and testosterone replacement should be undertaken by a suitably qualified specialist. KS is a non-heritable chromosomal disorder and so does not confer an elevated risk of transmission to offspring. It is paramount to assess, treat and monitor the androgen status of men with KS after fertility has been addressed. Men with KS experience high rates of various diseases, and therefore regular surveillance and management is critical (GS73).[64]

Cancer and male infertility

Risk of testicular cancer is increased in men with infertility. However, not all intratesticular lesions are malignant[27] and

some indeterminate lesions may be amenable to surveillance, with decision making facilitated by a multidisciplinary case discussion (GS74). In men who have a suspicious testicular tumour, an orchidectomy is standard of care.[65,66] Sperm cryopreservation should be attempted before orchidectomy for all men; some may be unable to provide an adequate sample at the first attempt of collection, and may therefore require repeated collections. Semen quality is often impaired in men with testicular cancer,[67] so concomitant extraction of sperm from testicular tissue at the time of orchidectomy should be discussed (GS76).[68]

All males from mid-puberty onwards who are about to embark on cancer treatment should be considered for fertility preservation, especially before commencing gonadotoxic therapy (GS77). Multiple factors affect decisions about appropriate timing of attempted conception after gonadotoxic therapies, so expert individualised guidance is recommended (GS78), but a specific timeframe is not prescribed.[69] After gonadotoxic treatment, a semen analysis is recommended for men seeking fertility, appreciating the variability in the potential recovery of semen parameters (GS79).[69] Further assessment by hormonal profiling may be necessary (GS79).[70] Some men have residual NOA that requires surgical sperm retrieval, ideally using micro-TESE (GS80).[71]

Conclusion

To our knowledge, these 80 guideline statements are the first set of evidence-based recommendations for management of male infertility in Australia. The comprehensive and broad scope of the guidelines serves as a framework for managing male infertility. The guidelines have been endorsed by key stakeholder organisations. We hope that this article will aid in raising awareness of this common condition.

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