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Review

An update on the management of male infertility

Stamatios Karavolos BSc MBBS MD MRCOG,[a]* **Nikoletta Panagiotopoulou** MSc (Oxon) MD (Res) MRCOG,[b] **Hisham Alahwany** MBBCh MSc PhD,[c] **Sarah Martins da Silva** MBChB DFFP MD MRCOG[d]

[a]Consultant Gynaecologist, Specialist in Reproductive Medicine and Surgery, Department of Gynaecology, Salford Royal NHS Foundation Trust, Salford M6 8HD, UK
[b]Consultant Gynaecologist, Subspecialist in Reproductive Medicine and Surgery, Manchester Fertility, Manchester SK8 3SB, UK
[c]PhD researcher, University of Nottingham and Royal Derby Hospital, Derby DE22 3DT, UK
[d]Senior Lecturer in Reproductive Medicine, Reproductive Medicine Research Group, Ninewells Hospital and Medical School, University of Dundee, Dundee DD1 9SY, UK
**Correspondence:* Stamatios Karavolos. Email: s.karavolos@doctors.org.uk

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Key content

- Male infertility underlies or contributes to up to 50% of infertility cases; current therapeutic interventions rely on assisted reproductive technology (ART), as medical or surgical treatments have limited value in enhancing semen quality or parameters.
- Lifestyle factors that affect male fertility could offer a therapeutic opportunity; however, their modification seems to be of variable benefit.
- In the quest for sperm functional assessment and selection tests, there is controversy over which patients, if any, should be tested for sperm DNA fragmentation, as well as which test to perform. Sperm selection techniques for intracytoplasmic sperm injection do not appear to significantly improve treatment outcomes or live birth rates.
- Routinely performed genetic tests are effective in determining aetiology in approximately 20% of infertile men; however, newer genetic tests could enhance diagnosis and change the future management of male infertility.

Learning objectives

- To summarise the key lifestyle factors that affect male fertility.
- To appraise the currently available investigations for sperm testing and selection.
- To describe the genetic tests currently available to identify the aetiology of male infertility, including emerging technologies in the field of genetics and personalised genomics.

Ethical issues

- How to deal with couples' requests for unproven medical interventions to manage male infertility?

Keywords: genetic testing / lifestyle factors / male infertility / sperm assessment / sperm selection

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Introduction

It is estimated that one in seven couples in the UK experiences difficulty conceiving,[1] with male factor as an underlying or contributory cause in up to half of these cases.[2] Male infertility is thought to affect 7% of all men;[3] evaluation of the male partner is therefore essential. A thorough history will highlight important medical and lifestyle issues that warrant investigation to diagnose specific underlying causes.

The prevalence of male infertility is difficult to estimate in the general population, mainly because of variations in the definitions used in different studies. Data from the Human Fertilisation and Embryology Authority[4] indicate that male infertility accounts for 37% of in vitro fertilisation (IVF) treatments, usually in combination with intracytoplasmic sperm injection (ICSI).

Male infertility can be attributed to several causes, including anatomical (congenital or acquired), endocrine, iatrogenic, behavioural, lifestyle factors and adverse environmental exposures.[5] Causes of male infertility can be classified into pretesticular, testicular and post-testicular.[6] However, it is worth noting that over 50% of cases of male infertility are idiopathic or unexplained, and therapeutic intervention is primarily by assisted reproductive technology (ART).

Although there have been advances in male reproductive health, from developments on in vitro spermatogenesis to better understanding the mature spermatozoon, progress in the arena of the management of male infertility has been limited. Several important questions in male infertility remain unanswered (Box 1).[7] Indeed, the most recent World Health Organization (WHO) manual regarding management of the infertile male was published in 2000, which means it is now 2 decades since an evidence-based update on best-practice recommendations.[8]

With the exception of male hypogonadotrophic hypogonadism, there is nothing that can currently be prescribed or added to sperm – in vivo or in vitro – to

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Box 1. Top 10 priorities in male infertility research by the Priority Setting Partnership for Infertility[25]

1. Are sperm tests other than the World Health Organization parameters useful in evaluating male fertility?
2. What are the emotional and psychological effects of male infertility?
3. Do environmental factors cause male infertility?
4. Does treating specific causes of male infertility improve outcomes?
5. Can we improve surgical sperm retrieval outcomes by prior use of endocrine stimulatory protocols?
6. What modifiable risk factors cause male infertility?
7. Does treating modifiable risk factors improve outcomes?
8. What comorbidities are associated with male infertility?
9. Does treating comorbidities improve outcomes?
10. Are nutraceuticals useful in improving male reproductive potential?

improve male fertility or sperm function.[9] Therefore, the mainstay treatment for male infertility remains ICSI, and the 2013 review paper published in *The Obstetrician & Gynaecologist*, which summarised causes and clinical management of male infertility,[7] remains current. However, several studies are underway that might change the management of male infertility in the near future.

This review paper highlights new advances in the field of male infertility, including the clinical management of lifestyle factors affecting male fertility, sperm assessment and selection and the latest advances in male reproductive genetics.

Lifestyle factors and male infertility

Although the causes of male infertility and impaired gametogenesis cannot often be readily identified, extrinsic factors, such as diet, physical activity, body habitus or environmental factors, have been linked to male infertility. Such extrinsic factors are modifiable and could offer a therapeutic opportunity. The recent refocus on holistic assessment and care of the infertile male, therefore, makes sense.

Obesity and weight loss

Recent large-scale data show statistically significant relationships between obesity and semen analysis parameters.[10] Obese men are more likely to be oligozoospermic or azoospermic compared with men who are within a normal weight range.[11] Paternal obesity is also acknowledged to negatively affect assisted reproduction outcomes.[12]

However, results are conflicting regarding the effect of significant weight loss on semen analysis parameters because 'improved',[13–17] 'no change'[18] and 'deterioration'[19,20] have all been reported.

It is certainly worth noting that weight loss intervention is complex; this perhaps explains the heterogeneity reported in various studies. It is also difficult to know whether observed improvements in sperm quality relate to weight loss per se, or other confounding factors, such as change in diet, increase in exercise or improved metabolic profiles.

Diet

Diets consisting of vegetables, fruits, fish, poultry, cereals and low-fat dairy products are positively associated with sperm quality.[21] Processed meat, full-fat dairy products, alcohol, coffee and sugar-sweetened beverages are associated with poor semen quality and lower fecundity rates.[22]

A systematic review and meta-analysis of the effect of nutrients and dietary supplements on semen characteristics found favourable effects of selenium, zinc, omega-3 fatty acids, coenzyme Q10 and carnitines. However, male fertility was not assessed and results should be cautiously interpreted because of the limited sample size and considerable interstudy heterogeneity.[21]

Vitamins and antioxidants

There is a considerable body of evidence to support the role of oxidative stress (OS) in sperm dysfunction,[23] which is proposed to affect the cell membrane, impair sperm motility and reduce the ability to fertilise the oocyte, as well as causing sperm DNA damage.[24] Antioxidants can protect cells from OS and, not surprisingly, antioxidant supplements have been investigated as potential treatments for male infertility. However, many existing trials are underpowered, have methodological flaws and/or are poorly reported.[7,25]

Many antioxidant supplements are now commercially available for the treatment of male infertility, although none has high-quality clinical data to support its use.[25] A 2019 Cochrane review suggests an increased live birth rate is associated with antioxidant use for male subfertility (odds ratio [OR] 1.79, 95% confidence interval [CI] 1.20–2.67).[25] However, this is based on seven randomised controlled trials (RCTs) comprising 750 men and only 124 live births. A further 11 trials (786 men) included in the analysis indicate that antioxidants may increase clinical pregnancy rate (OR 2.97, 95% CI 1.91–4.63). Overall, evidence from these trials is low quality and the authors have called for further large, well-designed RCTs reporting on pregnancy and live births to clarify the exact role of antioxidants.

Cigarette smoking and vaping

Cigarette smoking is widely acknowledged to negatively affect semen quality, although the underlying mechanisms have yet to be fully elucidated.[26–28] Despite no definite relationship between smoking and male infertility, available evidence on cigarette smoking and male fertility supports smoking cessation and minimising exposure to tobacco smoke among couples who are trying to conceive.

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Smoking is associated with reduced sperm count and motility and abnormal morphology, and causes a decline in sperm quality in both fertile and infertile men.[29] Subgroup analyses indicate that the effect is higher in infertile men than in the general population and that deterioration of semen quality is more pronounced in moderate and heavy smokers.[30] Oligozoospermia is also more prevalent in smokers (risk ratio [RR] 1.29, 95% CI 1.05–1.59; $P = 0.02$).[31]

Several cross-sectional studies show a significant effect of smoking on semen parameters and DNA fragmentation, as well as on gonadotrophin and testosterone levels.[32–36] Paternal smoking also significantly negatively influences ART outcomes.[37] Among former smokers, every additional year following smoking cessation of the male partner reduced the risk of treatment failure by 4%, particularly miscarriage.[38]

Electronic cigarettes (e-cigarettes) typically contain propylene glycol (a tasteless, odourless, colourless alcohol used in antifreeze), vegetable glycerine, a variable amount of nicotine, food-grade flavouring and water to generate an aerosol/vapour. Their use is commonly termed 'vaping' and is generally viewed to be less harmful than conventional smoking. Nonetheless, studies in animal models show detrimental effects on spermatogenesis and an increase in OS.[39,40]

Alcohol

Given that >50% of men regularly drink alcohol,[41] it is perhaps surprising that the effect of alcohol consumption on male fertility is not well understood. Overall, alcohol consumption has been associated with lower semen volume, but has a variable and probably dose-dependent effect on semen parameters.[29] Habitual alcohol consumption is associated with reduced semen quality and changes in reproductive hormones.[42] Similarly, semen volume, sperm count, motility and number of morphologically normal sperm were all significantly decreased in a study of those with heavy and chronic alcohol consumption.[43] In agreement with this, a recent meta-analysis indicated an effect of alcohol consumption on semen volume and sperm morphology. However, the review found no evidence for negative effects of occasional alcohol intake.[44]

Caffeine

Semen characteristics in most reported studies are apparently unaffected by caffeine intake from coffee, tea and cocoa drinks. However, male coffee drinking is associated with prolonged time to pregnancy in some studies. Conversely, data suggest a negative effect of cola-containing beverages and caffeine-containing soft drinks on semen volume, count and concentration. Caffeine intake may be associated with sperm aneuploidy and DNA breaks, but not with other markers of DNA damage.[45]

Stress

A large meta-analysis reported that psychological stress could lower sperm concentration and progressive motility and increase the fraction of sperm with abnormal morphology.[29] It is thought that effects of stress on male fertility are primarily caused by suppression of testosterone by raised corticosteroid levels.[46] An association has also been reported between stress/depression and male semen quality for those experiencing fertility issues.[47]

However, antidepressant drugs used to treat depression, anxiety disorders, chronic pain and other conditions have negative effects on sexual function and semen quality.[48] Nonetheless, there may be a place for non-pharmacological management of stress for infertile men, including cognitive behavioural therapy, psychotherapy and fertility counselling and support.[49]

Sleep

Sleep is increasingly recognised to influence a growing array of physiological processes. Sleep duration is associated with testis size in healthy young men.[50] Sleep disturbance is common, its prevalence is increasing[51] and it may contribute to male infertility.[52] Testosterone secretion follows a diurnal pattern, with a rise in testosterone coinciding with rapid eye movement (REM) sleep rather than changes in melatonin.[53] Prolactin secretion increases during sleep and levels are therefore sleep-dependent. It is worth considering the co-effects of stress/depression and poor sleep on semen analysis parameters.[54–57] Although pharmacotherapy is currently the most common treatment modality for insomnia, long-term use of hypnotics can be complicated by drug tolerance, dependence or rebound insomnia and are not recommended for male infertility.

Sperm assessment and selection

Semen analysis

Conventional semen analysis (SA) is essential in the evaluation of male fertility, and it remains the initial laboratory evaluation for infertile men. SA should be performed by an accredited andrology laboratory and to standards described by WHO for the examination and processing of human semen. WHO reference limits (the lower fifth centile of the fertile population) describe minimal standards of adequacy for semen characteristics (Table 1).[58]

A single SA is usually sufficient to determine the most appropriate management pathway. If the initial SA shows one or more abnormal parameters, a repeat should be considered.[25] Men with risk factors in their history or abnormal semen parameters should be referred to a male reproductive specialist for a full evaluation, including a detailed reproductive history and physical examination.

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Table 1. World Health Organization reference limits and 95% confidence intervals for semen parameters[58]

Parameter	Reference limit	95% confidence interval
Semen volume (ml)	1.5	1.4–1.7
Sperm concentration (10^6/ml)	15.0	12–16
Total number (10^6/ejaculate)	39.0	33–46
Total motility (PR+NP, %)	40.0	38–42
PR (%)	32.0	31–34
Normal forms (%)	4.0	3.0–4.0
Vitality (%)	58.0	55–63

NP = non-progressive motility; PR = progressive motility

Sperm DNA fragmentation

Even though SA is an essential part of the infertile male work-up, its diagnostic accuracy is limited because it lacks adequate discriminatory power[58,59] and does not predict ART outcomes.[60,61] The development of complementary tests is therefore desirable to provide data on sperm functionality. Given that DNA delivery to the oocyte at fertilisation is the main function of spermatozoa, sperm DNA integrity is key in determining its competence.[62] Several tests to evaluate sperm DNA fragmentation (SDF) are now available, including sperm chromatin structure assay (SCSA), sperm chromatin dispersion (SCD) test, terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick end-labelling (TUNEL) and the single cell gel electrophoresis (COMET) assay.[63]

Several studies using these tests have shown the percentage of spermatozoa with DNA fragmentation to be higher in infertile men than fertile men.[64] Current evidence supports the association between high SDF and poor reproductive outcomes in terms of natural conception[65] and intrauterine insemination,[66] although SDF has limited capacity to predict ART outcomes.[63] In addition, the observed association between high SDF and an increased risk of miscarriage following spontaneous conception[67] or ART[68,69] is of interest.

Nevertheless, current evidence is insufficient, neither to recommend routine DNA integrity testing for those undergoing ART, nor to predict pregnancy loss.[70] In addition, no treatment for high SDF has been proven to have clinical value, despite the proposal of several interventions, including oral antioxidant therapy, follicle-stimulating hormone treatment and the use of surgically retrieved testicular sperm.[71,72] Surgically retrieved testicular sperm avoids epididymal transit and this minimises exposure to reactive oxygen species,[73] which could contribute to a high SDF index. However, data regarding treatment outcomes, specifically live birth rate, are not robust. Furthermore, it is worth noting that sperm retrieval is an invasive procedure with potential complications. At present, this approach should be reserved for those with previous ART failure and when measures to correct underlying factors causing sperm DNA damage have failed.

New developments in sperm selection in ART

Sperm selection is a key step in ART that influences both the treatment success rate and offspring health.[74] Standard methods of sperm selection in ART treatment include density gradient centrifugation or swim-up. Both techniques isolate a population of highly motile, morphologically normal sperm and result in similar ART outcomes.[75]

However, the live birth rate following ICSI remains frustratingly static at 25–30% per (fresh) treatment cycle.[76] Various advanced sperm selection techniques have been proposed in the hope of improving this. Generally speaking, techniques either identify spermatozoa for ICSI by functional characteristics or by further purifying a prepared sperm sample.

Motile sperm organelle morphology evaluation (MSOME) involves real-time high-powered (x6600–13 000) observation of unstained sperm. Six organelles are assessed, namely the acrosome, post-acrosomal lamina, neck, tail, mitochondria and nucleus. MSOME selection of morphologically normal sperm incorporated with micromanipulation is termed intracytoplasmic morphologically selected sperm injection (IMSI). However, it has not been shown to robustly increase treatment success and its clinical use remains unclear.[77]

Hyaluronic acid is a major component of the extracellular matrix of the cumulus–oocyte complex. Physiological ICSI (PICSI) involves selection of mature sperm bound to hyaluronan microdots for oocyte injection. Findings from a recent, large RCT, which compared PICSI with conventional ICSI in 2772 couples, showed no significant improvement in live birth rate (27.4% PISCI versus 25.2% ICSI; OR 1.12, 95% CI 0.95–1.34). PICSI is therefore not recommended for routine clinical care.[78]

The hypo-osmotic swelling (HOS) test evaluates the functional integrity of the sperm plasma membrane and can be useful to assess sperm viability if motility is very poor. Live spermatozoa placed in hypo-osmotic media swell, particularly the tail, because water and small compounds influx into the cytoplasm. Importantly, this change is reversible and, because it does not damage or kill the sperm, it can be successfully used to identify viable sperm for ICSI.[79]

Microfluidic systems have been utilised for sperm purification or sorting.[80] While this technology is

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promising, a recent RCT showed no improvement in fertilisation, clinical pregnancy or live birth rates.[81]

Phosphodiesterase inhibitors (PDEIs) inhibit breakdown of cyclic AMP and/or cyclic GMP. This triggers sperm motility, allowing identification and selection of viable sperm for ICSI. Media containing theophylline, a relatively non-selective PDEI, is commercially available (SpermMobil; Gynemed, Lensahn, Germany) and has been reported to be clinically useful for sperm selection.[82,83]

Several other tests are also available, with variable success rates. Magnetic-activated cell sorting (MACS) depends on selecting preferred sperm based on membrane surface markers, with the aim of excluding apoptotic and DNA damaged sperm. However, MACS is not completely effective at reducing sperm DNA fragmentation[84] and improvement in ART outcomes are variable.[85–87]

Sperm with high negative surface electrical charge, named 'zeta potential', are mature and more likely to have intact chromatin. However, cell recovery rate using the zeta potential is low (typically <9%), making this method unsuitable for male factor. It is also time-dependent because sperm become less negatively charged during capacitation (acquisition of fertilising potential).[88]

Genetic testing in male infertility

Normal sperm production is the result of the aggregated action of up to 2300 genes.[89] In infertile men, genetic testing has made considerable advancements in recent years. Despite this, many genetic causes of male infertility remain unknown, even though it is recognised that rates of genetic abnormalities are likely to be increased among men requiring ART.[90,91] Genetic testing is currently recommended in specific circumstances, specifically the evaluation of the severely oligospermic or azoospermic male,[92–94] with the goal of testing being twofold. Firstly, it aims to identify genetic conditions that could be passed on to the offspring. Secondly, genetic testing could help to identify individuals who would likely benefit from surgical sperm retrieval procedures.[95]

Genetic tests routinely recommended in the evaluation of severe male factor infertility include karyotype, Y chromosome microdeletion analysis and cystic fibrosis transmembrane conductance regulator (CFTR) mutation analysis for men with congenital bilateral absence of the vas deferens (CBAVD). Recently, the adhesion G-protein coupled receptor G2 (*ADGRG2*) gene has been implicated in CBAVD[96] and should be considered in the genetic screening of such patients.

Karyotype testing can only detect DNA abnormalities that are 4 million base pairs or larger in size. Nonetheless, it can identify a genetic cause for a notable proportion of infertile men, particularly those with failure of spermatogenesis.[97] The most common aneuploidy is Klinefelter syndrome (47,XXY), which is identified in 11% of azoospermic males.[98] Less common abnormalities may include testicular disorder of sex development (46,XX), translocations (balanced or unbalanced), inversions, insertions or deletions. However, karyotype testing has limited resolution and cannot always provide detail regarding specific regions. One such region is the AZF region, located on the Y chromosome, part of which is deleted in 7% of azoospermic and 2.9% of oligospermic men.[99] Multiplex polymerase chain reaction (PCR) is used to amplify small portions of each one of the three regions of AZF (AZFa, proximal; AZFb, central; AZFc, distal) and identify microdeletions. This aids in patient counselling and their subsequent management because the specific location of the AZF microdeletion influences its effect on spermatogenesis. Microdeletions in the AZFc region of the Y chromosome are associated with good prognosis, with sufficient sperm being produced to justify testicular sperm extraction.[100] On the contrary, deletions involving the AZFb and AZFa regions predict a very poor prognosis for sperm retrieval, and this approach is not recommended.[101]

Unfortunately, karyotype, Y chromosome microdeletions and CFTR mutation analysis are only able to offer a diagnosis for 20% of men with infertility.[89] However, novel tests and diagnostic tools are in development, which aim to explain the other 80% of male factor infertility currently classified as 'idiopathic'. Such tests include spermatozoa genetic testing and epigenetic tests.

Direct genetic testing of spermatozoa currently includes DNA fragmentation testing (described above) and chromosome aneuploidy analysis using fluorescence in situ hybridisation (FISH) technology. Current data show that approximately 1% of the spermatozoa in an ejaculate of a fertile male are aneuploid when evaluated for five chromosomes (chromosomes 13, 18, 21, X and Y). This percentage is considerably higher in certain pathologies, such as severe morphological sperm defects; this might portend a severely poor prognosis.[102] Even though sperm chromosome aneuploidy testing could be of benefit to certain patients, it is not recommended as a screening tool because of the low incidence of significant sperm chromosome aneuploidy in the general population. There are also technical and cost issues associated with the use of multiple FISH probes. On the other hand, while epigenetic profiling of spermatozoa has not been implemented in clinical practice, the epigenome is transient and likely to be affected by numerous environmental influences, so it offers the promise of a major link between environmental influences and altered male fertility.[103]

Ethical considerations

Faced with the limitations of current ART interventions and treatments, individuals or couples with infertility often seek interventions with uncertain efficacy or questionable safety; for example, surgical sperm retrieval in cases of high SDF, or

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anti-estrogens or gonadotrophins for the management of non-obstructive azoospermia. Medical recommendations for or against an intervention are generally guided by a combination of ethical principles, namely autonomy, justice, beneficence and nonmaleficence.[104] The quality of evidence supporting an intervention and patient characteristics are also considered. However, when responding to requests for unproven interventions in an infertility setting, clinicians often face conflicting ethical principles. For example, the principle of beneficence may support the use of an unproven treatment in the absence of any alternatives, while the principle of nonmaleficence would support avoiding the use of an intervention with a dubious safety and/or efficacy profile.

To facilitate ethical discussion and collaborative action in response to unproven medical interventions, a shared decision-making approach is recommended. In this model, the clinician provides information on the medical aspects of the intervention and current best practice, answers patients' questions, ensures that the patient has expressed their own preferences in medical care and will eventually make a recommendation. This approach frequently allows a mutually acceptable consensus regarding the treatment plan to be reached. Moreover, it fosters open communication and contributes to a positive patient–clinician relationship.[105]

Conclusion

Infertility is a global health problem affecting one in seven couples. In half of these cases, male factor is, in part, responsible. As a general obstetrician and gynaecologist, it is important to be aware of modifiable lifestyle factors that provide opportunities for therapeutic intervention, as well as available sperm assessment and selection tests, including genetic tests, because these could alter clinical management in the not-so-distant future.

Disclosure of interests

NP is an Associate Editor of *The Obstetrician & Gynaecologist*; she was excluded from editorial discussions regarding the paper and had no involvement in the decision to publish.

Contribution to authorship

All authors contributed to the writing and review of the manuscript. SK supervised the review of the manuscript and did the final editing. All authors approved the final version.

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Infographic S1. Male infertility

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