Assessment of the infertile male

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Key content
• Male factors alone account for up to 30% of subfertile couples undergoing in vitro fertilisation.
• Male infertility may be due to problems with sperm production or transport and also sexual dysfunction. The underlying cause in most cases is idiopathic.
• Modifiable lifestyle factors can have an impact on male fertility, but medical treatments have a limited value in enhancing semen quality. Most treatments are based on assisted fertilisation techniques, rather than treatment of the underlying cause.
• The number and quality of sperm that can be recovered, either from the ejaculate or surgically, determines the available options for assisted conception.
• Intracytoplasmic sperm injection (ICSI) is considered relatively safe; however, because of the ability to bypass natural barriers to conception, there are concerns regarding its potential to transmit genetic defects.

Learning objectives
• To review appropriate practice in the assessment and investigation of the infertile male.
• To critically appraise the currently available investigations for male fertility.
• To summarise the treatment options for subfertile men.

Ethical issues
• Does ICSI propagate genetic causes of male infertility?
• Could there ever be a role for the use of artificial sperm in assisted reproduction?

Keywords: in vitro fertilisation / infertility / intracytoplasmic sperm injection / male / semen analysis


Introduction
It is estimated that one in seven couples in the UK experience some difficulty conceiving at some point in their reproductive life.1 Sixteen percent of couples will fail to conceive after 1 year of trying.1 A male factor alone is thought to contribute in up to 30% of these cases, with a combination of male and female factors affecting up to 40% of all infertile couples undergoing assisted reproduction.2–4

‘Normal’ reference values for semen quality were first published by McLeod5 in 1951. For several decades male infertility was considered an idiopathic and incurable condition, however, with advances in assisted reproductive technologies, effective treatments have now been developed and research into factors affecting sperm quality is increasing.

Epidemiology of male infertility
It is difficult to estimate the prevalence of male infertility in the general population, as reported fertility rates are dependent upon numerous factors, such as coital frequency, and do not necessarily reflect biological fertility. Studies in the early 1990s suggested a possible decline in semen quality,6 however, subsequent reports suggest that this finding is not universal.7 Demographic data on UK fertility rates provide evidence to suggest that male infertility is increasing.8 This, however, may be the result of increasing publicity of available treatments and thus reflect an increasing willingness of couples to seek advice and treatment. Long-term data from the Human Fertilisation and Embryology Authority (HFEA)9 analysing male factors as a cause for referral to fertility centres, has shown that the percentage of infertility attributable to male factors appears to have increased from 27.6% in 2000 to 32.5% in 2006, but since then it averages at approximately 30%.4 The evidence that sperm counts may be declining has been linked to the theory of testicular dysgenesis syndrome (TDS), which comprises a developmental disorder with increased rates of testicular cancer, undescended testes and congenital malformations.10 This may be due to environmental
factors. However, the validity of this theory has recently been questioned.\textsuperscript{11}

Box 1. Main causes of male factor infertility

<table>
<thead>
<tr>
<th>Pretesticular:</th>
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<tbody>
<tr>
<td><strong>Hypothalamic disease</strong></td>
</tr>
<tr>
<td>- Gonadotrophin deficiency (Kallman syndrome)</td>
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<tr>
<td><strong>Pituitary disease</strong></td>
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<tr>
<td>- Pituitary insufficiency (tumours, radiation, surgery)</td>
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<tr>
<td>- Hyperprolactinaemia</td>
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<tr>
<td>- Exogenous hormones (anabolic steroids, glucocorticoid excess, hyper- or hypothyroidism)</td>
</tr>
<tr>
<td>Testicular:</td>
</tr>
<tr>
<td><strong>Congenital</strong></td>
</tr>
<tr>
<td>Genetic</td>
</tr>
<tr>
<td>- Chromosomal (Kleinfeiter syndrome 47, XXY)</td>
</tr>
<tr>
<td>- Y chromosome microdeletions</td>
</tr>
<tr>
<td>- Noonan syndrome (male Turner syndrome 45, XO)</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>- Cryptorchidism</td>
</tr>
<tr>
<td><strong>Acquired</strong></td>
</tr>
<tr>
<td>- Injury (orchitis, torsion, trauma)</td>
</tr>
<tr>
<td>- Varicocele</td>
</tr>
<tr>
<td>- Systemic disease (renal failure, liver failure)</td>
</tr>
<tr>
<td>- Chemotherapy, radiotherapy</td>
</tr>
<tr>
<td>- Testicular tumours</td>
</tr>
<tr>
<td>- Idiopathic</td>
</tr>
<tr>
<td>Post-testicular (obstruction):</td>
</tr>
<tr>
<td><strong>Congenital</strong></td>
</tr>
<tr>
<td>- Cystic fibrosis, congenital absence of the vas deferens (CAVD)</td>
</tr>
<tr>
<td>- Young's syndrome</td>
</tr>
<tr>
<td><strong>Acquired</strong></td>
</tr>
<tr>
<td>- Vasectomy</td>
</tr>
<tr>
<td>- Infection (chlamydia, gonorrhoea)</td>
</tr>
<tr>
<td>- Iatrogenic vasal injury</td>
</tr>
<tr>
<td><strong>Disorders of sperm function or motility</strong></td>
</tr>
<tr>
<td>- Immotile cilia syndrome</td>
</tr>
<tr>
<td>- Maturation defects</td>
</tr>
<tr>
<td>- Immunological infertility</td>
</tr>
<tr>
<td>- Globozoospermia</td>
</tr>
<tr>
<td><strong>Sexual dysfunction</strong></td>
</tr>
<tr>
<td>- Timing and frequency</td>
</tr>
<tr>
<td>- Erectile/ ejaculatory dysfunction</td>
</tr>
<tr>
<td>- Diabetes mellitus, multiple sclerosis, spinal cord/pelvic injuries</td>
</tr>
</tbody>
</table>

Regulation of spermatogenesis

Sperm are formed in the seminiferous tubules, from germinal cells called spermatogonia. Spermatogonia divide by mitosis into primary spermatocytes, which in turn undergo two reduction divisions (meiosis I and II) to form spermatids. By the process of spermiogenesis, spermatids transform into mature cytoplasm-free sperm with condensed DNA in the head, an apical acrosome and a tail. Normal spermatogenesis is under the influence of follicular stimulating hormone (FSH) and testosterone. FSH binds to Sertoli cells and increases spermatogonial number and maturation to spermatocytes, but it is unable to complete spermatogenesis alone. Luteinising hormone (LH) is necessary for testosterone production by the Leydig cells, and plays an essential role in spermatid maturation. The entire spermatogenic process, including transit in the ductal testicular system takes approximately 3 months.\textsuperscript{12} This is important to bear in mind when advising individuals on the potential effect of lifestyle changes on semen quality improvement.

Causes of male infertility

Causes of male factor infertility can be classified into pretesticular, testicular and post-testicular (Box 1). Conditions that act at the pretesticular level tend to be hormonal in nature and most of these can be treated with hormone manipulation. Causes at the testicular level are largely irreversible, but can be treated with assisted reproductive technology (ART), if sperm is retrievable. Post-testicular causes can be treated with microsurgery or with ART. It is estimated that in about 50% of men with poor semen quality, no cause for this will be identified.\textsuperscript{13}

Male age

Male age has been shown to have an impact on fertility and offspring health.\textsuperscript{14} A UK study\textsuperscript{15} has shown that paternal age of >35 years halves the chance of achieving a pregnancy compared with a paternal age of <25 years. The effect of age on male fertility is more noticeable after the age of 50,\textsuperscript{16} with studies showing a concomitant increase in adverse outcome in the offspring.\textsuperscript{17,18} For this reason, the age of semen donors is limited to 40 or 45 years in some countries.\textsuperscript{19}

Environmental, occupational and lifestyle factors

There is increasing evidence from epidemiological studies that occupational exposures to certain chemicals can affect semen quality.\textsuperscript{20,21} More than 104 000 such chemicals and physical agents have been identified.\textsuperscript{1} These include heat, X-rays, heavy metals (lead, mercury), glycol ethers (highly volatile compounds used as solvents)\textsuperscript{22} and pesticides; a well documented example being dibromochloropropane (DBCP), a nematocide used in certain crops. The exact mechanism by which these occupational substances affect male fertility remains unclear.

Despite earlier reports, the level of environmental estrogens would not appear to be a threat to male reproductive health.\textsuperscript{23} Recent observational studies support
a dose-dependent decrease in semen parameters related to exposure to electromagnetic waves emitted from mobile phones. The clinical significance of this, however, remains unclear. Testicular hyperthermia may affect semen quality. However, there is no clear evidence that wearing loose-fitting underwear improves fertility. There is evidence that a sedentary lifestyle, most likely through elevated scrotal temperature, can affect sperm production.

Obesity is an important lifestyle factor that has been shown to be associated with poor semen quality. As the prevalence of obesity in Western countries is increasing, it is likely that it will have an increasing impact on male fertility. The mechanism by which obesity causes altered semen parameters is thought to be through an imbalance of reproductive hormone levels, as obese men have reduced sex hormone binding globulin and elevated estrogen levels. Altered metabolism of environmental toxins, sedentary lifestyle factors and increased risk of sexual dysfunction are also thought to contribute to reduced fertility in heavier men.

Anabolic-androgenic steroids may induce azoospermia by interfering with the hypothalamo-pituitary-gonadal (HPG) axis. They may also inhibit male reproductive function through loss of libido and erectile dysfunction secondary to low endogenous testosterone levels. Azoospermia may be reversed by conservative management when the drugs are discontinued, especially in non-heavy users, or by administration of human chorionic gonadotrophin and human menopausal gonadotrophin. Sperm quality tends to recover spontaneously within 4–12 months after discontinuation. However, persistent alterations in semen parameters can remain even after cessation of use. It is therefore important to encourage discontinuation of use immediately and to emphasise that even ‘steroid-free’ dietary supplements have been reported to be contaminated with traces of hormones.

Heavy alcohol consumption, but not moderate consumption, may affect sexual and reproductive performance in a reversible fashion. Tobacco smoking and cannabis consumption have been shown to reduce semen parameters, although the relationship between male smoking habits and fertility remains uncertain. Although smokers in general may not experience reduced fertility, men with suboptimal semen quality may benefit from quitting smoking and this should be strongly encouraged. Other recreational drugs such as cocaine, amphetamines and opiates may adversely affect reproductive performance due to decreased libido and erectile dysfunction.

According to some reports, sperm DNA damage secondary to oxidative stress may be the cause of between 30% and 80% of male subfertility cases. Recent evidence suggests that antioxidant supplementation in subfertile males, including carnitines, vitamin C, vitamin E, selenium, zinc and coenzyme Q10, improves semen quality and live birth rates in couples undergoing fertility treatment.

Pretesticular
Hypogonadotrophic hypogonadism is rare and accounts for ~1% of male factor fertility problems. It results from decreased production of FSH and LH secondary to hypothalamic or pituitary dysfunction, which leads to failure of spermatogenesis and testosterone secretion by the testes. It may be congenital or acquired. Causes include craniopharyngiomas, surgery for pituitary tumours, head trauma, haemochromatosis, Kallmann syndrome and other congenital genetic syndromes of reduced gonadotrophin releasing hormone (GnRH) secretion (Prader–Willi syndrome, Laurence–Moon–Biedl syndrome).

Testicular
Hypergonadotrophic hypogonadism results from testicular failure and leads to oligozoospermia and non-obstructive azoospermia with elevated LH and FSH levels. Also, the finding of normal testosterone and LH levels with an elevated FSH implies isolated spermatogenic failure without Leydig cell damage. Causes of testicular failure include bilateral cryptorchidism, genetic disorders, systemic disease, radiotherapy or chemotherapy (see Box 1). However, in the majority of cases (66%) the cause is unknown. The diagnosis is based on reduction in testicular size and elevation of serum FSH levels.

Varicocele
Varicoceles, a collection of dilated refluxing veins in the spermatic cord, are found in 11.7% of men with normal semen and 25.4% of men with abnormal semen. The exact mechanism by which a varicocele can affect fertility is not well understood but theories include increased scrotal heating and altered testicular steroidogenesis. The diagnostic significance of a varicocele is debatable.

Post-testicular
Obstruction, excluding vasectomy, accounts for up to 41% of causes of azoospermia. The diagnosis is based on normal serum FSH levels, normal testicular volume and evidence of complete spermatogenesis on biopsy. Causes include surgical trauma and vasectomy, infection (chlamydia, gonorrhoea, tuberculosis), and congenital bilateral absence of vas deferens (CBAVD).

Clinical management
History and physical examination together with the semen analysis provide the basic information for the initial evaluation of most men.
**Assessment of the infertile male**

**Box 2. Components of infertility history in the male**

**Medical history**
- Recent pyrexia/illness
- Systemic illness – diabetes mellitus, cancer, infection
- Genetic disorders – cystic fibrosis, Klenefelter syndrome

**Surgical history**
- Undescended testes, orchidopexy
- Hernia repair
- Testicular trauma, torsion
- Pelvic, bladder or retroperitoneal surgery

**Fertility history**
- Previous pregnancies – with current and previous partners
- Duration of infertility
- Previous infertility treatments

**Sexual history**
- Erection or ejaculation problems
- Frequency of intercourse

**Medication**
- Nitrofurantoin, cimetidine, sulfasalazine, spironolactone, β-blockers, methotrexate, colchicine, amiodarone, antidepressants, phenothiazines, chemotherapy

**Social history**
- Alcohol, smoking, anabolic steroids, recreational drugs
- Exposure to ionising radiation
- Chronic heat exposure
- Aniline dyes
- Pesticides
- Lead exposure

**History**
In addition to a normal general medical history, particular attention should be paid to history of undescended testes, pubertal development, genital surgery or infection, fertility in the current or previous relationships and coital frequency, erection or ejaculation problems. A list of information relevant to the infertility history is summarised in Box 2.

**Physical examination**
Examination of the male is important to identify any characteristics of men initiating natural conception within 12 months of unprotected intercourse, in a number of different countries. It is important to remember that these are not absolute limits and should always be interpreted in conjunction with relevant clinical information to provide guidance about the prospects of a particular couple’s fertility.

**Investigations**

**Semen analysis**
Semen analysis is the most important investigation of male subfertility. This is not a test for fertility but a guide for minimal standards of adequacy. What constitutes a ‘normal’ result has been a matter of debate, and recently the WHO48 normal ranges for semen parameters have changed (Table 1). These values represent the 5th percentile of semen characteristics of men initiating natural conception within 12 months of unprotected intercourse, in a number of different countries. It is important to remember that these are not absolute limits and should always be interpreted in conjunction with relevant clinical information to provide guidance about the prospects of a particular couple’s fertility.

NICE1 recommends that semen analysis should be performed according to the WHO methodology. This must be carried out in a qualified lab in accordance with the UK National External Quality Assessment Service (NEQAS) accreditation standards.49 One sample will suffice if normal. However, a man’s sperm count can vary considerably over time and therefore, if an abnormality is detected a repeat semen analysis should be performed after 3 months, or sooner if the initial test shows azoospermia. This reduces the likelihood of a transient illness causing misleading results.

It is important that clear instructions regarding the period of abstinence, method of production and transport of

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**Table 1. World Health Organization reference limits and 95% confidence intervals for semen parameters48**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reference limit</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semen volume (ml)</td>
<td>1.5</td>
<td>1.4–1.7</td>
</tr>
<tr>
<td>Sperm concentration (10^6/ml)</td>
<td>15.0</td>
<td>12–16</td>
</tr>
<tr>
<td>Total number (10^9/ejaculate)</td>
<td>39.0</td>
<td>33–46</td>
</tr>
<tr>
<td>Total motility (PR+NP,%)</td>
<td>40.0</td>
<td>38–42</td>
</tr>
<tr>
<td>Progressive motility (PR,%)</td>
<td>32.0</td>
<td>31–34</td>
</tr>
<tr>
<td>Normal forms (%)</td>
<td>4.0</td>
<td>3.0–4.0</td>
</tr>
<tr>
<td>Vitality (%)</td>
<td>58.0</td>
<td>55–63</td>
</tr>
</tbody>
</table>

NP = non-progressive motility; PR = progressive motility

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The scrotum should be carefully palpated with the patient standing. Testicular size and consistency should be noted. If one or other testicle is impalpable, the groin should be examined to see if it can be located. The presence and normality of the vasa deferentia should be confirmed. For size measurement, an orchidometer can be used for volume estimation. A mean volume of 20 ml in the adult is considered normal.47 Consistency can be described as firm (normal), soft or hard (abnormal). A soft or small testis can indicate impaired spermatogenesis. If an undescended testicle is diagnosed, the patient should be referred to a urologist for further management.

The epididymis should be examined for distension or induration. Engorgement of the pampiniform plexus of veins in the scrotum is indicative of a varicocele. Varicoceles are usually found on the left side and may be associated with atrophy of the left testis. Testicular size discrepancy and the feeling of a ‘bag of worms’ with a Valsalva manoeuvre should alert to this possibility. Varicoceles are best identified with the patient standing.

Penile and prostatic abnormalities may also be noted. Penile abnormalities such as micropenis or hypospadias may result in inadequate delivery of semen to the upper vagina. Rectal examination may reveal prostate abnormalities or seminal vesicle enlargement.
needed in this area to confirm the precise prognostic value for sperm recovery in AZFa and AZFb micro-deletions is poor and such individuals should not be offered surgical sperm retrieval. However, more studies are needed in this area to confirm the precise prognostic significance. CBAVD can be associated with cystic fibrosis carrier status and therefore men with non-palpable vas deferens should be tested for mutations in the cystic fibrosis gene, as indeed should all men with idiopathic obstructive azoospermia.

**Imaging**

Scrotal ultrasound should be performed if an abnormality such as a testicular tumour is detected on physical examination. Ultrasound can also be useful in the clinical diagnosis of varicocele, especially with the use of colour flow Doppler and demonstration of retrograde blood flow with a Valsalva manoeuvre. If an absent vas is detected on examination, a renal ultrasound scan is recommended, as up to 30% of such men may have a renal abnormality.

**Testicular biopsy**

Testicular biopsy can aid the diagnosis of severe oligospermia and azoospermia and facilitate sperm recovery for intracytoplasmic sperm injection (ICSI) use. Biopsy can be done by an open or percutaneous needle approach and is used to obtain a small piece of testicular tissue for histological examination. Testicular biopsy specimens can be classified histologically:

- normal (appropriate number of cells with complete spermatogenesis)
- hypospermatogenesis (all cell types present and in correct ratio but at reduced cell numbers)
- maturation arrest (failure of spermatogenesis beyond a certain stage; can be ‘early’ or ‘late’)
- sertoli cell-only (del Castille) syndrome (no germ cells).

In some cases complex mixtures of pathological patterns may be present.

**Other sperm function tests**

Routine semen analysis provides information about spermatogenesis and sperm delivery, but gives little information about the functional ability of sperm. A number of tests have been developed to assess this. These include the postcoital test, the sperm penetration assay (SPA) and the hemizona assay (HZA). There is some evidence to suggest that these tests can correlate with the outcome of natural conception or in vitro fertilisation (IVF), but the general consensus is that they are of limited value from a practical point of view. They are therefore not used routinely in clinical practice in the UK.

Sperm DNA fragmentation has been shown to be a robust predictor of assisted reproductive outcomes. Sperm DNA tests such as the sperm chromatin structure assay (SCSA), the comet assay and the TUNEL (terminal deoxynucleotidyl transferase-mediated dUTP nick end-labelling) assay, which assess sperm DNA integrity, show promise both as diagnostic...
tests for male infertility and prognostic tests for the outcome of assisted reproductive technologies.\textsuperscript{57} Their clinical application, however, needs further evaluation and improvement.\textsuperscript{55}

**Treatment options**

**Medical treatment**

Specific hormonal treatments can be effective in known endocrine disorders such as hyperprolactinaemia, hypothyroidism and congenital adrenal hyperplasia. Hypogonadotrophic hypogonadism can be treated successfully with GnRH or exogenous gonadotrophins. In general though, medical treatments have a limited role in idiopathic male infertility.

**Primary testicular failure**

There is no effective treatment to restore fertility in primary testicular failure. Men undergoing treatments that contribute to infertility, such as chemotherapy, should be offered the opportunity to cryopreserve semen.\textsuperscript{1} Alternatively, surgical sperm retrieval with assisted reproduction or donor sperm may be considered.\textsuperscript{1}

**Urological surgery**

**Reversal of vasectomy**

The success rates for vasectomy reversal depend on the skill of the operating surgeon, surgical technique and the time from the initial surgery. Patency rates seem to decline with increasing time due to the increasing rates of anti-sperm antibody development and secondary epididymal obstruction.\textsuperscript{58}

**Surgical sperm retrieval**

Sperm can be retrieved from the testes or the epididymis for use in IVF/ICSI. Common indications include obstructive causes, severe male factor infertility or ejaculatory failure. Techniques for sperm retrieval from the testes include testicular sperm aspiration (TESA), testicular sperm extraction (TESE) and microsurgical TESE (micro-TESE). The results of a single biopsy may not be indicative of the spermatogenic process in the whole of the testis and multiple biopsies may be necessary. Sperm from the epididymis can be retrieved by microsurgical (MESA) or percutaneous (PESA) epididymal sperm aspiration under local anaesthetic. Testicular biopsy should be done in a tertiary centre with facilities for sperm cryopreservation. Success rates for surgical sperm retrieval of almost 100% have been reported in obstructive cases, with lower rates of approximately 50% in non-obstructive cases. A meta-analysis of the use of surgical sperm retrieval in azoospermic men, showed the outcome of ICSI cycles in terms of fertilisation rates and clinical pregnancy rates to be significantly higher with the use of sperm from men with obstructive azoospermia as compared with non-obstructive azoospermia.\textsuperscript{59}

**Varicocele repair**

The degree to which varicocele repair improves pregnancy rates and the success of assisted reproductive technology remains controversial. NICE\textsuperscript{1} recommends that: ‘men should not be offered surgery for varicoceles as a form of fertility treatment because it does not improve pregnancy rates’.

However, recent evidence from a randomised control trial indicates that varicocelectomy in infertile men with impaired semen quality and palpable varicoceles, significantly improves semen characteristics and the chances of pregnancy within 1 year of follow-up.\textsuperscript{60} Overall, the evidence is stronger with regard to an improvement in sperm parameters, with less convincing evidence for this translating into higher spontaneous pregnancy rates.\textsuperscript{61} Varicocelectomy may also correct the serum testosterone deficit in men with varicocele and low testosterone levels.\textsuperscript{62}

**Assisted reproduction**

**Intrauterine insemination (IUI)**

IUI involves the placement of a washed pellet of ejaculated sperm within the uterine cavity, thus bypassing the cervical barrier. It can be performed with or without ovarian stimulation. Indications include mild male factor infertility, immunologic infertility and mechanical problems of sperm delivery such as erectile dysfunction or hypospadias. NICE recommends that IUI is used in mild forms of oligozoospermia,\textsuperscript{1} however, specific semen criteria for its use have not been standardised. Monthly conception rates of 8\textsuperscript{–}16% have been reported\textsuperscript{63} for IUI, however its efficacy has been questioned by recent studies.\textsuperscript{64,65} NICE\textsuperscript{1} currently recommends the use of up to six cycles of unstimulated IUI in mild cases of male factor infertility in order to reduce the rate of multiple pregnancies.

**In vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI)**

Although IVF can be used to treat milder forms of sperm abnormalities, more severe forms require ICSI. ICSI was originally described in 1988\textsuperscript{66} and has since revolutionised the treatment of male factor infertility. It involves the micromanipulation and injection of a single human sperm into the cytoplasm of the oocyte. ICSI requires ovarian stimulation, oocyte retrieval and sperm preparation as for IVF. It is used for un-correctable severe forms of male factor infertility including oligospermia and asthenoteratozoospermia, or following fertilisation failure in a previous IVF cycle. Average pregnancy rates of 33.0% per embryo transfer have been reported after ICSI.\textsuperscript{60,67}
Ethical issues

As ICSI bypasses the natural barriers to fertilisation, it raises one important matter of concern, which is the potential genetic risks associated with this procedure and the propagation of genetic defects that caused the infertility. This has ethical implications, especially with respect to the propagation of genetic defects that may re-surface in the male offspring of treatable infertile men. This could potentially lead to the creation of a population of subfertile men.

Recent data suggest that offspring born to infertile couples using ICSI have a higher incidence of chromosomal anomalies than do children who are naturally conceived. This may relate to the characteristics of the couples that require such treatment. The relationship between ICSI and the risk of congenital abnormality in the offspring remains unclear. In view of these concerns, and until robust evidence is available, couples should be fully counselled about these uncertainties prior to initiating treatment.

‘Artificial’ haploid gametes have been successfully created in vitro from embryonic stem cells in animal models. These gametes have been used to create live offspring in mice. The prospect of using artificially created human sperm to treat male fertility problems would raise important ethical issues.

Conclusion

Male infertility is a common problem that requires appropriate specialist referral. Assessment should include full clinical history and careful examination. Semen analysis remains the main initial investigation that guides further assessment of the infertile male. Over the past two decades, advances in research have increased the treatment options available for male infertility. The potential for ICSI to propagate genetic abnormalities warrants thorough counselling for couples regarding the possible implications of its use, prior to treatment starting. The health and wellbeing of children following ICSI requires long-term follow-up.

In the future, a better understanding of the causes of male infertility and new reproductive technologies may offer the possibility of novel treatments, but these need to be carried out within the appropriate ethical framework.

Conflict of interest

None declared.

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