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Assessment of male factor

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The assessment of male infertility is largely based around the examination of a freshly produced ejaculate by a trained technician according to laboratory methods agreed by the World Health Organization. Although many suggestions have been made to improve this approach, the basic techniques of semen analysis established in the 1950s are still being used. Although several putative tests of sperm function have been developed (e.g. the measurement of sperm hyperactivation, sperm acrosomal status, or sperm penetration through mucus or binding to zona pellucida), none have made it into routine clinical practice. Recently, several 'new' tests of sperm function and sperm selection have been developed. These include the use of microfluidic chambers, electrophoresis, the binding of sperm to hyaluronic acid, and high magnification sperm selection. Randomised-controlled trials are needed to evaluate these as a replacement or addition to routine semen analysis or current sperm preparation methods.

Background to male infertility

The incidence of infertility in men is difficult to establish reliably, but current evidence suggests that up to 20–25% of young men have poor semen quality and, in 30–50% of couples undergoing in-vitro fertilisation (IVF), a male factor contributes to infertility.[1] Unlike the situation in some cases of female infertility (e.g. amenorrhea), possible male infertility is not outwardly obvious because, macroscopically, the ejaculates of fertile and infertile men appear the same. It is only when couples fail to achieve conception, that male infertility may be suspected and laboratory tests (e.g. semen analysis) are clearly required to establish this reliably.[2]

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In recent years, whether or not the incidence of male infertility has increased has been furiously debated.[1] This has largely been based on the hypothesis that, as yet, unknown factors in the environment are affecting the testicular development of an increasing number of male babies before birth.[3] It is proposed that after puberty such affected individuals are more likely to produce ejaculates with reduced sperm count and consequently are less fertile. Direct evidence to support this hypothesis, however, is lacking; moreover, more recent prospective data have suggested that semen quality in young men is not declining[4] in the way that was originally proposed from an analysis of retrospective studies.[5] Although increasing rates of urogenital defects and incidence of testicular cancer have been demonstrated, lending some support to the original theory, the cause of such urogenital conditions is clearly more complex than was first proposed.[6]

As well as pre-natal exposures, the spermatogenesis of post-pubertal males can also be influenced by a number of medical and lifestyle factors.[7] For example, the ejaculates of men who have been treated with chemotherapy or radiotherapy typically have lower sperm concentrations than men not treated with these agents.[8] Similarly, men exposed to glycol ether in the workplace,[9] or men who have been infected with the sexually transmitted infection *Chlamydia trachomatis* have lower sperm concentrations.[10,11] Direct and independent effects on sperm motility, sperm morphology, or both, are less well described but equally important in their effect on male fertility.

Background to semen analysis

Antonie van Leeuwenhoek[12] first described human spermatozoa in 1678, although it wasn't until the 1950s when the first clinical descriptions of the relationship between semen quality and conception were made.[13–15] In 1980, the World Health Organization (WHO) then published an internationally agreed 'reference range' designed to help clinicians make decisions using data on semen quality[16]; over the next 30 years, four further updates[17–20] were produced as shown in Table 1.

As these 'ranges' became widely used in clinical practice, two issues became apparent. The first was how the variation in the technique used in different laboratories could affect the semen analysis results being reported significantly. This was illustrated in a series of studies in the UK[21,22] and the USA,[23] leading to the establishment of training programmes[24,25] and external quality-assurance programmes[26–28] in andrology. The second was that, even when semen analysis was carried out robustly, and with appropriate quality-control measures in place, a significant uncertainty could remain about the relationship between semen profile and the probability of conception.[29–31] As a consequence, commentators argued the need to further revise the WHO 'reference ranges'. To some extent, the publication of the 5th edition of the WHO manual in 2011[20] has addressed this problem in basing the reference ranges for the first time on 'real world' data.[32] This also introduced the importance of 'confidence intervals', allowing the user to understand the individual semen analysis values obtained in the context of measurement error (Table 2).

It has long been recognised that semen analysis only goes so far in providing a physical description of the ejaculate. Therefore, in an attempt to improve on this, many investigators have now turned their attention to the potential value of assessing aspects of sperm DNA either as a routine part of semen analysis or as a replacement to it.[33–35] This concept is underpinned by the logic that, although sperm

Table 1
World Health Organization reference ranges from 1980 to 2010 for the minimum semen quality thought to be compatible with unassisted conception.[16–20]

	1980	1987	1992	1999	2010
Semen volume (ml)	–	≥2.0	≥2.0	≥2.0	≥1.5
pH	–	7.2–7.8	7.2–7.8	7.2	–
Sperm concentration ($\times 10^6$/ml)	≥20	≥20	≥20	≥20	≥15
Total sperm number ($\times 10^6$)	–	≥40	≥40	≥40	≥39
Progressive Motility (%)	≥60	≥50	≥50	≥50	≥32
Normal morphology (%)	≥80	≥50	≥30	–	≥4
Vitality (% alive)	–	≥50	≥75	≥75	≥58
White blood cells	≤5.0	≤1.0	≤1.0	≤1.0	≤1.0
Antibody coated sperm (%)	–	≤10	≤20	≤50	≤50