Male fertility and infertility in 2011 and beyond

Allan A Pacey

Abstract

In 30—50% of sub-fertile couples the male partner has poor semen quality, either because of low sperm count, poorly motile sperm or sperm with abnormal size and shape (morphology). This may result from inherent genetic factors, poor pre-natal testicular development or adult exposure to gonadotoxic agents. There are few proven therapies to improve semen quality. Therefore, the number and quality of sperm that can be recovered from the ejaculate, or obtained by surgical sperm recovery, determines the available options for assisted conception. In recent years, the reliance upon donor sperm has reduced markedly as intracytoplasmic sperm injection can be attempted. Reproductive technologies are considered relatively safe, with healthy babies born; however, there are some concerns about potential reproductive problems in males conceived in this way. These may be related to the techniques used, or the underlying infertility of the parents, and are currently the subject of follow-up studies.

Keywords donor insemination; intra-cytoplasmic sperm injection; male fertility; semen analysis; spermatozoa

Introduction

In most males the onset of sperm production (spermarche) begins at puberty, typically between the ages of 13 and 15 years old. Once spermatogenesis has started, evidence suggests that in most males it continues almost constantly until death and the current consensus is that there is no significant reduction in the number, or concentration, of sperm ejaculated with age. Typically, the ejaculates of fertile men can contain up to several hundred million sperm per ml, although this is highly variable both within and between individuals.

The production of sperm takes approximately 3 months and is a consequence of both mitotic and meiotic activity leading to cell proliferation and a reduction in the number of chromosomes from diploid to haploid. An appreciation of the timeline of sperm production is important to recognize when attempting to advise patients of the potential benefit of lifestyle changes in improving semen quality, or when managing the use of endocrine therapy to initiate sperm production (e.g. in Kallman's syndrome).

Studies have attempted to characterize the sperm that are able to ascend the female reproductive tract, and bind to the unfertilized oocyte, and these provided the opportunity for scientists to establish the optimum size and shape of sperm. In comparison to most mammals, human sperm are very poor. A recent study of the semen quality of 889 men prior to vasectomy found that the mean percentage (± standard deviation) of normal sperm morphology was 17.57 ± 9.50. Similarly a recent analysis of over 1800 men whose partners conceived within 12 months found that 10% of them had a mean sperm morphology of less than 5.5%.

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Incidence of male infertility

Population estimates of male infertility are difficult to establish reliably. General census data of semen quality is always biased towards those with experience of infertility and few cross-sectional studies of the general (fertile) population are available. However, it is known that there is a male factor problem contributing to the infertility in 30—50% of all couples undergoing *in vitro* fertilization (IVF). Given that there are over 1000 cycles of IVF performed per million European inhabitants per year, male infertility is experienced by a substantial number of men.

Causes of male infertility

Male infertility may be due to a number of different reasons including:

- diseases of the hypothalamus and pituitary gland that affect the endocrine signals to the testes or prevent adequate testicular development at puberty (e.g. Kallman's syndrome)
- disorders at the testicular level that may affect the rate or the quality of sperm production
- dysfunction of the seminal ducts that prevents or inhibits sufficient numbers of sperm being ejaculated (e.g. congenital absence of the vas deferens)
- disorders of sexual function and/or ejaculation that interfere with intromission, such as spinal cord injury.

Each of these largely results in ejaculates containing either too few sperm (oligozoospermia), or insufficiently motile sperm (asthenozoospermia) or insufficient proportions of morphologically normal sperm (teratozoospermia) to allow any reasonable chance of unassisted conception occurring within 1 year. Less than 1% of men are truly sterile and do not produce any spermatozoa (i.e. are consistently azoospermic).

In recent years, concern has been growing over whether or not male infertility is becoming more common. This has been highlighted by studies and meta-analyses that have suggested in many parts of the world that there has been an apparent drop in semen quality alongside an increase in the incidence of developmental disorders of the male reproductive tract seen in newborns (e.g. cryptorchidism and hypospadias) and an increase in the incidence of germ cell tumours among young men. These pathologies are now thought to be linked by a common mechanism, termed testicular dysgenesis syndrome (TDS). This is thought to occur as a result of a disruption of gonadal development during critical neonatal stages (Figure 1).

Whether or not the apparent reduction in semen quality and associated increase in male reproductive problems is genetically or environmentally driven, some authors have suggested that a general decline in male fertility may explain why there has been a significant fall in the birth rate in many developing and industrialized countries. However, the fact that there is now a greater use of contraceptives among couples, as well as the active decision to wait until the female partner is older (and

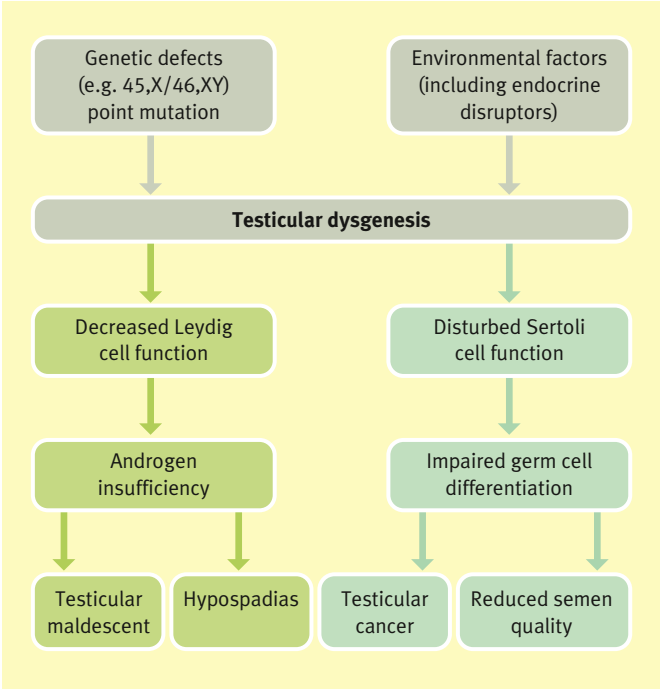

Figure 1 The theoretical pathogenetic links between the components and clinical manifestations of testicular dysgenesis syndrome (TDS) and how direct effects on the male foetus *in utero* can lead to the appearance of a suite of phenotypes such as reduced semen quality, testicular cancer or maldescent or hypospadias. Redrawn from Skakkaebaek et al. 2001 and reproduced with kind permission of Oxford University Press.

therefore less fertile herself) before they have children, makes it difficult to separate biology from social factors as an explanation for the apparent reduction in birth rate.

Diagnosis

The diagnosis of male infertility involves an exploration of the patient's medical history and physical examination followed by laboratory tests such as semen analysis (see below) and, if indicated, genetic tests such as karyotype and tests for cystic fibrosis carrier status. The World Health Organisation (WHO), the Royal College of Obstetricians and Gynaecologists (RCOG) and the National Institute for Health and Clinical Excellence (NICE) have each produced guidelines for the evaluation of the infertile male. However, Figure 2 shows an idealized algorithm followed by many gynaecologists with the results of semen analysis guiding the decision to undertake further tests, including surgical sperm retrieval. Many gynaecologists prefer not to examine men and rather rely on the results of semen analysis alone to guide their decisions. However, physical examination is always recommended to preclude the possibility of testicular cancer and also symptoms of sexually transmitted infection. As a typical rule of thumb, when an ejaculate contains less than 5 million sperm, then tests for cystic fibrosis carrier status and a karyotype should be performed.

Semen analysis

The laboratory techniques of semen analysis are defined by the WHO and the guidance was revised in 2010, including the publication of new references ranges. Historically, significant variation can exist in the data generated between laboratories that analyze aliquots of the same sample circulated for quality assurance purposes. It has been shown that the most precise measurements are made when semen analysis is performed in specialist andrology laboratories rather than general laboratories available in many hospitals (including embryology laboratories). The danger is that without adequate precision, the results may guide a doctor away from some of the supplementary tests outlined in Figure 2. Clinicians should, therefore, be aware of such variability and make efforts to understand the robustness of the measures generated in the laboratories they use to undertake semen analysis on their patients.

In spite of the problems in performing semen analysis, follow-up studies of couples attempting to conceive show that where semen analysis is performed robustly, there are good relationships between the individual measures of semen quality obtained (concentration, motility and morphology) and the probability of conception. A recent analysis of semen quality in over 1900 men whose partners had a time to pregnancy of less than 12 months has led to a revision of the WHO guidelines for the lower reference limits of semen quality. This is now based on the 5th centile of a fertile population and has led to a step-change in the definition that clinicians use to guide their decisions (see Table 1). Doctors should be aware of this change and make sure they are familiar with the methodology being undertaken in the laboratory that analyzes samples from their patients.

Other laboratory tests

In an attempt to improve the accuracy of laboratory tests, many researchers have developed more sophisticated tests designed to investigate specific aspects of sperm biology or to mimic in some way aspects of the journey sperm make to the site of fertilization. These are termed sperm function tests and include measuring the ability of sperm to:

- enter and make progression in mid-cycle cervical mucus (sperm mucus penetration tests)
- hyperactivate following capacitation
- bind to the zona pellucida
- undergo the acrosome reaction
- penetrate zona-free hamster eggs.

Although for each of these there is reasonable body of evidence to suggest correlations with outcome of IVF or unassisted conception, none of these tests has, to date, been universally incorporated into clinical practice.

Perhaps the tests with most current promise are those that examine the integrity of sperm DNA. However, many studies have suggested correlations between the integrity of sperm DNA and the probability of spontaneous conception, the outcome of assisted conception treatment, embryo quality and the probability of miscarriage and early pregnancy loss. However, both the American Society for Reproductive Medicine and the European Society for Human Reproduction and Embryology have recently reviewed the evidence base for sperm DNA testing and have concluded, for the time being at least, that there is insufficient evidence for such tests to be offered on a routine basis. As such, patients should only be offered the option to have their DNA quality tested in the context of an appropriately designed clinical trial.