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This may be a strange question to ask at the beginning of a book on male infertility but it is an important one and, as will become clear when we examine this subject in detail, it is a question that can be difficult to answer. However, it is important that we have some idea about what we mean when we use the words, “male infertility.”

What do we mean by fertility: male or female?

Infertility whether it is male or female is usually defined as lack of conception leading to a live birth after 1 year of regular coitus. Humans are, however, relatively infertile at least in relation to fertility among the domesticated species. In the human, only one in four cycles will result in a clinical pregnancy and not all of these conceptions will result in the birth of a live child. Indeed, about one in every eight clinical pregnancies results in fetal loss at some stage during gestation. Such a poor outcome would not be acceptable to those involved in animal husbandry.

The reason why the period of a year is used to define infertility is that at the end of 1 year a reduction in the frequency of conception among couples trying to achieve a pregnancy over that time will be seen. Moreover, after that interval an increase in the frequency of abnormalities in reproductive function can be found among couples that have been trying to conceive over that time period.

The longer the inability to conceive persists, the less likely it is that natural conception will occur. Thus, the duration of the infertility has an important bearing upon its management. For example, for a couple that has been trying to conceive for 1 year the chances of natural conception in the subsequent year may be as high as 50% but after 5 years of trying to conceive, spontaneous conception will only occur in about 5% of these couples. This reduction in the percentage of natural conceptions indicates the presence of more serious and persisting faults in reproductive function. These data have some meaningful pointers in relation to the chances of spontaneous conception without the use of any form of medical aid. Time may thus play a role in the definition of infertility in men as well as in women.

Age will also be an important factor in the determination of fertility. This is much more striking in women than it is in men and, indeed, it begins to play an important part when a woman reaches the age of 35 years.

The definition of male infertility thus cannot be determined simply by the male partner, as the ability to conceive will be determined also by the female partner.

Semen analysis as an indicator of male infertility

Semen analysis is the most common way in which male infertility is identified and for the most part it does this job fairly well. However, semen analysis is a poor determinant of the time to conception among infertile couples. The changes that may be seen in the seminal fluid of infertile men are largely non-specific and, except in rare circumstances, semen analysis almost never gives the clinician any idea of the causation of that infertility. Except for a few notable exceptions such as globozoospermia (where *only* semen analysis can provide the clinician with a diagnosis), the changes identified by semen analysis are of little value clinically.

One aspect of semen analysis that is often overlooked is that the concentration of sperm in an ejaculate relates inversely to the volume of fluid in which the sperm are contained. Thus to have “normal” values of sperm concentration when the volume of the ejaculate can vary between 2 and 10 ml is somewhat nonsensical, as is clearly demonstrated in Table 1.1.

In recent years, great emphasis has been placed upon quality assurance and accuracy in the performance of semen analysis. However, if one looks at the fate of the sperm present in an ejaculate, one wonders whether all this effort is really worthwhile. Indeed the difference between an ejaculate that results in conception compared with that where no conception occurs, involves only one sperm!

When semen is ejaculated into the vagina, many sperm will be lost from the vagina by the phenomenon of “flow-back.” In many species, at least half of the ejaculate will drain out of the vagina post-coitum. A large number of the sperm are also trapped in the coagulated seminal fluid and are then destroyed by the low pH of vaginal secretions at mid-cycle. The exact percentage that is lost in these ways is unclear but it is probably the fate of the majority of sperm in the ejaculate.

It is known, for example, that most of the sperm that are going to enter the cervical mucus and will thus be out of “harm’s way” from the toxic effects of the acidic vaginal secretions arrive in the cervical mucus within minutes of ejaculation and therefore cannot have been trapped by semen coagulation. Thus, at least some of the sperm in the cervical mucus may only get there due to their position in the ejaculate.

Table 1.1 Demonstration of the effect that changes in the volume of the seminal fluid will have on the sperm concentration. When the seminal fluid volume is low, the concentration of sperm will be high and when the volume of semen is high, the concentration of sperm will be low. However, the total number of sperm in an ejaculate will remain the same

Volume (ml)	Total sperm numbers (millions)	Concentration (million/ml)
0.5	50	100
1	50	50
2	50	25
5	50	10
10	50	5

There is little evidence that the number of sperm in the cervical mucus relates closely to the number of sperm in the ejaculate. At one time, it was thought that recolonization of the cervical mucus occurred after liquefaction, with the formation of a so-called “cervical reservoir” of spermatozoa. However, it has been shown in the rabbit that any extra sperm are no longer necessary for conception beyond 5 min after coitus, although this may be longer in the human. It is likely, therefore, that the number of sperm needed for conception is very much lower than that in an average ejaculate. There is little evidence for the presence of a cervical reservoir in the human. Nevertheless, the percentage of sperm that enter cervical mucus from an ejaculate is not known but is probably small.

Once within the cervical mucus, many sperm are also lost in the cervical canal. Sperm can become trapped within the folds of the epithelium of the cervical canal and may even enter the cervical glands. The number of sperm able to traverse cervical mucus and enter the uterus in the human is unknown but as a percentage of the ejaculate, it is quite small.

The number of sperm that enter the Fallopian tubes in the human is also unknown but is possibly small and a few thousand may enter each tube. Once in the tube, the extensive folding of the tubal epithelium must be a considerable barrier to the sperm’s progress. It is likely that the sperm:egg ratio, at least in the human, is very small and could at times be as little as 1:1. The picture of an egg surrounded by competing spermatozoa is likely to be simply an artifact of in vitro fertilization (IVF).

Having arrived in the ampulla of the Fallopian tube and in order to enter the oocyte, these sperm must now undergo changes to their movement known as hyperactivation, undergo the acrosome reaction, and penetrate both the zona pellucida of the oocyte as well as the perivitelline membrane.

As such a small number of sperm are involved in the actual process of fertilization, it is not surprising that an overview of the whole ejaculate will not be a very good indicator of fertility. The value of semen analysis in which the number of sperm is several orders of magnitude greater than the number reaching the Fallopian tubes is open to grave doubt – even when the reproducibility of those assessments is very acceptable. Thus, all one can say about semen analysis is that it gives the clinician an indication, but no certainty, of the fertility or infertility of a male patient. Only when the semen contains no sperm is infertility probably assured.

If one thinks about the problem, it is in fact surprising that semen analysis will even indicate the potential for fertility, as in a conception cycle all of the sperm, bar one, are lost. How one can predict this event by looking at the whole ejaculate is difficult to understand. However, it is likely that conception will fail when all the sperm in an ejaculate show a lack of some function, or some abnormality is present in every sperm, but this is a rare occurrence. At best, as was pointed out many years ago, all a semen analysis can do is provide the clinician with a probability of conception – the greater the number of normally functioning sperm present in an ejaculate, the greater the chances of a sperm arriving at the site of the oocyte and thus the greater the chances of conception.

Another aspect of semen analysis that often goes unrecognized is a result of faults in the collection of the sample of semen. Many clinicians, as well as laboratories, often do not understand the difficulties that patients may have in the collection of a semen sample and do not provide the patient with suitable surroundings for its production. Patients may be asked to produce semen samples in rooms that are not soundproofed in which it is possible

to hear conversations going on in the corridor outside. In such a situation, the ejaculate may be incomplete and the semen sample may thus not be representative of the patient's fertility potential.

“Normal” values in semen analysis

Pathology laboratories always like to provide clinicians with “normal” values in semen analysis. However, this is a confusing and unsound concept in relation to a semen sample. It is frequently stated that a semen sample that contains 20 million sperm per milliliter is compatible with fertility, while any sperm concentration below that value may be associated with difficulties in achieving conception. However, there are a large number of studies where semen analyses have been carried out on fertile men, particularly among men due to undergo vasectomy, where the vast majority are fertile but where the semen analysis would indicate the presence of infertility. Indeed, it is well known that the appearance of “infertility” is a very common finding among semen analyses from men of proven fertility. This phenomenon can also occur among men attending an infertility clinic thus making even the identification of male infertility very difficult.

There is, however, no doubt that the greater the number of normally functioning sperm present in an ejaculate, the greater the probability of conception. But the probability of pregnancy is the best a semen sample can give you even if every sperm function test known is applied to that sample. However, conception can also occasionally occur when miniscule numbers of sperm are present in a semen sample. Under no circumstance should a patient be promised a pregnancy, nor should a couple be told that a pregnancy cannot ever occur: in such a situation a couple must be told the probability of a pregnancy, as that is all that a semen analysis can tell a clinician.

The importance of diagnosis in the management of male infertility

Diagnosis is all-important in the management of male infertility but so rarely is it ever achieved. Infertility is not a diagnosis – it is a symptom. A low sperm count is not a diagnosis – it is a physical sign. The diagnosis is the cause of the low sperm count. Once the diagnosis is known, all that the low sperm count tells you is the severity of its cause.

Infertility is like anemia – it is a symptom of many different disorders. In order to treat anemia rationally, one must know its cause. The same applies to male infertility. Only when the cause of the infertility is known can it be treated rationally and only when the cause is known can anything be done to prevent its occurrence.

It is important that all male patients attending a fertility clinic, whether or not the semen analysis is deemed to be abnormal, should have a full clinical history taken and undergo a clinical examination. Many aspects of disturbed sexual function can thus be identified in this way, some features of which may have an important bearing on a couple's childlessness. A careful history can also provide the clinician with previously unknown causes of infertility.

Interactive factors in male infertility

It must always be remembered that infertility is a disorder of a couple, not of an individual. One could argue that there is no such thing as male or female infertility but *only* infertility

Table 1.2 Fictional patients demonstrate that improving the chances of conception in the female partner can greatly influence the “fertility” of the man without there being any change in his seminal profile

<i>Scenario 1</i>
Female: Ovulates 1 month in every 12 months
Male: Only produces a fertile semen sample during 1 month in 12
Monthly chances of conception = 1 in 144
<i>Scenario 2</i>
Female: Ovulates 1 month in every 12 months
Male: Fertile semen samples every month
Monthly chances of conception = 1 in 12
<i>Scenario 3</i>
Female: Ovulation induction 1 month in every 3 months
Male: Only produces a fertile semen sample for 1 month in every 2 months
Monthly chances of conception = 1 in 4

of a couple. It has also been made very clear that infertility in one partner can be overcome by high fertility in the other partner.

The same phenomenon can occur for an infertile man. If, for example, we treat a woman’s anovulation, at least minor degrees of infertility in the man can be converted to either a minor degree of infertility for the couple or even no infertility at all. Such an example emphasizes the need for the assessment of both partners, not just an individual. In addition, such interactions can only be assessed properly by looking at the patient, not just the semen analysis.

These interactions, however, happen in real life. For example, it is known that in women with endometriosis, a high sperm count in the male partner shortens the time to conception while a low sperm count prolongs it. It is also often said that infertile people marry each other, as factors that cause infertility are so often found in both partners. A fictitious example of this type of male/female interaction is demonstrated in Table 1.2. However, if we remember that, first, infertility is a fairly common problem and that factors that cause infertility can often be interactive, then it is no surprise that problems are frequently found in both partners of an infertile liaison.

Male infertility in relation to age

The occurrence of conception in the woman is very dependent upon age. However, although men can retain their fertility into old age, there is indeed a reduction in semen quality among men in their fifth and sixth decades together with a reduction in reproductive outcome. It is now also suggested that although it is not so marked as in women, there may be an increased incidence of congenital anomalies among the children of older men.

However, sexual function also deteriorates with some frequency as the male patient ages. The incidence of erectile dysfunction increases greatly over the age of 50 years and such a problem can seriously impact on the ability of an older couple to conceive. Testosterone also falls with age and this is associated with a reduction of bioavailable testosterone due to

a concomitant rise in the level of sex hormone binding globulin (SHBG). There is, however, no evidence in man for the catastrophic fall in hormone levels that occurs in women during the menopause and thus the term “andropause” should not be applied to the older man.

The availability of phosphodiesterase inhibitors, such as sildenafil, has helped greatly in the management of sexual dysfunction, and libido may also be improved by the use of low-dose testosterone. However, it must be remembered that exogenous testosterone will suppress luteinizing hormone (LH) levels and can thus render the patient either azoospermic or severely oligozoospermic, which may not be desirable among a couple seeking treatment for infertility.

The role of testicular biopsy in the management of male infertility

Sometimes the diagnosis of infertility is based upon abnormal histology that has been seen on a testicular biopsy; more frequently, however, a testicular biopsy is used to identify the presence of abnormal sperm production. One problem with the use of a testicular biopsy for any diagnostic purpose is that the changes in the testis tend to be focal in distribution. Thus the findings in a testicular biopsy may not be representative of what is occurring in the rest of the testis or indeed of that in the opposite testis. It thus may be possible to see normal testicular tissue in a man with a very low count or an abnormal biopsy in a man with a fertile semen analysis.

A testicular biopsy is thus not the first investigation that is used in the diagnosis of male infertility. However, as will be seen later in this book, a testicular biopsy can be of great value diagnostically in conditions such as carcinoma-in-situ of the testis, which is a pre-malignant condition that can be associated with infertility in the man. A testicular biopsy can also be used for the collection of sperm in azoospermic men for use within an IVF/intra-cytoplasmic sperm injection (ICSI) cycle.

As the result of the discussion posed in this chapter, it is clear that the definition of male infertility is not as easy as has been supposed in the past. In evaluating the infertile man, many factors must be taken into consideration and these include all the problems that may be present in the female partner.

Under no circumstances should a male patient be told that he is infertile when that statement is based on the examination of a single semen sample, especially when that sample only shows minor abnormalities. However, the more severe the abnormalities present in a semen sample, the more likely is it that the male partner is having an impact upon the inability of that couple to conceive.

Chapter
2

Anatomy and physiology of the male reproductive tract

In order to understand any aspect of clinical andrology or the pathologies that underlie male infertility, knowledge of the anatomy and basic physiology of the male genital tract is essential. Too often, clinicians have a poor concept of the abnormal physiology that relates to male infertility and thus may be unable to make even the simplest of diagnoses so essential to any rational treatment of these patients.

Anatomy of the male genital tract

The anatomy of the male genital tract is complex and consists of the gonads, their excurrent duct system, and accessory glands of the male genital tract. Unlike that in women, the male genital tract also shares part of that duct system with the urinary tract.

The scrotum

This cutaneous sac contains the testes and the lower portion of the spermatic cord. The skin is hair bearing and contains a cutaneous muscle called the dartos that is distributed throughout the skin of the scrotum. Contraction of this muscle gives the scrotum its corrugated appearance and will elevate the testis within the scrotum.

The scrotum is divided into two hemi-scrota. Each half contains one testis and its immediate excurrent duct systems (i.e. efferent ductules, epididymal duct, and proximal end of the vas deferens) contained within the lower end of the spermatic cord.

Each half of the scrotum is lined by the tunica vaginalis. This lining is simply an extension of the peritoneal cavity known as the processus vaginalis. It covers the wall of the scrotum as well as the epididymis and the scrotal portion of the spermatic cord (Figure 2.1).

In the fetus, this peritoneal extension is in fact continuous with the peritoneal cavity itself and known as the processus vaginalis. If such a processus persists into childhood, it may be associated with the formation of an inguinal hernia. In the rodent, the two cavities of the scrotum and the peritoneum continue to be connected into adulthood. Thus in these animals, each testis can always be fully retracted right into the abdominal cavity.

The testes

The testes are ovoid in shape and each lies on either side of the midline septum that divides the scrotum into its two halves.

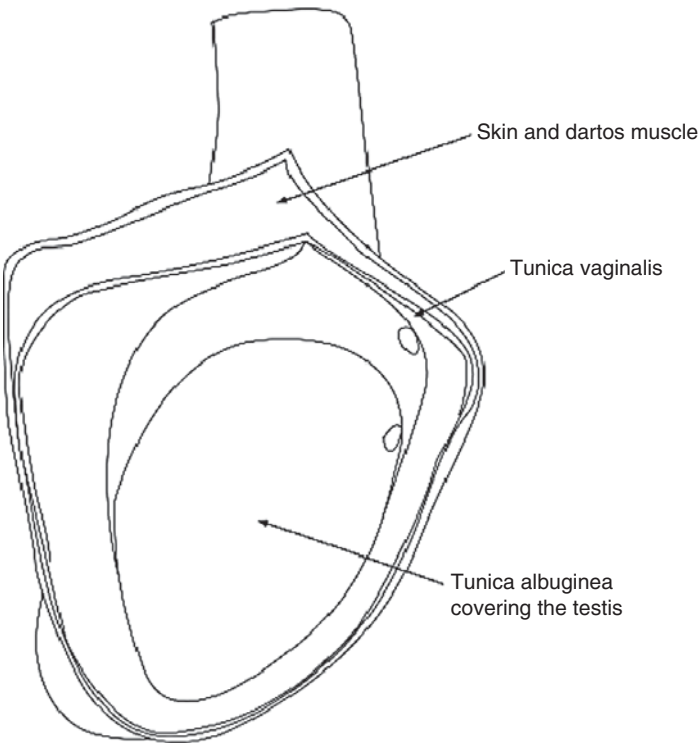


Figure 2.1 Coverings of the testis.

Each adult human testis is about 5 cm long and when normal has a volume of about 15–20 ml. A thick fibrous coat known as the tunica albuginea (due to its white coloring) covers the testis. This fibrous coat is thickened down the posteromedial border of each testis and forms the mediastinum testis (Figure 2.2). The tunica albuginea is penetrated along its posteromedial border by the testicular artery and vein.

It must be remembered that the tunica albuginea has very little distensibility and when some inflammatory condition affects the testis, the intra-testicular pressure will rise substantially. It is likely that when inflammatory problems do occur, testicular blood flow and testicular function could be severely compromised.

Beneath this thick fibrous covering lies the tunica vasculosa, made up of a vascular network suspended in fine connective tissue.

Also arising from the inner aspect of the mediastinum testis are thin, filamentous septa that spread out into the body of the testis to divide its cavity into about 100–200 lobules. Contained within each of these lobules are about two to three looped or blind-ended tubules known as the seminiferous tubules that contain spermatogenic epithelium in which spermatozoa develop and mature (Figure 2.3). These tubules are held together by loose connective tissue in which the Leydig cells are also suspended close to each of the tubules (Figure 2.4). The total length of the tubules may amount to as much as 1–2 m thus providing a large area of epithelium for sperm production.

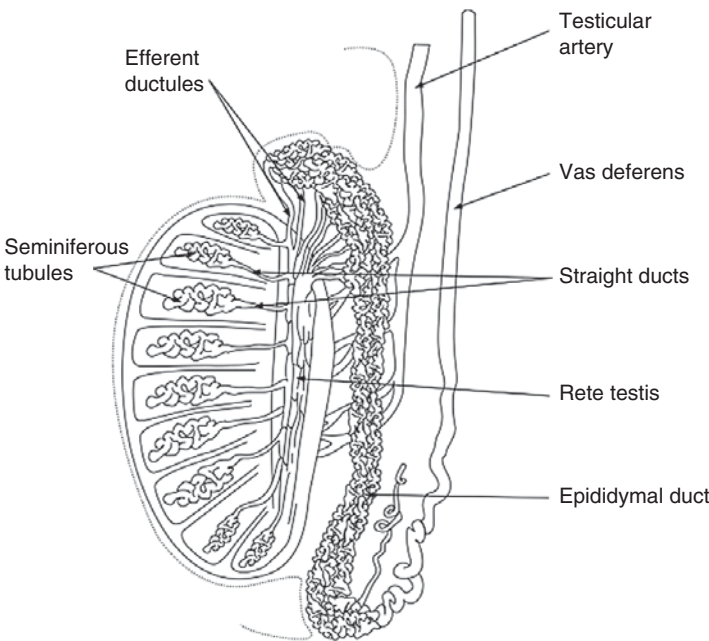


Figure 2.2 Diagram of the testis, epididymis, and vas deferens in the human.

Each tubule is convoluted and when this convolution is excessive, it may give rise to a form of partial obstruction that could result in oligozoospermia. This possibility will be discussed in more detail in a later chapter.

On freeing themselves from spermatogenic epithelium, sperm pass out of the coiled seminiferous tubules and into the straight ducts from where they pass into the rete testis. The mediastinum testis contains a network of channels known as the rete testis whose exact function is unclear. The epithelium of the rete testis is lined by a ciliated epithelium that may assist the passage of sperm out of the testis and into efferent ductules and on into the epididymal duct (Figure 2.5).

The sperm, now suspended in what is known as rete testis fluid, pass through the rete testis, and at the upper pole of the testis enter into efferent ductules from where sperm can now exit each testis.

The blood supply to each testis is by the spermatic artery that arises from the aorta at a point just below the origin of the renal artery on each side. Each artery descends the abdominal cavity and enters the spermatic cord to arrive in the scrotum posteriorly. It passes behind the epididymis to enter the testis as several branches at the same time sending branches to the epididymis. The arteries then pass into the interstitial tissue and tunica vasculosa. The tunica vasculosa covers the septa and inner surface of the tunica albuginea. The capillaries do not enter the seminiferous tubules but run in interstitial tissue in close proximity to basement membranes of the tubules.

The nerve supply to the testis accompanies the blood supply and is derived from the 10th and the 11th thoracic segments. Thus, testicular lesions can sometimes present with upper abdominal pain. As occurs with the ovary, there is a vagal supply to the testis and hence vomiting is commonly associated with testicular trauma.

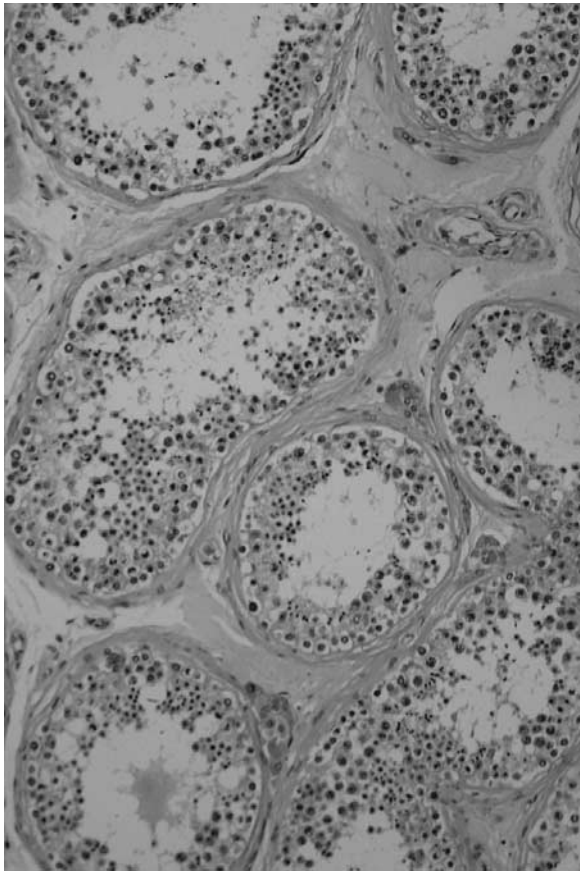


Figure 2.3 Normal testicular biopsy showing all the developmental stages of spermatozoa. (See plate section for color version)

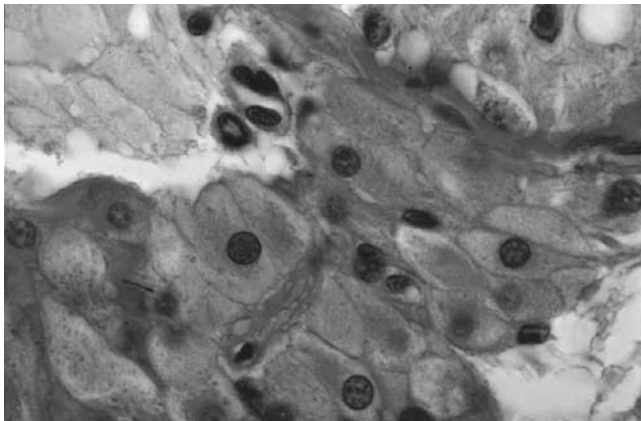


Figure 2.4 Histological section showing the Leydig cells that lie in groups in the interstitial space within the fine connective tissue. (See plate section for color version)