

## Chapter

# An overview of intrauterine insemination and ovulation induction

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## Introduction

Sperm preparation methods developed for in-vitro fertilization and embryo transfer (IVF-ET), such as the wash, swim-up and swim-down techniques, and the use of density gradients, have led to a resurgence of interest in intrauterine insemination (IUI). The use of washed prepared sperm for IUI has also resulted in a significant reduction in the side effects associated with the use of neat semen for IUI (which never should be used), such as painful uterine cramps, collapse and infection [1,2]. In view of the fact that IUI is a relatively simple procedure compared with in-vitro fertilization (IVF), its popularity as a treatment option for certain diagnostic groups of infertile couples is increasing, since it is intermediate between the simpler ovulation induction (OI) and the more “high tech” IVF. This is particularly so in developing countries, where facilities for IVF may be limited and the cost of treatment by IVF is a major issue.

The term “artificial insemination” (AI) covers a range of techniques for insemination: it may be intravaginal, intracervical, intrafallopian, intraperitoneal or intrauterine. AI has been used for many years for a number of different indications, and either the husband/partner’s sperm (AIH) or donor sperm (AID) may be used. It is almost 200 years since John Hunter advised a man with hypospadias to inject his seminal fluid into his wife’s vagina with a syringe, resulting in a normal pregnancy [3]. In the nineteenth century, Sims artificially inseminated six women who had negative postcoital tests. He used their husbands’ semen obtained from the vagina after intercourse; one pregnancy was achieved [4]. The first reported case of human donor insemination was by William Pankhurst from Philadelphia in the United States in 1884 [5].

The rationale for the use of IUI instead of intravaginal insemination (IVI) or intracervical insemination

(ICI) is to reduce the effect of factors such as vaginal acidity and cervical mucus hostility and to benefit from the deposition of a bolus of prepared motile, morphologically normal sperm as close as possible to the oocytes at the time of ovulation. There continues to be discussion in the literature about whether or not IUI should be complemented by OI – either with the oral medications clomiphene citrate (CC) or tamoxifen (TMX), or with the injectable gonadotropins. Most practitioners are of the opinion that IUI with OI does increase success rates, and many will initially try with CC or TMX, and move on to gonadotropins if there is no success within a few cycles of CC/IUI. The most appropriate time to move on from IUI to IVF is also a matter for debate, but most practitioners agree that the change should be made after no more than 4–6 cycles of IUI (see Chapters 7 and 8).

Before proceeding to artificial insemination, couples should undergo a complete assessment, of which a full description is given in Chapters 2 and 3. This includes a thorough medical history, clinical examination and appropriate investigations for any possible causes of a couple’s infertility, such as tubal damage, ovulatory disorder or a male factor. It is essential that couples should receive adequate counseling prior to starting treatment, especially when donor sperm is to be used. Couples should also be assured of complete confidentiality, and informed that all sperm donors are now comprehensively screened for genetic and infective conditions. Couples will wish to know how the donor is to be matched to their own characteristics, the cost of treatment, the probability of success, the potential for complications to occur and the likelihood of their occurrence. Medical professionals and couples can now make use of the internet to find a sperm donor that matches their desired physical, educational, religious and even national and ethnic

## Chapter 1: An overview of IUI and OI

characteristics (see Chapter 12). In countries with strict regulatory systems, such as the United Kingdom, couples using donor sperm must be made aware of any rules that may affect them when using donor sperm, particularly about parentage, registration of the birth of children and, in some countries, the removal of the right to anonymity of donors and therefore the right of a child to discover the identity of his or her true genetic father on reaching the age of 18 (see Chapter 17). The attitude of societies in general, certainly in the developed countries, towards the issue of single women and women in same-sex relationships having children has changed dramatically in the past decade or two. The demand for fertility treatment from these women is increasing, and practitioners are now more willing to provide donor IUI services to them. However, in many countries, mainly those in which the Roman Catholic or Islamic faiths predominate, donor insemination is forbidden.

The development of oocyte–sperm micromanipulation procedures, such as intracytoplasmic sperm injection (ICSI) and its introduction into IVF-ET programs [6], has made it possible to achieve fertilization and pregnancies when only very few spermatozoa are available. Prior to the development of techniques such as microsurgical epididymal sperm aspiration (MESA) [7], percutaneous epididymal sperm aspiration (PESA) [8] and testicular sperm extraction (TESE) [9], men with congenital bilateral absence of vas deferens (CBAVD), surgically unreconstructable vasa or other causes of vasal obstruction had very little chance of fathering their own children. Now, however, if these techniques are combined with ICSI, these men can be offered a very real chance of achieving paternity with their own sperm [10]. These methods have reduced the demand for AID; however, the cost of these procedures puts them beyond the means of many couples, and there is therefore a continuing need for AID, which is most effectively done by IUI using donor sperm.

## Indications for intrauterine insemination

There are a number of indications for IUI using the husband or partner's semen; these are summarized in Table 1.1. Ejaculatory failure is the classical indication, since the male partner is unable to ejaculate into the vagina, while cervical mucus hostility is a logical indication for IUI, as it bypasses the mucus in the cervical canal. The most common indications for IUI are the less severe forms of male-factor infertility and

**Table 1.1.** Indications for intrauterine insemination

<b>Effective</b>
Male subfertility
Cervical factor
Ejaculatory failure
Idiopathic/unexplained infertility
<b>Possibly effective</b>
Immunological infertility
Endometriosis

idiopathic or unexplained infertility. Other indications, for which conclusive evidence of effectiveness is lacking, are immunological causes of infertility and endometriosis.

The main indications for donor insemination are (1) gross male infertility or subfertility (azoospermia or severe oligoasthenoteratozoospermia), for couples who cannot afford IVF or reject IVF for other reasons, and (2) familial or genetic disease, such as Huntington's disease, hemophilia and severe Rhesus incompatibility. The use of cryopreserved semen in donor insemination programs is now mandatory in most countries, to minimize the possibility of the transmission of human immunodeficiency virus (HIV) and other infections to the recipients.

## Intrauterine insemination: natural and stimulated (OI) cycles

Treatment by IUI may be performed either in a natural or in a stimulated cycle. Many ovarian stimulation protocols have been devised for use with IUI, including: CC alone or in combination with gonadotropins and human chorionic gonadotropin (hCG); TMX alone or combined with gonadotropins; and the use of a gonadotropin-releasing hormone (GnRH) agonist or antagonist combined with gonadotropins. hCG is usually used at the end of the stimulation phase to achieve final maturation of the oocyte(s). Full descriptions of the different regimens for OI are given in Chapters 7 and 8.

The rationale for the use of OI with IUI is both to increase the "efficiency" and likelihood of ovulation and to increase the number of oocytes available for fertilization, and thus to improve the chance of pregnancy. Stimulation also enhances steroid production, which may improve the chance of fertilization and embryo implantation [11]. When considering whether or not to use ovarian stimulation with IUI, the

benefit of a potential increase in success rates that may be achieved, compared with natural cycle IUI, must be balanced against the increased cost of the medication and monitoring, as well as the potential complications of these medications, including ovarian hyperstimulation syndrome (OHSS) and the increased incidence of multiple pregnancies, with their associated maternal and neonatal complications [12] (see Chapters 14 and 15).

There are several methods available to time ovulation in both natural and stimulated cycles. These include simple methods such as the measurement of basal body temperature (BBT), which has been found to be the least accurate, and assessment of the cyclical changes that occur in cervical mucus. Templeton *et al.* showed that in 35% of cycles the optimum mucus score was observed on the day before the luteinizing hormone (LH) surge, in 44% of cycles it was optimum on the day of the LH surge and in 18% of cycles on the day after the LH surge, while in 3% it occurred two days after the LH surge [13]. However, the detection of the serum or urinary LH surge and ultrasound assessment of follicular growth and rupture have proved to be the most accurate methods of monitoring IUI and OI/IUI cycles. Vermesh *et al.* showed that use of a “dipstick” LH test kit predicted ovulation in 84% of cycles in his series [14]. In a stimulated cycle, if hCG is administered when the average diameter of the leading follicle is 18–20 mm, ovulation may be expected to occur 34–40 hours later.

## Sperm preparation

The ideal sperm preparation technique is the one which will achieve the largest number of morphologically normal motile spermatozoa in a small volume of physiological culture media, free from seminal plasma, leukocytes and bacteria [15]. There is more information than formerly about sperm quality and quantity necessary in an initial specimen for IUI to be successful, so that an informed decision can be made on whether to perform IUI or, instead, to recommend IVF with intracytoplasmic sperm injection (ICSI) or donor sperm [16]. Although there is no threshold of sperm concentration below which pregnancy is impossible, most conceptions occur when the number of inseminated motile sperm is  $4 \times 10^6$  or greater (see Chapter 6). The degree of motility and percentage of morphologically normal spermatozoa are other important variables in fertility prognosis.

There are several different sperm preparation techniques for IUI, and each has its own advantages and

disadvantages. Sperm preparation using the density gradient technique yields the highest number of motile spermatozoa when compared with simple washing or swim-up or swim-down methods, and significantly reduces bacterial contamination [17], but it should not be used when the initial specimen contains fewer than  $15 \times 10^6$  motile sperm (see Chapter 6). Equipment and materials necessary for semen analysis and preparation of husband/partner sperm for IUI are described in Chapters 4 and 6.

## Results of treatment by IUI and OI with husband/partner sperm

The results of IUI with husband/partner sperm in terms of pregnancy rates per treatment cycle vary considerably between clinics, and the evaluation of results is difficult because of the heterogeneity of the patient populations and the different ovarian stimulation protocols, if any, used in the studies. Although there are a large number of published studies on IUI, most of these are retrospective and/or on small numbers; only a few are prospective and randomized trials. There is an undoubted need for more large prospective randomized studies to evaluate the real effectiveness of IUI and to elicit which group of patients will benefit most from this treatment. Results of IUI and OI at Bourn Hall and the Fertility Institute of New Orleans are shown in Table 1.2.

Two European Society of Human Reproduction and Embryology (ESHRE) multicenter prospective studies compared ovulation induction alone with ovulation induction in conjunction with IUI, intraperitoneal insemination (IPI), gamete intrafallopian transfer (GIFT) and IVF [18,19]. In the treatment of unexplained infertility, the pregnancy rate achieved from superovulation alone was less than when combined with IUI, IPI, GIFT or IVF [18]. In the treatment of male subfertility, ovulation induction with IUI, GIFT and IVF gave better results than IPI and ovulation induction alone [19]. Martinez *et al.*, in an extensive review of the English-language literature from 1980 to 1991, showed that there was marked variation in the results of IUI between different clinics [20]. Retrospective analyses of IUI data using life-table analysis showed a relatively constant probability of becoming pregnant after each IUI treatment through four gonadotropin IUI cycles [21] or six IUI cycles without OI [22,23], and that thereafter it is hardly increased at all by continuing for longer. Most clinicians are now agreed that further evaluation and discussion of the other treatment options available

## Chapter 1: An overview of IUI and OI

**Table 1.2.** Pregnancy success rates related to cause of infertility

	Bourn Hall Clinic (1989–93) <sup>a</sup>	Fertility Institute of New Orleans (1983–98) [24]	Fertility Institute of New Orleans (1983–98) [25]
Medication	Mixed	Clomiphene	hMG/FSH
IUI cycles	> 1400	3381	4062
<b>Indication</b>	<b>Pregnancies per cycle (%)</b>	<b>Pregnancies per cycle (%)</b>	<b>Pregnancies per cycle (%)</b>
Ovulatory dysfunction	–	14.6	19.5
Cervical, unexplained	–	10.4	19.2
Idiopathic	12.3	–	–
Cervical	16.4	–	–
Endometriosis	–	8.1	16.1
Immunological	10.0	–	–
Male subfertility	21.0	11.4	16.9
Donor sperm	–	16.5	22.2
Ejaculatory failure	13.3	–	–

<sup>a</sup> Unpublished data

FSH, follicle-stimulating hormone; hMG, human menopausal gonadotropin.

to couples should be carried out after 4–6 cycles of IUI without OI. In IUI with OI, the probability of pregnancy per cycle and the number of cycles in which pregnancy rates remain constant, in patients treated at the Fertility Institute of New Orleans, depended on diagnosis, age, sperm source and the number of pre-ovulatory follicles that developed in response to CC (see Chapter 7, Table 7.1) [24] and human menopausal gonadotropin (hMG) or follicle-stimulating hormone (FSH) (see Chapter 8, Table 8.4) [25].

The United Kingdom results for donor insemination are reported yearly by the Human Fertilisation and Embryology Authority (HFEA) on their website ([www.hfea.gov.uk](http://www.hfea.gov.uk)). The data from all clinics show live birth rates for 2006 of 14.5% per donor insemination treatment cycle for women below the age of 35, reducing to 9.9% for women aged 35–39, 5.4% for ages 40–42 and just 1.2% for women aged 43–44, with no live births for women over the age of 44. Data from Bourn Hall Clinic for 2007, for all age groups combined, show a 22% clinical pregnancy rate per cycle started for IUI with husband/partner sperm and a 26% clinical pregnancy rate per cycle started for IUI with donor sperm ([www.bourn-hall-clinic.co.uk](http://www.bourn-hall-clinic.co.uk)). The majority of cycles are stimulated with CC or gonadotropins.

### Cost-effectiveness of IUI and OI

In a large retrospective analysis of 45 published reports on the treatment of couples with unexplained infertility,

Guzick *et al.* looked at the cost-effectiveness of no treatment, CC alone, CC+IUI, hMG alone, hMG+IUI, IVF, and GIFT [26]. Analysis of the data showed that CC+IUI was the most cost-effective treatment for idiopathic infertility (US\$10,000 per pregnancy), compared to hMG+IUI (US\$17,000 per pregnancy) and IVF (US\$50,000 per pregnancy). In their conclusions, they state that “on the highest level of evidence found in the data,” their recommendations for the cost-effective management of idiopathic infertility are: IUI does not appear to be effective without some form of superovulation; CC+IUI appears to be more cost-effective than hMG+IUI or IVF; IVF and GIFT are effective for couples who have not conceived after superovulation + IUI.

In a study from the Netherlands by Goverde *et al.*, 258 couples with a diagnosis of idiopathic or mild male-factor infertility were divided into three equal groups: (1) IUI alone, (2) IUI with mild ovarian stimulation using low-dose FSH, and (3) IVF [27]. Their conclusion was that stimulated IUI was as effective as IVF in achieving a pregnancy (31% vs. 33%), and was more cost-effective than IVF – cost per pregnancy resulting in a single live birth was US\$4,511–5,710 for stimulated IUI versus US\$14,679 for IVF. They concluded that patients should be counseled that IUI for these two diagnostic groups offers as good a chance of achieving a pregnancy as IVF and is more cost-effective. More controversially, they suggested that non-stimulated IUI should be the first-choice treatment, as it carries

fewer health risks, even though it is not as effective as stimulated IUI. Cohlen reviewed the literature looking at the evidence of the efficacy of IUI with “mild ovarian hyperstimulation” (MOH) as a treatment for cervical mucus hostility, moderate male-factor infertility and unexplained infertility [28]. His conclusion on the treatment of these three groups of patients was that “When multiple pregnancies are kept to a minimum, MOH/IUI is more cost-effective compared with in-vitro fertilization and embryo transfer.”

## Complications of treatment

There are few complications to treatment by IUI. Failure of the treatment could be said to be the most frequent, since pregnancy rates per cycle are reported at anywhere between 5% and 25%. The complication which causes couples the most concern, but which is almost certainly very rare, is the possibility that the patient might be inseminated with the wrong semen sample. Other complications include the possibility of transmission of venereal disease, HIV or hepatitis B or C. Proper adherence to protocols and the establishment of clinical and laboratory quality systems should almost eliminate these possibilities. Painful uterine contractions which may occur during insemination can usually be minimized by inseminating slowly. Intrauterine infection and anaphylaxis rarely may also occur, especially if neat semen is used – which it should never be.

The two most serious complications of OI are multiple pregnancy and ovarian hyperstimulation. There is increased awareness of the dangers of multiple pregnancy, including twins. Singleton birth is now the “gold standard” of IVF, and many countries in Europe now mandate single embryo transfer for most IVF patients. Twins occur in 10% of CC and 20% of gonadotropin OI cycles with or without IUI, and triplet and higher-order multiple pregnancies occur in as many as 20% of hMG/FSH IUI pregnancies in women younger than 32 who develop seven or more follicles [25]. Occurrence of multiple pregnancy and OHSS can be minimized by careful management and monitoring of treatment cycles and, if necessary, abandoning the cycle or converting it to an IVF cycle (see Chapters 14 and 15).

## Conclusion

IUI is an effective, non-invasive, relatively simple and cost-effective method of treatment for certain diagnostic groups of infertile couples. It can be provided more easily to more infertile couples in office practices and general hospitals than can the more specialized

techniques such as IVF, if there are adequate facilities for semen preparation and cycle monitoring and the clinic is staffed by adequately trained physicians and laboratory scientists. However, careful selection of patients suitable for IUI is important. Those who will benefit most are young women with patent fallopian tubes, with no ovulatory disorder, no endometriosis of more than moderate or severe degree and no severe degree of male-factor infertility in their partners. All couples require in-depth advice and counseling about the method, the effectiveness and the potential complications of treatment.

The main advantages of IUI over IVF are its simplicity and relative inexpensiveness. However, there are many advantages of IVF over IUI – principally those of a higher pregnancy rate, the ability to avoid multiple pregnancies by transferring a single embryo and cryopreserving any spare embryos generated in the IVF cycle, and the knowledge gained about the ability of the sperm to fertilize the oocytes. IVF or ICSI are the only realistic treatments for couples with severe male-factor infertility, as well as for severe endometriosis and infertility due to severe tubal damage. Although IUI can be performed outside of specialist units, a clinic with IVF facilities offers the best setting in which to perform IUI in case complications, such as an excessive follicular response or ovarian hyperstimulation, occur. If they do, then patients can be offered the chance to convert to IVF, with the chance to freeze any surplus embryos.

Finally, in an interesting paper on “Patients’ preferences for intrauterine insemination or in-vitro fertilization,” van Weert *et al.* [29] concluded that, when couples knew their cumulative chances of pregnancy at each stage, both at the start of treatment and after three cycles of IUI, the majority of couples wished to continue with IUI, but their preference changed to IVF after six cycles of IUI, in the knowledge that their chances of success were very much less at this stage [29].

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## Chapter 1: An overview of IUI and OI

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## Chapter

## 2

**Male causes of infertility: evaluation and treatment**

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**Introduction**

The male is solely responsible for the failure to conceive in about 20% of infertile couples, and contributory in another 30–40% [1]. Reduced male fertility can derive from congenital or acquired urogenital abnormalities, infection of male accessory glands, increased scrotal temperature, endocrine disturbances, genetic abnormalities or immunological factors [2]. However, no demonstrable etiology can be diagnosed in 48.5% of cases of male infertility. An abnormal semen analysis (SA) suggests the presence of a male factor; however, a normal SA does not preclude a male factor being present.

The goals of the evaluation of the infertile male are to identify [3]:

- potentially correctable conditions
- irreversible conditions amenable to assisted reproductive technologies (ART) using male gametes or donor insemination if the male partner's sperm is not procurable
- life- or health-threatening conditions that may underlie infertility and require medical attention
- genetic abnormalities that may affect the health of offspring if passed on via advanced reproductive techniques.

Traditionally, evaluation of infertility is postponed until one year of unprotected intercourse. However, it is justified to initiate an evaluation earlier if one of the following conditions is present [3]:

- defined male infertility risk factors
- female infertility risk factors, including advanced age (> 35 years)
- the male or female partner requests an earlier evaluation.

Initial evaluation of the male usually consists of two semen analyses separated by at least a month, a medical and reproductive history, and a focused physical examination by a urologist/andrologist. Additional tests may be required to further investigate underlying pathologies.

Semen analysis provides information on ejaculate volume, spermatozoa concentration, motility and morphology and also round-cell number (additional tests include determining fructose levels and staining for white blood cells in selected cases). Detailed laboratory protocols for each of these assays have been published by the World Health Organization (WHO) [4].

Except for patients with bilateral vasal agenesis or clinical signs of hypogonadism, patients with low ejaculate volume (< 1 mL) need their postorgasmic urine screened for retrograde ejaculation [3].

Hormonal evaluation, consisting of total testosterone and follicle-stimulating hormone (FSH) levels, is warranted if abnormally low sperm concentration, impaired sexual function or other clinical findings suggestive of specific endocrinologic dysfunction are identified. Any detected hormonal disturbance needs further confirmation and corroboration [3].

Imaging studies are not often required for a male infertility evaluation. In the presence of symptoms suggestive of ejaculatory duct obstruction, i.e. low ejaculate volume with severe oligoasthenospermia or azoospermia, transrectal ultrasonography is often performed. Similarly, in patients in whom physical examination of the scrotum is somewhat difficult or a testicular mass is suspected, scrotal ultrasonography has a high specificity for identifying scrotal pathology [3].

Specialized clinical tests (e.g. assays for antisperm antibodies, sperm viability or sperm–cervical mucus interaction) can be useful in a small cohort of patients.

**Chapter 2: Male causes of infertility**

They are reserved for special cases of unexplained infertility [3].

Men with non-obstructive azoospermia or severe oligospermia must be counseled for potential genetic abnormalities that may be transmitted to their offspring, and offered formal genetic screening prior to ART [3].

## Normal spermatogenesis and ejaculation

The sperm cycle is a complex series of events that requires approximately three months from the beginning of spermatogenesis to the antegrade ejaculation of semen. The physiology of sperm production and delivery is paramount to the diagnosis and treatment of male-factor infertility.

### Spermatogenesis and the testicle

Spermatogenesis occurs in the seminiferous tubules, which are the microscopic ducts made up primarily by Sertoli cells, germ cells and peritubular myoid cells [4]. The seminiferous tubules make up the bulk of the testicular cortex. Sertoli cells form the walls of the tubules and are connected by tight junctions; these form the blood–testis barrier that prevents macromolecules from entering the tubules from the lymph system, thus allowing spermatogenesis to occur in an immunologically privileged site [5]. Sertoli cells also play an important role in supporting the germ cells with nourishment and supplying high levels of androgens (20–50 × serum levels) in the seminiferous tubule lumen [6].

Germ cells lie within the tubule in an ordered fashion, beginning with the spermatogonia at the basement membrane, progressing to the mature spermatid at the lumen. Spermatogonia undergo several mitotic divisions to produce a large supply of stem cells, allowing for indefinite production of spermatozoa. The diploid spermatogonia undergo further mitotic division to produce the primary spermatocytes. After the first meiotic division the spermatocytes cross the blood–testis barrier into the adluminal compartment, becoming diploid secondary spermatocytes. Next, within the adluminal compartment, the secondary spermatocytes undergo the second meiotic division, each producing two round spermatids that mature by spermiogenesis into elongated flagellar cells before entering the seminiferous tubule lumen. Each primary spermatocyte produces four mature spermatids, which have compressed chromatin and acrosome in the head, with

a flagellar tail containing tightly packed mitochondria in the proximal portion. Spermatogenesis is heavily dependent on FSH and testosterone for initiation and maintenance [7,8].

### The epididymis

After release into the lumen, spermatids continue to mature. They are moved to the epididymis by active peristalsis by the peritubular myoid cells. When entering the epididymis, sperm are non-motile and unable to fertilize the oocyte via IUI. The maturation of spermatids within the epididymis largely occurs as a result of micro-environmental influence, and hence there is negligible protein synthesis within the spermatid itself. Most of the changes occur on the cell membrane by altering protein content, immunoexpression, net surface charge, integrity and fatty acid content [9]. These changes prepare the sperm for fertilization and are androgen-dependent. The epididymis also serves as a favorable storage environment for mature sperm.

### The vas deferens

After leaving the tail (or cauda) of the epididymis, sperm enter the thick, muscular, vas deferens. The vas is the major storage location of mature sperm prior to ejaculation, although it is not capable of preserving viability to the same degree as the epididymis. The physiology of the vas results in the recommended two-day optimal interval for intercourse, because more frequent intercourse produces less than optimal sperm counts and less frequent intercourse produces decreased sperm viability [10].

### Seminal vesicles and prostate

The seminal vesicles and prostate are the sexual accessory glands responsible for contributing to the fluid environment for sperm, with their secretions making up 95% of the normal ejaculate volume [5]. The seminal vesicles produce phosphorylcholine, ascorbic acid, flavin, prostaglandins, fructose and clotting factors. Prostaglandins relax the myometrium of the uterus and cervix; fructose is an energy source for sperm. The prostate is under regulation by androgens, specifically the potent dihydrotestosterone.

### Penis physiology

The penis is responsible for effective transportation of sperm and semen from the vas in an antegrade fashion to the cervical os, a process requiring erection and ejaculation. Erections occur from genital or central

stimulation. Genital stimulatory erections may be preserved in lesions above T10, although erections in spinal cord injury patients are usually short and uncontrolled [11]. Central-originating erections involve contributions from many different areas of the brain, involving memories, fantasy, visual and auditory stimuli. The flaccid penis is under constant sympathetic stimulation, causing constricted sinusoidal spaces within the corpora cavernosa. When parasympathetic stimulation increases from the pelvic plexus (*nervi erigentes*) these sinusoids relax under the influence of nitric oxide, causing an increase in the flow of blood into the penis, while simultaneously compressing the emissary veins (activation of the veno-occlusive mechanism) and decreasing blood outflow [12]. These processes produce a physiologic erection.

## Ejaculation

Ejaculation is a very quick and complex series of events that is crucial in the ability to deposit sperm in the vaginal canal. Ejaculation is the result of a combination of central and genital nervous stimulation. Penile sensory information is passed through the dorsal nerve to the spinal column, where it is integrated and sympathetic efferent signals are generated to initiate the ejaculatory reflex [5]. The threshold for this process can be lowered or raised by central modulation. Activation of the sympathetic ejaculatory pathway results in contraction of the vas deferens, bladder neck, seminal vesicles and prostate. Concurrent with seminal emission is a sense of general and localized pleasure, or orgasm. After emission of sperm into the posterior urethra, rhythmic contractions of the periurethral muscles result in an involuntary projectile ejaculation of the seminal fluid.

## Hypothalamo–pituitary–testicular axis in the adult male

The hypothalamo–pituitary–testicular axis is essential for human reproduction, especially spermatogenesis and erectile function. Gonadotropin-releasing hormone (GnRH), synthesized in the hypothalamus, is released into the portal system in a pulsatile fashion, stimulating the pituitary to synthesize and release FSH and luteinizing hormone (LH). LH stimulates the Leydig cells of the testicle to produce testosterone. The anterior pituitary production of LH is negatively inhibited by serum testosterone. Testosterone increases secretory production in the seminal vesicles and is converted by 5 $\alpha$ -reductase in

the prostate cells to stimulate growth and secretion. Within the testicle, testosterone drives spermatogenesis. FSH binds to Sertoli cells, initiating seminiferous tubule development during puberty, and is essential for continued spermatogenesis during adulthood. FSH is negatively inhibited by the Sertoli-cell-produced protein inhibin and, to a lesser extent, by testosterone. Physiologic levels of testosterone are required for adequate libido and spontaneous erections [13].

## Pathophysiology of male infertility

Semen quality can deteriorate with any of the recognized pathologies that may interfere with normal spermatogenesis. This section will focus on these pathologies and the treatment options for couples with such problems.

### Failure to produce adequate-quality spermatozoa

Production of spermatozoa is complicated by several mechanisms which are discussed below. Endocrine, testicular failure, anatomical, infectious, genetic and immunologic defects can impair the maturation of spermatogonia to produce quality sperm.

#### Endocrine/hormonal causes

The most common endocrine causes of male infertility are summarized in Table 2.1 [6].

#### Testicular causes

The most common testicular causes of male infertility are summarized in Table 2.2 [6].

#### Varicocele

Varicoceles are dilated tortuous testicular veins, classically described as “a bag of worms,” within the spermatic cord. They do not transilluminate when a pen light is held against the scrotal skin and usually do not collapse in the supine position. Subclinical varicoceles can be detected with scrotal ultrasound [14]. Varicocele is the most common correctable cause of male infertility, and 90% occur on the left side owing to the anatomy of entering the renal vein rather than the vena cava on the right side. The prevalence of varicocele in infertile men is 20–40% [15]. Authorities theorize that increased temperature, hypoxia and reflux of adrenal and renal metabolites may impair spermatogenesis in patients with varicocele.

**Chapter 2: Male causes of infertility****Table 2.1.** Endocrine causes of male infertility

Disease process	Characteristics
Pituitary disease	Tumors, infarcts, surgery, radiation, infiltrative or granulomatous disease.
Isolated hypogonadotropic hypogonadism (Kallmann syndrome)	Absence of gonadotropin-releasing hormone, associated with anosmia. Fertility can be achieved with LH and FSH replacement.
Fertile eunuch syndrome	LH is normal, but testosterone deficient. Patients have incomplete virilization, gynecomastia and reduced number of sperm.
Isolated FSH deficiency	Normal testes and virilization, does not respond to GnRH stimulation, azoospermic or oligospermic.
Androgen excess	Anabolic steroid abuse: 15% of high-school, 30% of college, and 70% of professional athletes. Temporary subfertility can result. Discontinue steroid use and re-evaluate in 3–6 months. Rarely caused by 21-hydroxylase deficiency characterized by precocious puberty.
Estrogen excess	Usually related to cirrhosis or obesity, which augment aromatase activity resulting in secondary pituitary suppression.
Prolactin excess	Secondary to pituitary adenoma, diagnosed by serum prolactin and CT/MRI of sella turcica. Check prolactin in end-stage renal disease or chronic renal insufficiency.
Thyroid abnormalities	Results in hypothalamic–pituitary dysfunction and alters sex hormone-binding globulin (SHBG) levels; < 0.5% of male infertility.
Glucocorticoid excess	Cushing's syndrome features, decreases spermatogenesis, suppresses LH, fertility improves with correction.

**Table 2.2.** Testicular causes of male infertility

Disease process	Characteristics
Bilateral anorchia	Secondary to torsion, trauma, infection or vascular injury. No effective ART.
Cryptorchidism	0.8% of boys at 1 year of age; germ-cell abnormalities begin to appear at 2 years of age. Increased risk for infertility and malignancy.
Testicular torsion	If testicle saved, predisposed to immunologic infertility. Contralateral testis is at risk for abnormalities.
Sertoli-cell-only syndrome	Germ-cell aplasia, azoospermia, normal virilization, small testes, elevated FSH. Extensive sampling and biopsy may find sperm suitable for ART.
Myotonic dystrophy	Adult-onset muscular dystrophy, cataracts, muscle atrophy, various endocrinopathies, elevated FSH and LH. Fertility has been reported.
Chemotherapy/ radiation	Dose-dependent, inverse relationship between radiation and sperm counts, primarily affecting spermatogonia; sperm counts rebound after therapy, no increased incidence in congenital defects. Alkylating agents are the most gonadotoxic chemotherapy agents, cytotoxic to spermatogonia, but no increased incidence of congenital defects. Patients should be advised to avoid conception until 6 months after the end of treatment. Consider sperm cryopreservation prior to treatment.
Medications	Discontinue all unnecessary medications: ketoconazole, spironolactone and alcohol inhibit testosterone synthesis, cimetidine is an androgen antagonist and some pesticides have estrogen-like activity.

Semen analysis in patients with varicocele demonstrate decreased motility, decreased sperm concentration and increased amorphous cells [16]. The majority of men who have varicoceles are fertile, but any subfertile man with varicocele should be considered for repair, as 70% of men receiving surgical repair have significant improvement in semen parameters. Motility improvements are most common (70%), followed by improved sperm densities (51%) and improved morphology (44%),

all of which increase the overall success rate of intrauterine insemination (IUI) [15]. Conception rates following varicocele repair average 40–50% when female factors are not present or have been appropriately treated.

### Infection

Infection of the male reproductive tract may be present in up to 23% of men seeking infertility evaluation [6]. Pyospermia is defined as  $> 1 \times 10^6$  leukocytes/mL of