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Reproductive Endocrinology Learning Guide

Abbott Diagnostics Fertility Educational Services

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Intended Audience

This learning guide is meant to serve the basic educational needs of health care professionals who are involved in the fields of laboratory medicine, obstetrics, gynecology, urology, and endocrinology. Anyone associated with the subspecialty of reproductive endocrinology will find this monograph of special interest.

Although anatomy, physiology, and infertility treatment will be discussed, the primary focus is on infertility diagnosis and hormone monitoring using immunoassays. Thus, laboratorians and those who use the laboratory's services will find this guide most useful. This includes laboratory technicians and technologists, laboratory supervisors and managers, nurses, and other physician office and laboratory support personnel.

Those at the doctorate level may find parts of this learning guide useful as well. If this monograph is to be made available to patients in part or in its entirety, prior review by the clinician is recommended.

How to Use This Learning Guide

To offer you the most benefit from this learning guide, each section begins with a Section Overview so you can quickly review its goal and content. Next you will find a set of Learning Objectives. These will help you focus on the key concepts presented in each section. There is a short Section Review quiz at the end of each section designed to help you recall the concepts introduced. If you answer a question incorrectly, review the appropriate portions of the text before moving to the next section.

A glossary and an explanation of acronyms are included at the end of this learning guide for quick reference.

Table of Contents

Introduction

By definition, **endocrinology** is the study of hormones and their modes of action. It follows then that reproductive endocrinology is the study of hormones and their impact on the reproductive system. It is a very interesting and exciting field still in its relative infancy.

Infertility is defined as the inability of a couple to conceive after one year of unprotected intercourse or the inability to carry a pregnancy to term. Although statistics vary, it is estimated that up to one in six couples will experience a degree of infertility at some point in their reproductive lives. With many of the factors causing infertility becoming increasingly prevalent in both economically-advanced and under-developed nations, the reported cases of infertility are not expected to decline in the foreseeable future.

Infertility is an area of interest not only because of its increasing prevalence, but also because of the dramatic scientific advances being made each year in its diagnosis and treatment. This makes reproductive endocrinology an area of medicine with high visibility and focus for both medical professionals and the general public.

Finally, the very nature of human reproduction is of inherent interest. It starts from the time we first recognize that mom or dad has body parts we do not and continues well into our adult lives. It is an area of medicine that can be readily understood at a basic level, yet remain intellectually challenging for a lifetime.

We hope this Reproductive Endocrinology Learning Guide from Abbott Diagnostics proves to be a useful tool to help you establish firm footing in this field of medicine.

Section 1

Human Reproductive Anatomy

This section will give you a general overview of both the male and female reproductive anatomy. Although not meant to be a comprehensive course in biology, it will give you the necessary knowledge to understand the rest of this learning guide.

Learning Objectives

After completing this section, you will be able to:

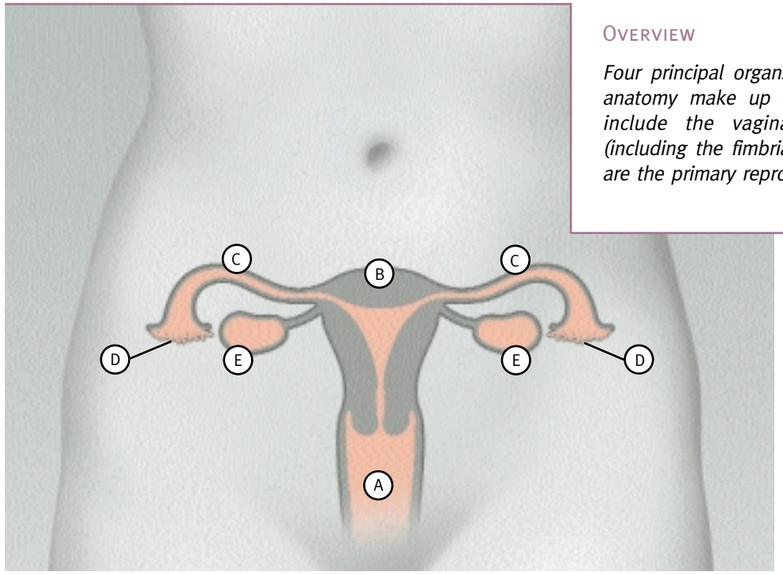
1. Name the four key female reproductive organs.
2. Define gonad and gamete.
3. Name the male and female gonads and indicate the function of each.
4. Name the male and female gametes.

Male and Female Common Links

Male and female reproductive anatomy begins with the gonads. Gonads are reproductive organs that produce gametes, sometimes called germ cells. In women, the gonad is the ovary. Gametes produced by the ovary are called ova (plural for ovum). These are also referred to as oocytes or eggs. In men, the gonad is the testis, and the germ cells it produces are called spermatozoa.

The male and female gonads have hormone-secreting (endocrine) functions in addition to their ability to produce germ cells. Hormones are chemical substances that circulate in the body and produce effects on the activity of cells remote from those they came from. Organs that secrete hormones or other substances are sometimes called "glands." The pituitary is an example of a gland found in both men and women. It will be discussed in further detail in Section II.

Female Reproductive Anatomy



Overview

Four principal organs of the female reproductive anatomy make up the reproductive tract. They include the vagina, uterus, fallopian tubes (including the fimbriae), and ovaries. The ovaries are the primary reproductive organs.

A) Vagina
B) Uterus
C) Fallopian Tube
D) Fimbria
E) Ovary

Figure 1-1 Graphic of Female Reproductive Anatomy

Next we'll discuss the ovaries, fallopian tubes, and uterus individually.

Ovaries

The female gonads are located within the pelvic cavity on either side of the uterus. Their upper poles are situated next to the ends of the fallopian tubes.

The ovaries are small at birth and increase in size rapidly at puberty. After menopause their size decreases and oocytes no longer develop. Although the ovaries atrophy (reduce in size) in old age, some hormone production still occurs.

There are two primary parts of the ovary: a cortical area that contains oocytes, and a medullary area that contains connective tissue and cells that produce hormones. At birth, there are between 200,000 and 400,000 oocytes in the cortical area of each ovary. This is the maximum number a woman will ever have, as no new ones are produced during her lifetime. Only a few hundred will mature and reach ovulation.

Each oocyte starts as a primordial follicle that develops into a secondary follicle containing the oocyte. A follicle is a cluster of granulosa cells surrounding the oocyte. A follicle with its oocyte grows in size as it develops. A mature follicle may be as much as two to three centimeters in diameter.

Fallopian Tubes

Adjacent to each ovary and leading to the uterus are two hollow structures called the fallopian tubes. The ends nearest the ovaries are flared with finger-like projections called fimbria. During ovulation, when an egg is released from the ovary, it passes to the fimbria, which sweep it into the fallopian tube. The lining of the tubes have small hair-like cells called cilia, which rhythmically move to propel the egg through the fallopian tube to the uterus. Fertilization usually takes place in a fallopian tube.

Uterus

The uterus, located in the lower abdomen, is an organ about the size of a human fist and is shaped like an inverted pear. The lining of the uterus, called the endometrium, is rich in blood vessels. The endometrium is where a fertilized egg is implanted. During pregnancy, the uterus expands as the fetus grows, eventually becoming large enough to accommodate a full-term baby. The fallopian tubes are attached to the uterus at the upper, wider end. At the lower, narrower end is the cervix, which leads to the vagina.

Male Reproductive Anatomy

The male gonad is the testis (the plural is testes). The gametes it produces are called spermatozoa, or sperm. Although there are many parts of the male reproductive anatomy that are critical to normal reproductive function, such as the vas deferens and seminal vesicle, our discussion will be limited to the testes and sperm.

Testis

The testes are located in the scrotum. The primary functions of the testis are to produce sperm in a process known as spermatogenesis, and to produce the major male hormone, testosterone. There are three primary types of cells in the testis: Leydig, Sertoli, and sperm cells. The Leydig cells are located in the connective interstitial tissue of the testis. They are responsible for the synthesis of androgens, primarily testosterone.

Sertoli cells are found in the seminiferous tubules. Seminiferous tubules are thread-like coiled tubes that make up the bulk of the testis. This is where sperm are actually produced and nourished by the Sertoli cells. Sertoli cells also act as the "blood-testis barrier." This means they separate mature and immature germ (sperm) cells and block the body's immune system from attacking the mature germ cells, which the body perceives as invaders.

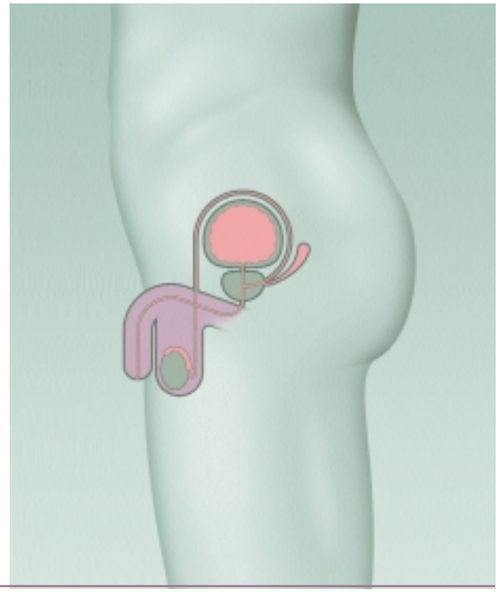
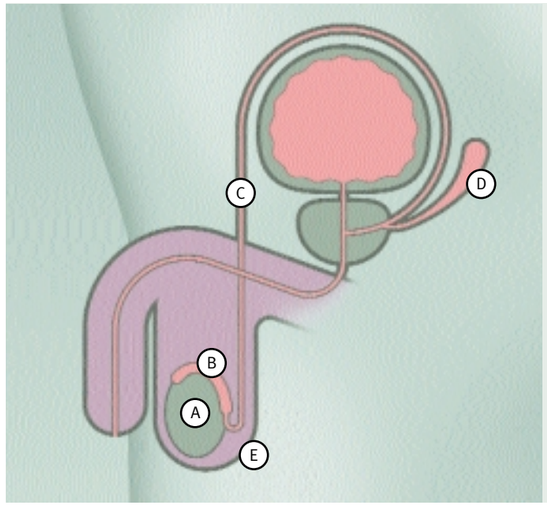


Figure 1-1 Graphic of Male Reproductive Anatomy



A) Testis
B) Epididymis
C) Vas deferens
D) Seminal vesicle
E) Scrotum

Sperm

The spermatozoa's primary function is to fertilize oocytes and thus achieve conception. Each sperm cell consists of a head, mid-piece, and tail. The head contains genetic material—normally 23 chromosomes. The mid-piece is where metabolism takes place, and the tail is responsible for the sperm's motility (movement). It takes 72-80 days for sperm cells to develop into mature sperm.

From the testes, the sperm pass into the channels of the epididymis, a coiled structure where the cells reach full maturity. They then pass into the vas deferens, a tube that connects the epididymis and the seminal vesicle.

Upon ejaculation, the sperm cells pass by the seminal vesicle where they are suspended in a fluid called semen. Semen helps the sperm cells move and nourishes them during their journey. During intercourse semen is ejaculated through the penis into the vagina. An average ejaculate of three milliliters (mL) of semen contains approximately 400 million sperm. A sperm count of less than 20 million per mL may be indicative of male infertility. Although it only takes one sperm cell to fertilize an egg, it is hypothesized that it takes this many to attain the volume of enzymes necessary to remove the barrier of granulosa cells that surround the ovum. Only then can a sperm penetrate and fertilize the egg. Sperm in cervical mucus remain capable of fertilizing an egg for up to 48 hours.

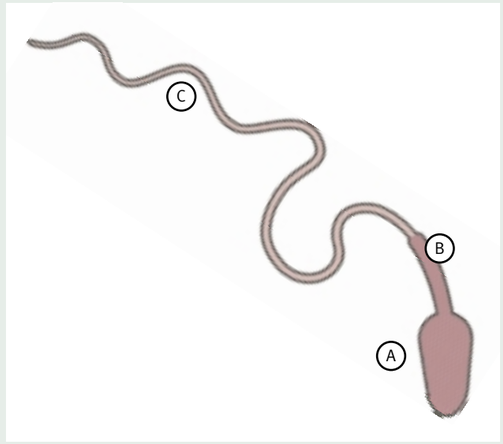


Figure 1-1 Graphic of Sperm

A) Head

B) Mid-piece

C) Tail

Review Questions • Section 1

1. Name the four key female reproductive organs:

1 _____ 3 _____

2 _____ 4 _____

2. Match the word with the correct definition:

(A)	Gonads	◯	Germ cells capable of initiating formation of a new individual by fusion with a gamete of the opposite sex.
(B)	Gametes	◯	Reproductive organs that in males produce sperm and in females produce eggs.

3. Complete the following:

The _____ is the female gonad.

The _____ is the male gonad.

4. Match the word with the correct definition:

(A)	Spermatozoa	◯	Fluid-filled sac that releases the female gamete upon maturation and ovulation
(B)	Ovum	◯	The female gamete (plural)
(C)	Ova	◯	The female gamete (singular); also referred to as egg or oocyte
(D)	Follicle	◯	The male gametes
(E)	Ovary	◯	Responsible for synthesis of testosterone
(F)	Leydig cells	◯	Primary female reproductive organ

Section 2

Endocrinology

This section will build on the concepts introduced in Section I by discussing key hormones responsible for sexual development and function. Here you will study the effect hormones have on the various organs just introduced. Together, these first two sections will prepare you for studying how conception occurs and how a baby develops—the topic of Section III: Pregnancy.

Learning Objectives

After completing this section, you will be able to:

1. Describe the reproductive axis in both males and females.
2. Name the four hormones that most affect female sexual development and reproduction.
3. Explain what reproductive steroid hormones are and where they are produced.

Male and Female Common Links

In addition to the testes and ovaries, there are two other organs that are critical for sexual development and reproductive function—the hypothalamus and pituitary. These are common to both males and females. Together with either the testis or ovary, they complete what is known as the reproductive or gonadal axis. In the male, this axis is referred to as the H-P-T (hypothalamus-pituitary-testis) axis and in the female the H-P-O (hypothalamus-pituitary-ovary) axis.

A) Hypothalamus
B) Pituitary

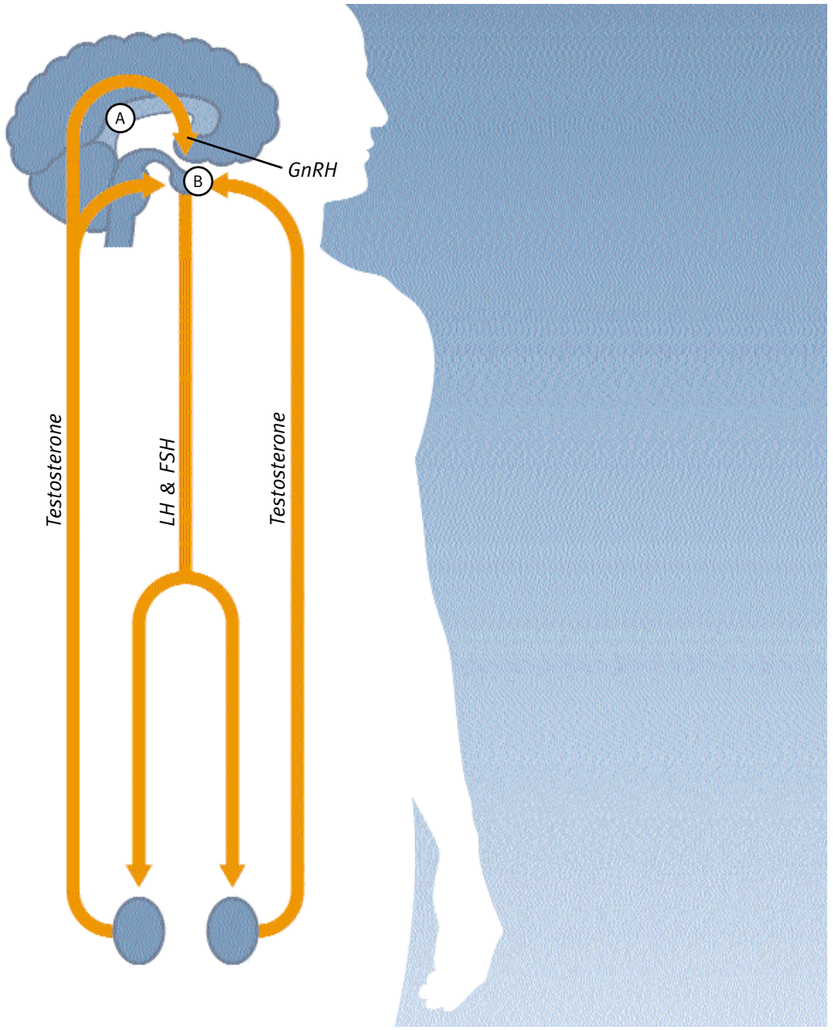


Figure 2-2 H-P-T Axis

The pituitary gland (sometimes called the hypophysis) lies at the base of the brain behind the nose. It is about one centimeter in diameter and is divided into anterior and posterior portions.

The pituitary produces several hormones including:

- Growth hormone (aids in growth through protein formation)
- Corticotropin (ACTH; stimulates adrenal hormone production)
- Thyroid-stimulating hormone (TSH; stimulates the thyroid gland)
- Follicle-stimulating hormone (FSH)
- Luteinizing hormone (LH)
- Prolactin (stimulates milk production)

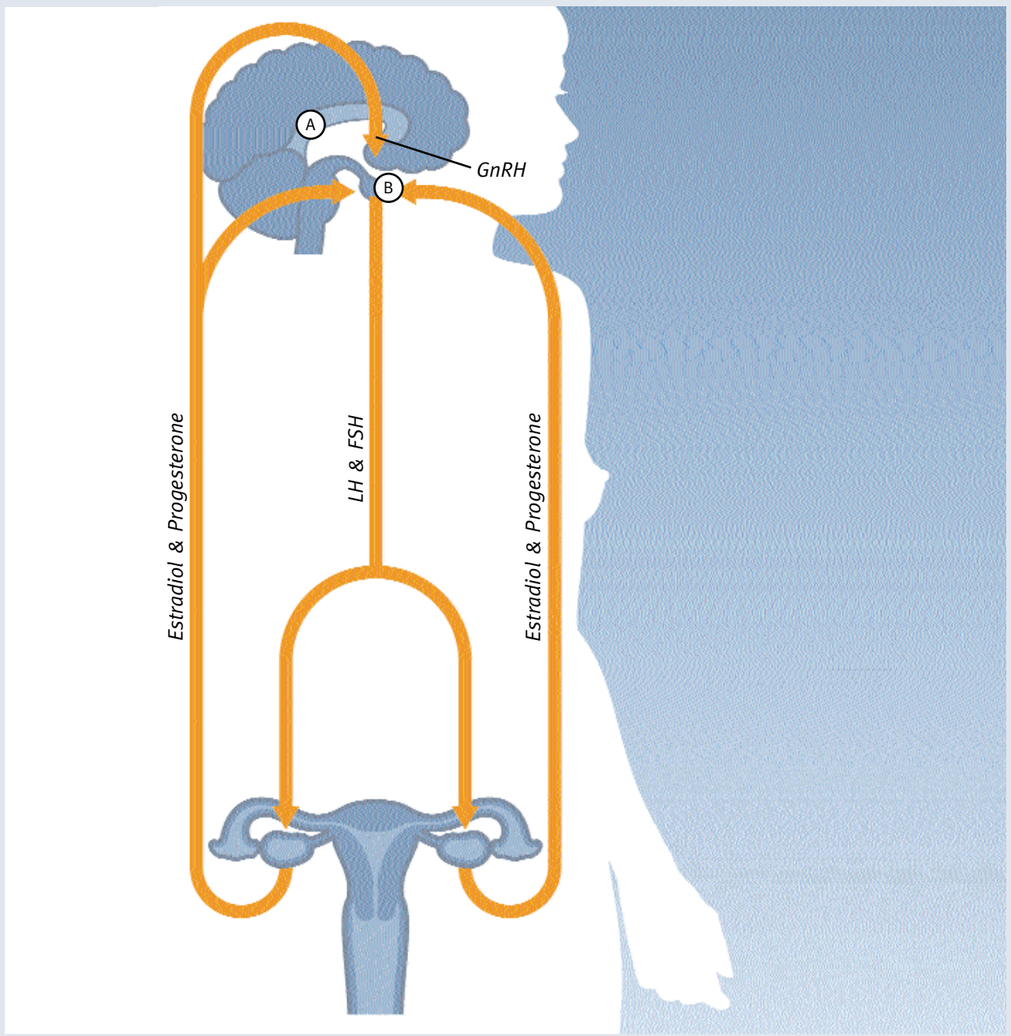
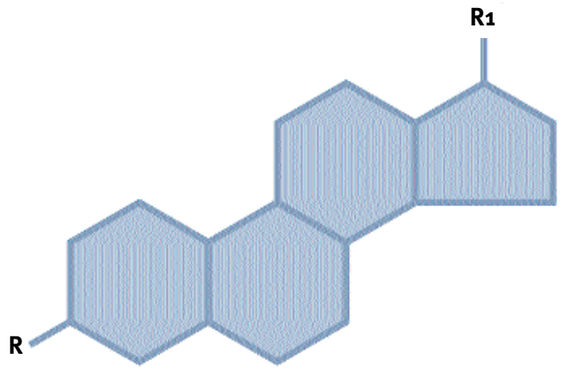


Figure 2-3 H-P-O Axis

A) Hypothalamus
B) Pituitary

The hypothalamus is located at the base of the brain. It produces GnRH (gonadotropin-releasing hormone) and other hormones. It is critical to the regulation of pituitary function and will be discussed in more detail later. Each hormone produced by the hypothalamus and pituitary has either an inhibiting or stimulating effect on an organ. This target organ may be either another endocrine gland or an "end organ." There are several types of hormones found in both males and females, among them a group of hormones known as steroids. A hormone is classified as a "steroid" if it is formed from cholesterol (the "precursor") and contains a 17-carbon, four-ring molecular structure. Steroids can sometimes be recognized because they end in "ol" or "one." Estradiol and progesterone are examples of steroid hormones. The reproductive steroids are synthesized in the gonad or in the adrenal gland. Steroids typically circulate bound to serum proteins. Sex hormone binding globulin (SHBG) and albumin are examples of these proteins. While most hormones are common to both males and females, some are more potent—or play a more significant role—in one of the sexes. LH and FSH, which will be discussed in more depth shortly, are very important to both men and women. Estrogens and androgens produced by the gonads are also present in both males and females. Estrogens, however, predominate and are most important in females, while androgens are most important and predominate in males. Hormones and their gender-specific roles are discussed next.



The 17-Carbon, four-ring molecular structure of a steroid hormone. The functional groups (R and R 1) differentiate one steroid from another.

Figure 2-4 Graphic of 17-Carbon

Female Hormone Physiology

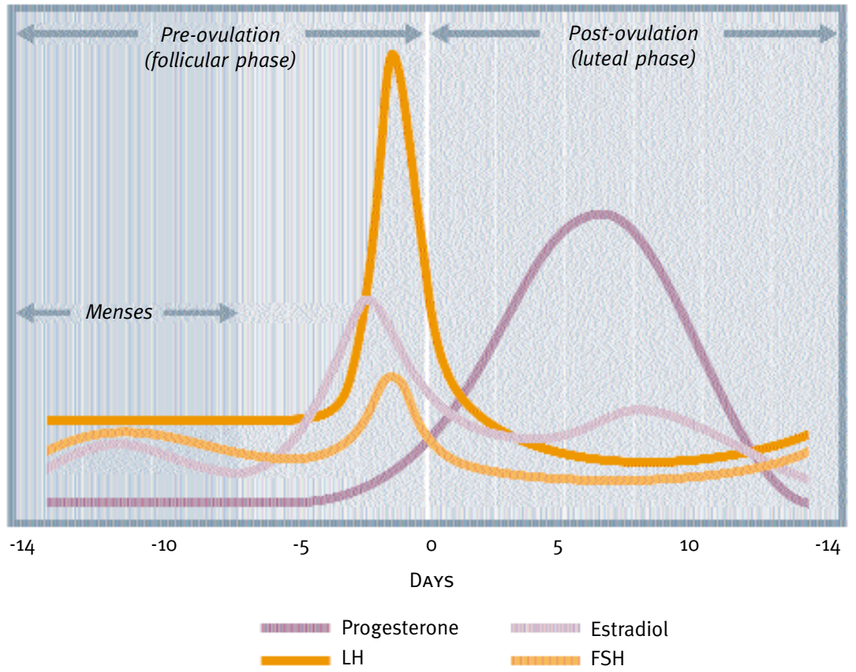
Control of the reproductive axis originates in the hypothalamus with the pulsatile, or intermittent release of gonadotropin-releasing hormone (GnRH). In response to GnRH, the pituitary gland releases LH and FSH. LH and FSH are known collectively as gonadotropins. In the female, LH and FSH induce the ovaries to produce estradiol and progesterone. This reproductive axis is regulated by both positive and negative feedback mechanisms from the ovaries. In general, estradiol and progesterone exert negative feedback to reduce levels of LH and FSH. The ovaries also produce proteins such as inhibin and activin, which can affect gonadotropin secretion.

The Menstrual Cycle

The feedback mechanisms just described are responsible for the female menstrual cycle (period). The menstrual cycle, also known as the ovarian cycle, averages 26-30 days. It is broken down into three phases: follicular, mid-cycle, and luteal.

The cycle is generally defined by the day of ovulation, which is the day the mature follicle ruptures to release the oocyte. The 14-15 days preceding the day of ovulation are known as the follicular phase, when the follicle is maturing, and the 14-15 days following ovulation are known as the luteal phase, when the corpus luteum is active.

Figure 2-5 Relative Hormone Serum Levels During Menstrual Cycle



As discussed, the hypothalamus secretes GnRH in pulses throughout the female menstrual cycle. These pulses stimulate the pituitary to release pulses of LH and FSH in a pattern that changes across the menstrual cycle. In the early follicular phase, at the time of menses (vaginal bleeding known as a period), the ovary has not yet selected a dominant follicle and estradiol levels are low. There is little feedback to shut down the hypothalamus and pituitary. Thus, FSH levels are higher than at any other time in the cycle, except during ovulation. FSH appears to be responsible for causing several follicles to grow so that eventually one becomes dominant. As the follicle grows and matures, the cells within it secrete more and more estradiol and follicular fluid.

Thus, the follicle becomes bigger. The rising estrogen levels induce increased amounts of cervical mucous and thickening of the endometrium. They also inhibit the hypothalamus and pituitary, so FSH levels are lower in the mid to late follicular phase.

At the end of the follicular phase, when the oocyte is mature, the feedback effect of estradiol on the hypothalamus and pituitary becomes positive instead of negative, and a surge of LH and FSH is released from the pituitary. This mid-cycle surge of LH is responsible for the final maturation of the oocyte. The LH surge also induces the follicle to rupture, releasing the oocyte so it can move down the fallopian tube, approximately 36 hours after the LH peak. (Because increasing amounts of LH are cleared in the urine as ovulation occurs, urine LH levels are often used for ovulation prediction in home tests.)

After the egg leaves the follicle, the cellular structure that surrounded and nourished it collapses to form the corpus luteum. The corpus luteum secretes progesterone. Progesterone causes organization of the endometrium so it can accept the fertilized egg if conception occurs.

Progesterone also causes the basal body temperature (BBT) to rise about half a degree, which is why some physicians ask women to make a BBT chart to determine if they have ovulated. Progesterone feeds back to the hypothalamus to slow the frequency of the GnRH pulses, so LH and FSH levels are relatively low during this luteal phase. In the absence of hCG produced by a developing placenta, the corpus luteum lasts about 14 days. After this time, the endometrium can no longer be maintained because the concentration of progesterone, produced by the corpus luteum, falls and menses occurs.

Refer to the chart on page 13 for a review of relative hormone concentrations during a normal menstrual cycle.

Male Hormone Physiology

Male hormone physiology is considerably easier to understand than its female counterpart because there is no monthly cycle. Male sex characteristics are brought about by a group of sex steroid hormones known as androgens. The most potent is testosterone. Much of what was just described about the female reproductive endocrinology system also applies to males. While GnRH stimulates LH and FSH production in the female, LH stimulates androgen production in the testes and then it is testosterone (instead of estradiol and progesterone) that acts as a negative feedback mechanism to the hypothalamus and pituitary. See page 10.

DHEA-S is another sex steroid from the group of hormones known as androgens, as is androstenedione. Both testosterone and androstenedione, however, are more potent than DHEA-S. The adrenal gland in both males and females increases DHEA-S production at puberty. This is why it is used as a tool to evaluate pubertal development, as will be seen in Section V. DHEA-S concentrations in both sexes fall gradually after age 30-40.

In both males and females, the proper sequence of hormone release is critical to normal sexual development and function. Understanding hormone physiology is particularly important because many infertility treatments rely on hormone manipulation as a primary tool. As medical science discovers more about hormone function and composition, further infertility treatment options become possible.

Review Questions • Section 2

1. In females, the reproductive axis is made up of what three organs?

1 _____

2 _____

3 _____

2. In males, the reproductive axis is made up of what three organs?

1 _____

2 _____

3 _____

3. Match the word with the correct definition:

(A) Hypophysis
(B) Androgens
(C) Gonadotopins
(D) Steroid
(E) Progesterone

◯ A class of hormone derived from cholesterol; includes Progesterone, testosterone, and estradiol.
◯ Luteinizine hormone (LH) and follicle-stimulating Hormone (FSH); peak during ovulation
◯ Male sex hormones
◯ The pituitary gland
◯ Secreted by the corpus luteum to sustain the endometrium

4. True or false:

True False A. LH and FSH play a key role in female physiology and are present, though not active, in males.

True False B. GnRH is produced by the pituitary gland.

True False C. Testosterone acts as a positive feedback mechanism to the hypothalamus a Negative feedback mechanism to the pituitary.

Section 3

Pregnancy

This section will build on the concepts introduced in Sections I and II by discussing how anatomy and hormone physiology act in unison to create a new life. With the fertility and pregnancy picture completed, Sections IV through VI will focus on some background facts about the field of infertility diagnosis, assay (test) utility, and treatment.

Learning Objectives

After completing this section, you will be able to:
1. Identify the three stages of fetal development.
2. Describe what happens to hormone levels in females when conception occurs and how these vary from hormone concentrations during a non-pregnant menstrual cycle.

Fetal Development

Conception is defined as the act of becoming pregnant through fertilization and implantation of the egg. It is considered to be the starting point of gestation (another word for pregnancy—generally lasting nine months in human beings). Conception occurs when the sperm fertilizes the egg. Only one sperm can penetrate an oocyte (egg). Once this occurs, the oocyte releases a substance that blocks any others from penetrating. After penetration, the sperm's head expands rapidly and forms a pronucleus. Soon thereafter, the 23 chromosomes located in the male pronucleus and the 23 in the pronucleus of the oocyte unite. This union forms the 23 pairs of chromosomes (46 in total) that determine the sex and other characteristics of the new individual.

A strand of DNA is made up of many genes. The genetic material of each chromosome consists of an extremely long stretch of DNA. Each cell contains an exact duplicate of the DNA.

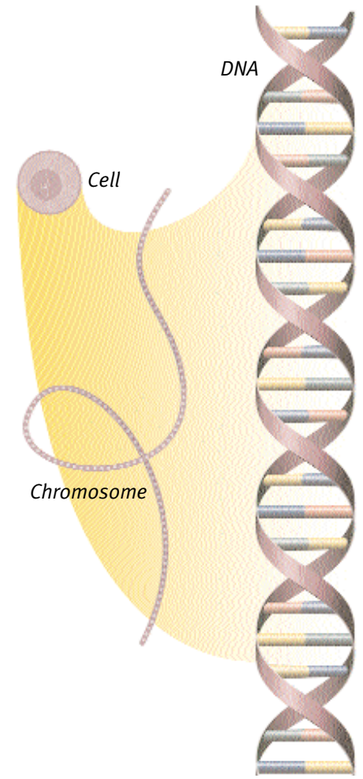


Figure 3-1 Graphic of cell / chromosome / DNA

The oocyte is fertilized just before or soon after entering the fallopian tubes. It generally takes eight days for the fertilized egg to reach the uterus and settle into the endometrium. At its earliest stage, a cell that is formed as a result of the male and female gametes fusing is called a zygote. This cell begins to divide and is then known as an embryo. Once the embryo develops its basic human structure, at about the third month, it is called a fetus.

At the very early stage of development, the embryo begins to form a hollow-centered sphere of cells known as a blastocyst. After implantation in the endometrial lining; cells from the blastocyst combine with those of the endometrium to form the placenta. The placenta is an organ that unites the embryo and the maternal uterus. It facilitates the exchange of nutrients and waste between mother and developing baby.

Maternal Hormone Physiology Upon Conception

During pregnancy, the placenta releases large quantities of human chorionic gonadotropin (hCG), estrogens (primarily estradiol), and progestins (primarily progesterone). All of these are required to sustain the pregnancy. The action of these hormones during pregnancy, plus prolactin and the gonadotropins, will be discussed next.

hCG

hCG was the first reproductive hormone discovered in the human body. It is produced by the trophoblastic cells of the placenta. hCG maintains corpus luteum function (prevents involution) for the first seven to ten weeks of pregnancy—primarily the production of estradiol and progesterone. This insures that shedding of the endometrium does not occur. hCG levels rise exponentially during the first few weeks of pregnancy, reaching peak levels between weeks seven and ten. At this time, the placenta is large enough to take over estrogen and progesterone production. hCG levels then decline steadily and plateau at the beginning of the fourth month of pregnancy.

Estrogens

Estrogens are a class of steroid hormones consisting primarily of estrone (E1), estradiol (E2), and estriol (E3). Estradiol is the most potent of the three. Rising estrogen levels induce increased amounts of cervical mucus and thickening of the endometrium in preparation for implantation. Estrogens are secreted by both the corpus luteum and the placenta. The placenta is responsible for the majority of estrogen production during pregnancy. During pregnancy, estradiol and estrone levels rise about 100-fold over average non-pregnant levels.

Progesterone

Along with estrogens, progesterone causes the endometrium to grow so it can support the developing fetus, instead of being sloughed off as happens during menstruation. Like estradiol, progesterone is secreted by the corpus luteum, although its main source during pregnancy is the placenta. Progesterone levels rise throughout pregnancy.

Prolactin

Prolactin is secreted by the pituitary. It is responsible primarily for milk production. Concentrations rise consistently throughout pregnancy and peak about one to two hours before birth. After dipping slightly, they again rise about one to two hours post-partum (after birth). This second rise is due to the loss of the inhibitory effect that progesterone and estradiol had while they were peaking prior to birth.

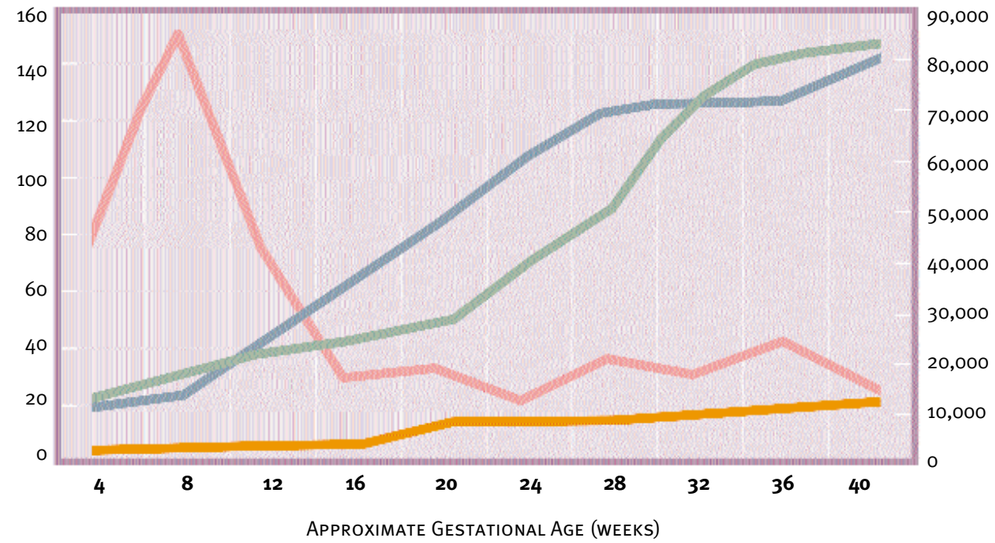
LH and FSH

As estradiol and progesterone levels rise during pregnancy, they exert their normal negative feedback on the production of LH and FSH. Consequently, gonadotropin levels are greatly suppressed during pregnancy.

Summary

The following chart shows average serum hormone levels during a normal pregnancy:

Figure 3-2 Gestational age (weeks)



The hormonal cycle in females is particularly important to understand because it can be manipulated to treat infertility. In the next section, we will cover some of the factors affecting infertility.

Review Questions • Section 3

1. Conception occurs (circle correct response):

A. Immediately upon fertilization of the egg by sperm.

B. Upon implantation of the blastocyst in the endometrial lining.

C. When the single-cell zygote divides into multiple cells and becomes an embryo.

2. The three stages of fetal development are:

1 _____

2 _____

3 _____

3. Match the word with the correct definition:

(A) hCG

(B) Zygote

(C) Embryo

(D) Fetus

◯ A single cell formed by the fusion of the male and female gametes.

◯ The term for a growing life once it develops its basic human structure; term generally applicable from months three to nine.

◯ The stage of development characterized by multiple cells without recognizable human structure.

◯ Rises rapidly during the first few weeks of pregnancy and peaks at weeks seven to ten.

4. True or false:

True False A. LH and FSH rise rapidly during pregnancy.

True False B. Progesterone is produced primarily by the corpus luteum during pregnancy and concentrations of it decline as the corpus luteum involutes.

True False C. Without hCG production by the placenta, the corpus luteum would involute. This would in turn cause decreased levels of estradiol and progesterone and ultimately menses would occur.

True False D. Prolactin is secreted by the hypothalamus and remains low until just prior to birth, when it increases to facilitate milk production.

Section 4

Factors Impacting Pregnancy & Fertility

In this section we will examine many of the social, gender-specific, and technological factors affecting fertility trends worldwide. This will help you understand the variety and scope of factors contributing to the incidence of infertility and build upon the knowledge gained in the first three sections. The financial impact to a couple seeking medical intervention for infertility will also be discussed.

Learning Objectives

After completing this section, you will be able to:

1. Distinguish between primary and secondary infertility.
2. Understand the widespread nature of infertility.
3. List the socio-economic factors affecting fertility.
4. Understand the relationship of infertility to age and sex.

Definition and Infertility Incidence

Infertility is defined as the inability of a couple to conceive after one year of unprotected intercourse or as the inability to carry a pregnancy to term. There are two types of infertility: primary and secondary. Primary infertility is when a couple has never achieved pregnancy. Secondary infertility is when a couple has achieved pregnancy in the past, but now can no longer do so.

For some couples infertility is due to the lack of mature follicles and available eggs, for some the problem is getting the sperm to the egg (as might be encountered with low sperm counts or blocked fallopian tubes), and for some it is a matter of the sperm not penetrating the egg. For still other couples the key concern is the fertilized egg not implanting properly in the endometrium. Implantation difficulties, possibly caused by uterine and genetic abnormalities, might lead to recurrent miscarriages. Finally, there is "idiopathic infertility"—infertility with an unknown cause.

It is estimated that infertility affects from one in six to one in seven of every couple during their reproductive lives. There are many factors that contribute to a couple's infertility and there are an increasing number of cases being reported.

Factors Affecting Increased Cases of Infertility

Demographic & Social Factors

Due to the "baby boom" that took place after World War II, the world population is aging. As reproductive organs age, they become less efficient and fertility decreases. Also, because there are more women working today, couples are delaying having children. As they wait, their reproductive organs age.

There is a direct correlation between a couple's ability to conceive and their age.

Age	Chance of Conception Over a 12 Month Period
20-24	86%
25-29	78%
30-34	63%
35-39	52%
40 and over	20%

Another reason for the rising number of infertility cases is the increased prevalence of sexually transmitted diseases (STDs). These often lead to pelvic inflammatory disease (PID), which may ultimately lead to infertility. Studies have shown that environmental toxins and nicotine may do the same.

Technological Factors

Another reason that reported infertility cases are on the rise is because of advances in both diagnostic and treatment technologies. As knowledge of these advances spreads, more couples seek medical intervention. With regard to treatment technologies, it is interesting to note that pregnancy success rates across infertility centers are very difficult to compare. This is because of differing criteria among clinics for accepting patients. For example, some centers may not accept women over 40 years old, which increases their probability of success and thus their claimed success rate. In another example, some centers use a broad range of treatment methods, including some experimental ones. This offers more couples an opportunity for success, yet the center's overall success rate may be lower.

Gender Contribution

Many people view infertility as a "woman's problem." In fact, the numbers are split fairly evenly between the number of cases contributed by male and female factors. Approximately 50 percent of causes are female-related and 40 percent are male-related. The remaining 10 percent are related to both partners or are unexplained.

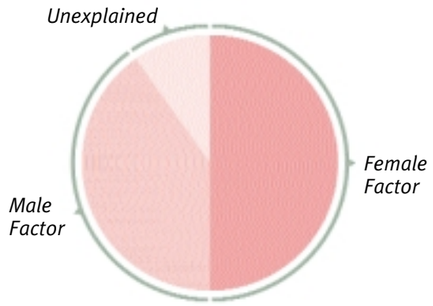


Figure 4-1 Gender Contribution

Economic Impact

The repercussions of infertility are not only emotionally draining to both partners, but are also financially so. The cost of diagnosis and treatment is very significant. In the United States, for example, a "cycle" of treatment (a one month attempt at achieving pregnancy via drug therapy, surgical techniques, or both) can run from $5,000-$20,000. Considering that many couples go through at least three cycles that are generally spaced at bi-monthly intervals, the investment can be significant.

Insurance and government coverage varies by locale. Because of the traditional lack of public funding to diagnose and treat infertility, medical assistance has often been limited to more affluent couples. Luckily, insurance coverage and public funding is becoming more accessible.

Summary

Today there is hope for infertile couples. Significant advances have been made in recent years with even more dramatic ones on the horizon. In most cases, the factors that reduce fertility can be identified and many of these conditions can be treated. Extensive evaluation may be required before treatment can be initiated by the physician. A full evaluation will probably require that a variety of assays (tests) be carried out. The regimen of tests ordered may vary by physician and will often be tailored to each couple's situation. Testing saves time and money because the results will help reveal which therapies are likely to be the most successful. In the next section, we will cover the most common laboratory tests and why they're important.

Review Questions • Section 4

1. Complete these statements.

A. Infertility is defined as:

_____

_____

B. Four of the factors discussed that contribute to the rising number of infertility cases are:

1 _____ 3 _____

2 _____ 4 _____

2. Match the word with the correct definition:

(A) Assay
(B) Male Factor
(C) Primary infertility
(D) Secondary infertility

◯ When an infertile couple has achieved pregnancy in the past
◯ When an infertile couple has never achieved pregnancy
◯ Responsible for 40 percent of infertility cases
◯ Laboratory test

3. True or false:

True False A) Female factor is the cause of infertility twice as often as male factor.

True False B) As many as one in six couples experience infertility at some time.

True False C) There is a direct correlation between a couple's ability to conceive and their age.

True False D) The number of couples seeking diagnosis and treatment of infertility is increasing in most parts of the world.

True False E) The cost of going through three treatment cycles may be equal to a couple's entire annual income.

Section 5

Assay Utility

In this section we will discuss the reasons for using assays (tests) in infertility diagnosis and treatment. We will examine how measuring various hormone levels in the blood can help evaluate the underlying causes of infertility and other health problems in both males and females. We will also discuss how proper use of test results can help determine a course of treatment and how they can help evaluate its efficacy (effectiveness).

Learning Objectives

After completing this section, you will be able to:

1. Comprehend the role of testing in an infertility workup.
2. Describe which hormones are measured and why.

The Infertility Workup (diagnosis) and Treatment Scheme

Although it will vary somewhat from physician to physician, the fertility workup should generally begin with patient counseling, a process which continues throughout the workup and subsequent treatment. The second step is obtaining a thorough medical history. Then both partners should undergo a physical exam, followed by or in conjunction with diagnostic tests. This will enable the physician to select an appropriate course of treatment.

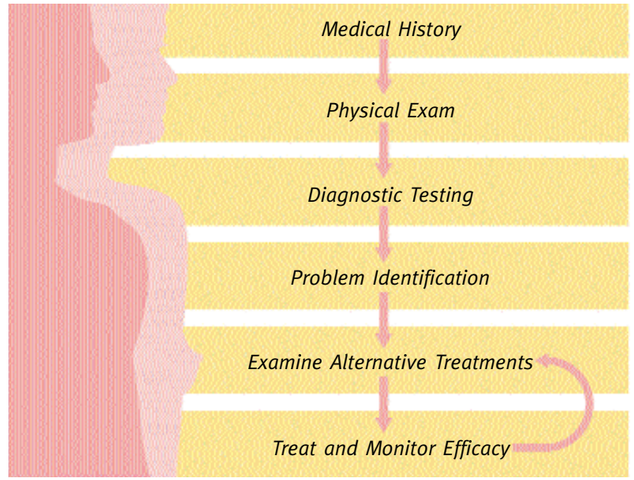


FIGURE 5-1 Patient Counseling Chart

Semen Testing

Andrology is the study of male fertility. One way to diagnose male infertility is by examining a fresh semen sample. In fact, semen analysis is often the first step taken during the diagnostic stage, often occurring prior to blood tests. The semen sample is evaluated for volume, color, pH, presence of white blood cells (indicating possible infection), viscosity, fructose, and sperm characteristics.

The characteristics of sperm that are analyzed are morphology (shape), motility (movement), and density (quantity, or count).

- Morphology—e.g. does the sperm have a tail and is it of sufficient length? Is the sperm head the right size and shape?
- Motility—e.g. does it swim the right way and with enough vigor to make it into the fallopian tube?
- Density—e.g. how many viable sperm per mL are there in the sample?

Hormone Testing with Immunoassays

An immunoassay is a laboratory test that identifies a substance through its ability to act as an antigen and bind with an antibody. LH, FSH, prolactin, estradiol, progesterone, hCG, testosterone, and dehydroepiandrosterone-sulfate (DHEA-S) tests make up about 90 percent of the requests for fertility and pregnancy immunoassays. In some laboratories the analysis of these hormones is performed in two separate specialty labs—a steroid hormone section and a peptide hormone section. All of these tests generally utilize serum. Serum is whole blood that has been allowed to clot and then centrifuged to remove clotting factors and red blood cells (RBCs).

Many of the test indications found in the following discussions are not related solely to infertility. In the case of ovarian tumor, for example, there is obviously good cause to treat it for reasons other than infertility. And for the older couple, the consequences of infertility may not even be an issue.

Next we will examine reasons for measuring key hormone concentrations.

Testing for LH (luteinizing hormone)

In women, LH peaks at ovulation and stimulates the ovaries to release eggs. In men, LH stimulates the production of testosterone, which in turn aids the production of sperm. LH is measured in milli-international units per milliliter (mIU/mL) or international units per liter (IU/L).

Following are key indications for ordering an LH test, along with expected results as compared to average concentrations. For LH and other assays to be discussed, each laboratory must establish its own reference ("normal") ranges. These will be dependent primarily on the assay used and, to a lesser extent, the local population. The information in the "Expected Assay Result" column should be considered relative to the laboratory's reference range. It is for general reference only and does not reflect the performance of any single manufacturer's assay on any one population.

Indication	Expected LH Results
Adult Female	Elevated
Menopause or Premature ovarian failure	Elevated
PCOS (polycystic ovarian syndrome)	Normal/Elevated
Hypothalamic amenorrhea	Suppressed
Hormone suppression therapy (e.g. with a GnRH agonist such as leuprolide acetate)	Initially elevated, then suppressed
Adult Male	
Gonadal failure	Elevated
Hypothalamic abnormality	Suppressed
Children	
Precocious (early onset) puberty	Normal/Elevated
Delayed puberty	Suppressed

LH is often ordered with FSH. With these two results, a ratio is acquired that offers further information to the clinician.

Testing for FSH (follicle stimulating hormone)

In women FSH concentrations usually run parallel with—although not equal to—LH levels. Like LH, they reach a peak during ovulation. Except for the surge at ovulation, FSH levels are highest at the very beginning of the follicular phase, then fall due to the negative feedback exerted by estradiol as it is secreted by developing follicles. FSH is measured in mIU/mL or IU/L units.

Indication	Expected FSH Results
Adult Female	
Ovulation	Elevated
Menopause or Premature ovarian failure	Elevated
PCOS (polycystic ovarian syndrome)*	Normal
Hypothalamic amenorrhea	Suppressed/Normal (generally>LH)
Adult Male	
Gonadal failure	Elevated
Hypothalamic abnormality	Suppressed
Children	
Precocious (early onset) puberty	Elevated
Delayed puberty	Suppressed

**The LH to FSH ratio for PCOS, when FSH reads normal, is generally greater than 2:1. This is very dependent, however, on the standardization of the assay used, the assay's antibody, protocol followed, and other factors.*

Testing for Prolactin (PRL)

Like hCG, prolactin is a hormone that plays an important role in female physiology once conception occurs. Prolactin helps the female body build and maintain a milk supply for the new baby. Prolactin levels rise gradually and significantly after conception and throughout pregnancy. Levels drop during active labor and are especially low two hours before delivery. At delivery prolactin levels surge, reaching a peak two hours post partum.

Abnormal prolactin levels can be a major disruption to both male and female physiology, although the incidence of abnormal prolactin levels in males is less commonly diagnosed as a problem. Abnormally elevated prolactin inhibits production of LH and FSH. Fortunately, medications such as bromocriptine can control over-production of prolactin in most patients.

Measuring prolactin can help evaluate and manage amenorrhea (lack of menstruation) or galactorrhea (abnormal production of milk), can aid in the diagnosis of infertility and gonadal disorders in both females and males, and can help diagnose pituitary dysfunction. Prolactin is measured in ng/mL units.

Indication	Expected PRL Result
Adult Males and Females	
Diagnose pituitary tumors	Elevated
Monitor therapy for hyperprolactinemia	Normal
Adult Female	
Evaluate amenorrhea or galactorrhea*	Elevated

**Abnormal milk production*

Testing for Estradiol (E2)

E2 concentrations are modest during most of the follicular phase and peak on the day before or the day of ovulation. After ovulation E2 declines only slightly, but increases if conception occurs. If conception does not occur, E2 levels decline and menstruation begins. E2 determinations are reported in picogram/mL (pg/mL) or picomole/liter (pmol/L) units.

Indication	Expected E2 Result
Adult Female	
Menopause or premature ovarian failure	Suppressed
Estrogen replacement therapy *	Suppressed or Elevated
Monitor follicular development/hormone induction therapy with exogenous gonadotropins (to be discussed in further detail next in Section VI)**	Normal/Elevated (degree of rise in values is the key)
Adult Male	
Gynecomastia (breast enlargement)	Normal/Elevated
Testicular, adrenal, or pituitary tumor	Normal/Elevated
Testicular dysfunction	Normal/Elevated
Children	
Precocious (early onset) puberty in girls	Elevated
Delayed puberty in girls	Suppressed

**The most common estrogen administered for the purposes of ERT is Premarin, which is made of equine-derived estrone sulfate and other equine estrogens. These equine estrogens are not measurable in assays meant for monitoring estradiol in human serum. Estrace" and Estraderm", however, are two other drugs administered for ERT and may be monitored using estradiol assays meant for use with human serum.*

***Estrogen levels help the clinician gauge medication dosages and timing of the stages of treatment. A treatment cycle for infertility may be canceled if ultrasound results of the developing follicles and serum estradiol levels indicate hyperstimulation or insufficient response has occurred.*

Testing for Progesterone

Progesterone peaks six to eight days after ovulation. This is why it may be ordered to confirm that ovulation has taken place. If conception does not occur, progesterone levels fall when the corpus luteum fails. It is ordered during the luteal phase to see if concentrations stay elevated long enough to sustain the endometrium should embryo implantation need to occur. Reduced progesterone levels signal the body to shed the endometrium, and the menstrual period begins. Progesterone levels are reported in nanogram/mL (ng/mL) or nanomole/L (nmol/L) units.

Indication	Expected Progesterone Result
Adult Female	
Post-ovulation confirmation	Elevated
Inadequacy of luteal phase to sustain pregnancy	Suppressed
PCOS	Suppressed
Ectopic or non-viable pregnancy	Suppressed (often used as a ratio with hCG)

Testing for hCG (human chorionic gonadotropin)

A rise in serum hCG is detectable seven to nine days following conception. Serum concentrations of hCG range from 50-250 mIU/mL at the time of the first missed menses (period) following conception. hCG concentrations continue to rise throughout the first two months of pregnancy, usually peaking between weeks eight and ten. Peak levels range from 50,000 to 2000,000 mIU/mL. Basal levels of less than five mIU/mL are found in normal males and non-pregnant females.

Because urinary concentrations of hCG are similar to those found in serum, urine tests for pregnancy are widely available.

hCG is sometimes administered to men with low LH levels to stimulate sperm production, because hCG is easier to purify than LH and has similar bioactivity.

Indication	Expected hCG Result
Adult Male & Female Cancer of lung, GI tract, and melanoma	Elevated (in minority of cases)
Adult Female	
Pregnancy*	Elevated
Threat of miscarriage	Suppressed (abnormal pattern of rise)
Hydatidiform molar pregnancy/ gestational trophoblastic disease**	Elevated
Fetal chromosomal abnormalities*** (e.g. Down's Syndrome)****	Elevated
Ecoptic pregnancy and spontaneous abortion	Elevated (doubling time compared to normal pregnancy suppressed; often used in combination with progesterone)
Ovarian and breast cancer	Elevated (in minority of cases)
Adult Male Testicular tumors*****	Elevated (in up to 70 percent of cases)

* *Values generally double every 24-48 hours from the beginning of gestation through weeks eight to ten. After peaking concentrations decline and plateau at about week 16 at one quarter the peak value.*

** *No hCG assay is FDA approved for this indication.*

*** *Only a few diagnostic companies have a Down's claim.*

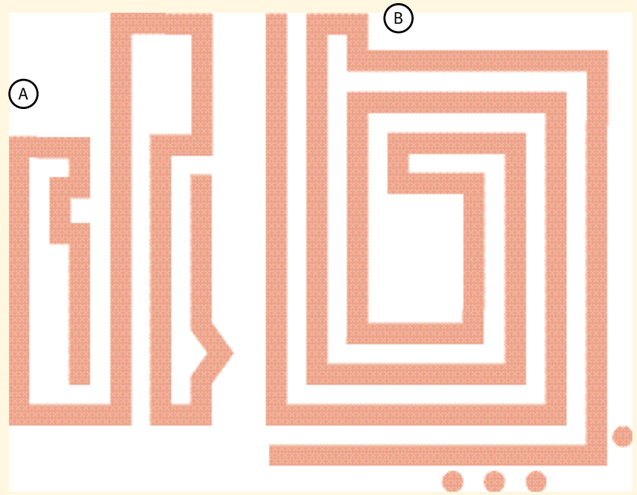
**** *Often tested with alpha-fetoprotein (AFP) and less frequently with estriol.*

***** *Often tested with AFP.*

Other hCG Testing Issues

There are multiple types of hCG assays. A "whole molecule" hCG assay measures the intact hCG molecule, which is composed of a chemically linked alpha and beta subunit. A "total beta" hCG assay measures not only the intact molecule, but also the free beta subunit.

Since the proportion of the free beta subunit to intact hCG is quite low following the first few weeks of gestation (sometimes as low as 0.5%), either assay method can be used to determine pregnancy. Both methods also aid in diagnosing ectopic pregnancy, spontaneous abortion, and multiple gestation. A small minority of trophoblastic disease patients secrete mainly or only hCG free beta subunits. These patients' samples would show falsely negative results if tested with an intact hCG assay.



A) Structure of alpha (∂) subunit of hCG molecule

B) Structure of beta (ß) subunit of hCG molecule

Testing for Testosterone

Testosterone levels are generally lower in females than in males, although testosterone is present in females and does play a physiologic role. In females, it acts as a precursor to estradiol and is produced primarily by the adrenal glands and ovaries.

Virilization, or the presence of male characteristics in females, can occur as a result of elevated testosterone levels. This can ultimately lead to infertility. In males, testosterone works in conjunction with LH and FSH to regulate sperm production. Testosterone also plays a significant role in the normal development of male characteristics during both gestation and puberty.

A decrease in testosterone secretion or sperm production is called hypogonadism. In boys at the age of puberty this can result in minimal pubic/body/facial hair, decreased muscle development, small penis, and possible breast enlargement. These characteristics are classified collectively as a female phenotype. The post-puberty onset of hypogonadism generally does not cause a regression of male characteristics, but will most likely result in a low libido (sex drive). Testosterone is measured in ng/mL or nmol/L units.

Indication	Expected Testosterone Result
Adult Males and Females Monitor androgen-suppressing drugs in cancer treatment	Normal/Suppressed
Adult Females	
Adrenal and ovarian tumors	Elevated
PCOS	Elevated or upper limit of normal
Virilization	Elevated
Monitor response to anti-androgen therapy	Normal
Testicular feminization	Elevated
Adult Males	
Hypogonadism	Suppressed

Testing for DHEA-S (dehydroepiandrosterone-sulfate)

Because of testosterone's dominance as the key androgen in males, measuring DHEA-S is not as important in males as it is in females. To evaluate DHEA-S levels, knowing age-specific reference ranges is very important. DHEA-S is the sulfated form of DHEA (DHEA is considered the "precursor" to DHEA-S). DHEA-S, however, is more commonly measured because it is not as pulsatile and thus its levels are more constant. DHEA-S levels are also higher than DHEA levels due to the stability (half-life) of DHEA-S, making it easier to measure accurately.

In females, elevated levels of DHEA-S are symptomatic of a variety of diseases: virilization (specifically hirsutism—excessive hair growth), alopecia (balding), PCOS, and hormone-secreting adrenal tumors. Low levels of DHEA-S can indicate pregnancy, use of oral contraceptives, or ovarian cancer. Low levels may also correlate with insulin resistance and cardiovascular disease. Other reasons to measure DHEA-S are to help assess delayed puberty and to indicate adrenal androgen output. DHEA-S is measured in micrograms per deciliter (µg/dL).

Indication	Expected DHEA-S Result
Adult Females Hyperandrogenicity to determine source (ovary, which normally makes very little DHEA-S, or the adrenal gland, which normally makes larger amounts)	Normal/Elevated
Virilizing congenital adrenal hyperplasia and adrenal cortical tumors	Elevated
Ovarian tumors	Normal/Suppressed
PCOS	Elevated (in about 50% of cases)
Virilization or hirsutism of adrenal origin	Elevated
Children Assess delayed puberty adrenal androgen output)	Suppressed

Panel Testing

Thus far, we have examined each of the immunoassays individually. In practice, however, a series of tests, known as a panel, are often run to give the clinician as much information as possible. Although the tests offered as part of a panel will vary from laboratory to laboratory, the following table outlines what a typical panel might include:

Indication	Tests often Included
Female infertility workup	LH, FSH, Estradiol, Progesterone, Prolactin, DHEA-S
Male infertility workup	LH, FSH, Prolactin, Testosterone
Monitoring response to ovulation induction therapy	Estradiol, LH
Impotency	Testosterone, Prolactin
Hirsutism	LH, FSH, Testosterone, DHEA-S, Prolactin

Finally, although beyond the scope of this monograph, there are testing decision trees (algorithms) that indicate further tiers of testing. These "reflex" tests or panels are not included in an initial set of test requests, but are ordered based on the data received from the first set of test results. Ordering select tests initially and reflexing with additional tests only if needed saves the entire health care system money.

Summary

Measuring hormone levels in the blood with immunoassays helps evaluate the causes of infertility and other problems in both males and females. Hormone imbalances, however, lead to infertility more frequently in females than in males due to the delicate nature of the menstrual cycle.

Testing for one or more of the compounds discussed can help determine a course of treatment and evaluate its effectiveness. Whether for diagnosis or monitoring treatment, hormone tests are often ordered in panels.

Finally, there are other analytes (compounds) that are evaluated during an infertility workup. These might include SHBG (sex hormone binding globulin) and androstenedione, as well as TSH (thyroid stimulating hormone). Because of the scope of this monograph, however, they are not discussed here.

Review Questions • Section 5

1. Complete these statements:

A. Sperm is analyzed for these three primary characteristics:

1 _____

2 _____

3 _____

B. The sex hormones may be divided into two classes:

_____ and _____

2. Match the word with the correct definition:

(A) Prolactin
(B) Estradiol
(C) Progesterone
(D) FSH
(E) hCG
(F) LH

( ) Peaks at ovulation, is elevated during ovarian failure, and is often used in a ratio with LH

( ) Sometimes used with hCG to diagnose ectopic pregnancies and confirms that ovulation has occurred

( ) Concentrations double every 24 to 48 hours form early pregnancy through weeks eight to ten

( ) Increased follicular growth viewed via ultrasound will be confirmed by increasing levels

( ) Stimulates the production of milk; if elevated may suppress menstrual cycle

( ) Determinations are elevated at ovulation and menopause

3. True or false:

True False A. DHEA-S is often elevated in women with hirsutism and alopecia.

True False B. SHBG, estrone, activin, TSH, and inhibin make up about 25 percent of the infertility diagnosis testing volume.

True False C. LH, FSH, and progesterone are often used to diagnose pubertal disorders.

True False D. hCG effectively aids in the diagnosis of molar pregnancies, where values will be elevated.

Section 6

Infertility Treatment

You should now have a basic understanding of reproductive anatomy and hormone physiology, the key factors contributing to infertility, and methods of infertility diagnosis. This final section will deal with infertility treatment for both men and women.

A variety of treatments will be discussed. These include hormone manipulation, surgical techniques, and a combination of both. Adoption and child-free living are also discussed. This section completes your basic knowledge of reproductive endocrinology as it relates to pregnancy and infertility diagnosis and treatment.

Learning Objectives

After completing this section, you will be able to:

1. Understand the most commonly used methods of ART (assisted reproductive technologies).
2. Discuss the role of ovarian stimulation in ART.
3. Identify methods used to retrieve gametes.
4. Discuss alternatives to medical intervention for treatment of infertility

Assisted Reproductive Technologies (ART)

ART is a general term used to describe methods of treatment for infertility. Although precise definitions vary, ART generally includes both invasive (surgical) and non-invasive methods of treatment.*

* *Some consider ART to include only IVF, GIFT, ZIFT, and related treatment techniques.*

In Vitro Fertilization (IVF) and Advanced Reproductive Technologies

In Vitro Fertilization (IVF) in humans was first successfully described in 1978 with the birth of Louise Brown in England. Since that time the technologies have advanced dramatically. Initially used in women with blocked tubes, the procedure is now indicated for couples with other anatomic causes for infertility such as endometriosis, severe male factor infertility, immunologic causes for infertility and unexplained infertility.

Monitoring Follicular Development

It is important to determine where a follicle is in terms of maturity. In other words, when the egg it contains is ready to be "harvested" or retrieved—ready to be fertilized. This can be accomplished in several ways:

- Ultrasound (sonograph) can image the ovary and show the follicles inside. Ultrasound can also be used to measure the thickness of the ripening endometrium lining:
- Estradiol levels may be measured in blood.
- LH levels can be measured in urine or blood (serum is used most often because it offers greater accuracy and helps monitor an early spontaneous LH surge, which is detrimental to the timing of oocyte retrieval and can cause the treatment cycle to be terminated).
- Physical examination of cervical mucus.

Several of these techniques are typically used together to give the physician a more complete picture.

Egg Retrieval

Once it is determined that eggs are ready to be fertilized, there are several ways of retrieving them. The most frequently used are laparoscopy and ultrasound-directed needle aspiration.

Laparoscopy

In laparoscopy, the laparoscope is inserted into a small incision made near the navel. The physician can then view the ovaries and other reproductive organs on a monitor. To retrieve the eggs, the physician makes another small incision, through which an aspiration needle is placed. Using the laparoscope, the needle can be accurately maneuvered to a mature follicle. The egg within the follicle is then drawn into the needle. This process is repeated until all mature follicles have been aspirated.

Ultrasound-Directed Needle Aspiration

In this technique an instrument called a vaginal transducer is placed in the vagina. This allows the physician to view ultrasound images of the reproductive organs. Alongside the transducer the physician directs an aspiration needle, monitoring the path with ultrasound. The needle is directed to mature follicles, and the eggs are drawn into the needle, again repeating the process until all of the visualized mature follicles have been aspirated.

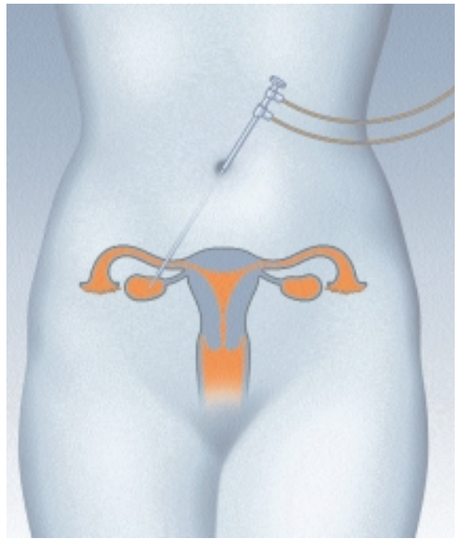


Figure 6-1 Graphic of Laparoscope

A laparoscope is used to view the ovaries

Ovulation Induction Through Ovarian Stimulation, Timed Intercourse and Intrauterine Insemination

If ovulation is not occurring in a woman (anovulation) or if it is occurring irregularly (oligomenorrhea), drug therapies can manipulate hormone levels, stimulating the ovaries to produce mature follicles. This is called ovulation induction (OI) therapy.

Once mature follicles have developed, attempts at fertilization may be accomplished through either well-timed sexual intercourse or the insertion of sperm into the uterus via mechanical methods, such as intrauterine insemination (IUI). Alternately, once OI has been used to develop mature follicles, the oocytes within the follicles may be surgically collected, or harvested, and used not only to produce mature follicles, but also to control ovulation timing.

The hormones administered in OI are either artificially produced or manufactured from native substances. They may be used individually or in combination.

Drug	DESCRIPTION & ROUTE of ADMINISTRATION
Synthetic GnRH	Stimulates the pituitary to secrete LH and FSH. Common trademark is Lutrepulse. Administered via intravenous or subcutaneous infusion pump.
Clomiphene citrate	Stimulates the pituitary to secrete LH and FSH by blocking inhibitory effect of estradiol. Usually administered from five to nine days from the start of menses to stimulate follicular growth. Often used when timed intercourse or IUI are to be attempted. Common trademarks are Clomid and Serophene. They are administered orally.
hMG (human menopausal gonadotropin)	Native LH and FSH often prepared from the extracts of urine or post menopausal women. May stimulate multiple eggs, which is the goal for IVF—ideally stimulates only one or two, which is the goal for ovulation induction without IVF; taken for seven to ten days to cause follicular growth. Usually used in conjunction with hCG. Common trademarks are Pergonal (FSH and LH) and Metrodin (primarily FSH). Administration is generally intramuscularly.
hCG	Administered 34-36 hours prior to egg aspiration or ovulation and after treatment with hMG. Mimics LH surge to trigger egg release. Often used in combination with clomiphene citrate, also. Common trademarks are Profasi and Pregnyl. Administration is intramuscularly.

Retrieval of Spermatozoa

Acquiring sperm samples through natural or surgical means is required to proceed with many ART techniques. In most cases, a masturbated sample is used. In some cases, infertility may be due to the obstruction of sperm delivery. This might be the case if pregnancy is desired after a vasectomy, if an attempted vasectomy reversal has not been successful, or in cases of trauma to the testicles or penis.

MESA (microsurgical epididymal sperm aspiration) is a common technique used when surgical means of acquiring sperm are necessary. With MESA, a needle is place in the area of the epididymis closest to the testes. Through it a sample of freshly-produced sperm, which is generally the most vigorous, may be obtained.

Surgical Methods of ART

There are many criteria used to decide what form of ART is most appropriate for a patient. Blocked fallopian tubes, for example, may indicate that IVF is more appropriate than GIFT, both of which will be discussed shortly.

Certain treatment techniques have a higher likelihood of success than others. With regard to success rates, however, it is important to note that not all procedures can be performed on all patients. Also, success rates for a particular method of ART vary by treatment center for several reasons as mentioned earlier. For all of these reasons it is difficult to compare methods for the purpose of determining the "best" technique. Success rates for surgical ART techniques generally range from 10-25% per cycle.

The following discussion describes some of the most common forms of ART using surgical means, their strengths and weaknesses, and what situations best indicate their use.

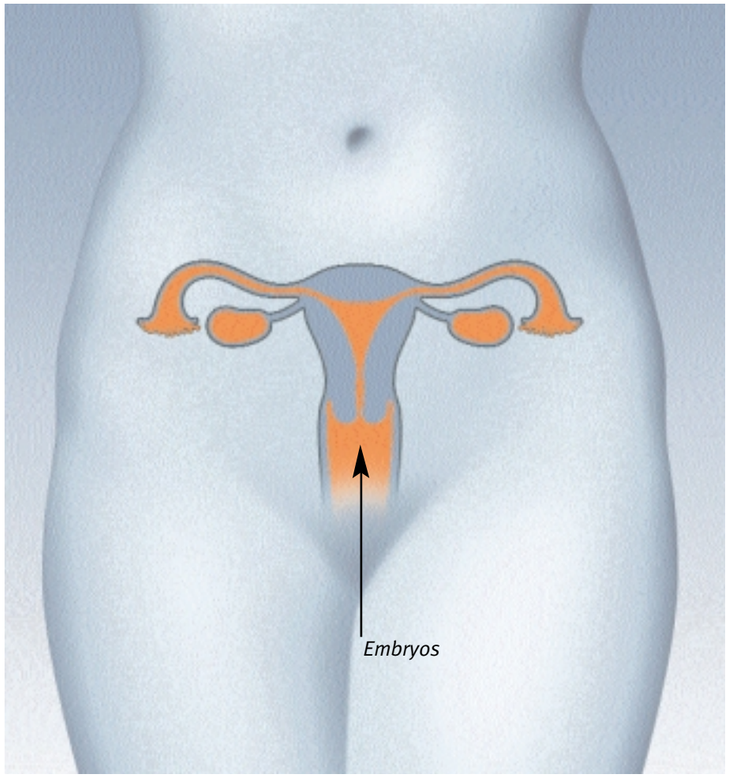
IVF

In vitro fertilization (IVF) is the most widely-known form of ART. The successful outcomes of this technique are often referred to as "test tube babies" in popular culture. It was this history-making process that resulted in the 1978 birth of Louise Brown in London, the first successful birth as a result of IVF.

IVF involves both OI and egg retrieval. It begins with a liquid called culture medium. The harvested eggs are placed into it and remain there for several hours. During this time, a semen sample is obtained, either from the husband or another donor. The semen is treated in several ways to obtain the most vigorous and motile sperm. These are then placed into the culture medium containing the eggs. After about 24 hours, they are examined through a microscope to see if fertilization has taken place. They are re-examined after 48 hours to evaluate the embryos for normal development. If fertilization is successful, embryo transfer (ET) is initiated.

In ET, a catheter is placed through the cervix into the uterus. Through this catheter, the embryos are moved into place where they may implant in the thickened endometrial lining.

IVF is appropriate when the fallopian tubes are blocked, when there are cervical problems or to overcome infertility due to immunologic problems.



In IVF, embryos are placed in the uterus

Figure 6-2 Graphic of Embryo placement into Uterus (IVF)

GIFT

Gamete intrafallopian transfer (GIFT) can be used when the woman's fallopian tubes are normal but for some reason fertilization has not occurred during prior attempts at conception. In GIFT, the ovaries are stimulated as previously discussed and eggs are retrieved at the appropriate stage, usually through laparoscopy. But before retrieval, a semen sample is obtained, prepared, and loaded into one part of a catheter. Eggs are retrieved, quickly examined and loaded into another part of the catheter. These two parts are then placed into the fallopian tube, where fertilization can occur in vivo (within the body). The fertilized egg can then travel to the uterus naturally.

GIFT is often the treatment of choice in cases of mild endometriosis, or when infertility is due to male factor, cervical problems, or immunologic factors. Because fertilization takes place within the woman's body, GIFT is considered the method of choice for individuals with particular religious or ethical beliefs who are concerned about the "in vitro" (outside of the body) aspects of other ART techniques.

ZIFT

Zygote intrafallopian transfer (ZIFT), also known as PROST (pronuclear stage transfer), is a process in which in vitro fertilization is conducted, but instead of placing the resulting embryo into the uterus as in ET, it is placed in the fallopian tube through laparoscopy. This process is called Tubal Embryonic Transfer (TET). Of course, the fallopian tubes must function normally for this procedure to be considered. The advantage of ZIFT over GIFT is that fertilization can be confirmed before introduction into the woman's body.

ZIFT is often the appropriate treatment in cases of mild endometriosis, or when infertility is due to male factor, cervical problems or immunologic factors.

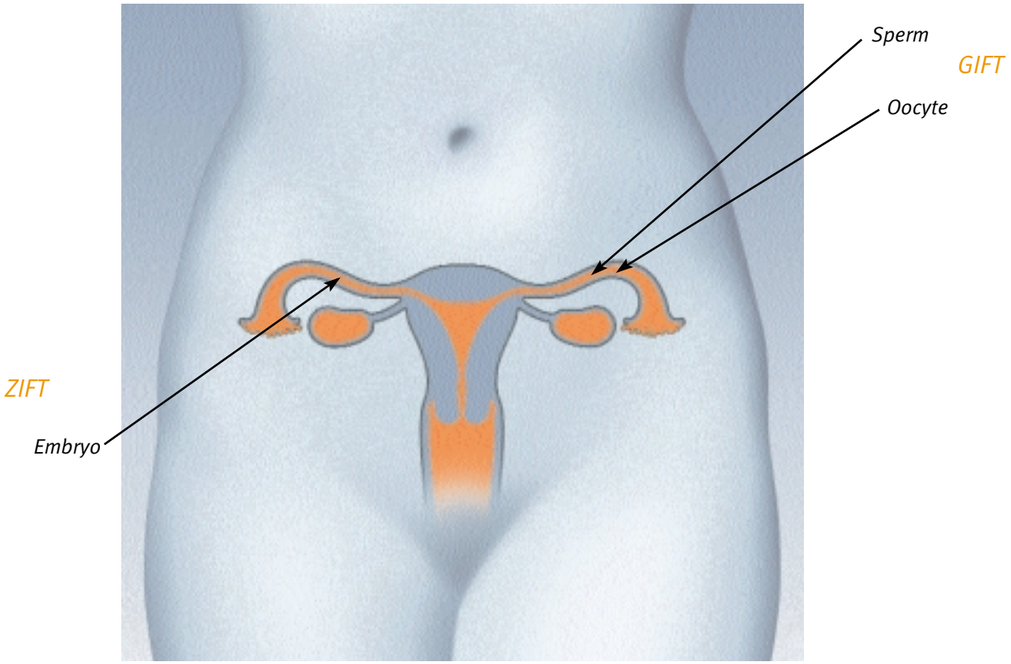


Figure 6-3 Graphic of GIFT / ZIFT

In GIFT, sperm and eggs are placed in the fallopian tube, where fertilization can occur in vivo.

In ZIFT, embryos are placed in the fallopian tube.

ART and Male Infertility

The treatment techniques discussed thus far have relied on the fact that properly functioning sperm are available—either from the husband or a donor (who would be considered the biological father). There are new and promising treatment techniques for male factor infertility due to low sperm count or immotility that might lessen the need for donor sperm. They are known as micro-manipulation. Because these techniques are new and still somewhat experimental, limited information is available on success rates.

Microsurgical Techniques

For couples with male factor infertility (low sperm count or sperm immotility) or who have failed IVF in the past, microsurgical techniques may be helpful.

With zona pellucida drilling and microinjection, an opening is formed in the outermost protective layer of the egg—the zona pellucida—and sperm are placed in direct contact with it. This opening may be formed with either a needle or an enzyme called a zona solvent. This gap makes it easier for sperm to enter the egg. One problem with this technique is a high possibility of more than one sperm penetrating the egg, which can result in polyploidy (chromosomally abnormal) embryos.

Further Options

Oocyte Donation

Just as donor sperm is an option to treat couples with male factor infertility, oocyte donation is an option when oocytes are not available from the female. Oocyte donation means that eggs from one woman are retrieved and transferred to the body of another woman. This technique may compensate for lack of ovarian function, failure to respond to ovarian stimulation, or genetically related recurrent miscarriage.

Surrogate Carriers

For a woman with normal ovaries but an abnormal or absent uterus, a surrogate carrier can be utilized to bring the pregnancy to term. In this process any of the assisted reproductive techniques can be used. Eggs and sperm are retrieved from the infertile couple and introduced into the body of the surrogate mother through IVF, GIFT, or ZIFT. The resulting baby is thus the genetic offspring of the infertile couple.

Cryopreservation of Eggs or Oocytes

Women undergoing ovulation induction therapy often produce large numbers of usable oocytes. When multiple eggs are harvested and fertilized, all of the resulting embryos may not be immediately required. Most ART procedures use three to four embryos. (The use of more than three to four embryos increases pregnancy rates, but will also increase the likelihood of multiple births.) Extra embryos can be frozen (cryopreserved) and stored for use at another time, or they may be implanted in another woman. Cryopreservation takes place after the formation of the zygote, or after the zygote has divided or developed into an embryo at the two to four cell stage.

About 60-80 percent of embryos will be viable after freezing. Human embryos stored for more than three years have resulted in healthy babies. One advantage is that such embryos usually can be transferred during a woman's normal ovulatory cycle, instead of a medication-induced cycle.

Cryopreservation is indicated when infertility has been a problem in the past, is anticipated to be a concern in the future, and the couple may want to have children beyond the current round of treatment. Cryopreservation may eliminate the future need to go through all the costly, time-consuming, and sometimes frustrating experience of achieving fertilization.

Adoption

Although many wondrous techniques have evolved to help the infertile couple, the success rate for achieving birth remains about 25 percent. Although far better than offering no hope at all, the fact remains the 75 percent of infertile couples can not currently be helped. Adoption offers a very satisfying solution to some infertile couples and should be closely examined as a treatment alternative. Not only will adoption give the infertile couple what they are seeking—a child to love and raise—but it will also give a child an opportunity to be raised in a manner that otherwise might not be possible.

Child-free Living

Finally, it must be recognized that ART techniques will not always be successful nor is adoption the answer in all cases. Child-free living should also be closely examined as a positive alternative to medical intervention.

Summary

All of the ART techniques discussed offer a new measure of hope to infertile couples. Not only have these techniques proven effective for younger couples, but also for those nearing what would be considered the end of their normal reproductive lives. We hope that this guide has given you the necessary background to understand the wonders of human reproduction and the role medicine can play in determining and treating causes of infertility.

Review Questions • Section 6

1. Complete these sentences

A. Four drugs most commonly used to stimulate the ovaries are:

1 _____ 3 _____

2 _____ 4 _____

B. Four techniques for monitoring egg development are:

1 _____ 3 _____

2 _____ 4 _____

2. Match the word with the correct definition:

(A) Laparoscopy	◯ Sperm and eggs are put into the fallopian tube before fertilization
(B) ET	◯ The freezing of embryos for use at another time
(C) ZIFT	◯ A procedure that allows the viewing of reproductive organs
(D) GIFT	◯ Fertilized eggs are put into the fallopian tubes
(E) Cryopreservation	◯ An embryo is transferred to the uterus after in vitro fertilization

3. True or false:

True	False	A. IVF was the first surgical form of ART successfully used.
True	False	B. Laparoscopy must always be used in ART.
True	False	C. Frozen and thawed embryos have resulted in healthy births.
True	False	D. Adoption and child-free living are two realistic and effective alternatives to medical intervention for dealing with infertility.

Correct Responses to Review Questions

Section 1 Review Correct Responses

1. Name the four key female reproductive organs: **Uterus Vagina Ovary Fallopian tube**

2. Match the word with the correct definition:

A. Gonad **B** - Germ cells capable of initiating formationof a new individual by fusion with a gamete of the opposite sex.
B. Gametes **A** - Reproductive organs that in males produce sperm and in females produce eggs.

3. Complete the following:

The **OVARY** is the female gonad. The **TESTIS** is the male gonad.

4. Match the word with the correct definition:

A. Spermatozoa **D** - Fluid-filled sac that releases the female gamete upon maturation and ovulation
B. Ovum **C** - The female gamete (plural)
C. Ova **B** - The female gamete (singular); also referred to as egg or oocyte
D. Follicle **A** - The male gametes
E. Ovary **F** - Responsible for synthesis of testosterone
F. Leydig cells **E** - Primary female reproductive organ

Section 2 Review Correct Responses

1. In females, the reproductive axis is made up of what three organs? **HYPOTHALAMUS, PITUITARY, OVARIES**

2. In males, the reproductive axis is made up of what three organs? **HYPOTHALAMUS, PTIUITARY, TESTES**

3. Match the word with the correct definition:

A. Hypophysis **D** - A class of hormone derived from cholesterol; includes progesterone, testosterone, and estradiol.
B. Androgens **C** - Luteinizine hormone (LH) and follicle-stimulating hormone (FSH); peak during ovulation
C. Gonadotropins **B** - Male sex hormones
D. Steroid **A** - The pituitary gland
E. Progesterone **E** - Secreted by the corpus luteum to sustain the endometrium

4. True or false:

A. LH and FSH play a key role in female physiology and are present, though not active, in males. **FALSE**
B. GnRH is produced by the pituitary gland. **FALSE**
C. Testosterone acts as a positive feedback mechanism to the hypothalamus a negative feedback mechanism to the pituitary. **FALSE**

Section 3 Review Correct Responses

1. Conception occurs (circle correct response):

Ⓐ **Immediately upon fertilization of the egg by sperm.**
B. Upon implantation of the blastocyst in the endometrial lining.
C. When the single-cell zygote divides into multiple cells and becomes an embryo.

2. The three stages of fetal development are: **ZYGOTE, EMBRYO, FETUS**

3. Match the word with the correct definition:

A. hCG **B** - A single cell formed by the fusion of the male and female gametes.
B. Zygote **D** - The term for a growing life once it develops its basic human structure; term generally applicable from months three to nine.
C. Embryo **C** - The stage of development characterized by multiple cells without recognizable human structure.
D. Fetus **A** - Rises rapidly during the first few weeks of pregnancy and peaks at weeks seven to ten.

4. True or false:

A. LH and FSH rise rapidly during pregnancy. **FALSE**
B. Progesterone is produced primarily by the corpus luteum during pregnancy and concentrations of it decline as the corpus luteum involutes. **FALSE**
C. Without hCG production by the placenta, the corpus luteum would involute. This would in turn cause decreased levels of estradiol and progesterone and ultimately menses would occur. **TRUE**
D. Prolactin is secreted by the hypothalamus and remains low until just prior to birth, when it increases to facilitate milk production. **FALSE**

Section 4 Review Correct Responses

1. Complete these statements.

A. Infertility is defined as: ***The inability of a couple to conceive after one year of unprotected intercourse or the inability to carry a pregnancy to term.***
B. Four of the factors discussed that contribute to the rising number of infertility cases are:
Aging population, Increased prevalence of sexually transmitted disease/PID, Environmental toxins, Nicotine, and Technological advances in infertility diagnosis and treatment

2. Match the word with the correct definition:

A. Assay **D** - When an infertile couple has achieved pregnancy in the past
B. Male Factor **C** - When an infertile couple has never achieved pregnancy
C. Primary infertility **B** - Responsible for 40 percent of infertility cases
D. Secondary infertility **A** - Laboratory test

3. True of false:

A. Female factor is the cause of infertility twice as often as male factor. **FALSE**
B. As many as one in six couples experience infertility at some time. **TRUE**
C. There is a direct correlation between a couple's ability to conceive and their age. **TRUE**
D. The number of couples seeking diagnosis and treatment of infertility is increasing in most parts of the world. **TRUE**
E. The cost of going through three treatment cycles may be equal to a couple's entire annual income. **TRUE**

Section 5 Review Correct Responses

1. Complete these statements:

A. Sperm is analyzed for these three primary characteristics: **MORPHOLOGY, MOTILITY, DENSITY**
B. The sex hormones may be divided into two classes: **STEROID HORMONES, PEPTIDE HORMONES**

2. Match the word with the correct definition:

A. Prolactin	**D** - Peaks at ovulation, is elevated during ovarian failure, and is often used in a ratio with LH
B. Estradiol	**C** - Sometimes used with hCG to diagnose ectopic pregnancies and confirms that ovulation has occurred
C. Progesterone	**E** - Concentrations double every 24 to 48 hours form early pregnancy through weeks eight to ten
D. FSH	**B** - Increased follicular growth viewed via ultrasound will be confirmed by increasing levels
E. hCG	**A** - Stimulates the production of milk; if elevated may suppress menstrual cycle
F. LH	**F** - Determinations are elevated at ovulation and menopause

3. True or false:

A. DHEA-S is often elevated in women with hirsutism and alopecia. **TRUE**
B. SHBG, estrone, activin, TSH, and inhibin make up about 25 percent of the infertility diagnosis testing volume. **FALSE**
C. LH, FSH, and progesterone are often used to diagnose pubertal disorders. **FALSE**
D. hCG effectively aids in the diagnosis of molar pregnancies, where values will be elevated. **TRUE**

Section 6 Review Correct Responses

1. Complete these sentences:

A. Four drugs most commonly used to stimulate the ovaries are: **GnRH, CLOMIPHENE CITRATE, Hmg, hCG**
B. Four techniques for monitoring egg development are: **ULTRASOUND, LH LEVELS, ESTRADIOL LEVELS, PHYSICAL EXAM**

2. Match the word with the correct definition:

A. Laparoscopy	**D** - Sperm and eggs are put into the fallopian tube before fertilization
B. ET	**E** - The freezing of embryos for use at another time
C. ZIFT	**A** - A procedure that allows the viewing of reproductive organs
D. GIFT	**C** - Fertilized eggs are put into the fallopian tubes
E. Cryopreservation	**B** - An embryo is transferred to the uterus after in vitro fertilization

3. True or false:

A. IVF was the first surgical form of ART successfully used. **TRUE**
B. Laparoscopy must always be used in ART. **FALSE**
C. Frozen and thawed embryos have resulted in healthy births. **TRUE**
D. Adoption and child-free living are two realistic and effective alternatives to medical intervention for dealing with infertility. **TRUE**

Glossary of Terms

Adrenal Glands – A pair of endocrine organs that produced steroids such as sex hormones, hormones concerned with metabolic functions, and epinephrine. They are located near the kidneys.

Amenorrhea – Absence of menstrual discharge.

Androgens – Male sex hormones such as testosterone.

Androstenedione – An androgen secreted by the testis, ovary, and adrenal glands.

Anovulation – Absence of ovulation.

Artificial Insemination (AI) – Introduction of semen into the uterus or oviduct (fallopian tube) by other than natural means.

Aromatization – In endocrinology, the final step in production of estrogens from other steroid hormones.

Assay – To analyze (verb); a laboratory test (noun).

Assisted Reproductive Technologies (ART) – Processes in which chances of conception are increased through medical intervention.

Axis – The hypothalamus and pituitary together with either the testis or ovary complete what is known as the reproductive gonadal axis. In the male, this axis is referred to as the H-P-T (hypothalamus-pituitary-testis) axis and in the female the H-P-O (hypothalamus-pituitary-ovary) axis.

Blastocyst – An early stage of embryo development consisting of a single layer of cells forming a hollow sphere with a fluid-filled cavity that merges with the endometrium to form the placenta.

Bromocryptine – A drug that inhibits the secretion of prolactin by the pituitary gland.

Cervix – The narrow outer end of the uterus.

Clomiphene Citrate – A synthetic anti-estrogen used to induce follicular development and ovulation.

Conception – The fertilization of a woman's egg by a man's sperm.

Corpus Luteum (CL) – Progesterone-secreting endocrine tissue which fills the cavity left by the ovum after discharge. If the ovum is not fertilized, the CL regresses quickly.

Cryopreservation – A method of preserving embryos by freezing them for use at another time.

Cyst – A closed sac with a distinct membrane that develops in a cavity or structure of the body.

Dehydroepiandrosterone (DHEA) – An androgenic ketosteriod that is one of several possible precursors for the synthesis of testosterone. Found in human serum, urine, and the adrenal cortex.

Dehydroepiandrosterone-Sulfate (DHEA-S) – The sulfated version of DHEA. A sex steroid hormone secreted by the adrenal glands in both males and females.

Donor Egg Transfer – Surgical removal of an egg from one woman and transfer to the fallopian tube or uterus of another.

Egg – A reproductive body, consisting of an ovum and its nutritive and protective envelopes, having the capacity to develop into a new individual capable of independent existence.

Embryo Transfer (ET) – The process of placing embryos into the uterus through a catheter.

Endometrial Lining – The membrane that lines the uterus.

Endometriosis – A disease state indicated by the presence of functioning endometrial tissue located where it is not normally found.

Endometrium – A mucous membrane lining the uterus. Also see endemetrial lining.

Estradiol (E2) – An estrogenic steroid hormone produced by the ovaries. The most potent female hormone.

Estrogen Replacement Therapy – Replacement of estrogens normally secreted by the ovaries. This is frequently beneficial to post-menopausal women. Usually estrogens are administered in the form of transdermal patches or tablets (pills).

Estrogens – Female sex steroid hormones which tend to promote the reproductive cycle and stimulate the development of female secondary sex characteristics. They are mainly produced by the ovaries.

Exogenous Gonadotropins – Natural or synthetic hormones that stimulate the gonads or sex glands. Exogenous means introduced from outside the body.

Fimbria – The fringed outer edges of the fallopian tubes, near the ovaries. During ovulation, the egg passes through the fimbria. The plural is fimbriae.

Female Factor – Infertility caused by any one of a number of female reproductive abnormalities.

Follicle – A cyst in the ovary which contains a developing egg surrounded by fluid and a covering of cells.

Follicular Phase – The first half of the menstrual cycle before ovulation, when the follicle matures and an egg becomes ready for release.

Follicle Stimulation Hormone (FSH) – A hormone from the pituitary which stimulates the growth and ripening of ovum-containing follicles in the ovary. In males it activates sperm-forming cells.

Free Hormones – Hormones not bound to proteins. Usually recognized as the biologically active component.

Gamete – A mature male or female sex cell that contains half a chromosome set and is capable of initiating formation of a new individual by fusion with a gamete of the opposite sex. Also called the egg or the sperm.

Gamete Intrafallopian Transfer (GIFT) – A medical assist to conception where a mature egg is retrieved by laparoscopy, mixed with sperm outside the woman's body, and subsequently reintroduced by laparoscopy to her fallopian tube, where fertilization may take place.

Gland – A group of cells that secrete or excrete material not related to their metabolism. An endocrine gland secretes hormones.

Gonad – A reproductive organ that produces gametes (egg or sperm).

Gonadotropin – A hormone which stimulates the gonads. In both males and females, the gonadotropins are LH and FSH.

Gonadotropin-Releasing Hormone (GnRH) – A hormone secreted by the hypothalamus to regulate gonadotropin production in the pituitary.

Granulosa Cells – A type of cell that surrounds the maturing egg inside the follicle and secretes estradiol.

Hirsutism – An excessive growth of hair with normal or abnormal distribution on the body or face. In women, this is often a symptom of PCOS (polycystic ovarian syndrome).

Hormone – A chemical substance secrete into the body fluids by one cell or a group of cells that exerts a physiological effect on other cells in the body.

Hormone Replacement Therapy (HRT) – The use of synthetic hormones to replace those that the body has ceased to produce.

Human Chorionic Gonadotropin (hCG) – A hormone released by the placenta during pregnancy. The primary function of hCG is to assure the female body does not initiate menstruation once implantation of the fertilized egg has occurred. Most pregnancy tests detect this hormone in either urine or serum to confirm pregnancy. hCG may also be administered to induce ovulation, mimicking the LH surge.

Human Menopausal Gonadotropin (hMG) – Gonadotropins purified from post-menopausal women. Used primarily for ovulation induction if females; sometimes used in males to treat infertility.

Hyperprolactinemia – An abnormally high concentration of prolactin in the blood. In women, this is associated with menstrual cycle disorders—periods may be irregular or absent. In men, this can cause low libido and low sperm counts.

Hypophysis – Another word for the pituitary gland.

Hypothalamic Amenorrhea – Absence of menstruation because of inadequate levels or the absence of hypothalamic secretion of GnRH.

Hypothalamus – Endocrine tissue which releases gonadotropin-release hormone (GnRH) which, in turn, regulates and controls hormones released by the pituitary gland. The hypothalamus is located at the base of the brain.

Inadequate Luteal Phase – A luteal phase which is shorter than normal or a luteal phase in which not enough progesterone is produced.

Inhibin – A hormone secreted by the testicles and ovaries which suppresses the level of follicle stimulating hormone (FSH).

Interstitial Cells – Cells of the testes that are situated between the germ cells of the gonads. One type of interstitial cell is the Leydig cell, which produces testosterone.

In Vitro Fertilization (IVF) – A procedure in which an egg is fertilized with sperm outside the woman's body.

Intrauterine Insemination (IUI) – The placement of large numbers of motile sperm high in the uterus near the time of ovulation. This is often used when infertility is due to cervical factors, male factors, or immunologic infertility.

Laparoscopy – Exploration of the abdomen by a surgical technique requiring a small incision into which is placed an optic device called a laparoscope. This technique is often used to view the internal female reproductive organs and may be used in certain assisted reproductive techniques.

Leydig Cells – Cells of the testes that are the source of testicular androgens and perhaps other hormones.

Libido – Sex drive.

Luteal Phase – The half of the menstrual cycle following ovulation. Indicated by a shift from the estrogen-dominated follicular phase to progesterone dominance.

Luteinizing Hormone (LH) – A hormone from the pituitary gland that works with follicle stimulating hormone (FSH) to induce ovulation and maintain the development of corpus lutea in the female. It also helps females to maintain progesterone production. In the male it stimulates the development of Leydig cells in the testis and thus the secretion of testosterone.

Male Factor – Infertility caused by any one of a number of male reproductive problems. Responsible for 40 percent of infertility.

Menopause – The period of natural cessation of menstrual activity, occurring usually between the ages of 45 and 55. It is associated with the depletion of oocytes from the ovary and therefore the cessation of estrogen production.

Menstruation – A discharging of blood, secretions, and tissue debris from the uterus at approximately monthly intervals in non-pregnant, reproductive-age females. Usually considered the readjustment of the uterus to the non-pregnant state.

Menstrual Cycle – The cycle of physiological changes from the beginning of one menstrual period to the beginning of the next. Also see "Ovulatory Cycle."

mIU/mL – Milli-international units per milliliter; a way of expressing concentration of one substance in another.

Oligomenorrhea – Abnormally infrequent or scanty menstrual flow.

Oocyte – An egg cell.

Ovary – The essential female reproductive organ that produces eggs and female sex hormones. There are usually two ovaries.

Ovulation – The discharge of a mature ovum from the ovary.

Ovulation Induction (OI) Therapy – Stimulation of follicle development and ovulation through external means in women who ovulate irregularly or who do not ovulate at all. The drugs commonly used to induce ovulation are clomiphene citrate, or combinations of gonadotropins such as FSH and LH to stimulate follicle development, and human chorionic gonadotropin to cause release of the ovum (ovulation).

Ovulatory Cycle – Also known as the menstrual cycle; averages 26-30 days. The cycle is generally defined by the day of ovulation, e.g. when the follicle matures and ruptures to release the ovum. It is broken down into three phases: the follicular phase (the 14-15 days preceding the day of ovulation), mid-cycle (ovulation), and luteal phase (the 14-15 days following ovulation).

Ovum – A mature egg; the female gamete.

Ova – The plural of ovum; more than one egg.

Peri-Menopause – The time period immediately before and immediately after menopause.

Pituitary – A small endocrine organ that produces various hormones which directly affect basic bodily functions and exert a controlling or regulating influence on other endocrine organs.

Polycystic Ovary Disease (POCD) – A condition of hormonal imbalance that causes infertility in women. The activity of the hormone FSH is inhibited by high levels of the hormone LH. Also known as Polycystic Ovary Syndrome.

Polycystic Ovary Syndrome (PCOS) – Another term for Polycystic Ovary Disease.

Premature Ovarian Failure – The occurrence of menopause in women under 40 years old. Because there are few to no oocytes remaining in the ovaries, they do not respond to stimulation by gonadotropins.

Progesterone – A steroid hormone which is produced by the corpus luteum after ovulation. During pregnancy it is also produced by the placenta.

Progestins – The family of steroid hormones which include progesterone as well as synthetic progesterone-like hormones.

Prolactin – A hormone which induces lactation. It is produced by the pituitary gland.

Prolactinoma – A non-cancerous tumor of the pituitary that produces or secretes prolactin.

Semen – A whitish fluid of the male reproductive tract composed of spermatozoa suspended in seminal fluid, which consists of secretions from the prostate and Cowper's glands.

Sex Hormone Binding Globulin (SHBG) – A serum protein which is typically bound to a sex steroid hormone to aid in carrying the hormone through the bloodstream.

Steroid – Compounds of 17-carbon 4-ring composition including various hormones.

Steroid Hormones – Any of the hormones with the characteristic ring structure of steroids, including sex hormones, cortisone, and adrenocortical hormones. Steroid hormone names often end in "-one" and "-ol" suffixes as in testosterone and estradiol.

Testis – The male reproductive gland in which sperm develop. Usually paired, the testis develops from the genital ridges of the embryo and normally descends into the scrotum before or shortly after birth.

Testosterone – A hormone responsible for inducing and maintaining secondary sex characteristics in males, although it is also found in females. It is produced by the testes, ovaries, and adrenals.

Theca Cells – Located in the ovaries, epithelial or lining cells surrounding the follicles that produce androgens, which the granulosa cells can use as a precursor for estrogen synthesis.

Tubal Embryo Transfer – The transfer of embryos into the fallopian tube through laparoscopy.

Tubal Factor – Infertility due to problems of the fallopian tubes. These may include obstructions of the tubes, adhesions, and endometriosis. An estimated 25 percent of infertility is caused by tubal factors.

Ultrasound – A technique for viewing internal organs using reflected high-frequency sound waves. It is frequently used to view the fetus in the uterus or the follicles in the ovaries. It is safe to use during pregnancy because it does not require damaging x-rays.

Uterus – An organ in females for containing and nourishing the fetus prior to birth. It is shaped like an inverted pear, usually with a pair of oviducts at the large section, and has a thick, non-striated muscular wall and an inner mucous coat containing numerous glands. During pregnancy it undergoes a remarkable increase in size and change in the condition of its walls. It is also called the womb.

Zygote – The resulting cell formed when a sperm cell fertilizes an egg.

Zygote Intrafallopian Transfer (ZIFT) – The transfer of a fertilized egg (or zygote) into the woman's fallopian tube, usually through laparoscopy.

Acronyms

Acronym	Definition
AI	Artificial insemination
BBT	Basal body temperature
BhCG	Beta (B) human chorionic gonadotropin
CL	Corpus luteum
DHEA	Dehydroepiandrosterone
DHEA-S	Dehydroepiandrosterone-sulfate
DHT	Dihydrotestosterone
E2	Estradiol
ERT	Estrogen replacement therapy
ET	Embryo transfer
FSH	Follicle stimulating hormone
GIFT	Gamete intrafallopian transfer
GnRH	Gonadotropin-releasing hormone
hCG	Human chorionic gonadotropin
hMG	Human menopausal gonadotropin
hGH	Human growth hormone
HRT	Hormone replacement therapy
ICSI	Intracytoplasmic sperm injection
IUI	Intrauterine insemination
IVF	In vitro fertilization
LH	Luteinizing hormone
MESA	Microsurgical epididymal sperm aspiration
OI	Ovulation induction
PG,P4, or P	Progesterone
PID	Pelvic inflammatory disease
PROST	Pronuclear stage transfer
SHBG	Sex hormone binding globulin
STD	Sexually transmitted disease
T	Testosterone
TET	Tubal embryonic transfer
ZIFT	Zygote intrafallopian transfer

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