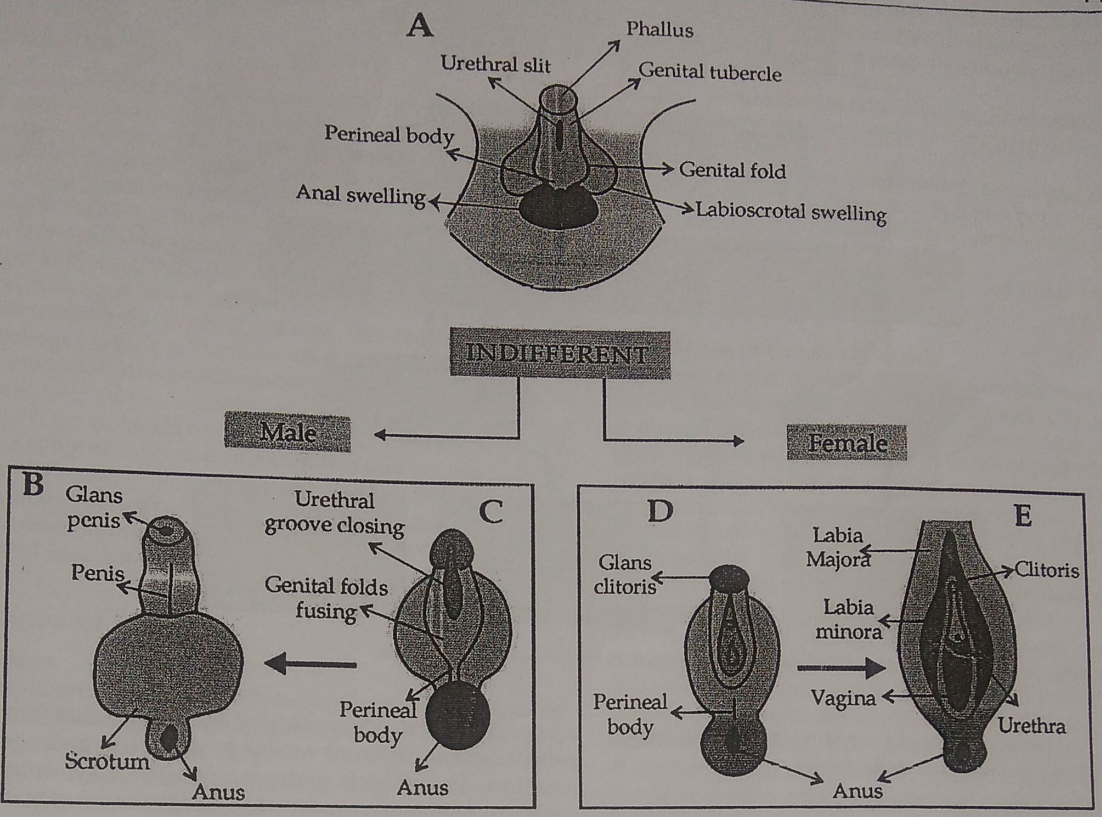


Figure 53.5 Differentiation of the male and female external genitalia. A: indifferent stage; B: male genitalia (7th to 8th week); C: male genitalia (at about 12th week); D: female genitalia (7th to 8th week); E: female genitalia (at about 12th week).

low rate during puberty and continue in a similar fashion thereafter. Therefore, the adult female plasma level of MIS is same as that of males. However, the exact role of MIS in adults, especially in females is not known.

Functions of MIS:

1. During early embryonic life, MIS inhibits development of female gonads by promoting regression of müllerian duct. Therefore, it helps in male gonadal development.
2. Later during fetal life in males, it helps in testicular descent.
3. In both sexes, it helps in maturation of germ cells.

Abnormalities of Sex Differentiation

The abnormalities of sex differentiation can be broadly ivided into two categories: chromosomal and develop-ıental abnormalities.

Chromosomal Abnormalities

he common chromosomal abnormalities are Turner's ndrome, Klinefelter's syndrome, testicular feminization ndrome, superfemales and true hermaphroditism.

Turner's Syndrome

This is otherwise known as **gonadal or ovarian dysgenesis**. It is characterized by diminished sexual development, dwarfism, and webbing of the neck in patients with no gonadal tissue or rudimentary gonads. The chromosomal **pattern of sex chromosomes is XO**, which means there are 44 autosomes and one X chromosomes (total 45 chromosomes). It results from nondisjunction of one of the X chromosomes during oogenesis. Usually, it presents with *primary amenorrhea*. No sexual maturation occurs at puberty.

Klinefelter's Syndrome

This is the most common sex chromosome abnormality. The syndrome is otherwise called **seminiferous tubule dysgenesis**. Typically, it is characterized by presence of feminine features in an apparent male with small testes. The patient is genetically female, but the presence of an extra Y chromosome causes development of the testis. Therefore, the **karyotype is 47 XXY** (44 autosomes + XX sex chromosomes + one extra Y chromosomes). They have male genitalia and at puberty male characteristics develop due to adequate testosterone. But, seminiferous tubules are not properly developed and therefore, infertility results. Thus, the syndrome usually presents with *primary*

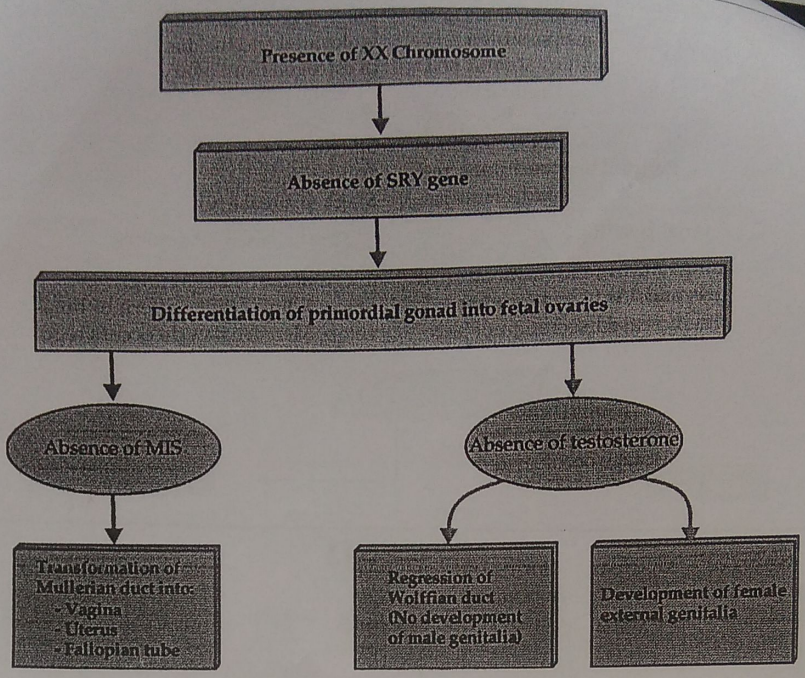


Figure 53.7 Mechanism of sex differentiation in female.

divided into **pseudohermaphroditisms** (both female and male patterns) and **enzyme deficiencies**.

Pseudohermaphroditisms

A **pseudohermaphrodite** is an individual with **genetic constitution and gonad of one sex**, but the **external genitalia of the other sex**. There are male and female pseudohermaphroditisms. In these conditions, the patients have normal gonadal development in accordance with their chromosomal sex, but afterward they develop heterosexual characteristics due to opposite hormonal excess.

Female Pseudohermaphroditisms: Male external genital development occurs in genetic females exposed to androgen during 8th to 13th week of gestation. Source of androgen is usually congenital virilizing adrenal hyperplasia of fetus or virilizing ovarian tumor of the mother. Sometimes it may be iatrogenically-induced following treatment of mother with androgens or progestational drugs. In a typical female pseudohermaphrodite, the individual possesses ovaries, oviducts, but there is varying degrees of masculine differentiation of external genitalia. The chromosomal sex is female.

Male Pseudohermaphroditisms: Development of female external genitalia in a genetic male is called male pseudohermaphroditism. It is usually due to defective testicular development. As MIS secreted from testis during early embryonic life prevents development of female gonads, in defective testicular development the internal genitalia are also of female pattern. Male pseudohermaphroditism could also be due to androgen resistance that usually occurs in deficiency of 5α-reductase, the enzyme that forms dehydroepiandrosterone or due to defects in androgen receptors. In complete androgen resistance syndrome (testicular feminizing syndrome), MIS is secreted as testes are normal; therefore, vagina ends blindly due to absence of internal genitalia.

Enzyme Deficiencies

Congenital **17α-hydroxylase deficiency** causes **male pseudohermaphroditism**. This also occurs in congenital adrenal hyperplasia in which enzyme defects block the formation of pregnenolone (for details, refer the chapter "Adrenal Cortex")

PUBERTY

Definition

The period of **transition from the non-reproductive state to the state of reproductive functions that allows procreation** is defined as puberty. During this period, the hypothalamo-pituitary-gonadal axis is activated to bring the gametogenic functions of the gonads to their threshold of reproductive maturation. Normally, gonads of both genders remain quiescent until the onset of puberty. Under the influence of gonadotropins secreted from pituitary, maturation of gonads occurs that in turn helps in maturation of the reproductive system. This period of maturation is known as puberty or **adolescence**. During this period the endocrine

and gametogenic functions of the gonads first develop to the point where the reproduction becomes possible.

Pubertal Age

The age of onset of puberty varies depending on various factors like socioeconomic and environmental conditions and genetic constitutions. In general, in developed countries, puberty occurs earlier than in the developing countries. In advanced nations, it occurs between the age of 8–13 in girls and 9–14 in boys. In developing nations, the age of onset of puberty is **11–16 years in girls** and **13–18 years in boys**.

The Initiating Stimulus: The increased secretion of adrenal androgen, called **adrenarche**, occurs about one to two years before the onset of puberty. This **increased adrenal androgen** is believed to stimulate the production of gonadal hormones that cause maturation of reproductive organs. As increase in adrenal androgen at this stage occurs without any alteration in ACTH or cortisol secretion, it is proposed that this is the primary and sole stimulus that heralds puberty. One hypothesis suggests that increased secretion of adrenal androgen before puberty occurs due to secretion of **adrenal androgen stimulating hormone** (AASH) from pituitary. But actual nature and mechanism of it are not known.

Stages of Puberty

In Boys

The pubertal development in males occurs in five stages (by **Tanner method**, modified). Usually it is completed within two to four years from its onset.

Stage 1: This is the preadolescent stage. There is no enlargement of external genitalia (penis, scrotum and testes). No pubic hair is present. However, secretion of adrenal androgen is increased (adrenarche).

Stage 2: Testes enlarges to more than 2.5 cm, which occurs due to growth of seminiferous tubules. Though this occurs due to the secretion of adrenal androgen (adrenarche), testicular androgen also contributes. Testicular testosterone secretion increases significantly. Pubic hairs appear in scanty at the root of the penis.

Stage 3: Penis enlarges in length. Scrotum and testes are further enlarged. Pubic hairs become darker and coarser above the pubis. Sperm first appears in the morning sample urine (spermarchy).

Stage 4: Penis enlarges in width and further in length. Scrotal and testicular enlargement continues. Pubic hair becomes adult type. Ejaculation of sperm occurs either in dreams, or on masturbation or by sexual act.

Stage 5: Full adult pattern of sexual features develops.

In Girls

The pubertal development in females also described in five stages (by **Tanner method**, modified). Usually it is completed within two to five years from its onset.

Stage 1: This is the preadolescent stage. There is no breast development. No pubic hair is present. However, secretion of adrenal androgen is increased (adrenarche).

Stage 2: Breast development starts (thelarche). Breast paillae is elevated and the diameter of areola is increased. Secretion of estrogen from ovary increases significantly. Sparse hairs appear along the labia majora.

Stage 3: Breast enlarges with enlargement of areola. Pubic hairs develop, grow and become dark (pubarche). Hairs appear in axilla.

Stage 4: Breast further enlarges with areola and papillae projecting out of it. Pubic hair becomes adult type, but covers smaller area. Menstrual cycle starts (menarche), but irregular at the beginning.

Stage 5: Full adult pattern of breasts and pubic hairs develop. Menstrual cycle occurs regularly.

Mechanism of Onset of Puberty

The hypothalamic neurons gradually mature to secrete more GnRH. This maturational process is genetically preprogrammed. Dehydroepiandrosterone secreted from adrenal gland plays some role in the **maturation of hypothalamic neurons**. The adipose tissue via secretion of leptin also plays some role in the determination of the time of onset of puberty (see below). Normally, the secretion of GnRH, LH and FSH is not pulsatile before the onset of puberty. It is clear that **until puberty the release of GnRH is non-pulsatile**, which prevents puberty to occur. It is not known what mechanism inhibits the GnRH pulse generator till puberty. However, before puberty, the GnRH is secreted in a **pulsatile pattern** that stimulates pulsatile secretion of LH and FSH. It is proposed that this **pulsatile secretion of GnRH** brings about the onset of puberty. This theory is supported by the fact that experimental pulsatile injection of GnRH in immature monkeys produces normal menstrual cycle and the cycles continue till the pulsatile injection continues.

Role of Leptin: It has been observed that body weight increases to a critical level before the onset of puberty, especially in females. It is also observed that the onset of puberty is delayed in girls with lower body weight. Leptin, the hormone secreted from adipose tissue cell is believed to help in the maturation of hypothalamogonadal axis. This is supported by the experimental evidence that injection of leptin in female mice results in precocious puberty. But, the exact role of leptin in the control of puberty is not known.

Abnormalities of Puberty

Abnormalities of puberty can be broadly classified into precocious puberty and delayed puberty.

Precocious Puberty

Precocious puberty may be of two types: true precocious puberty and precocious pseudopuberty.

True Precocious Puberty

Early development of **secondary sexual characteristics with premature development of gonads** is known as true precocious puberty. This occurs due to early pubertal pattern of secretion of gonadotropin from pituitary.

CHAPTER

58 Physiology of Contraception

Learning Objectives

On completion of study of this chapter, the student will be able to:

1. Classify contraceptives for males and females.
2. Give the mechanism of action of contraceptives.
3. Say which contraceptive will be better for which couple.

India is a highly populous nation. One of the major problems India facing in recent years is birth control. In April, 1976, India formulated its first 'National Population Policy', and 'National Population Policy–2000' is the latest in the series. All these policies primarily aim at reducing the birth rate.

When birth control procedures work prior to implantation of the fertilized egg, they are called **contraceptives**, and when work after implantation (cause death of the embryo), they are termed as **abortificients**.

Classification of Contraceptives

Contraceptive methods are classified into following categories:

1. Barrier methods
   - Physical methods
   - Chemical methods
2. Intrauterine devices
3. Hormonal methods
4. Post-conceptional methods
5. Permanent methods

Physical Methods

In Males

Condom is the most widely used barrier device in male. It prevents sperm to be deposited in the vagina. The biggest advantage is that it provides **protection against sexually transmitted diseases.**

In Females

Diaphragm is the most commonly used vaginal barrier. A **spermicidal jelly** is usually used along with the diaphragm. Another female barrier device is **vaginal sponge.**

Chemical Methods

Various spermicidal agents like foams, creams and suppositories are inserted manually into vagina before intercourse. These act as 'surface active agents' that attach themselves to sperms and decrease their oxygen uptake and kill them. They are not usually used due to their high failure rate.

Intrauterine Devices

Intrauterine devices (IUDs) are most effective contraceptive devices for a parous lady (who has borne at least one child).

The IUD are of **three generations**:

1. First generation IUD
   Lippes Loop
2. **Second generation IUD**
   Earlier devices: Copper–7; Copper T–200
   Newer devices: Copper T variants (T–Cu 220C; T–Cu 380A; T–Cu 380Ag)
3. Third generation IUD

Progestasert: a T shaped device filled with 38 mg of progesterone.

Leveonorgestrel–20 (LNG-20): a T shaped IUD releasing 20 mcg of leveonorgestrel, a synthetic steroid.

Mechanism of Action

IUD works by several mechanisms.

1. Usually, they work after fertilization has occurred but before implantation is completed. The presence of these small objects in the uterus brings about uterine changes that **interfere with the endometrial preparation** for acceptance of the blastocyst. Thus, implantation is prevented.
2. They also act as **foreign body** in the uterine cavity

...using cellular and biochemical changes in the endometrium and the uterine fluid that impair the viability of the gamete. Therefore, the chance of fertilization is reduced.

3. **Copper facilitates cellular reaction** in endometrium, composition of cervical mucous, impairs sperm motility and impairs capacitation of sperm.
4. Hormone releasing devices increase the viscosity of cervical mucous by releasing progesterone. They **make mucous thick**, so that sperm can not enter uterus. They also make the endometrium unfavorable for implantation.

Hormonal Contraceptives

1. **Oral contraceptive pills**
   - Combined pill
   - Progestogen only pill
   - Post-coital pill
   - Once-a-moth pill
   - Male pill
2. **Depots** (slow releasing formulations)
   - Injectable preparations
   - Subcutaneous implants
   - Vaginal rings

Oral Contraceptive Pills (OCPs)

Presently, OCPs contain 30-35 mcg of estrogen and 0.5 to 1 mg of progesterone. The pill is given for 21 days from 5th day of the cycle. Oral contraceptives are based on the principle that estrogen and progesterone **inhibit pituitary gonadotropin release**, thereby *preventing ovulation*. Only progesterone pill affects the composition of the cervical mucus, reducing the ability of the sperm to pass through the cervix, and inhibit the estrogen-induced proliferation of the endometrium, making it inhospitable for implantation.

Side effects of OCP

Though OCPs are 100% effective in preventing pregnancy, here are risks of few side effects, especially when consumed or many years.

Cardiovascular side effects: Myocardial infarction, cerebral hrombosis, venous thrombosis and hypertension have een reported. These side effects are more seen in aged nore than 35 years) woman and in smokers. Hypertension ccurs due to fluid retention and increased angiotensin vel. Estrogen increases renin-angiotensin activity and ereby increases angiotensin II production which is a tent vasoconstrictor.

rcinogenesis: Increased risks of cervical cancer and east neoplasia have been reported. Hepatic tumors oc- s rarely.

etabolic side effects: OCPs decrease HDL and alter od coagulability. These two factors facilitate atherosis and proneness to myocardial infarction and ke. They also cause glucose intolerance and insulin stance.

cellaneous: Other side effects include cholestatic jaun-, breast tenderness, weight gain and migraine.

Depots

Subcutaneous implants are contraceptive (progestogen) capsules (Norplant) implanted beneath the skin that releases hormone slowly and last for five years. Injectable forms (intra-muscular injection of progestogen substance like Depo-Provera every three months) are also available. Vaginal ring containing levonorgestrel has been found to be effective.

Post-Conceptional Pills

Contraceptives can be used within 72 h after intercourse (post-coital contraception). These pills interfere with ovulation, transport of the conceptus to the uterus, or implantation. Usually, high dose of estrogen, or two large doses (12 h apart) of a combined estrogen-progestin oral preparations are prescribed. Most effective with fewer side effects is the pill RU 486 (mifepristone), which antagonizes progesterone activity by binding competitively with progesterone receptors in the uterus. This causes the endometrium to erode and the contractions of the fallopian tubes and myometrium to increase.

Other Methods

The Rhythm (Safe Period) Method

The rhythm method is the **abstinence from sexual intercourse during the fertile period** of the cycle (near the time of ovulation). In 28 days regular cycles, normally ovulation occurs between 12th and 16th day (usually on 14th day). Functionally sperm can survive for two days and ovum for 3 days. Therefore, unprotected intercourse should be avoided during the **fertile period** of the cycle, which will fall between 2 days before and 3 days after ovulation i. e. from 10th day to 19th day of the cycle (refer Fig. 54.9; Chapter 54). Rest of the period in the cycle is considered to be **safe period**. However, the day of ovulation is not always fixed even in regular cycles and cycle length is also not always regular. Moreover, only the **length of luteal phase is constant**, which is 14 days from the day of ovulation, and practically it is difficult and tedious to know the day of ovulation. Therefore, in practice, **shortest cycle minus 18 days gives** the first day of fertile period and **longest cycle minus 10 days** gives the last day of fertile period. For example, if the duration of shortest cycle is 25 days (25 – 18 = 7th day) and duration of longest cycle is 32 days (32 – 10 = 22nd day), the unprotected intercourse should be avoided between 7th and 22nd day of any cycle. However, pregnancy has been documented due to intercourse on any day of the cycle. Therefore, it is believed that no period in any cycle, even during the bleeding phase is absolutely safe.

Coitus Interruptus

In this method, during fertile period, the male partner withdraws penis from vagina before ejaculation. Thus, sperm is not deposited in the female genital tract in the fertile period.

research about normal reproduction; investigation and treatment of infertility and recurrent abortion. It also includes evaluation of pregnancy termination (safe abortion) as a method of family limitation.

CONTRACEPTION

Contraception and fertility control are not synonymous. Fertility control includes both fertility inhibition (contraception) and fertility stimulation. While the fertility stimulation is related to the problem of the infertile couples, **the term contraception includes all measures temporary or permanent, designed to prevent pregnancy due to the coital act.**

Ideal contraceptive methods should fulfil the following criteria — widely acceptable, inexpensive, simple to use, safe, highly effective and requiring minimal motivation, maintenance and supervision. No one single universally acceptable method has yet been discovered.

CONTRACEPTIVE EFFECTIVENESS

The failure rate of any contraceptive is calculated in terms of pregnancy rate per hundred women years (H.W.Y) of use. It is calculated according to the following formula (Pearl index) :

$$\text{Pregnancy failure rate/H.W.Y} = \frac{\text{Number of accidental pregnancies} \times 1200^{*}}{\text{Number of patients observed} \times \text{months of use}}$$

* 1200 = Number of months in 100 years.

Example : If 100 couples have used a method for a period of 2 years and have resulted in 20 pregnancies, the pregnancy rate is calculated to be :

$$\frac{20 \times 1200}{100 \times 24} = 10$$

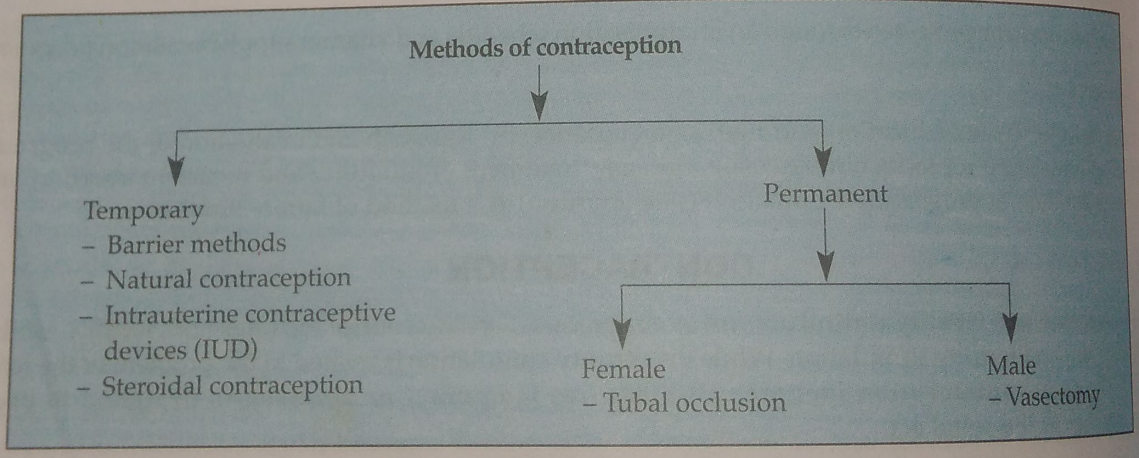
When the pregnancy rate is below 10, the effectiveness of the particular method is considered to be high. If it is more than 20, it is said to be low. The following are the effectiveness of the commonly used contraceptive methods.

Table 35.1 : Failure rate of contraceptive methods in first 12 months of use

Methods	Pregnancy rate per 100 women years (approx.)	Methods	Pregnancy rate per 100 women years (approx.)
No method	80	Combined oral pill	0.1
Rhythm	24	Progestin only pill	1
Coitus interruptus	19	DMPA and NET injectables	0.3
Lactational amenorrhoea	2	Norplant	0.1
Condom (male)	14	Vasectomy	0.15
Diaphragm	20	Tubectomy	0.5
IUCD	0.5 – 2		

Failure rate is further less when methods are used correctly and consistently

METHODS OF CONTRACEPTION



TEMPORARY

Temporary methods are commonly used to postpone or to space births. However, the methods are also frequently being used by the couples even though they have got strong desire for no more children.

BARRIER METHODS

These methods prevent sperm deposition in the vagina or prevent sperm penetration through the cervical canal. The objective is achieved by mechanical devices or by chemical means which produce sperm immobilisation, or by combined means. The following are used :

- *Mechanical*
  - Male — Condom
  - Female — Condom, Diaphragm, cervical cap