10. THE REPRODUCTIVE (GENITAL) SYSTEM

The reproductive system is responsible for the continuation of life. Both sexes share their part in the production of **gametes**, the reproductive cells that will fuse to produce the first new embryonal cell, the zygote. The male gametes are called **spermatozoa** and the female gametes **ovules** (or ova). The gametes of both sexes have *half the number of chromosomes*, compared to all the other cells of the body: they contain 22 single autosomal chromosomes plus one sexual chromosome (X or Y). The embryo's sex will be determined by the type of male gamete (spermatozoon) that will eventually fertilize the ovule. For example, if a spermatozoon contains 22+X chromosomes the embryo will be female, whereas if it contains 22+Y a male embryo will be formed.

The reproductive systems of the two sexes, although they look very different, share important similarities. First, the gonads are the organs that produce the gametes: the testicles in the male produce spermatozoa and the ovary in the female produces ovules. Both gonads also produce hormones that regulate the sexual characteristics of each gender and also facilitate the reproductive processes. Thus gonads act as endocrine glands. Gonads are "connected" with the rest of the sexual organs by designated tubes: the vas deferens (or deferent duct) in males and the ovarian (or Fallopian) tube in the female. These ducts are lined with ciliated epithelium that facilitates the movement of sperm or ovules.

An important difference between male and female gonads lies in the way they produce gametes. The testicles develop during the embryonic period but they only start to produce spermatozoa by the onset of puberty, usually at age 12. However, they retain the ability to continuously produce sperm until late at life. The primary male gametes, the spermatogones multiply through mitosis, keeping the number of the chromosomes stable. They afterwards go through meiosis, a procedure that produces gametes (spermatozoa) with half the number of chromosomes. On the other hand, the female primary gametes (the oocytes) have already been formed in the embryonic life in the ovary and remain in a nascent state until puberty. When the menstrual cycle appears, the primary oocytes are transformed into mature ovules by two consecutive meiosis that occur during the release of the ovule (**ovulation**).

The reproductive or genital organs can be separated as **internal** or **external**. In the female the reproductive system is practically internal, located in the pelvis. In the male, on the other hand, the genitals are practically exposed. However, the testicles are in fact *internal organs* that have been relocated in the scrotum (the skin pouch that hosts the testes outside the body). The reason for this exposure is that the testicles function ideally at a temperature *lower* than the internal (37.5-38 ^{0}C) temperature of the body. This descent normally occurs during the last trimester of pregnancy: the testicles move downwards to the **scrotum** following a fibrous band through a narrow opening between the abdominal muscles (the **inguinal canal**).

It is not rare for an infant to be born without the (one or both) testicles at the proper position in the scrotum. The situation is called **cryptorchidism** and is harmful for sperm production, because the testicle lies higher in the abdomen under higher temperature. Children should be operated before the age of 2 years if the testicle has not come down on its own. The **undescended testis** has also a higher chance to develop a tumor (testicular cancer) in later life.

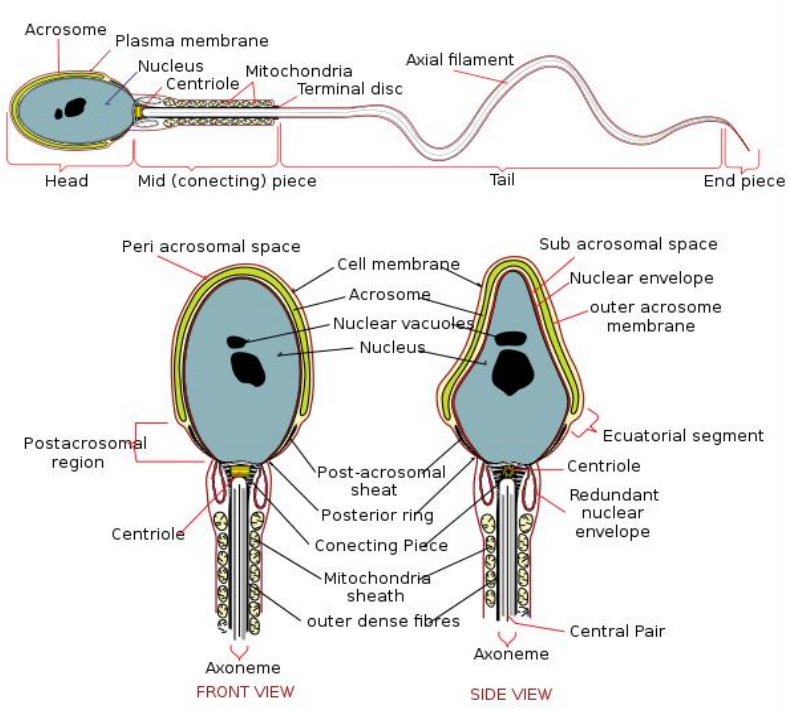

Fig. 10.1 Detailed structure of a spermatozoon.

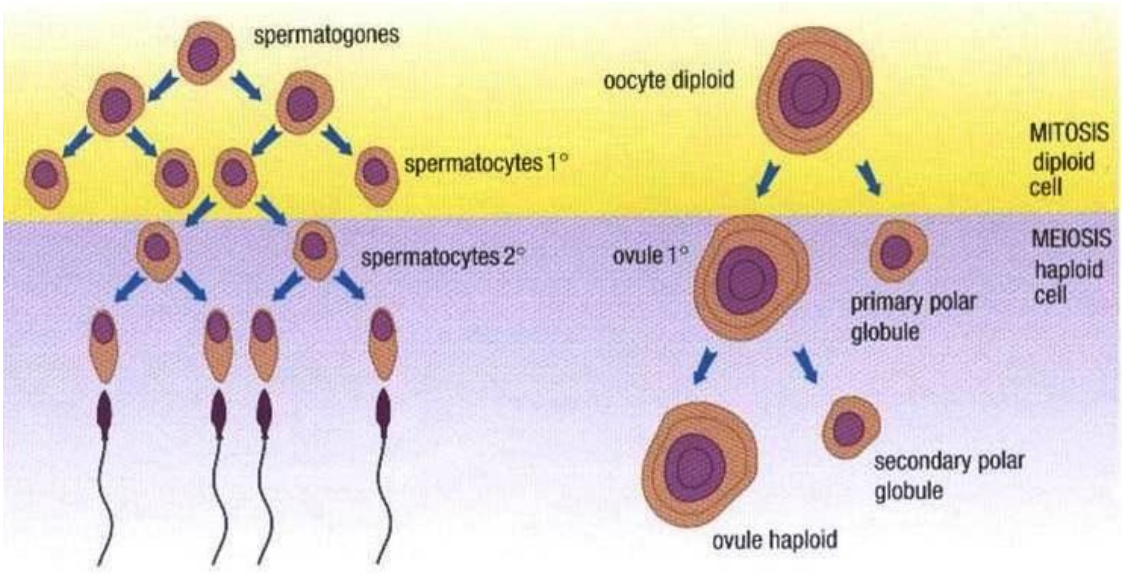

Fig. 10.2 Differences in production of spermatozoa and ovules.

The male genital system.

The **testicles** have an elongated, ovoid shape and are located vertically inside the scrotal sac. At the posterior aspect of the testis lies the **epididymis**, an elongated structure that eventually converts to a tube (**vas deferens**) that transports sperm towards the **urethra**. The surface of the testicle is covered by a dense, strong capsule (**tunica albuginea**). Inside the testicle is divided by several diaphragms into approximately 250 **lobules**. In the lobules lie the **seminiferous tubules**, closely packed microscopic tubes that harbor the primary gametes (spermatogonia or **germinal cells**) that will in time mature to spermatozoa. The developing sperm cells are "parked" on the surface of the **Sertoli's (supporting) cells**. In the interstitial tissue between the tubes lie clusters of cells **(Leydig cells**) that produce the male hormones (androgens). Movement of the maturing sperm cells are moving from the testis to the epididymis, the vas deferens and eventually, at the dilated end of the vas deferens (the **ampulla**) where they are stored until ejaculation.

During **ejaculation**, the spermatozoa in the ampulla are being expelled in the prostatic urethra, together with seminal fluid from the **seminal vesicles**. This occurs through the **ejaculatory ducts**, a common tube for the vas and the seminal vesicles that opens into the urethra on either side of the **verumontanum**. The fluid produced from the seminal vesicles is rich in *fructose*, providing energy for the spermatozoa. Secretions of the *prostate* gland are also added during ejaculation, providing the **semen** with liquefying enzymes and acid phosphatase.

Semen values vary widely between men; even between days for the same person. However, for semen to be fertile we need as many well-formed spermatozoa as possible, which also need to be quickly moving forward. The World Health Organization has set the following criteria of "normal" values:
VOLUME: 1.5-5ml
CONCENTRATION: >20 X 106/ml
MOTILITY: > 50%
MORPHOLOGY: >20% normal

The **prostate** gland is an accessory reproductive gland (the other two are the seminal vesicles and the Cowper's glands). It is a chestnut-shaped glandular structure that surrounds the prostatic part of the urethra, between the bladder neck and the urogenital diaphragm. The posterior aspect of the prostate is separated by a thin membrane from the rectum; this allows for easy digital palpation through the rectum (*digital rectal examination of the prostate*). The prostate comprises of four regions or zones: the central, transitional, peripheral and stromal zone. The *peripheral zone* in the normal gland accounts for approximately 65% of the total gland volume and is encapsulating the rest of the zones from behind. The prostate comprises of approx. 40 smaller glands that empty their secretions through their tubes (**acini**) in the prostatic urethra, in ~14-18 openings on either side of the verumontanum.

The most important substance secreted by the prostate is **PSA** (Prostate Specific Antigen). This is an enzyme that is responsible for dissolving seminal vesicle proteins and keeping the sperm in liquid phase. Most PSA is secreted in the semen, however tiny amounts are normally found in the blood circulation (0.5-4 ng/ml). An increase in the amount of PSA escaping in the blood stream may occur when prostate cancer is present. Thus, PSA is a useful and easy marker for prostate cancer screening.

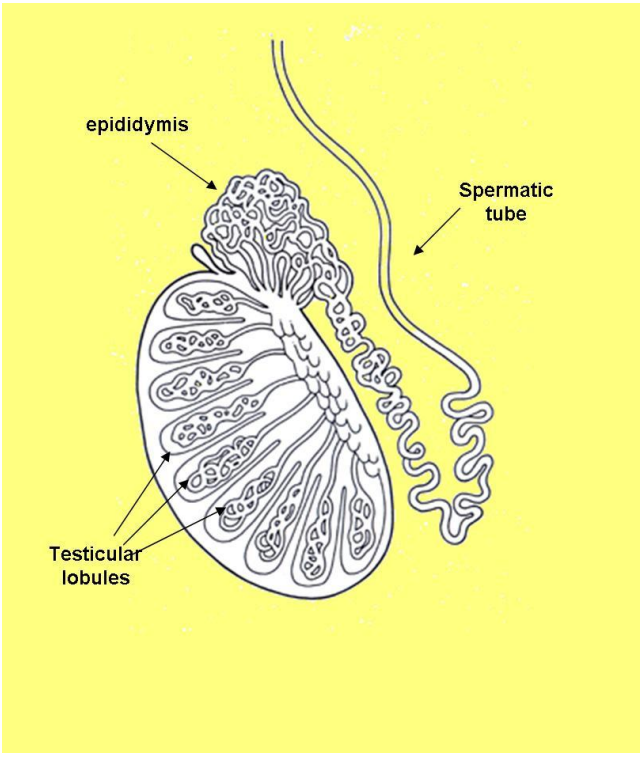

Fig. 10.3 Schematic representation of testicular anatomy.

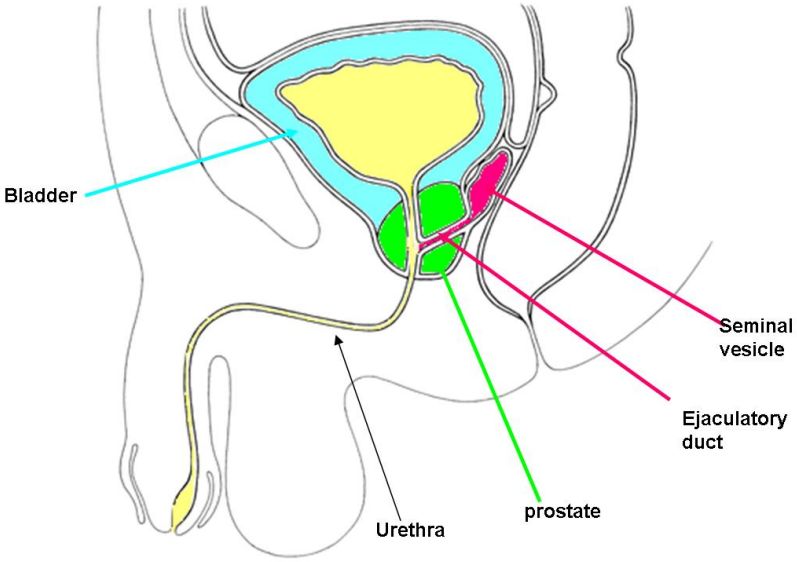

Fig. 10.4 Anatomical position of the prostate and seminal vesicles.

Digital examination of the prostate is easy to perform and may yield valuable information on the consistency of the gland (soft-hard). Most prostate cancers arise at the peripheral zone (which represents the back surface of the gland). Thus, these carcinomas may be palpated early by a digital examination, which should be performed regularly in men over 45-50 years.

The **Cowper's glands** are two tiny glands positioned in the **urogenital diaphragm** of the male. They empty their secretion in the urethra through two small ducts. Upon sexual stimulation, they produce a thin, mucous liquid that is useful for lubricating the urethra, cleaning microbes or dead cells and actually prepares the urethral tube for the passage of sperm. However, this liquid is not related to ejaculation and does not contain spermatozoa.

The **penis** acts as a copulation organ. It also accommodates the urethra, protecting it in the penile shaft but its main feature is **erection** (hardening of the penis). It comprises of two cylinders of highly vascularized spongy tissue (the cavernous bodies – **corpora cavernosa**) that lie side by side and a third cylinder (the spongiosum body- **corpus spongiosum**) that contains the urethra. The spongiosum ends up to the tip of the penis, forming the **glans** (the head of the penis), where the urethra opening lies (the external **urethral meatus**). The corpora are sponge-like tissues with spaces that fill with blood (**sinusoids**). The two corpora cavernosa are "enveloped" in a strong fibrous sheath called **tunica albuginea.**

The penis derives its blood supply from the ***internal pudendal artery***, a branch of the internal iliac artery. The main arteries of the penis are the two central **cavernosal arteries** that bring blood into the two corpora. Venous blood exits the corpora by small veins (**emissary veins**) that pierce through the tunica albuginea and drain into larger, circumferential veins. The blood supply for the corpus spongiosum is similar, by bulbar arteries and veins. It is important, however, that the whole corpus spongiosum (from the bulbar base to the glans) is not included in the hard sheath of the tunica albuginea.

Erection (or tumescence) is the procedure of penis enlargement as it fills with blood. A full erection is necessary for normal sexual intercourse. The mechanism is fired up by some sexual stimulus, either to the brain or directly to the penis. The stimulus is affecting the **erection centers** in the spinal cord and neural stimulation (via the **parasympathetic** system) of the cavernosal nerves occurs. That is leading to the release of **neurotransmitters** that eventually dilate the cavernosal arteries, leading to **increased blood supply** to the cavernosal (and the spongiosum) bodies. When the pressure in the cavernosal bodies is high enough, the **emissary veins are compressed** on the hard tunica albuginea and their lumen closes. That means that high pressure, arterial blood is entering the penis but the veins are occluded and the blood is entrapped in the corpora. That is the time when hard, full erection occurs (the **rigid** phase). After cessation of erotic stimuli or ejaculation, the action of **sympathetic** neural pathways leads to **contraction** of the smooth muscles in the sinusoids and the arterial wall; thus, the blood flow diminishes gradually until the penis reaches again the **flaccid state**.

Many factors may affect the ability of erection. **Erectile dysfunction** (ED) is a common problem between men, especially with advanced age. However, psychological problems, smoking, drugs, alcohol, medications and specific diseases may also affect erection even in younger men. A common cause of erectile dysfunction is failure of the arteries and sinusoids of the penis to fill with blood in high-pressure flow (arteriogenic or vasculogenic dysfunction). A revolution in the treatment of ED was the advent of medication that enhances blood supply to the penis, by relaxing the smooth muscles at the arteries and sinusoids. This is achieved by substances that block an enzyme called Phosphodiesterase 5 that is responsible for breakdown of **cGMP**, a molecule that enhances smooth muscle relaxation. The medications available in the market (VIAGRA™ being the most famous!) are generally called **PDE-5 inhibitors**.

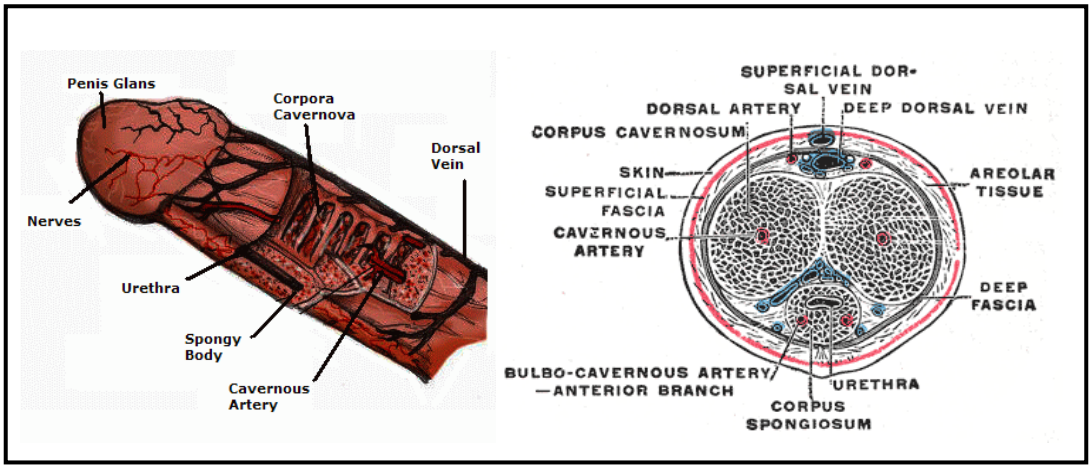

Fig. 10.5 The penis with transverse section of the penile shaft.

Fig. 10.6 The penis and scrotum: reaction of scrotum to cold (right).

The female genital system.

The female gonads, the **ovaries**, are located in the pelvis. They are small, egg-shaped structures that are positioned on each side of the **uterus**, hanging from ligaments that keep them in place. The ovaries are responsible not only for the production of **ova** but also for the female **hormones** (estrogen and progesterone).The uterine tubes (or **Fallopian tubes**) are close to the ovary, allowing for communication with the uterine cavity. The tubes are ~ 10 cm long and also serve as a conduit along which the sperm will travel and fertilize the ovule.

When a mature ovule is released from the surface of the ovary, the tentacle-like projections of the fallopian tube (**fibriae**) are moving in a rythmic way that "sucks" the ovule inside the tube, at the part called **infundibulum**. The inside lining of the uterine tube is covered by **ciliated epithelium**. Thanks to the movement of the cilia and the contractions of the muscle wall of the tube the ovule is first advanced to the **ampulla** of the tube (the most wide part of the tube where fertilization usually occurs) and then through the **isthmus** to the inside of the uterus (the **uterine cavity**). The whole journey of the ovule lasts usually 4-5 days.

The **uterus** is a pear-shaped, hollow organ with thick muscular walls. It is divided in 3 parts: the **fundus**, the **body** and the **cervix**. It is positioned in the pelvis, normally bending over the urinary bladder (this is called ***anteverted and anteflexed*** position). It is held in place by 3 ligaments: the *broad*, the *transverse* and the *round* ligaments. The wall of the uterus has two layers: the muscular wall (**myometrium**) and the mucosal lining of the uterine cavity (**endometrium**). The uterus serves as the site for implantation of a fertilized egg. Its inner lining (endometrium) also provides the nutrients to the developing embryo (via blood supply through the *placenta*). The uterine muscles grow in accordance with the embryo and finally assist during the delivery of the baby (**labor**).

The outmost part of the uterus (the **cervix**) is a narrow part that pierces the vaginal wall. It can be divided in two parts: the *supravaginal* (endocervix) and the *vaginal* portion. The cervical canal communicates with the vagina via an internal opening (**internal os**) and the uterine cavity via an external opening (**external os**). As the cervix protrudes into the vaginal tube, it forms two major spaces, one upwards (anterior fornix) and another downwards (posterior fornix). The **posterior vaginal fornix** is a larger pouch, useful in accommodating the sperm after ejaculation, with the female in the supine position.

The cervix is covered by **glandular, columnar** epithelium. Therefore it is not well protected against irritative factrors, compared to the vagina endothelium which is **squamous**. Hence, the cervix is extremely vulnerable to the development of **cancer**. Several factors such as infections, chronic inflammation, viruses (eg HPV) etc may cause dysplasia and eventually cancer of the cervix. However, these lesions can be easily diagnosed and cancer can be treated early by doing a simple test that examines the cytologic characteristics of the cervical cells. This test is called cervical smear test or Papanikolaou test (**Pap Test**). Every woman after onset of sexual relationships should have a Pap test annually.

The **vagina** is an elastic, fibromuscular tube that allows for **copulation** (sexual intercourse). When it is empty, the tube is slit-like as the anterior and posterior walls touch each other. However, it has the ability to expand, especially during delivery (childbirth). In virgin females, the opening to the **vulva** (vaginal orifice) is closed by a thin mucosal fold (the **hymen**) that usually is perforated at its center (to allow for menstruation blood to exit the vagina). After first sexual intercourse and especially after childbirth, the hymen consists only of small, mucosal tags.

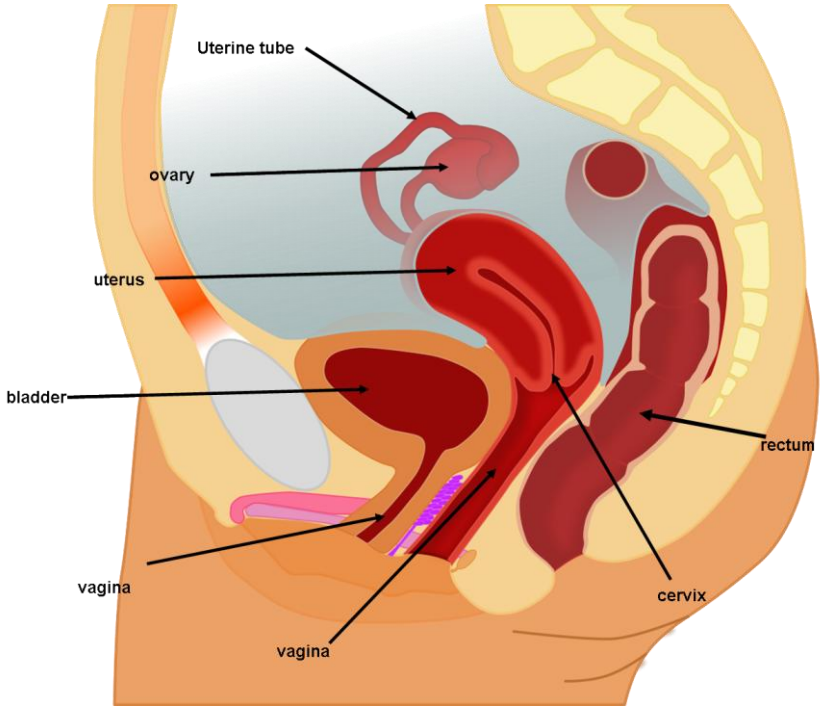

Fig. 10.7 The internal genital organs in the female.

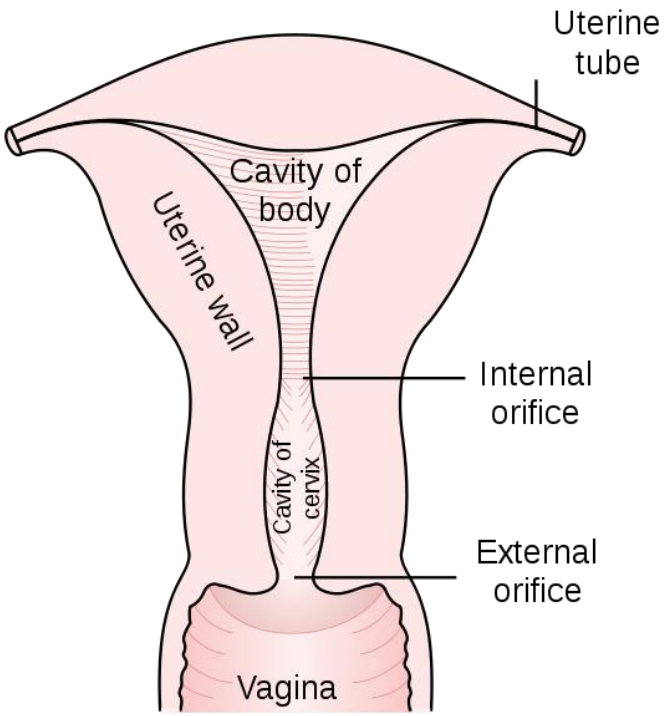

Fig. 10.8 The uterus and uterine cavity

The external genitalia.

The female genitalia consist of an opening for the urethra (the **meatus**) and an opening for the vagina in the **vulva** and the surrounding tissues. The **labia majora** are two skin folds that surround the vulva. They contain sebaceous and sudoriparous glands and possess hair, that is in continuation with the pubic hair, forming a triangle. Underneath the **labia majora**, on each side of the vulva, lie two masses of erectile tissue similar to the corpus spongiosum of the penis, called **vestibular bulbs**. The **labia minora** are smaller skin folds that surround the vaginal opening. Above the urethra meatus lies the **clitoris**, an organ analog to the male penis that contains similar erectile tissue (**corpora cavernosa of the clitoris**).
On each side of the lower part of the vulva lie two glands (**vestibular or Bartholin's glands**) that open up at the entrance of the vaginal opening (similar to the Cowper's glands in the male). Upon sexual arousal they produce a thick, mucous-like liquid necessary for vaginal **lubrication** during intercourse.

Although the internal genital organs are genetically determined (by the XX or XY chromosomes) the **external genital organs** share many similarities in both sexes. During the 7^{th}-8^{th} week of gestation, hormones that are produced by the embryo's gonads start influencing the formation of the external genital organs from the primary, embryonic structures that are common in both sexes. The male hormones (**androgens**) lead to a male phenotype while female hormones (**estrogens**) lead to female genitalia. However, congenital defects in the hormone production from the gonads or even external factors (e.g. consumption of substances with hormonal action by the mother) may lead to a state "in-between", called **ambiguous genitalia**.

The menstrual cycle.

The ovaries are responsible for the production of the female **hormones** that regulate the **menstrual (or ovarian) cycle**. A normal menstrual cycle usually lasts 28 days, with the 1^{st} day being the one that menstrual bleeding begins. This phase (**mestruation phase**) is due to the abrupt fall in the levels of estrogen and progesterone produced by the ovaries: this leads to a ***spasm*** of the endometrium vessels, necrosis of the mucosa and bleeding that lasts for 2-5 days. The next phase is called **proliferative phase** and is regulated by an *increase* mainly in estrogen production that allows for regeneration of the endometrium and thickening of the mucosa. That procedure lasts until the **ovulation**, which occurs usually on the 14^{th} day. After the ovule is released, the cells of the now empty follicle walls (**corpus luteum**) produce great amounts of estrogen **and** progesterone, further increasing the thickness of the endometrium and the storage of nutrients. This prepares the endometrium for possible implantation of a (theoritically) fertilized ovum. This third phase is called **secretory phase** and lasts usually 14 days. If no fertilization has occurred, the hormone levels will fall and menstruation will occur, as described above. In case of a fertilized ovum that implants in the endometrium successfully, another hormone is produced by the **trophoblastic** cells that surround the blastocyst: the **Human Chorionic Gonadotropin (HCG**). This hormone (which is often used in pregnancy tests) further activates the cells of the **corpus luteum** to continue producing estrogen and progesterone, in order to sustain the embryonic implantation and growth. That is sustained usually up to the point that the developing **placenta** will take over in the necessary hormone production at about the 3^{rd} to 4^{th} month of pregnancy.

The **ovarian cycle** is under regulation of hormones secreted by an endocrine gland called hypophysis (**pituitary gland**). This gland in turn is regulated by the hypothalamus under ***negative feedback*** control from the hormones released from the ovaries. The pituitary gland releases two hormones, the **Follicle Stimulating Hormone (FSH**) and the **Luteinizing Hormone (LH**). These products are responsible for the maturation of the follicles in the ovary and for timely ovulation.

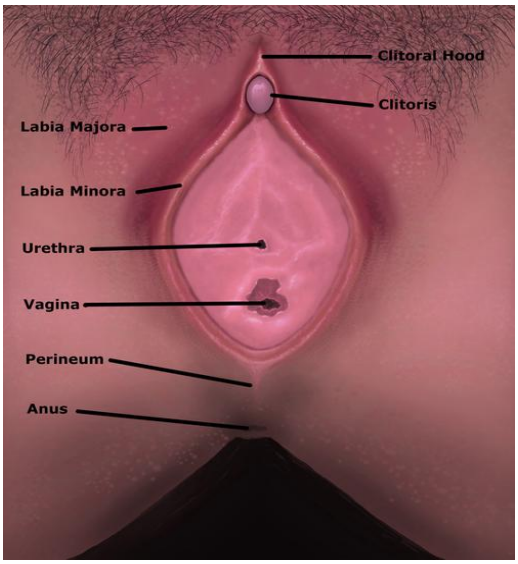

Fig. 10.9 External genitalia in the female.

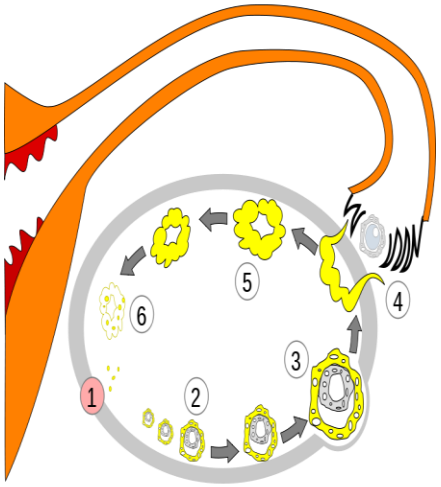

Fig. 10.10 The ovulation cycle.

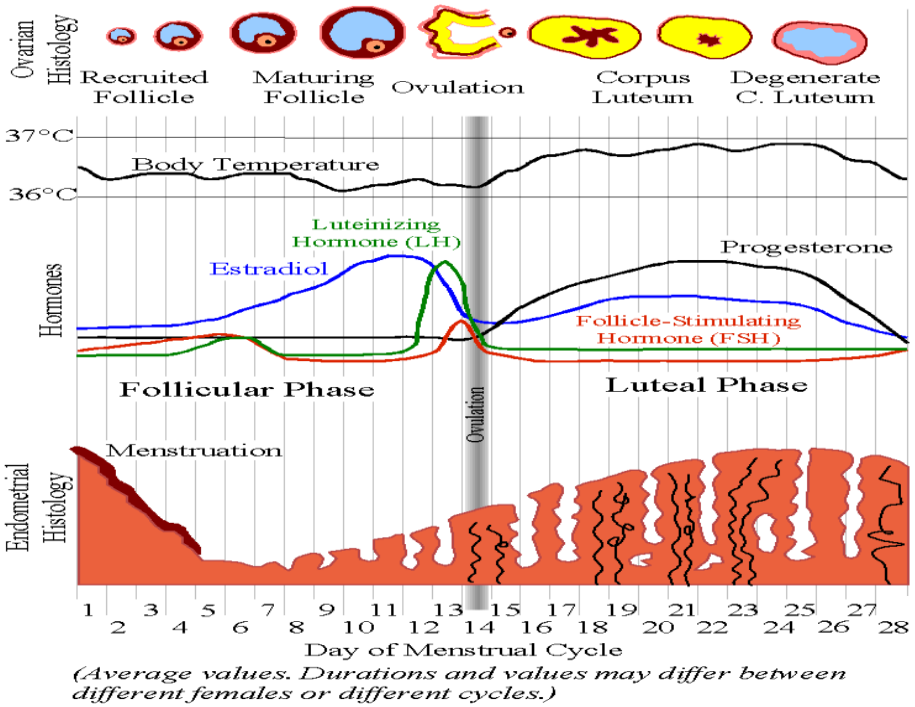

Fig. 10.11 Changes through the menstrual cycle.

Trying to avoid an unwanted pregnancy is called **contraception**. Measures can be taken by the male partner (e.g. condom use or interrupted coitus) or both partners (e.g. estimation of "fertile" days, temperature measurements etc). Another method is the use of an Intrauterine Device (IUD) which consists of insertion by the gynecologist of a small device (usually metal or plastic) in the endometrial cavity. This device prevents implantation of a fertilized ovum by irritating the endometrium. The use of the pill (contraceptive pill) is mainly for young, healthy, non-smoking women that wish to avoid a pregnancy with a high rate of success. The pill consists of low dose of hormones that act by influencing the normal ovarian cycle, the endometrium preparation or the thickness of the cervical mucous. More radical measures include surgical sterilization either to the male (vasectomy) or to the female (uterine tube ligation).

Gestation and childbirth.

The first step for the beginning of a new life is **fertilization** of the ovule by a single spermatozoon. This normally occurs in the ampulla of the uterine tube, creating the first "fused" embryonal cell: the **zygote**. Soon the zygote cell begins to multiply by mitosis and by the time it reaches the endometrial cavity consists of several cells forming the **embryoblast**, surrounded by a "cloud" of cells (the **trophoblast**) that will assist implantation. If **implantation** is successful, the embryo starts growing beneath the endometrium inside a sack called **amnion**. The growing embryo is "fed" from the mother through a newly formed organ (the **placenta**), which is responsible for the respiration, excretion and nutrition of the embryo.

A normal gestation lasts usually around 37 weeks (**full term pregnancy**), during which the embryo will grow and all systems and organs will fully develop. During gestation the uterus is developing and growing in accordance with the embryo. By the end of pregnancy, the estrogens have prepared the uterus, the pelvis and the vagina for childbirth. Immediately before delivery, an abrupt fall in progesterone and rise in estrogen levels stimulates **contraction** of the uterine muscles. **Dilation of the cervix** further assists contractions and eventually the baby will be expelled through the genital canal. Another hormone released by the pituitary gland (**oxytocin**) not only assists labor but also prepares the **breasts** for milk production.

The breast.

Although not a proper genital organ, the **breast** is (in a way) a part of the reproductive system, as a *secondary* sexual organ. Its growth is regulated by female hormones and plays an important role not only in the female sexual behavior but, most importantly, in the production of milk (**lactation**). The breast consists of a gland that has the ability to secrete milk upon stimulation by certain hormones, mainly **oxytocin** and **prolactin**. The **mammary gland** consists of 15-20 smaller glands, separated by **fibrous septa**, which are embedded in **fat** and empty their secretions in small lactiferous ducts on the surface of the **nipple**, at the center of the colored area called **areola**. The shape and size of the breasts varies widely between women; the most of their volume depends on the amount of fat (adipose) tissue. The breast is attached to the superficial fascia covering the chest wall and is held in place mainly by the skin and the underlying connective tissue.

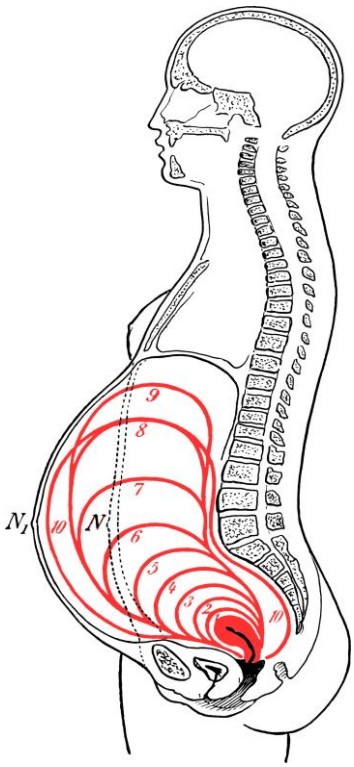

Fig. 10.12 Changes in uterine size and position during pregnancy.

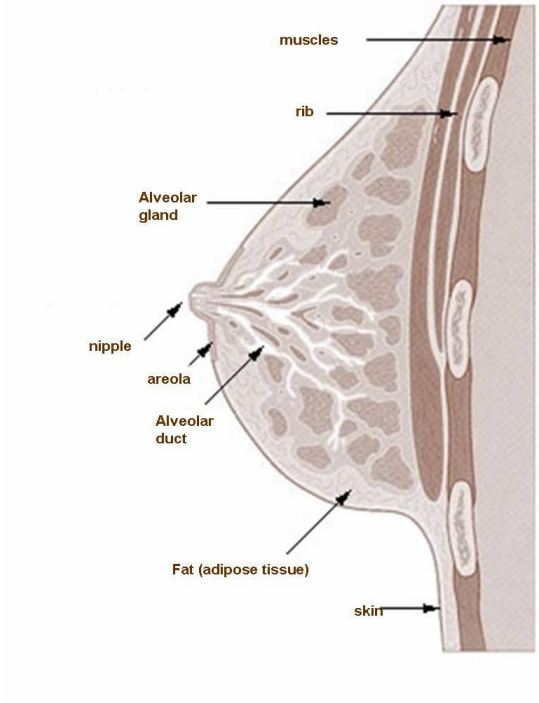

Fig. 10.13 The breast (mammary gland).