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Basics in Obstetrics and Gynaecology

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Basic sciences in obstetrics and gynaecology

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Structure and function of the genome

Chromosomes

The normal human genome is diploid and consists of 46 human chromosomes in 23 pairs. Chromosome abnormalities may be related to the number (aneuploidy) or structure of chromosomes. A karyotype describes the number of chromosomes and major structural abnormalities such as deletions, duplications, or translocations.

Meiosis is the cell division process in germline cells, resulting in the production of haploid gametes (ova and sperm). The process of meiosis generates four haploid cells, which can participate in fertilization. *Mitosis* is a process of the cell cycle in somatic cells resulting in the formation of two diploid daughter cells with identical genomes to that of the parental cell.

Genes and gene expression

A *gene* is a sequence of nucleotides in deoxyribonucleic acid (DNA) which codes for a protein. The sequence of nucleotides determines the amino acid sequence of the protein and its function. Each gene is represented twice (alleles) in the complement of genes known as the genome. Genes contain information that determines phenotype.

Genes are made up of exons and introns. Exons code for the protein and introns are spliced out during processing to messenger ribonucleic acid (mRNA). The length of the introns is far greater than that of the exons. The exact function of the introns is unclear. Although the exon sequence is highly conserved between individuals, the intron sequence is not.

Gene expression is the process by which information from a gene is used in the synthesis of a protein or another gene product such as transfer RNA (tRNA) or functional RNA. This process involves transcription of RNA from a DNA template and translation of mRNA into protein.

Although all cells in an organism have the same information in their DNA, only 3–5% of genes are active in a cell. Most of the genome is suppressed, a characteristic of gene expression.

Changes in gene regulation result in the expression of various gene products and the suppression of others. Methods for measuring RNA to evaluate gene expression include northern blot, ribonuclease protection assay, *in situ* hybridization, reverse-transcription quantitative polymerase chain reaction (PCR), and spotted complementary DNA arrays. Genome-wide methods for profiling gene expression include oligonucleotide arrays (microarrays) and transcriptome sequencing.

Epigenetics

Epigenetics is the study of heritable genome modifications in gene expression that are not due to alterations in DNA sequences. DNA methylation and histone modification (acetylation, methylation) are common epigenetic changes and can affect the process of transcription or silencing of gene expression.

Other epigenetic changes include modifications in non-coding RNAs and telomere length. Influences of environmental factors and epigenetic changes in the development of diseases such as cancer have been investigated in recent years. Such factors may include drugs, ultraviolet light, infection, and diet. Geographic differences in the incidence of autoimmune diseases have also been studied (1). Ageing and development of disease is another area of epigenetics involvement.

Molecular biology techniques

Molecular diagnostic tools in clinical genetics are applied for genotyping, detection of mutations, and assessment of chromosomal structural variants.

PCR technology is used to identify mutations. It requires prior knowledge of the DNA sequence of the fragment to be amplified. Real-time PCR allows the simultaneous detection and quantification of a DNA molecule and selection of mutant DNA. Deletion and insertion mutations can be identified using this technique.

PCR can detect organisms such as human immunodeficiency virus (HIV), methicillin-resistant *Staphylococcus aureus*, as well as chromosomal translocations associated with cancers.

Cytogenetic karyotype analysis by chromosomal banding, fluorescence *in situ* hybridization (FISH) on metaphase or interphase nuclei, or array comparative genomic hybridization (CGH) can identify structural variations. The resolution improves from karyotyping to interphase FISH and to array CGH. New sequence variants continue to be discovered with methods that allow analysis of entire genes or genomes.

Ovulation and ovarian function

Control of the hypothalamic–pituitary axis

The hypothalamus is part of the diencephalon. It is separated from the thalamus by the hypothalamic sulcus. Its external boundaries are rostrally the optic chiasm, laterally the optic tract, and posteriorly the mammillary bodies.

Its rostral boundary is a line through the optic chiasm, lamina terminalis, and anterior commissure and the caudal boundary extends from the posterior commissure to the caudal limit of the mammillary body. Dorsolaterally, the hypothalamus extends to the medial edge of the internal capsule (Figure 1.1) (2). The hypothalamus is associated with visceral, endocrine, autonomic, affective, and emotional behaviour.

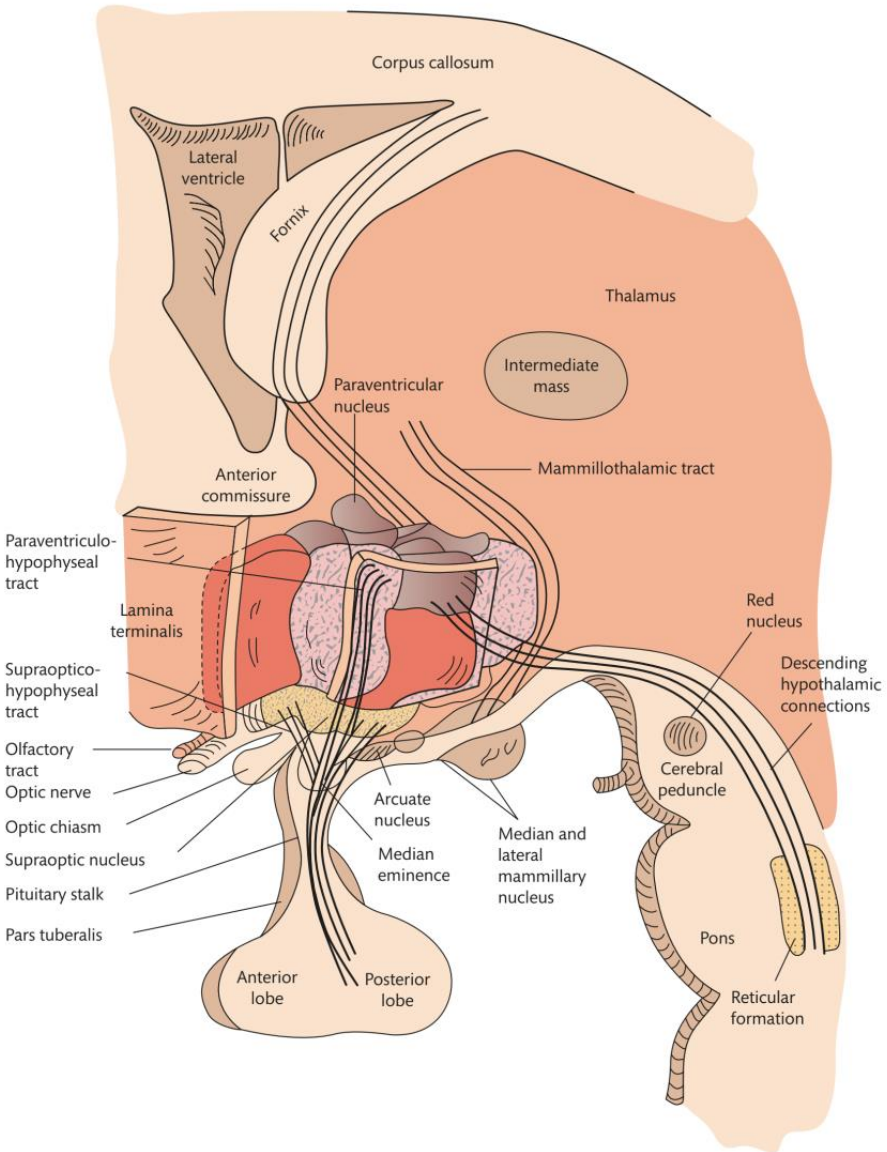

Figure 1.1 The hypothalamic nuclei and hypothalamic–hypophyseal tracts in relation to the thalamus, ventricular system, and brainstem.

Reproduced from Ignacio Bernabeu, Monica Marazuela, and Felipe F. Casanueva, General concepts of hypothalamus-pituitary anatomy, in: *Oxford Textbook of Endocrinology and Diabetes* 2e (eds: John Wass et al.), Oxford University Press, 2011, with permission from Oxford University Press.

The anterior pituitary is connected to the hypothalamus through a portal system. Hormones synthesized in the hypothalamus are transported to the nerve terminals on the hypophyseal portal capillaries. Hormones released into the hypophyseal portal system are transported to the anterior lobe of the pituitary. The posterior lobe of the pituitary consists of nerve terminals which lie in the supraoptic and paraventricular nuclei of the hypothalamus. Oxytocin and vasopressin are synthesized by the posterior pituitary.

Actions of pituitary and ovarian hormones

Gonadotropin-releasing hormone (GnRH) is synthesized in the preoptic area of the hypothalamus and is transported via portal vessels to the anterior pituitary where it stimulates the gonadotrophs to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH). These glycoproteins share a common alpha-subunit and a specific beta-subunit. They control the steroid synthesis of the testes and ovaries.

Oestrogen and progesterone are the major hormones secreted by the ovarian follicles and the corpus luteum (Figure 1.2).

Ovulation

A rise in FSH secretion stimulates the growth and differentiation of preantral and antral follicles, which in turn stimulates oestrogen secretion with a peak approximately 1 day before ovulation. Then, the mid-cycle surge occurs (3) and is associated with a change from negative feedback control of LH secretion by ovarian hormones to a positive feedback, resulting in a tenfold rise in serum LH and a smaller increase in FSH concentrations. The LH surge leads to substantial changes in the ovary. The oocyte in the dominant follicle completes its first meiotic division. The oocyte is subsequently released from the follicle at the surface of the ovary (4).

Before the release of the oocyte, the surrounding granulosa cells luteinize and produce progesterone. As a result, LH pulses become less frequent by the end of the surge (Figure 1.3).

The increasing serum progesterone concentrations have an effect on the endometrium, leading to cessation of mitoses and 'organization' of the glands.

Endometrial cycle

The average duration of the adult menstrual cycle is 28–35 days. The first day of menses represents the first day of the cycle. The cycle is then divided into two phases: follicular and luteal. The follicular

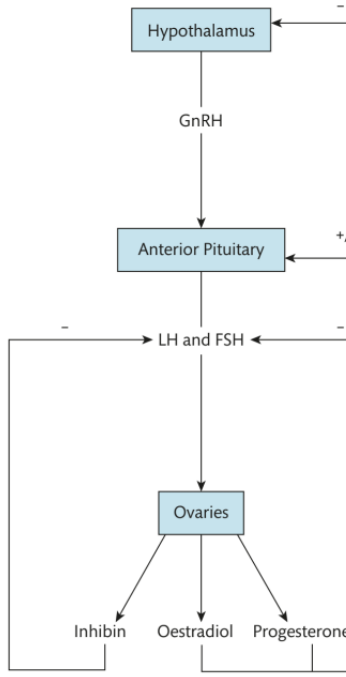

Figure 1.2 Hypothalamic–pituitary–ovarian axis.
Reproduced from S. Arulkumaran, Menstrual disorders, in: *Training in Obstetrics and Gynaecology* (eds. Ippokratis Sarris, Susan Bewley and Sangeeta Agnihotri), Oxford University Press, 2009, with permission from Oxford University Press.

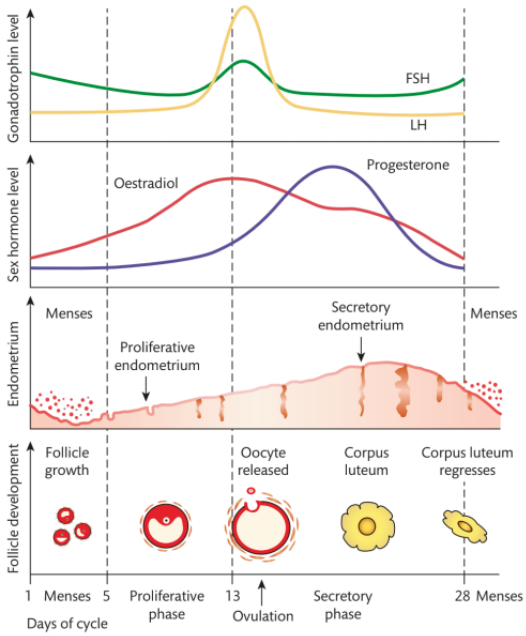

Figure 1.3 The hormonal and endometrial axis of the human menstrual cycle. After menstruation, rising levels of oestrogen exert a negative feedback, reducing follicle-stimulating hormone (FSH) release. Towards mid cycle, still higher levels of oestrogen then exert a positive feedback, causing a sudden peak release of luteinizing hormone (LH), which induces ovulation. An increased level in FSH also occurs. The endometrium during this phase has a thin surface epithelium and the glands are straight, short, and narrow (proliferative/follicular). In the luteal phase, LH levels maintain the corpus luteum, the source of progesterone. The endometrial glands become more tortuous during this phase (secretory/luteal) with secretion in the lumen and increasing fluid separating the stromal cells. If an embryo fails to implant, the corpus luteum deteriorates after about 7 days, with a resulting fall in progesterone and oestrogen concentrations.
Reproduced from S. Arulkumaran, Menstrual disorders, in: *Training in Obstetrics and Gynaecology* (eds. Ippokratis Sarris, Susan Bewley and Sangeeta Agnihotri), Oxford University Press, 2009, with permission from Oxford University Press.

phase begins with the onset of menses and ends on the day before the LH surge. The luteal phase begins on the day of the LH surge and ends at the onset of the next menses. The follicular phase lasts approximately 14–21 days and the luteal phase 14 days. Changes in the intermenstrual interval are primarily due to changes in the follicular phase. The luteal phase remains relatively stable. There is significantly more cycle variability during the first years after menarche and the 10 years before menopause. Menstrual cycle length peaks at the age of 25–30 years and then gradually declines. Between the ages of 20 and 40 years, there is relatively little cycle variability. Women in their 40s may have slightly shorter cycles (5).

During the menstrual cycle, endometrial changes include a proliferative phase and a secretory phase. The proliferative phase is characterized by an increased rate of mitotic division of endometrial glandular cells under the influence of oestradiol, leading to proliferation. The secretory phase is characterized by secretory activity following further proliferation under the influence of oestradiol and progesterone.

Luteinization of corpus luteum occurs 14 days after ovulation in the absence of conception. A rise in FSH is induced by the loss of negative feedback from oestradiol and progesterone, resulting in the start of another cycle. If, however, conception occurs, luteinization does not occur and the corpus luteum is maintained by human chorionic gonadotropin.

Puberty and menopause

Puberty is a process of physical and hormonal changes resulting in sexual maturity and capability of sexual reproduction. The two main physiological events include *gonadarche*, which is the activation of gonadal sex steroid production by the pituitary hormones FSH and LH, and *adrenarche*, which involves the increase in production of androgens by the adrenal cortex.

Thelarche is the appearance of breast tissue. *Menarche* is the onset of menstrual cycles. This is caused by the action of oestradiol on the endometrium and usually is not associated with ovulation. *Spermarche* is the onset of sperm production. *Pubarche* is the appearance of pubic hair, primarily due to the effects of androgens from the adrenal gland. The term also refers to the appearance of axillary hair (**Figure 1.4**).

In puberty, the increased frequency and amplitude of GnRH pulses stimulates secretion of FSH and LH and activates gonadal steroidogenesis.

Leptin is secreted by adipose tissues and along with kisspeptin plays a role in the onset of puberty. *Menopause* is defined as the permanent cessation of menstruation. It is an oestrogen- and progesterone-deficient state with an increase in the secretion of FSH and LH. The cessation of menstrual periods occurs as the ovary no longer contains follicles which are responsive to FSH. It is diagnosed retrospectively after 12 months of amenorrhea without any other cause (**Figure 1.5**).

Lack of oestrogen causes vasomotor symptoms including hot flushes and night sweats as well as mood swings and depression. Long-term effects include lower genital tract atrophy, osteoporosis, changes in lipid metabolism, and an increased risk of cardiovascular disease (6). Menopause usually occurs between 45 and 55 years of

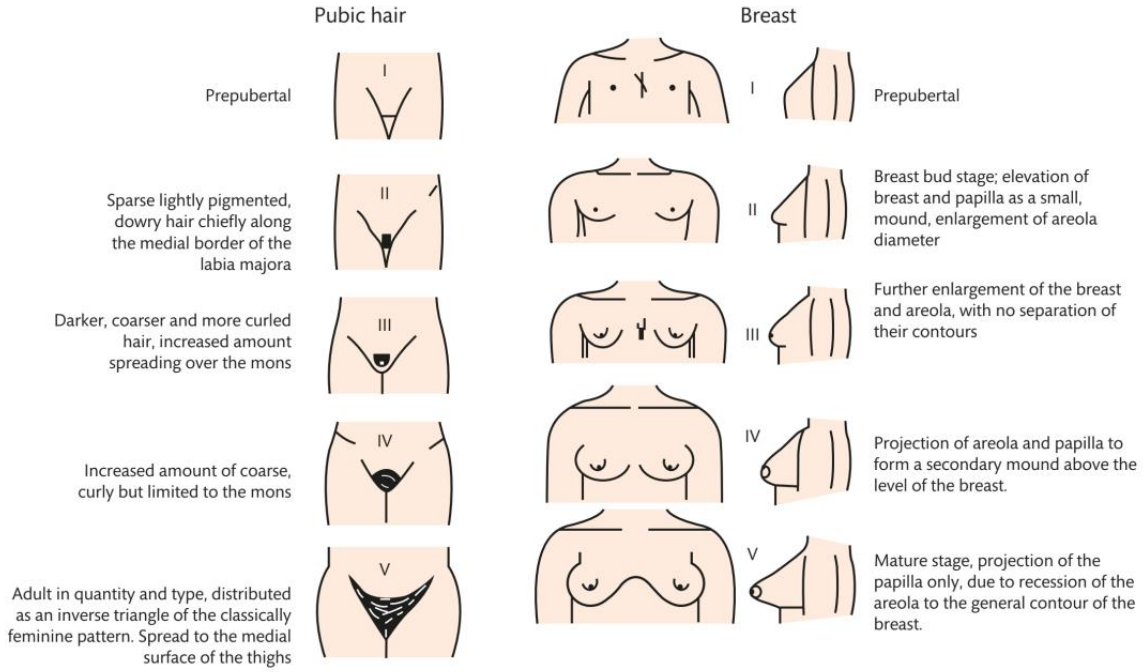

Figure 1.4 Marshall and Tanner stages of breast and pubic hair development.

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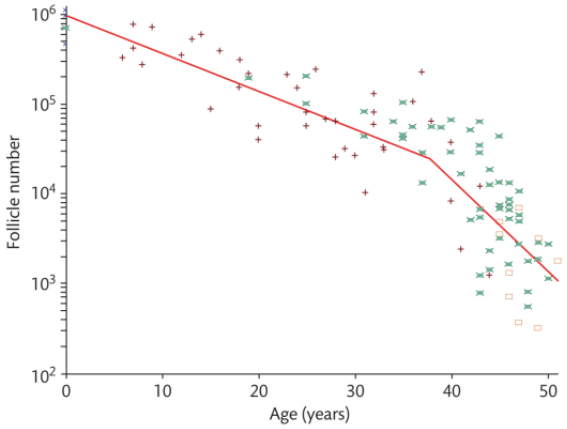

Figure 1.5 Decline in primordial follicle number with age.
Reproduced from Faddy MJ, Gosden RG. A mathematical model of follicle dynamics in the human ovary. *Hum Reprod*. 1995; 10: 770–5 with permission from Oxford University Press.

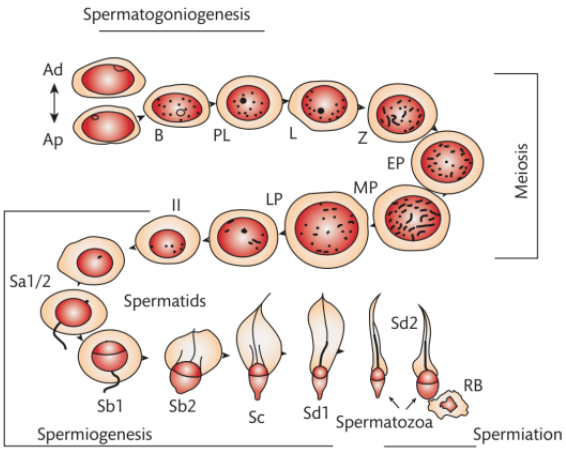

Figure 1.6 Schematic representation of the germ cell types and their development path during human spermatogenic process. Ad, A dark-spermatogonium; Ap, A pale-spermatogonium; B, B-spermatogonium; EP (early), MP (mid), and LP (late), pachytene spermatocyte; II, secondary spermatocyte; L, leptotene spermatocytes; M, mitochondria; PL, preleptotene spermatocytes; RB, residual body; Sa–Sd2, steps of spermatid differentiation (Sd2 spermatids are the mature testicular sperm). The developmental process from spermatogonium to formation of testicular sperm is considered to require at least 64 days (33–35).
Reproduced from C. Marc Luetjens and Gerhard F. Weinbauer, The male gamete: spermatogenesis, maturation, function, in: *Oxford Textbook of Endocrinology and Diabetes* 2e (eds: John Wass et al.), Oxford University Press, 2011, with permission from Oxford University Press.

age. In the United Kingdom, the average age of menopause is 51. Menopause before the age of 40 years is considered abnormal and is referred to as primary ovarian insufficiency (premature ovarian failure).

The transition to menopause, or perimenopause, is characterized by irregular menstrual cycles (7) and hormonal fluctuations, and a variable frequency and severity of symptoms such as hot flashes, sleep disturbances (8), mood changes, and vaginal dryness. It begins on average 4 years before the final menstrual period (9).

Fertilization and implantation

Gametogenesis

The full maturation of spermatozoa takes approximately 64–70 days. FSH causes stimulation of spermatogenesis and LH is responsible for stimulation of Leydig cells and testosterone production.

A large number of spermatogonia are produced by mitosis after puberty and are converted to spermatocytes in the testis. Following the first meiotic division, spermatozoa are released into the seminiferous tubules and then into the vas deferens. The second meiotic division is then completed (Figure 1.6).

Follicular development is characterized by enlargement of the ovum with aggregation of stromal cells to form the thecal cells. When a dominant follicle is selected, the innermost layers of granulosa cells become adherent to the ovum and form the *corona radiata*. A layer of gelatinous material around the ovum forms the *zona pellucida*. The follicle enlarges and bulges through the surface of the ovary and is released at the time of ovulation. The granulosa and the theca internal cells undergo luteinization. Formation of the *corpus luteum* occurs approximately 7 days after ovulation. Unless implantation occurs, it subsequently regresses.

Sperm transport

Once sperms arrive near the cervical os, sperm migration into the cervical mucous occurs with a rate normally of 6 mm/min. Motile spermatozoa reach the uterine cavity and subsequently the fimbrial end of the fallopian tube.

Capacitation and fertilization

Capacitation is the functional maturation of the spermatozoon. It takes place once sperm passes through the epididymis and seminal vesicles. This process continues in the uterus or fallopian tube. Capacitation allows penetration of the zona pellucida by the sperm. Enzymes such as beta-amylase or beta-glucuronidase may act on the membranes of spermatozoa and facilitate sperm penetration. The capacitation process also involves modifications of membrane lipids, loss of cholesterol from plasma membrane, activation of the cyclic adenosine monophosphate/protein kinase A (cAMP/PKA) pathway, increases in calcium (Ca^{2+}) uptake and pH, hyperpolarization of membrane potential, and tyrosine phosphorylation (10).

The process of *fertilization* involves the union of the ovum and spermatozoon. When a spermatozoon reaches the cumulus around the ovum, the acrosome reaction is initiated. The outer acrosomal membrane fuses with the plasma membrane surrounding the spermatozoon and lytic enzymes are released. This facilitates the penetration of the oocyte membrane. The sperm head fuses with the oocyte plasma membrane and by phagocytosis the sperm head and mid piece are engulfed into the oocyte. The tail piece is left outside the cell membrane of the oocyte.

The sperm head forms the male pronucleus and with the female pronucleus they form the zygote. After disintegration of the membranes of the pronuclei, fusion of the male and female chromosomes occurs. This is called *syngamy* and is followed by the first cleavage

division. After a series of divisions and at the 16-cell stage, a solid ball of cells called blastomeres forms within the zona pellucida. This is known as a *morula*. A fluid-filled cavity develops within the morula to form the blastocyst.

Implantation

Thirty-six hours after fertilization, the conceptus is transported through the fallopian tube and reaches the uterine cavity approximately 4 days later. The secretory endometrium is receptive to implantation. The second mitotic division of the oocyte is completed after fertilization and is followed by extrusion of the second polar body.

Six days after ovulation, the embryo becomes attached to the mid portion of the uterine cavity. By the seventh day, the blastocyst lies deep in the endometrium.

Physiology of coitus

The sexual response cycle described by Masters and Johnson has four phases in males and females. These phases are excitation, plateau, orgasmic, and resolution (Figure 1.7) (11, 12).

In the male, the excitation phase is associated with increased blood flow to the genitals and compression of venous channels of the penis resulting in erection. In the plateau phase, the penis remains in erection and the testes increase in size. Secretion of clear fluid may appear at the urethral meatus. In the orgasmic phase, reflex contractions of the bulbospongiosus (formerly bulbocavernosus) and ischiocavernosus muscles are followed by ejaculation of semen in spurts. During the resolution phase, penile erection subsides. During this phase, the male becomes refractory to further stimulation.

In the female, the excitation phase involves erection of the clitoris and swelling of the labia minora and vagina, vaginal lubrication, and nipple erection. The orgasmic phase is associated with narrowing of the vaginal introitus and contractions of the pelvic floor muscles. The plateau phase may be sustained in females and result in multiple orgasms. Following orgasm, congestion of the pelvic organs resolves rapidly.

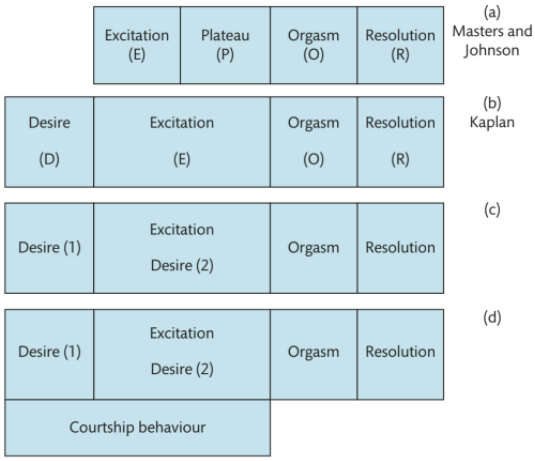

Figure 1.7 The development of the human sexual response model from (a) the original excitation, plateau, orgasmic, and resolution model of Masters and Johnson (11) through (b) the desire, excitation, orgasmic, and resolution model of Kaplan (12) to (c) the proposed modification with desire phase 1 (before initiation of the excitation phase and desire phase 2 during excitation phase) and finally (d) with added courtship behaviour.

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Embryology

Early embryo development

Cells differentiate into an outer layer, the *trophoblast*, and an *inner cell mass*, which will give rise to the *embryo proper*, the *amnion, yolk sac*, and *allantois*. Only two layers of cells intervene between the amniotic sac and yolk sac (Figure 1.8).

The layers of cells adjacent to the amniotic sac form the embryonic *ectoderm*. Ectodermal tissues of the fetus develop from these cells including skin, its appendages, neural tube, and its derivatives (brain, spinal cord, autonomic ganglia, and adrenal medulla). Cells adjacent to the yolk sac form the embryonic *endoderm*. Endodermal tissues include lining of the gut, epithelial cells of thyroid, parathyroid, trachea, lungs, liver, and pancreas. Between ectoderm and endoderm, a third layer of cells develops mainly from ectodermal proliferation. This middle layer forms the *mesoderm*. Mesodermal tissues are bones, muscles, cartilage, and subcutaneous tissues of the skin.

Organogenesis

Ectoderm, mesoderm, and endoderm initially take the form of a circular sandwich. Disproportionate growth of ectoderm results in elongation of the embryonic plate into an oval form. Each end of this plate curves, forming the head and tail folds. The amniotic sac enlarges and completely surrounds the developing embryo and the yolk sac. On the dorsal aspect of the ectoderm, a groove appears from the middle of the head to the tail and changes into the neural tube from which the nervous system develops.

Mesoderm starts to grow laterally and gives rise to the paraxial mesoderm, the intermediate cell mass, and the lateral plate mesoderm (Figure 1.9).

Endoderm grows first laterally and then ventrally to form the gut.

The lateral plate of the mesoderm divides into somatopleure, which remains adjacent to ectoderm, and the splanchnopleure, which grows around the developing gut. The space between the somatopleure and splanchnopleure form the coelomic cavity. This later becomes the pleural and peritoneal cavities.

The paraxial mesoderm develops into vertebrae, dura matter, and muscles of the body wall. The intermediate cell mass grows ventrally into the coelomic cavity and forms the urogenital system. See Figure 1.10.

Development of the genital organs

Genital and urinary systems arise from the intermediate mesoderm. The pronephros appears first and quickly disintegrates. At the caudal end of pronephros, the mesonephric duct (Wolffian duct) develops

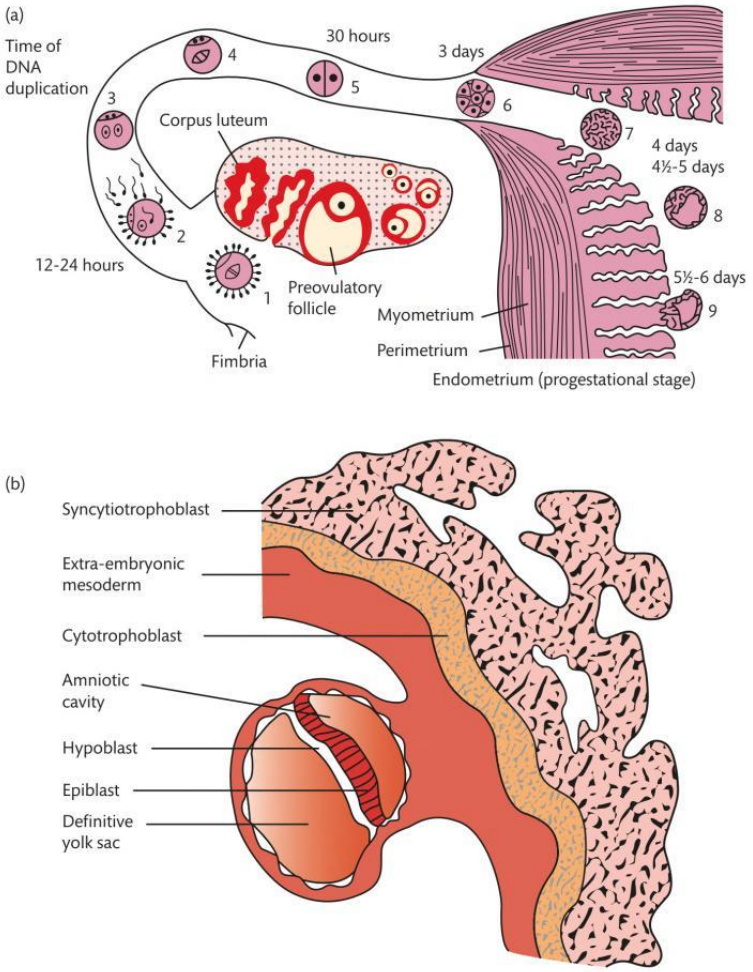

Figure 1.8 (a) Events of the first 6 days of development of a human embryo. 1: oocyte immediately after ovulation; 2: fertilization 12–24 h later results in the zygote; 3: zygote contains male and female pronuclei; 4: first mitotic division; 5: two-cell stage; 6: 3-day morula made up of up to 16 blastomeres; 7: morula stage (16–32 blastomeres) reaches the uterine lining; 8: early blastocyst; 9: implantation occurs at around day 6. (b) The site of implantation at the end of the second week.

and passes down the body to reach the cloaca. The mesonephros develops as a bulge in the dorsal wall of the coelom in the thoracic and lumbar regions. Two important structures appear on the coelomic surface of the mesonephros: (a) the genital ridge from which the gonad will form and (b) the paramesonephric (Mullerian) duct. The paramesonephric duct appears as a groove on the lateral aspect of the coelom and then becomes a tube. See Figures 1.11–1.14.

Placental development

Following implantation, the trophoblast completely surrounds the embryo in the form of proliferating cytotrophoblast and a syncytial layer. During the first trimester, a subset of trophoblast cells, the extravillous trophoblast (EVT) cells, become invasive and grow through the outer syncytium into the decidua where they invade maternal spiral arterioles. The trophoblast shell begins to break open, allowing maternal blood to enter the primitive intervillous space where it is utilized by the developing villous placenta and fetus. See Figure 1.15.

Development of membranes and amniotic fluid

The embryonic disc lies between the amniotic cavity and the primary yolk sac. The amniotic cavity develops between the embryonic ectoderm and cytotrophoblast. By the 12th postovulatory day, the base of this cavity is formed by embryonic ectoderm and the walls and roof are formed by the cytotrophoblast. Amniotic fluid is initially formed from the primitive cells around the amniotic vesicle.

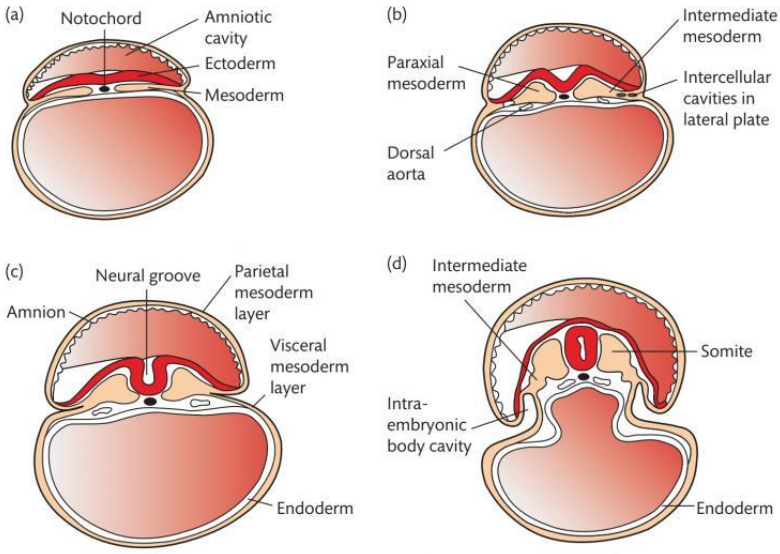

Figure 1.9 Transverse sections showing development of the mesodermal germ layer at days 17 (a), 19 (b), 20 (c), and 21 (d). The thin mesodermal sheet gives rise to paraxial mesoderm (future somites), intermediate mesoderm (future excretory units), and lateral plate, which is split into parietal and visceral mesoderm layers lining the intraembryonic cavity.

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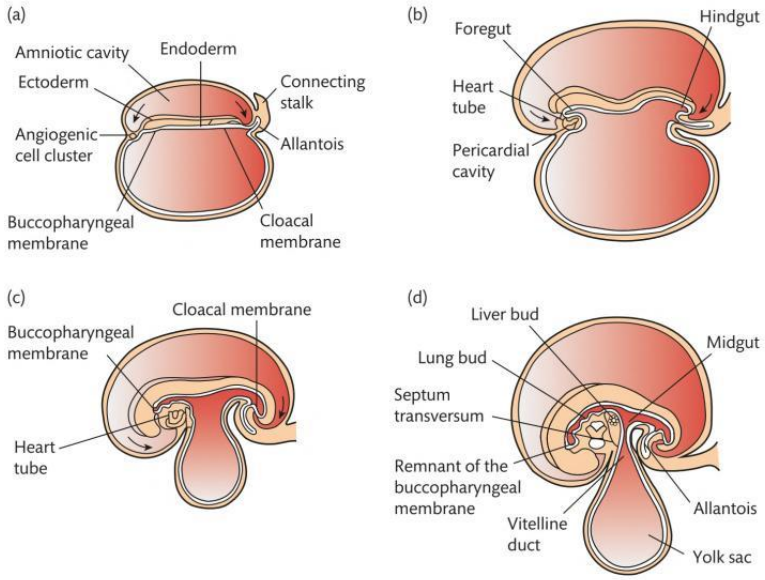

Figure 1.10 Sagittal midline sections of embryos at various stages of development demonstrating cephalocaudal folding and its effect on position of the endoderm-lined cavity. Presomite embryo (a), seven-somite embryo (b), 14-somite embryo (c), and 1-month embryo (d). Note the position of the angiogenic cell clusters in relation to the buccopharyngeal membrane.

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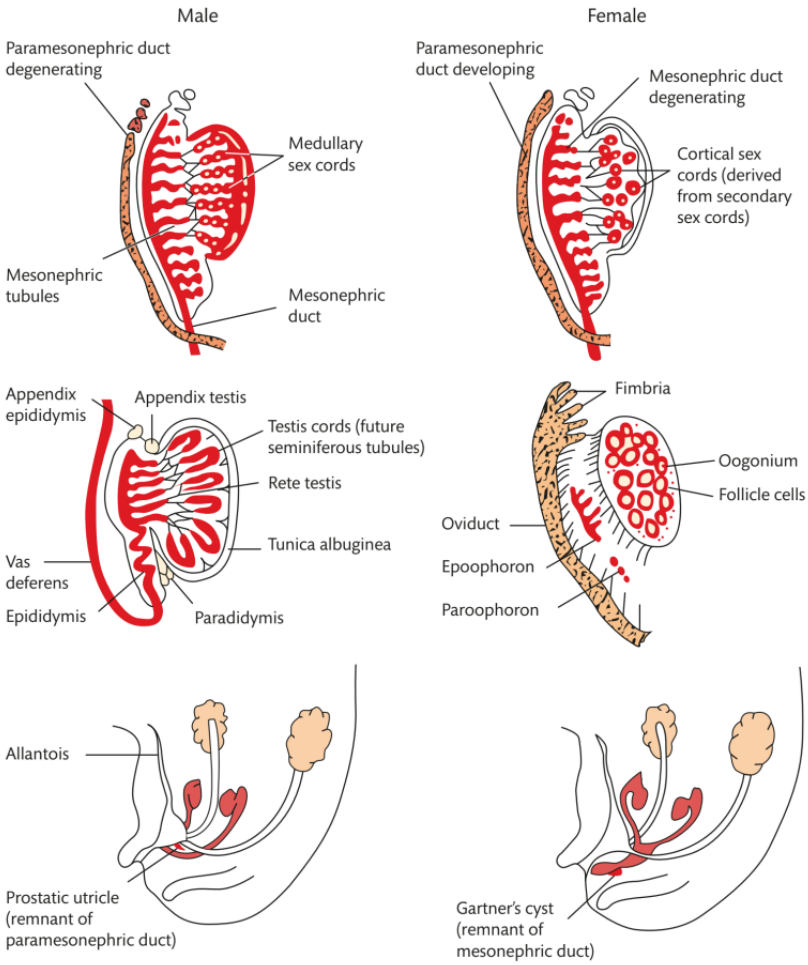

Figure 1.11 Male and female gonadal development. The male and female genital systems are virtually identical through the seventh week. In the male, SRY protein produced by the pre-Sertoli cells causes the medullary sex cords to develop into presumptive seminiferous tubules and rete testis tubules and causes the cortical sex cords to regress. Anti-Müllerian hormone produced by the Sertoli cells then causes the paramesonephric ducts to regress and Leydig cells also develop, which in turn produce testosterone, the hormone that stimulates development of the male genital duct system, including the vas deferens and the presumptive efferent ductules.

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Later on, fetal extracellular fluid (ECF) is passed through the fetal skin and umbilical cord.

Pathology

Response to tissue injury

Tissue injury is associated with reversible and irreversible changes of the cell membrane. Potassium is transferred out of the cell and sodium is transferred in accompanied by water. This leads to cellular oedema and a reduction in protein synthesis. There is a switch to anaerobic metabolism. Glycogen is used for energy resulting in lactate production and a drop in pH.

Intracellular enzymes including lactate dehydrogenase, troponins, and creatinine phosphokinase become activated in association with mitochondrial damage. Lysosomal rupture results in release of lysosomal enzymes and autolysis followed by nuclear death.

Tissue growth and differentiation

Growth and differentiation aim to maintain the normal structure of a particular tissue. In tissues with continuous cell loss (blood, skin, mucosa), lost cells are continuously replaced. Stem cells frequently differentiate into a mature form during this process. In the skin, as superficial keratinized cells are shed, basal cells proliferate to replace them. The newly produced basal cells differentiate into squamous cells. When the cell turnover rate is normal,

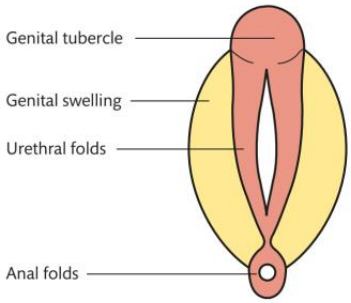

Figure 1.12 Indifferent stages of the external genitalia, approximately 6 weeks.

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the skin appears histologically normal but if the rate is greatly increased, cells do not fully mature, and abnormalities are seen both on physical examination and histologically. The rate of cell proliferation is determined by the cell cycle and controlled by a variety of growth factors and receptors, and regulated by growth control genes. Many of the cellular proto-oncogenes encode for growth factors for receptors.

Placental pathology

The placental involvement in the pathogenesis of pre-eclampsia and particularly the link between pre-eclampsia and reduced placental perfusion has long been recognized (13).

The main defect seems to be related to endovascular trophoblast invasion. In pre-eclampsia, myometrial arteries fail to adapt to physiological change. Trophoblast invasion is impaired. Acute atherosis is common. Blood flow into the intervillous space is therefore decreased in pre-eclampsia.

Fetal growth restriction is associated with reduced uteroplacental blood flow, which in turn can be secondary to defective placentation. Morphological abnormalities of the uterine arteries can be present in cases of fetal growth restriction.

Microbiology

Bacteriology

Bacteria are single-cell prokaryotic microorganisms. They have a single chromosome that is not enclosed in a nuclear membrane. They can have four shapes: cocci (spheres), bacilli (rods), spirilla (spirals), and vibrios (comma-shaped). Genetic information is encoded in the cell DNA. There are two types: chromosomal DNA and extrachromosomal DNA.

Bacterial metabolism is a balance between anabolic and catabolic functions. Their ability to utilize carbohydrates and convert them to glucose as well as oxygen requirement is used to characterize bacteria:

- Obligate anaerobes: oxygen is toxic.
- Aerotolerant anaerobes: anaerobic metabolism, but tolerant to the presence of oxygen.
- Facultative anaerobes: can grow in both anaerobic as well as aerobic conditions.
- Obligate aerobes: require oxygen to grow.
- Microaerophilic organisms: require low oxygen levels only; high levels may be inhibitory.

Bacteria can be Gram positive or Gram negative (**Figure 1.16**). Some bacteria can suspend growth and metabolism in adverse conditions and form resistant spores. Optimum temperature range is between 20°C and 40°C.

Bacteria have four phases of growth:

1. Initial lag phase
2. Exponential growth phase
3. Static phase
4. Death phase.

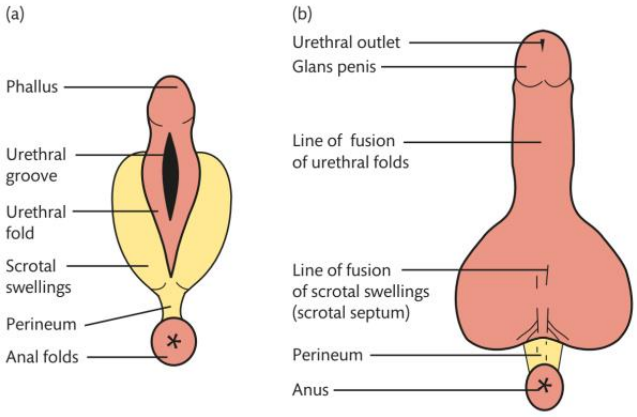

Figure 1.13 Development of the external genitalia in the male at (a) 10 weeks and (b) in the newborn. Genital tubercle extends rapidly to form the phallus, later the penis. Urethral folds close the urogenital sinus and genital swellings become scrotal swellings.

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