Block 11 - Tema: Congenital Abnormalities & Female Sex Hormones

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Sex determination & chromosome abnormalities

The reproductive system consists of the gonads, reproductive tract, and accessory sex glands.

- Reproduction depends on the union of male and female gametes. The reproductive systems of the two sexes are designed to enable this union. The female system is also the site of prenatal development.
- The primary reproductive organs are the pair of testis (male) and pair of ovaries (female). Both systems produce gametes (spermatozoa or ova) and secrete hormones, testosterone (male) or estrogen and progesterone (female).
- A reproductive tract plus accessory organs are found in either sex.
- Unique secondary sexual characteristics are found in each sex. These traits include differences in body configuration and distribution of body hair.

The reproductive system in each sex carries out essential functions.

- In the male these functions are production of sperm and delivery of sperm to the female.
- Functions in the female are production of ova, reception of sperm, transport of sperm and ova to a common site for union, maintenance of the developing fetus, parturition, and nourishing the infant.
- The product of fertilization in the embryo. After two months the developing being is a fetus.
- The ovaries and female reproductive tract are in the pelvic cavity. The two nearby oviducts pick up the ova after ovulation and are the site of fertilization.
- The uterus maintains the fetus during development. Its lowest part projects into the vagina. The vagina connects the uterus to the external environment.
- The vagina opens at the perineal region. It is partially covered by the hymen. The vaginal and urethral openings are surrounded by the labia majora and labia minora. The clitoris is anterior to the folds of the labia minora.
  - **See Figures 20-1 and 20-2**

Reproductive cells each contain a half set of chromosomes.

  - Human somatic cells have 46 chromosomes (23 homologous pairs). 46 is the diploid chromosome number.
  - Human gametes have the haploid chromosome number, 23. A sex cell has one chromosome of each kind, not two as in the diploid state.
- Gametogenesis occurs by meiosis.
  - Cell division involves the division of the nucleus and the division of the cytoplasm.
  - Mitosis (cell division) maintains the chromosome number, chromosome combination, and genetic identity of the chromosomes from the dividing parent cell to the two daughter cells produced. Mitosis produces somatic cells.
  - Meiosis produces gametes. Only one chromosome from each chromosome pair is inherited in each of the four daughter cells produced from a parent cells. The gametes have one-half the chromosome number.

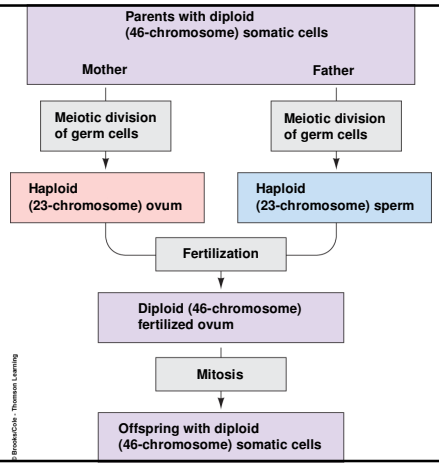

Figure 20.3
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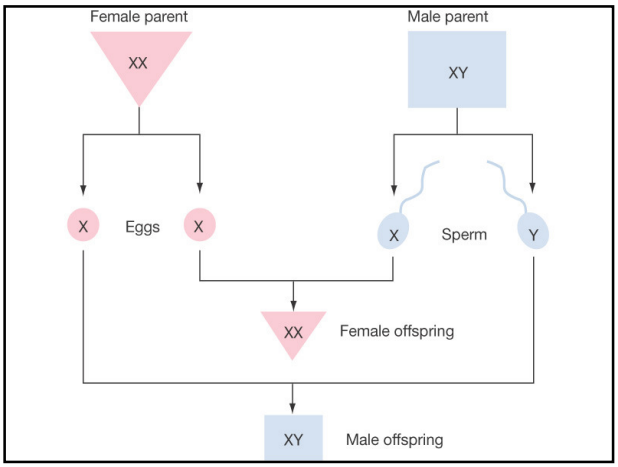

A combination of sex chromosomes determines the sex of an individual.

- 23 pairs of homologous chromosomes are separated during meiosis. The chromosomes of each pair are distributed to the sex cells by independent assortment.
- 22 pairs of the chromosome pairs are autosomes. The 23rd pair is either XX(female) or XY (male). A gamete normally receives one member from each pair (X or Y in male meiosis and X or X in female meiosis).
- Sex determination depends on the combination of chromosomes at fertilization. The fertilization of an ovum (X chromosome) with a sperm with an X chromosome produces an XX combination (female). The fertilization of an X with a Y produces XY (male).

Sexual differentiation in humans depends on the presence or absence of masculinizing determinants.

- The combination of sex chromosomes determines gonadal sex. A sex-determining region (SRY) of the Y chromosome influences gonadal specificity at the seventh week of intrauterine life. The region masculinizes the gonads.
- Females lack the SRY gene. Their gonadal cells do not receive a signal for testicular formation.
- Phenotypic sex is the apparent anatomic sex of an individual. By sexual differentiation, specific external genitalia and a specific reproductive tract develops in each sex. The male-type reproductive system is induced by androgens.

- Male and female external genitalia develop from the same embryonic tissue. The reproductive tracts also develop from a common source.
- Undifferentiated embryonic tissue develops into female structures unless actively signaled by masculinizing factors.
- Genetic and phenotypic sex are usually compatible. However several factors can produce errors in sexual differentiation.

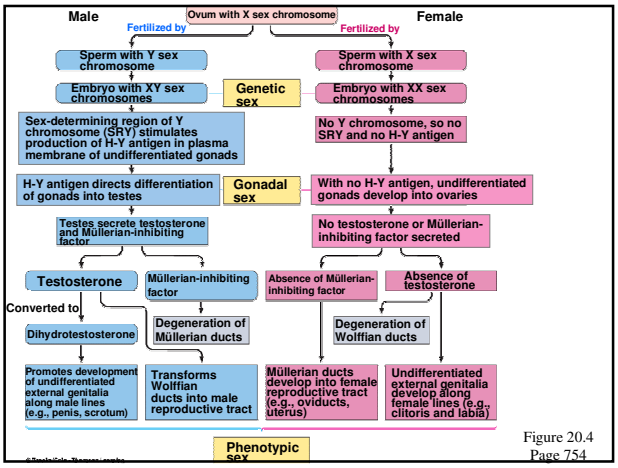

Figure 20.4
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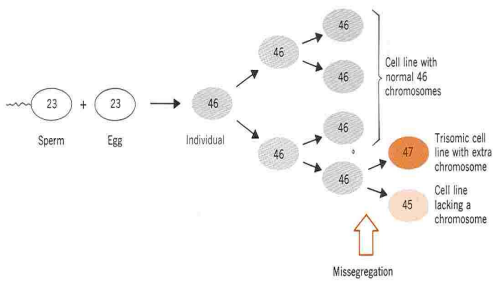
Chromosomal Abnormalities

1. Translocation defect – crossing over occurs between different chromosome pairs → gene at new location may not function normally
2. Trisomy – meiosis related → extra copy of chromosome
3. Extra or missing chromosomes

Trisomy

- An extra copy of one chromosome → 3 copies < 2 copies
- E.g. Trisomy 21 (number of the chromosome involved)

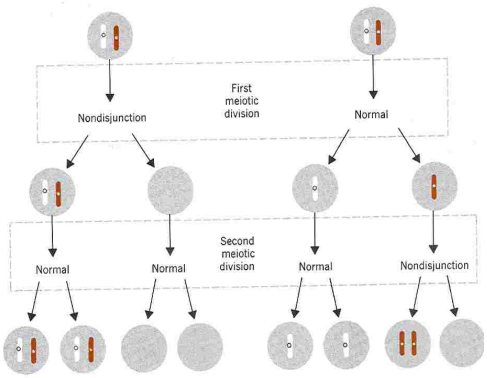


Abnormal Numbers of Sex Chromosomes – extra chrom

- E.g. Klinefelters (XXY)
- Extra X chromosome → reduced androgen production
- Phenotypically male
- Failure of testes to mature → sterile
- Enlarged breasts

Missing chromosome (deletion)

- Turner Syndrome → only single female sex chromosome (monosomy)
- Still female
- Maturational changes do not occur at puberty



Physiology of primary and secondary female sex organs

Female reproductive physiology is more complex than male reproductive physiology.

- There is a complex cycling of female sex hormones.
- The ovaries produce ova and produce estrogen and progesterone.
- The functions of estrogen include:
- maturation and maintenance of the female system
- establishment of female secondary sexual characteristics
- ova maturation and release
- transport of sperm from the vagina to the site of fertilization in the oviduct
- One important function of progesterone is to prepare a suitable environment for nourishing the developing embryo and fetus.

Oogenesis is gametogenesis in the female.

- Oogonia divide mitotically. These cells are undifferentiated primordial sex cells.
- The first meiotic division of an oogonium produces a primary oocyte (diploid). It is surrounded by a primary follicle. Only about 400 follicles will mature further and release ova. Most follicles never ovulate. Those that do ovulate may be arrested for years.
- From puberty to menopause some primary follicles develop into secondary follicles on a cyclical basis. These follicles and their primary oocytes enlarge.
- Just before ovulation the primary oocyte completes its first meiotic division. One product is a larger secondary oocyte. The other is the first polar body.
- The secondary oocyte is ovulated and possibly fertilized. Sperm entry into this oocyte triggers the second meiotic division. This meiosis produces a second polar body (haploid) and a haploid, mature ovum. If fertilized, it unites with a haploid sperm cell.

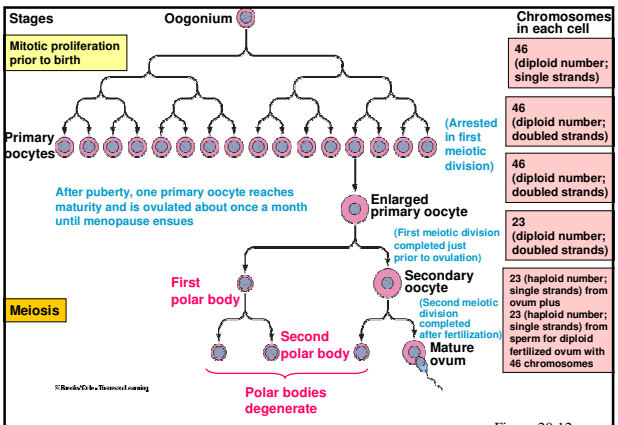


Figure 20.12
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Ovarian cycle

The ovarian cycle consists of alternating follicular and luteal phases.

- The follicular phase is dominated by maturing follicles. Over an average of 28 days the follicle operates the first half of the cycle.
- During the follicular phase the granulosa cells of some primary follicles proliferate. The oocyte inside each follicle is enlarging. Theca cells in the follicle secrete increased amounts of estrogen. This hormone circulates throughout the body.
- Rapid follicular growth continues during the follicular phase.
- One follicle usually grows more rapidly and matures about 14 days after the onset of follicular development. This follicle ruptures to release the oocyte from the ovary. This event is called ovulation.
- This released sex cell enters the oviduct where it may or may not be fertilized.
  - **See Figure 20-13**

The corpus luteum operates the last 14 days of the cycle.

- It is a the converted follicle left behind in the ovary after it loses its sex cell by ovulation.
- The corpus luteum secretes an increased amount of progesterone compared to the follicular phase. It also secretes estrogen.
- The corpus luteum degenerates 14 days after its formation unless fertilization and implantation occurs. If this occurs the corpus luteum continues to secrete its hormones.
- It is now called the corpus luteum of pregnancy.

The ovarian cycle is regulated by complex hormonal interactions.

- This is a summary of some of the major events.
- During the follicular phase a rise in FSH signals the ovarian follicle to secrete more estrogen.
- A rise is estrogen feeds back to inhibit FSH secretion which declines as the follicular phase proceeds.
- LH rises in the follicular phase. As it peaks in mid-cycle, it triggers ovulation. Estrogen output decreases and the mature follicle is converted to a corpus luteum.
- The corpus luteum secretes progesterone as well as estrogen during the luteal phase.
- Progesterone output inhibits the release of FSH and LH. With low LH the corpus luteum degenerates. With this breakdown, progesterone levels decline. FSH can start to rise again, initiating a new cycle.

There are concurrent changes in the uterus with the cyclical changes in the hormones during the female cycle.

- During the uterine menstrual cycle (beginning of the cycle) there is a sloughing off of the endometrium of the uterus. This is due to the low levels of estrogen and progesterone.
- An increased level of estrogen late in the follicular phase causes a thickening in the uterine lining (proliferative phase).
- After ovulation, progesterone produces further thickening of the uterine lining. This uterine secretory phase makes the uterine lining suitable for implantation.
- The degeneration of the corpus luteum starts a new ovarian follicular phase. Menstruation begins.

Oestrogen & Progesterone

Oestrogens

- These are major female sex hormones
- Apart from the small amounts produced by the adrenals, most oestrogens are synthesised by the cells of the corona radiata, theca interna & corpus lutuem
- During pregnancy the placenta produces large amounts.
- Some oestrogen is formed - circulating testosterone.
- Ovary produces 2 oestrogens, viz. oestradiol & oestrone
- Large quantities of both oestradiol and oestrone are hydroxylated at C_{16} & thus converted to oestriol (liver).

- Another major pathway for catabolism of oesrtogens is hydroxylation at C_2 & C_4
- Oestrogens contain 18 carbon atoms.
- Main steps in their biosynsthesis – fig 19.3
- In plasma 90% of circulating oestrogens are bound to albumin and sex hormone-binding globulin
- Oestrogens and their metabolites are conjugated to glucuronic acid or sulphate in liver.
- Most of these soluble conjugates are excreted by the kidneys, but some are secreted in bile and reabsorbed from the intestines

Functions

- Promote follicle development & ovulation
- Stimulate proliferation of epithelial cells of uterine tubes, uterus & vagina
- Stimulate proteins synthesis
- Reduce membrane potential of myometrial muscle fibres
- Stimulate duct growth in mammary glands
- Are largely responsible for development of female characteristics
- Are invloved in skeletal growth & maintenance of structural integrity of bones

Progestrogens

- Term designates any substance possessing progestational activity.
- Natural ones are progesterone and 17-hydroxyprogesterone
- Both are 21-carbon compounds-progesterone plays the major role
- Non-pregnant females - Predominantly produced by corpus luteum; small amounts are produced by developing follicle & adrenals
- Pregnancy - large amounts are produced by corpus lutuem & placenta
- Binds mainly to albumin & transcortin; it is converted to pregnanediol and excreted.

Functions

- Stimulates secretory activity of uterine tubes, uterus & vagina
- Is responsible for the progestational changes in the endometrium
- ↑ membrane potential of myometrial muscle fibres
- Prevents ovulation when present in high concentration
- ↓ no. of oestrogen receptors
- Promtes protein anabolism
- Responsible for rise in body temperature – ovulation
- Stimulates alveolar formation in breasts
- Stimulates respiration
- Antagonises action of aldosterone on kidney

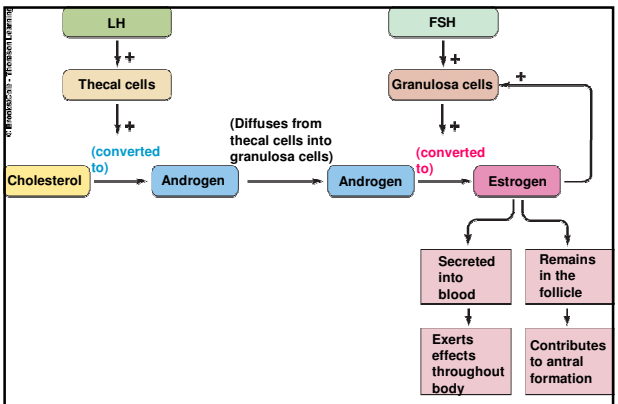

Figure 20.16
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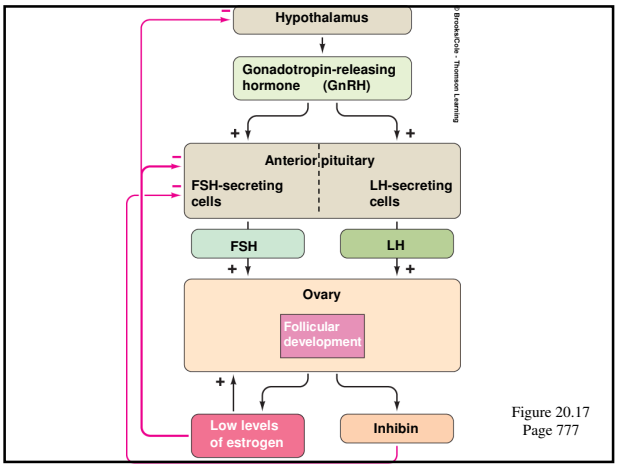

Figure 20.17
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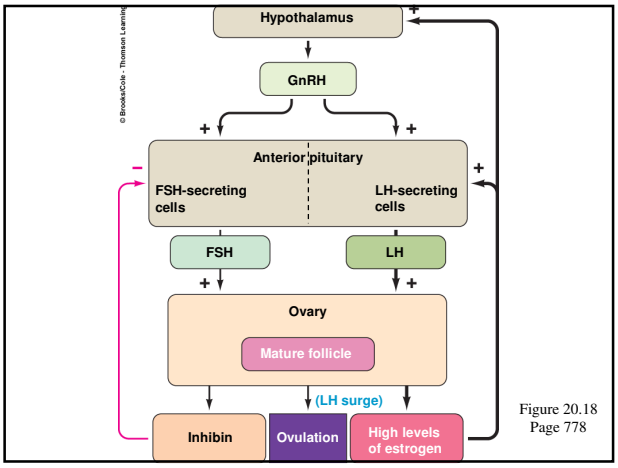

Figure 20.18
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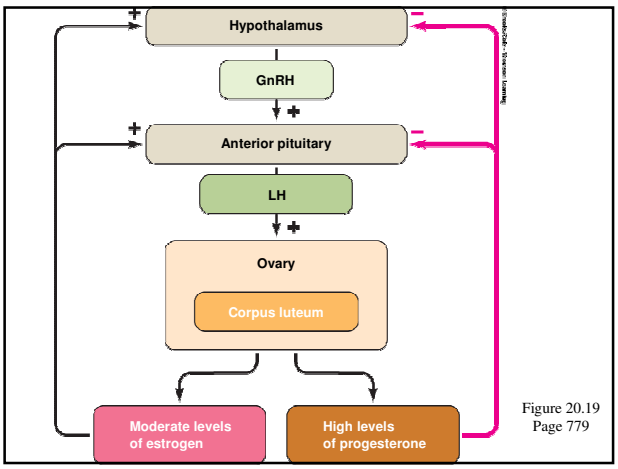

Figure 20.19
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Other facts of the female cycle include:

- Fluctuating estrogen and progesterone levels produce cyclical changes in the cervical mucus.
- Pubertal changes in females are similar to those in males. GnRH secretion increases at the onset of puberty. GnRH stimulates the release of hormones from the anterior pituitary. Estrogen release promotes many changes in the female reproductive system and in other body characteristics.
- Menopause is unique in females. A mid-life hypothalmic change may cause the onset of menopause. It is characterized by increasingly irregular cycles and dwindling estrogen levels. This has widespread physiological actions.

The oviduct is the site of fertilization.

- It normally occurs in the upper third of this structure. The dilated end of the oviduct contains fimbriae which attract the female sex cell into the oviduct.
- Fertilization must occur within 24 hours after ovulation.
- Sperm cells can survive up to five days in the female reproductive tract.
- By abnormal sites of fertilization, ectopic pregnancy can occur.
- Sperm cells deposited in the vagina travel through the cervical canal, uterus, and into the upper third of the oviduct for fertilization.
- Sperm migration is helped by the female tract. One example is the contractions of the myometrium (smooth muscle layer) of the uterus and antiperistaltic contractions of the oviduct. Acrosomal enzymes break down barriers surrounding the ovum.
- Chemical changes around the ovum allow only one sperm to penetrate the ovum.

A blastocyst implants in the endometrium.

- It does this by the action of trophoblastic enzymes.
- The zygote (fertilized egg) forms a morula by mitosis. This occurs in the oviduct.
- The morula descends into the uterus, living for three or four days. The secretory phase of the uterus is preparing the lining of the uterus for possible implantation.
- The morula continues to divide, forming a blastocyst. This is a single-layered ball of cells. Its outer trophoblast accomplishes implantation. The fluid-filled blastocoele of the blastocyst will become the amniotic sac.
- The cells of the trophoblast secrete enzymes that digest proteins on the uterine lining. This carves a hole in the endometrium for implantation.
- The endometrium undergoes additional changes to support the developing embryo. These include increase nutrient storage and increased vascularization.

The placenta is the organ of exchange between the maternal and fetal blood.

- It is derived from trophoblastic and decidual tissue.
- The development of the placenta involves many changes. Maternal and fetal structures interlock.
- Fingerlike projections of the chorionic tissue form placental villi. They extend into the maternal blood.
- Fetal capillaries branch off an umbilical artery and project into the placental villi. Fetal and maternal blood are separated here by a thin chorionic layer that forms the placental villi.
- An exchange can occur between the maternal and fetal blood. The fetal blood leaves through an umbilical vein.
- Maternal blood exists through maternal venules.
  - **See Figure 20-26**

Hormones secreted by the placenta play an important role in the maintenance of pregnancy.

- This is a summary of some of the hormones and their efffects.
- hCG maintains the corpus luteum of pregnancy.
- Estrogen stimulates the growth of the myometrium, strengthening it for partuition.
- Progesterone suppresses uterine contractions.
- Relaxin softens the cervix to prepare it for cervical dilation at partuition.
- Placental PTHrp increases plasma calcium ions in the maternal blood.
- Overall the maternal body systems respond to the increased demands of gestation. The changes include uterine enlargement and an increase in the amount of blood.

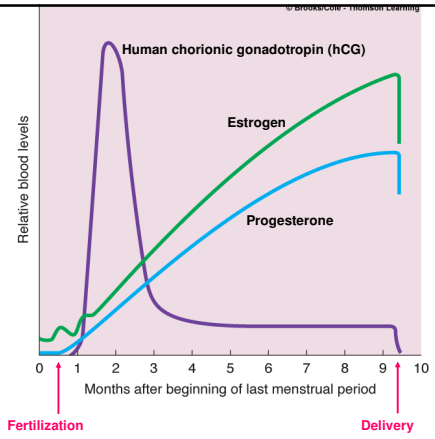

Figure 20.27
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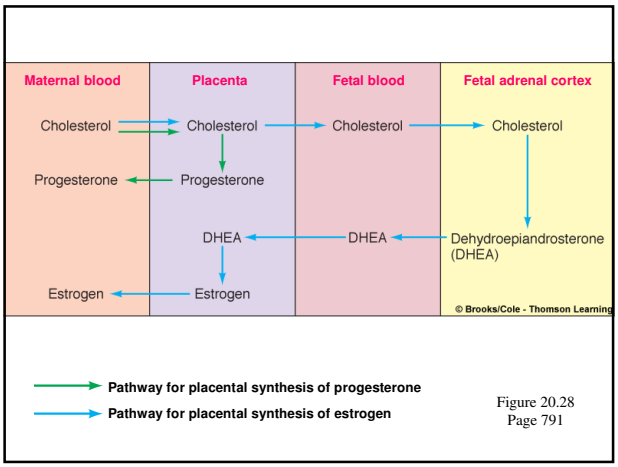

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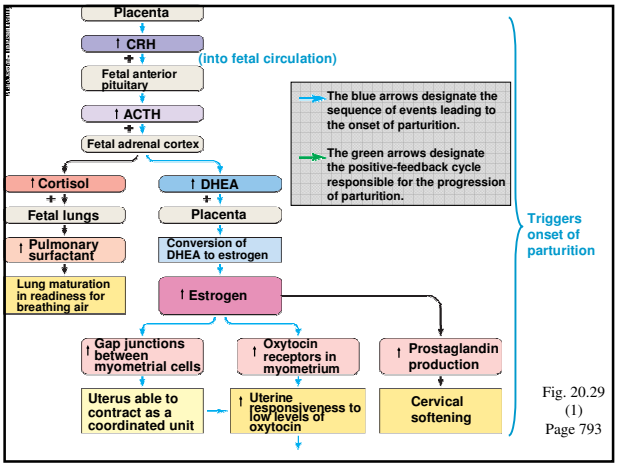

Fig. 20.29
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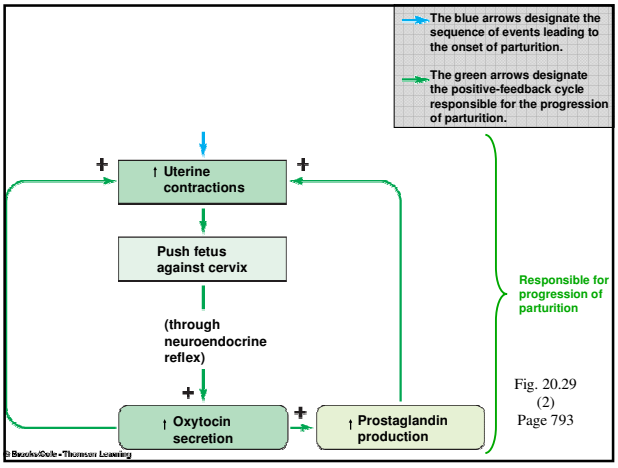

Fig. 20.29
(2)
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Changes in later gestation prepare for partuition.

- Partuition is birth. During the last trimester the uterus becomes more excitable. Mild contractions occur.
- The cervix begins to soften near partuition.
- The fetus shifts downward, with its head contacting the cervix.
- Rhythmic contractions begin at the onset of labor. There are high levels of estrogen at this time.
- Factors triggering the onset of parturition are not well understood.
- Oxytocin plays a key role as labor progresses. It is a powerful muscle stimulant.
- CRH plays a major role. It drives the manufacture of placental estrogen. It also promotes changes in the fetal lungs.

Partuition is accomplished by a positive feedback cycle.

- As labor proceeds the uterine contractions become more frequent and powerful. Continued dilation of the cervix triggers the release of more and more oxytocin.
- Labor occurs over three stages. The first stage is cervical dilation.
- The second stage is the birth of the baby. This occurs when cervical dilation is complete.
- After the birth of the baby a second series of uterine contractions separates the placenta from the myometrium and expels it through the vagina. This is the third stage.
- After delivery involution of the uterus occurs.

Lactation requires multiple hormonal inputs.

- High estrogen secretion promotes extensive duct development in the breasts. Progesterone stimulates alveolar-lobular development. Prolactin also contributes to mammary gland development.
- An abrupt decline in estrogen and progesterone with the loss of the placenta initiates lactation.
- Prolactin promotes milk secretion. Oxytocin induces milk ejection.
- Breast-feeding has advantages for the infant. These include an abundance of immune cells and many substances such as lactoferrin.
- There are also advantages of breast-feeding for the mother. Oxytocin release hastens involution of the uterus.
- There is a cessation of production at weaning.