9. Reproduction

The sexual differences between male and female depend ultimately on differences in their chromosomes. In most mammalian species the female has two X sex chromosomes while the male has one X and one Y sex chromosome, in addition to their autosomal chromosomes (22 pairs in humans). It is possible to determine the sex-chromosomal pattern by laboratory examination of cell smears since the female pattern can be conveniently recognized by the presence of an extra piece of chromatin called the 'sex chromatin' or 'Barr's body'. Sex-chromosome abnormalities, such as XXY (Klinefelter's syndrome) and XO (Turner's syndrome), result in incomplete development of the gonads. The XXX ('superfemale') pattern, however, does not seem to bee characterized by abnormal sexual development.

A fundamental difference between the female and the male is that the former undergoes obvious cyclic variations in reproductive activity. *Female* mammals have an *ovarian cycle* with a characteristic mean frequency for each species, i.e., 4 days in rats and 28 days in women. In women and in some other primates the cycle is marked by a period of menstrual bleeding, which is due to the shedding of the endometrial lining of uterus. Other female mammals do not menstruate although they show a phase called *oestrus*, or 'heat' as it is commonly known, when the female becomes receptive to the male just before ovulation. In some species, i.e., the cat and rabbit, ovulation is triggered by copulation. In most mammals, however, ovulation is regulated by an intrinsic rhythm controlled by interactions between the hypothalamus, pituitary and gonads.

9.1 Sexual Development

In humans the 'indifferent' gonads of both sexes are identical until differentiation begins at about the sixth week of fetal life. In the genetic male the *testes* form and begin to secrete the hormone testosterone; in the genetic female the *ovaries* develop more slowly. At this stage the fetus has primordial genital ducts for both the male (*Wolffian ducts*) and the female (*Mullerian ducts*). In the genetic male the Wolffian ducts develop to form the male internal genitalia and the Mullerian ducts regress; in the genetic female the opposite happens. The external genitalia are similarly bipotential at this stage. The development of male or female genitalia appears to depend on the presence or absence of testosterone and a protein called Mullerian-inhibiting factor (MIF). In the genetic male androgens stimulate the development of Wolffian ducts and MIF inhibits the development of the Mullerian ducts. Androgens also induce male differentiation of the external genitalia. In the absence of these factors female genitalia develop.

The secretion of testosterone and MIF is not all that is required for the development of the male phenotype. The tissues must have the necessary androgen receptors to respond. Otherwise a defect known as *testicular feminization* (androgen-insensitivity syndrome) will result in which genetic males appear as phenotypic females with abdominal testes. Moreover, some fetal tissues require testosterone for differentiation and some, i.e., the prostate and the penis, require dihydrotestosterone. The conversion of testosterone to dihydrotestosterone in such tissues requires the presence of the enzyme, 5 alpha-reductase. In *5 alpha-reductase deficiency* the affected males at birth have testes, but lack a prostate gland, and their external genital organs resemble those of the female. Another defect caused by an inborn error of

metabolism is *congenital adrenal hyperplasia* which is associated with masculinization of the female fetus.

After birth reproductive development is dormant until *puberty* when the reproductive organs in both sexes are reactivated. This coincides with accelerated growth of the body and the development of the *secondary sexual characteristics.* The onset of puberty usually occurs at about 13 years of age in both boys and girls, although this may vary considerably depending on genetic and environmental influences. Puberty is signified by the *menarche* or first menstrual bleeding in the female and by the first ejaculation in the male. At about 50 years of age in women the *menopause* occurs: the ovary ceases to respond to gonadotrophins, the sexual cycles gradually disappear and menstruation eventually stops. In contrast the production of sperm in males continues throughout life although it may gradually diminish.

9.2 The Male Reproductive System

The *primary* reproductive organs or gonads of the mal are the *testes* which produce *spermatozoa* and also secrete the male sex hormone, *testosterone.* In addition there are the *accessory* reproductive ducts and secretory glands (*seminal vesicles, prostate gland and bulbouretral glands*) which are involved in the transport and delivery of spermatozoa to the female. A few weeks before birth the two developing testes pass out of the abdominal cavity into the scrotal sac. Failure of either or both testes to descend into the scrotum (*cryptorchidism*) may result in infertility because production of spermatozoa (*spermatogenesis*) depends on a temperature about 4°C below body temperature. The scrotum can contract or relax to move the testes closer to or further away from the body so that this temperature can be maintained.

Spermatogenesis

Spermatozoa are produced in the *seminiferous tubules* of the testes. These tubules are lined with maturing spermatozoa and also with *Sertoli cells* which appear to provide nutrients for the developing spermatozoa. In response to gonadotrophic hormones released by the anterior pituitary, spermatogenesis is initiated at puberty and occurs continuously thereafter. Germinal cells called *spermatogonia* divide to form *primary spermatocytes* which undergo meiosis to form *secondary spermatocytes.* During meiosis there is a reduction in the number of chromosomes from 46 to 23. The haploid secondary spermatocytes then divide to form *spermatides* which differentiate to give rise to the *spermatozoa*. The process of spermatogenesis from spermatogonium to release of spermatozoa into the lumen of the seminiferous tubule takes about 75 days.

When spermatozoa are released into the seminiferous tubules, they are non-motile and incapable of fertilizing an ovum. From the seminiferous tubules spermatozoa pass into the *epididymis* where they mature and are stored until ejaculation takes place. The production of spermatozoa is a continuous process and spermatozoa not ejaculated eventually deteriorate and are reabsorbed by phagocytosing epididymal cells.

The *mature sperm* consists of a head, middle piece and long tail. The head is composed mainly of the nucleus and is covered by a cap known as the *acrosome.* Thee

acrosome contains lytic enzymes which may enable the sperm to penetrate the ovum. The middle piece consists of helical sheath of mitochondria surrounding a core of contractile filaments which extend into the tail. Thee mitochondria provide energy for motility of the spermatozoon which depends on a wave-like movement of the tail.

Testosterone

The principal androgenic hormone produced by the testis is *testosterone.* This steroid hormone is secreted by the *interstitial cells of Leydig* which lie scattered between the seminiferous tubules. Its synthesis is similar to the formation of androgens in the adrenal cortex. Once released into the blood it is bound to a specific carrier globulin. In some of its target tissues testosterone appears to be converted to a more potent androgen called dihydrotestosterone.

Testosterone promotes the *development of the reproductive system* and the *secondary sexual characteristics* of the male. The most obvious effects of testosterone are seen at puberty, namely, enlargement of the penis and testes, increased rate of growth of muscle and bone, appearance of facial, axillary and pubic hair, and change in the pitch of the voice. Castration or removal of the testes in childhood prevents most of these changes from occurring. Castrated males do not become bald and the presence of testosterone seems necessary for baldness to occur in males genetically predisposed to this condition. Testosterone also promotes libido or sexual drive.

Control of Male Reproductive Activity

The anterior pituitary gonadotrophic hormones - *follicle-stimulating hormone (FSH)* and *luteinizing hormone (LH)* - control respectively spermatogenesis and synthesis of testosterone. The release of the gonadotrophic hormones occurs in a pulsatile manner and is controlled by a common hypothalamic neurohormones - *luteinizing hormone releasing hormone (LHRH).* Both testosterone and FSH are necessary for normal spermatogenesis. Testosterone inhibits secretion of LH in a typical negative-feedback manner but has little effect on FSH secretion at physiological concentrations. There is evidence to suggest that *inhibin,* a protein produced in the testes, has a negative-feedback effect on secretion of FSH.

Semen

The ejaculated fluid or semen contains spermatozoa and secretions of the seminal vesicles, prostate gland and bulbourethral glands. The average volume of ejaculate in man is about 3 mL and this contains approximately 100 million spermatozoa per mL. The secretions of these accessory glands comprise the bulk of the semen and assist in the transport and nourishment of the sperm. The seminal fluid contains high concentrations of *fructose,* which serves as an energy substrate for the spermatozoa, and also high concentrations of *prostaglandins* which may increase motility of the uterus, thus promoting transport of spermatozoa in the female genital tract. Fertility depends on the quality of the semen, the two most important factors being the number and motility of the spermatozoa. A count of less than 20 million spermatozoa per mL is generally considered incompatible with fertility.

Erection

The erection of the penis, which is necessary for coitus and delivery of semen to the female, is due to the engorgement of the penis with blood. Erection may be initiated by psychic stimuli and by tactile stimulation of the glans penis. Failure of erection, i.e., *impotence,* may be due to psychological disturbances. In erection a spinal reflex arc is involved in which impulses pass along afferent nerves to integrating centres in the *sacral* spinal cord, there to initiate impulses which travel back along parasympathetic fibres. Excitation of the *parasympathetic fibres* causes *arteriolar dilatation* in the penis so that the venous sinusoids of the corpora cavernosa and corpus spongiosum become engorged with blood, thus producing an erection.

Ejaculation

This is a reflex action involving movement (*emission*) of spermatozoa and glandular secretions into the *urethra* followed by the sudden ejection of the semen from the urethra. Emission of the glandular secretions occurs in a definite sequence. During erection the secretion of the bulbourethral glands is discharged to lubricate the urethra. During ejaculation the alkaline secretion of the prostate is discharged first to neutralize the acidity of the male urethra and the vagina. This is followed by the discharge of spermatozoa and finally the secretion of the seminal vesicles is added.

Ejaculation is triggered by stimulation of tactile receptors in the glans penis causing impulses to pass along afferent nerves to centres in the *lumbar* spinal cord and initiate impulses which return along sympathetic fibres. This *sympathetic activity* leads to contraction of the smooth muscle of the epididymis, vas deferens and secretory glands propelling spermatozoa and glandular secretions into the urethra. At the same time the internal sphincter of the urethra constricts, preventing semen from entering the bladder. Contraction of the bulbospongiosus and ischiocavernosus muscles due to reflex activity in *somatic motor nerves* then leads to pulsatile emission of the seminal fluid from the urethra.

Vasectomy

This procedure, in which the vasa deferentia are cut and tied, is an effective means of contraception in the male. Spermatogenesis continues after vasectomy but without an outlet the spermatozoa degenerate and are reabsorbed in the epididymis. Since less than 10% of semen consists of spermatozoa, the volume of the ejaculate is little affected by vasectomy.

9.3 The Female Reproductive System

The *primary reproductive organs* of the female are the two *ovaries,* which produce ova and secrete sex hormones, oestrogen and progesterone. The *accessory reproductive structures* comprise the two oviducts (Fallopian tubes), the *uterus,* the *cervix* and the *vagina.*

The Ovary

The formation of germ cells or *oogonia* is completed during fetal development of the ovary. Many of the oogonia undergo the first stage of meiosis to form diploid *primary oocytes.* Others degenerate. At birth each human ovary contains approximately one million oocytes. The number surviving in both ovaries at puberty is less than about 400000 and continues to decline so that at the time of menopause few viable cells remain. Although the first stage of meiosis occurs before birth, it is not until ovulation that meiosis is completed with the formation of the haploid *secondary oocyte.* In this process most of the cytoplasm is retained by the oocyte and a smaller rudimentary cell called the first polar body is split off. After a second division during passage in the oviduct, a second polar body is eliminated and the mature *ovum* is formed.

In the ovary the primary oocytes are arranged in *primary follicles.* Each primary follicle consists of an oocyte surrounded by a single layer of *granulosa cells.* From puberty onwards, in response to the gonadotrophic hormones, FSH and LH, several follicles begin to develop during each cycle but normally only one of these reaches the stage of ovulation. The rest degenerate. Only about 400 of the primary follicles develop into ova during the reproductive life of a woman. As a follicle matures the granulosa cells proliferate and secrete mucopolysaccharides which form a translucent halo called the *zona pellucida* around the oocyte. Soon after, the developing follicle becomes surrounded by a capsule of ovarian tissue made up of an inner cellular layer, the *theca interna,* and a more fibrous outer layer, the *theca externa.* With further maturation fluid accumulates amongst the granulosa cells to form a central cavity filled with fluid called the *antrum.* In the mature *Graafian follicle* the oocyte embedded in a mass of granulosa cells protrudes into the antrum. Up to this time oestrogens, secreted mainly by the cells of the theca interna and also by the granulosa cells, comprise the bulk of the hormones liberated by the ovary. About the middle of the ovarian cycle, ovulation occurs: the follicle ruptures and the secondary oocyte together with its surrounding granulosa cells is extruded into the peritoneal cavity. It is then swept by the movement of the cilia into the open end of the oviduct which is closely applied to the ovary.

After ovulation, the granulosa cells remaining in the ruptured follicle, together with cells of the theca interna, proliferate to form a new endocrine structure, the *corpus luteum.* This goes on secreting oestrogen but also produces the hormone *progesterone.* The corpus luteum is functional for about 12 days after ovulation. Thereafter, unless fertilization of the ovum and implantation have occurred, the corpus luteum regresses, causing a decline in the secretion of oestrogen and progesterone, the onset of menstruation and the initiation of a new cycle of ovarian activity.

Gonadotrophic Hormones

Maturation of follicles in the ovary requires the presence of the *gonadotrophic hormones, FSH* and *LH,* which is secreted by the anterior pituitary. The secretion of both gonadotrophic hormones is stimulated by LHRH, also known as gonadotrophin-releasing hormone. LHRH is produced in the medial basal area of the hypothalamus and is released in a pulsatile manner with a periodicity of 1-4 h.

FSH and LH are glycoproteins and each can be dissociated into two subunits called alpha and beta. The alpha subunits of FSH and LH are identical in structure and specificity is determined by the beta subunit. Their actions are mediated by cyclic AMP. FSH, together with LH, promotes *development of the follicle* and LH is needed for the *secretion of oestrogen* by the ovary. The sudden peak in the LH secretion of mid-cycle appears to be responsible for *triggering ovulation.* Ovulation can be induced in infertile women by treatment with gonadotrophic extracts from the pituitary or urine. To be effective, such extracts must contain FSH for follicular development and LH for the production of oestrogen and ovulation. LH is also required for normal corpus luteum function.

Menstrual Cycle

The average length of the menstrual cycle is 28 days but it may vary considerably. The first signs of bleeding signal the start of a new menstrual cycle and bleeding may continue for 3 to 5 days. During this period the *ovarian follicles* begin to develop and secrete increasing quantities of *oestrogen.* Oestrogen acts on the uterus to stimulate regeneration and growth of the *endometrium* from the remnants left over from the previous menstrual cycle, causing a two- or three-fold increase in the thickness of the endometrium. The first 2 weeks of the menstrual cycle are therefore referred to as the *follicular phase* with respect to the ovary and as the *proliferative phase* with respect to the uterus. The variation that occurs in the duration of the menstrual cycle is usually due to variation in the first half of the reproductive cycle. Ovulation occurs at about the mid-point of the cycle, i.e., around day 14.

During the second half of the reproductive cycle the *corpus luteum* develops and secretes both *oestrogen* and *progesterone.* Oestrogen continues to promote proliferative activity in the endometrium while, under the action of progesterone, the endometrial glands become distended with secretory products including *glycogen*, which is an important nutrient for he developing embryo should implantation take place. Endometrial blood flow increases and the spiral arteries become more tightly coiled and twisted. The second half of the cycle is therefore referred to as the *luteal phase* with respect to the ovaries and as the *secretory phase* with respect to the uterus. If implantation does not occur, the corpus luteum regresses, there is a rapid fall in secretion of oestrogen and progesterone and, for reasons which are unclear, the endometrium undergoes shrinkage due to the loss of extracellular water and constriction of spiral arteries. This causes a reduction in blood flow to the endometrium with cell death and weakening of the walls of blood vessels. As the phase of vasoconstriction wears off, blood leaks from the damaged vessels to initiate *menstrual bleeding* and eventually all but the basal layer of endometrium is detached from the uterus. A second phase of vasoconstriction of the spiral arteries minimizes loss of blood from the arteries.

Ovarian Hormones: Oestrogen and Progesterone

Oestradiol is the main oestrogen and progesterone the main progestin produced in the ovary. Oestrone is also secreted in significant amounts but its biological activity is less than that of oestradiol. These steroid hormones are transported in the blood bound to plasma proteins. They are degraded in the liver and their metabolites ar excreted by the kidney. Like other steroid hormones, oestrogen and progesterone are thought to cause their effects in responsive tissues by combining with cytoplasmic receptors in cells to be translocated to the

nucleus to induce increased production of messenger RNA with subsequent increase in synthesis of the effector proteins.

Oestrogen is secreted by the theca interna and the granulosa cells of the follicles and is also produced after ovulation by the corpus luteum. The peak of LH that occurs at ovulation is preceded by a rise in oestrogen secretion which is thought to stimulate LH secretion, i.e., a high level of oestrogen has a *positive-feedback* effect on LH (and FSH) secretion at this point in the cycle. During the secretory phase of the menstrual cycle, oestrogen and progesterone exert a *negative-feedback* effect on the secretion of the *gonadotrophic hormones.* It is now believed that the primary site of the positive and negative feedback actions of oestrogen is the pituitary, although it is likely that the hypothalamus is also a site of action. The negative-feedback effect diminishes as the concentrations of oestrogen and progesterone fall with regression of the corpus luteum.

In addition to its positive and negative effects on gonadotrophin secretion, oestrogen:

(i) sensitizes the ovaries to the effects of gonadotrophins;

(ii) stimulates growth of the endometrium and contractility of the myometrium:

(iii) stimulates the output of mucus from the cervical glands and causes changes in the properties of the mucus which assist entry of spermatozoa;

(iv) causes the vaginal epithelium to proliferate and show increased cornification;

(v) stimulates the growth and development of breasts, particularly of the lactiferous ducts;

(vi) promotes the growth of bones and skeletal muscle and helps to bring about the characteristic female patterns of distribution of body hair and adipose tissue;

(vii) promotes closure of the epiphyses at the end of the period of linear skeletal growth.

Progesterone, which is present in significant amounts only during the luteal phase of each menstrual cycle, acts on tissues which have already been stimulated by oestrogen. In addition to having inhibitory effects on gonadotrophin secretion and follicular development during the luteal phase, progesterone:

(i) transforms the endometrium to its secretory phase and decreases the spontaneous electrical activity of the myometrium;

(ii) modifies the composition of cervical mucus, making it more viscous and resistant to penetration by spermatozoa;

(iii) causes further changes in the vaginal epithelium with regression of cornification;

(iv) promotes development of the breasts, particularly of the secretory units; and

(v) causes an increase in basal body temperature after ovulation, which may be useful clinically to indicate that ovulation is occurring.

Control of the Female Reproductive Cycle

The blood levels of the gonadotrophic and ovarian hormones throughout the ovarian cycle are shown in the figure. A marked peak in the level of gonadotrophins occurs at the mid-point of the menstrual cycle and coincides with the time of ovulation. Because it is difficult to pin-point the time of ovulation, it has been standard practice to designate the peak in blood LH as day zero in the cycle. Just before the beginning of each cycle there is a small rise in FSH. This rise in FSH stimulates follicular development and, together with LH, leads to an increase in oestrogen secretion. Oestrogen plays an important role in the maturation process because it sensitizes the granulosa cells, and perhaps the theca interna cells, to the effects of gonadotrophins and thus increases their capacity to produce more oestrogen. The surge in oestrogen secretion that occurs just prior to ovulation has a positive-feedback effect on the anterior pituitary, and possibly the hypothalamus, causing a marked rise in LH and FSH secretion. The peak in LH secretion triggers ovulation. After ovulation the increase in oestrogen and progesterone that parallels the development of the corpus luteum prepares the endometrial lining of the uterus for implantation. If implantation does not occur, the levels of oestrogen and progesterone fall in parallel with the demise of the corpus luteum. The fall in ovarian hormone causes menstruation to occur and also removes the negative-feedback influence on the secretion of the gonadotrophic hormones. The resultant rise in output of FSH triggers development of a new batch of follicles and the beginning of a new cycle of uterine and ovarian function.

Hormonal Contraception

The oral contraceptive pill is a very effective means of preventing pregnancy. Hormonal contraception is the outcome of research into the negative-feedback effects of the sex hormones. However, natural oestrogens and progestins are not effective when taken orally, and it was not until the development of synthetic oestrogens and progestins that hormonal contraception was widely adopted. The most commonly used contraceptive pill is a combination of synthetic oestrogen and progestin taken daily but withdrawn towards the end of the month. It acts primarily through feedback inhibition of FSH and LH secretion to suppress follicular development and ovulation. Preparations containing progestin also produce changes in the cervical secretions making it more difficult for sperm to penetrate the uterus. This appears to be the main basis of action of the progestin-only contraceptive which is not withdrawn and is administered continuously, either orally, or by the slow release of hormone from a vaginal suppository or intramuscular injection.

Hyperprolactinaemia

Prolactin is required in mammals for breast development and lactation. In some rodents it prolongs the life of the corpus luteum and so has been called luteotrophic hormone. It may also play a normal role in reproductive activity in humans, as suggested in clinical studies of hyperprolactinaemia due for example to a pituitary tumour. In these studies it was found that elevated prolactin levels caused infertility and amenorrhoea in women and impotence in men. The mechanism of this action is unknown.

Pineal Gland

This gland, situated in the centre of the brain, secretes the hormone *melatonin.* In experimental animals the administration of melatonin inhibits ovulation by preventing the release of LHRH and consequently LH. In some mammals the secretion of melatonin fluctuates in relation to light (and hence day length) and so it is thought that the pineal gland plays a role in determining the seasonal breeding patterns of such animals.

Melatonin is synthesized from serotonin and its synthesis is controlled by the enzyme hydroxyindole-O-methyltransferase (HIOMT). Light suppresses the synthesis of this enzyme in those animals in which there is a 24 h (circadian) rhythm of melatonin release. Light energy is transduced to nerve impulses in the eye and relayed by a complex pathway to the spinal cord and thence to the pineal gland via sympathetic nerve fibres relaying in the superior cervical ganglion. The release of noradrenaline by these postganglionic sympathetic fibres during daylight suppresses the synthesis of HIOMT and hence of melatonin.

The pineal gland may also play a role in reproductive activity in man. Hypersecretion of melatonin due to a pinealoma can suppress gonadal activity and delay the onset of puberty. Conversely, hyposecretion of melatonin may lead to early sexual maturity.

9.4 Pregnancy

The duration of pregnancy (or gestation) in women is approximately 40 weeks from the last menstruation. Sperm can survive for a few days in the female reproductive tract. The ovum remains fertile for less than a day. Therefore, fertilization can occur if sperm are deposited in the female reproductive tract a few days before ovulation. Sperm need to spend some period of time in the female reproductive tract before they are capable of fertilizing the ovum. This process is known as *capacitation* of the sperm. Only one of the many hundreds of thousands of sperm deposited in the vagina can fertilize the ovum.

Fertilization occurs in the oviduct and the *zygote* begins to divide as it makes its way to the uterus. By the time (about 3 days) it reaches the uterus it is a small mass of cells called a *morula.* Identical twins may arise if the morula separates into two parts during this stage. The morula develops into the *blastocyst* which is composed of an outer layer of trophoblastic cells separated from an inner mass of embryonic cells. The *trophoblastic layers* forms part of the *chorion* which gives rise to the fetal part of the placenta. *Implantation* of the blastocyst in the uterine wall occurs about 7 days after fertilization.

At about 9 days after fertilization the trophoblastic layer begins to secrete the hormone, *human chorionic gonadotrophin (HCG).* HCG prolongs the life of the corpus luteum so that it continues to secrete oestrogen and progesterone which are necessary for the continuation of pregnancy during the first trimester. Thereafter, the role of the corpus luteum is supplanted by the placenta. The *placenta* is not only a means for exchanging respiratory gases, nutrients and waste products between fetal and maternal circulations, it also serves as an *endocrine gland* in its own right. The placenta secretes both protein and steroid hormones necessary for the continuation of pregnancy during the second and third trimesters.

Placental Hormones

The placenta secretes at least *five* hormones. Three of these hormones are *proteins,* namely *human chorionic gonadotrophin (HCG), human placental lactogen (HPL)* and *human placental thyrotrophin,* while two are *steroids,* namely *oestrogen* and *progesterone.* The maternal plasma levels of HCG, oestrogen and progesterone during pregnancy are shown in the figure.

Human chorionic gonadotrophin (HCG). It is a glycoprotein (MW 30000) secreted by the trophoblastic cells of the placenta. It is chemically and biologically similar to LH. It is secreted in large quantities during the first trimester and its main role is to maintain the corpus luteum during the early part of pregnancy. Since HCG is secreted as early as 9 days after fertilization, its detection by radioimmunoassay provides a simple test for pregnancy.

Human placental lactogen (HPL). It is a protein (MW 18500) also secreted by trophoblastic cells. It is structurally similar to human growth hormone. The level of HPL in the maternal circulation increases steadily throughout pregnancy but its functions are not well defined. It has a diabetogenic action, promoting maternal lipid mobilization and inhibiting glucose uptake. As its name implies it also promotes mammary development in preparation for lactation.

Human placental thyrotrophin. This is a glycoprotein that is chemically similar to pituitary thyroid-stimulating hormone. Its physiological role in pregnancy is not understood.

Progesterone. During pregnancy the maternal plasma levels of progesterone reach a peak 3-4 weeks after fertilization and then decline before increasing up until the time of parturition. The initial peak reflects the development of the corpus luteum and the later rise is due to secretion by the placenta. Progesterone is required throughout pregnancy to maintain the endometrium and to suppress spontaneous contractions of the myometrium of the uterus. Progesterone also stimulates the development of the mammary glands.

Oestrogen. Several oestrogens, namely oestradiol, oestrone and oestriol, are secreted by the placenta. Oestriol is secreted in the greatest amounts. The maternal plasma levels of this hormone are shown in the figure. The placenta cannot form the precursor steroid, 17-hydroxyprogesterone, and thus depends on the availability of steroid precursors synthesized by the fetus. Thus the fetus and the placenta complement each other in the synthesis of oestrogen and are said to function as the *fetoplacental unit.* This is important clinically because it is possible to monitor the well-being of the fetus by measuring the maternal levels of oestrogen. Although the total plasma levels of oestrogen may increase some fifty-fold during pregnancy, the levels of free oestrogen are not greatly increased because of a corresponding rise in the sex hormone-binding globulin. Oestrogen is required during pregnancy for the uterus to develop to accommodate the growing fetus and also for the development of the mammary glands.

Parturition

The exact trigger for parturition in women has not been established. A fall in *progesterone* secretion would be expected to enhance uterine contractions but such a fall does not appear to take place immediately prior to delivery. An increase in *oxytocin* release would likewise be expected to stimulate uterine contractions. Oxytocin is indeed released at parturition in response to stimulation of stretch receptors in the uterus and cervix and is used clinically to induce labour. Nevertheless, parturition can still be initiated in women with hypothalamic damage who lack oxytocin. *Prostaglandins* will also induce labour but again there is insufficient evidence that they provide the trigger for parturition in women. In sheep, however, it has been established that the fetus determines thee time of delivery by increasing its release of ACTH and hence cortisol. The increase in fetal cortisol secretion causes a change in placental steroid synthesis that somehow initiates uterine contractions through the release of prostaglandins.

Towards the end of pregnancy *relaxin*, a polypeptide hormone, can be extracted from the ovary, uterus and placenta. Relaxin and other similar polypeptides appear to play a role in parturition by promoting relaxation of the birth canal.

Lactation

Mammary glands provide both milk for nourishment and antibodies for protection of the young. Milk is produced by epithelial cells lining the alveoli which drain into slender ducts. *Development of the alveoli and ducts* require the presence of several hormones - *oestrogen, progesterone, growth hormone, cortisol and insulin.* During the latter part of pregnancy *prolactin* is required for *full maturation of the mammary glands and milk production.* The initiation of copious lactation occurs shortly after parturition, although the reason for this is not fully understood. While prolactin stimulates milk production, *milk let-down* depends on the release of *oxytocin* which is induced by suckling. Suckling is also necessary for the continued release of prolactin because it stimulates nerve endings in the nipples which in turn send impulses to the hypothalamus that inhibit the release of prolactin-inhibiting factor. In the absence of suckling, prolactin secretion is reduced and lactation ceases. The suckling stimulus also inhibits secretion of gonadotrophins and this presumably accounts for the suppression of ovulation that often occurs in nursing women.