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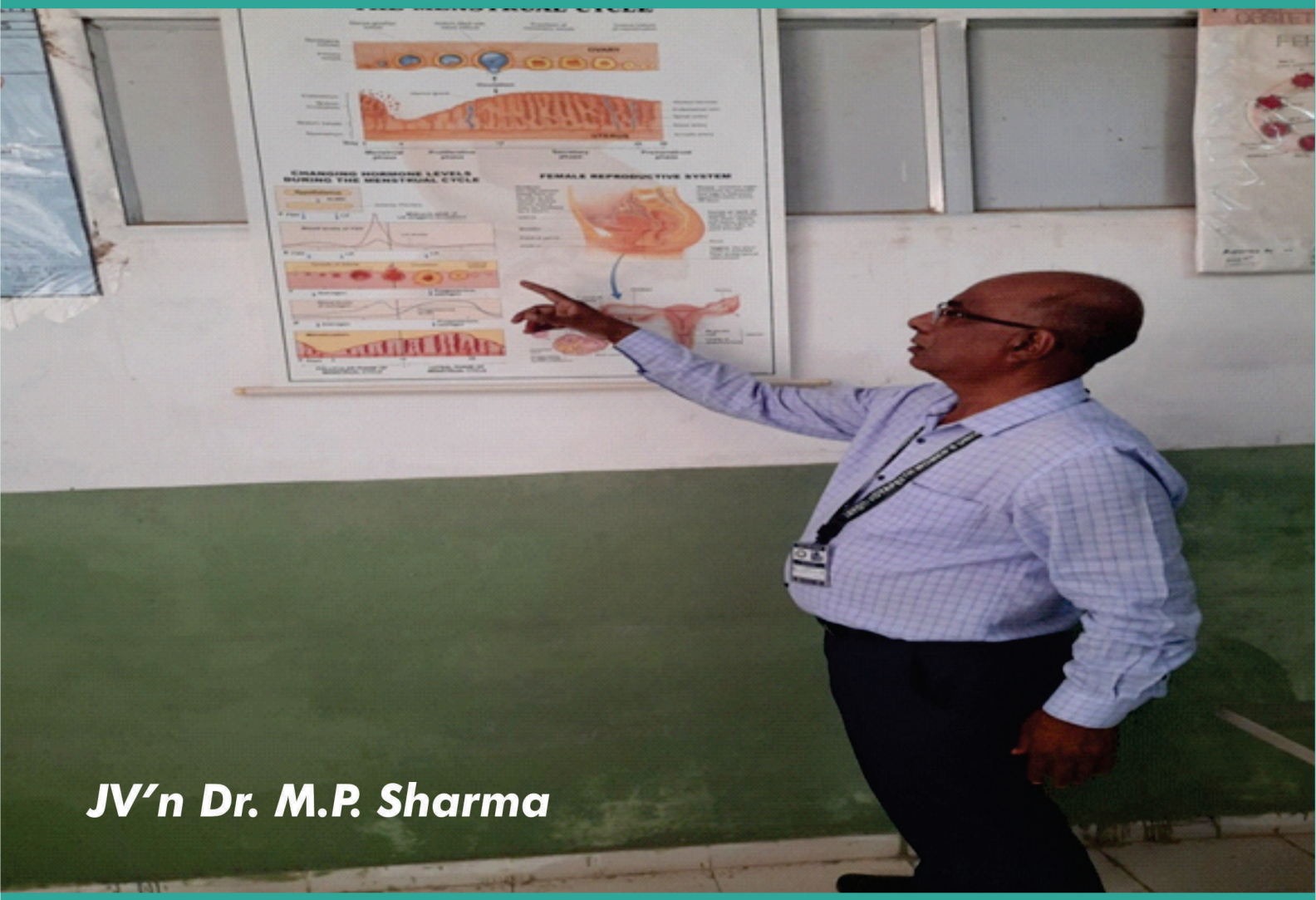
A HANDBOOK OF FEMALE REPRODUCTIVE SYSTEM



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FEMALE REPRODUCTIVE SYSTEM

INTRODUCTION-

The female reproductive system is framed to perform different functions. It creates egg cells that are essential for reproduction known as ova. The system is organized to deliver the ova to the region of fertilization. The egg fertilization takes place in the Fallopian tubes along with the sperm. The implanting in the walls of the uterus and initiating the stages of pregnancy is the next step of fertilized eggs. Apart from the above-mentioned functions, the female reproductive system is also involved in the production of female sex hormones to maintain the reproductive cycle.

The female reproductive system is composed of a pair of ovaries along with oviducts, vagina, cervix, uterus, and the external genitalia that are located in the pelvic region. These parts along with a pair of mammary glands that are integrated both functionally and structurally also support the process of ovulation, fertilization, birth and finally the child care.

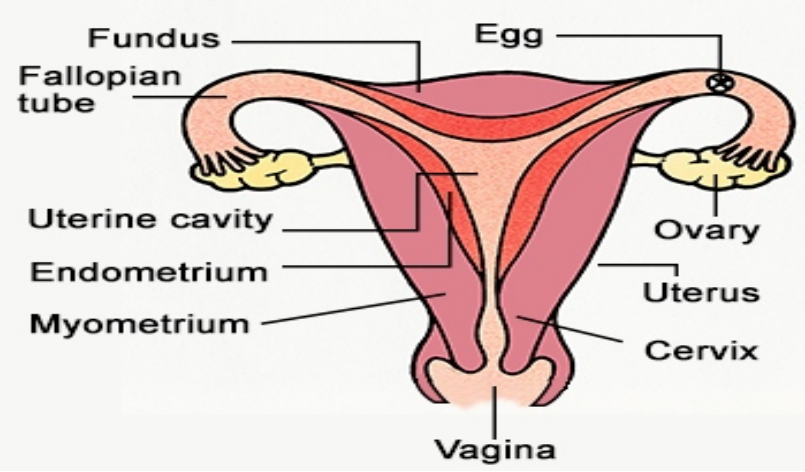
Physiology of female reproductive system-

The **female reproductive system** is made up of the internal and external sex organs that function in reproduction of new offspring. In humans, the female reproductive system is immature at birth and develops to maturity at puberty to be able to produce gametes, and to carry a foetus to full term. The internal sex organs are the uterus, Fallopian tubes, and ovaries. The uterus or womb accommodates the embryo which develops into the foetus. The uterus also produces vaginal and uterine secretions which help the transit of sperm to the Fallopian tubes. The ovaries produce the ova (egg cells). The external sex organs are also known as the genitals and these are the organs of the vulva including the labia, clitoris, and vaginal opening. The vagina is connected to the uterus at the cervix.

At certain intervals, the ovaries release an ovum, which passes through the Fallopian tube into the uterus. If, in this transit, it meets with sperm, a single sperm (1-cell) can enter and merge with the egg or ovum (1-cell), fertilizing it into a zygote (1-cell).

Fertilization usually occurs in the Fallopian tubes and marks the beginning of embryogenesis. The zygote will then divide over enough generations of cells to form a blastocyst, which implants itself in the wall of the uterus. This begins the period of gestation and the embryo will continue to develop until full-term. When the foetus has developed enough to survive outside the uterus, the cervix dilates and contractions of the uterus propel the newborn through the birth canal (the vagina).

Vulva- The vulva consists of all of the external parts and tissues and includes the mons pubis, pudendal cleft, labia majora, labia minora, Bartholin's glands, clitoris, and vaginal opening.



Internal organ

Vagina

Main article: Vagina

The vagina is a fibromuscular (made up of fibrous and muscular tissue) canal leading from the outside of the body to the cervix of the uterus or womb. It is also referred to as the birth canal in the context of pregnancy. The vagina accommodates the male penis during sexual intercourse. Semen containing spermatozoa is ejaculated from the male at orgasm, into the vagina potentially enabling fertilization of the egg cell (ovum) to take place.

Cervix

The cervix is the neck of the uterus, the lower, narrow portion where it joins with the upper part of the vagina. It is cylindrical or conical in shape and protrudes through the upper anterior vaginal wall. Approximately half its length is visible, the remainder lies above the vagina beyond view. The vagina has a thick layer outside and it is the opening where the fetus emerges during delivery.

Uterus

The uterus or womb is the major female reproductive organ. The uterus provides mechanical protection, nutritional support, and waste removal for the developing embryo (weeks 1 to 8) and fetus (from week 9 until the delivery). In addition, contractions in the muscular wall of the uterus are important in pushing out the fetus at the time of birth.

The uterus contains three suspensory ligaments that help stabilize the position of the uterus and limits its range of movement. The uterosacral ligaments keep the body from moving inferiorly and anteriorly. The round ligaments restrict posterior movement of the uterus. The cardinal ligaments also prevent the inferior movement of the uterus.

The uterus is a pear-shaped muscular organ. Its major function is to accept a fertilized ovum which becomes implanted into the endometrium, and derives nourishment from blood vessels which develop exclusively for this purpose. The fertilized ovum becomes an embryo, develops into a fetus and gestates until childbirth. If the egg does not embed in the wall of the uterus, a female begins menstruation.

Fallopian tube

The Fallopian tubes are two tubes leading from the ovaries into the uterus. On maturity of an ovum, the follicle and the ovary's wall rupture, allowing the ovum to escape and enter the Fallopian tube. There it travels toward the uterus, pushed along by movements of cilia on the inner lining of the tubes. This trip takes hours or days. If the ovum is fertilized while in the Fallopian tube, then it normally implants in the endometrium when it reaches the uterus, which signals the beginning of pregnancy. The fallopian tubes made up of cillated columnar epithelium tissues

Ovaries

The ovaries are small, paired organs located near the lateral walls of the pelvic cavity. These organs are responsible for the production of the egg cells (ova) and the secretion of hormones. The process by which the egg cell (ovum) is released is called ovulation. The speed of ovulation is periodic and impacts directly to the length of a menstrual cycle.

After ovulation, the egg cell is captured by the Fallopian tube, after traveling down the Fallopian tube to the uterus, occasionally being fertilized on its way by an incoming sperm. During fertilization the egg cell plays a role; it releases certain molecules that are essential to guiding the sperm and allows the surface of the egg to attach to the sperm's surface. The egg can then absorb the sperm and fertilization can then begin The Fallopian tubes are lined with small hairs (cilia) to help the egg cell travel.

Physiology-

The reproductive tract (or genital tract) is the lumen that starts as a single pathway through the vagina, splitting up into two lumens in the uterus, both of which continue through the Fallopian tubes, and ending at the distal ostia that open into the abdominal cavity.

In the absence of fertilization, the ovum will eventually traverse the entire reproductive tract from the fallopian tube until exiting the vagina through menstruation.

The reproductive tract can be used for various transluminal procedures such as fertiloscopy, intrauterine insemination, and transluminal sterilization

Development of the reproductive system-

Chromosome characteristics determine the genetic sex of a fetus at conception. This is specifically based on the 23rd pair of chromosomes that is inherited. Since the mother's egg contains an X chromosome and the father's sperm contains either an X or Y chromosome, it is the male who determines the fetus's sex. If the fetus inherits the X chromosome from the father, the fetus will be a female. In this case, testosterone is not made and the Wolffian duct will degrade thus, the Müllerian duct will develop into female sex organs. The clitoris is the remnants of the Wolffian duct. On the other hand, if the fetus inherits the Y chromosome from the father, the fetus will be a male. The presence of testosterone will stimulate the Wolffian duct which will bring about the development of the male sex organs and the Müllerian duct will degrade.

OVARY -

The ovary is an organ found in the female reproductive system that produces an ovum. When released, this travels down the fallopian tube into the uterus, where it may become fertilized by a sperm. There is an ovary (from Latin ovarium, meaning 'egg, nut') found on each side of the body. The ovaries also secrete hormones that play a role in the menstrual cycle and fertility. The ovary progresses through many stages beginning in the prenatal period through menopause. It is also an endocrine gland because of the various hormones that it secretes

Structure

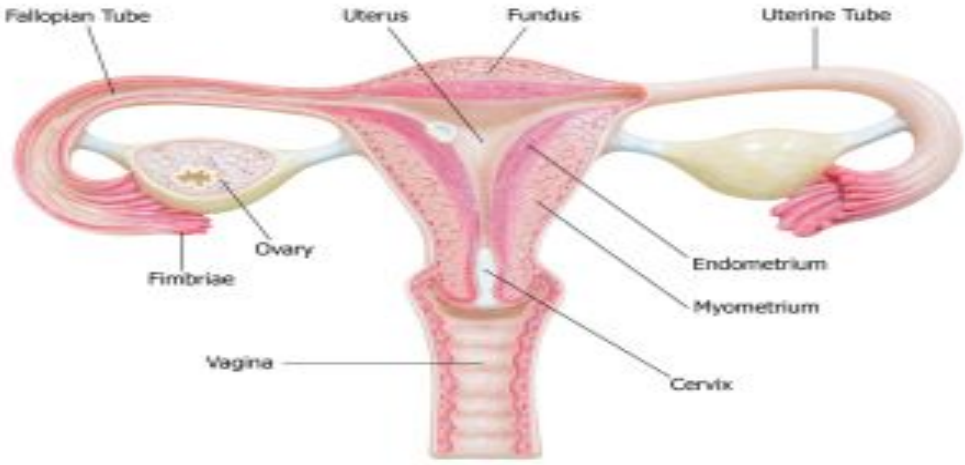
The ovaries are considered the female gonads. Each ovary is whitish in color and located alongside the lateral wall of the uterus in a region called the ovarian fossa. The ovarian fossa is the region that is bounded by the external iliac artery and in front of the ureter and the internal iliac artery. This area is about 4 cm x 3 cm x 2 cm in size.

The ovaries are surrounded by a capsule, and have an outer cortex and an inner medulla The capsule is of dense connective tissue and is known as the tunica albuginea.

Usually, ovulation occurs in one of the two ovaries releasing an egg each menstrual cycle.

The side of the ovary closest to the fallopian tube is connected to it by infundibulopelvic ligament, and the other side points downwards attached to the uterus via the ovarian ligament.

Other structures and tissues of the ovaries include the hilum.



Ligaments

The ovaries lie within the peritoneal cavity, on either side of the uterus, to which they are attached via a fibrous cord called the ovarian ligament. The ovaries are uncovered in the peritoneal cavity but are tethered to the body wall via the suspensory ligament of the ovary which is a posterior extension of the broad ligament of the uterus. The part of the broad ligament of the uterus that covers the ovary is known as the mesovarium.

The ovarian pedicle is made up part of the fallopian tube, mesovarium, ovarian ligament, and ovarian blood vessels

OVARIAN HORMONES -

The ovary is a dynamic endocrine organ. The follicle cells interact in a highly integrated manner to produce several steroid and peptide hormones. Steroidogenesis requires effectual delivery, uptake, and use of sterol by an array of steroidogenic enzymes. Steroid hormones play a central role in the reproductive system. Physiological effects of steroid hormones are mediated via their nuclear receptors that belong to a superfamily of ligand-dependent transcription factors. The two isoforms of ER and PR (α and β) are differentially expressed in different tissues, leading to tissue-specific responses. Furthermore, the differences in gene expression depend on interactions with protein cofactors, the coactivators, and corepressors. A better understanding of the effect that the cell environment has on nuclear receptors and their coregulators led to the discovery and understanding of the mechanism of action of antiestrogens and selective receptor modulators.

Virtually all steps in steroid biosynthesis require the action of LH and FSH and are influenced by endocrine, autocrine, and paracrine actions of several intraovarian peptide hormones,

growth factors, cytokines, and neuropeptides. In recent years, research has shown that these growth factors affect various cell processes, such as cytodifferentiation, mitogenesis, and apoptosis in a variety of ways. Activins, inhibins, and follistatins, members of the transforming growth factor (TGF)β (beta) family, were first discovered as gonadal peptide hormones that have actions on FSH production by pituitary gonadotropes to maintain normal reproductive axis. Follistatin also produced by the pituitary gonadotropes binds and modulates bioactivity of activin. Inhibins produced by the ovary also antagonize activin signaling via interaction with type II activin/BMP receptors and prevent the recruitment of type I receptor or via binding to betaglycans. They act along with other members of the TGFβ (beta) family, including TGFβ (beta) and a subset of BMPs and numerous growth factors (IGFs) and cytokines (interleukin 1 and 6), in concert with LH/FSH via a complex network of intracellular signaling to mediate their actions. Furthermore, another member of the TGFβ (beta) family, AMH produced by granulosa cells of early developing follicles, inhibits the FSH-induced primordial follicle growth and serves as a marker of ovarian reserve.

OVULATION -

Estrogen levels peak towards the end of the follicular phase. This, by positive feedback, causes a surge in levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). This lasts from 24 to 36 hours, and results in the rupture of the ovarian follicles, causing the oocyte to be released from the ovary.

Through a signal transduction cascade initiated by LH, proteolytic enzymes are secreted by the follicle that degrades the follicular tissue at the site of the blister, forming a hole called the stigma. The secondary oocyte leaves the ruptured follicle and moves out into the peritoneal cavity through the stigma, where it is caught by the fimbriae at the end of the fallopian tube. After entering the fallopian tube, the oocyte is pushed along by cilia, beginning its journey toward the uterus.

By this time, the oocyte has completed meiosis I, yielding two cells: the larger secondary oocyte that contains all of the cytoplasmic material and a smaller, inactive first polar body. Meiosis II follows at once but will be arrested in the metaphase and will so remain until fertilization. The spindle apparatus of the second meiotic division appears at the time of ovulation. If no fertilization occurs, the oocyte will degenerate between 12 and 24 hours after ovulation. Approximately 1-2% of ovulations release more than one oocyte. This tendency increases with maternal age. Fertilization of two different oocytes by two different spermatozoa results in fraternal twins.

The mucous membrane of the uterus, termed the functionalis, has reached its maximum size, and so have the endometrial glands, although they are still non-secretory

Disorders of ovulation are classified as menstrual disorders and include oligoovulation and anovulation:

- Oligoovulation is infrequent or irregular ovulation (usually defined as cycles of greater than 36 days or fewer than 8 cycles a year)
- Anovulation is absence of ovulation when it would be normally expected (in a post-menarchal, premenopausal female). Anovulation usually manifests itself as irregularity of menstrual periods, that is, unpredictable variability of intervals, duration, or bleeding. Anovulation can also cause cessation of periods (secondary amenorrhea) or excessive bleeding (dysfunctional uterine bleeding).

The World Health Organization (WHO) has developed the following classification of ovulatory disorders:

- WHO group I: Hypothalamic–pituitary-gonadal axis failure
- WHO group II: Hypothalamic–pituitary-gonadal axis dysfunction. WHO group II is the most common cause of ovulatory disorders, and the most common causative member is polycystic ovary syndrome (PCOS).
- WHO group III: Ovarian failure
- WHO group IV: Hyperprolactinemia

PLACENTA -

The **placenta** is a temporary organ that connects the developing fetus via the umbilical cord to the uterine wall to allow nutrient uptake, thermo-regulation, waste elimination, and gas exchange via the mother's blood supply; to fight against internal infection; and to produce hormones which support pregnancy. Placentas are a defining characteristic of placental mammals, but are also found in marsupials and some non-mammals with varying levels of development.

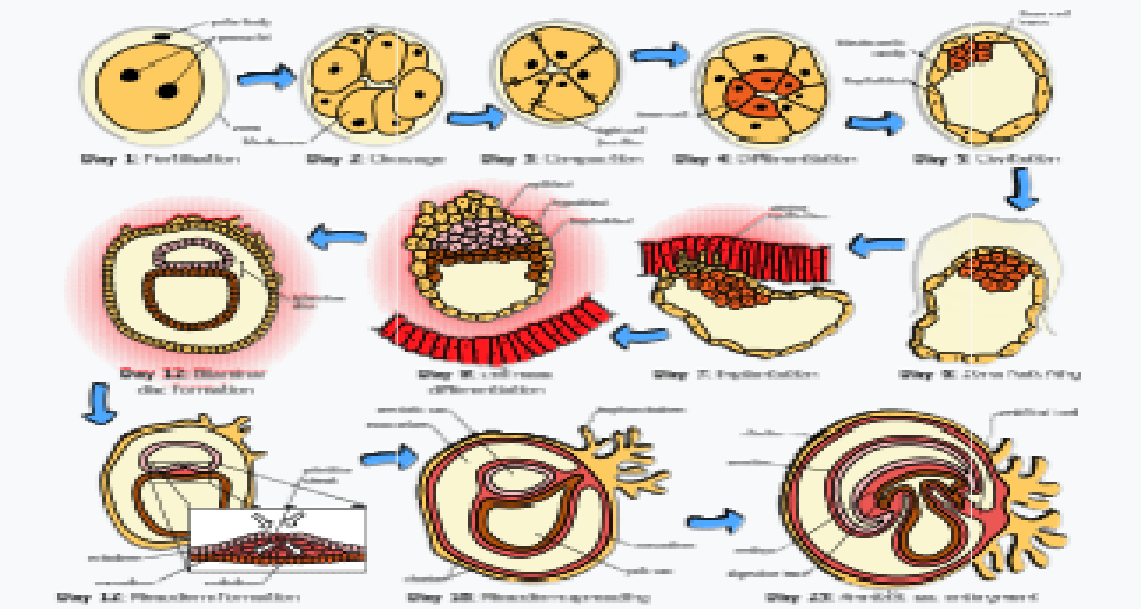
The placenta functions as a fetomaternal organ with two components: the **fetal placenta** (Chorion frondosum), which develops from the same blastocyst that forms the fetus, and the **maternal placenta** (Decidua basalis), which develops from the maternal uterine tissue. It metabolizes a number of substances and can release metabolic products into maternal or fetal circulations. The placenta is expelled from the body upon birth of the fetus.

Placentas probably first evolved about 150 million to 200 million years ago. The protein syncytin, which makes up the physical barrier between mother and baby in the syncytiotrophoblast, has a certain RNA signature in its genome that has led to the hypothesis that it originated from an ancient retrovirus: essentially a "good" virus that helped pave the transition from egg-laying to live-birth.

The word placenta comes from the Latin word for a type of cake, from Greek πλακόεντα/πλακοῦντα plakóenta/plakoúnta, accusative of πλακόεις/ πλακούς plakóeis/ plakoús, "flat, slab-like", in reference to its round, flat appearance in humans. The classical plural is placentae, but the form placenta is common in modern English and probably has the wider currency at present.

Development

Placenta



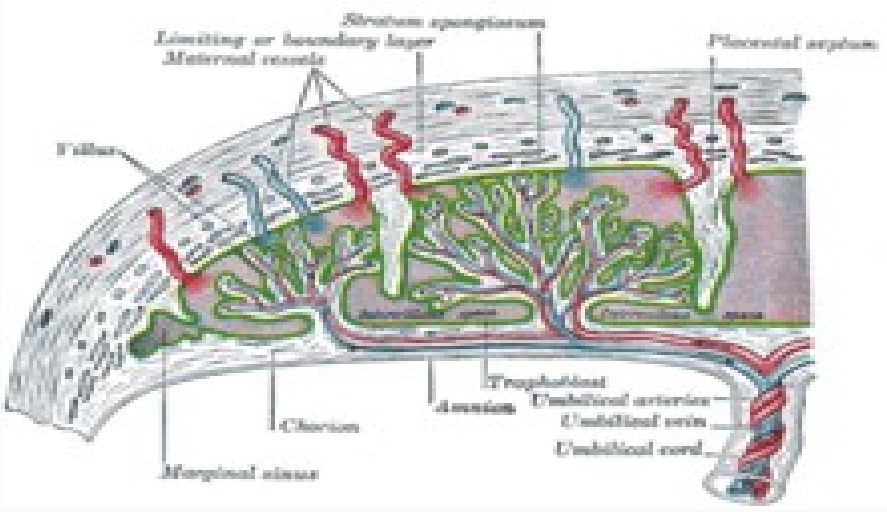
The initial stages of human embryogenesis.

Further information: Placentation

The placenta begins to develop upon implantation of the blastocyst into the maternal endometrium. The outer layer of the blastocyst becomes the trophoblast, which forms the outer layer of the placenta. This outer layer is divided into two further layers: the underlying cytotrophoblast layer and the overlying syncytiotrophoblast layer. The syncytiotrophoblast is a multinucleated continuous cell layer that covers the surface of the placenta. It forms as a result of differentiation and fusion of the underlying cytotrophoblast cells, a process that continues throughout placental development. The syncytiotrophoblast (otherwise known as syncytium), thereby contributes to the barrier function of the placenta.

The placenta grows throughout pregnancy. Development of the maternal blood supply to the placenta is complete by the end of the first trimester of pregnancy week 14 (DM).

Placental circulation



Maternal blood fills the intervillous space, nutrients, water, and gases are actively and passively exchanged, then deoxygenated blood is displaced by the next maternal pulse.

Maternal placental circulation

In preparation for implantation of the blastocyst, the endometrium under goes decidualization. Spiral arteries in the decidua are remodeled so that they become less convoluted and their diameter is increased. The increased diameter and straighter flow path both act to increase maternal blood flow to the placenta. There is relatively high pressure as the maternal blood fills intervillous space through these spiral arteries which bathe the fetal villi in blood, allowing an exchange of gases to take place. In humans and other hemochorial placentals, the maternal blood comes into direct contact with the fetal chorion, though no fluid is exchanged. As the pressure decreases between pulses, the deoxygenated blood flows back through the endometrial veins.

Maternal blood flow is approximately 600–700 ml/min at term.

This begins at day 5 - day 12

Fetoplacental circulation

Deoxygenated fetal blood passes through umbilical arteries to the placenta. At the junction of umbilical cord and placenta, the umbilical arteries branch radially to form chorionic arteries. Chorionic arteries, in turn, branch into cotyledon arteries. In the villi, these vessels eventually branch to form an extensive arterio-capillary-venous system, bringing the fetal blood

extremely close to the maternal blood; but no intermingling of fetal and maternal blood occurs ("placental barrier").

Endothelin and prostanoids cause vasoconstriction in placental arteries, while nitric oxide causes vasodilation. On the other hand, there is no neural vascular regulation, and catecholamines have only little effect.

The fetoplacental circulation is vulnerable to persistent hypoxia or intermittent hypoxia and reoxygenation, which can lead to generation of excessive free radicals. This may contribute to pre-eclampsia and other pregnancy complications. It is proposed that melatonin plays a role as an antioxidant in the placenta.

This begins at day 17 - day 22

Birth

Placental expulsion begins as a physiological separation from the wall of the uterus. The period from just after the child is born until just after the placenta is expelled is called the "third stage of labor". The placenta is usually expelled within 15–30 minutes of birth.

Placental expulsion can be managed actively, for example by giving oxytocin via intramuscular injection followed by cord traction to assist in delivering the placenta. Alternatively, it can be managed expectantly, allowing the placenta to be expelled without medical assistance. Blood loss and the risk of postpartum bleeding may be reduced in women offered active management of the third stage of labour, however there may be adverse effects and more research is necessary.

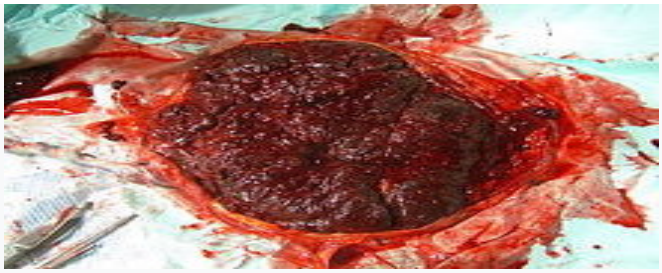
The habit is to cut the cord immediately after birth, but it is theorised that there is no medical reason to do this; on the contrary, it is theorized that not cutting the cord helps the baby in its adaptation to extrauterine life, especially in preterm infants.

Microbiome

The placenta is traditionally thought to be sterile, but recent research suggests that a resident, non-pathogenic, and diverse population of microorganisms may be present in healthy tissue. However, whether these microbes exist or are clinically important is highly controversial and is the subject of active research.

Functions

Nutrition and gas exchange



Maternal side of a placenta shortly after birth.

The placenta intermediates the transfer of nutrients between mother and fetus. The perfusion of the intervillous spaces of the placenta with maternal blood allows the transfer of nutrients and oxygen from the mother to the fetus and the transfer of waste products and carbon dioxide back from the fetus to the maternal blood. Nutrient transfer to the fetus can occur via both active and passive transport.[24] Placental nutrient metabolism was found to play a key role in limiting the transfer of some nutrients.[25] Adverse pregnancy situations, such as those involving maternal diabetes or obesity, can increase or decrease levels of nutrient transporters in the placenta potentially resulting in overgrowth or restricted growth of the fetus.

Excretion

Waste products excreted from the fetus such as urea, uric acid, and creatinine are transferred to the maternal blood by diffusion across the placenta.

Immunity

IgG antibodies can pass through the human placenta, thereby providing protection to the fetus in utero. This transfer of antibodies begins as early as the 20th week of gestational age, and certainly by the 24th week. This passive immunity lingers for several months after birth, thus providing the newborn with a carbon copy of the mother's long-term humoral immunity to see the infant through the crucial first months of extrauterine life. IgM, however, cannot cross the placenta, which is why some infections acquired during pregnancy can be hazardous for the fetus.

Furthermore, the placenta functions as a selective maternal-fetal barrier against transmission of microbes. However, insufficiency in this function may still cause mother-to-child transmission of infectious diseases.

Endocrine function

- The first hormone released by the placenta is called the human chorionic gonadotropin hormone. This is responsible for stopping the process at the end of menses when the Corpus luteum ceases activity and atrophies. If hCG did not interrupt this process, it would lead to spontaneous abortion of the fetus. The corpus luteum also produces and releases progesterone and estrogen, and hCG stimulates it to increase the amount that it releases. hCG is the indicator of pregnancy that pregnancy tests look for. These tests will work when menses has not occurred or after implantation has happened on day's seven to ten. hCG may also have an anti-antibody effect, protecting it from being rejected by the mother's body. hCG also assists the male fetus by stimulating the testes to produce testosterone, which is the hormone needed to allow the sex organs of the male to grow.
- Progesterone helps the embryo implant by assisting passage through the fallopian tubes. It also affects the fallopian tubes and the uterus by stimulating an increase in secretions necessary for fetal nutrition. Progesterone, like hCG, is necessary to prevent spontaneous abortion because it prevents contractions of the uterus and is necessary for implantation.
- Estrogen is a crucial hormone in the process of proliferation. This involves the enlargement of the breasts and uterus, allowing for growth of the fetus and production of milk. Estrogen is also responsible for increased blood supply towards the end of pregnancy through vasodilation. The levels of estrogen during pregnancy can increase so that they are thirty times what a non-pregnant woman mid-cycles estrogen level would be.
- Human placental lactogen is a hormone used in pregnancy to develop fetal metabolism and general growth and development. Human placental lactogen works with Growth hormone to stimulate Insulin-like growth factor production and regulating intermediary metabolism. In the fetus, hPL acts on lactogenic receptors to modulate embryonic development, metabolism and stimulate production of IGF, insulin, surfactant and adrenocortical hormones. hPL values increase with multiple pregnancies, intact molar pregnancy, diabetes and Rh incompatibility. They are decreased with toxemia, choriocarcinoma, and Placental insufficiency.

Immunological barrier

The placenta and fetus may be regarded as a foreign body inside the mother and must be protected from the normal immune response of the mother that would cause it to be rejected. The placenta and fetus are thus treated as sites of immune privilege, with immune tolerance.

PREGNANCY -

Pregnancy, also known as **gestation**, is the time during which one or more offspring develops inside a woman. A multiple pregnancy involves more than one offspring, such as with twins. Pregnancy can occur by sexual intercourse or assisted reproductive technology. A pregnancy may end in a live birth, a miscarriage, an induced abortion, or a stillbirth. Childbirth typically occurs around 40 weeks from the start of the last menstrual period (LMP). This is just over nine months, where each month averages 31 days.When measured from fertilization it is about 38 weeks.[An embryo is the developing offspring during the first eight weeks following fertilization, after which, the term fetus is used until birth. Symptoms of early pregnancy may include missed periods, tender breasts, nausea and vomiting, hunger, and frequent urination.] Pregnancy may be confirmed with a pregnancy test.

Pregnancy is divided into three trimesters, each lasting for approximately 3 months. The first trimester includes conception, which is when the sperm fertilizes the egg. The fertilized egg then travels down the fallopian tube and attaches to the inside of the uterus, where it begins to form the embryo and placenta. During the first trimester, the possibility of miscarriage (natural death of embryo or fetus) is at its highest. Around the middle of the second trimester, movement of the fetus may be felt. At 28 weeks, more than 90% of babies can survive outside of the uterus if provided with high-quality medical care. Prenatal care improves pregnancy outcomes. Prenatal care may include taking extra folic acid, avoiding drugs and alcohol, regular exercise, blood tests, and regular physical examinations. Complications of pregnancy may include disorders of high blood pressure, gestational diabetes, iron-deficiency anemia, and severe nausea and vomiting among others. In the ideal childbirth labor begins on its own when a woman is "at term". Babies born before 37 weeks are "preterm" and at higher risk of health problems such as cerebral palsy. Babies born between weeks 37 and 39 are considered "early term" while those born between weeks 39 and 41 are considered "full term" Babies born between weeks 41 and 42 weeks are

considered "late term" while after 42 week they are considered "post term". Delivery before 39 weeks by labor induction or caesarean section is not recommended unless required for other medical reasons

Sign and symptoms

The usual symptoms and discomforts of pregnancy do not significantly interfere with activities of daily living or pose a health-threat to the mother or baby. However, pregnancy complications can cause other more severe symptoms, such as those associated with anemia.

Common symptoms and discomforts of pregnancy include:

- Tiredness
- Morning sickness
- Constipation
- Pelvic girdle pain
- Back pain
- Braxton Hicks contractions. Occasional, irregular, and often painless contractions that occur several times per day.
- Peripheral edema swelling of the lower limbs. Common complaint in advancing pregnancy. Can be caused by inferior vena cava syndrome resulting from compression of the inferior vena cava and pelvic veins by the uterus leading to increased hydrostatic pressure in lower extremities.
- Low blood pressure often caused by compression of both the inferior vena cava and the abdominal aorta (aortocaval compression syndrome).
- Increased urinary frequency. A common complaint, caused by increased intravascular volume, elevated glomerular filtration rate, and compression of the bladder by the expanding uterus.
- Urinary tract infection.
- Varicose veins. Common complaint caused by relaxation of the venous smooth muscle and increased intravascular pressure.
- Hemorrhoids (piles). Swollen veins at or inside the anal area. Caused by impaired venous return, straining associated with constipation, or increased intra-abdominal pressure in later pregnancy.

- Regurgitation, heartburn, and nausea.
- Stretch marks
- Breast tenderness is common during the first trimester, and is more common in women who are pregnant at a young age.
- Melasma, also known as the mask of pregnancy, is a discoloration, most often of the face. It usually begins to fade several months after giving birth.

Chronology

The chronology of pregnancy is, unless otherwise specified, generally given as gestational age, where the starting point is the beginning of the woman's last menstrual period (LMP), or the corresponding age of the gestation as estimated by a more accurate method if available. Sometimes, timing may also use the fertilization age which is the age of the embryo.

Start of gestational age

Gestational age

According to American Congress of Obstetricians and Gynecologists, the main methods to calculate gestational age are.

- Directly calculating the days since the beginning of the last menstrual period.
- Early obstetric ultrasound, comparing the size of an embryo or fetus to that of a reference group of pregnancies of known gestational age (such as calculated from last menstrual periods), and using the mean gestational age of other embryos or fetuses of the same size. If the gestational age as calculated from an early ultrasound is contradictory to the one calculated directly from the last menstrual period, it is still the one from the early ultrasound that is used for the rest of the pregnancy.
- In case of in vitro fertilization, calculating days since oocyte retrieval or co-incubation and adding 14 days.

Trimesters

Pregnancy is divided into three trimesters, each lasting for approximately 3 months. The exact length of each trimester can vary between sources.

- The **first trimester** begins with the start of gestational age as described above, that is, the beginning of week 1, or 0 weeks + 0 days of gestational age (GA). It ends at week 12 (11 weeks + 6 days of GA) or end of week 14 (13 weeks + 6 days of GA).

- The **second trimester** is defined as starting, between the beginning of week 13 (12 weeks +0 days of GA) and beginning of week 15 (14 weeks + 0 days of GA). It ends at the end of week 27 (26 weeks + 6 days of GA) or end of week 28 (27 weeks + 6 days of GA).
- The **third trimester** is defined as starting, between the beginning of week 28 (27 weeks + 0 days of GA) or beginning of week 29 (28 weeks + 0 days of GA). It lasts until childbirth.

MENOPAUSE-

Menopause, also known as the **climacteric**, is the time in most women's lives when menstrual periods stop permanently, and they are no longer able to bear children. Menopause typically occurs between 49 and 52 years of age. Medical professionals often define menopause as having occurred when a woman has not had any menstrual bleeding for a year. It may also be defined by a decrease in hormone production by the ovaries. In those who have had surgery to remove their uterus but still have ovaries, menopause may be considered to have occurred at the time of the surgery or when their hormone levels fell. Following the removal of the uterus, symptoms typically occur earlier, at an average of 45 years of age.

In the years before menopause, a woman's periods typically become irregular, who means that periods may be longer or shorter in duration or be lighter or heavier in the amount of flow. During this time, women often experience hot flashes; these typically last from 30 seconds to ten minutes and may be associated with shivering, sweating, and reddening of the skin. Hot flashes often stop occurring after a year or two. Other symptoms may include vaginal dryness, trouble sleeping, and mood changes. The severity of symptoms varies between women. While menopause is often thought to be linked to an increase in heart disease, this primarily occurs due to increasing age and does not have a direct relationship with menopause. In some women, problems that were present like endometriosis or painful periods will improve after menopause.

Menopause is usually a natural change. It can occur earlier in those who smoke tobacco. Other causes include surgery that removes both ovaries or some types of chemotherapy. At the physiological level, menopause happens because of a decrease in the ovaries' production of the hormones estrogen and progesterone. While typically not needed, a diagnosis of menopause can be confirmed by measuring hormone levels in the blood or urine. Menopause is the opposite of menarche, the time when a girl's periods start

Specific treatment is not usually needed. Some symptoms, however, may be improved with treatment. With respect to hot flashes, avoiding smoking, caffeine, and alcohol is often recommended. Sleeping in a cool room and using a fan may help. The following medications may help: menopausal hormone therapy (MHT), clonidine, gabapentin, or selective serotonin reuptake inhibitors Exercise may help with sleeping problems. While MHT was once routinely prescribed, it is now only recommended in those with significant symptoms, as there are concerns about side effects. High-quality evidence for the effectiveness of alternative medicine has not been found. There is tentative evidence for phytoestrogens

During early menopause transition, the menstrual cycles remain regular but the interval between cycles begins to lengthen. Hormone levels begin to fluctuate. Ovulation may not occur with each cycle.

The term menopause refers to a point in time that follows one year after the last menstruation. During the menopausal transition and after menopause, women can experience a wide range of symptoms.

Vagina and uterus

During the transition to menopause, menstrual patterns can show shorter cycling (by 2–7 days); onger cycles remain possible. There may be irregular bleeding (lighter, heavier, spotting). Dysfunctional uterine bleeding is often experienced by women approaching menopause due to the hormonal changes that accompany the menopause transition. Spotting or bleeding may simply be related to vaginal atrophy, a benign sore (polyp or lesion), or may be a functional endometrial response. The European Menopause and Andropause Society has released guidelines for assessment of the endometrium, which is usually the main source of spotting or bleeding.

In post-menopausal women, however, any genital bleeding is an alarming symptom that requires an appropriate study to rule out the possibility of malignant diseases.

Symptoms that may appear during menopause and continue through postmenopause include:

- painful intercourse
- vaginal dryness
- atrophic vaginitis – thinning of the membranes of the vulva, the vagina, the cervix, and the outer urinary tract, along with considerable shrinking and loss in elasticity of all of the outer and inner genital areas.

MAMMARY GLAND -

A **mammary gland** is an exocrine gland in humans and other mammals that produces milk to feed young offspring. Mammals get their name from the Latin word mamma, "breast". The mammary glands are arranged in organs such as the breasts in primates (for example, humans and chimpanzees), the udder in ruminants (for example, cows, goats, and deer), and the dugs of other animals (for example, dogs and cats). Lactorrhea, the occasional production of milk by the glands, can occur in any mammal, but in most mammals, lactation, the production of enough milk for nursing, occurs only in phenotypic females who have gestated in recent months or years. It is directed by hormonal guidance from sex steroids

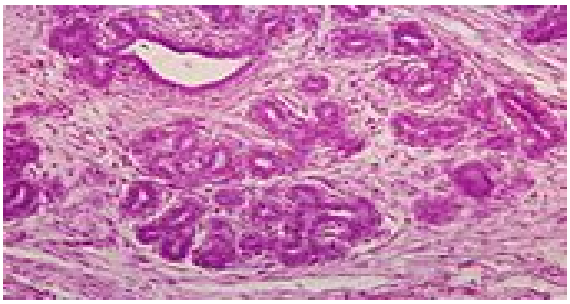
Structure

The basic components of a mature mammary gland are the alveoli (hollow cavities, a few millimeters large) lined with milk-secreting cuboidal cells and surrounded by myoepithelial cells. These alveoli join to form groups known as lobules. Each lobule has a lactiferous duct that drains into openings in the nipple. The myoepithelial cells contract under the stimulation of oxytocin, excreting the milk secreted by alveolar units into the lobule lumen toward the nipple. As the infant begins to suck, the oxytocin-mediated "let down reflex" ensues and the mother's milk is secreted — not sucked from the gland — into the baby's mouth.

All the milk-secreting tissue leading to a single lactiferous duct is called a "simple mammary gland"; in a "complex mammary gland" all the simple mammary glands serve one nipple. Humans normally have two complex mammary glands, one in each breast, and each complex mammary gland consists of 10–20 simple glands. The presence of more than two nipples is known as polythelia and the presence of more than two complex mammary glands as polymastia.

Maintaining the correct polarized morphology of the lactiferous duct tree requires another essential component – mammary epithelial cells extracellular matrix (ECM) which, together with adipocytes, fibroblast, inflammatory cells, and others, constitute mammary stroma. Mammary epithelial ECM mainly contains myoepithelial basement membrane and the connective tissue. They not only help to support mammary basic structure, but also serve as a communicating bridge between mammary epithelia and their local and global environment throughout this organ's development.

Histology



Light micrograph of a human mammary gland during estrous cycle. Sprouting gland tissue can be seen in the upper left field (haematoxylin eosin staining)

A mammary gland is a specific type of apocrine gland specialized for manufacture of colostrum when giving birth. Mammary glands can be identified as apocrine because they exhibit striking "decapitation" secretion. Many sources assert that mammary glands are modified sweat glands. Some authors dispute that and argue instead that they are sebaceous glands. n

Development

Mammary glands develop during different growth cycles. They exist in both sexes during embryonic stage, forming only a rudimentary duct tree at birth. In this stage, mammary gland development depends on systemic (and maternal) hormones, but is also under the (local) regulation of paracrine communication between neighboring epithelial and mesenchymal cells by parathyroid hormone-related protein (PTHrP). This locally secreted factor gives rise to a series of outside-in and inside-out positive feedback between these two types of cells, so that mammary bud epithelial cells can proliferate and sprout down into the mesenchymal layer until they reach the fat pad to begin the first round of branching. At the same time, the embryonic mesenchymal cells around the epithelial bud receive secreting factors activated by PTHrP, such as BMP4. These mesenchymal cells can transform into a dense, mammary-specific mesenchyme, which later develop into connective tissue with fibrous threads, forming blood vessels and the lymph system. A basement membrane, mainly containing laminin and collagen, formed afterward by differentiated myoepithelial cells, keeps the polarity of this primary duct tree. These components of the extracellular matrix are strong determinants of duct morphogenesis.

Biochemistry

Estrogen and growth hormone (GH) are essential for the ductal component of mammary gland development, and act synergistically to mediate it. Neither estrogen nor GH is capable

of inducing ductal development without the other. The role of GH in ductal development has been found to be mostly mediated by its induction of the secretion of insulin-like growth factor 1 (IGF-1), which occurs both systemically (mainly originating from the liver) and locally in the mammary fat pad through activation of the growth hormone receptor (GHR). However, GH itself also acts independently of IGF-1 to stimulate ductal development by upregulating estrogen receptor (ER) expression in mammary gland tissue, which is a downstream effect of mammary gland GHR activation. In any case, unlike IGF-1, GH itself is not essential for mammary gland development, and IGF-1 in conjunction with estrogen can induce normal mammary gland development without the presence of GH. In addition to IGF-1, other paracrine growth factors such as epidermal growth factor (EGF), transforming growth factor beta (TGF-β), amphiregulin, fibroblast growth factor (FGF), and hepatocyte growth factor (HGF) are involved in breast development as mediators downstream to sex hormones and GH/IGF-1.

During embryonic development, IGF-1 levels are low, and gradually increase from birth to puberty. At puberty, the levels of GH and IGF-1 reach their highest levels in life and estrogen begins to be secreted in high amounts in females, which is when ductal development mostly takes place. Under the influence of estrogen, stromal and fat tissue surrounding the ductal system in the mammary glands also grows. After puberty, GH and IGF-1 levels progressively decrease, which limits further development until pregnancy, if it occurs. During pregnancy, progesterone and prolactin are essential for mediating lobuloalveolar development in estrogen-primed mammary gland tissue, which occurs in preparation of lactation and nursing.

Androgens such as testosterone inhibit estrogen-mediated mammary gland development (e.g., by reducing local ER expression) through activation of androgen receptors expressed in mammary gland tissue, and in conjunction with relatively low estrogen levels, are the cause of the lack of developed mammary glands in males.

Before birth

Mammary gland development is characterized by the unique process by which the epithelium invades the stroma. The development of the mammary gland occurs mainly after birth. During puberty, tubule formation is coupled with branching morphogenesis which establishes the basic arboreal network of ducts emanating from the nipple.

Developmentally, mammary gland epithelium is constantly produced and maintained by rare epithelial cells, dubbed as mammary progenitors which are ultimately thought to be derived from tissue-resident stem cells.

Embryonic mammary gland development can be divided into a series of specific stages. Initially, the formation of the milk lines that run between the fore and hind limbs bilaterally on each side of the midline occurs around embryonic day 10.5 (E10.5). The second stage occurs at E11.5 when placode formation begins along the mammary milk line. This will eventually give rise to the nipple. Lastly, the third stage occurs at E12.5 and involves the invagination of cells within the placode into the mesenchyme, leading to a mammary anlage (biology).

The primitive (stem) cells are detected in embryo and their numbers increase steadily during development.

Growth

Postnatally, the mammary ducts elongate into the mammary fat pad. Then, starting around four weeks of age, mammary ductal growth increases significantly with the ducts invading towards the lymph node. Terminal end buds, the highly proliferative structures found at the tips of the invading ducts, expand and increase greatly during this stage. This developmental period is characterized by the emergence of the terminal end buds and lasts until an age of about 7–8 weeks.

By the pubertal stage, the mammary ducts have invaded to the end of the mammary fat pad. At this point, the terminal end buds become less proliferative and decrease in size. Side branches form from the primary ducts and begin to fill the mammary fat pad. Ductal development decreases with the arrival of sexual maturity and undergoes estrous cycles (proestrus, estrus, metestrus, and diestrus). As a result of estrous cycling, the mammary gland undergoes dynamic changes where cells proliferate and then regress in an ordered fashion.

Pregnancy

During pregnancy, the ductal systems undergo rapid proliferation and form alveolar structures within the branches to be used for milk production. After delivery, lactation occurs within the mammary gland; lactation involves the secretion of milk by the luminal cells in the alveoli. Contraction of the myoepithelial cells surrounding the alveoli will cause the milk to be ejected through the ducts and into the nipple for the nursing infant. Upon weaning of the

infant, lactation stops and the mammary gland turn in on itself, a process called involution. This process involves the controlled collapse of mammary epithelial cells where cells begin apoptosis in a controlled manner, reverting the mammary gland back to a pubertal state.

Postmenopausal

During postmenopause, due to much lower levels of estrogen, and due to lower levels of GH and IGF-1, which decrease with age, mammary gland tissue atrophies and the mammary glands become smaller.

Hormonal control

Lactiferous duct development occurs in females in response to circulating hormones. First development is frequently seen during pre- and postnatal stages, and later during puberty. Estrogen promotes branching differentiation, whereas in males testosterone inhibits it. A mature duct tree reaching the limit of the fat pad of the mammary gland comes into being by bifurcation of duct terminal end buds (TEB), secondary branches sprouting from primary ducts and proper duct lumen formation. These processes are tightly modulated by components of mammary epithelial ECM interacting with systemic hormones and local secreting factors. However, for each mechanism the epithelial cells' "niche" can be delicately unique with different membrane receptor profiles and basement membrane thickness from specific branching area to area, so as to regulate cell growth or differentiation sub-locally. Important players include beta-1 integrin, epidermal growth factor receptor (EGFR), laminin-1/5, collagen-IV, matrix metalloproteinase(MMPs), heparan sulfate proteoglycans, and others. Elevated circulating level of growth hormone and estrogen get to multipotent cap cells on TEB tips through a thin, leaky layer of basement membrane. These hormones promote specific gene expression. Hence cap cells can differentiate into myoepithelial and luminal (duct) epithelial cells, and the increased amount of activated MMPs can degrade surrounding ECM helping duct buds to reach further in the fat pads. On the other hand, basement membrane along the mature mammary ducts is thicker, with strong adhesion to epithelial cells via binding to integrin and non-integrin receptors. When side branches develop, it is a much more “pushing-forward” working process including extending through myoepithelial cells, degrading basement membrane and then invading into a periductal layer of fibrous stromal tissue. Degraded basement membrane fragments (laminin-5) roles to lead the way of mammary epithelial cells migration. Whereas, laminin-1 interacts with non-integrin receptor dystroglycan negatively regulates this side branching process in case of cancer. These

complex "Yin-yang" balancing crosstalks between mammary ECM and epithelial cells "instruct" healthy mammary gland development until adult.

There is preliminary evidence that soybean intake mildly stimulates the breast glands in pre- and postmenopausal women.

Pregnancy

Secretory alveoli develop mainly in pregnancy, when rising levels of prolactin, estrogen, and progesterone cause further branching, together with an increase in adipose tissue and a richer blood flow. In gestation, serum progesterone remains at a stably high concentration so signaling through its receptor is continuously activated. As one of the transcribed genes, Wnts secreted from mammary epithelial cells act paracrinely to induce more neighboring cells' branching. When the lactiferous duct tree is almost ready, "leaves" alveoli are differentiated from luminal epithelial cells and added at the end of each branch. In late pregnancy and for the first few days after giving birth, colostrum is secreted. Milk secretion (lactation) begins a few days later due to reduction in circulating progesterone and the presence of another important hormone prolactin, which mediates further alveologenesis, milk protein production, and regulates osmotic balance and tight junction function. Laminin and collagen in myoepithelial basement membrane interacting with beta-1 integrin on epithelial surface again, is essential in this process.[44][45] Their binding ensures correct placement of prolactin receptors on the basal lateral side of alveoli cells and directional secretion of milk into lactiferous ducts. Suckling of the baby causes release of the hormone oxytocin, which stimulates contraction of the myoepithelial cells. In this combined control from ECM and systemic hormones, milk secretion can be reciprocally amplified so as to provide enough nutrition for the baby.

Weaning

During weaning, decreased prolactin, missing mechanical stimulation (baby suckling), and changes in osmotic balance caused by milk stasis and leaking of tight junctions cause cessation of milk production. It is the (passive) process of a child or animal ceasing to be dependent on the mother for nourishment. In some species there is complete or partial involution of alveolar structures after weaning, in humans there is only partial involution and the level of involution in humans appears to be highly individual. The glands in the breast do secrete fluid also in nonlactating women. In some other species (such as cows), all alveoli and secretory duct structures collapse by programmed cell death (apoptosis)

and autophagy for lack of growth promoting factors either from the ECM or circulating hormones. At the same time, apoptosis of blood capillary endothelial cells speeds up the regression of lactation ductal beds. Shrinkage of the mammary duct tree and ECM remodeling by various proteinase is under the control of somatostatin and other growth inhibiting hormones and local factors. This major structural change leads loose fat tissue to fill the empty space afterward. But a functional lactiferous duct tree can be formed again when a female is pregnant again.

Clinical significance

Tumorigenesis in mammary glands can be induced biochemically by abnormal expression level of circulating hormones or local ECM components, or from a mechanical change in the tension of mammary stroma. Under either of the two circumstances, mammary epithelial cells would grow out of control and eventually result in cancer. Almost all instances of breast cancer originate in the lobules or ducts of the mammary glands

INFERTILITY -

Infertility is the inability to become pregnant after one year of intercourse without contraception involving a male and female partner. There are many causes of infertility, including some that medical intervention can treat. Estimates from 1997 suggest that worldwide about five percent of all heterosexual couples have an unresolved problem with infertility. Many more couples, however, experience involuntary childlessness for at least one year: estimates range from 12% to 28%. Male infertility is responsible for 20–30% of infertility cases, while 20–35% are due to female infertility, and 25–40% are due to combined problems in both parts. In 10–20% of cases, no cause is found. The most common cause of female infertility is ovulatory problems, which generally manifest themselves by sparse or absent menstrual periods. Male infertility is most commonly due to deficiencies in the semen, and semen quality is used as a surrogate measure of male fecundity.

Women who are fertile experience a natural period of fertility before and during ovulation, and they are naturally infertile for the rest of the menstrual cycle. Fertility awareness methods are used to discern when these changes occur by tracking changes in cervical mucus or basal body temperature.

- Primary infertility is defined as the absence of a live birth for women who desire a child and have been in a union for at least 12 months, during which they have not

used any contraceptives. The World Health Organisation also adds that 'women whose pregnancy spontaneously miscarries, or whose pregnancy results in a still born child, without ever having had a live birth would present with primarily infertility'.

- Secondary infertility is defined as the absence of a live birth for women who desire a child and have been in a union for at least 12 months since their last live birth, during which they did not use any contraceptives.
- Thus the distinguishing feature is whether or not the couple have ever had a pregnancy which led to a live birth.

Causes

Immune infertility

Antisperm antibodies (ASA) have been considered as infertility cause in around 10–30% of infertile couples. In both men and women, ASA production are directed against surface antigens on sperm, which can interfere with sperm motility and transport through the female reproductive tract, inhibiting capacitation and acrosome reaction, impaired fertilization, influence on the implantation process, and impaired growth and development of the embryo. The antibodies are classified into different groups: There are IgA, IgG and IgM antibodies. They also differ in the location of the spermatozoon they bind on (head, mid piece, tail). Factors contributing to the formation of antisperm antibodies in women are disturbance of normal immunoregulatory mechanisms, infection, and violation of the integrity of the mucous membranes, rape and unprotected oral or anal sex. Risk factors for the formation of antisperm antibodies in men include the breakdown of the blood-testis barrier, trauma and surgery, orchitis, varicocele, infections, prostatitis, testicular cancer, failure of immunosuppression and unprotected receptive anal or oral sex with men.

Sexually transmitted infections

Infections with the following sexually transmitted pathogens have a negative effect on fertility: Chlamydia trachomatis and Neisseria gonorrhoeae. There is a consistent association of Mycoplasma genitalium infection and female reproductive tract syndromes. M. genitalium infection is associated with increased risk of infertility.

Genetic

Mutations to NR5A1 gene encoding Steroidogenic Factor-1 (SF-1) have been found in a small subset of men with non-obstructive male factor infertility where the cause is unknown. Results of one study investigating a cohort of 315 men revealed changes within the hinge region of SF-1 and no rare allelic variants in fertile control men. Affected individuals displayed more severe forms of infertility such as azoospermia and severe oligozoospermia.

Other causes

Factors that can cause male as well as female infertility are:

- DNA damage
    - DNA damage reduces fertility in female ovocytes, as caused by smoking, other xenobiotic DNA damaging agents (such as radiation or chemotherapy) or accumulation of the oxidative DNA damage 8-hydroxy-deoxyguanosine
    - DNA damage reduces fertility in male sperm, as caused by oxidative DNA damage, smoking. Other xenobiotic DNA damaging agents (such as drugs or chemotherapy) or other DNA damaging agents including reactive oxygen species, fever or high testicular temperature. The damaged DNA related to infertility manifests itself by the increased susceptibility to denaturation inducible by heat or acid or by the presence of double-strand breaks that can be detected by the TUNEL assay.
- General factors
    - Diabetes mellitus, thyroid disorders,undiagnosed and untreated coeliac disease, adrenal disease
- Hypothalamic-pituitary factors
    - Hyperprolactinemia
    - Hypopituitarism
    - The presence of anti-thyroid antibodies is associated with an increased risk of unexplained subfertility with an odds ratio of 1.5 and 95% confidence interval of 1.1–2.0.
- Environmental factors

- Toxins such as glues, volatile organic solvents or silicones, physical agents, chemical dusts, and pesticides. Tobacco smokers are 60% more likely to be infertile than non-smokers.

German scientists have reported that a virus called adeno-associated virus might have a role in male infertility, though it is otherwise not harmful. Other diseases such as chlamydia, and gonorrhea can also cause infertility, due to internal scarring (fallopian tube obstruction).

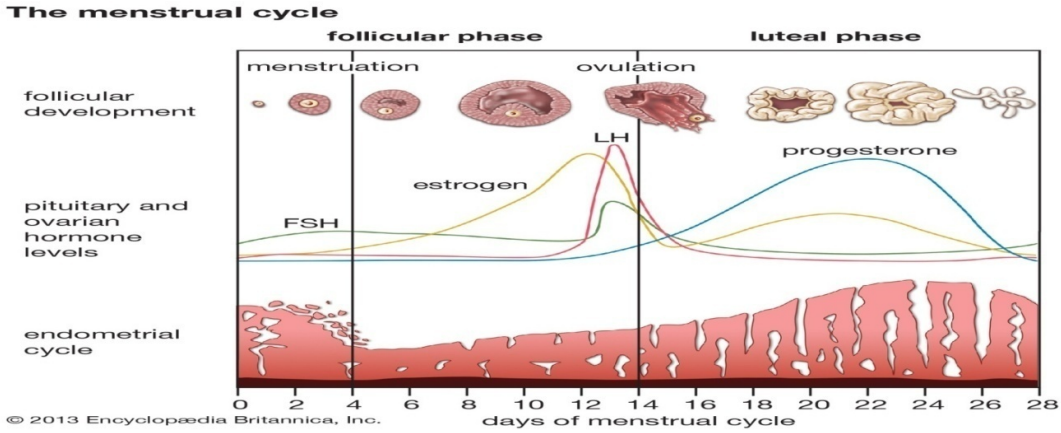
MENSTRUAL CYCLE -

The **menstrual cycle** is the regular natural change that occurs in the female reproductive system (specifically the uterus and ovaries) that makes pregnancy possible. The cycle is required for the production of oocytes, and for the preparation of the uterus for pregnancy. The menstrual cycle occurs due to the rise and fall of estrogen. This cycle results in the thickening of the lining of the uterus, and the growth of an egg, (which is required for pregnancy). The egg is released from an ovary around day fourteen in the cycle; the thickened lining of the uterus provides nutrients to an embryo after implantation. If pregnancy does not occur, the lining is released in what is known as menstruation or a "period".

Up to 80% of women report having some symptoms during the one to two weeks prior to menstruation. Common symptoms include acne, tender breasts, bloating, feeling tired, irritability and mood changes. These symptoms interfere with normal life and therefore qualify as premenstrual syndrome in 20 to 30% of women. In 3 to 8%, they are severe.

The first period usually begins between twelve and fifteen years of age, a point in time known as menarche. They may occasionally start as early as eight, and this onset may still be normal. The average age of the first period is generally later in the developing world and earlier in developed world. The typical length of time between the first day of one period and the first day of the next is 21 to 45 days in young women and 21 to 35 days in adults (an average of 28 days. Menstruation stops occurring after menopause which usually occurs between 45 and 55 years of age. Bleeding usually lasts around 3 to 7 days.

The menstrual cycle is governed by hormonal changes. These changes can be altered by using hormonal birth control to prevent pregnancy. Each cycle can be divided into three phases based on events in the ovary (ovarian cycle) or in the uterus (uterine cycle).The ovarian cycle consists of the follicular phase, ovulation, and luteal phase whereas the uterine cycle is divided into menstruation, proliferative phase, and secretory phase.



Menstrual disorders

Infrequent or irregular ovulation is called oligoovulation. The absence of ovulation is called anovulation. Normal menstrual flow can occur without ovulation preceding it: an anovulatory cycle. In some cycles, follicular development may start but not be completed; nevertheless, estrogens will be formed and stimulate the uterine lining. Anovulatory flow resulting from a very thick endometrium caused by prolonged, continued high estrogen levels is called estrogen breakthrough bleeding. Anovulatory bleeding triggered by a sudden drop in estrogen levels is called withdrawal bleeding. Anovulatory cycles commonly occur before menopause (perimenopause) and in women with polycystic ovary syndrome.

Very little flow (less than 10 ml) is called hypomenorrhea. Regular cycles with intervals of 21 days or fewer are polymenorrhea; frequent but irregular menstruation is known as metrorrhagia. Sudden heavy flows or amounts greater than 80 ml are termed menorrhagia. Heavy menstruation that occurs frequently and irregularly is menometrorrhagia. The term for cycles with intervals exceeding 35 days is oligomenorrhea. Amenorrhea refers to more than three to six months without menses (while not being pregnant) during a woman's reproductive years. The term for painful periods is dysmenorrhea.

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