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PHARMACOLOGY

 (1)Lactation period: Lactation is the secretion and yielding of milk by females after giving birth. The milk is produced by the mammary glands, which are contained within the breasts. The physiology of lactation is divided into mammogenesis, lactogenesis, galactokinesis and galactopoesis.

Mammogenesis: Mammogenesis is the process of growth and development of the mammary gland in preparation for milk production. This process begins when the mammary gland is exposed to estrogen at puberty and is completed during the third trimester of pregnancy. Before pregnancy, the breast is predominantly adipose tissue without extensive glandular or ductal development. Under the influence of uninterrupted and rising concentrations of estrogen, progesterone, and prolactin during pregnancy, the breast increases in water, electrolyte, and fat content. This increase in overall breast volume amounts to approximately 3/4 lb (0.338 kg) per breast. The increase in volume is accompanied by a marked increase in the vascular supply to the breast; the dilated subcutaneous mammary veins become prominent, and the blood flow increases twofold. Size and pigmentation of the nipples also increase under the influence of rising estrogen concentrations. The sebaceous glands of Montgomery on the periphery of the areolae greatly enlarge; during lactation, they produce a secretion important for nipple conditioning and lubrication.

 Hormonal Effects

Total estrogen excretion increases from 20–20,000 mg per 24 hours between early and late pregnancy. This reflects the rising plasma estrogen levels, which greatly stimulate the ductal arborization begun at puberty and the differentiation of epithelial cells into ductal, acinar, and myoepithelial elements. In addition to its effect on the mammary cells themselves, estrogen stimulates the synthesis and release of prolactin from the pituitary lactotrophs. Rising prolactin levels appear to be necessary for estrogen to exert its biologic effects on the mammary gland. In addition, prolactin induces the enzymes necessary for the acinar secretory activity seen after delivery. Prolactin levels increase from 20–200 ng/ml during pregnancy. Progesterone secretion increases from 3–300 mg/day during pregnancy. In the presence of estrogen and prolactin, progesterone stimulates acinar proliferation and inhibits lactose synthesis. The high plasma concentrations of estrogen and progesterone present before delivery inhibit the active secretory effects of prolactin on mammary alveolar epithelium. Human placental lactogen (HPL), also called human chorionic somatomammotropin, is a placental protein hormone that has both lactogenic and somatotropic effects that may facilitate mammogenesis directly or act by competitively inhibiting prolactin receptors in the mammary tissue during pregnancy to delay milk production until after delivery.

The initial stimulation of mammary epithelium occurs during the first few weeks of pregnancy. By the second trimester, colostrum, the first milk, appears in the alveoli of the acinar glands in small quantities, reflecting the beginning of protein synthesis under the influence of prolactin. By the third trimester, the alveoli contain significant amounts of colostrum, the epithelial cells are laden with fat droplets, and the adipose tissue of the breast has been markedly reduced and replaced by functioning glandular units.

Lactogenesis: Lactogenesis is the onset of milk secretion and includes all of the changes in the mammary epithelium necessary to go from the undifferentiated mammary gland in early pregnancy to full lactation sometime after parturition.it is divided into 2 stages.

Stage I occurs during pregnancy, when the gland becomes sufficiently differentiated to secrete small quantities of specific milk components, such as casein and lactose. In humans, stage I occurs at approximately midpregnancy and can be detected by the measurement of increased plasma concentrations of lactose and α-lactalbumin. After lactogenesis stage I has been achieved the gland is sufficiently differentiated to secrete milk, but secretion is held in check by high circulating plasma concentrations of progesterone and, possibly, in some species such as humans, estrogen. The secretion product, often called colostrum, which can be extracted from the breasts of pregnant women, contains relatively high concentrations of sodium; chloride; and protective substances, such as immunoglobulins and lactoferrin. Casein is not present and the lactose concentration is low at this time.

Stage II is the onset of copious milk secretion associated with parturition. In many species, such as cows, goats, and rats, this stage begins before birth of the young, brought about by the sharp decrease in plasma progesterone that also initiates parturition. In humans, the progesterone level does not decrease prepartum but decreases approximately 10-fold during the first 4 days after birth, accompanied by a programmed transformation of the mammary epithelium, which leads to transfer to the infant of 500 to 750 mL/d of milk by day 5 postpartum. This transformation requires a concerted change in several processes, including changes in the permeability of the paracellular pathway between epithelial cells; changes in the secretion of protective substances, such as immunoglobulins, lactoferrin, and complex carbohydrates; and an increased rate of secretion of all milk components. Lactogenesis stage II can be monitored by changes in milk composition and volume in women and other species in which large milk samples can easily be obtained.The terms colostrum and transitional milk, traditionally used to describe the mammary secretion product during the first 4 days postpartum and from days 4 to 10 postpartum, respectively, do not define clear-cut temporal changes in milk composition and are not useful distinctions. Rather, the changes in milk composition that occur postpartum should be viewed as part of a continuum wherein rapid changes in composition occur during the first 4 days postpartum followed by slow changes in various components of milk throughout the course of lactation.

Galactokinesis : Discharge of milk from the mammary glands of breast depends upon the suction exerted by the baby during suckling.

Contractile mechanism also helps by expressing the milk from alveoli into the ducts.

During suckling, a conditioned nervous reflex is set up by SUCKLING REFLEX.

Hormonal Control of Galactokinesis

Prolactin

Produced by the AP

Acts on the breast by binding

to mammary epithelial cell receptors

stimulates synthesis of mRNA of milk proteins producing milkTakes several minutes of the infant sucking at the breast to cause prolactin secretion

Oxytocin

produced by the PP

Suckling at the breast stimulates the release of oxytocin in an intermittent manner.

Acts on the myoepithelial cells of breast to produce milk ejection

Galactopoesis: is the maintenance of lactation once lactation has been established. Two key interrelated components contribute to the maintenance of lactation, galactopoietic hormones and removal of accumulated milk. Because of the importance of galactopoietic hormones in milk production, sometimes the word galactopoiesis also is used to indicate enhancement of lactation, especially in dairy animals. Inhibition of secretion of key galactopoietic hormones will depress milk production to varying degrees depending on the species, stage of lactation, and the particular hormone being suppressed. The role of galactopoietic hormones such as prolactin in maintenance of lactation is well established. Prolactin is released at the time of milk removal in ruminants and nonruminants, and it remains a key systemic modulator of milk secretion during lactation. Conversely, growth hormone is generally considered to be the predominant galactopoietic hormone in ruminants. Inhibition of prolactin secretion or administration of prolactin to lactating cows has little effect on milk yields.

Regardless of the hormones involved, all attempts to evaluate milk secretion must account for continued removal of milk. This is a reminder of the critical role of local mammary factors in maintenance of milk secretion. One such factor that plays a major role in regulating milk secretion in many species is a feedback inhibitor of lactation (FIL) found in milk. FIL is thought to be produced by the mammary cells as they synthesize and secrete milk. Accumulation of FIL in the milk-producing alveoli results in feedback inhibition of milk synthesis and secretion.

Frequent removal of milk from the gland minimizes local inhibitory effects of FIL and increases milk secretion. Milk removal involves several mechanisms that impact milk production, including removal of local inhibitory components, regulation of local blood flow, and even physical factors in the alveolus. The effects of frequency of milk removal are tied closely with the local regulation of milk secretion.

(2) Gestation period: The average gestation period in humans is 280 days or 40 weeks. The gestation period begins on the first day of the woman's last menstrual period. Full-term babies are born from 37 weeks to 42 weeks of the estimated date of birth.

The stages of human gestation are broken into three trimesters that are 3 months long each. The first trimester runs until the 12th week of pregnancy. The second trimester begins in week 13 and ends in week 28. The third and final trimester begins at week 29 and ends when the baby is born. Babies born before 37 weeks of gestation are considered to be premature. Irregular menstrual cycles can make it hard to determine the length of gestation.

Pregnancy causes physiologic changes in all maternal organ systems; most return to normal after delivery. In general, the changes are more dramatic in multifetal than in single pregnancies.

Cardiovascular

Cardiac output (CO) increases 30 to 50%, beginning by 6 weeks gestation and peaking between 16 and 28 weeks (usually at about 24 weeks). It remains near peak levels until after 30 weeks. Then, CO becomes sensitive to body position. Positions that cause the enlarging uterus to obstruct the vena cava the most (eg, the recumbent position) cause CO to decrease the most. On average, CO usually decreases slightly from 30 weeks until labor begins. During labor, CO increases another 30%. After delivery, the uterus contracts, and CO drops rapidly to about 15 to 25% above normal, then gradually decreases (mostly over the next 3 to 4 weeks) until it reaches the prepregnancy level at about 6 weeks postpartum.

Hematologic

Total blood volume increases proportionally with cardiac output, but the increase in plasma volume is greater (close to 50%, usually by about 1600 mL for a total of 5200 mL) than that in red blood cell (RBC) mass (about 25%); thus, hemoglobin (Hb) is lowered by dilution, from about 13.3 to 12.1 g/dL. This dilutional anemia decreases blood viscosity. With twins, total maternal blood volume increases more (closer to 60%).

WBC count increases slightly to 9,000 to 12,000/mcL. Marked leukocytosis (≥ 20,000/mcL) occurs during labor and the first few days postpartum.

Iron requirements increase by a total of about 1 g during the entire pregnancy and are higher during the 2nd half of pregnancy—6 to 7 mg/day. The fetus and placenta use about 300 mg of iron, and the increased maternal RBC mass requires an additional 500 mg. Excretion accounts for 200 mg. Iron supplements are needed to prevent a further decrease in Hb levels because the amount absorbed from the diet and recruited from iron stores (average total of 300 to 500 mg) is usually insufficient to meet the demands of pregnancy.

Urinary

Changes in renal function roughly parallel those in cardiac function. Glomerular filtration rate (GFR) increases 30 to 50%, peaks between 16 and 24 weeks gestation, and remains at that level until nearly term, when it may decrease slightly because uterine pressure on the vena cava often causes venous stasis in the lower extremities. Renal plasma flow increases in proportion to GFR. As a result, blood urea nitrogen (BUN) decreases, usually to < 10 mg/dL (< 3.6 mmol urea/L), and creatinine levels decrease proportionally to 0.5 to 0.7 mg/dL (44 to 62 micromole/L). Marked dilation of the ureters (hydroureter) is caused by hormonal influences (predominantly progesterone) and by backup due to pressure from the enlarged uterus on the ureters, which can also cause hydronephrosis. Postpartum, the urinary collecting system may take as long as 12 weeks to return to normal.

Postural changes affect renal function more during pregnancy than at other times; ie, the supine position increases renal function more, and upright positions decrease renal function more. Renal function also markedly increases in the lateral position, particularly when lying on the left side; this position relieves the pressure that the enlarged uterus puts on the great vessels when pregnant women are supine. This positional increase in renal function is one reason pregnant women need to urinate frequently when trying to sleep.

Respiratory

Lung function changes partly because progesterone increases and partly because the enlarging uterus interferes with lung expansion. Progesterone signals the brain to lower carbon dioxide (CO2) levels. To lower CO2 levels, tidal and minute volume and respiratory rate increase, thus increasing plasma pH. oxygen consumption increases by about 20% to meet the increased metabolic needs of the fetus, placenta, and several maternal organs. Inspiratory and expiratory reserve, residual volume and capacity, and plasma PCO2 decrease. Vital capacity and plasma PCO2 do not change. Thoracic circumference increases by about 10 cm.

Considerable hyperemia and edema of the respiratory tract occur. Occasionally, symptomatic nasopharyngeal obstruction and nasal stuffiness occur, eustachian tubes are transiently blocked, and tone and quality of voice change.

Mild dyspnea during exertion is common, and deep respirations are more frequent.

Gastrointestinal (GI) and hepatobiliary

As pregnancy progresses, pressure from the enlarging uterus on the rectum and lower portion of the colon may cause constipation. GI motility decreases because elevated progesterone levels relax smooth muscle. Heartburn and belching are common, possibly resulting from delayed gastric emptying and gastroesophageal reflux due to relaxation of the lower esophageal sphincter and diaphragmatic hiatus. Hydrochloric acid production decreases; thus, peptic ulcer disease is uncommon during pregnancy, and preexisting ulcers often become less severe.

Incidence of gallbladder disorders increases somewhat. Pregnancy subtly affects hepatic function, especially bile transport. Routine liver function test values are normal, except for alkaline phosphatase levels, which increase progressively during the 3rd trimester and may be 2 to 3 times normal at term; the increase is due to placental production of this enzyme rather than hepatic dysfunction.

Endocrine

Pregnancy alters the function of most endocrine glands, partly because the placenta produces hormones and partly because most hormones circulate in protein-bound forms and protein binding increases during pregnancy.

The placenta produces the beta subunit of human chorionic gonadotropin (beta-hCG), a trophic hormone that, like follicle-stimulating and luteinizing hormones, maintains the corpus luteum and thereby prevents ovulation. Levels of estrogen and progesterone increase early during pregnancy because beta-hCG stimulates the ovaries to continuously produce them. After 9 to 10 weeks of pregnancy, the placenta itself produces large amounts of estrogen and progesterone to help maintain the pregnancy.

The placenta produces a hormone (similar to thyroid-stimulating hormone) that stimulates the thyroid, causing hyperplasia, increased vascularity, and moderate enlargement. Estrogen stimulates hepatocytes, causing increased thyroid-binding globulin levels; thus, although total thyroxine levels may increase, levels of free thyroid hormones remain normal. Effects of thyroid hormone tend to increase and may resemble hyperthyroidism, with tachycardia, palpitations, excessive perspiration, and emotional instability. However, true hyperthyroidism occurs in only 0.08% of pregnancies.

The placenta produces corticotropin-releasing hormone (CRH), which stimulates maternal adrenocorticotropic hormone (ACTH) production. Increased ACTH levels increase levels of adrenal hormones, especially aldosterone and cortisol, and thus contribute to edema.

Increased production of corticosteroids and increased placental production of progesterone lead to insulin resistance and an increased need for insulin, as does the stress of pregnancy and possibly the increased level of human placental lactogen. Insulinase, produced by the placenta, may also increase insulin requirements, so that many women with gestational diabetes develop more overt forms of diabetes.

The placenta produces melanocyte-stimulating hormone (MSH), which increases skin pigmentation late in pregnancy.

The pituitary gland enlarges by about 135% during pregnancy. The maternal plasma prolactin level increases by 10-fold. Increased prolactin is related to an increase in thyrotropin-releasing hormone production, stimulated by estrogen. The primary function of increased prolactin is to ensure lactation. The level returns to normal postpartum, even in women who breastfeed.

Dermatologic

Increased levels of estrogens, progesterone, and MSH contribute to pigmentary changes, although exact pathogenesis is unknown. These changes include

Melasma (mask of pregnancy), which is a blotchy, brownish pigment over the forehead and malar eminences

Darkening of the mammary areolae, axilla, and genitals

Linea nigra, a dark line that appears down the midabdomen

Melasma due to pregnancy usually regresses within a year.

Incidence of spider angiomas, usually only above the waist, and of thin-walled, dilated capillaries, especially in the lower legs, increases.