Name: Obiadi Ginika

Department: Anatomy

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Assignment

1. Physiology of lactation and details on the physiology of pregnancy in a normal woman

A. Physiology of lactation

Physiology of lactation is a process that begins to take effect well before the initial latch of the newborn infant. It requires the breast to change in composition, size, and shape during each stage of female development. Development includes puberty, pregnancy, and lactation. These stages are influenced by a cascade of physiologic changes that are crucial to successful breastfeeding.

The process of lactation and breastfeeding can be negatively affected by anything that interrupts the normal development of the female breast, or that interferes with the production of milk. Women who have had breast augmentation may experience issues with lactation and breastfeeding, but this is dependent on the location of the incision. Incisions made in the armpit are more favorably for normal breastfeeding; whereas, the "smile" incision around the areola increases the woman's risk of having breastfeeding issues.

In the post-partum period, some women may experience difficulty with lactation if they have inadequate milk production, poor milk extraction, and insufficient caloric intake to meet demands. Current recommendations for lactating women are to have a minimum excess of 500 calories per day to meet the caloric demands for milk production. Women are also encouraged to empty the breast as often as possible, typically every 2 to 3 hours to maintain milk supply.

Issues of concern regarding lactation include the infant’s inability to latch, nipple pain, mastitis, or plugged ducts. The normal breast consists of two major structures (ducts and lobules), two types of epithelial cells (luminal and myoepithelial), and two types of stroma (interlobular and intralobular). Six to ten major duct orifices open onto the skin surface of the nipple. The uppermost portion is lined with keratinized squamous cells that abruptly change to the double-layered epithelium (luminal and myoepithelial) of the remainder of the duct and lobule system. Large ducts will eventually lead to the terminal duct lobular unit, and these terminal ducts will then branch into grape-like clusters of small acini to form a lobule.

There are three types of lobules, type 1, 2, and 3 which form at different stages in a woman's development. Lobules increase progressively in number and size, and by the end of pregnancy, the breast is composed almost entirely of lobules separated by small amounts of the stroma. Only with the onset of pregnancy does the breast become completely mature and functional.

During puberty, lobule type 1 is formed. Changes in the level of estrogen and progesterone during each menstrual cycle stimulate lobule 1 to produce new alveolar buds and eventually evolve to more mature structures, known as type-2 and type-3 lobules. Once puberty is complete, no further changes occur to the female breast until pregnancy.

During pregnancy, stage-II mammogenesis (alveolar development and maturation of the epithelium) occurs largely in response to higher levels of progesterone. The increased volume of breast tissue during pregnancy is a result of the proliferation of secretory tissue. In early pregnancy, lobule type 3 is formed due to the influence of chorionic gonadotropin. These newly formed lobules have larger size and number of epithelial cells composing each acinus. In late

pregnancy, the proliferation of new acini is reduced, and the lumen becomes distended with secretory material or colostrum.

During labor and lactation, further growth and differentiation can be seen in the lobule along with milk secretion. The glandular component of the breast has now increased to the point where it is mainly formed of epithelial elements and very little stroma. This will persist throughout lactation.

Finally, the involution of mammary glands occurs with the cessation of lactation and requires a combination of lactogenic hormone deprivation and local autocrine signals that signal apoptotic cell death and tissue remodeling. Full regression does not occur, and pregnancy causes a permanent increase in the size and number of lobules. Following lactation, there is always the potential of the glands to produce milk in response to regular stimulation.

Normal lactation involves the female breast, anterior lobe of the pituitary, and the posterior lobe of the pituitary. Their roles in lactation are;

- Breast milk provides ideal nutrition for infants with vitamins, proteins, and fats that are more easily digested than formula.

-Breast milk contains antibodies from the mother that help babies fight off viruses and bacteria. Other anti-infective factors it provides include immunoglobulin (IgA in particular), white blood cells, whey protein (lysozyme and lactoferrin), and oligosaccharides.

-It also lowers the baby's risk of asthma, allergies, ear infections, respiratory illnesses, bouts of diarrhea, and the risk of diabetes and obesity.

Lactogenesis is the process of developing the ability to secrete milk and involves the maturation of alveolar cells. It takes place in 2 stages: secretory initiation and secretory activation.

- Stage I lactogenesis (secretory initiation) takes place during the second half of pregnancy. The placenta supplies high levels of progesterone which inhibit further differentiation. In this stage, small amounts of milk can be secreted by week 16 gestation. By late pregnancy, some women can express colostrum.
- Stage II lactogenesis (secretory activation) starts with copious milk production after delivery. With the removal of the placenta at delivery, the rapid drop in progesterone, as well as the presence of elevated levels of prolactin, cortisol, and insulin, is what stimulate this stage.

Lactation is maintained by regular removal of milk and stimulation of the nipple, which triggers prolactin release from the anterior pituitary gland and oxytocin from the posterior pituitary gland. For the ongoing synthesis and secretion of milk, the mammary gland must receive hormonal signals; and although prolactin and oxytocin act independently on different cellular receptors, their combined action is essential for successful lactation.

Prolactin is a polypeptide hormone synthesized by lactotrophic cells in the anterior pituitary and is structurally similar to growth hormone and placental lactogen. Prolactin is both positively and negatively regulated, but its main control comes from hypothalamic inhibitory factors such as dopamine which act on the D2 subclass of dopamine receptors present in lactotrophs. Prolactin stimulates mammary gland ductal growth and epithelial cell proliferation and induces milk protein synthesis. Emptying of the breast by the infant's suckling is thought to be the most important factor. Prolactin concentration increases rapidly with suckling of the nipple which stimulates nerve endings.

Oxytocin is involved in the milk ejection or letdown reflex. The tactile stimulation of the nipple-areolar complex by suckling leads to afferent signals to the hypothalamus that trigger release of oxytocin. This results in contraction of the myoepithelial cells, forcing milk into the ducts from the alveolar lumens and out through the nipple. Oxytocin also has a psychological effect, which includes inducing a state of calm, and reducing stress. It may also enhance feelings of affection between mother and child, an important factor in bonding.

Once lactation is established and maintained, production is regulated by the interaction of both physical and biochemical factors. If milk is not removed, elevated intramammary pressure and accumulation of a feedback inhibitor of lactation reduce milk production and initiate mammary involution. If breast milk is removed, the inhibitor is also removed, and secretion will resume. The role of the feedback inhibitor of lactation is to regulate the amount of milk produced which is determined by how much the baby takes, and therefore by how much the baby needs.

B.

The physiology of pregnancy in a normal woman.

Pregnancy is considered to last 266 days from the time of conception or 280 days from the first day of the last menstrual period if periods occur regularly every 28 days. Delivery date is estimated based on the last menstrual period. Delivery up to 2 weeks earlier or later than the estimated date is normal. Delivery before 37 weeks gestation is considered preterm; delivery after 42 weeks gestation is considered postterm.

The earliest sign of pregnancy and the reason most pregnant women initially see a physician is missing a menstrual period. For sexually active women who are of reproductive age and have regular periods, a period that is ≥ 1 week late is presumptive evidence of pregnancy.

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 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 pre-pregnancy level at about 6 weeks postpartum.

The increase in CO during pregnancy is due mainly to demands of the uteroplacental circulation; volume of the uteroplacental circulation increases markedly, and circulation within the intervillous space acts partly as an arteriovenous shunt. As the placenta and fetus develop, blood flow to the uterus must increase to about 1 L/min (20% of normal CO) at term. Increased needs of the skin (to regulate temperature) and kidneys (to excrete fetal wastes) account for some of the increased CO.

To increase CO, heart rate increases from the normal 70 to as high as 90 beats/min, and stroke volume increases. During the 2nd trimester, blood pressure (BP) usually drops (and pulse pressure widens), even though CO and renin and angiotensin levels increase, because uteroplacental circulation expands (the placental intervillous space develops) and systemic vascular resistance decreases. Resistance decreases because blood viscosity and sensitivity to angiotensin decrease. During the 3rd trimester, BP may return to normal. With twins, CO increases more and diastolic BP is lower at 20 weeks than with a single fetus. Exercise increases CO, heart rate, oxygen consumption, and respiratory volume/min more during pregnancy than at other times.

The hyperdynamic circulation of pregnancy increases frequency of functional murmurs and accentuates heart sounds. X-ray or ECG may show the heart displaced into a horizontal position, rotating to the left, with increased transverse diameter. Premature atrial and ventricular beats are common during pregnancy. All these changes are normal and should not be erroneously diagnosed as a heart disorder; they can usually be managed with reassurance alone. However, paroxysms of atrial tachycardia occur more frequently in pregnant women and may require prophylactic digitalization or other antiarrhythmic drugs. Pregnancy does not affect the indications for or safety of cardioversion.

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 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 hemoglobin 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.

Changes in renal function roughly parallel those in cardiac function. Glomerular filtration rate 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 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; that is 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.

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 (CO_2) levels. To lower CO_2 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 PCO_2 decrease. Vital capacity and plasma PCO_2 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.

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.

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, 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, which stimulates maternal adrenocorticotropic hormone (ACTH) production. Increased ACTH levels increase levels of adrenal hormones, especially aldosterone and cortisol, and thus contribute to edema.

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. 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.

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

Pregnancy may cause breasts to be engorged because of increased levels
of estrogen (primarily) and progesterone an extension of premenstrual breast engorgement. Nausea, occasionally with vomiting, may occur because of increased secretion of estrogen and the beta subunit of human chorionic gonadotropin (beta-hCG) by syncytial cells of the placenta, beginning 10 days after fertilization. The corpus luteum in the ovary, stimulated by beta-hCG, continues secreting large amounts of estrogen and progesterone to maintain the pregnancy. Many women become fatigued at this time, and a few women notice abdominal bloating very early.
Women usually begin to feel fetal movement between 16 and 20 weeks.

During late pregnancy, lower-extremity edema and varicose veins are common; the main cause is compression of the inferior vena cava by the enlarged uterus. Pelvic examination findings include a softer cervix and an irregularly softened, enlarged uterus. The cervix usually becomes bluish to purple, probably because blood supply to the uterus is increased. Around 12

weeks gestation, the uterus extends above the true pelvis into the abdomen; at 20 weeks, it reaches the umbilicus; and by 36 weeks, the upper pole almost reaches the xiphoid process.

-Urine beta-hCG test

Usually urine and occasionally blood tests are used to confirm or exclude pregnancy; results are usually accurate several days before a missed menstrual period and often as early as several days after conception. Levels of beta-hCG, which correlate with gestational age in normal pregnancies, can be used to determine whether a fetus is growing normally. The best approach is to compare 2 serum beta-hCG values, obtained 48 to 72 hours apart and measured by the same laboratory. In a normal single pregnancy, beta-hCG levels double about every 1.4 to 2.1 days during the first 60 days then begin to decrease between 10 and 18 weeks. Regular doubling of the beta-hCG level during the 1st trimester strongly suggests normal growth.