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PHYSIOLOGY

Phs 204

Question: Discuss the physiology of lactation and gestation on a normal woman

1. **PHYSIOLOGY OF LACTATION ON A NORMAL WOMAN**

## INTRODUCTION

The normal 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. This article will review the development of the mammary gland (mammogenesis), the process by which the mammary gland develops the ability to secrete milk (lactogenesis), and the process of milk production (lactation).

## Cellular

It is important to learn the normal anatomy and cellular composition of breast tissue to understand the physiologic process of lactation. The normal breast consists of 2 major structures (ducts and lobules), 2 types of epithelial cells (luminal and myoepithelial), and 2 types of stroma (interlobular and intralobular). Six to 10 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 3 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.

## Development

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 are 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.

## Organ Systems Involved

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

## Function

The decision to breastfeed or to provide breast milk via expression is a decision that every mother must make. Clinicians must inform our patients about all the benefits that breast milk can provide to their newborn. 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.

## Pathophysiology

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, are what stimulate this stage. Usually, at days 2 or 3 postpartum, most women experience swelling of the breast along with copious milk production. In primiparous women, the secretory activation stage is slightly delayed, and early milk volume is lower. Lower milk volume is also observed in women who had cesarean births compared with those who delivered vaginally. Late onset of milk production has also been seen in women who have had retained placental fragments, diabetes, and stressful vaginal deliveries. With retained placental fragments, lactogenesis stage II could be inhibited by the continued secretion of progesterone and would continue to be inhibited until removal of the remaining placental fragments.

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 located there.

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.

## Clinical Significance

The normal development of the female breast is the foundation for mammogenesis, lactogenesis, and lactation. Clinicians who possess an understanding of the physiology of lactation will have the tools necessary to educate their patients to maximize chances of successful breastfeeding.

2) **PHYSIOLOGY OF GESTATION ON A NORMAL WOMAN**

### INTRODUCTION

Pregnancy in the human female is an unusual state in which virtually all maternal systems are dramatically altered to permit the sustenance and growth of the intrauterine conceptus. In very real ways, the maternal organism is life-adapted.

Although pregnancy is unique in many ways, it is particularly so in being limited in time. Pregnancy is a temporary state with a definite point of onset and an equally definite termination. The duration of pregnancy in humans, marked from the first day of the last menstrual period, is classically 280 days. Recent studies, however, using computerized day-counting techniques, show an average duration of 284.2 days.[1](https://www.glowm.com/section_view/heading/Physiology%20of%20Pregnancy/item/103#r1) Table 1 shows the mean values and statistical dispersion of gestational duration as well as a number of other gestational milestones.

Table 1. Mean observed intervals to delivery date for last menstrual period (LMP) and obstetric milestones\*

| **Milestone** | **Mean interval to delivery (days)** | **Standard deviations (days)** |
| --- | --- | --- |
| Known LMP | 284.2 | 14.6 |
| Quickening | 156.3 | 18.0 |
| Fetal heart audible | 136.2 | 17.0 |
| Uterus at umbilicus | 140.8 | 14.9 |

The changes brought about in the maternal organism by the state of pregnancy are important, because in many instances they mimic pathophysiologic responses to disease. If the constellation of changes occurring normally in pregnancy are misinterpreted as signs of disease processes, the gravid or puerperal woman may be subjected to diagnostic and therapeutic interventions that are not only unnecessary but may also be dangerous to mother and fetus.

Because so many system-specific changes occur in the course of pregnancy, it is difficult to develop a total physiologic overview. There are, however, a number of well-described adaptive physiologic states that produce changes in human systems similar to those seen in pregnancy. These adaptive states may be used as models or constructs to help integrate the diverse alterations in physiologic systems that occur during the course of normal gestation. Among the physiologic states that produce adaptive changes similar to those seen in pregnancy are the presence of a moderate-sized arteriovenous fistula, acclimation to increased environmental or internal heating, and adjustments to increasing levels of circulating progesterone.

### MODELS OF PREGNANCY AS A PHYSIOLOGICALLY ADAPTED STATE

Model I: Pregnancy as an Arteriovenous Fistula

In 1938, Burwell and associates[2](https://www.glowm.com/section_view/heading/Physiology%20of%20Pregnancy/item/103#r2) suggested that there are strong similarities between the physiologic alterations seen in normal pregnancy and those seen in patients with large arteriovenous fistulas. Patients on chronic renal dialysis who have peripheral shunts constructed for purposes of dialysis typically have flow rates in their shunts of approximately 600 ml/minute.[3](https://www.glowm.com/section_view/heading/Physiology%20of%20Pregnancy/item/103#r3) Because uteroplacental flow rates at term (nearly 600 ml/minute[4](https://www.glowm.com/section_view/heading/Physiology%20of%20Pregnancy/item/103#r4)) are essentially the same as those in the artificially produced shunts, it is not surprising that there are similarities between the cardiovascular changes in the shunted patients and cardiovascular alterations in the pregnant woman, particularly as she approaches term.

In both of these circumstances there is evidence of increased peripheral circulation, decreased peripheral resistance, increased heart rate, increased cardiac output, and increased plasma volume. This particular model can be used to explain a number of other changes related not directly to the shunting mechanism but to secondary changes produced by increased peripheral circulation, such as increased renal plasma flow and the physiologic alterations associated with increased renal perfusion.

Model II: Pregnancy as a State of Heat Adaptation

Abrams and associates and others[5](https://www.glowm.com/section_view/heading/Physiology%20of%20Pregnancy/item/103#r5),[6](https://www.glowm.com/section_view/heading/Physiology%20of%20Pregnancy/item/103#r6) have shown that there is a considerable temperature gradient between the mother and fetus. Aortic temperature measurements made in the pregnant ewe indicate that the fetal core temperature exceeds that of the mother by 0.5°C, which is a significant amount. Thermodynamics and the physics of heat transfer suggest that because of this temperature difference, the flow of heat from the fetus to the mother is relatively constant. As a result, the maternal organism must adjust her thermoregulatory system to permit increased heat loss to the environment. Aside from physical considerations, the need for maternal thermoregulatory adjustments is suggested by the observation that homeothermic mammals function within a very narrow range of internal temperatures. Extremes in either direction produce significant alterations in the function of fundamental systems responsible for the maintenance of life.

Responses of the homeothermic mammal to internal and environmental heating produce similar physiologic alterations. These include increased respiratory rate, increased cardiac output, increased heart rate, expansion of plasma volume, increased peripheral circulation, and a number of other changes similar to those seen in normal human gestation.

Model III: Pregnancy as a Hyperprogestational State

With the onset of normal gestation, all maternal systems are subjected to increasing levels of circulating progesterone. At first the corpus luteum of pregnancy, and later the placenta, produce large amounts of this hormone. At term, serum levels may be as high as 2.5 times those considered normal in the menstruating woman.

Increased basal body temperature and changes in the smooth muscle dynamics of the uterus, the vascular system, the urinary system, the gastrointestinal system, and the respiratory system in pregnancy have often been explained on the basis of increasing levels of serum progesterone. The mechanism proposed to explain many of these changes relates to the effect of progesterone on the electrochemical gradient at the cell membrane of individual smooth muscle fibers.[7](https://www.glowm.com/section_view/heading/Physiology%20of%20Pregnancy/item/103#r7) According to this hypothesis, progesterone acts to hyperpolarize the cell membrane, depressing the resting electrical potential at the membrane to a level below that of the normal activation threshold. This effectively puts the muscle at rest, because much greater levels of stimulation are required to produce depolarization and subsequent muscle contraction. Decreased tone and overall decrease in contractile activity is seen in most of the structures that depend on smooth muscle for their action. This includes the uterus, gut, respiratory system, ureters, and peripheral vascular system.

Volume expansion of the intravascular space, decreased peripheral resistance, increased heart rate, and a number of other alterations associated with the pregnant state could theoretically be explained on the basis of progesterone's effect on smooth muscle.

Overall, it seems unlikely that a single model can be invoked to explain the varied changes that take place in the human female during the course of gestation. It is more likely that all of these mechanisms contribute, along with other factors still unidentified, to the myriad changes that constitute the physiologic alterations associated with the normal human gestation. Each model, nonetheless, helps the clinician to anticipate and integrate the changes in many of the altered systems. The constructs described permit the alterations in individual systems to be fused into a more coherent overview.

### METABOLIC CHANGES

Basal metabolic studies carried out in the 1920s and 1930s by Sandiford and Wheeler[8](https://www.glowm.com/section_view/heading/Physiology%20of%20Pregnancy/item/103#r8) and Rowe and Boyd[9](https://www.glowm.com/section_view/heading/Physiology%20of%20Pregnancy/item/103#r9) demonstrated that pregnancy is characterized by increased metabolic activity as measured by the basal metabolic rate. In these studies, done on a small group of women throughout gestation, they found that the basal metabolic rate increased by approximately 20% as the pregnancy approached term. This trend is pictured in Figure 1. The researchers hypothesized that this increase in metabolic activity primarily represented increased fetal and placental metabolic work, with only a small fraction being attributable to increased maternal metabolic activity. At term, the products of gestation were estimated to be responsible for approximately 13% of the 20% increase in total metabolic activity. More modern studies[10](https://www.glowm.com/section_view/heading/Physiology%20of%20Pregnancy/item/103#r10),[11](https://www.glowm.com/section_view/heading/Physiology%20of%20Pregnancy/item/103#r11) using oxygen consumption measures and indirect calorimetry estimate the energy output of an average-sized pregnant woman at 36 weeks' gestation to be approximately 98 W (8443 ± 243 kJ/day). This compares with an energy output of approximately 81 W (6971 ± 172 kJ/day) for a similar-sized, nonpregnant, nonlactating woman. Although the more recent studies used different methodologies, they all support the results of the earlier work.