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Level: 300L[Carry over Student]

Course Code: PHS 204

Course Title: Endocrinology and Reproductive Physiology

Assignment Question(s): Discuss lactation and gestation period in a normal female

LACTATION AND GESTATION IN A NORMAL FEMALE

Lactation, 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 breasts, unlike most of the other organs, continue to increase in size after childbirth. Although mammary growth begins during pregnancy under the influence of ovarian and placental hormones, and some milk is formed, copious milk secretion sets in only after delivery. Since lactation ensues after a premature birth, it would appear that milk production is held back during pregnancy. The mechanism by which this inhibitory effect is brought about, or by which lactation is initiated at delivery, has long been the subject of an argument that revolves around the opposing actions of estrogen, progesterone, and prolactin, as studied in laboratory animals, goats, and cattle. During pregnancy the combination of estrogen and progesterone circulating in the blood appears to inhibit milk secretion by blocking the release of prolactin from the pituitary gland and by making the mammary gland cells unresponsive to this pituitary hormone. The blockade is removed at the end of pregnancy by the expulsion of the placenta and the loss of its supply of hormones, as well as by the decline in hormone production by the ovaries, while sufficient estrogen remains in circulation to promote the secretion of prolactin by the pituitary gland and so favour lactation.

human nutrition: Pregnancy and lactation

A woman’s nutritional status before and during pregnancy affects not only her own health but also the…

For lactation to continue, necessary patterns of hormone secretion must be maintained; disturbances of the equilibrium by the experimental removal of the pituitary gland in animals or by comparable diseased conditions in humans quickly arrest milk production. Several pituitary hormones seem to be involved in the formation of milk, so that it is customary to speak of a lactogenic (“milk-producing”) complex of hormones. To some degree, the role of the pituitary hormones adrenocorticotropin, thyrotropin, and growth hormone in supporting lactation in women is inferred from the results of studies done on animals and from clinical observations that are in agreement with the results of animal studies. Adrenal corticoids also appear to play an essential role in maintaining lactation.

The stimulus of nursing or suckling supports continued lactation. It acts in two ways: it promotes the secretion of prolactin (and possibly other pituitary hormones of value in milk formation), and it triggers the release of yet another hormone from the pituitary gland—oxytocin, which causes the contraction of special muscle cells around the alveoli in the breast and ensures the expulsion of milk. It is in this way that a baby’s sucking at one breast may cause an increase in milk flow from both, so that milk may drip from the unsuckled nipple. About 30 seconds elapse between the beginning of active suckling and the initiation of milk flow.

The nerve supply to the mammary glands is not of great significance in lactation, for milk production is normal after the experimental severing of nerves to the normal mammary glands in animals or in an udder transplanted to the neck of a goat. Milk ejection, or “the draught,” in women is readily conditioned and can be precipitated by the preparations for nursing. Conversely, embarrassment or fright can inhibit milk ejection by interfering with the release of oxytocin; alcohol, also, is known to block milk ejection in women, again by an action on the brain. Beyond its action on the mammary glands, oxytocin affects uterine muscle, so that suckling can cause contractions of the uterus and may sometimes result in cramp. Since oxytocin release occurs during sexual intercourse, milk ejection in lactating women has been observed on such occasions. Disturbance of oxytocin secretion, or of the milk-ejection reflex, stops lactation just

as readily as a lack of the hormones necessary for milk production, for the milk in the breast is then not extractable by the infant. Many instances of nursing failure are due to a lack of milk ejection in stressful circumstances; fortunately, treatment with oxytocin, coupled with the reassurance gained from a successful nursing, is ordinarily successful in overcoming the difficulty.

Suckling can initiate lactation in nonpregnant women. This has been seen most often in women of childbearing age but also has been observed in older persons. A baby who had lost his mother was suckled by his 60-year-old grandmother, who had borne her last child 18 years before. The grandmother produced milk after a few days and continued to nurse the baby until he was a year old and could walk. Rarely, lactation has been reported to set in after operations on the chest; in such instances it is attributed to injury or irritation of the nerves in this region. Such observations argue against the possibility that lactation continues simply as a consequence of emptying the breasts.

Composition And Properties Of Milk

Milk can be regarded as an emulsion of fat globules in a colloidal solution of protein together with other substances in true solution. Two constituents of milk—the protein casein and milk sugar, or lactose—are not found elsewhere in the body.

Breastfeeding is particularly advantageous because of the nutritional, immunologic, and psychological benefits. Human breast milk is superior to modified cow's milk formulas, which may lack essential and beneficial components and are not absorbed as easily or as quickly by the infant. Maternal breast milk provides vitamins, minerals, protein, and anti-infectious factors; antibodies that protect the infant's gastrointestinal tract are supplied, resulting in a lower rate of enteric infection in breast-fed than in bottle-fed babies. The bonding that is established through breast-feeding is advantageous to building the parent-child relationship.

The nutritional status of the mother is important throughout this period. The mother's daily caloric intake must increase significantly in order to replenish the mother's nutrient and energy stores. The use of drugs or smoking by the mother can adversely affect the infant; many drugs are secreted in breast milk, and smoking reduces breast milk volume and decreases infant

growth rates.

The milk released from the breast when lactation starts differs in composition from the mature milk produced when lactation is well established. The early milk, or colostrum, is rich in essential amino acids, the protein building blocks essential for growth; it also contains the proteins that convey immunity to some infections from mother to young, although not in such quantity as among domestic animals. The human infant gains this type of immunity largely within the uterus by the transfer of these antibody proteins through the placenta; the young baby seldom falls victim to mumps, measles, diphtheria, or scarlet fever. For a short time after birth, proteins can be absorbed from the intestine without digestion, so that the acquisition of further immunity is facilitated. The growth of harmful viruses and bacteria in the intestines is probably inhibited by immune factors in human milk. After childbirth the composition of milk gradually changes; within four or five days the colostrum has become transitional milk, and mature milk is secreted some 14 days after delivery.

Some variations between human colostrum, transitional milk, and mature milk and cow’s milk are shown in Table 2. The greater amount of protein in unmodified cow’s milk is largely responsible for its dense, hard curd, which the infant cannot digest; the difficulty can be avoided by heat treatment or dilution of the milk. Ordinarily, when cow’s milk is fed to young infants, it is modified so as to match its composition as far as possible to breast milk.

Some constituents of human colostrum, transitional, and mature milk and of cow's milk

(average values per 100 millilitres whole milk)

colostrum (1–5 days) transitional (6–14 days) mature (after 14 days) cow's milk

*Kilocalorie; sufficient energy to raise the temperature of 1 kilogram of water 1 degree Centigrade.

energy, kcal*	58	74	71	69
total solids, g	12.8	13.6	12.4	12.7
fat, g	2.9	3.6	3.8	3.7
lactose, g	5.3	6.6	7.0	4.8
protein, g	2.7	1.6	1.2	3.3

casein, g	1.2	0.7	0.4	2.8	
ash, g	0.33	0.24	0.21	0.72	
calcium, mg	31	34	33	125	
magnesium, mg		4	4	4	12
potassium, mg		74	64	55	138
sodium, mg	48	29	15	58	
iron, mg	0.09	0.04	0.15	0.10	

Weaning And The Cessation Of Lactation

There is no typical age at which human infants are weaned, for this varies from country to country and among the social classes of a nation. In India women in the higher socioeconomic groups tend to use artificial feeding, while the reverse relationship holds in Britain and the United States. Most commonly, weaning is a gradual process, with a gradual increase in the proportion of solid food supplied to the infant together with breast milk. Pediatricians in general have concluded that, on the basis of present knowledge, no nutritional superiority or psychological benefits result from the introduction of solid foods into the infant diet earlier than the age of 21/2 to 31/2 months and that normal full-term infants can be expected to thrive for the first six months of life on a diet consisting exclusively of milk, either normal human milk or properly modified milk from other sources.

With the reduced demand of the baby, lactation slowly declines and stops. Estrogen treatment is often used to suppress lactation, and the high doses used may accomplish this; but there is often a rebound effect at the end of treatment. Lactation may be slightly depressed when oral contraceptives are being taken in high dosage. Although ovulation is less frequent during lactation, it does occasionally occur. Breast-feeding should not, therefore, be used as a method of contraception. Menstruation usually resumes within six to eight weeks in women who are not breast-feeding; the length of its absence varies in women who breast-feed.

Bernard Thomas Donovan

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Overview of Lactation

Lactation is the secretion of milk from specialized glands (mammary glands) to provide nourishment to offspring.

Lactation is a hallmark feature of female mammals.

Lactation is under endocrine control. The two main hormones involved are prolactin and oxytocin.

Lactogenesis, or the process of changes to the mammary glands to begin producing milk, begins during the late stages of pregnancy. The delivery of the placenta and the resulting dramatic reduction in progesterone, estrogen, and human placental lactogen levels stimulate milk production.

Colostrum is the first milk a breastfed baby receives. It contains higher amounts of white blood cells and antibodies than mature milk and is especially high in immunoglobulin A. This immunoglobulin coats the lining of the baby's immature intestines, helping to prevent pathogens from invading the baby's system.

witch's milk: Witch's milk or neonatal milk is milk secreted from the breasts of some newborn human infants of either sex. Neonatal milk secretion is considered a normal physiological occurrence and no treatment or testing is necessary.

mammary gland: A gland that secretes milk for suckling an infant or offspring.

lactation: 1. The secretion of milk from the mammary gland of a female mammal. 2. The process of providing the milk to the young, such as breastfeeding. 3. The period of time that a

mother lactates to feed her young; the lactation period.

human placental lactogen: A hormone closely associated with prolactin that is

instrumental in breast, nipple, and areola growth before birth.

colostrum: A form of milk produced by the mammary glands in late pregnancy and the few days after giving birth. Human and bovine colostrum is thick and yellowish. In humans, it has high concentrations of nutrients and antibodies, but it is small in quantity.

Lactation describes the secretion of milk from the mammary glands and the period of time that a mother lactates to feed her young. The process occurs in all female mammals, although it predates the origin of mammals.

In humans the process of feeding milk is called breastfeeding or nursing.

The chief function of lactation is to provide nutrition and immune protection to the young after birth. In almost all mammals, lactation induces a period of infertility, which serves to provide the optimal birth spacing for survival of the offspring.

In most species, milk comes out of the mother's nipples; however, the platypus (a non-placental mammal) releases milk through ducts in its abdomen. In only one species of mammal, the dayak fruit bat, is milk production a normal male function.

In some other mammals, the male may produce milk as the result of a hormone imbalance. This phenomenon may also be observed in newborn infants as well (for instance, witch's milk).

Galactopoiesis is the maintenance of milk production. This stage requires prolactin and oxytocin.

Preparation for Lactation

By the fifth or sixth month of pregnancy, the breasts are ready to produce milk. During the latter part of pregnancy, the woman's breasts enter into the lactogenesis I stage. This is when the breasts make colostrum, a thick, sometimes yellowish fluid.

At this stage, high levels of progesterone inhibit most milk production. It is not a medical concern if a pregnant woman leaks any colostrum before her baby's birth, nor is it an indication of future milk production.

At birth, prolactin levels remain high, while the delivery of the placenta results in a sudden drop in progesterone, estrogen, and human placental lactogen levels. This abrupt withdrawal of progesterone in the presence of high prolactin levels stimulates the copious milk production of the lactogenesis II stage.

When the breast is stimulated, prolactin levels in the blood rise and peak in about 45 minutes, then return to the pre-breastfeeding state about three hours later. The release of prolactin triggers the cells in the alveoli to make milk.

Colostrum

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This is an illustration of the positive feedback loop that is created to ensure that milk production continues as long as the infant continues to breastfeed. The increase in milk production causes an increase in infant suckling.

Lactation: A positive feedback loop ensures continued milk production as long as the infant continues to breastfeed.

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Physiology of Lactation

Physiology, Lactation

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Publication Details

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).[1][2][3]

Issues of Concern

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 is 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.[4][5][6][7]

Other issues of concern regarding lactation include the infants inability to latch, nipple pain, mastitis, or plugged ducts.

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.[8]

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.

P

Physiological changes occur in pregnancy to nurture the developing foetus and prepare the mother for labour and delivery. Some of these changes influence normal biochemical values while others may mimic symptoms of medical disease. It is important to differentiate between normal physiological changes and disease pathology. This review highlights the important changes that take place during normal pregnancy.

During pregnancy, the pregnant mother undergoes significant anatomical and physiological changes in order to nurture and accommodate the developing foetus. These changes begin after conception and affect every organ system in the body.1 For most women experiencing an uncomplicated pregnancy, these changes resolve after pregnancy with minimal residual effects. It is important to understand the normal physiological changes occurring in pregnancy as this will help differentiate from adaptations that are abnormal.

Plasma volume increases progressively throughout normal pregnancy.2 Most of this 50% increase occurs by 34 weeks' gestation and is proportional to the birthweight of the baby. Because the expansion in plasma volume is greater than the increase in red blood cell mass, there is a fall in haemoglobin concentration, haematocrit and red blood cell count. Despite this haemodilution, there is usually no change in mean corpuscular volume (MCV) or mean corpuscular haemoglobin concentration (MCHC).

The platelet count tends to fall progressively during normal pregnancy, although it usually remains within normal limits. In a proportion of women (5–10%), the count will reach levels of 100–150 × 109 cells/l by term and this occurs in the absence of any pathological process. In practice, therefore, a woman is not considered to be thrombocytopenic in pregnancy until the platelet count is less than 100 × 109 cells/l.

Pregnancy causes a two- to three-fold increase in the requirement for iron, not only for haemoglobin synthesis but also for for the foetus and the production of certain enzymes. There is a 10- to 20-fold increase in folate requirements and a two-fold increase in the requirement for vitamin B12.

Changes in the coagulation system during pregnancy produce a physiological hypercoagulable state (in preparation for haemostasis following delivery).3 The concentrations of certain clotting factors, particularly VIII, IX and X, are increased. Fibrinogen levels rise significantly by up to 50% and fibrinolytic activity is decreased. Concentrations of endogenous anticoagulants such as antithrombin and protein S decrease. Thus pregnancy alters the balance within the coagulation system in favour of clotting, predisposing the pregnant and postpartum woman to venous thrombosis. This increased risk is present from the first trimester and for at least 12 weeks following delivery. In vitro tests of coagulation [activated partial thromboplastin time (APTT), prothrombin time (PT) and thrombin time (TT)] remain normal in the absence of anticoagulants or a coagulopathy.

Venous stasis in the lower limbs is associated with venodilation and decreased flow, which is more marked on the left. This is due to compression of the left iliac vein by the left iliac artery and the ovarian artery. On the right, the iliac artery does not cross the vein.

Cardiac changes

Changes in the cardiovascular system in pregnancy are profound and begin early in pregnancy, such that by eight weeks' gestation, the cardiac output has already increased by 20%. The primary event is probably peripheral vasodilatation. This is mediated by endothelium-dependent factors, including nitric oxide synthesis, upregulated by oestradiol and possibly vasodilatory prostaglandins (PGI2). Peripheral vasodilation leads to a 25–30% fall in systemic vascular resistance, and to compensate for this, cardiac output increases by around 40% during pregnancy. This is achieved predominantly via an increase in stroke volume, but also to a lesser extent, an increase in heart rate. The maximum cardiac output is found at about 20–28 weeks' gestation. There is a minimal fall at term.

An increase in stroke volume is possible due to the early increase in ventricular wall muscle mass and end-diastolic volume (but not end-diastolic pressure) seen in pregnancy. The heart is physiologically dilated and myocardial contractility is increased. Although stroke volume declines towards term, the increase in maternal heart rate (10–20 bpm) is maintained, thus preserving the increased cardiac output. Blood pressure decreases in the first and second trimesters but increases to non-pregnant levels in the third trimester

There is a profound effect of maternal position towards term upon the haemodynamic profile of both the mother and foetus. In the supine position, pressure of the gravid uterus on the inferior vena cava (IVC) causes a reduction in venous return to the heart and a consequent fall in stroke volume and cardiac output. Turning from the lateral to the supine position may result in a 25% reduction in cardiac output. Pregnant women should therefore be nursed in the left or right lateral position wherever possible. If the woman has to be kept on her back, the pelvis should be rotated so that the uterus drops to the side and off the IVC, and cardiac output and uteroplacental blood flow are optimised. Reduced cardiac output is associated with a reduction in uterine blood flow and therefore in placental perfusion, which could compromise the foetus.

Although both blood volume and stroke volume increase in pregnancy, pulmonary capillary wedge pressure and central venous pressure do not increase significantly. Pulmonary vascular resistance (PVR), like systemic vascular resistance (SVR), decreases significantly in normal pregnancy. Although there is no increase in pulmonary capillary wedge pressure (PCWP), serum

colloid osmotic pressure is reduced by 10–15%. The colloid osmotic pressure/pulmonary capillary wedge pressure gradient is reduced by about 30%, making pregnant women particularly susceptible to pulmonary oedema. Pulmonary oedema will be precipitated if there is either an increase in cardiac pre-load (such as infusion of fluids) or increased pulmonary capillary permeability (such as in pre-eclampsia) or both.

Labour is associated with further increases in cardiac output (15% in the first stage and 50% in the second stage) Uterine contractions lead to an auto-transfusion of 300–500 ml of blood back into the circulation and the sympathetic response to pain and anxiety further elevate the heart rate and blood pressure. Cardiac output is increased between contractions but more so during contractions.

Following delivery there is an immediate rise in cardiac output due to relief of the inferior vena cava obstruction and contraction of the uterus, which empties blood into the systemic circulation. Cardiac output increases by 60–80%, followed by a rapid decline to pre-labour values within about one hour of delivery. Transfer of fluid from the extravascular space increases venous return and stroke volume further.

Those women with cardiovascular compromise are therefore most at risk of pulmorary oedema during the second stage of labour and the immediate postpartum period. Cardiac output has nearly returned to normal (pre-pregnancy values) two weeks after delivery, although some pathological changes (e.g. hypertension in pre-eclampsia) may take much longer.

The above physiological changes lead to changes on cardiovascular examination that may be misinterpreted as pathological by those unfamiliar with pregnancy. Changes may include a bounding or collapsing pulse and an ejection systolic murmur, present in over 90% of pregnant women. The murmur may be loud and audible all over the precordium, with the first heart sound loud and possibly sometimes a third heart sound. There may be ectopic beats and peripheral oedema.

Normal findings on ECG in pregnancy that may partly relate to changes in the position of the heart include:

atrial and ventricular ectopics

Q wave (small) and inverted T wave in lead III

ST-segment depression and T-wave inversion in the inferior and lateral leads

left-axis shift of QRS.

Adaptive changes in renal vasculature

The primary adaptive mechanism in pregnancy is a marked fall in systemic vascular resistance (SVR) occurring by week six of gestation. The 40% fall in SVR also affects the renal vasculature.4 Despite a major increase in plasma volume during pregnancy, the massive decrease in SVR creates a state of arterial under-filling because 85% of the volume resides in the venous circulation.5 This arterial under-filling state is unique to pregnancy. The fall in SVR is combined with increased renal blood flow and this is in contrast to other states of arterial under -filling, such as cirrhosis, sepsis or arterio-venous fistulas.3,6

Relaxin, a peptide hormone produced by the corpus luteum, decidua and placenta, plays an important role in the regulation of haemodynamic and water metabolism during pregnancy. Serum concentrations of relaxin, already elevated in the luteal phase of the menstrual cycle, rise after conception to a peak at the end of the first trimester and fall to an intermediate value throughout the second and third trimester. Relaxin stimulates the formation of endothelin, which in turn mediates vasodilation of renal arteries via nitric oxide (NO) synthesis.7

Despite activation of the renin–angiotensin–aldosterone (RAA) system in early pregnancy, a simultaneous relative resistance to angiotensin II develops, counterbalancing the vasoconstrictive effect and allowing profound vasodilatation.8 This insensitivity to angiotensin II may be explained by the effects of progesterone and vascular endothelial growth factormediated prostacyclin production, as well as modifications in the angiotensin I receptors during pregnancy.9 The vascular refractoriness to angiotensin II may also be shared by other vasoconstrictors such as adrenergic agonists and arginine vasopressin (AVP).10 It is possible that in the second half of pregnancy, the placental vasodilatators are more important in the maintenance of the vasodilatatory state.6

Changes in renal anatomy and function

As a consequence of renal vasodilatation, renal plasma flow and glomerular filtration rate (GFR) both increase, compared to non-pregnant levels, by 40–65 and 50–85%, respectively. In addition, the increase in plasma volume causes decreased oncotic pressure in the glomeruli, with a subsequent rise in GFR.11 Vascular resistance decreases in both the renal afferent and efferent arterioles and therefore, despite the massive increase in renal plasma flow, glomerular hydrostatic pressure remains stable, avoiding the development of glomerular hypertension. As the GFR rises, both serum creatinine and urea concentrations decrease to mean values of about 44.2 μmol/l and 3.2 mmol/l, respectively.

The increased renal blood flow leads to an increase in renal size of 1–1.5 cm, reaching the maximal size by mid-pregnancy. The kidney, pelvis and calyceal systems dilate due to mechanical compressive forces on the ureters. Progesterone, which reduces ureteral tone, peristalsis and contraction pressure, mediates these anatomical changes.11 The increase in renal size is associated with an increase in renal vasculature, interstitial volume and urinary dead space. There is also dilation of the ureters, renal pelvis and calyces, leading to physiological hydronephrosis in over 80% of women.12 There is often a right-sided predominance of hydronephrosis due to the anatomical circumstances of the right ureter crossing the iliac and ovarian vessels at an angle before entering the pelvis. Urinary stasis in the dilated collecting system predisposes pregnant women with asymptomatic bacteriuria to pyelonephritis.12

There are also alterations in the tubular handling of wastes and nutrients. As in the non-pregnant state, glucose is freely filtered in the glomerulus. During pregnancy, the reabsorption of glucose in the proximal and collecting tubule is less effective, with variable excretion. About 90% of pregnant women with normal blood glucose levels excrete 1–10 g of glucose per day. Due to the increases in both GFR and glomerular capillary permeability to albumin, the fractional excretion of protein may increase up to 300 mg/day and protein excretion also increases. In normal pregnancies the total protein concentration in urine does not increase above the upper normal limit. Uric acid excretion also increases due to increased GFR and/or decreased tubular reabsorption.11

Body water metabolism

Arterial under-filling in pregnancy leads to the stimulation of arterial baroreceptors, activating the RAA and the sympathetic nervous systems. This results in a non-osmotic release of AVP from the hypothalamus. These changes lead to sodium and water retention in the kidneys and

create a hypervolaemic, hypoosmolar state characteristic of pregnancy.6 Extracellular volume increases by 30–50% and plasma volume by 30–40%. Maternal blood volume increases by 45% to approximately 1 200 to 1 600 ml above non-pregnant values. By the late third trimester the plasma volume increases by more than 50–60%, with a lower increase in red blood cell mass, and therefore plasma osmolality falls by 10 mosmol/kg. The increase in plasma volume plays a critical role in maintaining circulating blood volume, blood pressure and uteroplacental perfusion during pregnancy.13

Activation of the RAA system leads to increased plasma levels of aldosterone and subsequent salt and water retention in the distal tubule and collecting duct. In addition to the increased renin production by the kidneys, ovaries and uteroplacental unit produce an inactive precursor protein of renin in early pregnancy.14 The placenta also produces oestrogens that stimulate the synthesis of angiotensinogen by the liver, resulting in proportionally increased levels of aldosterone compared to renin. Plasma levels of aldosterone correlate well with those of oestrogens and rise progressively during pregnancy. The increase in aldosterone is responsible for the increase in plasma volume during pregnancy.13 Progesterone, which is a potent aldosterone antagonist, allows natriuresis despite the sodium-retaining properties of aldosterone. The rise in GFR also increases distal sodium delivery, allowing excretion of excess sodium. Progesterone has antikaliuretic effects and therefore excretion of potassium is kept constant throughout pregnancy due to changes in tubular reabsorption, and total body potassium increases during pregnancy.6,15

Hypothalamic AVP release increases early in pregnancy as a result of increased relaxin levels. AVP mediates an increase in water reabsorption via aquaporin 2 channels in the collecting duct. The threshold for hypothalamic secretion of AVP and the threshold for thirst is reset to a lower plasma osmolality level, creating the hypo-osmolar state characteristic of pregnancy. These changes are mediated by human chorionic gonadotropin (hCG) and relaxin.11,16

In middle and late pregnancy there is a four-fold increase in vasopressinase, an aminopeptidase produced by the placenta. These changes enhance the metabolic clearance of vasopressin and regulate the levels of active AVP. In conditions of increased placental production of vasopressinase, such as pre-eclampsia or twin pregnancies, a transient diabetes insipidus may develop.17 As a consequence of this volume expansion, the secretion of atrial natriuretic peptides increases by 40% in the third trimester, and rises further during the first week postpartum. The levels of natriuretic peptides are higher in pregnant women with chronic hypertension and pre-eclampsia.18

Respiratory changes

There is a significant increase in oxygen demand during normal pregnancy. This is due to a 15% increase in the metabolic rate and a 20% increased consumption of oxygen. There is a 40–50% increase in minute ventilation, mostly due to an increase in tidal volume, rather than in the respiratory rate. This maternal hyperventilation causes arterial pO2 to increase and arterial pCO2 to fall, with a compensatory fall in serum bicarbonate to 18–22 mmol/l (see Table 1). A mild fully compensated respiratory alkalosis is therefore normal in pregnancy (arterial pH 7.44).

Table 1

1. Reference ranges for respiratory function in pregnancy

Normal values

Investigations	Pregnant	Non-pregnant
pH	7.40–7.47	7.35–7.45
pCO2, mmHg (kPa)	≤ 30 (3.6–4.3)	35–40 (4.7–6.0)
pO2, mmHg (kPa)	100–104 (12.6–14.0)	90–100 (10.6–14.0)
Base excess	No change	+2 to −2
Bicarbonate (mmol/l)	18–22	20–28

Diaphragmatic elevation in late pregnancy results in decreased functional residual capacity but diaphragmatic excursion and therefore vital capacity remain unaltered. Inspiratory reserve volume is reduced early in pregnancy, as a result of increased tidal volume, but increases in the third trimester, as a result of reduced functional residual capacity (see Fig. 1). Peak expiratory flow rate (PEFR) and forced expiratory volume in one second (FEV1) are unaffected by pregnancy.

Fig. 1.

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Physiological changes in respiratory function in pregnancy.

Pregnancy may also be accompanied by a subjective feeling of breathlessness without hypoxia. This is physiological and is most common in the third trimester but may start at any time during gestation. Classically, the breathlessness is present at rest or while talking and may paradoxically improve during mild activity.

Adaptive changes in the alimentary tract

Nausea and vomiting are very common complaints in pregnancy, affecting 50–90% of pregnancies.19 This might be an adaptive mechanism of pregnancy, aiming at preventing pregnant women from consuming potentially teratogenic substances such as strong-tasting fruits and vegetables. The exact underlying mechanism is not clear but pregnancy-associated hormones such as human chorionic gonadotropin (hCG), oestrogen and progesterone could to be involved in the aetiology. The levels of hCG peak at the end of the first trimester when the trophoblast is most actively producing hCG, correlating with the nausea symptoms. Nausea is also more frequent in pregnancies with high levels of hCG, such as in twin pregnancies.

Thyroid hormones may also be involved in the development of nausea symptoms, as a strong association with nausea and abnormal thyroid function tests has been found. Thyroid-stimulating hormone (TSH) and hCG have similar biomolecular structures and therefore hCG cross-reacts with TSH, stimulating the thyroid gland.18 Psychological causes, genetic incompatibility, immunological factors, nutritional deficiencies as well as Helicobacter pylori infection have been proposed as aetiological factors of nausea and vomiting during pregnancy.20

The nausea symptoms usually resolve by week 20 but about 10–20% of the patients experience symptoms beyond week 20 and some until the end of the pregnancy.21 In most cases minor dietary modification and observation of electrolyte balance is sufficient. About 0.5–3% of pregnant women develop hyperemesis gravidum, a severe form of nausea and excessive vomiting, often resulting in dehydration, electrolyte imbalance, ketonuria, weight loss and vitamin or mineral deficiencies.19,21 In these cases intravenous fluid and vitamin substitution is commonly required. Thiamine supplementation is important in order to avoid the development of Wernicke’s encephalopathy.22

As pregnancy progresses, mechanical changes in the alimentary tract also occur, caused by the growing uterus. The stomach is increasingly displaced upwards, leading to an altered axis and increased intra-gastric pressure. The oesophageal sphincter tone is also decreased and these factors may predispose to symptoms of reflux, as well as nausea and vomiting.23

Changes in oestrogen and progesterone levels also influence the structural alterations in the gastrointestinal tract. These include abnormalities in gastric neural activity and smooth muscle function, leading to gastic dysrhythmia or gastroparesis. The alterations are pronounced in women with pre-existing gastrointestinal diseases such as gastroesophageal reflux disease, diabetic gastroparesis, gastric bypass surgery or inflammatory bowel disease.21,23

Endocrine changes

Thyroid

There is an increase in the production of thyroxine-binding globulin (TBG) by the liver, resulting in increased levels of thyroxine (T4) and tri-iodothyronine (T3). Serum free T4 (fT4) and T3 (fT3) levels are slightly altered but are usually of no clinical significance. Levels of free T3 and T4 do however decrease slightly in the second and third trimesters of pregnancy and the normal ranges are reduced.24 Free T3 and T4 are the physiologically important hormones and are the main determinants of whether a patient is euthyroid.

Serum concentrations of TSH are decreased slightly in the first trimester in response to the thyrotropic effects of increased levels of human chorionic gonadotropin. Levels of TSH increase again at the end of the first trimester, and the upper limit in pregnancy is raised to 5.5 μmol/l compared with the level of 4.0 μmol/l in the non-pregnant state (Table 2).

Table 2

Reference ranges for thyroid function in pregnancy37

Thyroid function	Non-pregnant	1st trimester	2nd trimester	3rd trimester
fT4 (pmol/l)	9–26	10–16	9–15.5	8–14.5
fT3 (pmol/l)	2.6–5.7	3–7	3–5.5	2.5–5.5
TSH (mU/l)	0.3–4.2	0–5.5	0.5–3.5	0.5–3.5

Pregnancy is associated with a relative iodine deficiency. The causes for this are active transport of iodine from the mother to the foeto-placental unit and increased iodine excretion in the urine. The World Health Organisation recommends an increase in iodine intake in pregnancy from 100 to 150–200 mg/day.24 If iodine intake is maintained in pregnancy, the size of the thyroid gland remains unchanged and therefore the presence of goiter should always be

investigated. The thyroid gland is 25% larger in patients who are iodine deficient.

Adrenal gland

Three types of steroids are produced by the adrenal glands: mineralocorticoids, glucocorticoids and sex steroids. The RAA system is stimulated due to reductions in vascular resistance and blood pressure, causing a three-fold increase in aldosterone levels in the first trimester and a 10 -fold increase in the third trimester.25,26 Levels of angiotensin II are increased two- to four-fold and renin activity is increased three to four times that of non-pregnant values.

During pregnancy there is also an increase in serum levels of deoxycorticosterone, corticosteroid-binding globulin (CBG), adrenocorticotropic hormone (ACTH), cortisol and free cortisol. These changes cause a state of physiological hypercortisolism and may be clinically manifested by the striae, facial plethora, rising blood pressure or impaired glucose tolerance.27 Total cortisol levels increase at the end of the first trimester and are three times higher than non -pregnant values at the end of pregnancy. Hypercortisolism in late pregnancy is also the result of the production of corticotropin-releasing hormone by the placenta – one of the triggers for the onset of labour. Diurnal variations in ACTH and cortisol levels are maintained. The hypothalamic–pituitary axis response to exogenous glucocorticoids is blunted during pregnancy.

Pituitary gland

The pituitary gland enlarges in pregnancy and this is mainly due to proliferation of prolactin-producing cells in the anterior lobe. Serum prolactin levels increase in the first trimester and are 10 times higher at term. The increase in prolactin is most likely due to increasing serum oestradiol concentrations during pregnancy. Levels of follicle-stimulating hormone (FSH) and luteinising hormone (LH) are undetectable during pregnancy due to the negative feedback from elevated levels of oestrogen, progesterone and inhibin.28 Pituitary growth hormone production is decreased but serum growth hormone levels are increased due to growth hormone production from the placenta.

The posterior pituitary produces oxytocin and arginine vasopressin (AVP). Oxytocin levels increase in pregnancy and peak at term. Levels of antidiuretic hormone (ADH) remain unchanged but the decrease in sodium concentration in pregnancy causes a decrease in osmolality. There is therefore a resetting of osmoreceptors for ADH release and thirst.29

Glucose metabolism

Pregnancy is a diabetogenic state and the adaptations in glucose metabolism allow shunting of glucose to the foetus to promote development, while maintaining adequate maternal nutrition.30 Insulin-secreting pancreatic beta-cells undergo hyperplasia, resulting in increased insulin secretion and increased insulin sensitivity in early pregnancy, followed by progressive insulin resistance.31

Maternal insulin resistance begins in the second trimester and peaks in the third trimester. This is the result of increasing secretion of diabetogenic hormones such as human placental lactogen, growth hormone, progesterone, cortisol and prolactin. These hormones cause a decrease in insulin sensitivity in the peripheral tissues such as adipocytes and skeletal muscle by interfering with insulin receptor signalling.32 The effect of the placental hormones on insulin sensitivity is made evident postpartum when there is a sudden decrease in insulin resistance.33

Insulin levels are increased in both the fasting and postprandial states in pregnancy. Fasting glucose levels are however decreased due to:

increased storage of tissue glycogen

increased peripheral glucose use

decrease in glucose production by the liver

uptake of glucose by the foetus.34

Insulin resistance and relative hypoglycaemia results in lipolysis, allowing the pregnant mother to preferentially use fat for fuel, preserving the available glucose and amino acids for the foetus and minimising protein catabolism. The placenta allows transfer of glucose, amino acids and ketones to the foetus but is impermeable to large lipids. If a woman’s endocrine pancreatic function is impaired, and she is unable to overcome the insulin resistance associated with

pregnancy then gestational diabetes develops.

Lipid metabolism

There is an increase in total serum cholesterol and triglyceride levels in pregnancy. The increase in triglyceride levels is mainly as a result of increased synthesis by the liver and decreased lipoprotein lipase activity, resulting in decreased catabolism of adipose tissue. Low-density lipoprotein (LDL) cholesterol levels also increase and reach 50% at term. High-density lipoprotein levels increase in the first half of pregnancy and fall in the third trimester but concentrations are 15% higher than non-pregnant levels.

Changes in lipid metabolism accommodate the needs of the developing foetus. Increased triglyceride levels provide for the mother's energy needs while glucose is spared for the foetus. The increase in LDL cholesterol is important for placental steroidogenesis.

Protein metabolism

Pregnant women require an increased intake of protein during pregnancy. Amino acids are actively transported across the placenta to fulfill the needs of the developing foetus. During pregnancy, protein catabolism is decreased as fat stores are used to provide for energy metabolism.

Calcium metabolism

The average foetus requires about 30 g of calcium to maintain its physiological processes. Most of this calcium is transferred to the foetus during the third trimester and is derived from increased dietary absorption by the mother.35 There is a decrease in total serum calcium concentration during pregnancy. This is mainly due to a decrease in serum albumin levels due to haemodilution, resulting in a decrease in the albumin-bound fraction of calcium. However the physiologically important fraction, serum ionised calcium, remains unchanged.36 Therefore maternal serum levels of calcium are maintained during pregnancy and foetal needs are met by increased intestinal absorption, which doubles from 12 weeks' gestation. However the peak demand for calcium is only in the third trimester. This early increase in calcium absorption may allow the maternal skeleton to store calcium in advance.17

Serum levels of 25-hydroxyvitamin D increase and this is metabolised further into 1.25-

dihydroxyvitamin D. The increase in 1.25-dihydroxyvitamin D is directly responsible for the increase in intestinal calcium absorption.36

Increased calcium absorption is associated with an increase in calcium excretion in the urine and these changes begin from 12 weeks. During periods of fasting, urinary calcium values are low or normal, confirming that hypercalciuria is the consequence of increased absorption.35 Pregnancy is therefore a risk factor for kidney stones.

Skeletal and bone density changes

There is controversy regarding the effect of pregnancy on maternal bone loss. Although pregnancy and lactation are associated with reversible bone loss, studies do not support an association between parity and osteoporosis in later life.25 Bone turnover is low in the first trimester and increases in the third trimester when foetal calcium needs are increased. The source of the calcium in the third trimester is previously stored skeletal calcium.36

A study of bone biopsies in pregnancy has shown a change in the micro-architectural pattern of bone in pregnancy but not overall bone mass.36 The changes reflect the need for the maternal skeleton to be resistant to bending forces and biochemical stresses needed to carry the growing foetus.

Other musculoskeletal changes seen in pregnancy include:

exaggerated lordosis of the lower back, forward flexion of the neck and downward movement of the shoulders

joint laxity in the anterior and longitudinal ligaments of the lumbar spine

widening and increased mobility of the sacroiliac joints and pubic symphysis.