INVITED ARTICLE

Physiological Changes in Pregnancy

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Abstract

Pregnancy is a dynamic process, which induces a multitude of anatomic, physiological, biochemical, and psychological changes. Physiological changes during pregnancy allow the body to meet the increased metabolic demands of the mother and fetus by maintaining adequate uteroplacental circulation, and ensure fetal growth and development. These changes begin early in the first trimester and are brought on by the increased circulating levels of progesterone and estrogen, which are produced by the ovary in the first 12 weeks of pregnancy and thereafter by the placenta. While some of these cause a change in biochemical values, others may mimic symptoms of medical disease. For instance, cardiac changes such as sinus tachycardia, systolic heart murmurs, and cardiac enlargement could be interpreted as signs of heart disease. It is thus crucial, to differentiate between normal physiological changes and pathological changes, particularly for clinicians involved in the care of pregnant patient.

Keywords: Blood volume, Cardiac changes, Hemodynamic changes, Normal pregnancy, Physiological changes, Pregnant patient.

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Introduction

The physiological changes of pregnancy are caused by the hormones secreted by the placenta. These changes lead to a series of adaptations, affecting all the systems, and enable adequate oxygen and nutrient delivery to both the mother and developing fetus.[1] These physiological changes induce a change in the biochemical test results. Additionally, decompensation leading to unmasking of preexisting diseases in pregnancy is also common.[2] Understanding these changes, with respect to each trimester, allows an accurate interpretation of physiological changes and laboratory parameters, identification of abnormalities if any, and implementation of appropriate measures. In this article, we highlight the salient changes occurring in all the systems (Table 1).

Fluid and Electrolyte Changes

The so-called physiological anemia of pregnancy is a result of a differential increase in plasma, red cell, and white cell volumes. The plasma volume increases by 40–50%, whereas the red cell volume increases by only 15–20%, leading to hemodilution, and decreased blood viscosity by approximately 20%. Mediators such as renin–angiotensin–aldosterone, atrial natriuretic peptide, estrogen, progesterone, and nitric oxide are postulated to cause the increase in total body water and, consequently, plasma volume.[1–3] This expansion in total body fluid volume is about 6.5–8.5 L at term and is distributed throughout the maternal–fetal unit. These changes are helpful in protecting the mother and fetus from the disastrous effects of peripartum hemorrhage.[4] The increased plasma volume increases the volume of distribution of some drugs and impacts their clearance.[1,2]

The osmotic threshold for thirst and antidiuretic hormone release is lowered by 10 mosmol, leading to an increased water intake and retention of electrolytes. This causes a cumulative retention of approximately 500–900 mmol sodium and 350 mmol potassium over the course of the pregnancy. However, despite retention of these electrolytes, increase in plasma volume leads to lower mean serum sodium (3–4 mEq/L) and potassium concentrations (0.2 mEq/L) after 12 weeks of gestation.[4]

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Acid–Base Regulation[5]

In order to ensure efficient oxygen delivery to the growing fetus, there is 30% increase in 2,3-diphosphoglycerate (2,3-DPG), which leads to a rightward shift in the oxyhemoglobin dissociation curve. In contrast, increased minute ventilation leads to respiratory alkalosis due to a decrease in $PaCO_2$ and a left shift of the same curve. Labor that causes maternal hyperventilation is associated with an acute left shift of the oxyhemoglobin dissociation curve. This reduces the oxygen delivery to the fetus. However, prolonged labor leads to an increase in oxygen consumption and basic metabolic rate, which can result in lactic acidosis, a right shift of the oxyhemoglobin dissociation curve, and a decrease in maternal oxygen uptake.

Hematological System

Hematological changes in pregnancy lead to adaptations, which increase the risks for anemia, thromboembolism, and consumptive coagulopathies. The levels of clotting factors I, VII, VIII, IX, X, and XII and fibrinogen are elevated (Table 2). Platelet production and aggregation are also increased. The levels of endogenous

Table 1: Overview of changes in the various systems[1,2]

Organ system	*Effects*
Cardiovascular system	Increased heart rate, stroke volume, and cardiac output Left ventricular hypertrophy Regurgitant murmurs Decreased systemic vascular resistance
Respiratory system	Increased minute volume (increased tidal volume and respiratory rate), increased PaO_2, decreased $PaCO_2$ Decreased functional residual capacity
Gastrointestinal system	Decreased lower esophageal sphincter tone, increased risk of aspiration, decreased liver enzymes (ALT, AST, GGT), increased alkaline phosphatase
Renal system	Increased renal blood flow and GFR, decreased plasma urea and creatinine, increased urinary protein and glucose Increased risk of UTI
Musculoskeletal system	Increased ligamentous laxity, increased risk of dislocation
Endocrine system	Increased progesterone and estrogen, thyroid hyperplasia Transient hyperthyroidism, insulin resistance, increased cortisol secretion, placental secretion of relaxin, human placental lactogen, human chorionic gonadotropin
Neurological	Increased CSF pressure, engorgement of epidural veins, increased sensitivity to local anesthetic, decreased minimum alveolar concentration
Dermatological	Hyperpigmentation of face, neck, abdomen due to melanocyte-stimulating hormone, Striae gravidarum
Ophthalmological	Decreased aqueous humor and intraocular pressure
Metabolic/acid–base balance	30% increase in 2,3-diphosphoglycerate (DPG), increased metabolism of carbohydrates, proteins, and fats

Table 2: Effect on clotting factors[4]

Coagulation factor	*Change*
Antithrombin III	No change
Plasma fibrinogen (factor I)	Increase
Factor II	No change
Factor V	No change
Factor VII	Increase
Factor VIII	Increase
Factor IX	No change
Factor X	Increase
Free protein S	Decrease
Plasminogen activator inhibitor 1	Increase
Plasminogen activator inhibitor 2	Increase
Protein C	No change
von Willebrand factor	Increase

anti-coagulants like protein S are increased, and resistance to activated protein C develops.[1] Additionally, the placenta generates plasminogen activator inhibitor (PAI), thus impairing fibrinolysis. This creates an overall state of hypercoagulability. Though this is meant to prevent bleeding at the time of delivery, there is a higher risk of thromboembolic phenomena.[3]

The red cell mass increases by 20–30%, but coupled with a disproportionate increase in plasma volume, a state of anemia exists during pregnancy. The white blood count remains on the higher side throughout pregnancy, but a sharp rise is seen during labor and immediately after.[3] After delivery, "autotransfusion" leads to approximately 500 mL of blood returning to circulating volume. This autotransfusion has the potential to complicate the peripartum course in women with cardiac disease and pre-eclampsia.[2] These changes are outlined in Table 3.

Respiratory System

The pregnancy hormones affect the vasculature of the respiratory tract mucosa and cause capillary engorgement and swelling, resulting in nasal congestion, voice change, and infections of the upper respiratory tract. This means smaller endotracheal tubes are required for intubation and there is increased potential for bleeding on manipulating the airway.

The total lung capacity of the lungs decreases slightly due to a significant upward displacement (4 cm) of the diaphragm by the gravid uterus, which is offset by a compensatory increase in transverse and anteroposterior chest diameters by 5–7 cm as well as flaring of the ribs.[3] As the pregnancy advances, there is a progressive decrease in the expiratory reserve volume, residual volume, and functional residual volume, which reaches approximately 20% at term (Table 4).[1] Progesterone-induced muscle relaxation also reduces the airway resistance, and lung compliance remains unchanged.[3]

There is a 40% rise in tidal volume and a 15% rise in respiratory rate, leading to progressive increase in minute ventilation to about 50% above normal by the second trimester. Alveolar ventilation increases to about 70% higher, than pre-pregnancy values by the end of gestation.[3] Hyperventilation leads to respiratory alkalosis, with decreased alveolar and arterial carbon dioxide levels. As an involuntary response to pain, hyperventilation is further augmented in labor and could lead to marked alkalosis and a shift to left of the oxygen dissociation curve, thus reducing the release of oxygen to the fetus. Similarly, oxygen consumption also increases to an additional 20% at term, which further increases to >60% during labor.

Cardiovascular System

The heart size increases due to both chamber hypertrophy and dilation, which can lead to movement of the apical impulse upward and laterally and a mild tricuspid regurgitation.[6] The systemic

Table 3: Changes in hematological factors[3]

Decreased	*Unchanged*	*Increased*
Hematocrit 35–45%	Mean corpuscular hemoglobin concentration	Blood volume 30–45%
Plasma protein 10–14%	Lymphocyte/T cell (although function reduced)	Plasma volume 45%
Antithrombin III	Bleeding time	Red cell mass 33%
Platelets		White cell count 8%
Plasma oncotic pressure (hemodilution)		Clotting factors (I, VII, VIII, X, XII, prekallikrein, von Willebrand factor, thrombin)
		Activated partial thromboplastin time
		Prothrombin time
		Fibrinogen levels 50–80%
		Renal erythropoietin/reticulocyte count
		RBC 2,3-diphosphoglycerate (rightward shift in oxygen–hemoglobin dissociation curve)
		Serum albumin concentration
		Hydrostatic pressure
		Erythrocyte sedimentation ratio
		Serum lipids 40–60%

Table 4: Changes in lung volumes[2]

Lung volume	*Effect*
Tidal volume	Increase by 30–40%
Functional residual capacity	Decrease by 20%
Expiratory reserve volume	Decrease by 20–30%
Residual volume	Decrease by 20%
Vital capacity (VC)/forced expiratory volume in 1 second (FEV1)	Unchanged

vascular resistance (SVR) decreases steadily over the course of the pregnancy, while the pulmonary artery pressure remains normal. In addition to progesterone, nitric oxide leads to smooth muscle relaxation and fall in SVR. There is decrease in vascular sensitivity to vasoconstrictor agents well.[3] The vascular tone is more dependent on sympathetic control, so hypotension develops more readily and more markedly consequent to sympathetic blockade.[6]

The central venous and brachial venous pressures remain unchanged, but femoral venous pressure is progressively increased due to mechanical factors. Thus, there is a reduction in afterload and an increase in preload, which, together with the increase in blood volume, may produce functional murmurs, in addition to those due to the anatomic changes.

Cardiac output (CO) increases to 30–40% higher levels, than in the non-pregnant state in the first trimester. This increase in cardiac output can be attributed to increase in both the stroke volume (35%) and heart rate (15%).[3] CO is highest in knee-chest and left lateral positions and least in standing and supine positions.[6] CO increases even further during labor in response to catecholamine secretion due to pain and addition of 300–500 mL of blood into the venous system by the contracting uterus. After delivery, there is a further increase in the blood volume by autotransfusion, leading to an increase in the cardiac output by 50%, which makes this a hazardous time for the parturients with heart disease.[3]

Gastrointestinal System[7]

Increasing levels of human chorionic gonadotropin (hCG) cause estrogen production leading to nausea and vomiting, which occurs in the first trimester in up to 70% of the patients. It resolves on its own, with supportive therapy in about 60% by the end of the first trimester, and 90% by 20 weeks of gestation. A small fraction of women may suffer from persistent vomiting, profound dehydration, electrolyte imbalance, and weight loss, often necessitating hospitalization, in a condition called hyperemesis gravidarum.[4]

Progesterone induces relaxation of the lower esophageal sphincter and upward displacement of the stomach due to the enlarging uterus, leading to progressive increase in reflux and heartburn (up to 80% patients at term).[5] The intestinal emptying time increases however, leading to an increased propensity for constipation. Therefore, in spite of a normal gastric emptying time throughout pregnancy, women remain at a higher risk of aspiration. This, however, changes during labor, where the gastric emptying time also increases significantly, increasing the risk of aspiration exponentially.[1] This reverts to pre-pregnancy risk values in 24–48 hours after delivery. There is impaired motility of gallbladder, with delayed emptying; this leads to the development of biliary sludge and gallstones.[1] Thus, pregnant women have progressive increase in residual volume of gallbladder throughout the pregnancy, which returns to normal volume shortly after delivery. Contrary to the popular belief, there is high incidence of biliary colic in pregnant women, which gets better with conservative management. If intervention is required, however, it is best done in the second trimester and is generally well tolerated.[8]

Though the blood supply to liver does not increase significantly through the pregnancy, its activity and synthetic capacity increase tremendously.[4] With respect to the level of enzymes, there appears to be a discrepancy in what the literature suggests. While some papers suggest that hepatic transaminases, γ-glutamyl transferase, bilirubin, and lactate dehydrogenase are increased slightly in

pregnancy, some others suggest that these enzymes levels reduce during pregnancy.[2,4,5] Alkaline phosphatase is markedly elevated due to placental production. Spider naevi and palmar erythema may occur without clinically significant liver disease.[5]

Renal System

Increased CO leads to an increase in the renal plasma flow and the glomerular filtration rate by up to 50% at term. As a result, the plasma blood urea nitrogen (BUN) and creatinine concentrations reduce by about 40–50%. Increased GFR overwhelms the capacity of the renal tubules to reabsorb glucose, and amino acids might not be absorbed as efficiently; hence, mild glycosuria (up to 300 mg/day) and aminoaciduria may develop in normal gestation. Physiological diuresis during the postpartum period occurs between the second and fifth days. The glomerular filtration rate and BUN concentration slowly return to nonpregnant values by the sixth postpartum week.[1]

After the 12th week of gestation, progesterone-induced relaxation leads to dilation and atony of the renal calyces and ureters. This promotes urinary stasis and, combined with mechanical obstruction due to the growing uterus, increases the risk of urinary tract infections.[3]

Central and Peripheral Nervous System

Both the central and peripheral nervous systems display an increased sensitivity to anesthetic agents, which is reflected as decreased minimum alveolar concentration (MAC) and a more profound and prolonged block, with a decreased dose requirement of local anesthetics for peripheral blocks. Due to venous engorgement, there is a reduction in the epidural space and increased CSF pressures. This reduces the amount of local anesthetic that is required for epidural blockade (recommendation is for 20–30% reduction).[2]

Endocrine System

Increased pregnancy hormones change the internal milieu and thus lead to a change in hormone levels. B-HCG stimulates thyroid-stimulating hormone (TSH) receptors, leading to transient hyperthyroidism, and thus follicular hyperplasia, causing an increase in size. There is an increase in thyroid-binding globulin, but normal free T3 and T4 levels are seen.

Fasting blood sugar is lower in pregnant than nonpregnant women, but tolerance to a glucose load, which causes early glycosuria, may be somewhat impaired due to the actions of placental lactogen, producing a mild diabetogenic state. In addition, lower fasting blood sugars in pregnant patients mask an underlying insulin resistance, secondary to placental secretion of human placental lactogen (hPL).[2] Occasionally, this progresses to gestational diabetes. Glucose responses return to normal promptly after delivery of the placenta.[1,2] Unlike insulin, glucose readily crosses the placenta. Babies of diabetic mothers thus run a higher risk of higher birth weights (macrosomia) and may potentially develop both hypoglycemia and even hypoglycemic seizures soon after they are born.

Secretion of corticosteroid hormones by the adrenal gland is increased, and there is adrenal cortical hyperplasia. Higher cortisol levels can also lead to further insulin resistance and increased skin pigmentation.[2]

Metabolic Changes

To provide for the growing fetus and increased basal metabolic rate and oxygen consumption of the mother, protein, fat, and carbohydrate metabolism is increased. The presence of high concentrations of human placental lactogen, progesterone, prolactin, and cortisol, in presence of reduced glucokinase and phosphofructokinase activities, cause an insulin-resistant state.[3]

Musculoskeletal System

Relaxin and estrogen are responsible for increased ligamentous laxity, especially in the pelvis. While the laxity enables the fetus to be accommodated easily, it can also contribute to musculoskeletal pain and poses an increased risk of subluxation or dislocation.[1]

Dermatological System

Hyperpigmentation of certain parts of the body such as the face, neck, and midline of the abdomen is not uncommon during pregnancy. Melanocyte-stimulating hormone is responsible for this change.[1] Striae gravidarum are also seen toward the end of pregnancy.

Ocular Changes

Increased progesterone levels, relaxin, and decreased production of aqueous humor lead to decreased intraocular pressures, which in turn could lead to visual disturbances and contact lens intolerance.[1]

Conclusion

It is not only important for a physician to be aware of the various changes that occur during normal pregnancy, but also when these changes are likely to occur, so that protective or preventative measure can be instituted without delays when any abnormalities are noted. This is particularly true in women who have preexisting diseases, since their disorders are likely to get aggravated through the course of the pregnancy and require urgent medical attention.

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