UDK: 618.3-008

PHYSIOLOGICAL CHANGES DURING PREGNANCY

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During pregnancy, in response to the growing fetus, various changes occur. This affects various organic systems, cardiovascular, respiratory, gastrointestinal, urinary. Factors leading to changes in these systems include changes in hormonal levels, fetal size and physiological needs of the pregnant woman and fetus. Most of the physiological changes return to normal in the postpartum period. It should be pointed out that much of these changes are more pronounced in multiparous patients.

Affected Organic Systems

Endocrine System

Many of the physiological changes associated with pregnancy are due to changes in hormones produced by the placenta. One such hormone is human chorionic gonadotropin (hCG), more specifically, its beta subunit (β-hCG). This hormone is produced by the placental syncytiotrophoblast. It is responsible for stimulating the yellow body to produce progesterone. Progesterone itself is essential in maintainingthe pregnancy (1). β-hCG stimulates and maintains the yellow body, thereby preventing new ovulations. By the end of the first trimester (approximately up to 10–12 gestational weeks), ovaria produce increased levels of estrogens and progesterone. After the first trimester the placenta is mature enough to take over the production of these hormones (2).

In non-pregnant women, the hypothalamus produces and releases thyrotropic releasing hormone (TRH).It stimulates the release of thyroid stimulating hormone (TSH) and prolactin (PRL) from the anterior pituitary gland. In pregnant women, the placenta releases additional TRH, which leads to greater release of TSH and PRL. The production of thyroid hormones in pregnancy increases by about 50%, but free T_3 and free T_4 remain unchanged. This is due to the simultaneous release of thyroid-binding globulin (TBG) (3). These additional thyroid hormones are required for normal brain development and thyroid function of the growing fetus (4).

In pregnancy, the pituitary gland expands by about 135%. This is due to lactotrophic hyperplasia and further raises the level of circulating prolactin (5). Its level increases 10 times during pregnancy. This results in growth of the glandular tissue of the breasts and the production of milk (6).

Relaxin is a peptide hormone that is released from the yellow body in both pregnant and non-pregnant women. In addition, in pregnant women it is releasedfrom the placenta and the decidua. This hormone allows remodeling of the connective tissue and consistent softening of the birth canal. It affects the growth and differentiation of the mammary glands and inhibitsthe uterine contractile activity (7). Relaxin also mediates the release of nitrogen oxide (NO), allowing systemic vasodilation and reducing the blood pressure in pregnancy.

Free cortisol levels are about 2.5 times higher during pregnancy compared to the pre-pregnancy period (9). Increased cortisol levels are particularly important for the normal development of the fetal brain. However, excessive values of maternal glucocorticoids may be neurotoxic to the fetus, resulting in impaired neuronal development (10).

Concentrations of endorphins and enkephalins also increase during pregnancy. This leads to anincrease in the pain threshold whichis necessary to counter the pain that will be present during birth (11).

Cardiovascular System

The cardiovascular system of pregnant women undergoes significant physiological changes. There is an increase in heart frequency, impact volume, cardiac output and decrease in vascular resistance (12). An increase in the chamber wall, heart contraction and compliance can also be seen.

During the first trimester, vasodilator effects of NO, prostaglandins and progesterone occur. They cause peripheral vasodilation. By the 8^{th}gestational week, it leads to a 20% increase in cardiac output (CO). Additionally, peripheral vasodilation reduces systemic vascular resistance (SVR). This is compensatedby an increase in CO by about 40% during pregnancy. Peripheral vasodilation also leads to a decrease in blood pressure early during pregnancy. The lowest blood pressure values are reached during the 20–24 gestational weeks, leading to physiological hypotension.

Cardiacoutput is a product of the heart frequency and the impact volume. The increase in the cardiac output is mainly due to an increase in the impact volume, and in a smaller percentage of the increase of the heart rate (13). In early pregnancy, the impact volume is responsible for maintaining increased CO. While during the third trimester, the increase in heart frequency becomes responsible for the elevated CO. This directs the blood to the uterus, placenta, kidneys, skin and limbs. During late pregnancy, the blood flow through the uterus increases up to 10 times. The renal blood flow increases by 50%. The blood flow to the liver and brain is minimally affected. Skin flow and flow to the limbs increases the temperature of the mother's skin. This is a mechanism of maternal thermoregulation.

During the active stage of birth, uterine contractions cause "autotransfusion" of approximately 500ml of blood, back into the mother's circulation. Even after childbirth, as a result of a decrease in the compression of the inferior vena cava, the cardiac output increases by 75% (14).

More than 90% of pregnant women will develop systolic murmur in pregnancy that will disappear after childbirth. 18% of pregnant women will develop diastolic murmur. Third heart sound occurs in more than 80% of pregnant women. Fourth heart sound occurs in about 16% of pregnant women (15).

In pregnancy, normal ECG findings can be a small Q-spikes and inverse T-waves in the III line, ST-segment depression and inversion of T-wave into lateral and lower lines, as well as shifting the axis of the QRS complex to the left (13).

Respiratory System

Functional residual capacity (FRC) consists of expiratory reserve volume (ERV) and residual volume (RV). During pregnancy, due to the growing uterus, the rest position of the diaphragm shifts upwards by about 5cm. This reduces ERV and FRC. Vital capacity (VC) remains unchanged, and the reduced ERV is accompanied by increased inspiratory reserve volume (IRV).

Increased concentrations of progesterone, starting in the first trimester, cause the respiratory volume to increase by about 30–50%. The respiratory volume and respiratory frequency product gives the minute ventilation, which will increase by 30–50%.

Progesterone stimulates respiration and can lead to hyperventilation. As a result, arterial partial oxygen pressure (PaO_2) will be up to 105mmHg, while arterial partial carbon dioxide pressure ($PaCO_2$) approximately 30mmHg (16). This change in blood gases results in mild respiratory alkalosis. It is metabolically compensated by increased bicarbonate excretion by the kidneys, approximately 20mEq/L (17). These metabolic changes lead to moving the dissociative curve of oxyhemoglobin to the right. It means that the dissociation of oxygen and oxygen transport through the placenta is facilitated.

During childbirth, minute ventilation increases even by 140–200%, depending on the stage of birth. This causes an even greater decrease in $PaCO_2$ (18). Metabolic oxygen consumption increases, as a result of contractions of the uterus, sympathetic activity and maternal Valsalva maneuver. As oxygen demand exceeds the oxygen supply during the active stage of birth, an anaerobic phase of metabolism and lactate formation occurs (19).

Hematological Changes

In a pregnant woman, renin values in plasma grow, and there is a tendency to reduce the level of atrial natriuretic protein. This leads to systemic vasodilation and increased vascular capacitation. These physiological changes, without compensation, would lead to an unfulfilled vascular

system. To compensate for this phenomenon, as well as potential blood loss during birth, the mother's blood volume increases by about 1.5l. The production of maternal erythropoietin increases, leading to an increase in erythrocyte mass by approximately 30%. This increase in plasma volume is greater than the erythrocyte mass, and results in dilutional anemia, or physiological anemia in pregnancy (20).

The increase in erythrocyte mass, combined with increased blood flow through the uterus, leads to optimization of oxygen transport to the fetus. However, increasing erythrocyte mass also means an increase in the physiological need for iron during pregnancy. Approximately 1000mg (1gr) of iron is required during pregnancy. Two-thirds are for the needs of the pregnant woman, and one-third is for placenta-fetal tissue growth and needs. In the first trimester, the iron needs are lower (0.8mg/day). While during the third trimester, the daily iron needs increase (3.0–7.5mg/day) (21).

Pregnancy is a hypercoagulable condition, with increased values of coagulation factors. This is caused by increased levels of estrogens, which play a role as mediators in protein synthesis. As pregnancy progresses, coagulation factors VII, VIII, X, XII, vWF and fibrinogen values significantly increase. As a result of the increase in factor VIII, the activated partial thromboplastic time (aPTT) is typically shortened.The prothrombin time (PT) and thrombin time (TT) remain unchanged. As a result of this hypercoagulable condition, pregnant women are up to five times more likely to develop deep vein thrombosis (DVT) compared to non-pregnant women [22].

Renal Changes

As previously noted, the increase in the heart output leads to an increase in the renal blood flow. Glomerular filtration rate (GFR) increases by about 50% and renal plasma flow (RPF) increases by 80%. This increased GFR leads to a decrease in serum concentrations of creatinine, urea and uremic acid. Due to water containment, the kidneys increase in size and physiological hydronephrosis occurs. As a result of the influence of progesterone and relaxin on smooth muscles, there is a dilatation of the renal collecting system, which can lead to urinary retention. This phenomenon increases the predisposition to urinary tract infections and pyelonephritis with asymptomatic bacteriuria during pregnancy (23).

Typically, during normal pregnancy, an increase in the level of regulation of the renin-angiotensin-aldosterone system (RAAS) occurs. The formation of estrogen by the placenta stimulates the synthesis of angiotensinogen in the liver. This leads to an increase in the values of angiotensin II. Renin is released from the ovaries and the decidua of the uterus. Approximately around the eighth gestational week, aldosterone values increase. Up to the third trimester of thepregnancythey continue to rise up to 3–6 times from the upper limit of their normal values. The result of these events is a total increase in approximately 1.5l of water in the pregnant woman's body (23).

Gastrointestinal Changes

Gastroesophageal reflux (GER) is a common occurrence in pregnant women as a result of several factors. Increased progesterone values during pregnancy lead to a decrease in muscle tone at rest and the lower esophageal sphincter. It also leads to delayed gastric emptying and an increase in the transit time through the small intestines. These changes, added to the pressure caused by the pregnant uterus, predispose to the appearance of GER (24).

Skin Changes

Increased hormone values of estrogen and progesterone during pregnancy may stimulate increased melanin synthesis. It causes hyperpigmentation of the face, known as melasma. As one of the hyperpigmentation associated with pregnancy is also the dark line, a hyperpigmented line that goes along the middle line of the abdominal wall. It is usually associated with the appearance of hyperpigmentation of areolas, armpits and genitals (25).

Clinical Significance

It is important to remember that many changes in pregnant women during pregnancy affect the pharmacodynamic and pharmacokinetic characteristics of certain drugs (absorption, distribution, metabolism and elimination). If mothers' physiological adjustments during pregnancy are not taken into account, it may lead to an increase in maternal morbidity due to pre-or sub-dosing of a pregnant woman.

Increased renal clearance during pregnancy may increase the elimination of some drugs that have renal elimination. For example, ampicillin, cefazolin, cefuroxime, piperacillin, digoxin, atenolol, lithium.

As soon as pregnancy is confirmed, hypothyroid patients who needed levothyroxine should increase their dose by 30%, and the values of serum thyrotropin should be closely monitored.

Additionally, it is important to understand physiological hypotension during pregnancy, especially when it comes to a pregnant patient who is already hypertensive and receives antihypertensive therapy.

It is important that doctors from all medical specialties, especially those in family medicine, cardiology, obstetrics or obstetric anesthesia, understand the physiological changes that occur in pregnant women and appropriately adapt the approach and treatment of these patients.

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Abbreviations:

- β-hCG, beta human chorionic gonadotropin
- TRH, thyrotropic releasing hormone
- TSH, thyroid stimulating hormone
- PRL, prolactin
- TBG, thyroid-binding globulin
- NO, nitrogen oxide
- CO, cardiac output
- SVR, systemic vascular resistance
- FRC, functional residual capacity
- ERV, expiratoryreserve volume
- RV, residual volume
- VC, vital capacity
- IRV, inspiratory reserve volume
- PaO_2, arterial partial oxygen pressure
- $PaCO_2$, arterial partial carbon dioxide pressure
- aPTT, activated partial thromboplastic time
- PT, prothrombin time
- TT, thrombin time
- DVT, deep vein thrombosis
- GFR, glomerular filtration rate
- RPF, renal plasma flow
- RAAS, renin-angiotensin-aldosterone system
- GER, gastroesophageal reflux

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