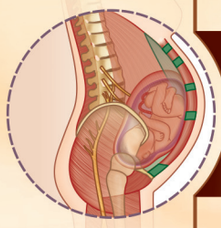


1 Physiological Changes in Pregnancy

Physiological changes during pregnancy facilitate the adaptation of the whole body systems to adjust to the increased metabolic needs of the mother and enable adequate delivery of oxygenated blood to peripheral tissues and the fetus. Changes occur not only in the genital organs responsible for the pregnancy to carry forward but also all other systems including circulating blood volume (affecting preload), peripheral vascular compliance and resistance (affecting afterload), myocardial function and contractility, heart rate, and sometimes heart rhythm and the neurohormonal system.

CARDIOVASCULAR SYSTEM

Changes in Antepartum Period

An increase in blood volume and heart rate as well as a reduction in systemic vascular resistance bring about the increase in cardiac output necessary to sustain pregnancy.

Circulating Blood Volume

An increase in blood volume of varying magnitude is observed from 12 weeks of pregnancy. The increased blood volume delivered to the ventricle during pregnancy increases the preload. Blood volume begins to increase from 6th week of gestation and by the end of pregnancy it will have reached approximately 50% more than in the prepregnant state. The increase in blood volume is more pronounced in twin pregnancies.

Red cell mass increases as much as 40% above pre-pregnancy levels. The plasma volume increase is proportionally greater than the increase in red blood cell mass and the resulting hemodilution explains the so-called 'physiological anemia of pregnancy'. Reduced plasma volume expansion has been associated with low birth weight and intrauterine growth retardation.

In normal pregnancy, there is an increase in the left ventricular end-diastolic volume, which can be noted by 10 weeks' gestation and peaks during the third trimester. There are also increases in the left atrial, right atrial and right ventricular diastolic dimensions. Preload is influenced by maternal position; the supine position results in compression of the inferior vena cava and consequent obstruction of venous return and decreased cardiac output. The effect is more profound in twin pregnancy.

The heart rate variability falls in normal pregnancy because of increase of 10–15 beats/min in the resting baseline rate. The heart is rotated forward and pushed upward as the diaphragm rises so that apex beat appears in the fourth rather than the fifth intercostal space. The cardiac volume rises by about 12% which appears to result from the rise in venous filling rather than from hypertrophy (Fig. 1.1).

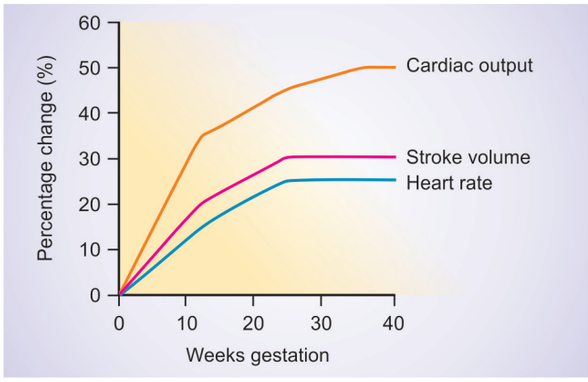


Fig. 1.1: Maternal cardiovascular changes

The blood pressure in the upper extremities changes very little during pregnancy, but pressure in the lower extremities increases. This is accompanied by pedal edema. The venous pressure in the legs rise from 9 cm H_2O in early pregnancy to 24 cm H_2O by term. Because of extra blood flow, variation in the auscultated heart sounds may occur, such as murmurs, a wider split between the first and second heart sounds, or an S_3 gallop. Some nonspecific ST-segment changes may occur in ECG. The following is a summary of cardiovascular changes:

- Systolic blood pressure level decreases by 4–6 mmHg.
- Diastolic blood pressure level decreases by 8–15 mmHg.
- Mean blood pressure level decreases by 6–10 mmHg.
- Heart rate increases by 12–18 beats per minute.
- Stroke volume increases to 10–30%.
- Cardiac output increases by 1.5 L/min.
- Heart size increases to 12%.
- Physiological ejection murmurs in precordium.
- Flat or inverted T in lead III due to positional heart changes.
- Pulse pressure increases.
- Pulmonary BP remains unchanged.
- Blood flow to uterus increases by 500 ml/min.
- Blood flow to kidneys increase by 400 ml/min.
- Blood flow to skin increases by 300–400 ml/min.
- Blood flow to breasts increases by 200 ml/min.

RESPIRATORY SYSTEM

Respiratory system undergoes marked physiological changes in pregnancy (Fig. 1.2). The shape of the chest changes during pregnancy as the lower ribs flare out and subcostal angle widens dramatically. The diaphragm rises and the respiration becomes more diaphragmatic in nature.

The vital capacity is little increased in pregnancy but tidal volume rises by 40% from 500 to 700 ml. Inspiratory capacity increases by 300 ml. The residual volume falls by 20%. There is increase in oxygen consumption between 30 and 40 ml/min by late pregnancy, from a baseline level of 220 ml/min. In early pregnancy, the minute ventilation rises by about 30% with a slow rise to a maximum of 40–50% above nonpregnant values at term mainly by increase in tidal volume rather than by respiratory rate. FEV_1 and peak expiratory flow rate is not affected by pregnancy. This is probably due to high concentration of progesterone, uterine muscle relaxant and PGE_1 and prostacyclin which act as bronchodilators. This counteracts the reduction in total lung capacity and bronchoconstrictor effect of $PGF_{2\alpha}$.

The fall in maternal pCO_2 in pregnancy is due to hyperventilation because of stimulatory effect of progesterone on carbonic anhydrase which facilitates carbon dioxide transfer and wash out of CO_2 from the lungs. By term, the maximum pCO_2 rises to about 30 mm Hg which is largely contributed from the fetus. Due to marked sensitivity a 1 mmHg rise in pCO_2 results in ventilation of 6 L/min during pregnancy.

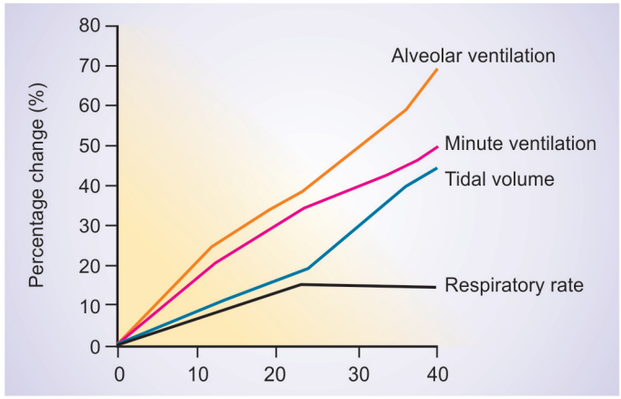


Fig. 1.2: Maternal respiratory changes

The fall in maternal pCO_2 allows more efficient placental transfer of carbon dioxide from the fetus which has a pCO_2 value of 55 mmHg and the mother can experience dyspnea and increased respiratory effort. Regular moderate physical exercise during mild to late pregnancy reduces ventilatory efforts. The increased alveolar ventilation results in smaller rise of pO_2 than the fall in pCO_2 which help in transfer of oxygen to fetus from maternal erythrocytes by 2,3-DPG.

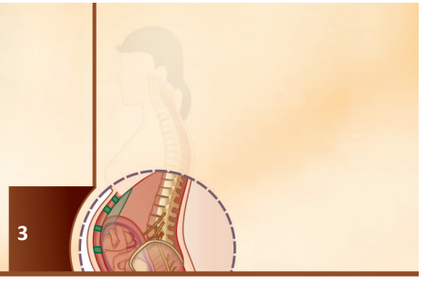
Pregnant women experience nasal stuffiness due to estrogen-induced hypersecretion of mucus. Epistaxis is also common. The following is a summary of respiratory changes:

- Respiratory rate does not change.
- Tidal volume increases by 0.1–0.2 L.
- Expiratory reserve volume (ERV) decreases by 200 ml (15%).
- Residual volume decreases by 300 ml or 20%.
- Vital capacity does not change.
- Inspiratory capacity increases by 300 ml (5%).
- Functional reserve capacity decreases by 18%.
- Minute volume increases by 40% or 3 L/min
- Oxygen requirement increases by 30–40 ml/min.
- Carbon dioxide pressure decreases from 35–40 mmHg to 28–30 mmHg.
- Oxygen pressure increases to 100–104 mmHg.
- pCO_2 decreases to 30–31 mmHg.
- pH has a mild increase from 7.35 to 7.38.

Weight Gain

Guidelines for weight gain during pregnancy are as follows:

- Underweight women (BMI <18.5) should gain 20–40 pounds (14–20 kg).



- Normal-weight women (BMI, 18.5–24.9) should gain 25–35 pounds (10–15 kg).
- Overweight women (BMI, 25–29.9) should gain 15–20 pounds (7–10 kg).
- Obese women (BMI, 30 or higher) should gain 11–14 pounds (5–7 kg).

Distribution of Weight Gain

- 7.5 pounds (3.5 kg)—average baby's weight
- 7.0 pounds (3.5 kg)—extrastored nutrients like fat, protein, etc.
- 4.0 pounds (2.0 kg)—extra blood
- 4.0 pounds (2.0 kg)—extra body fluids
- 2.0 pounds (1 kg)—amniotic fluid surrounding the baby
- 2.0 pounds (1 kg)—breast enlargement
- 2.0 pounds (1 kg)—enlargement of uterus
- 1.5 pounds (500–750 gm)—placenta

RENAL SYSTEM

The kidneys increase in size during pregnancy. By the third trimester, renal parenchymal volume rise by about 70% and the kidneys weigh 20% greater than its nonpregnant weight and are increased by 1–2 cm in length. There is marked dilatation of the calyces, renal pelvis and ureters in majority of women with kinking of ureters. The ureters are dilated above the brim of the bony pelvis. They also elongate, widen and become more curved. Thus there is an increase in urinary stasis which may lead to infection.

The exact cause of hydronephrosis and hydroureter in pregnancy is unknown. There may be several factors contributing to these:

1. Elevated progesterone level contributes to hypotonia of smooth muscles of the ureter.
2. The engorged ovarian venous plexus in the suspensory ligament of the ovary may compress the ureter at the brim to produce hydroureter above the brim.
3. Dextrorotation of uterus on the right side causes more dilatation of right ureter than the left.
4. Hyperplasia of the smooth muscle in the distal one-third of the ureter reduces the size of the lumen.

Renal Function

- The glomerular filtration rate (GFR) increases by about 50%.
- Renal plasma flow rate increases by 25–50%.
- Even though GFR increases dramatically during pregnancy, volume of urine passed each day is not increased.
- Concentration of urea and creatinine is decreased in pregnancy due to high renal clearance. Plasma creatinine falls from 73 mmol/L to a nadir of 47 mmol/L and plasma urea falls from 4.3 to 3.1 mmol/L.
- Glycosuria in pregnancy is explained by increase in GFR with impaired tubal absorption capacity for filtered glucose. Increased level of urinary glucose also contributes to increased susceptibility to UTI in pregnancy.
- Proteinuria is common in pregnancy but more than 300 mg/day may be pathological.
- Serum uric acid concentration falls by 25% in early pregnancy due to decrease in tubular reabsorption and slight increase in its excretion.
- Pregnancy accumulates 950 mmol sodium during the course of pregnancy due to high concentration of progesterone and aldosterone from activated renin–angiotensin system.
- About 350 mmol of potassium is retained in pregnancy.
- Bladder is displaced upward and flattened in anteroposterior diameter by the enlarged uterus. Pressure from the uterus leads to increase in urinary frequency. Bladder vascularity increases in pregnancy and detrusor tone decreases with increase in capacity of 1500 ml.

GASTROINTESTINAL SYSTEM

- Appetite is usually increased, sometimes with specific cravings.
- Progesterone causes relaxation of the lower esophageal sphincter and increased reflux, making many women prone to heartburn.
- GI motility is reduced and transit time is consequently longer. This allows increased nutrient absorption. Constipation is common.
- The gallbladder may dilate and empty less completely. Pregnancy also predisposes to the precipitation of cholesterol gallstones.
- Gums become spongy, friable and prone to bleeding. Good dental care is important.
- The histological picture of liver does not change in pregnancy. Albumin concentration falls by 22% from 3.5 to 2.5 gm/dl. Its synthesis rises between 12 and 28 weeks so that total albumin mass increases by 19%.
- Serum alkaline phosphatase concentration rises to almost double in pregnancy though most of them are isoenzyme of placental origin. Transaminase values remain unaltered in pregnancy though upper limit of normal is reduced by 2.5%.

- Total globulin as well as hormone binding globulin increases.
- Cholestasis is stasis of bile in dilated biliary canaliculi with no cellular necrosis or alteration in the secretion of bile. Cholestasis is associated with generalized pruritus which responds to treatment with cholestyramine. Very rarely it produces jaundice. It is probably a hormonal effect and is associated with raised postprandial glucose.

ENDOCRINE SYSTEM

The placenta is the main source of hormone production from the early days of gestation. The placental trophoblast can synthesize human chorionic gonadotrophins from the very conceptual period. It also synthesize adrenocorticotrophic hormone (ACTH), progesterone, parathyroid and renin.

Pituitary

The increase in size and weight of the pituitary in pregnancy is due to increase in number of several secretory cells. The number of lactotrophs is increased while the number of growth hormone and gonadotrophin-secreting cell is reduced. Plasma prolactin increases in pregnancy and by term it is raised 10–20 times.

TSH secretion is low in first trimester, but remains unchanged throughout rest of the pregnancy. It responds normally to TRH from hypothalamus. The secretion of other anterior pituitary hormones remain unchanged or lowered.

- FSH/LH falls to low levels due to blunting of GnRH response by hCG.
- ACTH and melanocyte-stimulating hormone increase. The placental production of ACTH and CRH is not suppressible by exogenous steroids.
- Maternal CRH concentration is mostly bound though the free CRH rises rapidly in pregnancy towards term suggesting its role in parturition.
- Prolactin increases from early pregnancy and then comes back to a little above baseline till the end of pregnancy.

Thyroid and Parathyroid

- Thyroxine-binding globulin (TBG) concentrations rise due to increased oestrogen levels.
- T_4 and T_3 increase over first half of pregnancy but there is a normal to slightly decreased amount of free hormone due to increased TBG-binding.
- TSH production is stimulated, although in healthy individuals this is not usually significant. A large rise in TSH is likely to indicate iodine deficiency or subclinical hypothyroidism.
- Serum calcium levels decrease in pregnancy which stimulates an increase in parathyroid hormone (PTH).
- Cholecalciferol (vitamin D_3) is converted to its active metabolite, 1,25-dihydroxycholecalciferol, by placental 1α-hydroxylase.

Adrenal and Pancreas

- Cortisol levels increase in pregnancy which favours lipogenesis and fat storage.
- Insulin response also increases so blood sugar should remain normal or low.
- Peripheral insulin resistance may also develop over the course of pregnancy and gestational diabetes is thought to reflect a pronounced insulin resistance.

Parathyroid Glands

- The main function of PTH is to regulate the renal synthesis of 1,25 dihydroxyvitamin D. This is an active metabolite of vitamin D. It increases calcium absorption from the kidney and gut and mobilizes calcium from bone.
- There is transplacental loss of 6.5 mmol/day of calcium and 4.6 mmol/day of inorganic phosphate.
- There is marked increase in urinary calcium excretion due to raised GFR
- PTH level falls in pregnancy but level of 1,25-dehydroxyvitamin D and calcitonin rises.
- The increase in serum 1,25-dihydroxyvitamin D provides for increased calcium requirement in pregnancy.

CHANGES IN REPRODUCTIVE ORGANS

Changes in the body during pregnancy are most obvious in the organs of the reproductive system.

Uterus

1. Changes in the uterus are phenomenal. By the time pregnancy has reached term, uterus will have five times increase of its normal size. It increases:
   a. In length from 6.5 to 32 cm.
   b. In depth from 2.5 to 22 cm.
   c. In width from 4 to 24 cm.
   d. In weight from 50 to 1000 grams.
   e. In thickness of its walls from 1 to 0.5 cm.
2. The capacity of the uterus expands to accommodate a term fetus and placenta, the umbilical cord, 500 to 1000 ml of amniotic fluid and the fetal membranes.
3. The abdominal contents are displaced to the sides as the uterus grows in size, which allows for ample space for the uterus within the abdominal cavity.

4. The size of the uterus usually reaches its peak at 38 weeks gestation. The uterus may drop slightly as the fetal head settles into the pelvis, preparing for delivery. This dropping is referred to as 'lightening.' This is more noticeable in a primigravida than a multigravida.

Cervix

1. The cervix undergoes a marked softening which is referred to as 'Goodell's sign.'
2. A mucus plug, known as 'operculum' is formed in the cervical canal. This is the result of enlarged and active mucus glands of the cervix. It serves to seal the uterus and to protect the fetus and fetal membranes from infection. The mucus plug is expelled at the end of the pregnancy. This may occur at the onset of labor or precede labor by a few days. When the mucus is blood-tinged, it is referred to as a 'bloody show'.
3. Additional changes and softening of the cervix occur prior to the beginning of labor.

Vagina

Increased circulation to the vagina early in pregnancy changes the color from normal light pink to a purple hue which is known as the 'Chadwick's sign'.

Ovaries

1. The follicle-stimulating hormone (FSH) ceases its activity due to the increased levels of estrogen and progesterone secreted by the ovaries and corpus luteum. This prevents ovulation and menstruation.
2. The corpus luteum enlarges during early pregnancy and may even form a cyst on the ovary. The corpus luteum produces progesterone to help maintain the lining of the endometrium in early pregnancy. It functions until about the 10th to 12th week of pregnancy when the placenta is capable of producing adequate amounts of progesterone and estrogen. It slowly decreases in size and function after the 12 weeks.

BREAST CHANGES IN PREGNANCY

There are many changes in breast during pregnancy particularly evident in primigravida (Fig. 1.3).

- **Sore breasts:** Early in the first trimester, breasts are sore or tender because of their heaviness due to proliferation of their glands and ducts.
- **Nipple changes:** They become larger and darker as pregnancy progresses. There will have pimple like white areas on the areola. These are normal. They are called Montgomery's tubercles.

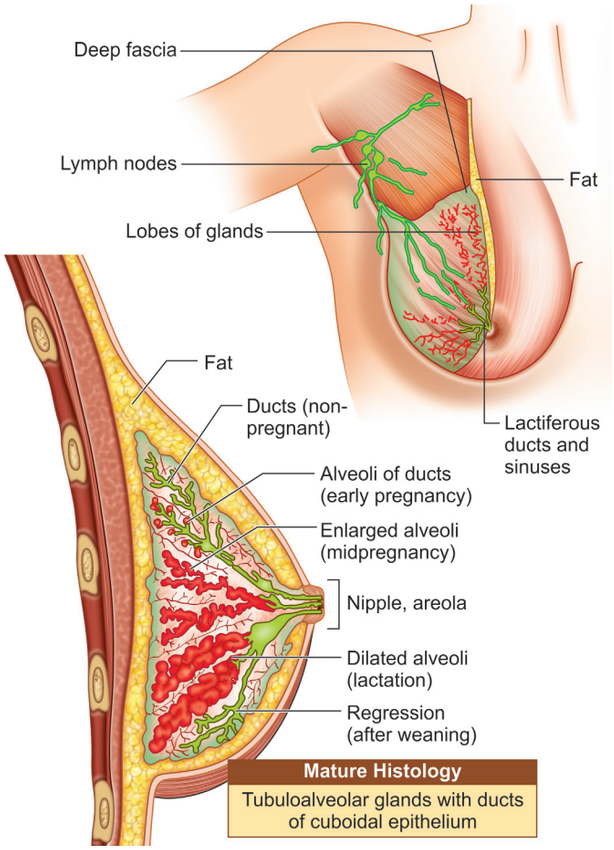


Fig. 1.3: Breast structure and changes in pregnancy

- **Larger breasts:** Toward the end of the first trimester or the beginning of the second trimester, breasts enlarge and grow further and become heavy. This is for the glands getting prepared for nursing.
- **Leaking colostrum:** Colostrum is the first milk body makes. It will provide baby with everything which is needed to start life, including gut immunities apart from highly concentrated nutrients. Toward the end of pregnancy, breasts may start leak colostrums.
- **No breast changes:** There may have only slight symptoms or no symptoms and signs of breast changes in pregnancy. It is normal and will have successful pregnancy or lactation.

CHANGES OF SKIN DURING PREGNANCY

Alterations in hormonal balance and mechanical stretching are responsible for several changes in the integumentary system. The following changes occur during pregnancy:

a. *Linea nigra.* This is a dark line that runs from the umbilicus to the symphysis pubis and may extend

as high as the sternum. It is a hormone-induced pigmentation. After delivery, the line begins to fade, though it may not ever completely disappear.

b. *Mask of pregnancy (chloasma).* This is the brownish hyperpigmentation of the skin over the face and forehead. It gives a bronze look, especially in dark-complexioned women. It begins about the 16th week of pregnancy and gradually increases, then it usually fades after delivery.

c. *Striae gravidarum (stretch marks).* This may be due to the action of the adrenocorticosteroids. It reflects a separation within underlying connective tissue of the skin. This occurs over areas of maximal stretch—the abdomen, thighs, and breasts. It will usually fade after delivery although it never completely disappear.

d. *Sweat glands.* Activity of the sweat glands throughout the body usually increases which causes the woman to perspire more profusely during pregnancy.

NUTRITION

Pregnant women require 300 calories extra in addition to the normal daily requirement. The nutrition recommendations, although variable from country-to-country, suggest universal addition of protein, iron, and other mineral and vitamin supplements for fetal and maternal welfare during the course of gestation. Antepartum nutrition, continues to be an area of great interest because the feeding of pregnant women is a simple intervention that may have a significant impact on the outcome of reproduction.

The current recommendations proposed by the Food and Nutrition Board of the US National Science Foundation are listed in Table 1.1.

Table 1.1: Recommended dietary allowances (revised in 2005)

Nutrient	*For nonpregnant woman*	*For pregnant woman*
Protein	45 gm/day	+30 gm/day
Calories	2100	+300
Calcium	1000 µg/day supplementation	No
Iron	18 mg/day	+9 mg/day
Folic acid	400 µg/day	+200 µg/day
Ascorbic acid	75 mg/day	+10 mg/day

Caloric Requirements

Maternal mass increases by approximately 20% during the course of normal gestation. This increase in mass and the metabolic needs of the fetus require 300 additional calories above the recommended daily allowance. A pregnant woman of average size requires approximately 2200 calories/day.

Protein Requirements

Food and Nutrition Board has recommended that an extra 30 gm of protein be supplied to pregnant women in addition to the basic requirement based on age and size. In the average-sized woman, this constitutes a total daily protein ration of 44–46 gm/day (0.88 gm/kg/day) plus the 30 gm supplement.

Lipid Metabolism

Lipid concentration in the serum is markedly increased in pregnancy. Triglycerides, phospholipids, cholesterol, and free fatty acids increase markedly in amount. The increase in serum cholesterol seems to occur regardless of the dietary habits of the gravida; vegetarians show the same increase as those who eat meat (Fig. 1.4).

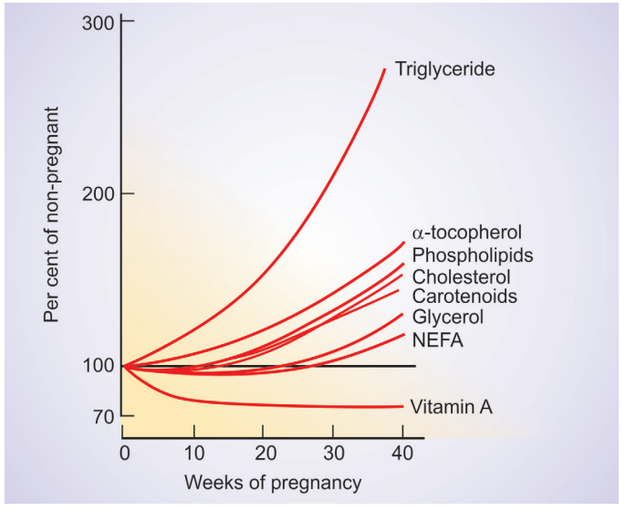


Fig. 1.4: Lipid metabolism in pregnancy

Carbohydrate Metabolism

Carbohydrate metabolism is altered in the course of normal pregnancy and the pregnant state is diabetogenic. Previously undiscovered diabetes may be unmasked during the course of pregnancy, or a woman may develop diabetic levels of blood glucose as a response to pregnancy.

In the fasting state, glucose is transferred to the fetus from the maternal circulation, producing a decrease in maternal serum glucose levels. The major effects of pregnancy on glucose metabolism are related to the fact that the fetus withdraws glucose from the maternal circulation. The rate of delivery of glucose to the fetal circulation is controlled by the difference in serum concentrations between maternal and fetal serum levels.

Glucose also seems to be transferred across the placenta by means of facilitated diffusion. Placental transfer of glucose and other materials related to carbohydrate handling in pregnancy is pictured in Fig. 1.5.

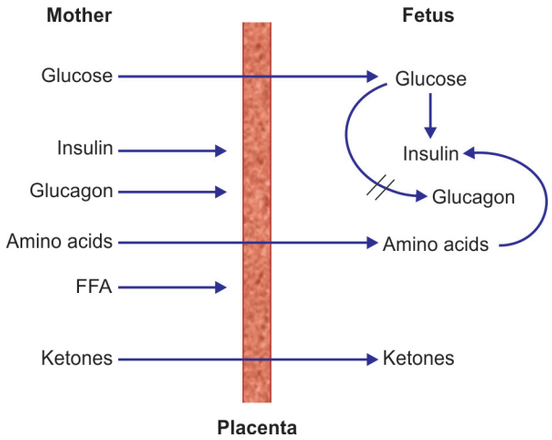


Fig. 1.5: A schematic representation of maternal–fetal nutrient and hormone exchange across the placenta in pregnancy. Glucose, amino acids, and ketones move freely into the fetal circulation, whereas insulin, glucagon, and free fatty acids (FFA) do not.

Fetus uses glucose at a rate of 6 mg/kg/minute at term. This rate is quite high compared with that in the normal adult, which is approximately 2.5 mg/kg/minute. In addition to glucose, amino acids are freely transported across the placenta into the fetal circulation. This transfer produces maternal hypoaminoacidemia, particularly of alanine, an important precursor of glucose in gluconeogenesis. In pregnancy, feeding produces hyperglycemia, an increase in serum insulin levels, and hypertriglyceridemia. There is also a diminished response to insulin. These changes are related to protection of fetal tissues from fluctuations in glucose by switching the maternal tissues over to free fatty acid and triglyceride metabolism. The placental production of lactogen, a substance known to have lipolytic properties, is responsible for this.

Iron and Mineral Requirements

Physiologic iron requirements are three times higher in pregnancy than they are in menstruating women. Approximately 1200 mg must be acquired from the body iron store or from the diet by the end of pregnancy to meet both the requirements of the mother for the expansion of circulating red cell mass and demands of the developing fetus. The average requirement for a menstruating woman for the same period of time is 400 mg. The increased requirement is, therefore, 800 mg.

The demand for additional iron is not spread evenly throughout pregnancy. In the first trimester, requirements are actually reduced because menstruation has ceased, the demands of the fetus are still small and the expansion of the maternal red cell mass has not yet started to occur. The need for additional iron commences early in the second trimester and reaches a peak toward the end of the third trimester, when requirements rise to between 4 and 6 mg/day.

The relative importance of iron stores on one hand and increased iron absorption on the other is best illustrated by examining iron balance during pregnancy in women from industrialized countries. They enter pregnancy with adequate stores. The additional iron is derived from both the stores and increased absorption. The serum ferritin level is the best measure of the size of iron stores; 1 µg/L serum ferritin = 8 mg storage iron in an adult. The 50th percentile for serum ferritin concentrations is 36 µg/L . This value predicts a mean iron store of 300 mg. Therefore, the average size of iron stores for women entering pregnancy is 300 mg. Because the estimated total additional requirement during pregnancy is 800 mg, the average woman must absorb 500 mg (2 mg/day) more iron than she required while menstruating to avoid a negative iron balance.

However, iron absorption is regulated by the size of body iron stores. The operation of this important regulatory process is not affected by the advent of pregnancy. Women who enter pregnancy with adequate iron stores absorb relatively little iron during the first trimester. Stores are utilized first as the demand for iron increases in the second trimester. Absorption is accelerated only after there has been a substantial fall in the size of the iron store. At the time of the greatest need in late pregnancy, stores are essentially exhausted in most women. Virtually, all of the iron is derived from absorption.

Pregnant women consume a bioavailable diet that supply about 12 mg nonheme iron/day. The results show that the women utilize iron stores first. Absorption increase markedly only after most of the storage iron has been used. At the time of highest iron requirement in the third trimester, virtually all of the iron is derived from absorption. The diets of women in developing countries do not contain sufficient bioavailable iron to meet these needs during the second and third trimesters even if iron stores are adequate at the beginning of pregnancy. Supplementation will be necessary in the second and third trimesters of pregnancy, even if supplementation before conception improves iron storage status in the first trimester.

MUSCULOSKELETAL CHANGES (Fig. 1.6)

During pregnancy, women gain 25 to 35 pounds, on average, and undergo multiple hormonal changes and biomechanical alterations that strain the axial skeleton and pelvis.

Musculoskeletal consequences that ensue as a result of weight gain and hormonal changes include:

- Force across pelvic joints is increased up to twofold.
- Exaggerated lordosis of the lower back, forward flexion of the neck, and downward movement of the shoulders typically occur to compensate for the enlarged uterus and change in center of gravity.
- Stretching, weakness, and separation of abdominal muscles further impede neutral posture and place even more strain on paraspinal muscles.
- Joint laxity in the anterior and posterior longitudinal ligaments of the lumbar spine creates more instability in the lumbar spine and can predispose to muscle strain.
- There is widening and increased mobility of the sacroiliac joints and pubic symphysis in preparation for the fetus for passage through the birth canal.
- A significant increase in the anterior tilt of the pelvis occurs with increased use of hip extensor, abductor, and ankle plantar flexor muscles. Stance is widened to maintain trunk movement.

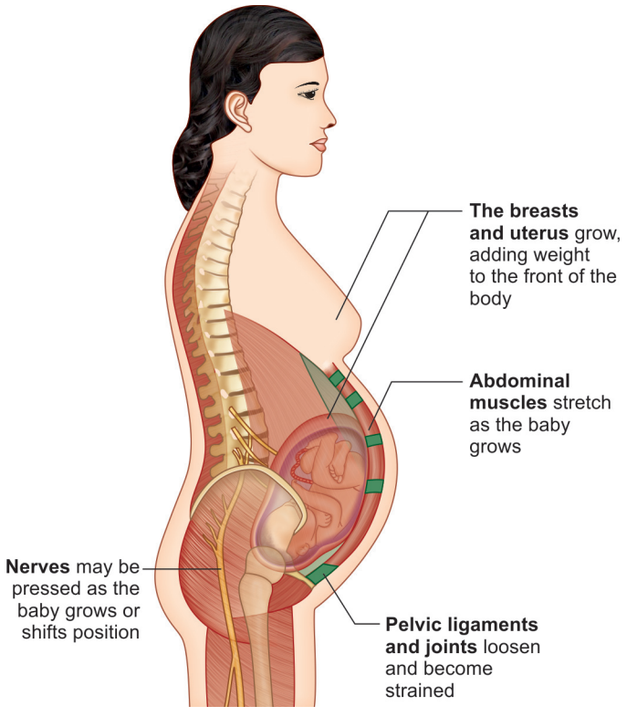


Fig. 1.6: Late pregnancy—musculoskeletal changes

- Fluid retention can cause compression of certain nerves such as the median nerve under flexor retinaculum over wrist.