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Developmental Physiology

The fertilized egg contains the genetic material that directs cell multiplication and differentiation and guides development of the fetus. However, extrinsic factors also play a role. During the first half of pregnancy, the fetus' own genetic program is the primary determinant of growth. During the second half of pregnancy, the patterns of growth and development are more variable. The four primary epigenetic factors at work during the second half of pregnancy are placental, hormonal, environmental (e.g., maternal nutrition, disease, drugs, altitude), and metabolic (e.g., diabetes).

Development of the Organ Systems

The gross structure of the organ systems is usually established by the 4th month of pregnancy. However, cellular development in the organs requires the remaining 5 months of gestation to complete. Even at birth, some organ systems (particularly the nervous system, kidneys, and liver) lack full development.

Circulatory system. The heart begins to beat during the 4th week after fertilization. By this point, the fetus is a multicellular organism that requires a circulatory system to deliver nutrients to the developing organs. Many tissues produce red blood cells in the fetus that lose the ability to generate blood cells by birth, including the endothelium of blood vessels, the liver, and lymphoid organs. Early in development, many of the red blood cells are nucleated. The hemoglobin of fetal red blood cells differs from that of postnatal individuals in that it has a higher affinity for oxygen. By the end of the first postnatal year, genetic programming causes the fetal hemoglobin to be replaced by normal human hemoglobin.

Respiratory system. The development of the respiratory system occurs over a relatively long period of time, such that the respiratory system is not adequately developed to sustain life until just before the end of a normal pregnancy. For example, the development of the alveolar membranes and the interdigitation of capillaries into the membranes does not occur until after ~24 weeks gestation. A number of hormones, particularly glucocorticoids, stimulate the formation of type II alveolar cells and the secretion of surfactant. Fetal cortisol levels rise steadily during the third trimester and surge just before birth. Two thirds of this cortisol is of fetal origin; the rest crosses the placenta from the mother. Most infants delivered before 30 weeks of gestation have insufficient surfactant to permit adequate breathing, and require artificial ventilation.

Because glucocorticoids stimulate surfactant production, women with risky pregnancies at 24-34 weeks gestation are provided steroid therapy to induce surfactant production. Surfactant can also be injected into the trachea of the newborn to ease the work of breathing. Together, glucocorticoid therapy and infusion of surfactant in the newborn have greatly reduced the incidence of respiratory distress syndrome.

Nervous system. Most reflexes that involve the spinal cord and brainstem are present by 4 months of gestation. However, cortical development lags behind, and is far from complete at birth. Cortical development requires feedback from the environment, and occurs progressively through the first years of life.

Renal system. The fetal kidneys begin to secrete urine during the second trimester, and fetal urine accounts for 70-80% of the amniotic fluid. However, control of fluid and ion balance in the extracellular space, and particularly acid-base balance, is not fully developed until well after birth. At birth, the infant cannot concentrate urine nearly as much as an adult, and loses considerable fluid through urine. Thus, the newborn infant must consume ample quantities of milk to avoid dehydration.

Gastrointestinal system. The GI system begins to function relatively normally, with some exceptions, by the middle of pregnancy. At this point, the fetus consumes amniotic fluid and excretes the residue combined with waste products from the GI tract (mucus, dead cells, GI secretions); this waste is called *meconium.*

Liver function in the infant is greatly diminished until at least a week after birth. Prior to birth, the fetus acquires a number of plasma proteins, and eliminates bilirubin (the breakdown product of red blood cells), through the placenta. At birth, the lack of the ability of the infant to conjugate bilirubin with glucuronic acid for elimination in bile can result in infant jaundice, resulting in a yellow discoloration of the skin. Usually liver function increases and bilirubin levels drop within a week, before any physiological consequences occur. However, since bilirubin is toxic to brain cells, a rare complication after birth is the development of *bilirubin encephalopathy.*

Diminished liver function at birth also results in a drop of plasma proteins as well as clotting factors during the first weeks of life. In some cases, this can result in edema since filtration exceeds absorption in capillaries.

A major problem soon after birth is a lack of ability of the liver to engage in gluconeogenesis. As a result, the infant must feed often to avoid a drop in blood glucose levels. Unfed infants can have a blood glucose level that is only ~40% of normal.

Metabolism. Until near the time of delivery, the tissues of the fetus do not require insulin to transport glucose. However, insulin is an important growth hormone in the fetus, such that development does not occur normally without insulin. In mothers with untreated Type 1 diabetes, hyperglycemia results in superfluous insulin production by the fetus, which stimulates body growth. In mothers with Type 2 diabetes, high levels of blood insulin are conveyed to the fetus, also stimulating growth. Thus, the child of a diabetic mother is larger than a normal child, which can result in problems at birth.

Infants of mothers with untreated Type 1 diabetes often have elevated insulin production due to fetal stimulation of pancreatic β-cells. As a result, these infants may suffer from hypoglycemia.

Insulin-like growth factors are secreted from the fetal liver independent from the levels of growth hormone (recall that in adults, growth hormone regulates the levels of insulin-like growth factors). Insulin-like growth factors are essential to stimulate mitosis and development of the fetus. Curiously, anencephalic fetuses grow normally without the existence of an anterior pituitary and any production of growth hormone.

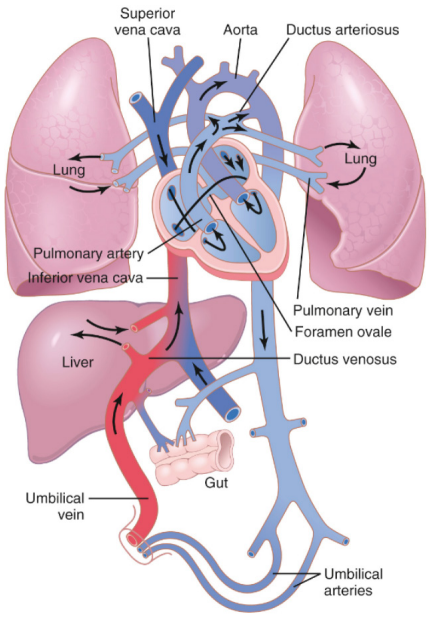
As noted in previous lectures, thyroid hormone is essential for normal fetal development. Prior to the second trimester, and the development of the hypothalamic-pituitary portal system, the thyroid hormone that stimulates development comes from the mother. Although severely hypothyroid mothers rarely get pregnant, modestly hypothyroid mothers often have children with serious birth defects, particularly diminished intelligence.

Mothers with an autoimmune disease that attacks the thyroid gland pass the defective antibodies to the fetus. Those antibodies attack the fetal thyroid gland, resulting in defective fetal development.

Iodine deficiency during pregnancy leads to diminished thyroid hormone secretion by both the mother and fetus. This almost always results in severe *cretinism.* The World Health Organization estimated in 2000 that 20 million people had some degree of brain damage due to iodine deficiency in fetal life.

Physiological Changes at Birth

A variety of cardiovascular specializations are present in the fetus to receive oxygen and nutrients from the placenta, and to bypass the lungs, which are not functional. These specializations must be replaced at birth with the normal circulatory structure.



Blood returning from the placenta through the *umbilical vein* passes through *the ductus venosus*, mainly bypassing the liver. Most of this blood is directed across the right atrium and through *foramen ovale* into the left atrium. Thus, most of the oxygenated blood from the placenta is delivered to the left heart, and is pumped to the arteries of the upper body.

Blood entering the right atrium from the superior vena cava tends to flow through the tricuspid valve into the right ventricle. Most of this blood is directed through *ductus arteriosus* into the descending aorta, and much of that blood reaches the placenta, where it is oxygenated.

Only ~12% of the blood passes through the lungs of the fetus. Of the blood entering the aorta, ~55% is directed to the placenta, ~18% to the lower body, and ~15% to the upper body and head.

As discussed during the Respiratory Lectures, a variety of changes in this circulatory pattern occur at birth. Loss of the placental circulation increases systemic vascular resistance, resulting in increases in aortic pressure. The pulmonary vascular resistance drops precipitously, as the first breath of the infant causes the pO_2 in the lungs to rise, thereby resulting in dilation of the pulmonary arterioles. This drop in pulmonary resistance causes right atrial pressure to drop. The rise in left atrial pressure (due to increased return of blood from the lungs) and the drop in right atrial pressure result in the closure of foramen ovale. The new pressure differential in the atria causes a flap of tissue on the left side to cover the opening, preventing back-flow into the right atrium. Within a few months, a solid tissue barrier usually forms in the atrial septum.

The ductus arteriosus also closes at birth, but for different reasons. Note that in the fetus, the high pulmonary resistance favors blood flow from the pulmonary artery into the descending aorta through the ductus arteriosus. After birth, aortic pressure becomes higher than pulmonary artery pressure, so the direction of blood flow reverses. The high level of oxygen in the arterial blood serves as a paracrine that causes constriction of smooth muscle in ductus arteriosus. Loss of prostaglandin E_2 from the placenta, which induces dilation of smooth muscle in ductus arteriosus, also contributes to its closure. Administration of prostaglandin synthesis inhibitors such as indomethacin can aid in closure of ductus arteriosus if this does not occur naturally.

Ductus venosus, which shunts blood from the placenta away from the liver, also closes within a few hours of birth. The closure of this vessel permits portal blood flow through the liver. The mechanisms contributing to the closure of ductus venosus are currently unknown.

The First Breath

Fetal breathing movements commence near the end of the first trimester. It appears that hypoxia and tactile stimulation of the fetus promote these breathing movements, which occupy less than half of any 24-hour period. Near term, breathing movements are regular, similar to those found after birth. However, just before labor, fetal breathing decreases, for an unknown reason.

In utero, the alveoli and airways of the fetal lung are filled with fluid. The onset of labor is accompanied by increases in catecholamines and arginine vasopressin, which decrease fluid production by the fetal lung and initiate its active reabsorption. The pulmonary circulation absorbs the majority of the fluid, and the pulmonary lymphatics absorb some as well. A small portion of the lung fluid is forced out of the trachea as the fetus passes through the birth canal.

The first breath is the defining event for the newborn, and is triggered by hypoxia and hypercapnia as well as cold skin and tactile stimulation. Not only does it inflate the lungs, but as noted above it triggers circulatory changes that convert the fetal pattern of blood flow to the adult pattern.

The first breath is normally also the most difficult inspiration of a lifetime. A considerable negative pressure within the intrapleural space is necessary to overcome the effects of surface tension. The newborn's first ventilatory effort creates an air-water interface for the first time, opening the alveoli. Breathing becomes far easier once the alveoli are open and the type II alveolar pneumocytes deliver surfactant to the air-water interface.

Immunity

The placenta actively transports the small IgG immunoglobulins from mother to fetus, so that fetal IgG levels are even higher than those in the mother. These maternal IgG antibodies ward off infection by viruses and some bacteria. However, maternal IgA (which is primarily present in secretions), IgE, and IgM antibodies generally do not cross the placenta in appreciable amounts, and the baby is generally born with very low levels of these other immunoglobulins.

In addition to high prenatal levels of maternal IgG, the newborn receives copious amounts of secretory IgA antibodies in colostrum and breast milk. However, the blood levels of maternal IgG antibodies progressively fall, and IgG levels in the infant's blood reach a nadir at ~3 months of age. After that time, the infant's own production of IgG antibodies causes total IgG levels to increase gradually. However, even at 1 year of age, IgG levels—as well as the levels of IgA, IgM, and IgE—are still only half of adult levels.

Antibodies obtained in utero from the mother protect against most childhood diseases, including diphtheria, measles, and poliomyelitis. The persistence of antibodies—at levels high enough for protection—varies considerably from one disease to another. For example, maternal measles antibodies are so persistent that vaccinations against measles often fail if they are attempted before 15 months of age. In contrast, maternal antibodies against whooping cough (pertussis) are generally inadequate to protect the infant beyond 1 to 2 months. The infant normally receives a first DTP immunization (diphtheria, tetanus, and pertussis), as well as a first poliomyelitis immunization, at 2 months of age.

Physiological Effects of Aging

The extent of aging-related physiological changes among individuals range from barely perceptible to very marked. A subset of individuals shows minimal physiological deterioration during aging. Many individuals show marked deterioration with age in all physiological systems, whereas other individuals exhibit little or no deterioration in one or more systems. Although the nature of the aging process is similar in the two sexes—except, of course, for the reproductive system—important quantitative differences exist. For example, women lose bone mass much faster with increasing age than do men. Because of the great reserve capacity or redundancy of some physiological systems, the effect of aging on a physiological process is often not apparent until either the individual faces an unusual challenge or function has fallen to less than some critical level.

Changes in height and weight during aging.

Women reach peak height by age 16 to 17 years and men by 18 to 19 years. After these peaks, height starts to decline, primarily because of compression of the cartilaginous disks between the vertebrae and loss of vertebral bone. By the age of 70 years, height has fallen 2.5% to 5% lower than peak level. In most Americans, body mass increases until middle age in both sexes and begins to decrease after age 70 years. Both fat-free mass and lean body mass progressively decrease over most of adult life in both sexes. Although a sedentary lifestyle may contribute to this loss, lifelong athletes also show a progressive age-associated loss in fat-free mass and lean body mass.

Adipose tissue fat mass increases with adult age, but the extent differs markedly among individuals. Although a sedentary lifestyle may be a factor, even physically fit individuals who do not exhibit an age-associated increase in body mass show a small but progressive increase in adipose tissue fat mass (in parallel with the decrease in fat-free body mass).

Changes in muscle.

A steady loss in skeletal muscle mass occurs with aging, particularly beyond 50 years, and it primarily reflects a loss of number and, to a lesser extent, size of muscle fibers. The loss of muscle partly results from inactivity, but it is also caused by a progressive loss of the motor neurons. With loss of their neural innervation, affected muscle fibers either atrophy and die or become innervated by a sprout that emerges from a healthy axon nearby. This process of reinnervation ultimately results in larger motor units and thus a decrement in fine motor control.

Changes in bone.

Remodeling of bone occurs throughout adult life; it involves the coordinated activity of *osteoclasts*, which resorb bone, and *osteoblasts*, which form bone. Until middle age, bone resorption and formation are in balance. However, starting in middle age, resorption exceeds formation, thus leading to a progressive loss in bone mass. In women, bone loss accelerates during the first few years following menopause. Bone loss can progress to osteoporosis, which carries a heightened risk of bone fractures.

With increasing adult age, joint flexibility declines, mainly because of the aging of articular cartilage. This cartilage thins and exhibits altered mechanical features, including decreases in tensile stiffness, fatigue resistance, and strength. The age-related changes in joint cartilage undoubtedly play a major role in the development of osteoarthritis.

Changes in cardiovascular function.

Aging decreases the distensibility of arteries. The decreased compliance results in increased systolic pressure and slightly decreased diastolic pressure. Consequently, there is a tendency for mean blood to increase with aging. The increased afterload causes thickening of the left ventricular wall, which involves an increase in size but not number of myocytes.

At the same time, venous compliance increases. This tends to result in an increase in peripheral blood pooling, and increased susceptibility for orthostatic hypotension.