21. BIRTH: FETUS TO NEONATE

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RECOMMENDED READING: Larsen, 3rd edition, pp. 149-151 (lung maturation), 217, 220-222 (changes in circulatory system), 481-484, 487 – 489 (Rh Factor).

SUMMARY: Normal gestation in humans requires 38 weeks, (266 days) from the time of fertilization. During the first two months, the embryonic period, the essential organ systems are established. This is the time of highest risk of teratogenic effects. During the remainder of the pregnancy, the fetal period, there is general growth and maturation and most systems are less prone to developmental anomalies. However, the brain and sensory systems undergo significant development over this time and so are highly sensitive. At birth when placental circulation is terminated, there are major accommodations to extra uterine life involving changes particularly in the circulatory and respiratory systems. The age at which a fetus is viable is primarily a function of the time at which gas exchange can occur with the air medium within alveoli of the lungs, no earlier than 26 weeks.

Parturition and the hormones of pregnancy will be discussed in the topic of the female reproductive system in Science Basic to the Practice of Medicine and Dentistry.

GLOSSARY:

Apgar score: rating of general condition of neonate based on five components: heart rate, respiratory effort, muscle tone, reflex irritability, and color, each of which is given a score of 0 through 10.

Embryonic period: third through eighth weeks of pregnancy

Fetal period: ninth week to birth

Lanugo hair: first fetal hair, very fine, most prominent 7th and 8th months, typically shed before birth

Meconium: contents of lower ileum and colon beginning at 4th month; a combination of desquamated intestinal cells and components of swallowed amniotic fluid including lanugo hair, desquamated skin and various secretions including bile

Rh factor: red cell surface molecule that if missing in the mother (Rh negative) results in her developing antibodies that can cross the placenta in subsequent pregnancies and cause breakdown of fetal red cells (*erythroblastosis fetalis*)

Vernix caseosa: secretory product of sebaceous glands that covers the fetus and offers protection against infection during parturition

LEARNING OBJECTIVES:

This lecture provides a summary of developmental processes in the various organ systems. At the end of the lecture you should be able to:

1. Discuss the significance of designating embryonic and fetal periods in development.
2. Discuss progressive changes in the digestive, urinary, respiratory, endocrine and nervous systems and describe the general status of the fetus in the early, middle and late periods of development.
3. Describe the major changes in the circulatory and respiratory systems that occur at the time of birth.

TEXT

Intrauterine development is divided into an embryonic period extending through the eighth week in which all the rudiments of the major organ systems form, and a fetal period from the ninth week until birth in which growth and maturation are the defining processes.

Fetal growth and development

At the beginning of the fetal period the fetus weighs about 8 g and the head makes up about one half of its crown-rump length (**Figure 21-1**). At birth the head is about one fourth of crown-heel length and the fetus weighs about 3400 g (**Figure 21-2**).

Fig. 21-1. Early fetus (60 days), head as large as body, tail has regressed, digits present, gut herniated into umbilical cord. Hamilton, WJ, and Mossman, HW Human Embryology 4th ed. Williams & Wilkins, Baltimore, 1972, p. 184.
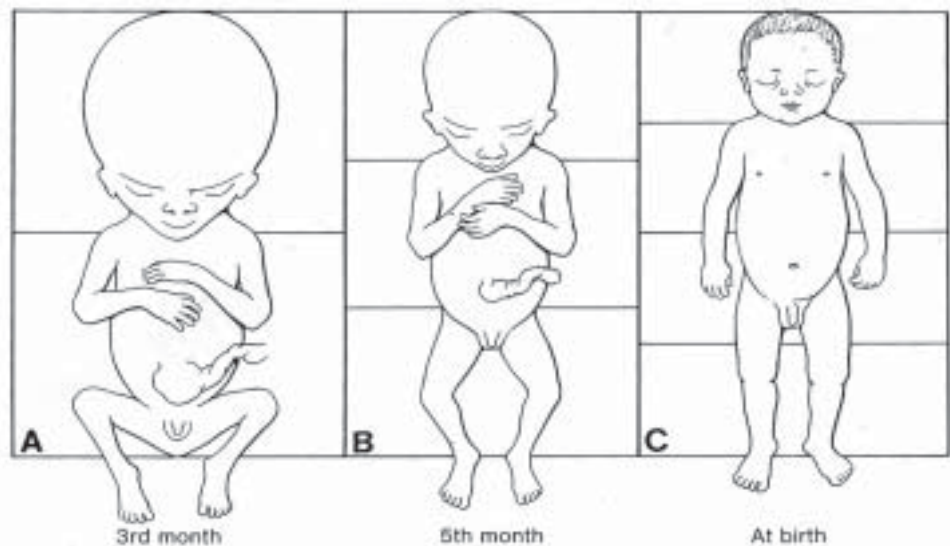

A   3rd month   B   5th month   C   At birth

Fig. 21-2. Relative size of head over fetal development. Sadler, TW Langman's Medical Embryology 8th ed. Lippincott Williams & Wilkins 2000 Baltimore, MD, p. 114.

Teratology

The risks of malformation due to genetic flaws and environmental insults are highest in the embryonic period. Errors in development that arise in the fetal period may be severe, but are usually more restricted. This is the period during which most of the development and maturation of the brain and nervous system occur. Insults to these systems can result in functional and behavioral problems. Teratogenic agents include the rubella virus, which if present during the first trimester can cause defects in the eyes, ears and heart. Thalidomide, a highly effective sedative, is no longer prescribed as it was
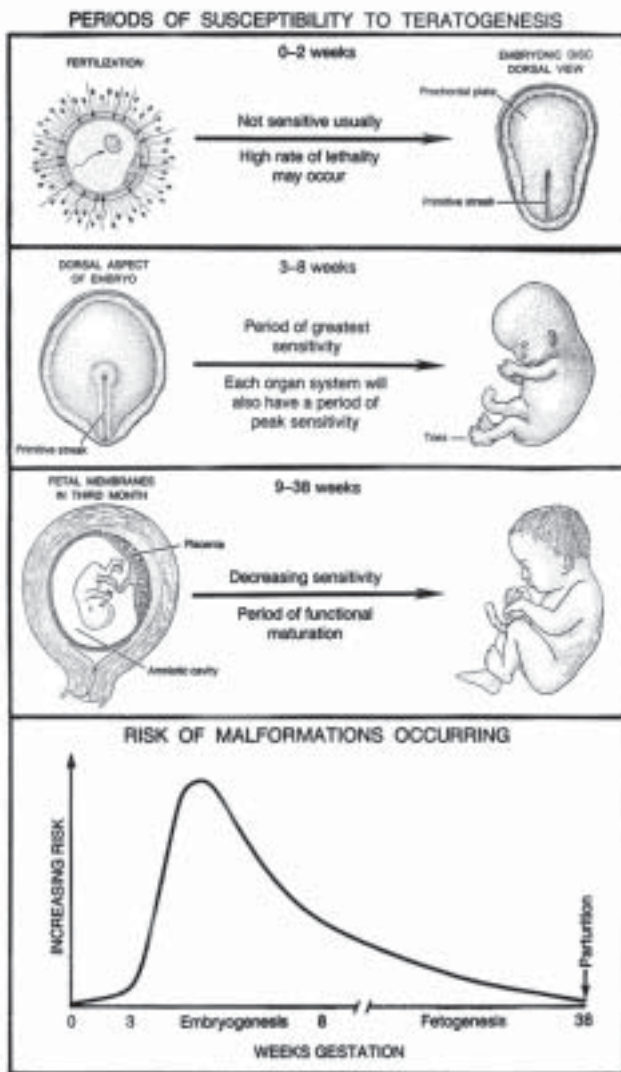
Fig. 21-3. Periods of susceptibility. Sadler TW, Langman's Medical Embryology 8th ed. Lippincott Williams & Wilkins 2000 Baltimore, MD, frontispiece.

found to cause serious defects in limb development if used during the first six weeks. Deficiency in folic acid in the maternal diet can result in a range of defects in the nervous system from anencephaly (lack of brain) to failure of neural tube closure. For most organs there is a peak period of susceptibility while the nervous system with its long period of maturation has a prolonged period of risk (**Figure 21-3, and Introductory Chapter, Figure p. 6**).

Maturation of organ systems during fetal period

At the beginning of the fetal period all the major organ systems are in place, but only the heart and circulatory system are truly functional. The blood that is delivered to the fetus is well oxygenated and carries products of maternal digestion that are ready to be utilized.

The following is a description of critical developmental landmarks in the various organ systems during the fetal period and the changes that occur at birth that allow the neonate to survive without the support of the umbilical circulation. While anomalies and malformations may occur, and it is important to understand their embryological origins, this discussion will focus on normal development.

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Digestive System

There is an oral to aboral gradient in the development of the specific regional characteristics of the lining of the gut. The secondarily occluded lumen becomes recanalized by the 9th week.

Esophagus and stomach: The mucosal epithelia of the esophagus and stomach differentiate by about 4 months. Parietal cells and chief cells are evident by as early as 11 and 12 weeks respectively; however these cells may not be actively secretory during fetal life as the lumen of the stomach remains at about normal pH until birth. Within a few hours after birth gastric acid production increases greatly and the stomach contents become acid.

Intestine: Development of villi begins within the duodenum at the beginning of the fetal period. This is followed in the next two weeks by the elaboration of crypts. By 16 weeks villi and crypts are forming along the length of the intestine, even in the colon where the villi will regress and are eliminated by the 8th month. While no major digestive function occurs until after birth, Brunner's glands appear early in the second trimester. At this time most intestinal cell types are present. Not surprisingly, lactase is one of the first enzymes to be synthesized.

Liver: The diverse functions of the liver begin at various times. Hematopoiesis begins here as early as 4 weeks, and this becomes the major site of blood formation by the beginning of the fetal period. Early on, the liver synthesizes serum albumin and begins to store glycogen. At 12 weeks hepatocytes can produce bile, largely through the breakdown of hemoglobin. These cells also begin to make enzymes for the synthesis of urea from nitrogenous metabolites.

Contractility and peristalsis: Neuromuscular components of the gastrointestinal tract develop along an oral to aboral gradient. The first spontaneous rhythmical activity in the small intestine occurs at the 7th week when the inner circular layer of the muscularis externa has developed, but peristaltic movements do not begin until the 4th month.

Swallowing and sucking: Swallowing can be detected first at 11 weeks. Towards the end of gestation the fetus swallows between 200 and 750 ml or more of amniotic fluid per day. This may contain growth factors that facilitate the differentiation of epithelial cells in the GI tract. Taste seems to affect fetal swallowing. Saccharin introduced into the amnion increases fetal swallowing and noxious chemicals reduce swallowing. Sucking begins only at about 32 weeks. From 32 to 36 weeks, there are short bursts of sucking that are not associated with swallowing.

Meconium: The intestine (lower ileum and colon) contains meconium by the end of the 4th month. This is a mixture of desquamated intestinal cells, swallowed lanugo hair and various secretions. It is greenish due to the presence of bile pigments. After 3-4 weeks the fetus can pass meconium in utero. The presence of significant quantities of meconium in amniotic fluid can signal fetal distress. In newborns with neurodevelopmental problems meconium is sometimes analyzed as an indicator of prenatal exposure to noxious agents such as drugs, alcohol and tobacco.

Urinary System

The urinary system develops in stages as described in Chapter 13. (Note that excretory function is performed throughout pregnancy by the placenta. Waste products including urea, creatinine and bilirubin are transferred from fetal blood vessels across plancental villi.) The mesonephros is functional during the embryonic period and produces small amounts of dilute urine by the 5th week. It regresses late in the 3rd month when the metanephric tubules are taking shape. Between the 9th and 12th weeks the metanephric kidneys begin to function and by 14 weeks the loops of Henle are performing resorptive function. The product of the fetal kidney is hypotonic to plasma. One of the mechanisms for concentrating the urine is the action of antidiuretic hormone (ADH). This hormone is released by the neural lobe of the pituitary (see below) beginning at the 11th week.

Amnion

Amniotic fluid increases until the 7th month and then decreases such that the total volume at birth is about 1 liter. It is initially produced by transport of fluid across the amniotic membrane. Beginning at 16 weeks fetal urine contributes substantially to the fluid. (This urine does not contain metabolic waste as this is carried via the placental circulation back to the mother.) Amniotic fluid is constantly being resorbed, largely through the fetal gut after it is swallowed.

Respiratory System

The development of the respiratory system is discussed in Chapter 12. Briefly, respiratory bronchioles begin to sprout from terminal bronchioles by about the 16th week, and by 26 weeks give rise to terminal sacs (future alveoli). During the last trimester of pregnancy fluid constitutes 90% to 95% of the total weight of the lungs. The fluid is a combination of secretions of pulmonary epithelial cells and amniotic fluid. Total fluid volume is related to breathing movement. Mechanical stretching stimulates proliferation of lung epithelium. The fetus begins to make gross breathing movements as early as 11 weeks. These are periodic gasps. Periods of rapid breathing occur mostly during rapid eye movement

sleep (REM) and alternate with periods of cessation (apnea).

Type II pneumocytes secrete small quantities of pulmonary surfactant at 6 months. Major changes in the lungs take place during the last 2 months. This includes thinning of the walls of the maturing alveoli and increased secretion of surfactant. There is not sufficient surfactant for spontaneous respiratory function until 36 weeks.

Endocrines (Figure 21- 4)

Note: The endocrine glands and the hormones of pregnancy and lactation are discussed later in SBPMD.

Most peripheral endocrine glands (e.g., thyroid, pancreatic islets, adrenals, parathyroids, gonads) form early in the second month as the result of epithelial-mesenchymal interactions. As they differentiate late in the 2nd or early in the 3rd month, the glands develop the intrinsic capacity to synthesize their specific hormonal products, though in small amounts. The regulation of endocrine secretion depends on stimulation by higher order centers, e.g., pituitary gland and hypothalamus.

The **pituitary** gland is a two-part organ (**Figure 21-5**). Its anterior lobe (adenohypophysis) develops as a dorsal outpocketing of oral ectoderm beginning at the 4th week. This lobe is the source of hormones, some of which stimulate the peripheral endocrine glands. These include thyroid stimulating hormone (TSH) the gonadotropins (luteinizing hormone, LH and follicle stimulating hormone, FSH) and adrenocorticotropic hormone (ACTH) as well as growth hormone and prolactin. The cell types that produce these hormones differentiate over the course of the fetal period. The posterior lobe of the pituitary forms as a downgrowth of the diencephalon, and as central nervous tissue, is called the neurohypophysis. It is the site of the axon terminals of cells in the hypothalamus whose secretions are antidiuretic hormone (ADH, also known as vasopressin) and oxytocin.

Beginning at about 12 weeks a neurovascular connection is established between the pituitary and the brain, allowing for the delivery of hormones from the hypothalamus that stimulate or inhibit the cells of the pituitary. Negative feedback systems develop such that there is interplay between the endocrine glands and higher centers. The **thyroid** gland (Chapter 10) illustrates this mechanism. In the fully functional system, signals (TSH) from the anterior lobe of the pituitary gland that are delivered to the thyroid gland via the bloodstream stimulate both the synthesis and release of thyroid hormone. Thyroid hormone, in addition to stimulating metabolic activity at sites around the body, acts back on the hypothalamus where it inhibits the release of thyrotropin releasing hormone(TRH) a stimulator of TSH that is delivered through the hypothalamic-pituitary neurovascular portal system. The effect is to decrease the synthesis and release of TSH by the anterior pituitary.

The **adrenal** is a two part gland. Its medulla is derived from neural crest (Chapter 4) and is essentially a modified sympathetic ganglion but its cells secrete epinephrine as well as norepinephrine. The cortex is the source of steroid hormones including mineralocorticoids, glucocorticoids and weak androgens. The role of the adenal in the development of the urogenital system is discussed in Chapters 13 and 14.
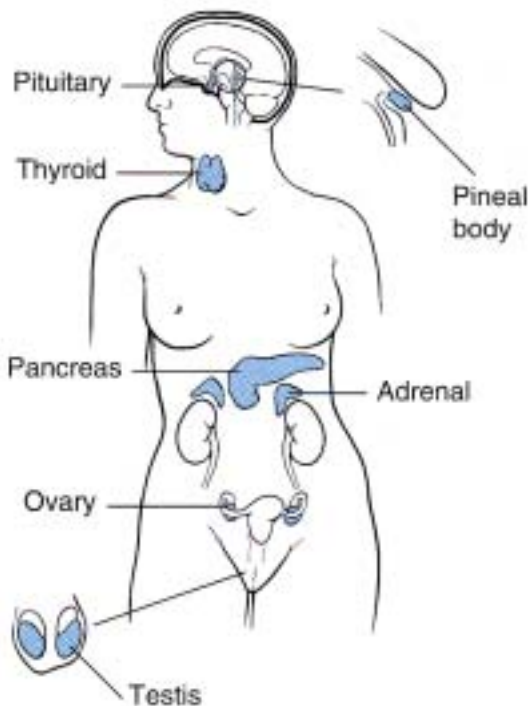

Fig. 21-4. Major endocrine organs. Bergman RA, Afifi AK, Heidger Jr PM, Histology 1996 WB Saunders, Philadelphia (1996), p. 259.
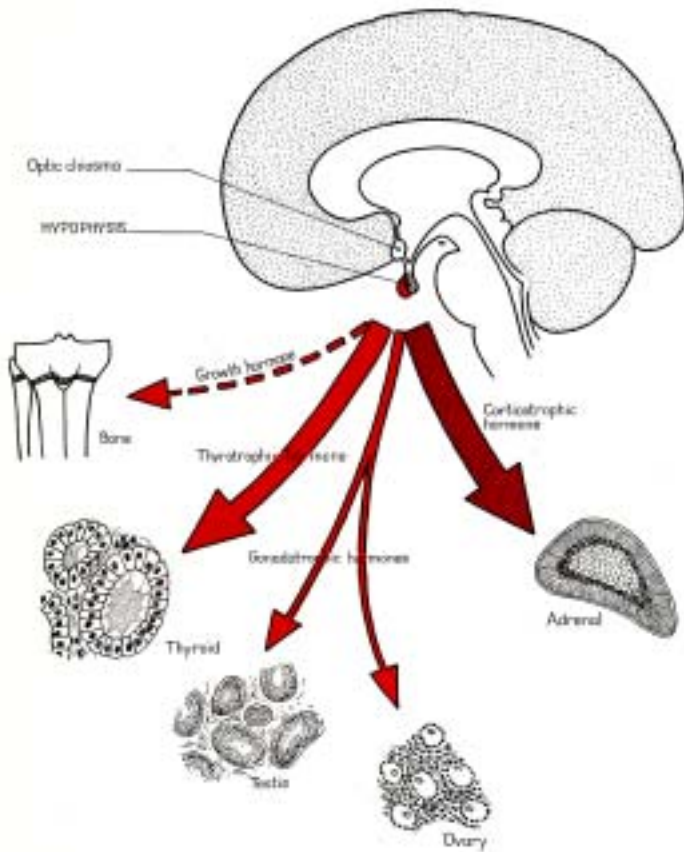
The placenta itself is a major source of peptide, protein and steroid hormones (notably progesterone and estrogen). Progesterone and estrogen are produced by a complex process requiring products from the maternal side as well as the fetal adrenal (to be discussed in SBPMD). The hormones produced include placental lactogen (hPL), human chorionic thyrotropin and corticotropin, insulin-like growth factors, prolactin, relaxin and corticotropin-releasing homone.

Brain, nervous system and behavior (Figure 21-6)

At the end of the embryonic period, the five divisions of the brain are apparent: the telencephalon, diencephalon, mesencephalon, metencephalon and myelencephalon and the flexures have occurred. The lateral cerebral vesicles (future cerebral hemispheres) have formed as diverticula of the telencephalon and the olfactory bulbs are present. The diencephalon has differentiated into a thalamus with overlying epithalamus containing the pineal gland and an underlying hypothalamus. The pituitary gland has begun

Fig. 21-5 Hormones of the anterior pituitary and their targets. Tuchmann-Duplessis H, Auroux M, Haegel P, Illustrated Human Embryology, Vol. 3, Nervous System and Endocrine Glands Springer-Verlag, NY, 1975, p. 127.

to develop. Emanating from the diencephalon are the optic vesicles (the future retinae and optic nerves). The cerebellum is forming in the roof of the metencephalon.

The cerebral cortex appears smooth until about 6 months. It subsequently develops gyri (bulges) and sulci (grooves) as the volume of the gray matter increases. The central sulcus is recognizable by 6 months as are the major lobes of the cerebral cortex (frontal, parietal, temporal and occipital).

The spinal cord initially extends throughout the length of the vertebral column, but as the embryo grows, its terminal regresses such that by 9 months, the tip of spinal cord is at L3. Postnatal growth results in its adult position between L1 and L2.
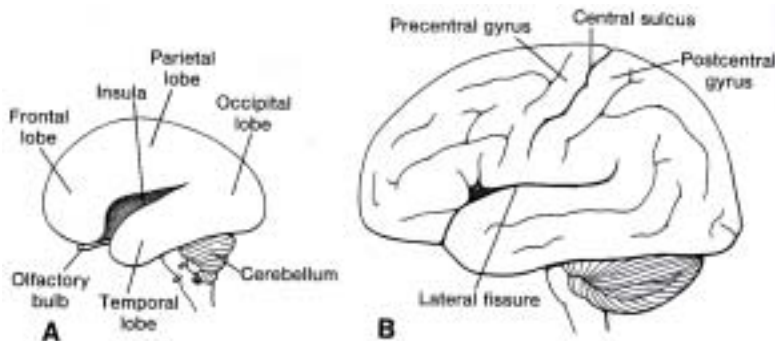
Myelination of axons begins in the motor roots of the peripheral nervous system,

Fig.21-6. Brain development. A. 7 months, B. 9 months. Sadler, TW Langman's Medical Embryology 8th ed. Lippincott Williams & Wilkins 2000 Baltimore, MD, p 438.

followed by sensory roots in the second month. Myelination of axons within the spinal cord begins at 11 weeks at the cranial end of the cord. The functional maturation of individual tracts is dependent upon their myelination, which continues into young adulthood. Myelination within the brain begins in the third trimester and continues into young adulthood.

The fact that the nervous system develops and matures over a long period makes it uniquely vulnerable to teratogenic agents.   Ethanol is a common cause of mental retardation (fetal alcohol syndrome, FAS).

Fetal movements (Figure 21-7)

The undisturbed embryo does not show any indication of movement until about 7 - 8 weeks. The earliest movement is startle, characterized as a quick (one second) generalized movement that starts in the limbs and may spread to the trunk and neck. Early on the fetus can move an arm or leg and can move its head. It can hiccup by about 10 weeks and yawn by 12. Diurnal rhythms in fetal activity appear at 20 to 22 weeks. Movement is highest in early evening when maternal blood glucocorticoid levels are lowest, and lowest in the early morning when glucocorticoid peaks.

Sensory systems

The fetus in utero is able to respond to sounds in the amniotic fluid after about 20 weeks. The pathway by which sound reaches and activates the fetal inner ear is not entirely known. The auditory ossicles are not free to vibrate until just before birth. It is thought that transmission of sound is predominately by vibrations in skull bones induced by a sound field in the amniotic fluid that result in vibrations within the fetal cranial cavity (brain and cerebrospinal fluid). This apparently reaches the fetal inner ear through fluid communication channels connecting the cranial cavity and the inner ear.   Near term fetuses are responsive to 2000 Hz stimuli when in a state of wakefulness, but are unresponsive during periods

Fig. 21-7. Timetable for onset of movements. Carlson, Bruce M. Human Embryology and Developmental Biology, 2nd ed., Mosby, St. Louis, 1999, p. 454.

of sleep. Loud vibroacoustic stimuli applied to the maternal abdomen produce a fetal response consisting of an eye blink, a startle reaction, and an increase in heart rate.

The eyes are covered by the fused eyelids from the end of the embryonic period until somewhere between the 5th and 7th months. Although the fetus is in the dark, there is a pupillary light reflex by about 30 weeks.

Antibodies and immunity

Maternal antibodies are transferred across the placenta and enter the fetal circulation. This results in passive immunity for the first few months after birth against a number of agents including smallpox, diphtheria and rubella (German measles). The passage of antibodies can also cause problems for the fetus as in the case of maternal-fetal incompatibility in the Rh factor. This is a red blood cell surface molecule that is present in the majority of the population.   If the mother is Rh negative, but the fetus is Rh positive, this may cause problems because a few red cells from the fetus inevitably escape into the mother's circulation. She will then develop antibodies to the Rh factor. This is not usually a problem in the first pregnancy with an Rh + fetus, as only a few antibodies will have been formed. But in subsequent pregnancies, large numbers of antibodies are generated by the Rh-negative mother. When these cross into the fetal circulation, they form antigen-antibody complexes that result in hemolysis of the fetal red cells, a condition known as *erythroblastosis fetalis*. This can be prevented by transfusions

of Rh-negative blood to the fetus in utero and to the newborn so there is a substantial population of red cells that will not be destroyed. More recently it has become common practice to administer anti-Rh antibodies to the mother after a pregnancy with an RH+ baby so that Rh antibodies that she has developed will be destroyed.

Appearance of the fetus

The 5-month-old fetus is covered by lanugo hairs.   At 7 months the skin is slightly wrinkled, there are scalp hairs in addition to lanugo, eyelashes are well developed and the eyelids begin to open. By 8 months there is enough subcutaneous fat storage that the skin is pink and smooth. (Brown fat is deposited beginning at the 17th week and is a major site of heat production in the newborn.) Fingernails have reached the tips of the fingers. The testes are descending into the scrotum.

By 9 months the testes have usually completed their descent. Toenails reach the ends of the toes and most of the lanugo hairs are shed by this time. The skin is covered by vernix caseosa. This waxy substance is a product of sebaceous glands and offers some protection against infection during the birth process. The attachment of the umbilical cord becomes central in the abdomen. The breasts protrude and produce "witches milk".

Birth

The stages of birth are illustrated in **Figure 21-8**. In the first stage (A and B) the cervix dilates, and the amnion and chorion enter the birth canal. In the second stage (C to E) the fetus passes through the cervix and vagina. In the third stage (F) the uterus continues to contract causing the placenta to fold and pull away from the uterine wall and a hematoma forms. The placenta and associated membranes are subsequently expelled by further contractions.

At birth the health of the neonate is usually rated based on the basis of its Apgar score on heart rate,
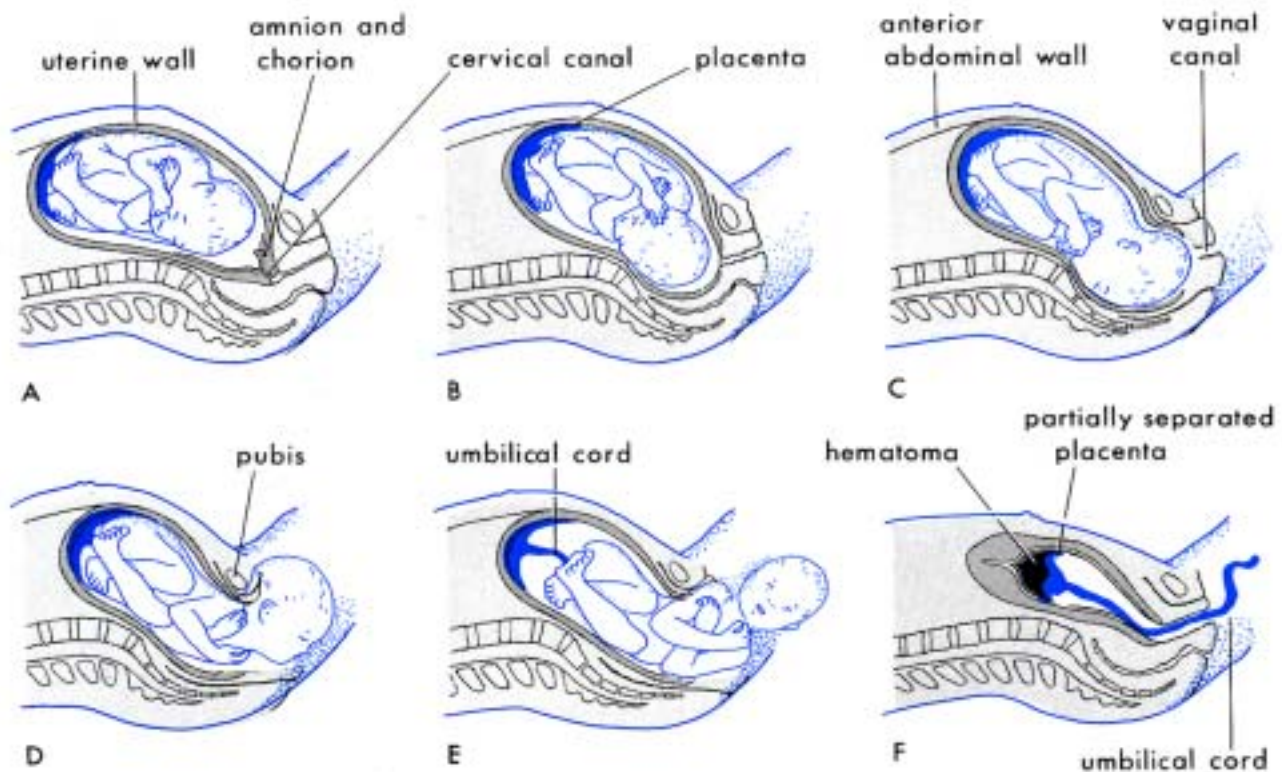

Fig. 21-8. Stages of birth. Moore, KL, Before We Are Born 3rd ed., WB Saunders, Philadelphia, 1989, p. 96.

respiration, muscle tone, reflex response and color. On a scale of 0-10, anything above 7 is considered within normal range.

Changes in the circulatory system
Dramatic changes occur in the circulatory (and respiratory) system at birth, allowing the neonate to survive without support from the placenta. These are discussed in Chapters 7, 12 and 22. See **Figures 7-14 and 7-15.**

Some landmarks in fetal development

1. **Beginning of fetal period – 9 weeks**
    The gut recanalizes, the midgut is herniated into the umbilical cord, the heart is partitioned, definitive aortic arches are formed, hematopoiesis is ongoing in the liver, the diaphragm has formed, ossification has begun (clavicle), teeth are cap stage, the tail has regressed, the external genitalia are indifferent, the head is half of the crown rump length, there is a startle response.
2. **Beginning of the second trimester – 12 weeks**
    The midgut is no longer herniated, dilute urine is produced by the metanephros, the liver produces serum albumin, stores glycogen, secretes bile and is hematopoietic, the endocrine glands are formed but are not fully functional, myelination of spinal roots and spinal cord has begun, the lungs are gland like, the fetus can hiccup, gasp, swallow and yawn, gender differences are visible externally.
3. **The earliest time of possible survival – 26-28 weeks**
    The gut has developed villi and crypts, peristalsis is present, surfactant is secreted in the lungs, the alveolar walls are thinning, hematopoiesis occurs in liver, spleen and bone marrow, there is coordination of endocrines by the pituitary, there is some myelination in the brain, gyri and sulci are forming, the fetus responds to sound, and is covered by lanugo hair.
4. **End of fetal development**
    The pH of the stomach becomes acid, some digestive enzymes are present (e.g., lactase), there is meconium in the bowel, hematopoiesis only in bone marrow, the testes are descended, there is myelination of corticospinal tracts to the level of the medulla, lanugo hair is replaced with adult hair, vernix caseosa covers the body, the fetus can suck and the pupillary light reflex is present.

A video of a birth will be shown at the conclusion of this lecture.