First Trimester Embryology: An Overview

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Introduction

Normal human development is a continuum. In particular, the first trimester of pregnancy is a period of rapid change from a fertilized egg to an embryo with a clearly recognizable human form. Interruptions in this process can result in abnormal development and congenital fetal anomalies. These anomalies can be the result of a variety of etiologic factors (Table 5.1) [1]. Up to 3% of human pregnancies are complicated by congenital abnormalities and it is anticipated that the majority of these abnormalities can be identified by prenatal ultrasound as early as the first trimester. The purpose of this chapter is to provide the clinician or sonographer with a basic understanding of embryonic and fetal development in the first trimester. Knowledge of normal and abnormal human embryology is critical to adequate evaluation of the first trimester fetus, whether normal or with anatomical abnormalities.

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Table 5.1 Causes of malformations in the fetus/infant[a]

Chromosomal	10.0%
Single gene	3.0%
Familial	14.5%
Multifactorial	23.0%
Teratogens	3.2%
Uterine anomalies	2.5%
Twinning	0.4%
Unknown	

[a] Based on data from Ref. [1]

Signaling Pathways Identified for Embryologic Development

Embryonic development in the first trimester is complex and extensive. A small number of totipotent stem cells are responsible for cellular differentiation and organ formation. It is important to be aware that these complex processes are controlled by *cell signaling* pathways, which guide development both by the location of their expression and by the specific time at which they are actively expressed in the embryo and its surrounding tissues. Detailed information on signaling pathways is beyond the scope of this chapter but are well described in other texts [2–6].

Development of the Bilaminar Embryo (Weeks 1–2)

After successful fertilization, the resulting zygote quickly undergoes cleavage and progresses

J. S. Abramowicz, R. E. Longman (eds.), *First-Trimester Ultrasound*,
https://doi.org/10.1007/978-3-031-24133-8_5

through the morula stage. The morula, a solid ball of dividing cells, will separate into an inner cell mass (the embryoblast or future embryo) and an outer cell mass (the trophoblastic component of the placenta).

The embryoblast further differentiates into a bilaminar embryonic disc, consisting of dorsal epiblast and ventral hypoblast. This occurs around day 14 post-fertilization, around the time of implantation [6].

Embryonic Weeks 3–4

During the 3rd week of life (i.e., 5 weeks after the last menstrual period), the dorsal epiblast goes on to develop an elongated primitive streak, which marks the start of gastrulation or conversion into the trilaminar embryonic disc, comprised of the three critical germ layers in the human embryo—ectoderm, mesoderm, and endoderm [7, 8]. From these three layers, all fetal tissues and organs will develop (Fig. 5.1).

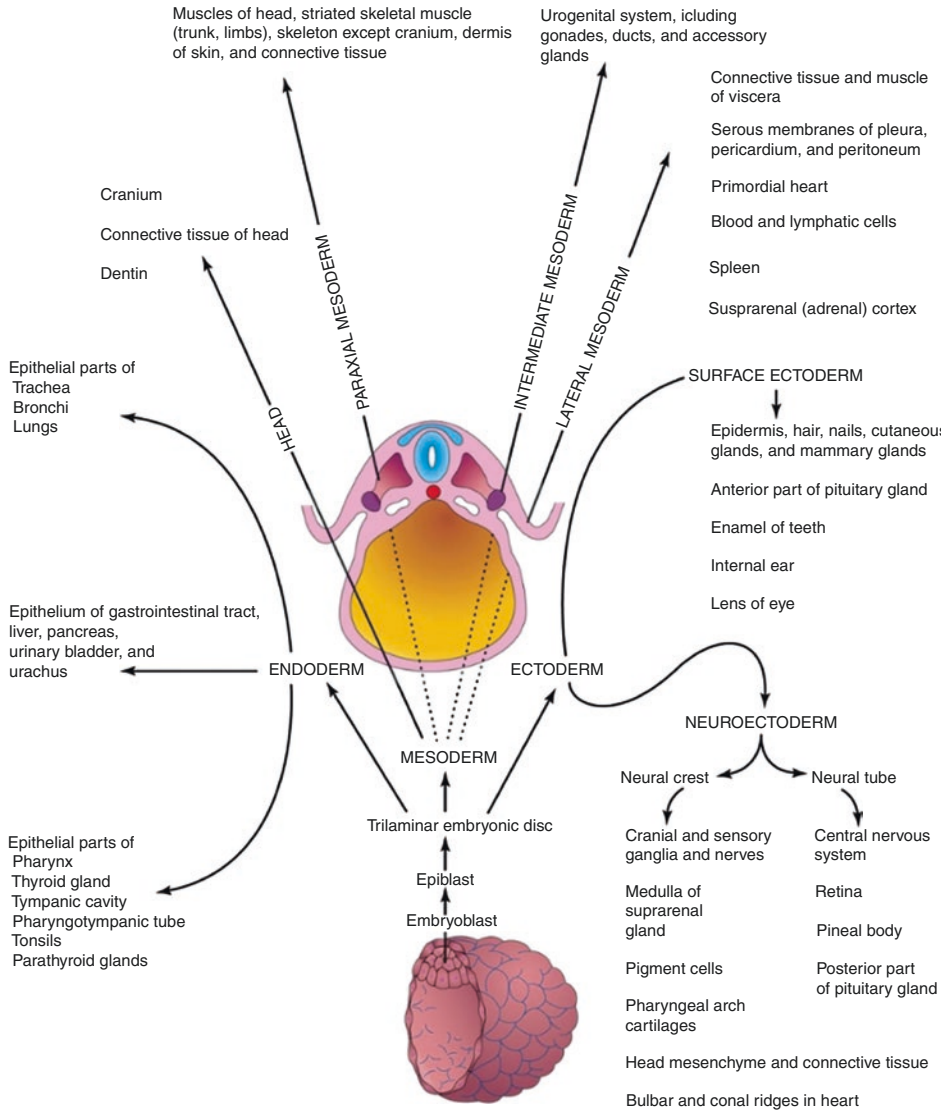

Fig. 5.1 Schematic of the derivatives of the three germ layers of the trilaminar embryonic disc: ectoderm, endoderm, and mesoderm. (This figure was published in The Developing Human: Clinically Oriented Embryology, 11th ed., Moore KL, Persaud TVN, Torchia MG, page 70, copyright Elsevier 2020)

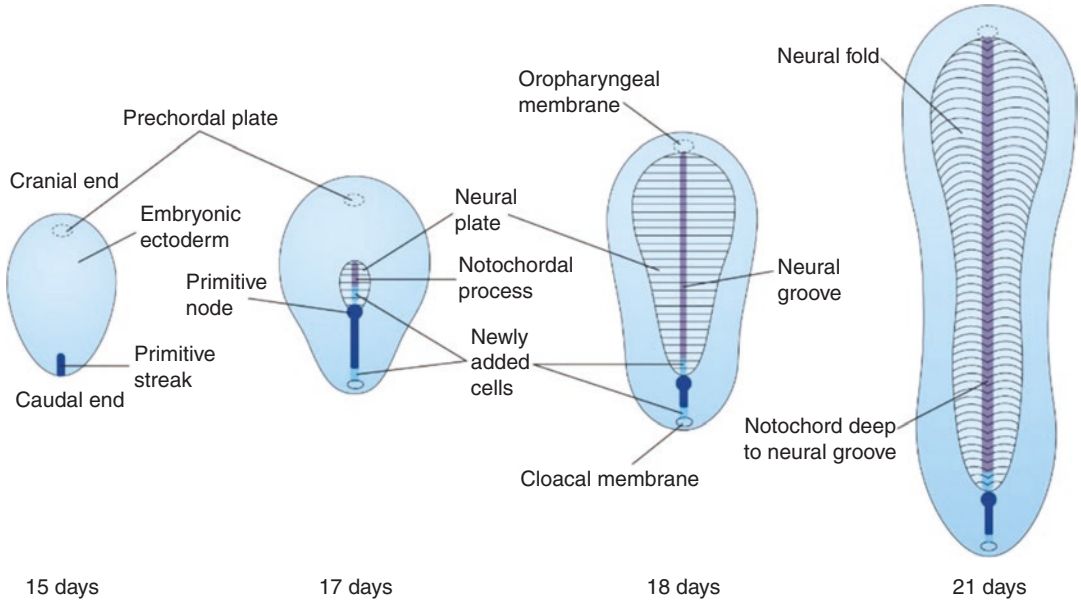

Fig. 5.2 Development of the primitive streak and notochord. The embryo begins to lengthen and change shape in the 3rd embryonic week. The primitive streak lengthens by adding cells at its caudal end, while the notochord lengthens by migration of cells from the primitive node. This process is the embryonic basis of the central nervous system. (This figure was published in The Developing Human: Clinically Oriented Embryology, 11th ed., Moore KL, Persaud TVN, Torchia MG, page 51, copyright Elsevier 2020)

The mesoderm also aids in the orientation of extraembryonic components such as the amniotic cavity, yolk sac, and the primary umbilical vesicle. In addition, gastrulation marks the beginning of morphogenesis, which is the shaping of an organism by the differentiation of cells, tissues, organs, and organ systems [9].

As the primitive streak develops (Fig. 5.2), it gives rise to the primitive node. This is critical for the development of mesenchyme, an embryonic tissue which will go on to serve as the progenitor for many supporting tissues of the fetus. Although the totipotent cells of the primitive streak typically regress by week 4 of embryonic development, remnants are believed to lead to the formation of a unique fetal tumor, the sacrococcygeal teratoma [10]. Newly formed mesenchyme cells will migrate through the streak and become a chord of tissue known as the notochord. The notochord determines the axis of the embryo and becomes a rod-like support for further axial development. Through notable signaling pathways that include sonic hedgehog (Shh) and bone morphogenetic proteins (BMPs), the notochord and the overlying neural tube will orchestrate the establishment of the axial musculoskeletal system as well as the development and segmentation of the central nervous system [11]. In addition, the paraxial mesoderm (mesoderm located on each side of the developing neural tube) divides into intermediate and lateral mesoderm, which gives rise to the components of the musculoskeletal system and the urinary tract [6].

Formation of the Neural Tube

This vital component of embryonic development begins during the 4th embryologic week. As the notochord develops, signaling pathways support the formation of the neural plate, which will give rise to the brain and spinal cord. The neural plate becomes a groove and folds in a process known as neurulation [12]. Fusion of the neural groove into a neural tube occurs in a zipper-like fashion, beginning in the middle and progressing in both cranial and caudal directions. Failure to fuse at any site in the process is known as a neural tube defect, which can range from small defects that are functionally unim-

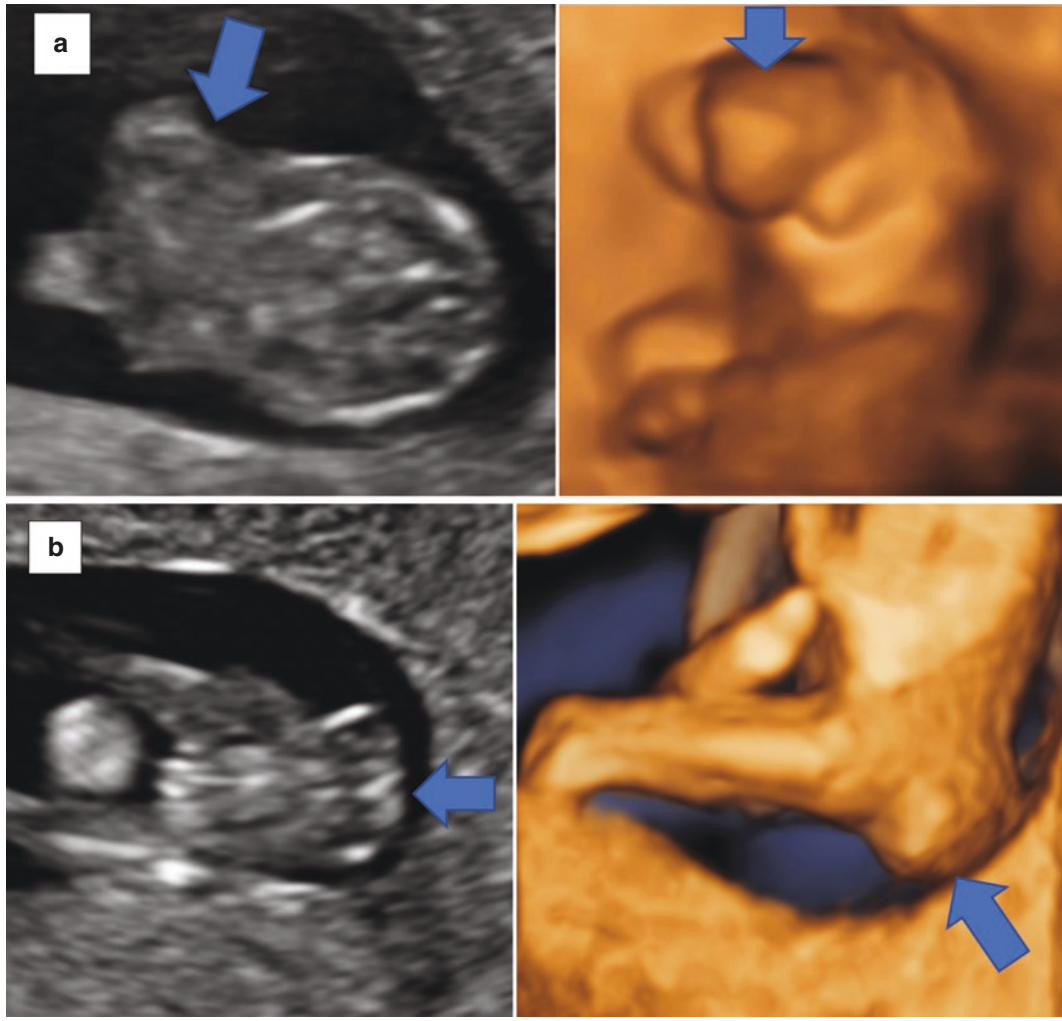

Fig. 5.3 (**a**) Ultrasound images (2D left, 3D right) at 11 weeks gestation with acrania, resulting from failure of the rostral neuropore to close. This results in the absence of a skull or cranium. Prolonged exposure of the fetal brain (blue arrows) to amniotic fluid can eventually lead to the destruction and degeneration of the brain or anencephaly. (**b**) Ultrasound images (2D left,3D right) at 14 weeks gestation of a sacral neural tube defect (blue arrows). This results from failure of the neural tube to close at the 5-6th week of gestation. (Courtesy of Dr. Cresta Jones, Division of Maternal Fetal Medicine, University of Minnesota, Minneapolis, MN)

portant (spina bifida occulta) to severe defects located at the cranial tube (acrania and anencephaly) (Fig. 5.3a) or further caudally (spina bifida) (Fig. 5.3b) [13].

Formation of the Fetal Brain

The fetal brain begins to develop from the most cranial portion of the neural tube during the 3rd embryologic week. Three primary brain vesicles (forebrain, midbrain, and hindbrain) will further divide into five secondary brain vesicles during the 5th embryonic week. Abnormalities in brain division and migration can result in abnormalities, which have the potential to cause significant challenges for normal neonatal neurodevelopmental outcomes.

Neural crest cells can be found alongside both sides of the neural tube. These cells are critical to normal development, as they migrate throughout the embryo to give rise to components of the heart, head, and face, and to ganglia of the spine and autonomic nervous system, pigment cells,

adrenal glands, and the medulla [14]. Abnormal development or migration of neural crest cells is believed to influence the development of disorders such as neurofibromatosis and CHARGE association [15].

Embryonic Weeks 5–8

After the formation of the neural tube, the embryo enters a period in which many major body structures are developed. This period extends from the 5th to 8th week of embryonic development (7–10 postmenstrual weeks) [6]. This critical phase of development is the time at which the conceptus is most vulnerable to abnormal development due to teratogen exposure. Unfortunately, it is also a time at which many pregnant people might not yet be aware that they are pregnant, and thus exposure to environmental teratogens may be increased.

Individual organ systems and structures, as formed during the first trimester, will next be addressed individually.

Development of the Embryonic Cavities and Diaphragm

The primordium or the earliest recognizable body cavities is called intraembryonic coelom and is divided into individual cavities during the 4th and 5th embryonic weeks. These cavities include one pericardial cavity, two pericardioperitoneal cavities, and one peritoneal cavity. As the fetus begins to develop and fold cranially, the heart and pericardial cavity are located near the developing foregut and remain in direct communication with the paired pericardioperitoneal cavities [6]. As development continues, the peritoneal cavity becomes isolated, while the remaining cavities fuse and expand to establish separate pleural and peritoneal cavities, which will contribute to the creation of the diaphragm. Development of the diaphragm is dependent on the coordinated development of four separate components: the pleuroperitoneal membranes, the mesentery of the developing esophagus, the muscular ingrowth from the lateral body wall, and the septum transversum, an outgrowth of the dorsal body wall [16]. Defects in any of these components can result in a congenital diaphragmatic hernia (CDH) (Fig. 5.4). The most common cause of a CDH is the abnormal formation or fusion of the pleuroperitoneal membranes with the other components of the diaphragm and occurs on the left side of the fetus in 90% of cases [17].

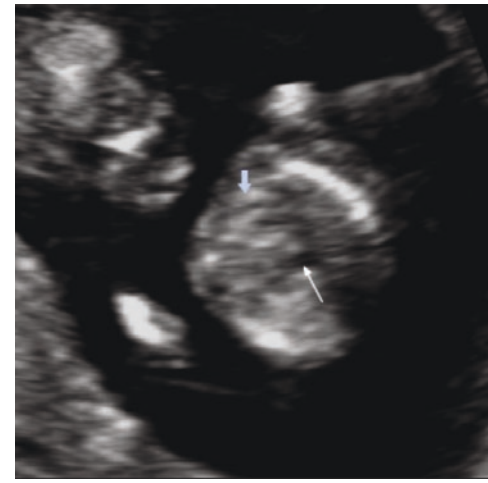

Fig. 5.4 Ultrasound image at 11 weeks with a congenital diaphragmatic hernia. The white arrow identified the fetal stomach in the chest, alongside the fetal heart (gray arrow). This results from a developmental defect of the diaphragm, with abdominal contents migrated into the fetal chest. (Courtesy of Dr. Cresta Jones, Division of Maternal Fetal Medicine, University of Minnesota, Minneapolis, MN)

Development of the Fetal Face

The development of the fetal face begins with embryonic primordia around the primordial fetal mouth or stomodeum. Facial development is dependent on the formation of five structures: a frontonasal prominence and paired maxillary and mandibular prominences. Appropriate migration and fusion are essential for normal facial and palate development [18]. Abnormalities in these processes can result in cleft lip and palate or more severe clefting of the fetal face. Clefting can also be associated with other midline anomalies such as holoprosencephaly (Fig. 5.5), often due to inappropriate signaling which prevents normal component migration and fusion. Such facial hypoplasia is often seen in trisomy 13.

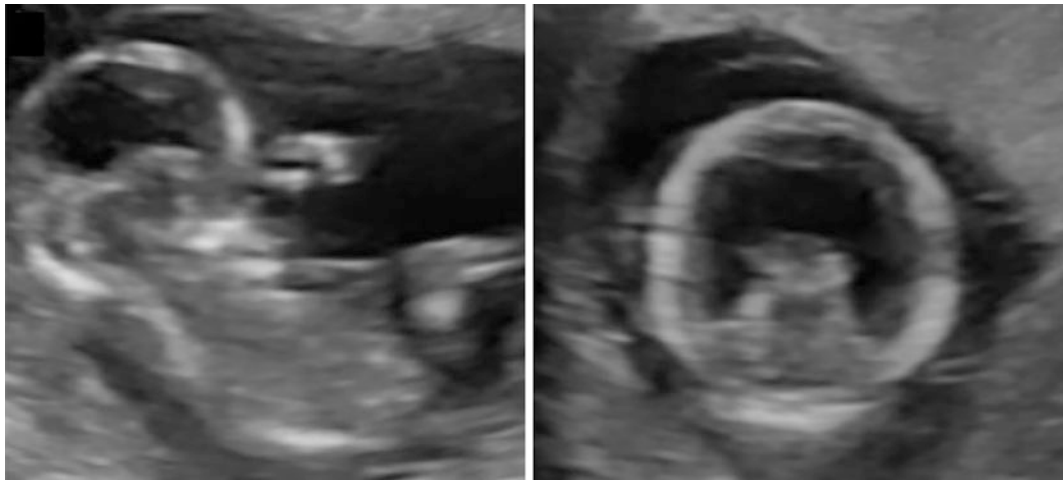

Fig. 5.5 Ultrasound images at 13 weeks gestation demonstrating the midline developmental defect of the embryonic forebrain called holoprosencephaly. This defect results in incomplete development of essential brain structures and is also associated with midline facial clefs. (Courtesy of Dr. Cresta Jones, Division of Maternal Fetal Medicine, University of Minnesota, Minneapolis, MN)

Development of the Respiratory System

The respiratory system also begins to develop during the 4th embryonic week, as the respiratory diverticulum buds from the primitive foregut. Subsequent migration of splanchnic mesoderm over the diverticulum results in the development of respiratory buds, which will further divide and differentiate over the course of fetal development and after birth. An important step in the respiratory system formation is the separation of the foregut and the esophagus from the trachea, through the development of tracheoesophageal folds. These folds will fuse to form the tracheoesophageal septum. Inappropriate or incomplete development of this septum can result in various types of tracheoesophageal fistulas (TEF). TEF is associated with incomplete formation of the esophagus in 85% of cases (esophageal atresia) [6] and can lead to an ultrasound finding of excess amniotic fluid, also known as polyhydramnios, and is secondary to the fetus' inability to swallow appropriately [19].

Development of the Gastrointestinal Tract

The primordial gut tube begins to form in the 4th embryonic week as a portion of the yolk sac is incorporated into the embryo as it folds. Cell proliferation will initially obliterate the lumen of the tube, which will then recanalize and differentiate into foregut, midgut, and hindgut components [6]. Incomplete recanalization can result in areas of stenotic or atretic intestine [20]. The foregut is divided into the trachea and esophagus as addressed in the prior section. Additional components of the foregut include the stomach, which will dilate and rotate to its normal physiologic location in the left upper quadrant, as well as the liver and duodenum [21].

At approximately the 6th embryonic week, the midgut forms a U-shaped loop, which will herniate through the umbilical ring of the embryo, causing physiologic gut herniation (Fig. 5.6a), which is a normal step in embryonic development. The loop will rotate 270° and then return to the abdomen by embryonic week 11. Abnormalities in hernia reduction can result in persistent bowel herniation into a sac at the umbilical cord insertion into the fetal abdomen, known as an omphalocele (Fig. 5.6b). Omphalocele is associated with an increased risk of fetal aneuploidy [22]. This contrasts with gastroschisis (Fig. 5.6c) which is defined by a defect located to the right of the umbilicus. Subsequently, the bowel and other structures can herniate through this defect. The speculated etiologies for

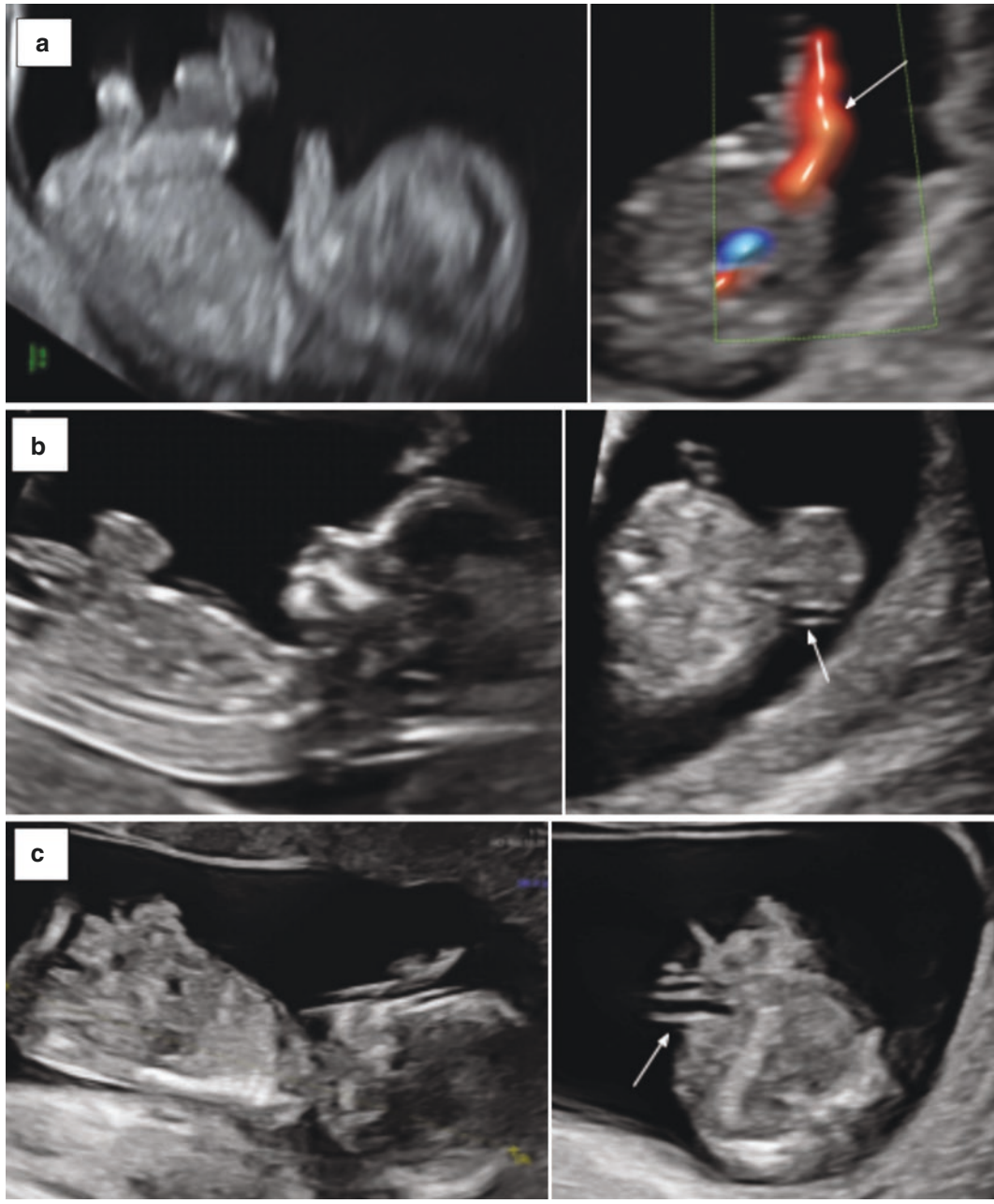

Fig. 5.6 Physiologic gut herniation and midline abdominal wall defects. (**a**) Ultrasound images at 9 weeks gestation with physiologic gut herniation, which occurs between 7 and 12 weeks. In the transverse plane (image on right), the gut is visualized directly alongside the umbilical cord vessel (arrow). (**b**) Ultrasound images at 13 weeks gestation with omphalocele. In the transverse (image on right) the herniation is central with the umbilical cord (arrow) inserted in the hernia sac. An omphalocele is frequently associated with other congenital anomalies. (**c**) Ultrasound images at 13 weeks gestation with gastroschisis. In the transverse plane (image on right), the umbilical cord (arrow) is located to the left of the herniated bowel. Gastroschisis is rarely associated with other congenital anomalies. (Courtesy of Dr. Cresta Jones, Division of Maternal Fetal Medicine, University of Minnesota, Minneapolis, MN)

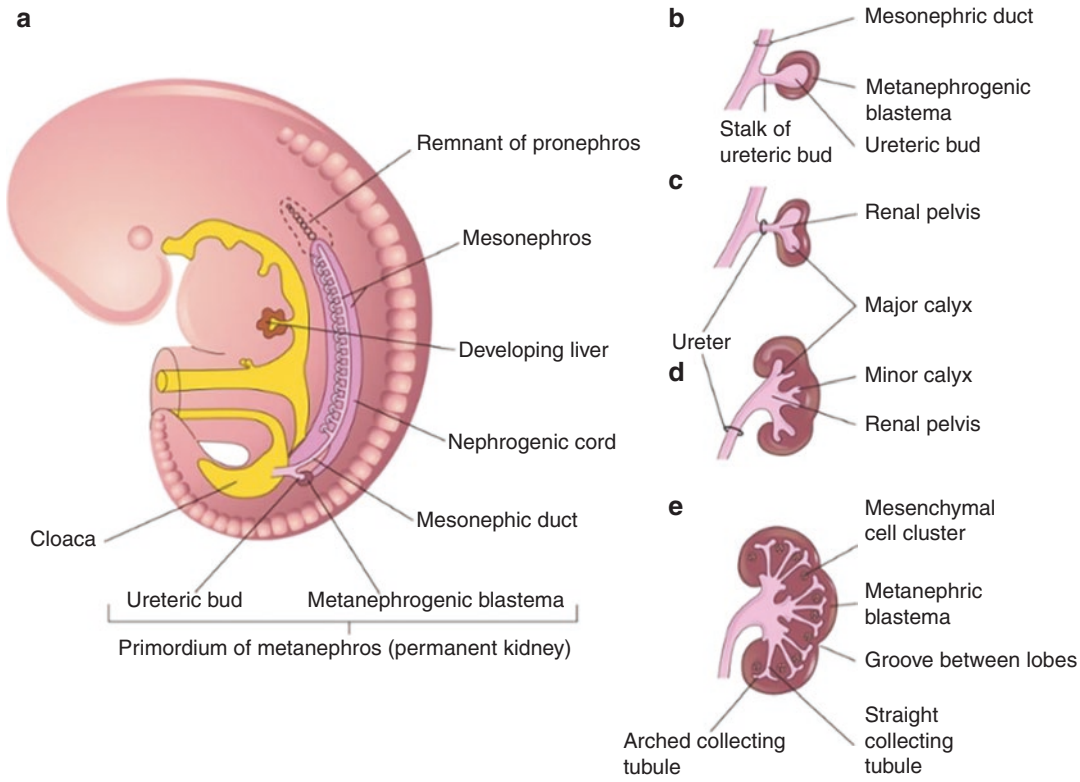

Fig. 5.7 Development of the permanent kidney. (**a**) Five week human embryo showing the developing metanephros and ureteric bud. (**b–e**) Successive stages in the development of ureteric bud (5th to 8th weeks). (This figure was published in The Developing Human: Clinically Oriented Embryology, 11th ed., Moore KL, Persaud TVN, Torchia MG, page 228, copyright Elsevier 2020)

this defect include the agenesis of the right omphalomesenteric artery, or the early disappearance of the right umbilical vein resulting in non-fusion of the lateral folds of the embryo [6]. Gastroschisis is typically not associated with an increased risk of fetal genetic abnormalities [23].

Development of the Urogenital System

The fetal renal system progresses through three separate functioning kidney structures [6]. All three originate primarily from the intermediate mesoderm, which develops into the nephrogenic cord. The initial fetal renal structure, the pronephros, disappears by week 5 of embryonic life. It is replaced by the mesonephros and mesonephros (Wolffian) duct, which also plays a critical role in the development of the male reproductive system. At 10 embryonic weeks, the permanent renal structure, the metanephros, is formed and functional. It develops from an outgrowth of the mesonephros (ureteric bud), and this bud induces the formation of the metanephros (Fig. 5.7). Lack of development of the ureteric bud will result in absence of permanent fetal kidneys, or renal agenesis. This anomaly can be lethal if bilateral and is identified by a lack of amniotic fluid, also known as anhydramnios, typically identified in the second trimester of pregnancy [24].

Highlights of Cardiac Development

Highlights of cardiac development are reviewed in the section. A detailed review of the development of the human heart is beyond the scope of this chapter, due to the level of complexity of its formation.

Early Cardiac Development

The cardiovascular system is the first organ system to begin functioning at 3–4 weeks of embryonic age. It is primarily derived from splanchnic mesoderm, paraxial and lateral mesoderm, and pharyngeal mesoderm, but also involves the migration of neural crest cells [6]. Paired angiogenic cords, formed from the cardiogenic mesoderm, undergo fusion and canalization to form a simple tube, the initial heart structure. Blood begins flowing through the cardiac tube at approximately 4 weeks of embryonic age. The outside of the single tube becomes the myocardium, and the inside of the tube becomes the endocardium. The epicardium (visceral pericardium) is derived from mesothelial cell proliferation from the external surface of the sinus venosus, which is a predecessor of the cardiac atria [25]. Folding of the head results in a heart location, which is ventral to the foregut and caudal to the developing mouth.

After the formation of a single cardiac tube, partitioning of the heart begins at the end of the 4th embryonic week and continues into the 9th week [6]. The developing heart begins to bend and constrict, resulting in the formation of five segmental primitive heart dilations: the truncus arteriosus, bulbus cordis, primitive ventricle, primitive atrium, and sinus venosus. The truncus arteriosus gives rise to the precursors of the aorta and pulmonary trunk, the bulbus cordis and primitive ventricle given risk to the ventricles, and the primitive atrium and sinus venosus given rise to the atria and the coronary sinus. Dextral (right-handed) cardiac looping is also initiated during this period and is believed to primarily occur during embryonic weeks 5–7 [25]. The process results in a U-shaped loop and determines the normal axis of the heart (Fig. 5.8).

When the heart tube loops left, rather than right, the heart is displaced and its great vessels are reversed, creating a mirror image of the normal heart structure, called dextrocardia. Dextrocardia

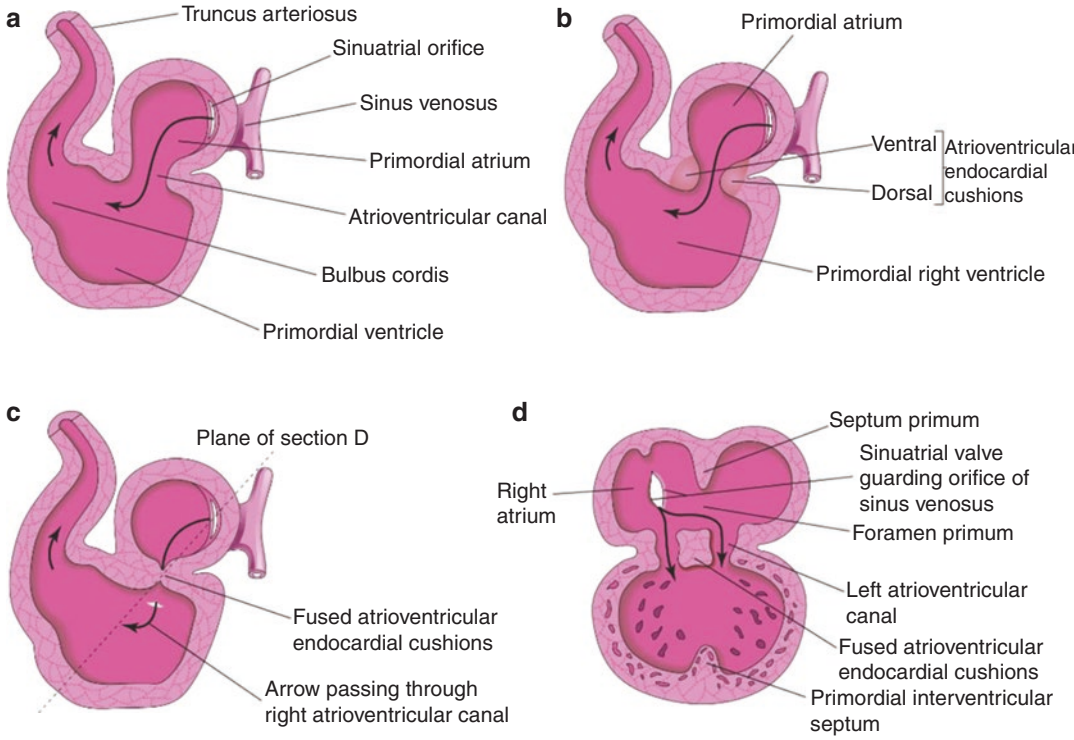

Fig. 5.8 (**a**, **b**) Sagittal sections of the heart during the 4th and 5th weeks, illustrating blood flow and division of the atrioventricular canal. (**c**) Fusion of the atrioventricular endocardial cushions. (**d**) Coronal section of the plane shown in (**c**). (This figure was published in The Developing Human: Clinically Oriented Embryology, 11th ed., Moore KL, Persaud TVN, Torchia MG, page 273, copyright Elsevier 2020)

can be associated in some cases with an increased risk of severe cardiac abnormalities [26].

Cardiac Septae Formation and Valvular Development

Multiple separate cell migration and signaling pathway processes are involved in the development of appropriate cardiac septae.

Atrioventricular (AV) Septum

The AV endocardial cushions develop from a specialized extracellular matrix (cardiac jelly) within the walls of the AV canal. These cushions move toward each other and eventually fuse to form the AV septum with separation of a common AV canal into left and right AV canals. The cushions then function as the precursor to AV valves until further differentiation occurs, resulting in definitive valve structures. Inductive signals from the myocardium of the AV canal cause epithelial-mesenchymal transformation, which changes the endocardial cushions and ultimately contributes to the development of the definitive AV valves and membranous septum of the heart [26].

Numerous cardiac anomalies are attributable to the abnormal development of the endocardial cushions. Failure of cushion fusion is responsible for a persistent common AV canal, in which there is no true septal division of the heart, and a single common AV valve in place of the tricuspid and mitral valves (Fig. 5.9). Inadequate amounts of cushion are also believed to be associated with abnormal development of the tricuspid valve, including abnormal location (Ebstein's anomaly) or congenital absence of the valve, the results of which can have devastating consequences for long-term cardiac function [26].

Atrial Septum

Partitioning of the atria begins at the end of the 4th embryonic week [6]. The right and left atria are created by fusion of the two septae, the septum primum and the septum secundum. The septum primum has an initial foramen or hole, termed the foramen primum, and subsequently develops the foramen secundum. As the septum secundum develops, an incomplete septation occurs resulting in the foramen ovale [27]. The inferior aspect of the septum primum becomes the flap (valve) of the foramen ovale, which should fuse anatomically shortly after birth. Excessive resorption of either the septum primum or septum secundum results in an atrial septal defect or persistent foramen ovale, which are among the most common congenital heart abnormalities. The female to male ratio for atrial septal defects is 3:1 [28].

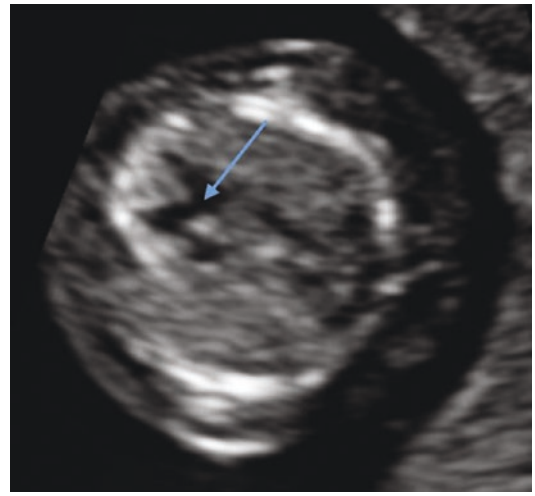

Fig. 5.9 US image at 12 weeks gestation of a transverse view through a persistent common atrioventricular canal defect (arrow). This is complication of abnormal endocardial cushion development. (Courtesy of Dr. Cresta Jones, Division of Maternal Fetal Medicine, University of Minnesota, Minneapolis, MN)

Ventricular Septum

Partitioning of the ventricles also involves septation, accomplished by fusion of the muscular portion of the interventricular (IV) septum with the membranous area of the septum [6]. Until the 7th embryonic week, a defect is noted in the IV septum between the free edge of the muscular portion and the lower component of the AV cushions. Closure of the defect typically occurs at the end of the 7th week and involves fusion of the membranous portion of the IV septum with the muscular component [27]. Failure of this closure to occur results in ventricular septal defects (VSDs), which are the most common form of congenital heart disease, making up approximately 25% of cases [29]. Typically, the defect results from failure of the membranous portion of the septum to close, although defects in

other locations do occur. Many small VSDs close during embryonic and fetal development, although larger defects can result in cardiac dysfunction and require postnatal surgical management.

Aorticopulmonary (AP) Septum

The septation of the truncus arteriosus and bulbus cordis is critical to normal cardiac development as well as to normal outflow through the pulmonary trunk and the aorta. This occurs during the 5th embryonic week [6]. The AP septum is believed to be formed by mesenchyme derived from migrating neural crest cells, which invade the truncus arteriosus and bulbus cordis [27]. As the cells migrate, they develop in a spiral fashion, fusing to form the AP septum and separating the pulmonary and aortic outflow tracts. Membranous tissue from the interventricular septum also fuses with the aorticopulmonary septum, resulting in a normal anatomic relationship, where the pulmonary artery arises from the right ventricle and the aorta arises from the left ventricle. If neural crest cell migration does not proceed appropriately, the AP septum may not develop properly. This includes a condition called truncus arteriosus, which results from limited development of the AP septum, with only one large vessel leaving the heart. Abnormal or absent spiraling of the septum can cause transposition of each vessel from its appropriate ventricular outflow, called transposition of the great arteries. Unequal division of the truncus arteriosus is also believed to contribute to the development of Tetralogy of Fallot, in which pulmonary artery stenosis, ventricular septal defect, overriding aorta, and right ventricular hypertrophy occur together [26].

Development of the Lymphatic System

Development of the lymphatic system begins at the end of the 6th embryonic week after the cardiovascular system has developed [30]. It develops with a process like that for fetal blood vessels, with a series of small lymphatic tubes joining to form a lymphatic network. Lymphatic drainage encompasses six primary lymph sacs and many lymph nodes. Draining occurs first from the cranial and caudal aspects of the embryo and then primarily into the right lymphatic duct. A small measurable area filled with lymphatic fluid is typically seen behind the fetal neck at 10–14 weeks gestation and is known as the nuchal translucency (Fig. 5.10a). Abnormalities in lymphatic drainage, due to a blocked or malformed lymphatic sac or channel, may cause a thickened nuchal translucency (Fig. 5.10b) or even larger swellings around the fetal neck known as cystic hygroma (Fig. 5.10c). The presence of a cystic hygroma is associated with an increased risk of fetal genetic abnormalities, cardiac malformations, and other fetal developmental problems [31, 32].

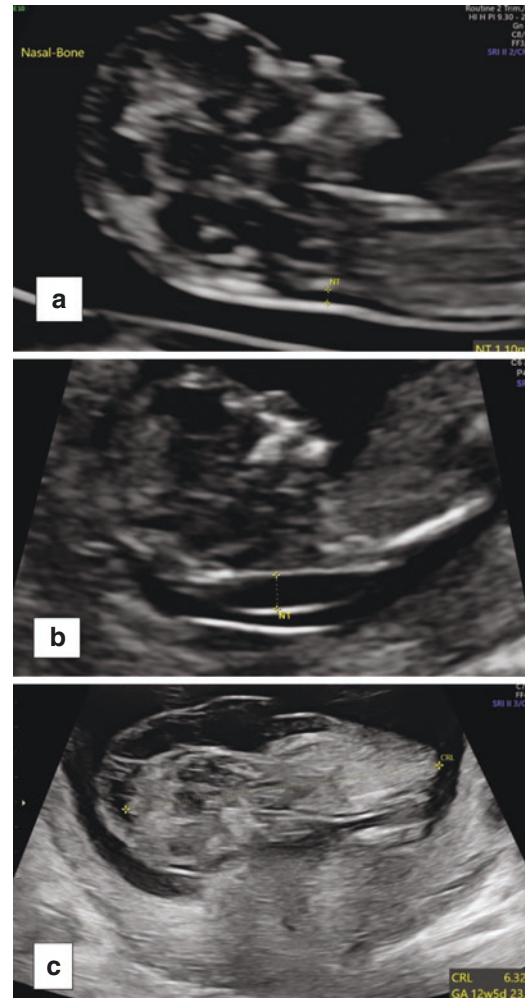

Fig. 5.10 First trimester images of nuchal translucency and related abnormalities. (**a**) Ultrasound image at 12 weeks gestation with a normal nuchal translucency. (**b**) Ultrasound image at 13 weeks gestation with a thickened nuchal translucency. (**c**) Ultrasound image at 12 weeks gestation with a cystic hygroma. (Courtesy of Dr. Cresta Jones, Division of Maternal Fetal Medicine, University of Minnesota, Minneapolis, MN)

Summary

The human embryo undergoes remarkable development in the first trimester of pregnancy, progressing from several cells to an organism with clear organ structure and function. This formation is in large part affected by a complex system of embryonic cell signaling and the fetus' surrounding environment. Abnormalities in signaling function and cell migration, including those resulting from first trimester teratogen exposure or genetic abnormalities can have long-term complications for the developing fetus and newborn.

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