First-Trimester Embryology: An Overview

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Introduction

Normal human development is a continuum. In particular, the first-trimester pregnancy development is a period of rapid progression from a fertilized egg to an embryo with a clearly identified human form. Interruptions in this ongoing process can result in abnormal development and subsequent congenital anomalies. These anomalies can be the result of many etiologic factors (Table 4.1) [1]. Approximately 3 % or greater of pregnancies are complicated by congenital anomalies, and it is anticipated that many of these anomalies will be identified by prenatal ultrasound, often in the first trimester. The purpose of this chapter is to provide the clinician or sonographer with the essential basics of embryological and fetal development, to better understand mechanisms of normal and abnormal first-trimester human development. Understanding of these mechanisms is imperative for adequate evaluation of the first-trimester fetus in the ultrasound laboratory.

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Signaling Pathways Identified for Normal Embryo Development

Embryonic development in the first trimester is extensive, with a small group of totipotent (able to differentiate into any cell within the organism) stem cells located in the inner cell mass of the blastula responsible for cellular differentiation and subsequent organ formation. It is important to be aware that this complex formation appears to be controlled by *cell signaling* pathways, which guide normal development both by the location of their expression as well as the specific time at which they are active in the embryo and surrounding tissues. Detailed descriptions of all signaling pathways are 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 to rapidly progress through the blastula and morula stages. The morula

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Table 4.1 Causes of malformations in fetuses/infants[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	43.2 %

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

will separate into an inner cell mass (the embryoblast, or future embryo) and an outer cell mass (the trophoblast component of the placenta).

The embryoblast differentiates into a *bilaminar embryonic disc*, consisting of dorsal epiblast and ventral hypoblast. This typically occurs around day 14 after fertilization, around the time of completion of implantation [6]. A new layer of cells is derived from the epiblast, the extraembryonic mesoderm, and proceeds to aid in the origins of extraembryonic components such as the amniotic cavity and the umbilical vesicle.

Embryonic Weeks 3–4

During this period, all the major organ systems of the embryo and fetus will begin to develop. During the third week of embryonic development (5 weeks after the last menstrual period), the most notable processes include the development of the primitive streak and notochord [7], and the creation of the three germ layers of the *trilaminar embryonic disc* (Fig. 4.1).

The process of *gastrulation* results in the development of the three critical germ layers of the human embryo—endoderm, ectoderm, and mesoderm [8]. From these three simple layers will develop all fetal tissues and organs (Fig. 4.2). In addition, gastrulation marks the beginning of *morphogenesis*, the shaping of an organism by the differentiation of cells, tissues, and organs and organ systems, according to its genetic direction [9].

During this time, the *primitive streak* develops (Fig. 4.3) and will give rise to the primitive node. This is critical to allow the development of mesenchyme, 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 4 weeks of development, remnants are believed to lead to the formation of a unique fetal tumor, the *sacrococcygeal teratoma* [10]. Newly formed mesenchyme 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 signaling pathways that include sonic hedgehog (Shh) and bone morphogenetic proteins (BMPs), the *notochord* and overlying developing neural tube will orchestrate the establishment of the axial central nervous system and axial musculoskeletal system, as well as the segmentation of the nervous system [11]. Furthermore, the paraxial mesoderm (mesoderm located on each side of the developing neural tube) divides into intermediate and lateral mesoderm, which will give rise to components of the musculoskeletal system and the urinary tract [6].

Formation of the Neural Tube

This critical component of embryonic development begins during the fourth embryologic week. As the notochord develops, signaling pathways induce the formation of the neural plate, which will give rise to the future brain and spinal cord. The neural plate becomes a groove and subsequently folds begin to form, a process known as *neurulation* [12]. Fusion of the neural groove into the neural tube occurs in a zipper-like fashion, beginning in the midline and progressing in both cranial and caudal directions. Non-fusion at any site is known as *spina bifida*, which can range from small defects that are functionally unimportant (*spina bifida occulta*) to severe defects, which are incompatible with life such as *anencephaly* (Fig. 4.4) [13].

During the development of the neural tube, *neural crest* cells are differentiating as columns of cells along both sides of the neural tube. These cells are critical to normal embryonic development, as they migrate throughout the embryo to

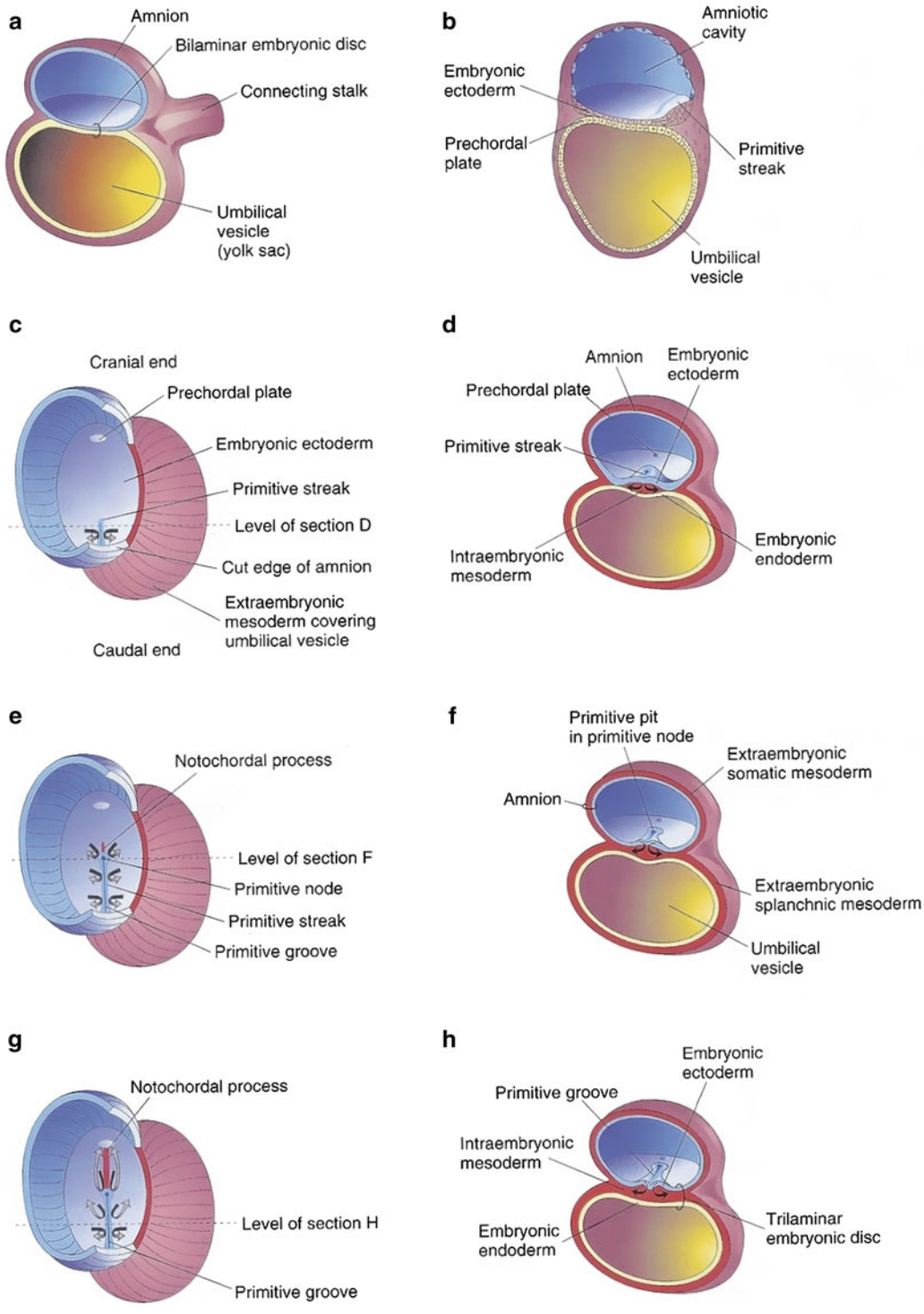

Fig. 4.1 The formation of the trilaminar embryonic disc. The *arrows* indicate invagination and migration of mesenchymal cells from the primitive streak. (**c**, **e**, **g**) Dorsal views of the trilaminar disc early in week 3, exposed by removal of the amnion. (**a**, **b**, **d**, **f**, **h**) Transverse sections through the embryonic disc, with the level of each section indicated in (**c**), (**e**), and (**g**). This figure was published in The Developing Human: Clinically Oriented Embryology, 9th ed., Moore KL, Persaud TVN, Torchia MG, Copyright Elsevier 2013

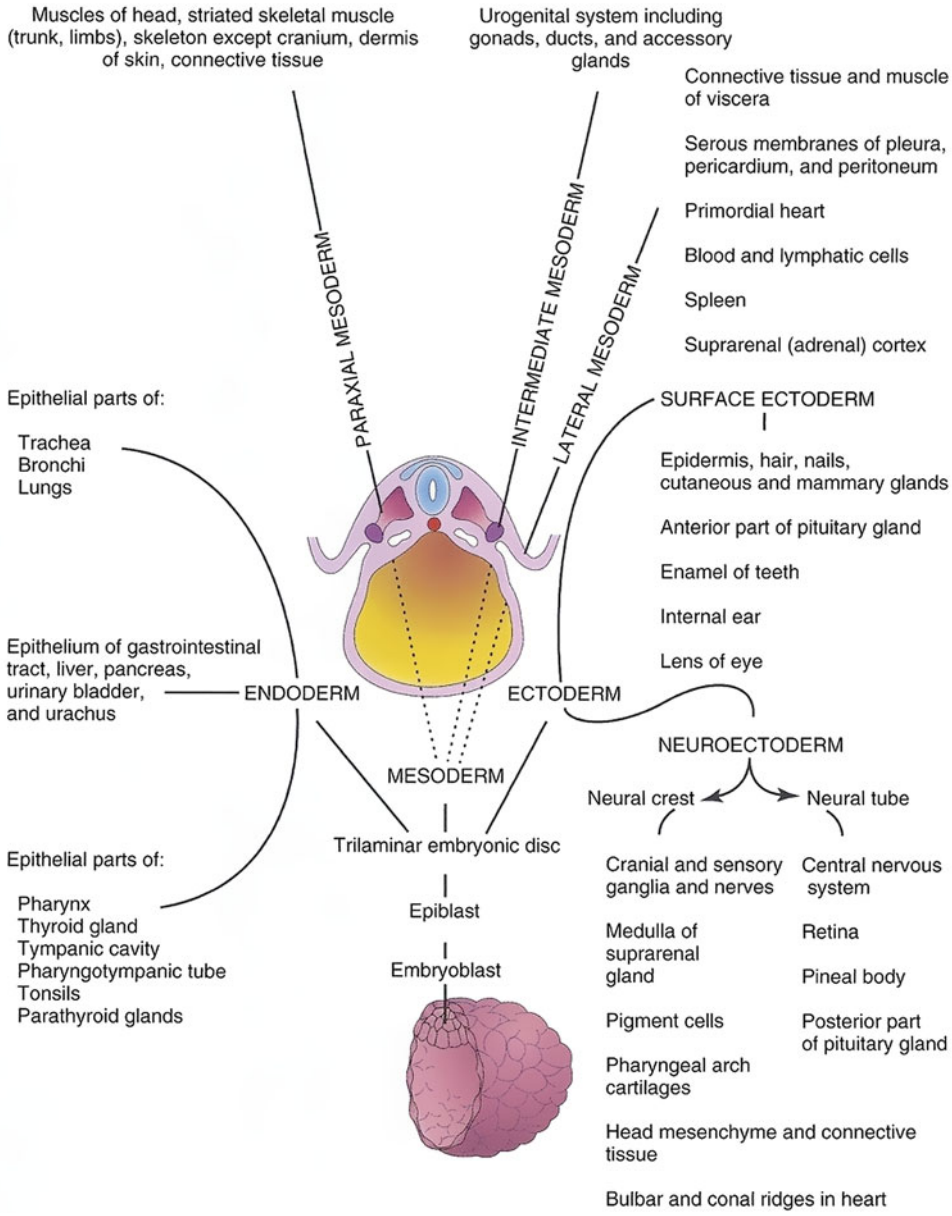

Fig. 4.2 Schematic of the derivatives of the three germ layers of the trilaminar embryonic disc: ectoderm, endoderm, and mesoderm. This figure was published in The Developing Human: Clinically Oriented Embryology, 9th ed., Moore KL, Persaud TVN, Torchia MG, Copyright Elsevier 2013

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 and or migration of the neural crest cells are believed to influence the development of such disorders 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 external and internal body structures are developed. This period extends from the fifth to eighth week of embryonic development (7–10 postmenstrual weeks) [6].

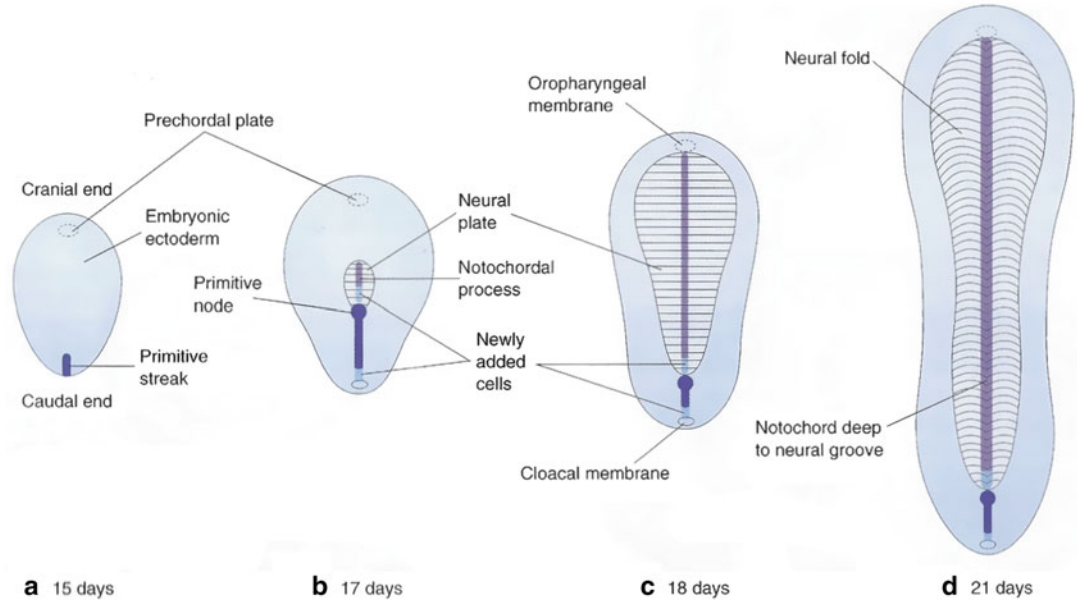

Fig. 4.3 Development of the primitive streak and notochord. The embryo begins to length and change shape in the third embryonic week. The primitive streak lengthens by adding cells at its caudal end, while the notochord lengthens by migration of cells from the primitive node. The notochordal process and adjacent mesoderm induce overlying ectoderm to form the neural plate, which is the embryonic basis of the central nervous system. This figure was published in The Developing Human: Clinically Oriented Embryology, 9th ed., Moore KL, Persaud TVN, Torchia MG, Copyright Elsevier 2013

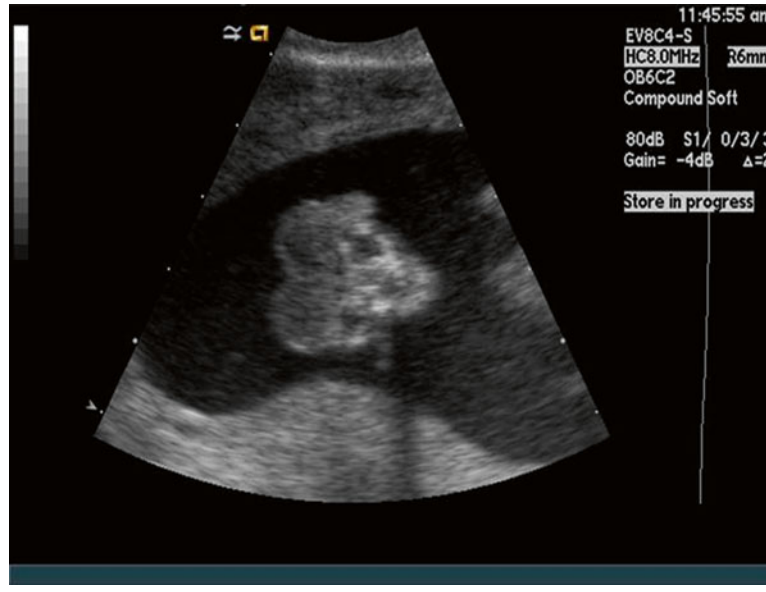

Fig. 4.4 Ultrasound image at 12 week gestation, with anencephaly, a lethal abnormality in which a large portion of the fetal brain is absent, as is the superior portion of the fetal skull, due to incomplete closure of the rostral neuropore during spinal cord formation. Courtesy of Dr. Randall Kuhlmann, Division of Maternal Fetal Medicine, Medical College of Wisconsin, Milwaukee, WI

This critical phase of development is the time at which the conceptus is most vulnerable to teratogens potentially leading to abnormal development. Unfortunately, it is also a time at which many women might not yet be aware that they are pregnant, and thus exposure to environmental agents, which might alter embryonic development, may be increased. Individual organ systems and structures, as formed during the first trimester, are now addressed individually.

Division of the Embryonic Cavities and Diaphragm

The primordium of the body cavities, or intraembryonic coelom, is divided into cavities during the fourth and fifth week. These include the pericardial cavity, two pericardioperitoneal cavities and a single peritoneal cavity. As the fetus begins to 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 will become isolated, and fusion and expansion of the remaining cavities will establish separate pleural and peritoneal cavities, and will contribute to the creation of the diaphragm. Development of the definitive diaphragm, which is also occurring at this time, is dependent on coordinated development of four separate components: the pleuroperitoneal membranes, the mesentery of the developing esophagus, muscular ingrowth from the lateral body wall, and the septum transversum, an outgrowth from the dorsal body wall (Fig. 4.5) [16]. Defects in any of these components can result in a congenital diaphragmatic hernia, which is most often caused by defective formation or fusion of the pleuroperitoneal membranes with the other three parts of the diaphragm, and occurs on the left side of the fetus in up to 90 % of cases [17].

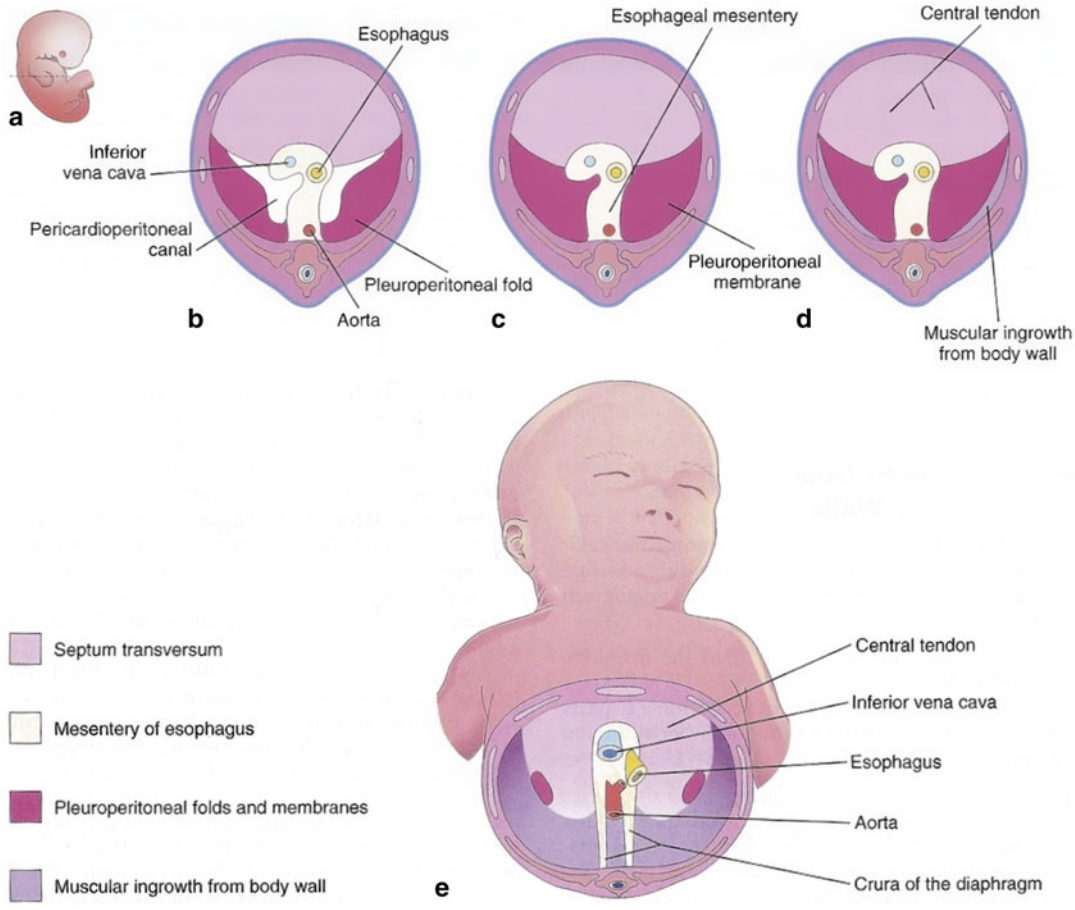

Fig. 4.5 Development of the diaphragm. (**a**) Lateral view of the embryo at the end of the fifth embryonic week, indicating the level of the transverse sections in (**b**), (**c**), and (**d**). (**b**) Transverse section of the pleuroperitoneal membranes prior to fusion. (**c**) Similar section at the end of the sixth embryonic week. (**d**) Transverse section at 12 embryonic weeks. (**e**) Inferior view of the diaphragm in a neonate, identified the embryologic origin of its components. This figure was published in The Developing Human: Clinically Oriented Embryology, 9th ed., Moore KL, Persaud TVN, Torchia MG, Copyright Elsevier 2013

Development of the Fetal Face

The development of the fetal face begins with embryonic primordial around the developing fetal mouth or stomodeum. Facial development is dependent on the formation of five structures: frontonasal prominences, maxillary prominences, and mandibular prominences. Appropriate migration and fusion are vital to allow for normal facial and palatal development (Fig. 4.6) [18].

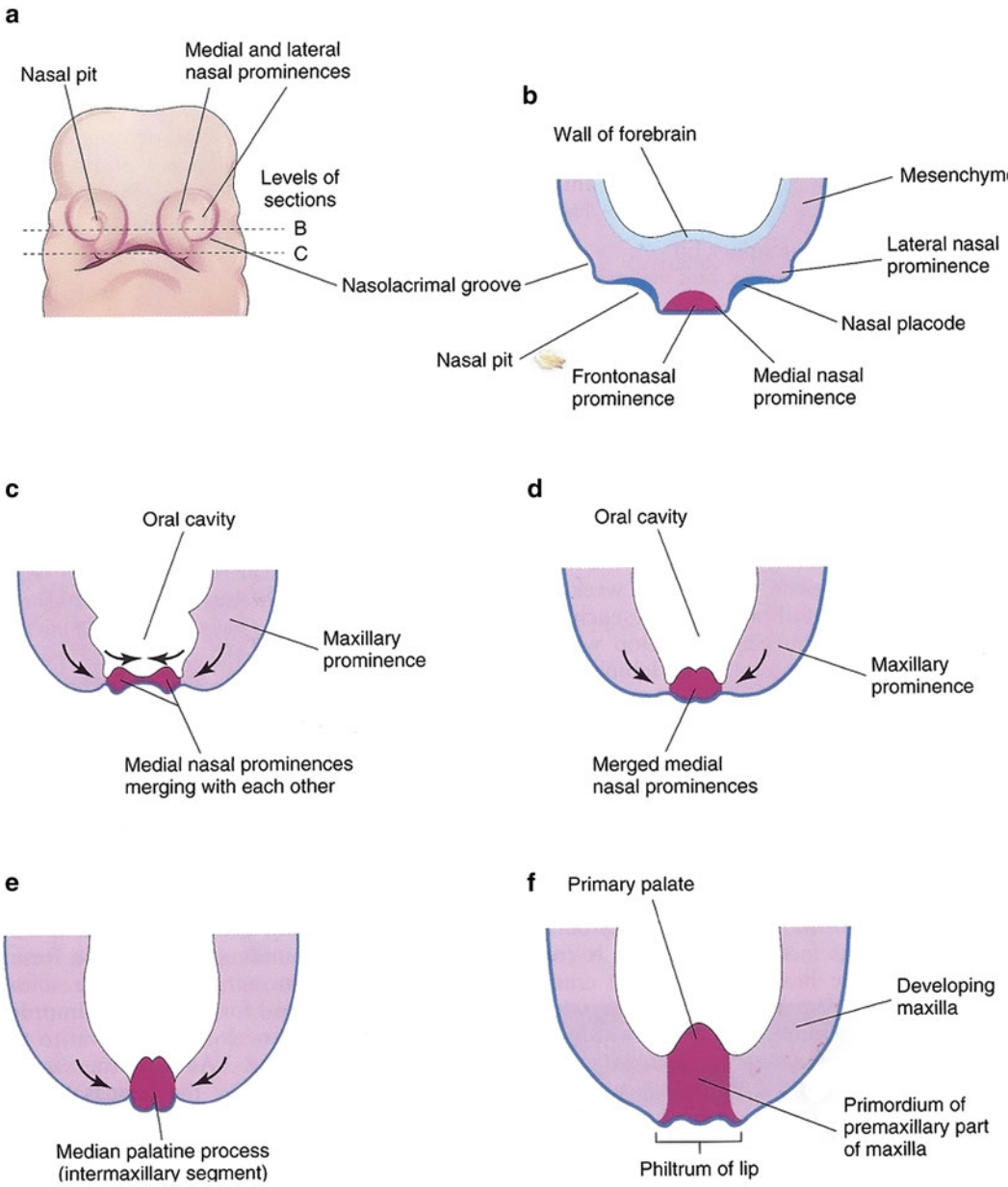

Fig. 4.6 Early development of the maxilla, palate and upper lip. (**a**) Facial view of a fifth embryonic week embryo. (**b**, **c**) Horizontal sections at the levels shown in (**a**). The *arrows* in (**c**) indicate growth of the maxillary and median nasal prominences. (**d**–**f**), Similar sections of older embryos identifying merging of the medial nasal prominences and maxillary prominences to form the upper lip. This figure was published in The Developing Human: Clinically Oriented Embryology, 9th ed., Moore KL, Persaud TVN, Torchia MG, Copyright Elsevier 2013

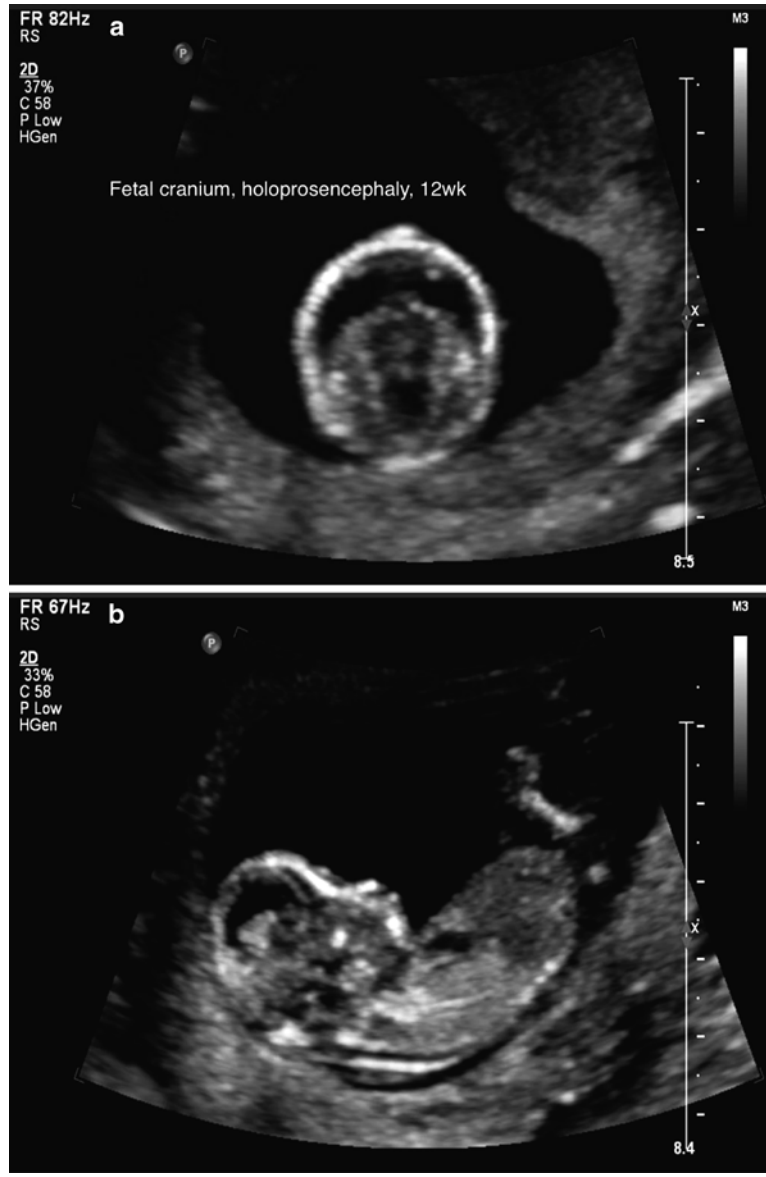

Fig. 4.7 Ultrasound scan of a fetal face at 12 weeks gestation with holoprosencephaly (**a**) and flattened facial profile (**b**) suggestive of severe facial clefting, which was identified in the second trimester. This fetus was ultimately diagnosed with trisomy 13 and midline facial clefting. Courtesy of Dr. Randall Kuhlmann, Division of Maternal Fetal Medicine, Medical College of Wisconsin, Milwaukee, WI

Abnormalities in these processes can result in cleft lip and cleft palate or more severe major clefting of the fetal face. Clefting can also be associated with other midline anomalies such as holoprosencephaly, often due to inappropriate signaling to allow normal component migration and fusion. Such facial hypoplasia is often seen in trisomy 13 (Fig. 4.7a, b).

Development of the Respiratory System

The respiratory system also begins to develop during the fourth 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. An important step in the respiratory system's formation is the separation of the foregut and esophagus from the trachea through the development of the tracheoesophageal folds, which will fuse to form the tracheoesophageal septum [6]. Inappropriate or incomplete development of this septum can result in various types of tracheoesophageal fistulae (TEF). This abnormal passage is associated with incomplete formation of the esophagus (esophageal atresia) in 85 % of cases [6] and can lead to ultrasound findings of excess amniotic fluid, as the fetus is unable to swallow and assimilate appropriately during gestation [19].

Development of the Gastrointestinal Tract

The primordial gut tube begins to form in the fourth embryonic week as a portion of the yolk sac is incorporated into the embryo as it folds. Initially cell proliferation will obliterate the lumen of the tube, which will then recanalize and differentiate into foregut, midgut, and hindgut components [6]. Incomplete recanalization can result in subsequent areas of stenotic or atretic intestine [20]. The foregut is divided into the trachea and esophagus as addressed in the previous 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 sixth embryonic week, the midgut forms a U-shaped loop, which will herniate through the umbilical ring of the embryo, causing physiologic gut herniation, which is a normal step in embryonic development (Fig. 4.8). The loop will rotate 270°, allowing for hernia reduction by embryonic week 11. Abnormalities in hernia reduction can result in persistent bowel herniation into a sac at the umbilical cord insertion in the fetal abdomen, known as omphalocele (Fig. 4.9a, b). Omphaloceles are associated with an increased risk of fetal aneuploidy [22]. This contrasts with gastroschisis (Fig. 4.10a, b), which is defined by a defect located to the right of the umbilicus. Subsequently, the bowel and other structures are allowed to herniate through this defect. The etiologies speculated for this defect include agenesis of the right omphalomesenteric artery, or early disappearance of the right umbilical vein resulting in non-fusion of the lateral folds

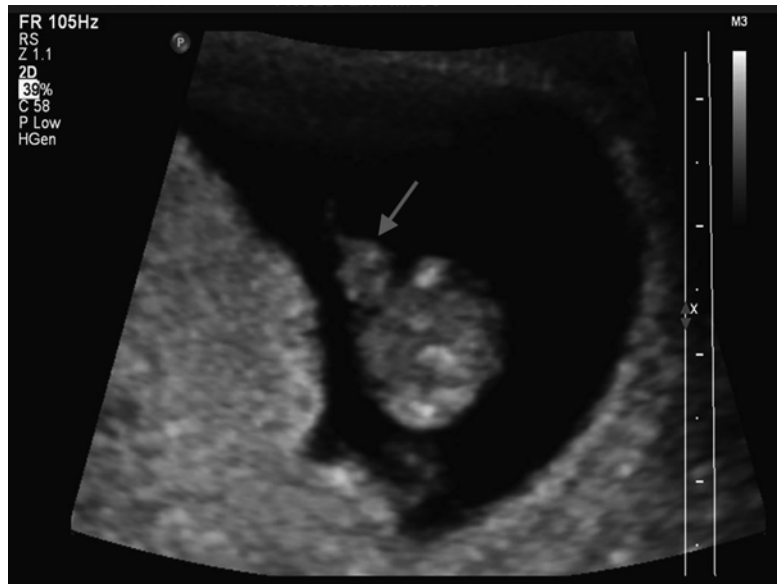

Fig. 4.8 A transverse ultrasound image at 10 weeks through the fetal abdomen demonstrates normal physiological gut herniation. The *arrow* indicates area of herniation. Courtesy of Dr. Randall Kuhlmann, Division of Maternal Fetal Medicine, Medical College of Wisconsin, Milwaukee, WI

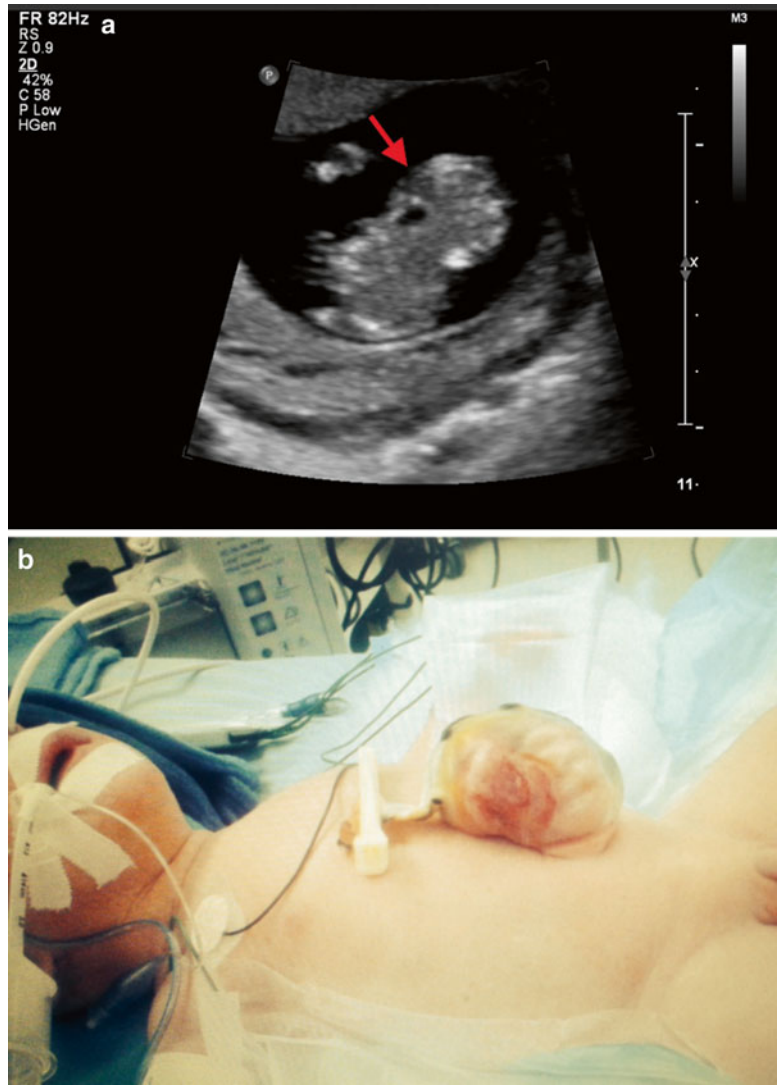

Fig. 4.9 (**a**) Ultrasound at 13 weeks, transverse fetal abdomen with *arrow* indicating large omphalocele. (**b**) Neonate with an omphalocele. Courtesy of Dr. Randall Kuhlmann, Division of Maternal Fetal Medicine, Medical College of Wisconsin, Milwaukee, WI

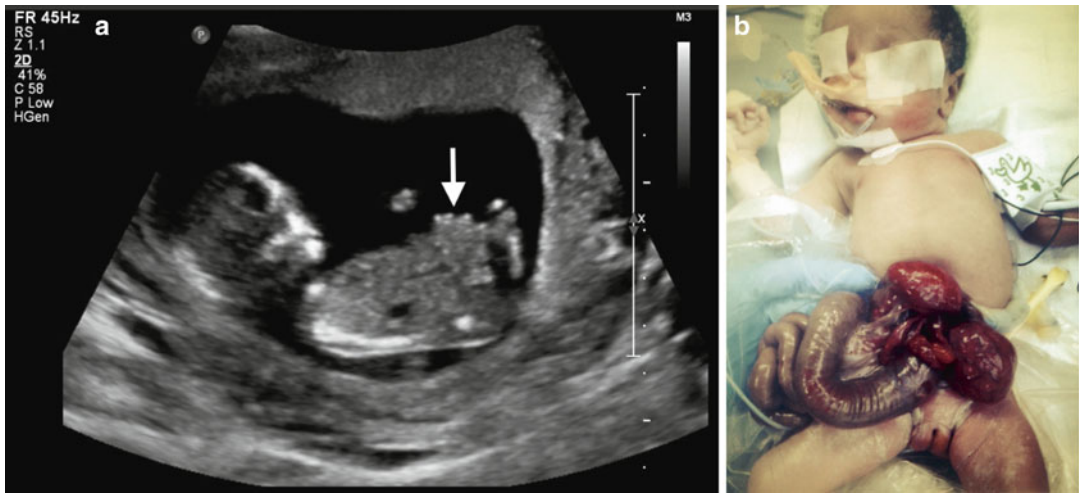

Fig. 4.10 (**a**) Ultrasound at 12 weeks, longitudinal fetus with *arrow* indicating gastroschisis. (**b**) Neonate with gastroschisis. Courtesy of Dr. Randall Kuhlmann, Division of Maternal Fetal Medicine, Medical College of Wisconsin, Milwaukee, WI

of the embryo [6]. Some authors feel that this may represent a ruptured omphalocele. 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 have their origins primarily from 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 mesonephric (Wolffian) duct, which will play a critical role in development of the male reproductive system. At 10 embryonic weeks, the permanent renal structure, the metanephros is functional. It develops from an outgrowth of the mesonephros (ureteric bud), and this bud induces the formation of the metanephros (Fig. 4.11). Lack of development of the ureteric bud will result in absence of permanent fetal kidneys, or renal agenesis. This anomaly is lethal if bilateral and is identified by a lack of amniotic fluid in the second trimester of pregnancy [24].

Highlights of Cardiac Development

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. Highlights of cardiac development are reviewed in this section.

Early Cardiac Development

The cardiovascular system is the first organ system to begin functioning at 3–4 weeks of embryonic age. The cardiovascular system is primarily derived from splanchnic mesoderm, paraxial and

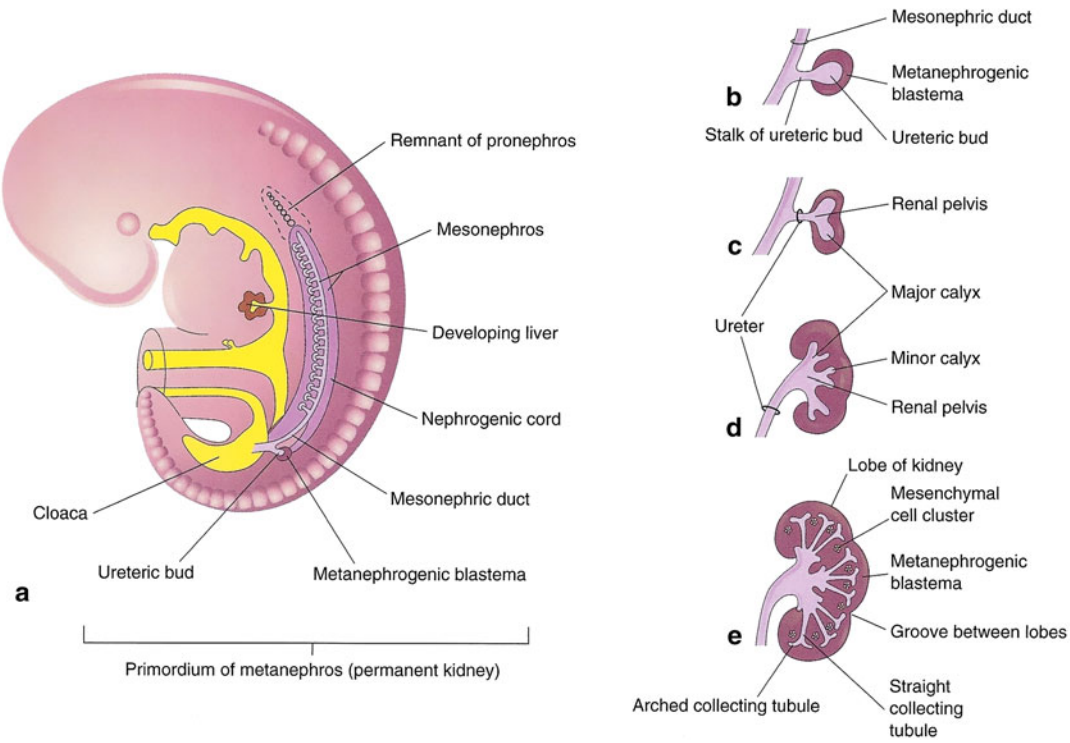

Fig. 4.11 Development of the permanent kidney. (**a**) Five-week human embryo showing the developing metanephros and ureteric bud. (**b**–**e**) Successive stages in the development of the ureteric bud. This figure was published in The Developing Human: Clinically Oriented Embryology, 9th ed., Moore KL, Persaud TVN, Torchia MG, Copyright Elsevier 2013

lateral mesoderm, and pharyngeal mesoderm, but also involves 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 cardiac structure. Blood begins flowing through the cardiac tube at approximately 4 weeks 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 the heart location 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 fourth embryonic week, continuing until the eighth to ninth week [6]. The developing heart begins to bend and constrict, resulting in the formation of five segmental primitive heart dilatations—the truncus arteriosus, bulbus cordis, primitive ventricle, primitive atrium, and sinus venosus. The truncus arteriosus give rise to the precursors of the aorta and pulmonary trunk, the bulbous cordis and primitive ventricle give rise to the ventricles, and the primitive atrium and sinus venosus to the atria and coronary sinus. Dextral (right handed) cardiac looping is also initiated during this developmental period, believed to primarily occur during embryonic weeks 5–7 [25]. This looping results in a U-shaped loop, which has as its end result the normal axis of the heart (Fig. 4.12).

When the heart tube bends left, rather than right, the heart is displaced to the right and its great vessels are reversed, creating a mirror image of the

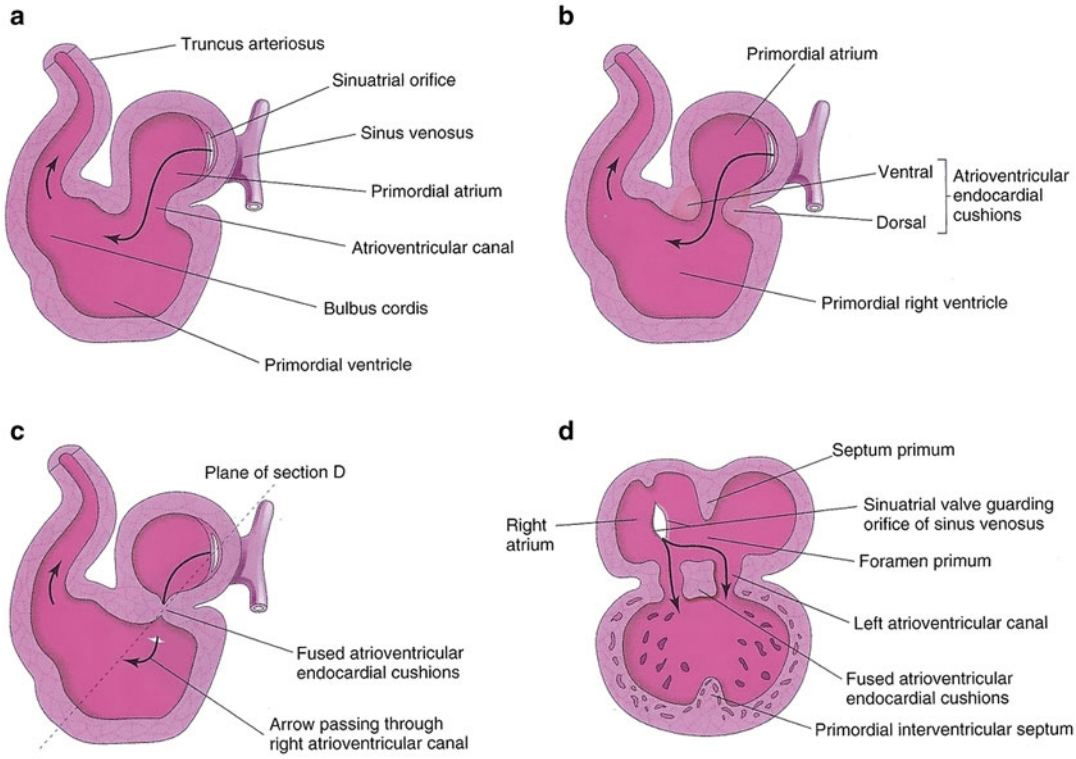

Fig. 4.12 Development of cardiac looping and atrioventricular (AV) septum development. (**a**, **b**) Sagittal sections of the heart at 4–5 embryonic weeks. (**c**) Fusion of the endocardial cushions to form the AV septum. (**d**) Coronal section of the heart at the place shown in (**c**). This figure was published in The Developing Human: Clinically Oriented Embryology, 9th ed., Moore KL, Persaud TVN, Torchia MG, Copyright Elsevier 2013

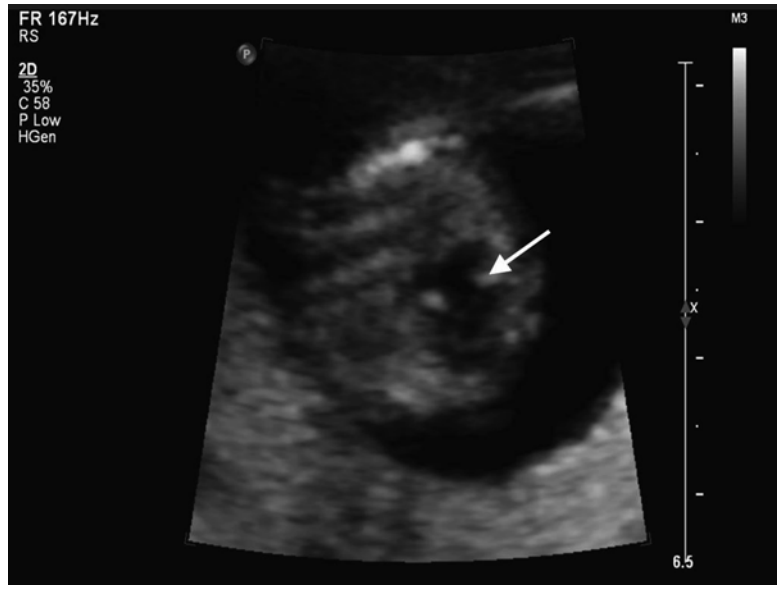

Fig. 4.13 Fetal persistent common atrioventricular (AV) canal at 13 weeks, a complication of abnormal endocardial cushion function or location. The *arrow* indicates the site of the absent AV septum, with a single shared AV valve for both sides of the heart. Courtesy of Dr. Randall Kuhlmann, Division of Maternal Fetal Medicine, Medical College of Wisconsin, Milwaukee, WI

normal heart structure, called dextrocardia which can be associated in some cases with an increased risk of severe cardiac defects [26].

Cardiac Septae Formation and Valvular Development

Multiple separate cell migration and signaling pathway processes are involved in the complex 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 towards each other and eventually fuse to form the AV septum with separation of a common AV canal into left and right AV canals (see Fig. 4.12). The cushions then function as the AV valves until further differentiation occurs resulting in definitive valve structure. Inductive signals from the myocardium of the AV canal causes epithelial–mesenchymal transformation, which transforms 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 abnormal development of the endocardial cushions. Failure of cushion fusion is responsible for persistent common AV canal, in which there is no true septal division of the heart, and a single common atrioventricular valve in place of the tricuspid and mitral valves (Fig. 4.13). Inadequate amounts of endocardial 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 result of which can have devastating consequences for long term cardiac function [26].

Atrial Septum

Partitioning of the atria begins at the end of the fourth embryonic week [6]. The right and left atria are created by the fusion of two septae, the septum primum and septum secundum. The septum primum has an initial foramen, termed the foramen primum, and, subsequently, also 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 several of the

most common congenital heart abnormalities. The female to male ratio for atrial septal defects is 3:1 [28].

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 seventh week of gestation 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 week seven, and involves fusion of the membranous portion of the IV septum with the muscular component [27]. Ventricular septal defects (VSDs) are the most common form of congenital cardiac abnormality, making up approximately 25 % of cases [29]. Typically the defect results from failure of the membranous portion of the septum to close, although other defects also 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

Septation of the truncus arteriosus and bulbus cordis is critical to the normal cardiac development and outflow through the pulmonary trunk and the aorta. This occurs during the fifth 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 (Fig. 4.14). 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 from the left ventricle (see Fig. 4.14). If neural crest cell migration does not proceed appropriately, the AP septum may not develop properly. This includes limited development of AP septum, with only one large vessel leaving the heart, called truncus arteriosus, as well as abnormal or absent spiraling of the septum causing transposition of each vessel from it appropriate ventricular outflow, called transposition of the great arteries. Unequal division of the truncus arteriosus is also believed to contribute to tetralogy of Fallot, in which pulmonary artery stenosis, ventricular septal defect, overriding aorta, and right ventricular hypertrophy are all identified [26].

Development of the Lymphatic System

Development of the lymphatic system begins and the end of the sixth embryonic week, *after* the cardiovascular system has developed [30]. It develops with a process similar to that for fetal blood vessels, with a series of small lymphatic tubes joining to form a lymphatic network (Fig. 4.15). Lymphatic drainage encompasses six primary lymph sacs, and many lymph nodes. Drainage occurs first from the cranial and caudad aspects of the embryo/fetus and then primarily into the right lymphatic duct. Abnormalities in lymphatic drainage, due to a blocked lymph sac or failure to establish appropriate lymphatic channels, may cause large swellings in the area of the fetal neck known as cystic hygromas (Fig. 4.16). The presence of a cystic hygroma is associated with and increased risk of fetal genetic abnormalities, cardiac malformations, and other fetal developmental problems [31, 32].

Summary

The human embryo and fetus undergoes remarkable development in the first trimester, from several cells to an embryo with clear organ structure and function. This formation is in large part affected by a complex system of embryonic cell signaling. Abnormalities in appropriate 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.

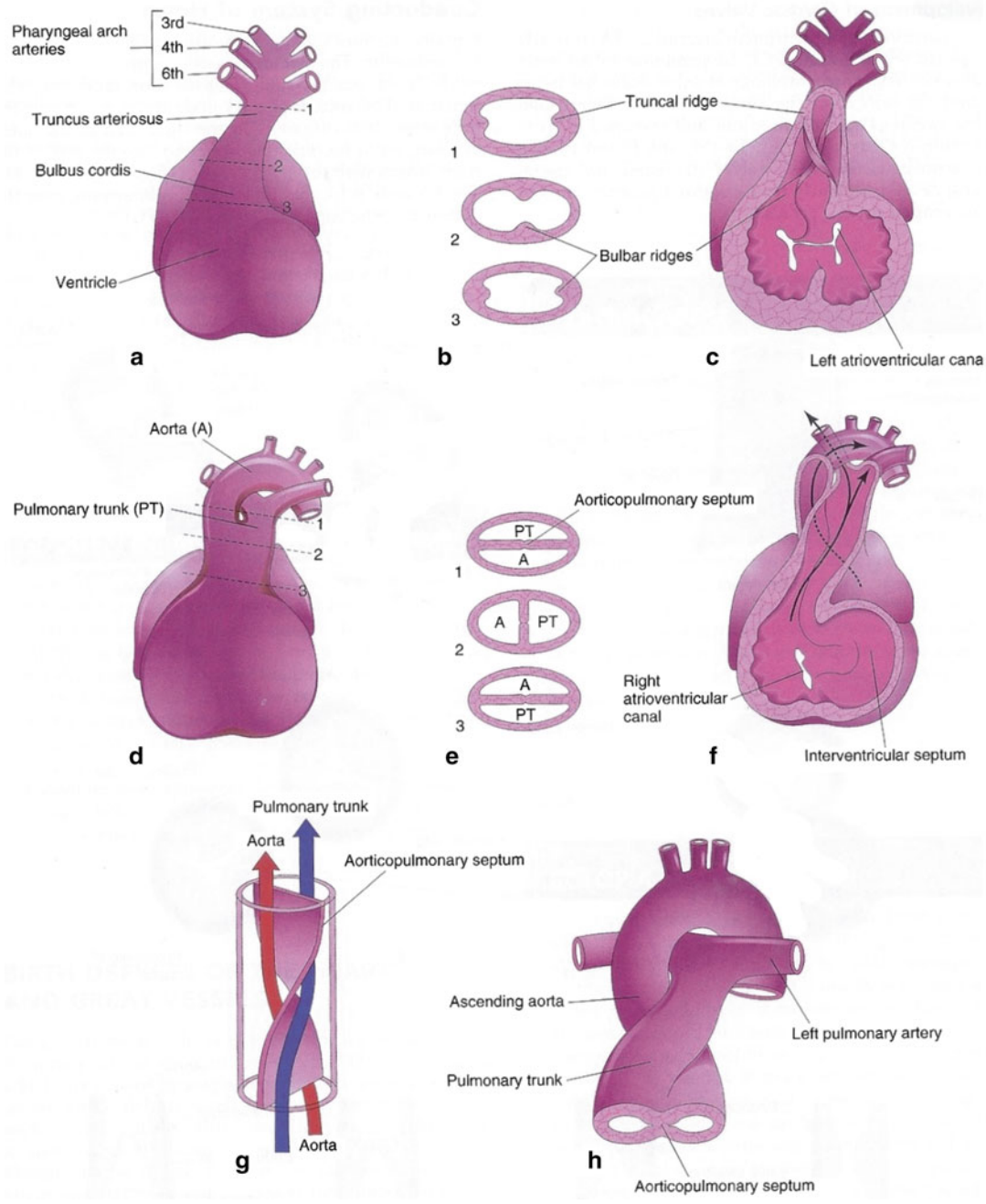

Fig. 4.14 Partitioning of the bulbus cordis and truncus arteriosus to form the great arteries. (**a**) Ventral view of the fetal heart at 5 weeks. *Broken lines* indicate the levels of the sections shown in (**b**). (**b**, **c**) Identification of the bulbar and truncal ridges forming the pulmonary and aortic outflow. (**d**–**f**) Ventral view of the fetal heart at 6 weeks after the aorticopulmonary (AP) septum is formed. (**g**) Spiral form of the AP septum, further illustrated in (**h**). This figure was published in The Developing Human: Clinically Oriented Embryology, 9th ed., Moore KL, Persaud TVN, Torchia MG, Copyright Elsevier 2013

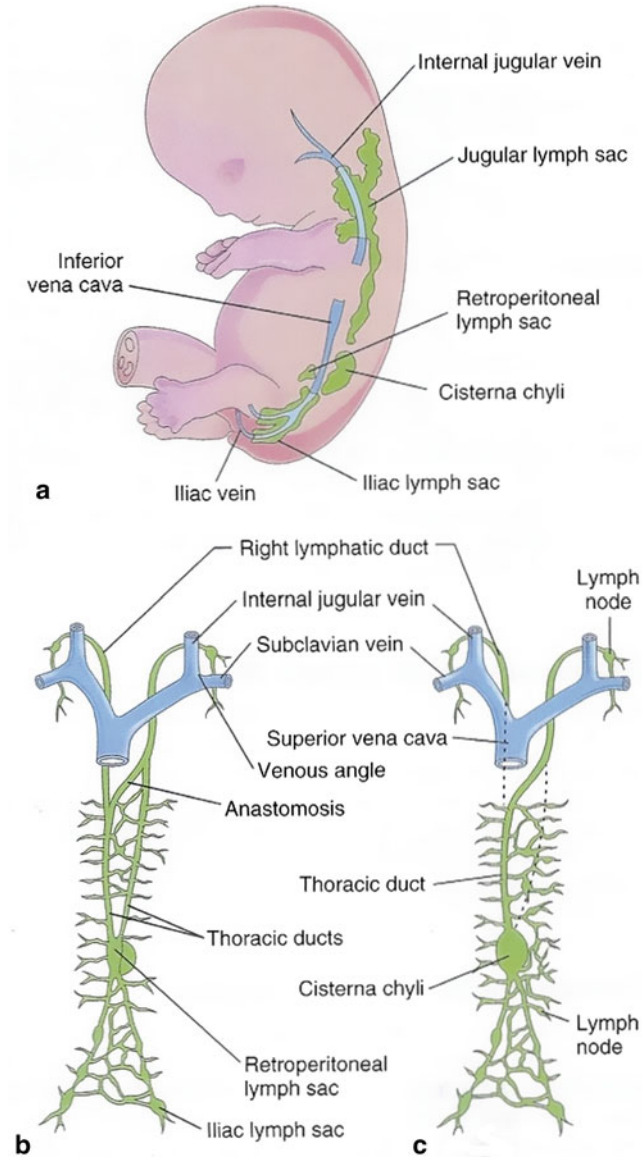

Fig. 4.15 Development of the lymphatic system. (**a**) Fetal embryo at 7 weeks showing primary lymph sacs. (**b**) Ventral view of lymphatic system at 9 weeks. (**c**) Formation of the thoracic and right lymphatic ducts later in gestation. This figure was published in The Developing Human: Clinically Oriented Embryology, 9th ed., Moore KL, Persaud TVN, Torchia MG, Copyright Elsevier 2013

Teaching Points

- Three percent of all pregnancies are complicated by a congenital anomaly.
- Signaling pathways are essential for normal morphogenesis
- The three germ layers are ectoderm, endoderm, and mesoderm; these are the building blocks for normal morphogenesis.
- The notochord is paramount to normal neurulation, axial orientation, and segmentation during early embryological development.
- Normal diaphragm development is dependent upon normal partitioning of the embryo and normal relationship of the septum transversum, dorsal mesentery of the esophagus, pleuroperitoneal membranes, and muscular ingrowth from the lateral body wall.
- Gastroschisis is believed to be the result of lack of fusion of the lateral folds of the embryo.

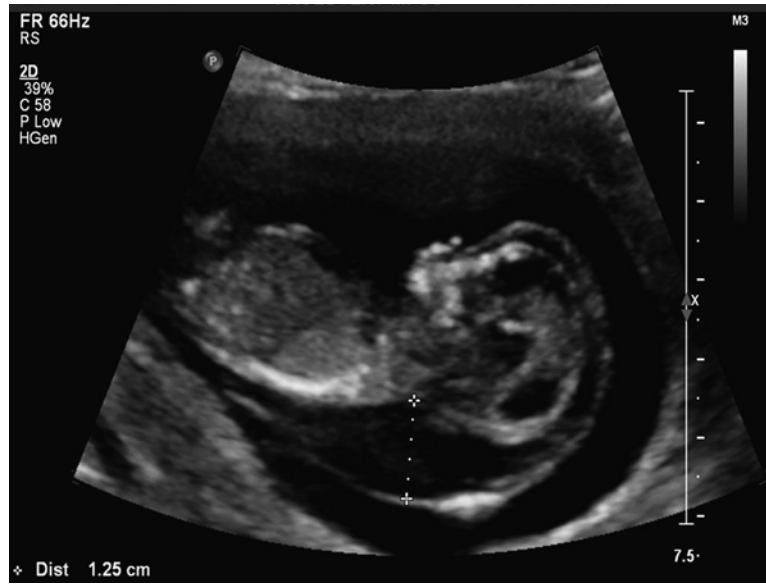

Fig. 4.16 Eleven-week ultrasound image of a fetus with longitudinal view of a cystic hygroma. Courtesy of Dr. Randall Kuhlmann, Division of Maternal Fetal Medicine, Medical College of Wisconsin, Milwaukee, WI

- Failure of endocardial cushion fusion results in various degrees of cardiac septal defects ranging from a membranous ventriculoseptal defect (VSD), to complete nonfusion and a common atrioventricular (AV) canal.

References

1. Nelson K, Holmes LB. Malformations due to presumed spontaneous mutations in newborn infants. N Engl J Med. 1989;320(1):19–23.
2. Hubaud AH, Pourquie O. Signalling dynamics in vertebrate segmentation. Nat Rev Mol Cell Biol. 2014;15:709–21.
3. Patthey C, Gunhaga L. Signaling pathways regulating ectodermal cell fate choices. Exp Cell Res. 2014; 321(1):11–6.
4. Dutta D. Signaling pathways dictating pleuropotency in embryonic stem cells. Int J Dev Biol. 2013; 57(9-10):667–75.
5. Sui L, Bouwens L, Mfopou JK. Signaling pathways during maintenance and definitive endoderm differentiation of embryonic stem cells. Int J Dev Biol. 2013;57(1):1–12.
6. Moore KL, Persaud TVN, Torchia MG. The developing human: clinically oriented embryology. 9th ed. Philadelphia, PA: Elsevier Saunders; 2013.
7. Downs KM. Enigmatic primitive streak: prevailing notions and challenges concerning the body axis of mammals. Bioessays. 2009;31(8):892–902.
8. Solnica-Krezel L, Sepich DS. Gastrulation: making and shaping germ layers. Annu Rev Cell Dev Biol. 2012;28:687–717.
9. Hardin J, Waston T. Models of morphogenesis: the mechanism of and mechanics of cell rearrangement. Curr Opin Genet Dev. 2004;14:399–406.
10. Flake AM. The fetus with sacrococcygeal teratoma. In: Adzick NS, Holzgrev W, editors. The unborn patient: the art and science of fetal therapy. 3rd ed. Philadelphia, PA: WB Saunders; 2001.
11. Ruiz I, Altaba A. Induction and axial patterning of the neural plate: planar and vertical signals. J Neurobiol. 1993;24(10):1276–304.
12. Greene ND, Copp AJ. Development of the vertebrate central nervous system: formation of the neural tube. Prenat Diagn. 2009;29(4):303–11.
13. Copp AJ, Greene ND. Genetics and development of neural tube defects. J Pathol. 2010;220(2):217–30.
14. Mayor R, Theveneau E. The neural crest. Development. 2013;140(11):2247–51.
15. Takahashi Y, Sipp D, Enomoto H. Tissue interactions in neural crest development and disease. Science. 2013;341(6148):860–3.
16. Mayer S, Metzger R, Kluth D. The embryology of the diaphragm. Semin Pediatr Surg. 2011;20(3):161–9.
17. Clugston RD, Greer JJ. Diaphragmatic development and congenital diaphragmatic hernia. Semin Pediatr Surg. 2007;16(2):94–100.
18. Hinrichsen K. The early development of morphology and patterns of the face of human embryos. Adv Anat Embryol Cell Biol. 1985;98:1–79.
19. Holinger LD. Congenital anomalies of the larynx. Congenital anomalies of the trachea and bronchi. In: Behrman RE, Kliegman RM, Jenson HB, editors. Nelson's textbook of pediatrics. 17th ed. Philadelphia, PA: WB Saunders; 2004.
20. Magnuson DK, Parry RL, Chwals WJ. Selected abdominal gastrointestinal anomalies. In: Martin RJ, Fanaroff AA, Walsh MC, editors. Fanaroff and

Martin's Neonatal-perinatal medicine: diseases of the fetus and infant. 8th ed. Philadelphia, PA: Mosby; 2006.
21. Persaud TVN, Hay JC. Normal embryonic and fetal development. In: Reece EA, Hobbins JC, editors. Clinical obstetrics: the fetus and mother. 3rd ed. Oxford: Blackwell Publishing; 2006.
22. Jones KL. Smith's recognizable patterns of human malformation. 7th ed. Philadelphia, PA: Elsevier/WB Saunders; 2006.
23. Bronschstein M, Blazer S, Zimmer EZ. The fetal gastrointestinal tract and abdominal wall. In: Callen PW, editor. Ultrasonography in obstetrics and gynecology. 5th ed. Philadelphia, PA: WB Saunders; 2008.
24. Kerecuk L, Schreuder MF, Woolf AS. Renal tract malformations: perspectives for nephrologists. Nat Clin Pract Nephrol. 2008;4(6):312–25.
25. Manner J. The anatomy of cardiac looping: a step towards the understanding of the morphogenesis of several forms of cardiac malformations. Clin Anat. 2009;22(1):21–35.
26. Bajolle F, Zaffran S, Bonnet C. Genetics and embryological mechanisms of congenital heart disease. Arch Cardiovasc Dis. 2009;102(1):59–63.
27. Vincent SD, Buckingham ME. How to make a heart: the origin and regulation of cardiac progenitor cells. Curr Top Dev Biol. 2010;90:1–41.
28. Moore KL, Persaud TVN, Torchia MG. Before we are born: essentials of embryology and birth defects. 8th ed. Philadelphia, PA: Elsevier Saunders; 2013.
29. Penny DJ, Vick GW. Ventricular septal defect. Lancet. 2011;377(9771):1103–12.
30. Yang Y, Oliver G. Development of the mammalian lymphatic vasculature. J Clin Invest. 2014;124(3):888–97.
31. Nadel A, Bromley B, Benacerraf BR. Nuchal thickening or cystic hygroma in first- and early second-trimester fetuses: prognosis and outcome. Obstet Gynecol. 1993;82(1):43–8.
32. Brady AF, Pandya PP, Yuksel B, Greenough A, Patton MA, Nicolaides KH. Outcome of chromosomally normal livebirths with increased fetal nuchal translucency at 10-14 weeks' gestation. J Med Genet. 1998;35(3):222–4.