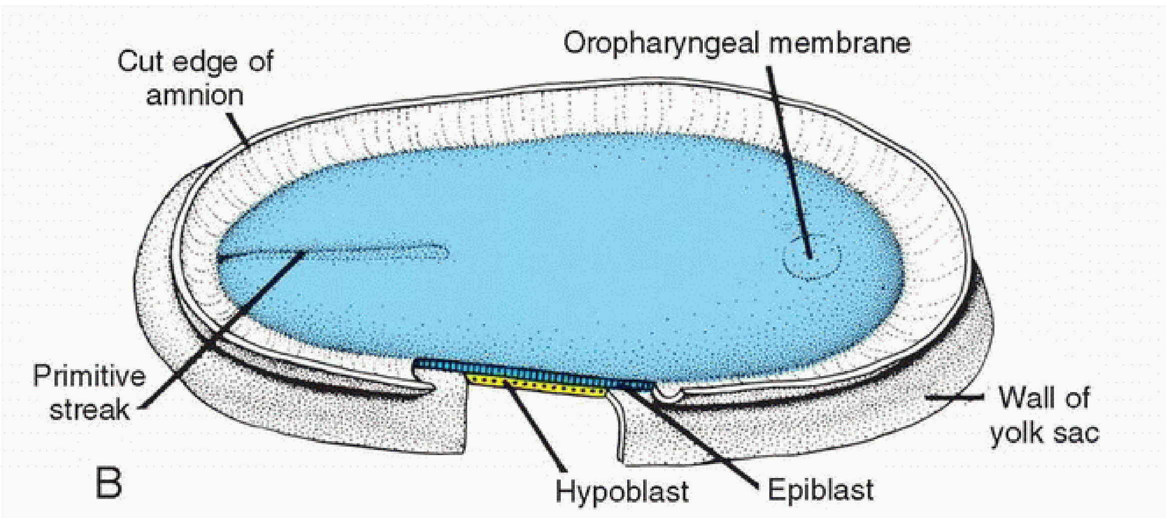
Medical Embryology

Alaa Hachem (DPhil)

Third Week of Development: Trilaminar Germ Disc

☒ Gastrulation: Formation of Embryonic Mesoderm and Endoderm

The most characteristic event occurring during the third week of gestation is **gastrulation,** the process that establishes all three **germ layers (ectoderm, mesoderm,** and **endoderm)** in the embryo. Gastrulation begins with formation of the **primitive streak** on the surface of the epiblast. Initially, the streak is vaguely defined, but in a 15- to 16-day embryo, it is clearly visible as a narrow groove with slightly bulging regions on either side. The cephalic end of the streak, the **primitive node,** consists of a slightly elevated area surrounding the small **primitive pit**. Cells of the epiblast migrate toward the primitive streak. Upon arrival in the region of the streak, they become flask-shaped, detach from the epiblast, and slip beneath it. This inward movement is known as **invagination.** Once the cells have invaginated, some displace the hypoblast, creating the embryonic **endoderm,** and others come to lie between the epiblast and newly created endoderm to form **mesoderm.** Cells remaining in the epiblast then form **ectoderm.** Thus, the epiblast, through the process of gastrulation, is the source of all of the germ layers, and cells in these layers will give rise to all of the tissues and organs in the embryo.



As more and more cells move between the epiblast and hypoblast layers, they begin to spread laterally and cephalad. Gradually, they migrate beyond the margin of the disc and establish contact with the extraembryonic mesoderm covering the yolk sac and amnion. In the cephalic direction, they pass on each side of the **prechordal plate.** The prechordal plate itself forms between the tip of the notochord and the **buccopharyngeal membrane** and is derived from some of the first cells that migrate through the node in a cephalic direction. Later, the prechordal plate will be important for induction of the forebrain. The buccopharyngeal membrane at the cranial end of the disc consists of a small region of tightly adherent ectoderm and endoderm cells that represents the future opening of the oral cavity.

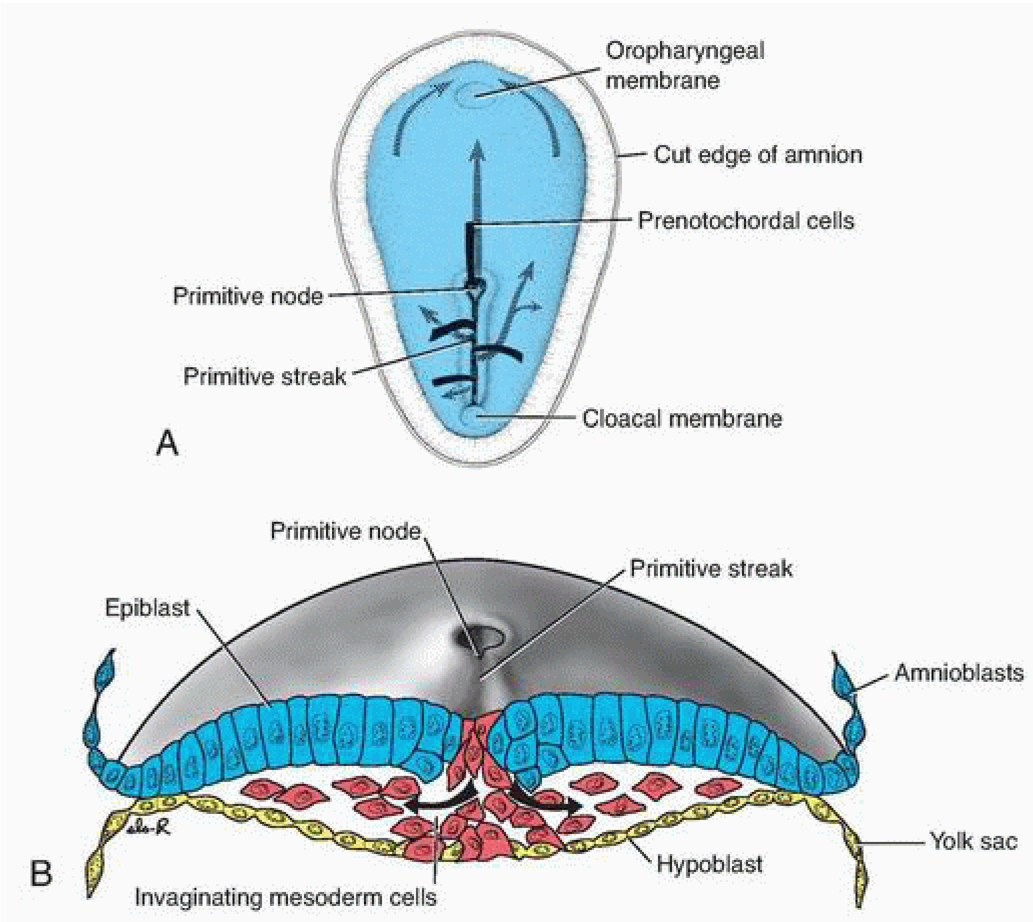
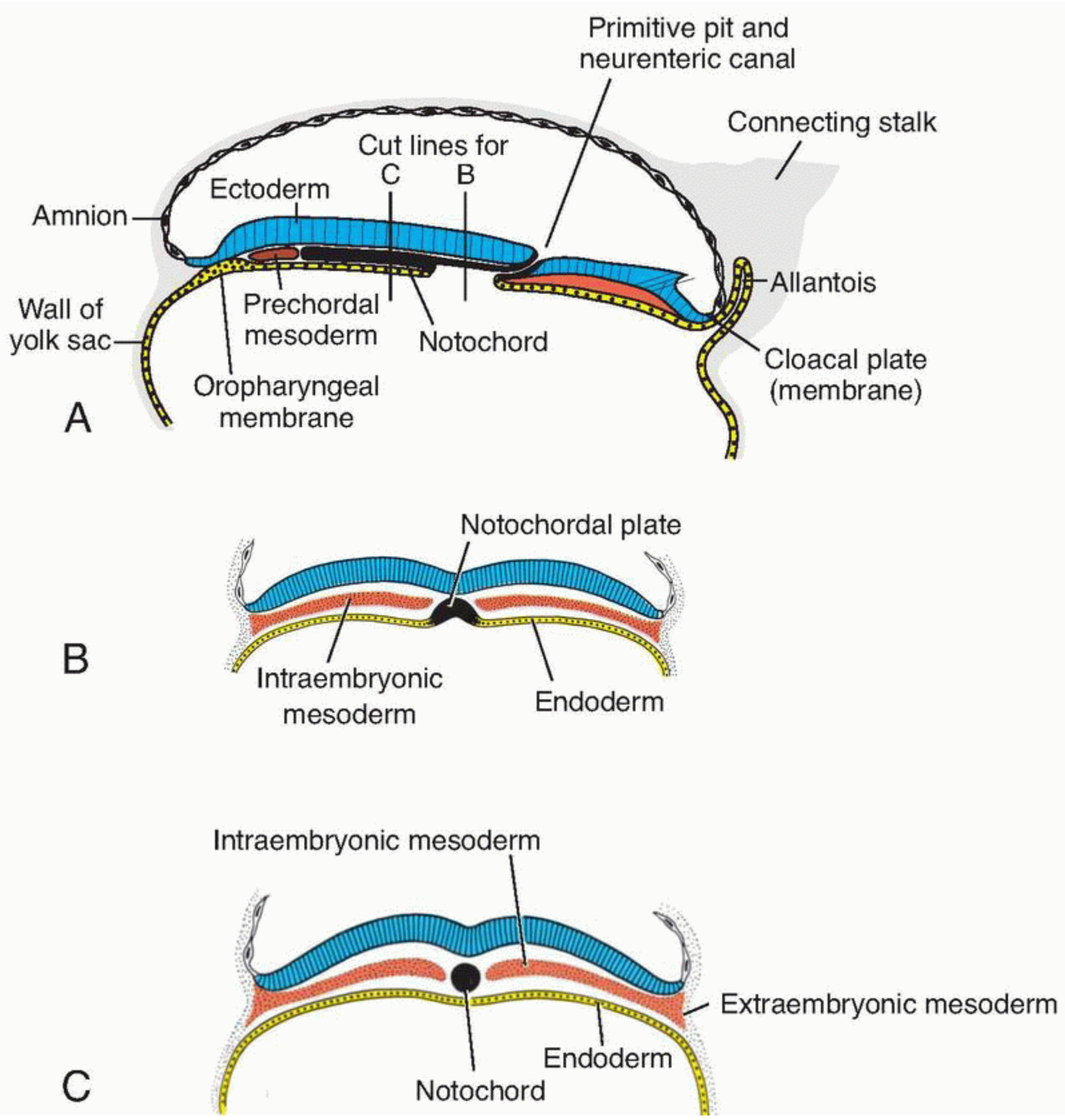


Figure 5.2 A. Dorsal side of the germ disc from a 16-day embryo indicating the movement of surface epiblast cells (solid black lines) through the primitive streak and node and the subsequent migration of cells between the hypoblast and epiblast (broken lines). B. Cross section through the cranial region of the streak at 15 days showing invagination of epiblast cells. The first cells to move inward displace the hypoblast to create the definitive endoderm. Once definitive endoderm is established, inwardly moving epiblast forms mesoderm.

☒ Formation of the Notochord

Prenotochordal cells invaginating in the primitive pit move forward cephalad until they reach the **prechordal plate**. These prenotochordal cells become intercalated in the hypoblast so that, for a short time, the midline of the embryo consists of two cell layers that form the **notochordal plate.** As the hypoblast is replaced by endoderm cells moving in at the streak, cells of the notochordal plate proliferate and detach from the endoderm. They then form a solid cord of cells, the **definitive notochord**, which underlies the neural tube and serves as the basis for the axial skeleton. Because elongation of the notochord is a dynamic process, the cranial end forms first, and caudal regions are added as the primitive streak assumes a more caudal position. The notochord and prenotochordal cells extend cranially to the prechordal plate (an area just caudal to the buccopharyngeal membrane) and caudally to the primitive pit. At the point where the pit forms an indentation in the epiblast, the **neurenteric canal** temporarily connects the amniotic and yolk sac cavities.

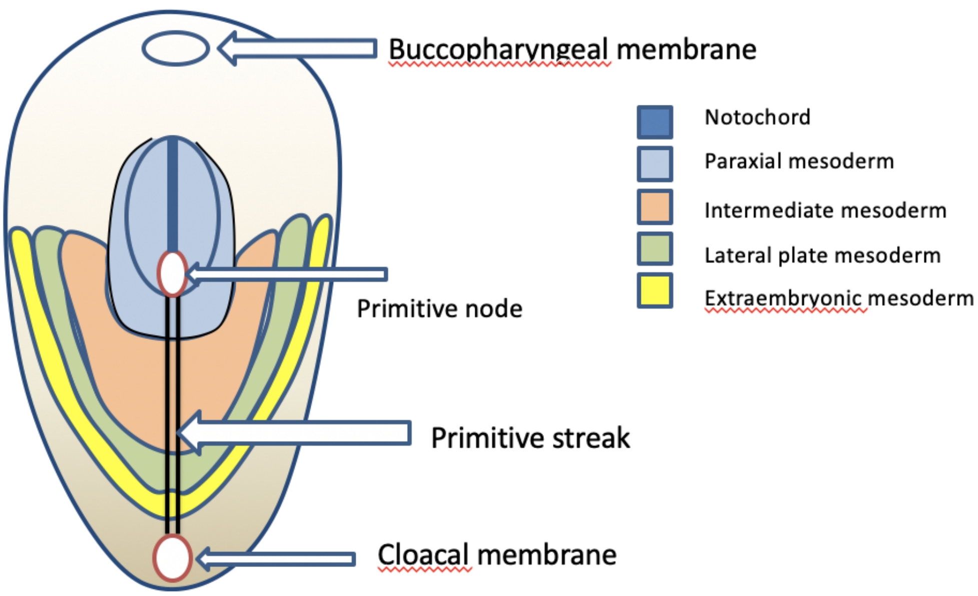
The cloacal membrane is formed at the caudal end of the embryonic disc. This membrane, which is similar in structure to the buccopharyngeal membrane, consists of tightly adherent ectoderm and endoderm cells with no intervening mesoderm. When the cloacal membrane appears, the posterior wall of the yolk sac forms a small diverticulum that extends into the connecting stalk. This diverticulum, the **allantoenteric diverticulum,** or **allantois,** appears around the 16th day of development. Although in some lower vertebrates the allantois serves as a reservoir for excretion products of the renal system, in humans it remains rudimentary but may be involved in abnormalities of bladder development.


Primitive pit and
neurenteric canal
Connecting stalk
Cut lines for
C
B
Ectoderm
Amnion
Allantois
Wall of
yolk sac
Prechordal
mesoderm
Notochord
Cloacal plate
(membrane)
Oropharyngeal
membrane
A
Notochordal plate
B
Intraembryonic
mesoderm
Endoderm
Intraembryonic mesoderm
Extraembryonic mesoderm
Endoderm
Notochord
C

☒ Fate Map Established During Gastrulation

Regions of the epiblast that migrate and ingress through the primitive streak have been mapped and their ultimate fates determined. For example, cells that ingress through the cranial region of the node become notochord; those migrating at the lateral edges of the node and from the cranial end of the streak become **paraxial mesoderm;** cells migrating through the midstreak region become **intermediate mesoderm;** those migrating through the more caudal part of the streak form **lateral plate mesoderm;** and cells migrating through the caudal-most part of the streak contribute to extraembryonic mesoderm (the other source of this tissue is the primitive yolk sac [hypoblast]; see day 11 and day 12 of the development).

Fate Map Established During Gastrulation



☒ Growth of the Embryonic Disc

The embryonic disc, initially flat and almost round, gradually becomes elongated, with a broad cephalic and a narrow caudal end. Expansion of the embryonic disc occurs mainly in the cephalic region; the region of the primitive streak remains more or less the same size. Growth and elongation of the cephalic part of the disc are caused by a continuous migration of cells from the primitive streak region in a cephalic direction. Invagination of surface cells in the primitive streak and their subsequent migration forward and laterally continues until the end of the fourth week. At that stage, the primitive streak shows regressive changes, rapidly shrinks, and soon disappears. That the primitive streak at the caudal end of the disc continues to supply new cells until the end of **the fourth week** has an important bearing on development of the embryo. In the cephalic part, germ layers begin **their specific differentiation by the middle of the third week**, whereas in the caudal part, differentiation **begins by the end of the fourth week.** Thus gastrulation, or formation of the germ layers, continues in caudal segments while cranial structures are differentiating, causing the embryo to develop cephalocaudally.

☒ Clinical correlates

Teratogenesis Associated with Gastrulation

The beginning of the third week of development, when gastrulation is initiated, is a highly sensitive stage for teratogenic insult. At this time, fate maps can be made for various organ systems, such as the eyes and brain anlage, and these cell populations may be damaged by teratogens. **For example, high doses of alcohol at this stage kill cells in the anterior midline of the germ disc, producing a deficiency of the midline in craniofacial structures and resulting in holoprosencephaly.** In such a child, the forebrain is small, the two lateral ventricles often merge into a single ventricle, and the eyes are close together (hypotelorism). Because this stage is reached 2 weeks after fertilization, it is approximately 4 weeks from the last menses. Therefore, the woman may not recognize she is pregnant; having assumed that menstruation is late and will begin shortly. Consequently, she may not take precautions she would normally consider if she knew she was pregnant.

Gastrulation itself may be disrupted by genetic abnormalities and toxic insults. In **caudal dysgenesis (sirenomelia),** insufficient mesoderm is formed in the caudal-most region of the embryo. Because this mesoderm contributes to formation of the lower limbs, urogenital system (intermediate mesoderm), and lumbosacral vertebrae, abnormalities in these structures ensue. Affected individuals exhibit a variable range of defects, including hypoplasia and fusion of the lower limbs, vertebral abnormalities, renal agenesis, imperforate anus, and anomalies of the genital organs. In humans, the condition is associated with maternal diabetes and other causes.

Situs inversus is a condition in which transposition of the viscera in the thorax and abdomen occurs.

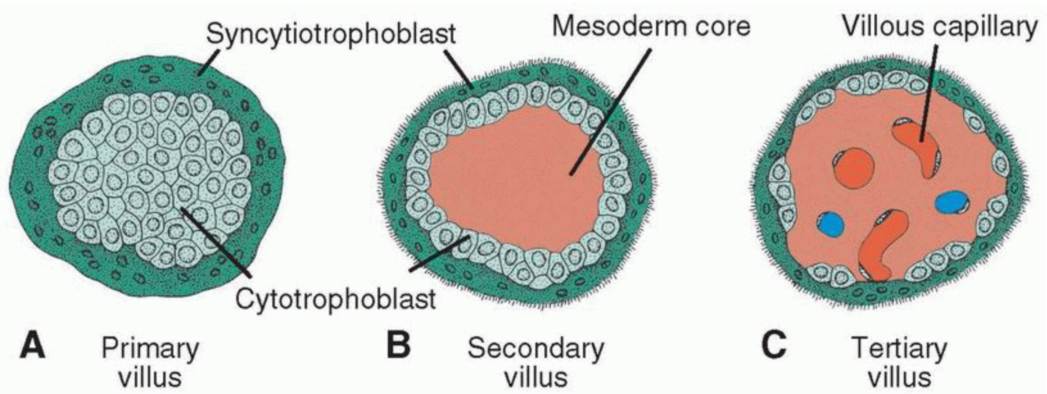
Other conditions of abnormal sidedness are known as **laterality sequences.** Patients with these conditions do not have complete situs inversus but appear to be predominantly bilaterally left sided or right sided. The spleen reflects the differences; those with left-sided bilaterality have polysplenia, and those with right-sided bilaterality have asplenia or hypoplastic spleen. Patients with laterality sequences also are likely to have other malformations, especially heart defects.

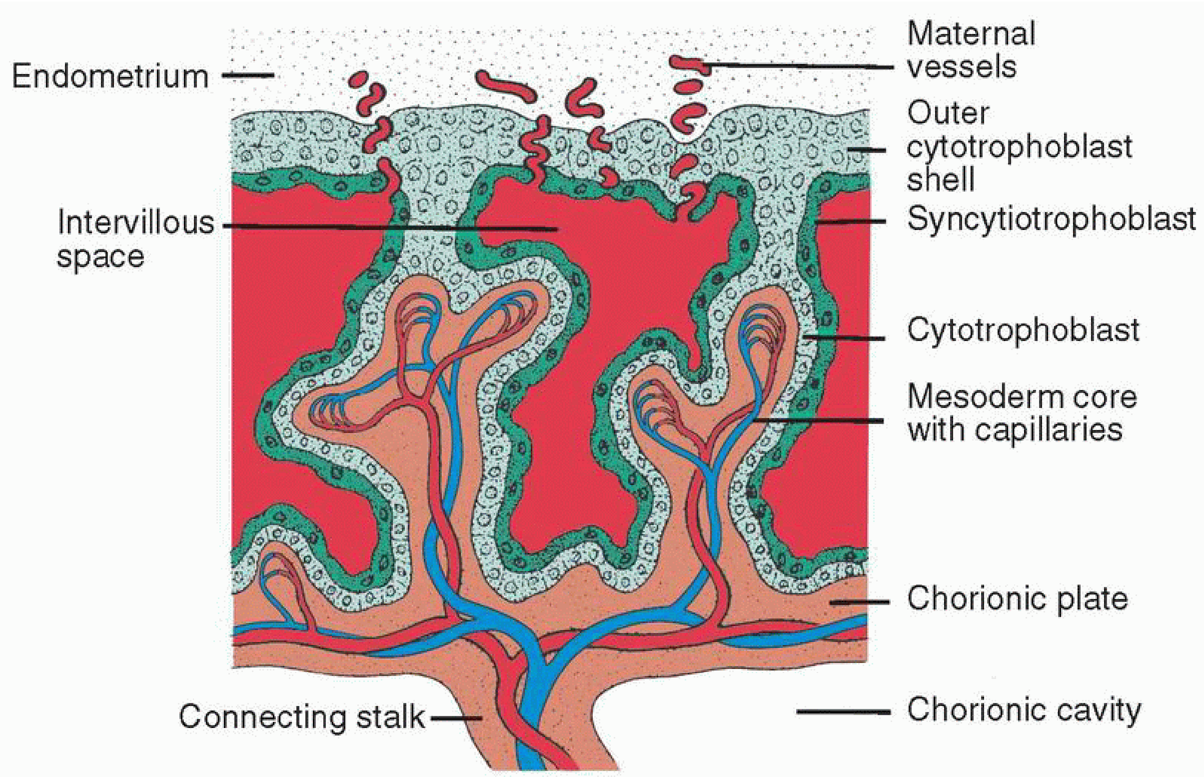
☒ Further Development of the Trophoblast

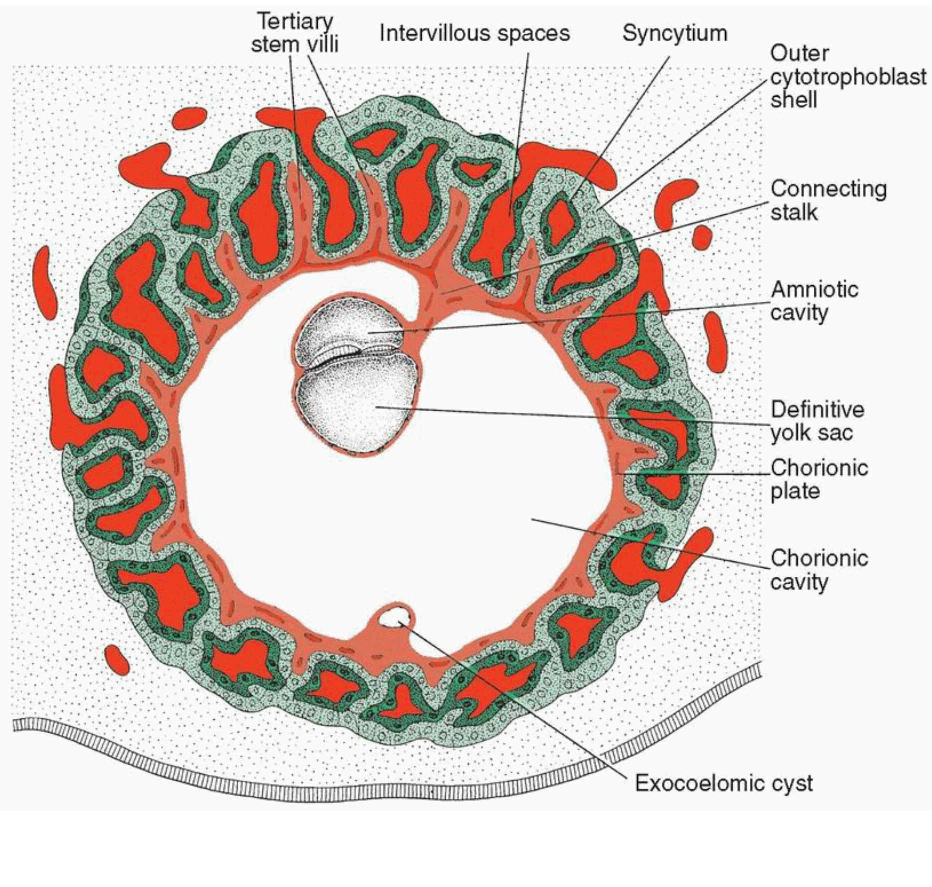
By the beginning of the third week, the trophoblast is characterized by **primary villi** that consist of a cytotrophoblastic core covered by a syncytial layer. During further development, mesodermal cells penetrate the core of primary villi and grow toward the decidua. The newly formed structure is known as a **secondary villus**.

By the end of the third week, mesodermal cells in the core of the villus begin to differentiate into blood cells and small blood vessels, forming the villous capillary system. The villus is now known as a **tertiary villus** or **definitive placental villus.** Capillaries in tertiary villi make contact with capillaries developing in mesoderm of the chorionic plate and in the connecting stalk. These vessels, in turn, establish contact with the intraembryonic circulatory system, connecting the placenta and the embryo. **Hence, when the heart begins to beat in the fourth week of development**, the villous system is ready to supply the embryo proper with essential nutrients and oxygen.

Meanwhile, cytotrophoblastic cells in the villi penetrate progressively into the overlying syncytium until they reach the maternal endometrium. Here they establish contact with similar extensions of neighboring villous stems, forming a thin **outer cytotrophoblast shell**. This shell gradually surrounds the trophoblast entirely and attaches the chorionic sac firmly to the maternal endometrial tissue. Villi that extend from the **chorionic plate** to the **decidua basalis (decidual plate:** the part of the endometrium where the placenta will form) are called **stem** or **anchoring villi.** Those that branch from the sides of stem villi are **free (terminal) villi,** through which exchange of nutrients and other factors will occur. The chorionic cavity, meanwhile, becomes larger, and by the 19th or 20th day, the embryo is attached to its trophoblastic shell by a narrow **connecting stalk**. The connecting stalk later develops into the **umbilical cord,** which forms the connection between placenta and embryo.




Endometrium
Maternal
vessels
Outer
cytotrophoblast
shell
Intervillous
space
Syncytiotrophoblast
Cytotrophoblast
Mesoderm core
with capillaries
Chorionic plate
Connecting stalk
Chorionic cavity


Tertiary
stem villi
Intervillous spaces
Syncytium
Outer
cytotrophoblast
shell
Connecting
stalk
Amniotic
cavity
Definitive
yolk sac
Chorionic
plate
Chorionic
cavity
Exocoelomic cyst