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Formation of the Bilaminar Embryonic Disc: Second Week



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Formation of the Bilaminar Embryonic Disc: Second Week ■ 43

Implantation of the blastocyst is completed during the second week. As this process occurs, morphologic changes in the embryoblast produce a bilaminar embryonic disc composed of epiblast and hypoblast (Fig. 3-1A). The **embryonic disc** gives rise to the germ layers that form all the tissues and organs of the embryo. Extraembryonic structures forming during the second week are the amniotic cavity, amnion, umbilical vesicle (yolk sac), connecting stalk, and chorionic sac.

COMPLETION OF IMPLANTATION AND CONTINUATION OF EMBRYONIC DEVELOPMENT

Implantation of the blastocyst is completed by the end of the second week. It occurs during a restricted time period 6 to 10 days after ovulation. As the blastocyst implants (see Fig. 3-1), more trophoblast contacts the endometrium and differentiates into

- The cytotrophoblast, a layer of cells that is mitotically active and forms new cells that migrate into the increasing mass of syncytiotrophoblast, where they fuse and lose their cell membranes
- The syncytiotrophoblast, a rapidly expanding, multinucleated mass in which no cell boundaries are discernible

The erosive **syncytiotrophoblast** invades the endometrial connective tissue, and the blastocyst slowly embeds itself in the endometrium. Syncytiotrophoblastic cells displace endometrial cells at the implantation site. The endometrial cells undergo **apoptosis** (programmed cell death), which facilitates the invasion. The molecular mechanisms of implantation involve synchronization between the invading blastocyst and a receptive endometrium. The microvilli of endometrial cells (pinopodes), cell adhesion molecules, cytokines, prostaglandins, homeobox genes, growth factors, and matrix metallo-proteins play a role in making the endometrium receptive. The connective tissue cells around the implantation site accumulate glycogen and lipids and assume a polyhedral appearance. Some of these cells—**decidual cells**—degenerate adjacent to the penetrating syncytiotrophoblast. The syncytiotrophoblast engulfs these degenerating cells, providing a rich source of embryonic nutrition.

The syncytiotrophoblast produces a hormone—**human chorionic gonadotrophin** (hCG), which enters the maternal blood via lacunae (Latin, hollow cavities) in the syncytiotrophoblast (see Fig. 3-1C). hCG maintains the hormonal activity of the corpus luteum in the ovary during preg-

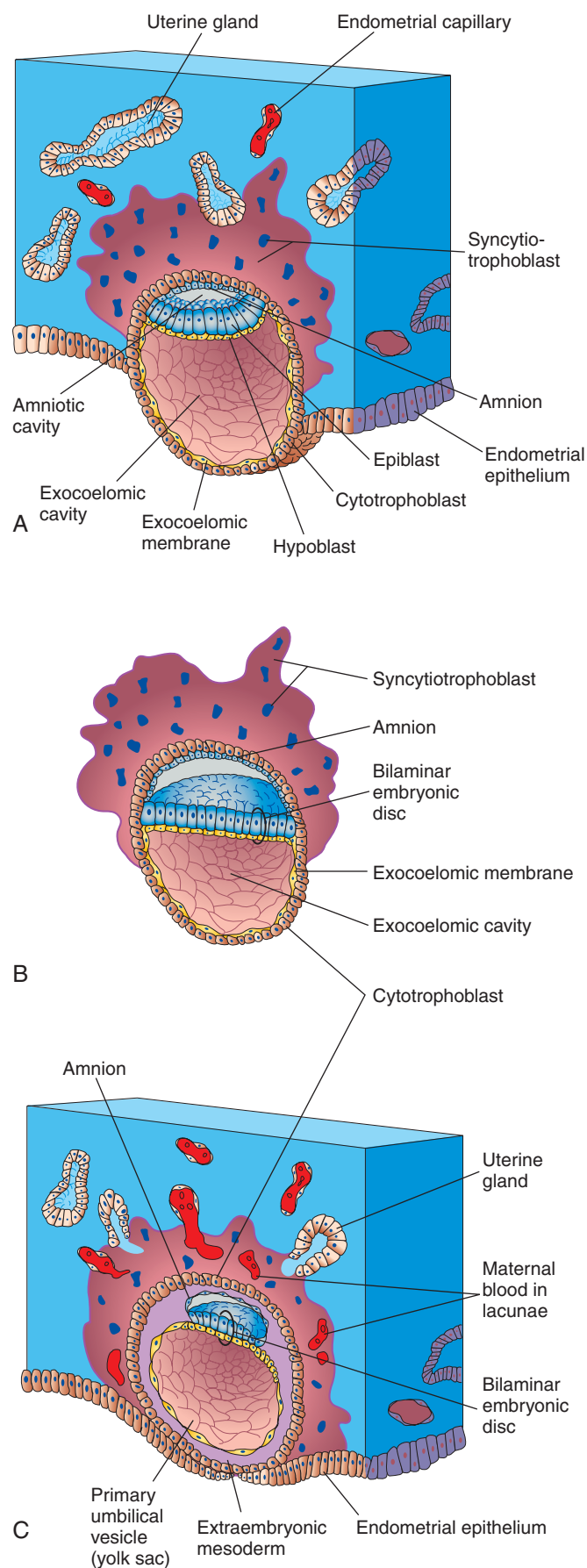


FIGURE 3-1. Implantation of a blastocyst in the endometrium. The actual size of the conceptus is 0.1 mm, approximately the size of the period at the end of this sentence. **A**, Drawing of a section through a blastocyst partially implanted in the endometrium (approximately 8 days). Note the slitlike amniotic cavity. **B**, An enlarged three-dimensional sketch of a slightly older blastocyst after removal from the endometrium. Note the extensive syncytiotrophoblast at the embryonic pole (side of the blastocyst containing the embryonic disc). **C**, Drawing of a section through a blastocyst of approximately 9 days implanted in the endometrium. Note the lacunae appearing in the syncytiotrophoblast. The term *yolk sac* is a misnomer because it contains no yolk.

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nancy. The corpus luteum is an endocrine glandular structure that secretes estrogen and progesterone to maintain the pregnancy. Highly sensitive radioimmunoassays are available for detecting hCG and pregnancy and forms the basis for *pregnancy tests*. Enough hCG is produced by the syncytiotrophoblast at the end of the second week to give a positive pregnancy test, even though the woman is probably unaware that she is pregnant.

FORMATION OF THE AMNIOTIC CAVITY, EMBRYONIC DISC, AND UMBILICAL VESICLE

As implantation of the blastocyst progresses, a small space appears in the embryoblast. This space is the primordium of the **amniotic cavity** (see Fig. 3-1A). Soon amniogenic (amnion-forming) cells—*amnioblasts*—separate from the epiblast and form the **amnion**, which encloses the amniotic cavity (see Fig. 3-1B and C). Concurrently, morphologic changes occur in the embryoblast that result in the formation of a flat, almost circular bilaminar plate of cells, the **embryonic disc**, consisting of two layers (Fig. 3-2A):

- **Epiblast**, the thicker layer, consisting of high columnar cells related to the amniotic cavity
- **Hypoblast**, consisting of small cuboidal cells adjacent to the exocoelomic cavity

The epiblast forms the floor of the amniotic cavity and is continuous peripherally with the amnion. The hypoblast forms the roof of the **exocoelomic cavity** and is continuous with the thin exocoelomic **membrane** (see Fig. 3-1B). This membrane, together with the hypoblast, lines the **primary umbilical vesicle**. The embryonic disc now lies between the amniotic cavity and the umbilical vesicle (see Fig. 3-1C). Cells from the vesicle endoderm form a layer of connective tissue, the **extraembryonic mesoderm** (see Fig. 3-2A), which surrounds the amnion and umbilical vesicle. This mesoderm continues to form from cells that arise from the primitive streak (see Fig. 4-3). The umbilical vesicle and amniotic cavities make morphogenetic movements of the cells of the embryonic disc possible.

As the amnion, embryonic disc, and primary umbilical vesicle form, isolated cavities—**lacunae**—appear in the syncytiotrophoblast (see Figs. 3-1C and 3-2). The lacunae soon become filled with a mixture of maternal blood from ruptured endometrial capillaries and cellular debris from eroded uterine glands. The fluid in the lacunar spaces—*embryotroph* (Greek, *trophe*, nourishment)—passes to the embryonic disc by diffusion and provides nutritive material to the embryo.

The communication of the eroded endometrial capillaries with the lacunae establishes the **primordial uteroplacental circulation**. When maternal blood flows into the lacunae, oxygen and nutritive substances are available to the embryo. *Oxygenated blood* passes into the lacunae from the *spiral endometrial arteries*, and *poorly oxygenated blood* is removed from them through the endometrial veins.

The 10-day human conceptus (*embryo and extraembryonic membranes*) is completely embedded in the endometrium (see Fig. 3-2A). For approximately 2 days, there is a defect in

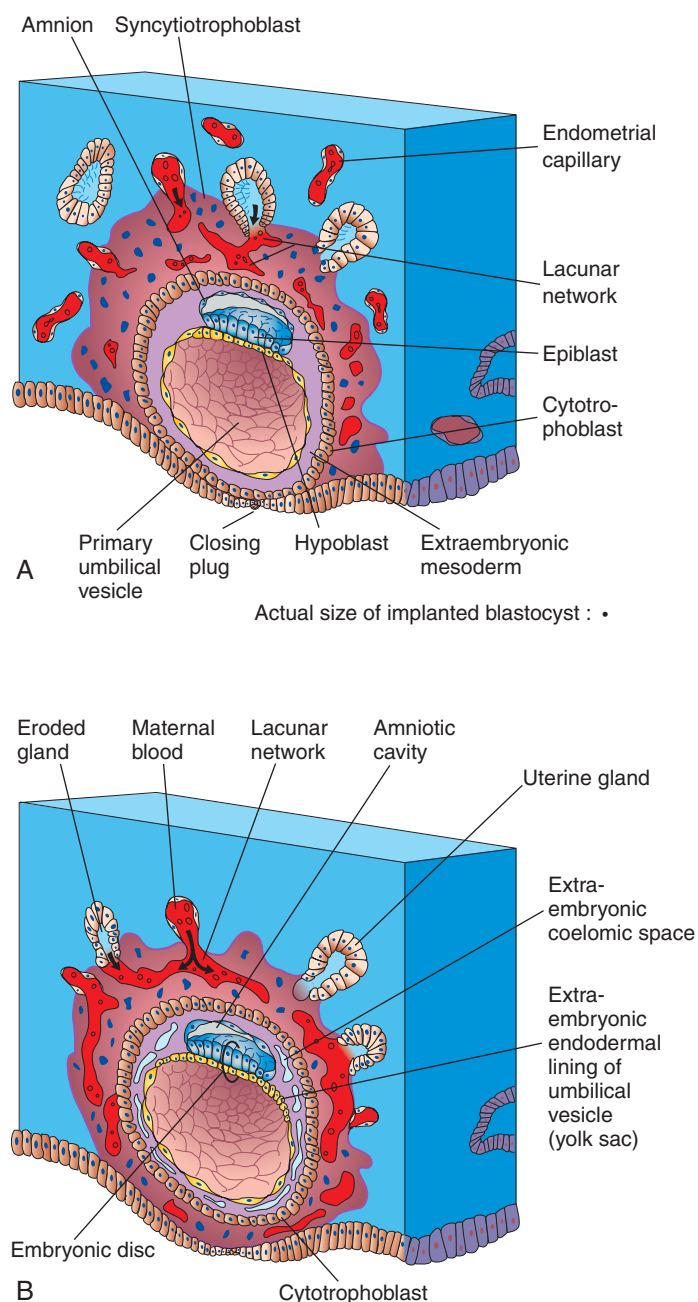


FIGURE 3-2. Implants of blastocysts. **A**, At 10 days; **B**, at 12 days. This stage of development is characterized by communication of the blood-filled lacunar networks. Note in **B** that coelomic spaces have appeared in the extraembryonic mesoderm, forming the beginning of the extraembryonic coelom.

the endometrial epithelium that is filled by a **closing plug**, a fibrinous coagulum of blood. By day 12, an almost completely regenerated uterine epithelium covers the closing plug (see Fig. 3-2B). As the conceptus implants, the endometrial connective tissue cells undergo a transformation, the **decidual reaction**. After the cells swell because of the accumulation of glycogen and lipid in their cytoplasm, they are known as **decidual cells**. The primary function of the decidual reaction is to provide nutrition for the early embryo and an immunologically privileged site for the conceptus.

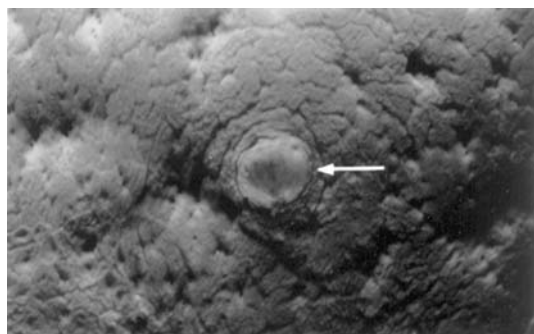


FIGURE 3-3. Photograph of the endometrial surface of the uterus, showing the implantation site of the 12-day embryo shown in Figure 3-4. The implanted conceptus produces a small elevation (arrow) (×8). (From Hertig AT, Rock J: *Contrib Embryol Carnegie Inst* 29:127, 1941. Courtesy of the Carnegie Institution of Washington.)

In a **12-day embryo**, adjacent syncytiotrophoblastic lacunae have fused to form **lacunar networks** (see Fig. 3-2B), giving the syncytiotrophoblast a spongelike appearance. The lacunar networks, particularly obvious around the embryonic pole, are the primordia of the intervillous spaces of the placenta (see Chapter 7). The endometrial capillaries around the implanted embryo become congested and dilated to form **sinusoids**, thin-walled terminal vessels that are larger than ordinary capillaries. The syncytiotrophoblast erodes the sinusoids, and maternal blood flows freely into the lacunar networks. The trophoblast absorbs nutritive fluid from the lacunar networks, which is transferred to the embryo. Growth of the bilaminar embryonic disc is slow compared with growth of the trophoblast (see Figs. 3-1 and 3-2). The implanted 12-day embryo produces a minute elevation on the endometrial surface that protrudes into the uterine lumen (Figs. 3-3 and 3-4).

As changes occur in the trophoblast and endometrium, the extraembryonic mesoderm increases and isolated **extraembryonic coelomic spaces** appear within it (see Figs. 3-2 and 3-4). These spaces rapidly fuse to form a large isolated cavity, the **extraembryonic coelom** (Fig. 3-5A). This fluid-filled cavity surrounds the amnion and umbilical vesicle, except where they are attached to the **chorion** by the **connecting stalk**. As the extraembryonic coelom forms, the primary umbilical vesicle decreases in size and a smaller **secondary umbilical vesicle** forms (see Fig. 3-5B). This smaller vesicle is formed by extraembryonic endodermal cells that migrate from the hypoblast inside the primary umbilical vesicle (Fig. 3-6). During formation of the secondary umbilical vesicle, a large part of the primary umbilical vesicle is pinched off (see Fig. 3-5B). *The umbilical vesicle contains no yolk*; however, it has important functions (e.g., it is the *site of origin of primordial germ cells* [see Chapter 12]). It may have a role in the selective transfer of nutrients to the embryo.

DEVELOPMENT OF THE CHORIONIC SAC

The end of the second week is characterized by the appearance of **primary chorionic villi** (Figs. 3-5 and 3-7). Proliferation of cytotrophoblastic cells produces cellular extensions that grow into the syncytiotrophoblast. The

growth of these extensions is thought to be induced by the underlying **extraembryonic somatic mesoderm**. The cellular projections form primary chorionic villi, the first stage in the development of the chorionic villi of the placenta.

The extraembryonic coelom splits the extraembryonic mesoderm into two layers (see Fig. 3-5A and B):

- **Extraembryonic somatic mesoderm**, lining the trophoblast and covering the amnion
- **Extraembryonic splanchnic mesoderm**, surrounding the umbilical vesicle

The extraembryonic somatic mesoderm and the two layers of trophoblast form the **chorion** (see Fig. 3-7B). *The chorion forms the wall of the chorionic sac*, within which the embryo and its amniotic sac and umbilical vesicle are suspended by the connecting stalk. The extraembryonic coelom is now called the chorionic cavity. The amniotic sac and the umbilical vesicle can be thought of as two balloons pressed together (at the site of embryonic disc) and suspended by a cord (connecting stalk) from the inside of a larger balloon (chorionic sac). *Transvaginal ultrasonography* (endovaginal sonography) is used for measuring the chorionic (gestational) sac diameter (Fig. 3-8). This measurement is valuable for evaluating early embryonic development and pregnancy outcome.

The **14-day embryo** still has the form of a flat bilaminar embryonic disc (see Fig. 3-9), but the hypoblastic cells in a localized area are now columnar and form a thickened circular area—the **prechordal plate** (see Fig. 3-5B and C), which indicates the future site of the mouth and an important organizer of the head region.

IMPLANTATION SITES OF BLASTOCYSTS

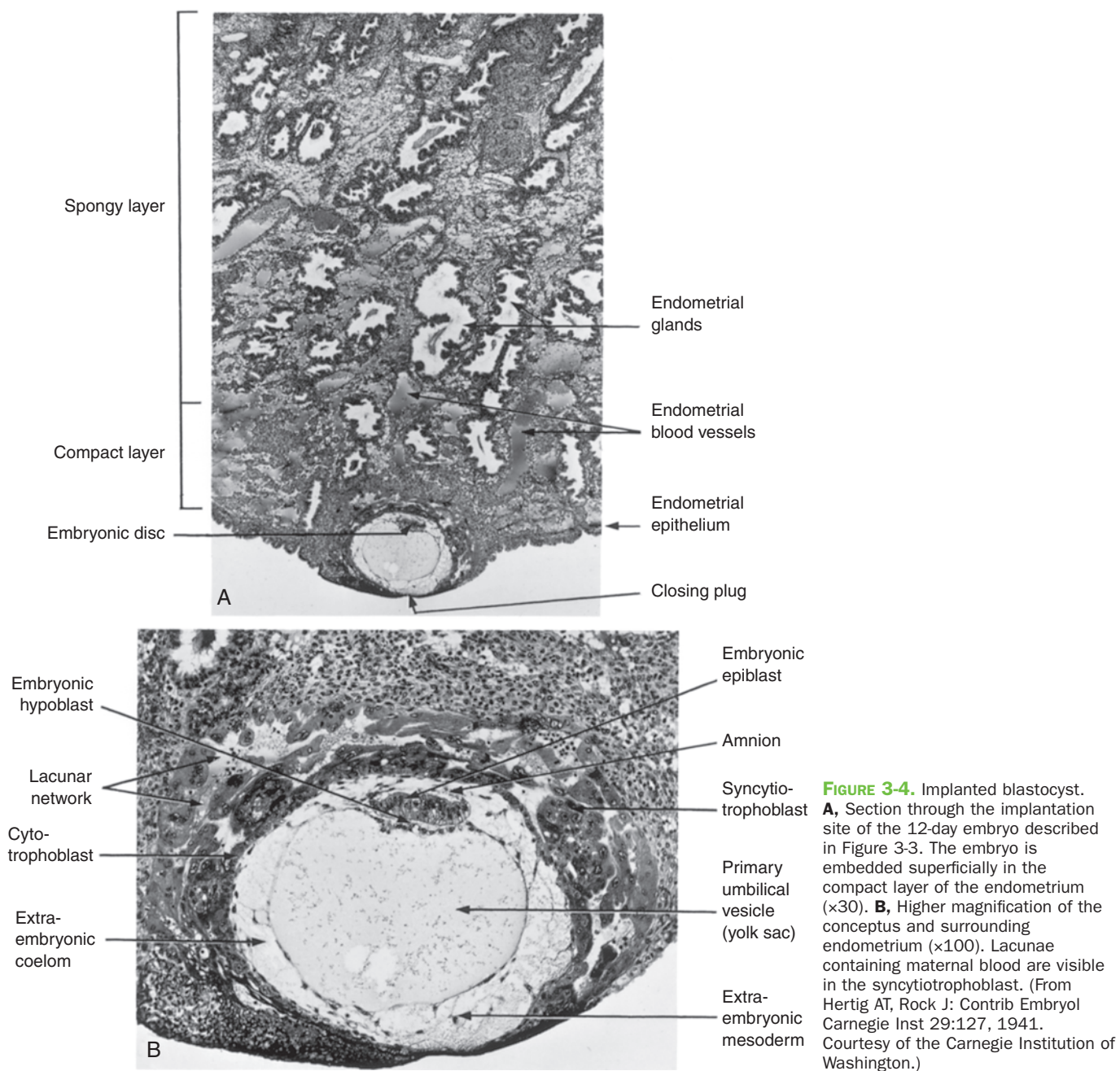
Implantation of blastocysts usually occurs in the endometrium of the uterus, superior in the body of the uterus, slightly more often on the posterior than on the anterior wall. Implantation of a blastocyst can be detected by ultrasonography and highly sensitive radioimmunoassays of hCG as early as the end of the second week.

EXTRAUTERINE IMPLANTATION

Blastocysts may implant outside the uterus. These implantations result in **ectopic pregnancies**; 95% to 98% of ectopic implantations occur in the uterine tubes, *most often in the ampulla and isthmus* (Figs. 3-10 to 3-12). The incidence of ectopic pregnancy has increased in most countries, ranging from 1 in 80 to 1 in 250 pregnancies, depending on the socioeconomic level of the population. In the United States, the frequency of ectopic pregnancy is approximately 2% of all pregnancies, and it is the main cause of maternal deaths during the first trimester.

A woman with a **tubal pregnancy** has signs and symptoms of pregnancy (e.g., misses her menstrual period). She may also experience abdominal pain

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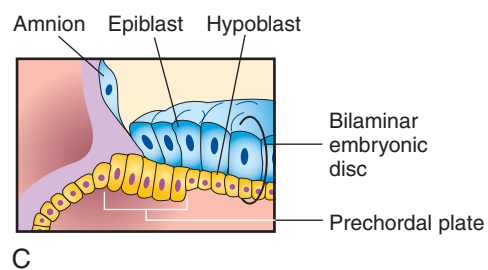
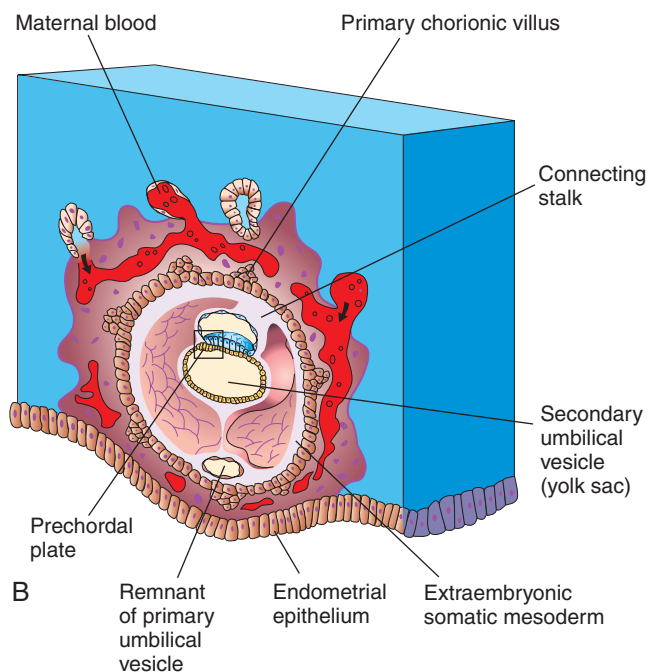
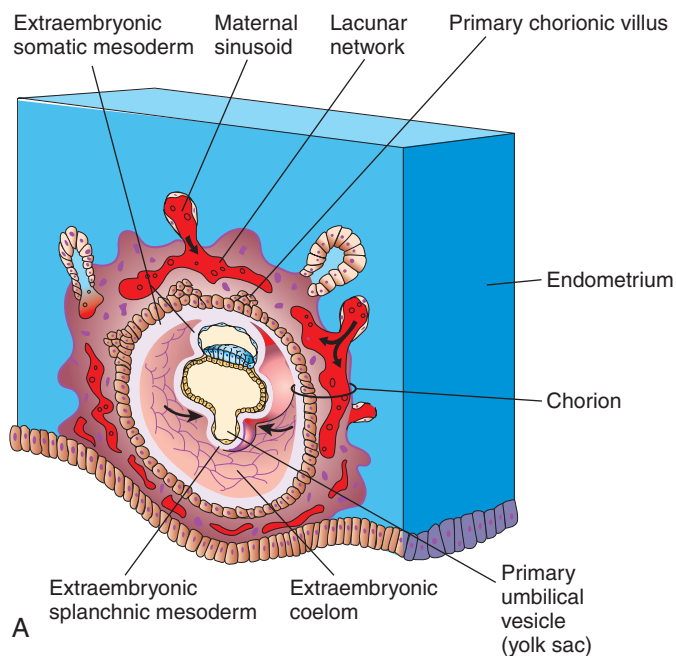
and tenderness because of distention of the uterine tube, abnormal bleeding, and irritation of the pelvic peritoneum (peritonitis). The pain may be confused with *appendicitis* if the pregnancy is in the right uterine tube. Ectopic pregnancies produce β -human chorionic gonadotropin at a slower rate than normal pregnancies; consequently β -human chorionic gonadotropin assays may give false-negative results if performed too early. *Transvaginal ultrasonography is very helpful in the early detection of ectopic tubal pregnancies.*

There are several causes of tubal pregnancy, but they are often related to factors that delay or prevent

transport of the cleaving zygote to the uterus, for example, by mucosal adhesions in the uterine tube or from blockage of it that is caused by scarring resulting from *pelvic inflammatory disease*. Ectopic tubal pregnancies usually result in rupture of the uterine tube and hemorrhage into the peritoneal cavity during the first 8 weeks, followed by death of the embryo. Tubal rupture and hemorrhage constitute a threat to the mother's life. The affected tube and conceptus are usually surgically removed (see Fig. 3-12).

When blastocysts implant in the isthmus of the uterine tube (see Fig. 3-11D), the tube tends to

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rupture early because this narrow part of the tube is relatively unexpandable, and often with extensive bleeding, probably because of the rich anastomoses between ovarian and uterine vessels in this area. When blastocysts implant in the uterine (intramural) part of the tube (see Fig. 3-11E), they may develop beyond 8 weeks before expulsion occurs. When a uterine tubal pregnancy ruptures, it usually bleeds profusely.

Blastocysts that implant in the ampulla or on fimbriae of the uterine tube may be expelled into the peritoneal cavity where they commonly implant in the rectouterine pouch. In exceptional cases, an **abdominal pregnancy** may continue to full term and the fetus may be delivered alive through an abdominal incision. Usually, however, the placenta attaches to abdominal organs (Fig. 3-11G) and causes considerable intraperitoneal bleeding. Abdominal pregnancy increases the risk of maternal death from hemorrhage by a factor of 90 when compared with intrauterine pregnancy, and seven times more than that for tubal pregnancy. In very unusual cases, an abdominal conceptus dies and is not detected; the fetus becomes calcified, forming a “stone fetus”—*lithopedion* (Greek, *lithos*, stone, + *paidion*, child).

Simultaneous intrauterine and extrauterine pregnancies are unusual, occurring approximately 1 in 7000. The ectopic pregnancy is masked initially by the presence of the uterine pregnancy. Usually the ectopic pregnancy can be terminated by surgical removal of the involved uterine tube without interfering with the intrauterine pregnancy (see Fig. 3-12). *Cervical implantations are unusual* (see Fig. 3-11); in some cases, the placenta becomes firmly attached to fibrous and muscular tissues of the cervix, often resulting in bleeding and requiring subsequent surgical intervention, such as *hysterectomy* (excision of uterus).

FIGURE 3-5. Drawings of sections through implanted human embryos, based mainly on Hertig and colleagues (1956). Observe that (1) the defect in the endometrial epithelium has disappeared; (2) a small secondary umbilical vesicle has formed; (3) a large cavity, the extraembryonic coelom, now surrounds the umbilical vesicle and amnion, except where the amnion is attached to the chorion by the connecting stalk; and (4) the extraembryonic coelom splits the extraembryonic mesoderm into two layers: extraembryonic somatic mesoderm lining the trophoblast and covering the amnion and the extraembryonic splanchnic mesoderm around the umbilical vesicle. **A**, At 13 days, illustrating the decrease in relative size of the primary umbilical vesicle and the early appearance of primary chorionic villi. **B**, At 14 days, showing the newly formed secondary umbilical vesicle and the location of the prechordal plate in its roof. **C**, Detail of the prechordal plate outlined in **B**.

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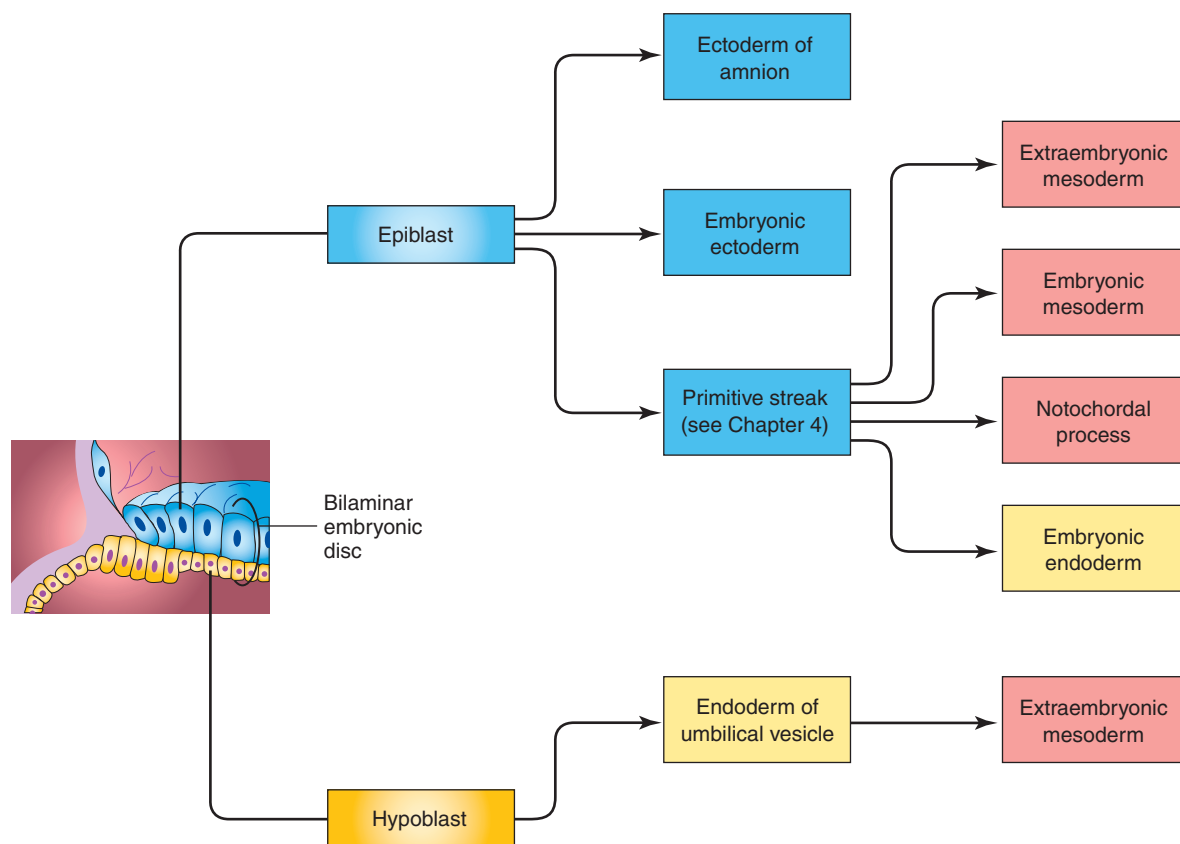


FIGURE 3-6. Origin of embryonic tissues. The colors in the boxes are used in drawings of sections of conceptuses.

SUMMARY OF IMPLANTATION

Implantation of the blastocyst begins at the end of the first week and is completed by the end of the second week. The cellular and molecular events relating to implantation are complex. It involves a receptive endometrium and hormonal factors, such as estrogen, progesterone, prolactin, as well as cell adhesion molecules, growth factors, and HOX genes. Implantation may be summarized as follows:

- The zona pellucida degenerates (*day 5*). Its disappearance results from enlargement of the blastocyst and degeneration caused by enzymatic lysis. The lytic enzymes are released from the acrosomes of the sperms that surround and partially penetrate the zona pellucida.
- The blastocyst adheres to the endometrial epithelium (*day 6*).
- The trophoblast differentiates into two layers: the syncytiotrophoblast and cytotrophoblast (*day 7*).
- The syncytiotrophoblast erodes endometrial tissues, and the blastocyst starts to embed in the endometrium (*day 8*).
- Blood-filled lacunae appear in the syncytiotrophoblast (*day 9*).
- The blastocyst sinks beneath the endometrial epithelium, and the defect is filled by a closing plug (*day 10*).

- Lacunar networks form by fusion of adjacent lacunae (*days 10 and 11*).
- The syncytiotrophoblast erodes endometrial blood vessels, allowing maternal blood to seep in and out of lacunar networks, thereby establishing a uteroplacental circulation (*days 11 and 12*).
- The defect in the endometrial epithelium is repaired (*days 12 and 13*).
- Primary chorionic villi develop (*days 13 and 14*).

PLACENTA PREVIA

Implantation of a blastocyst in the inferior segment of the uterus near the internal os results in placenta previa, a placenta that partially or completely covers the os (see Fig. 3-11). Placenta previa may cause bleeding because of premature separation of the placenta during pregnancy or at delivery of the fetus (see Chapter 7).

SPONTANEOUS ABORTION OF EMBRYOS

Most spontaneous abortions of embryos occur during the first 3 weeks. *Sporadic and recurrent*

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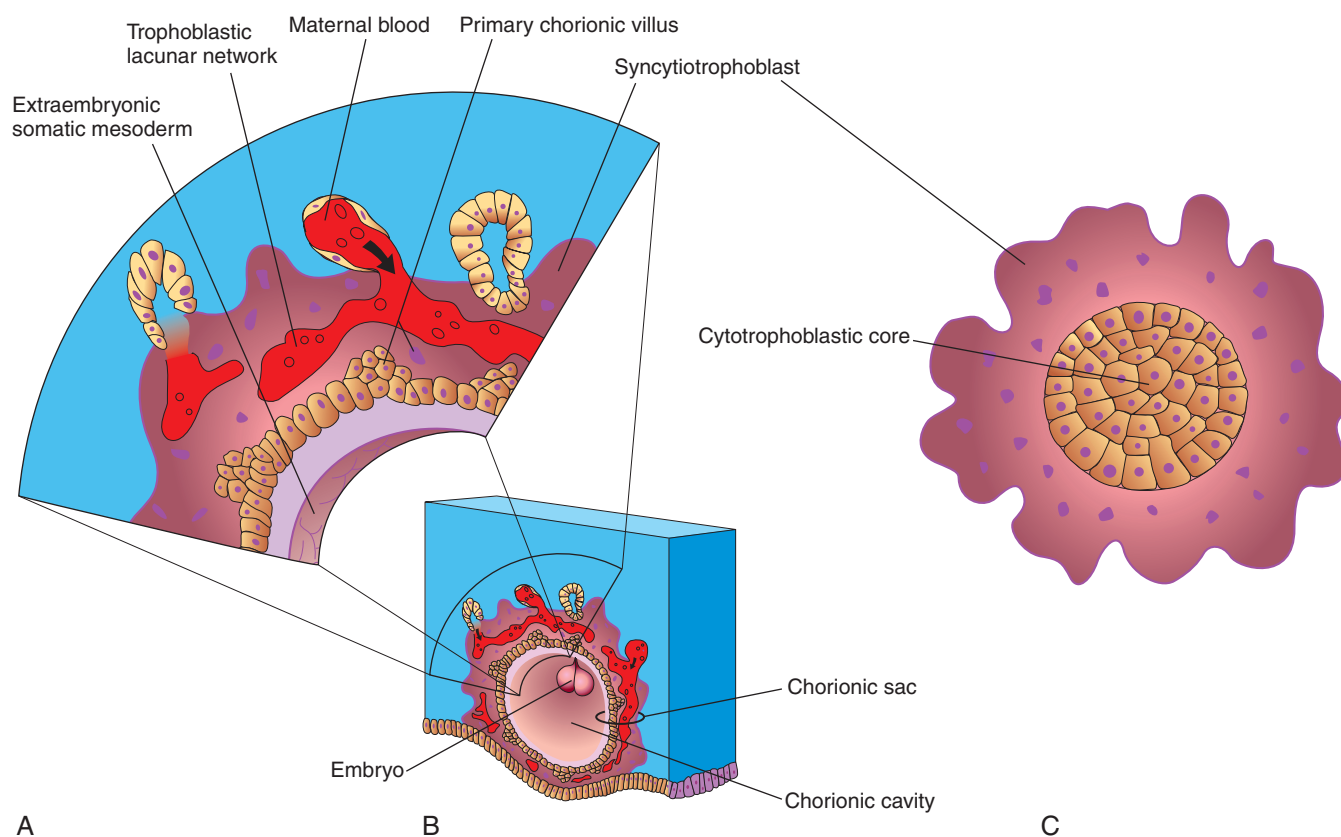


FIGURE 3-7. **A**, Detail of the section (outlined in **B**) of the wall of the chorionic sac. **B**, Sketch of a 14-day conceptus illustrating the chorionic sac and the shaggy appearance of it created by the primary chorionic villi. **C**, Drawing of a transverse section through a primary chorionic villus.

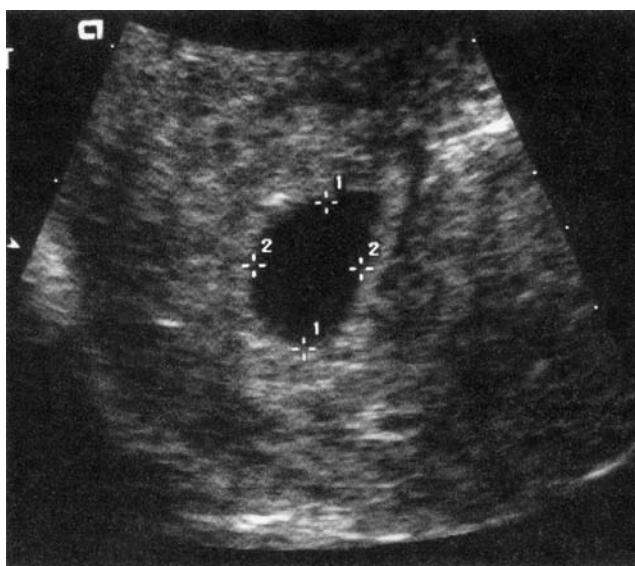
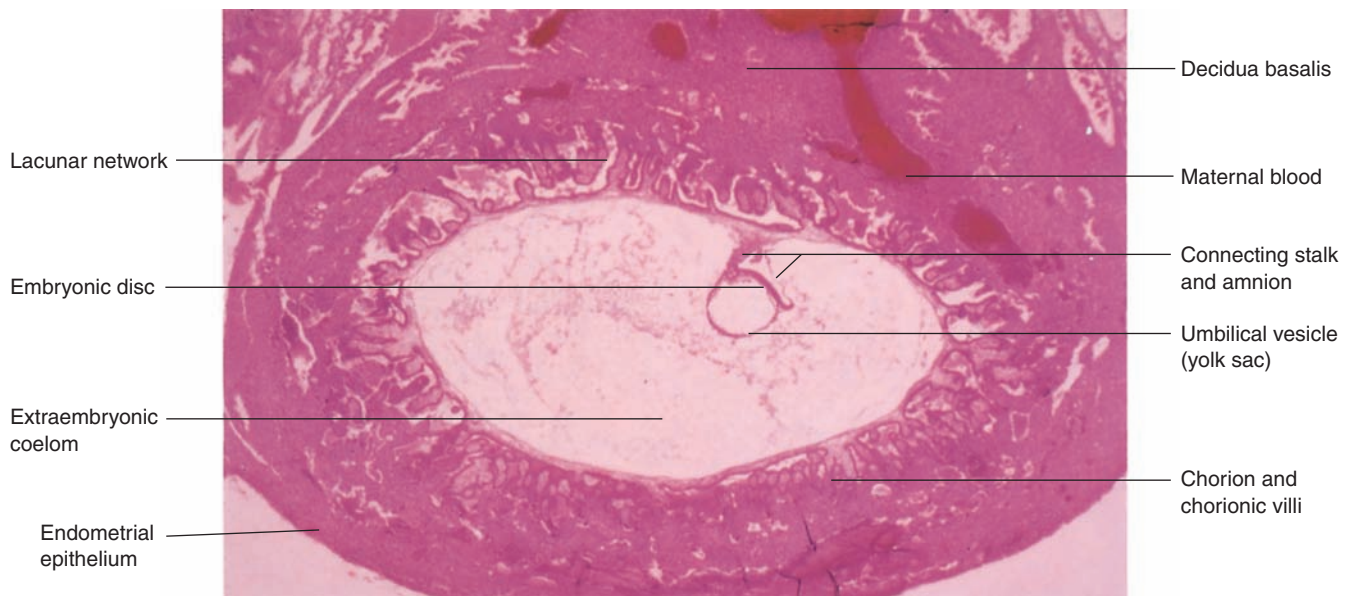


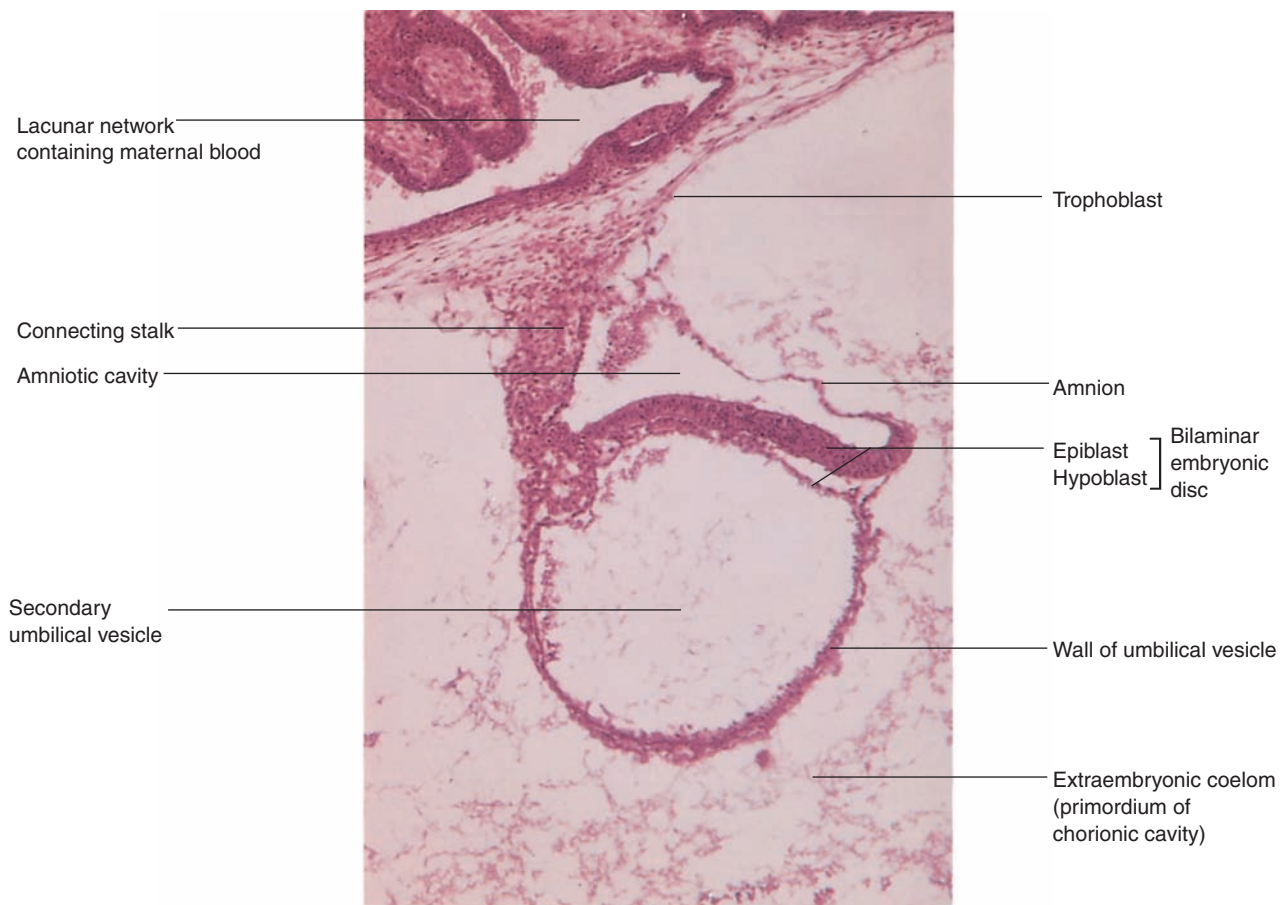
FIGURE 3-8. Endovaginal sonogram of an early chorionic (gestational) sac. The mean gestational sac diameter is determined by adding the three orthogonal dimensions (length, depth, and width) and dividing by 3. (From Laing FC, Frates MC: Ultrasound evaluation during the first trimester of pregnancy. In Callen PW [ed]: *Ultrasonography in Obstetrics and Gynecology*, 4th ed. Philadelphia, WB Saunders, 2000.)

spontaneous abortions are two of the most common gynecologic problems. The frequency of early abortions is difficult to establish because they often occur before a woman is aware that she is pregnant. An abortion occurring several days after the first missed period is very likely to be mistaken for a delayed menstruation. Detection of a conceptus in the menses (menstrual blood) is very difficult because of its small size.

Study of most early spontaneous abortions resulting from medical problems reveals abnormal conceptuses. More than 50% of all known spontaneous abortions result from chromosomal abnormalities. The higher incidence of early abortions in older women probably results from the increasing frequency of *nondisjunction* during oogenesis (see Chapter 2). It has been estimated that from 30% to 50% of all zygotes never develop into blastocysts and implant. Failure of blastocysts to implant may result from a poorly developed endometrium; however, in many cases, there are probably lethal chromosomal abnormalities in the embryo. There is a higher incidence of spontaneous abortion of fetuses with neural tube defects, cleft lip, and cleft palate.



A



B

FIGURE 3-9. Photomicrographs of longitudinal sections of an implanted embryo at Carnegie stage 6, approximately 14 days. Note the large size of the extraembryonic coelom. **A**, Low-power view (x18). **B**, High-power view (x95). The embryo is represented by the bilaminar embryonic disc composed of epiblast and hypoblast. (From Nishimura H [ed]: Atlas of Human Prenatal Histology. Tokyo, Igaku-Shoin, 1983.)

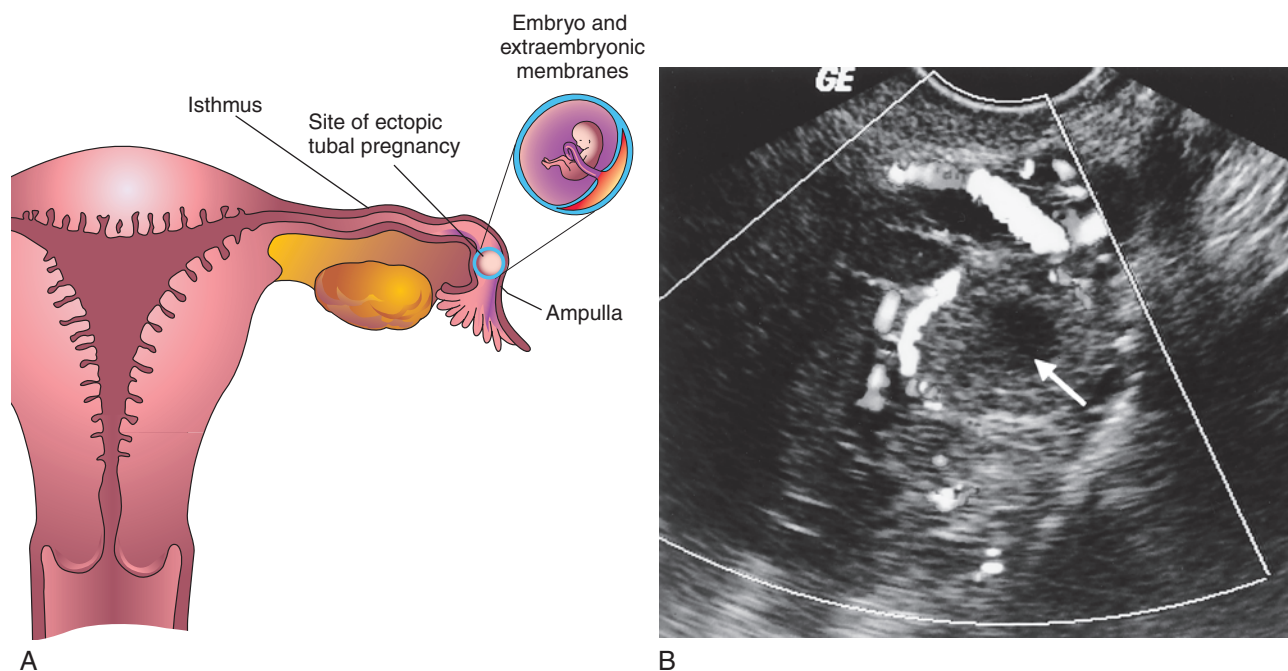


FIGURE 3-10. **A**, Frontal section of the uterus and left uterine tube, illustrating an ectopic pregnancy in the ampulla of the tube. **B**, Ectopic tubal pregnancy. This axial sonogram through the left adnexa (placenta and extraembryonic membranes) of a 6-week pregnant patient shows a small chorionic or gestational sac (arrow) in the left uterine tube with prominent vascularity in its periphery. This is characteristic of an ectopic tubal pregnancy. The incidence of tubal pregnancy ranges from 1 in 80 to 1 in 250 pregnancies. Most ectopic implantations (95% to 97%) occur in the uterine tube, usually in the isthmus or ampulla. (Courtesy of E.A. Lyons, MD, Professor of Radiology and Obstetrics and Gynecology, Health Sciences Centre, University of Manitoba, Winnipeg, Manitoba, Canada.)

INHIBITION OF IMPLANTATION

The administration of relatively large doses of progestins and/or estrogens (“morning-after pills”) for several days, beginning shortly after unprotected sexual intercourse, usually does not prevent fertilization but often prevents implantation of the blastocyst. A high dose of *diethylstilbestrol*, given daily for 5 to 6 days, may also accelerate passage of the cleaving zygote along the uterine tube. Normally, the endometrium progresses to the secretory phase of the menstrual cycle as the zygote forms, undergoes cleavage, and enters the uterus. The large amount of estrogen disturbs the normal balance between estrogen and progesterone that is necessary for preparation of the endometrium for implantation.

An intrauterine device inserted into the uterus through the vagina and cervix usually interferes with implantation by causing a local inflammatory reaction. Some intrauterine devices contain progesterone that is slowly released and interferes with the development of the endometrium so that implantation does not usually occur.

SUMMARY OF THE SECOND WEEK

- Rapid proliferation and differentiation of the trophoblast occurs as the blastocyst completes its implantation in the endometrium.
- The endometrial changes resulting from the adaptation of these tissues in preparation for implantation are known as the **decidual reaction**.
- Concurrently, the *primary umbilical vesicle* (yolk sac) forms and **extraembryonic mesoderm** develops. The extraembryonic coelom forms from spaces that develop in the extraembryonic mesoderm. The coelom later becomes the **chorionic cavity**.
- The primary umbilical vesicle becomes smaller and gradually disappears as the **secondary umbilical vesicle** develops.
- The **amniotic cavity** appears as a space between the cytotrophoblast and the embryoblast.
- The **embryoblast** differentiates into a **bilaminar embryonic disc** consisting of *epiblast*, related to the amniotic cavity, and *hypoblast*, adjacent to the blastocyst cavity.
- The **prechordal plate** develops as a localized thickening of the hypoblast, which indicates the future

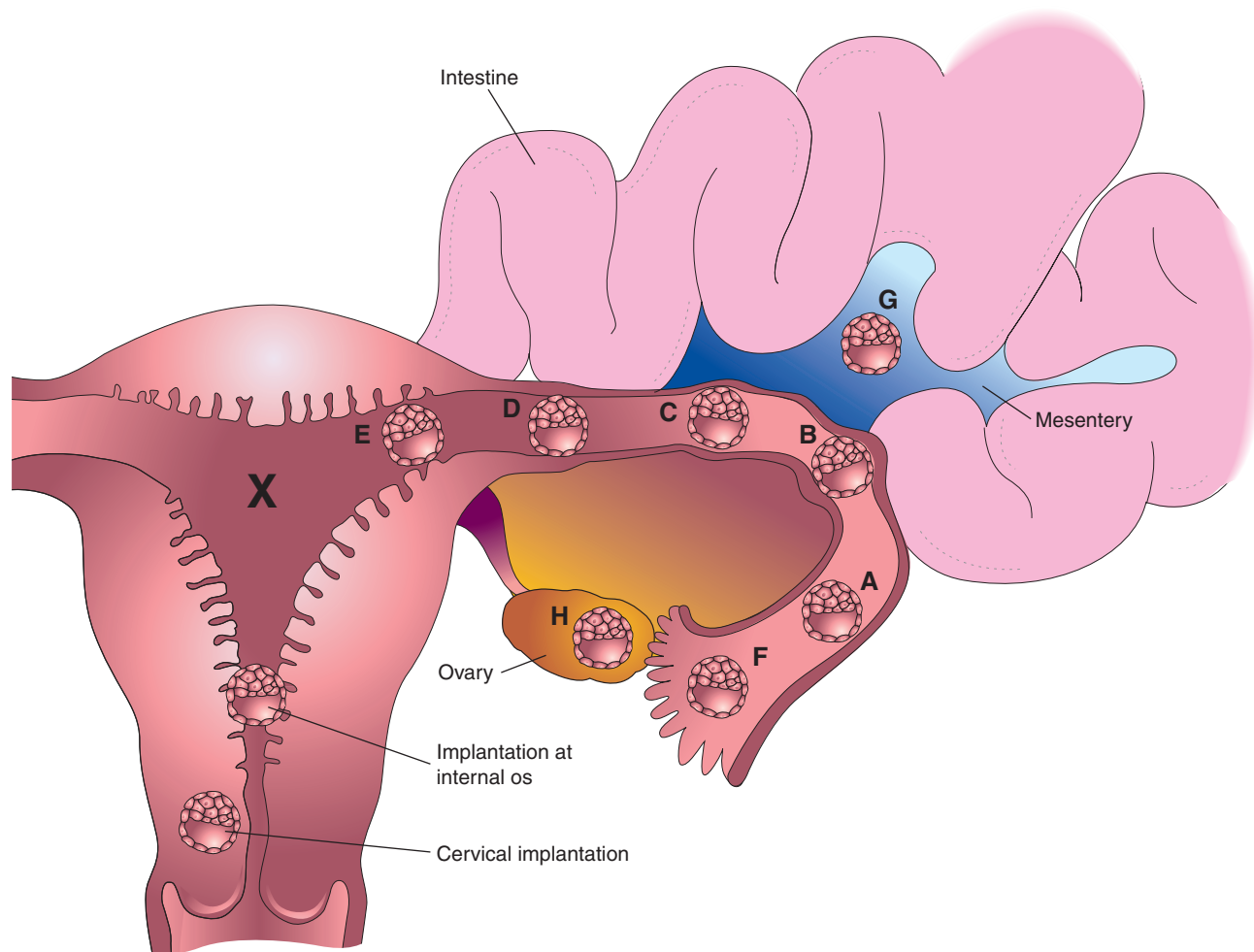


FIGURE 3-11. Implantation sites of blastocysts. The usual site in the posterior wall of the uterus is indicated by an X. The approximate order of frequency of ectopic implantations is indicated alphabetically (A, most common, H, least common). **A** to **F**, tubal pregnancies; **G**, abdominal pregnancy; **H**, ovarian pregnancy. Tubal pregnancies are the most common type of ectopic pregnancy. Although appropriately included with uterine pregnancy sites, a cervical pregnancy is often considered to be an ectopic pregnancy.

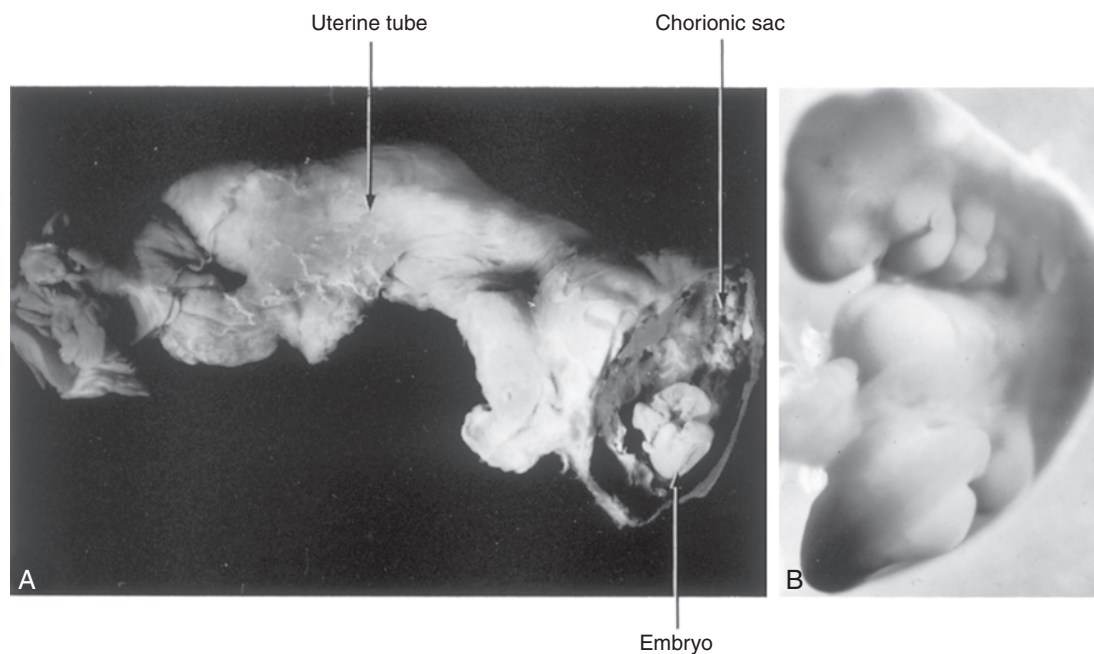


FIGURE 3-12. A tubal pregnancy. **A**, The uterine tube has been surgically removed and sectioned to show the conceptus implanted in the mucous membrane ($\times 3$). **B**, Enlarged photograph of the normal-appearing 4-week embryo ($\times 13$). (Courtesy of Professor Jean Hay [retired], Department of Anatomy and Cell Science, University of Manitoba, Winnipeg, Manitoba, Canada.)

cranial region of the embryo and the future site of the mouth; the prechordal plate is also an important organizer of the head region.

CLINICALLY ORIENTED PROBLEMS

CASE 3-1

A 22-year-old woman who complained of a severe “chest cold” was sent for a radiograph of her thorax.

- Is it advisable to examine a healthy female’s chest radiographically during the last week of her menstrual cycle?
- Are birth defects likely to develop in her conceptus if she happens to be pregnant?

CASE 3-2

A woman who was sexually assaulted during her fertile period was given large doses of estrogen twice for 1 day to interrupt a possible pregnancy.

- If fertilization had occurred, what do you think would be the mechanism of action of this hormone?
- What do lay people call this type of medical treatment? Is this what the media refer to as the “abortion pill?” If not, explain the method of action of the hormone treatment.
- How early can a pregnancy be detected?

CASE 3-3

A 23-year-old woman consulted her physician about severe right lower abdominal pain. She said that she had missed two menstrual periods. A diagnosis of ectopic pregnancy was made.

- What techniques might be used to enable this diagnosis to be made?
- What is the most likely site of the extrauterine gestation?
- How do you think the physician would likely treat the condition?

CASE 3-4

A 30-year-old woman had an appendectomy toward the end of her menstrual cycle; 8½ months later, she had a child with a congenital anomaly of the brain.

- Could the surgery have produced this child’s congenital anomaly?
- What is the basis for your views?

CASE 3-5

A 42-year-old woman finally became pregnant after many years of trying to conceive. She was concerned about the development of her baby.

- What would the physician likely tell her?
- Can women over 40 have normal babies?
- What tests and diagnostic techniques would likely be performed?

Discussion of these problems appears at the back of the book.

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