

# 3

## Pregnancy, Abortion, and Ectopic Pregnancy

Endometrial Glands and Stroma in Pregnancy . . . . .	35
Early Gestational Endometrium (1 to 3 Weeks Postfertilization) . . . . .	35
Endometrium in Later Pregnancy (4 or More Weeks Postfertilization) . . . . .	37
Arias-Stella Reaction . . . . .	39
Other Glandular Changes in Pregnancy . . . . .	41
Trophoblast and Villi . . . . .	43
Trophoblastic Cells . . . . .	44
Immunohistochemistry of Trophoblastic Cells . . . . .	46
Placental Implantation Site . . . . .	48
Exaggerated Placental Implantation Site . . . . .	53
Placental Site Nodules . . . . .	54
Chorionic Villi and Villous Trophoblast in the First Trimester . . . . .	57
Hydropic Change and Other Pathologic Changes in Abortions . . . . .	58
Chorionic Villi and Villous Trophoblast After the First Trimester . . . . .	59
Placental Polyps . . . . .	61
Placenta Accreta . . . . .	62
Endometrium Associated with Ectopic Pregnancy . . . . .	62
Clinical Queries and Reporting . . . . .	63

Recognition of the features of gestational endometrium, trophoblast, and villi, as well as the pathologic changes in chorionic tissues, is an important part of endometrial biopsy interpretation. The presence of intrauterine products of conception generally excludes the diagnosis of ectopic pregnancy and can help explain other

pathologic states such as abnormal bleeding or chronic endometritis.

An abortion before the 16th week of pregnancy is the usual source of endometrial tissue specimens that show apparent gestational changes. The different types of abortions are defined as follows. “Spontaneous abortions” are unexpected and unplanned interruptions of pregnancy that present with bleeding and passage of tissue. Approximately 15% to 20% of early pregnancies end in a spontaneous abortion.<sup>1-4</sup> In addition, many other early pregnancies spontaneously abort before pregnancy is recognized by the woman and are occult.<sup>5,6</sup> Most spontaneous abortions occur before 12 weeks of pregnancy, and at least half of these are attributable to a genetic (karyotypic) anomaly. An “incomplete abortion” is a spontaneous abortion in which the conceptus and decidua are incompletely passed, thus requiring curettage. A “missed abortion” refers to an abortion with retained products of conception but no abnormal bleeding for 5 to 8 weeks after death of the embryo or fetus. The criteria for diagnosis of a missed abortion vary among practitioners and institutions. “Therapeutic abortions” are those in which the pregnancy is electively terminated.

Besides abortions, several other complications of pregnancy, such as retained placenta or placental implantation site, ectopic pregnancy, or gestational trophoblastic disease, lead to the need for endometrial curettage (Table 3.1). Specimens from patients with these conditions show either trophoblastic tissue, the effects of trophoblastic tissue on the endometrium, or a

TABLE 3.1. Complications of pregnancy.

Spontaneous abortion
Missed abortion
Retained placental tissue/implantation site
Ectopic pregnancy
Placenta accreta, increta, and percreta
Gestational trophoblastic disease

combination of trophoblastic tissue and its effects.

This chapter first reviews the physiologic changes of the endometrium in pregnancy, especially early pregnancy. This is followed by a discussion of normal placental implantation and growth, as well as benign and pathologic trophoblast conditions. Chapter 4 reviews the closely related topic of gestational trophoblastic disease.

## Endometrial Glands and Stroma in Pregnancy

### Early Gestational Endometrium (1 to 3 Weeks Postfertilization)

Fertilization occurs in the fallopian tube soon after ovulation, and implantation (nidation) of the developing blastocyst takes place on day 20 or 21 (postovulatory day 6 or 7). Implantation occurs on the surface of the endometrium, usually on the midportion of the posterior wall. The ovulatory cycle, during which fertilization and implantation take place, is called the cycle of conception. Immediately after implantation, subtle changes begin to appear in the glands and stroma, although the tissue retains the overall characteristics of the mid- to late secretory phase for several days. An endometrial biopsy or curettage performed inadvertently at this time, usually during infertility evaluation, may not include trophoblast or disrupt the early gestation, yet will show very early pregnancy-related changes. These changes include recrudescence or accentuation of glandular secretions, distension of the glands, edema, and an extensive predecidual reaction.<sup>7-10</sup> The coiled glands show secretory activity and a serrated lumen, but they appear distended or wider than those in the late secretory phase of a menstrual cycle (Fig. 3.1). Vascular promi-

nence with engorgement and dilation of superficial veins and capillaries also occurs,<sup>8</sup> and the spiral arteries develop thicker walls.

Other reported changes in the cycle of conception include persistent basal cytoplasmic vacuoles in late secretory phase glands,<sup>9</sup> a disparity between development of the glands and stroma,<sup>11</sup> or a histologic date earlier than the cycle date as determined by basal body temperature or luteinizing hormone (LH) surge.<sup>11-14</sup> One study reported that in the cycle of conception pronounced stromal edema and vascular engorgement of capillaries and small veins correlated better with pregnancy than did the glandular changes.<sup>7</sup> Because menstruation does not occur, there is no substantial change in the number of true granular lymphocytes at this time. Practically, however, the morphologic changes during the first 1 to 2 weeks after conception are subtle. It is difficult to decide whether the vacuolated cytoplasm within glandular epithelium reflects normal persistence of vacuoles in the late secretory phase or the changes of pregnancy. It usually is not possible to be certain of pregnancy-related changes until 2 weeks or more after conception, when decidua, as opposed to predecidua, is fully developed (see later).

Within 10 to 15 days of fertilization, the endometrium gradually begins to show more characteristic changes of pregnancy as differentiation of stromal cells into decidua progresses (Table 3.2). As compared to predecidual cells, decidual cells are larger and contain more abundant eosinophilic to amphophilic cytoplasm that may contain faint vacuoles (Figs. 3.2 and 3.3). These cells become more clearly polyhedral with well-defined cell membranes. Nuclei of the decidualized stromal cells are round to oval and uniform, with smooth outlines, finely dispersed chromatin, and indistinct nucleoli (compare with Fig. 3.15). Occasional decidualized stromal cells are binucleate. Stromal granular lymphocytes persist in early pregnancy and are clearly evident among decidual cells. The presence of granular lymphocytes may suggest a chronic inflammatory infiltrate, but the granular lymphocytes, in contrast to inflammatory cells, have characteristic lobated nuclei and plasma cells are not present.

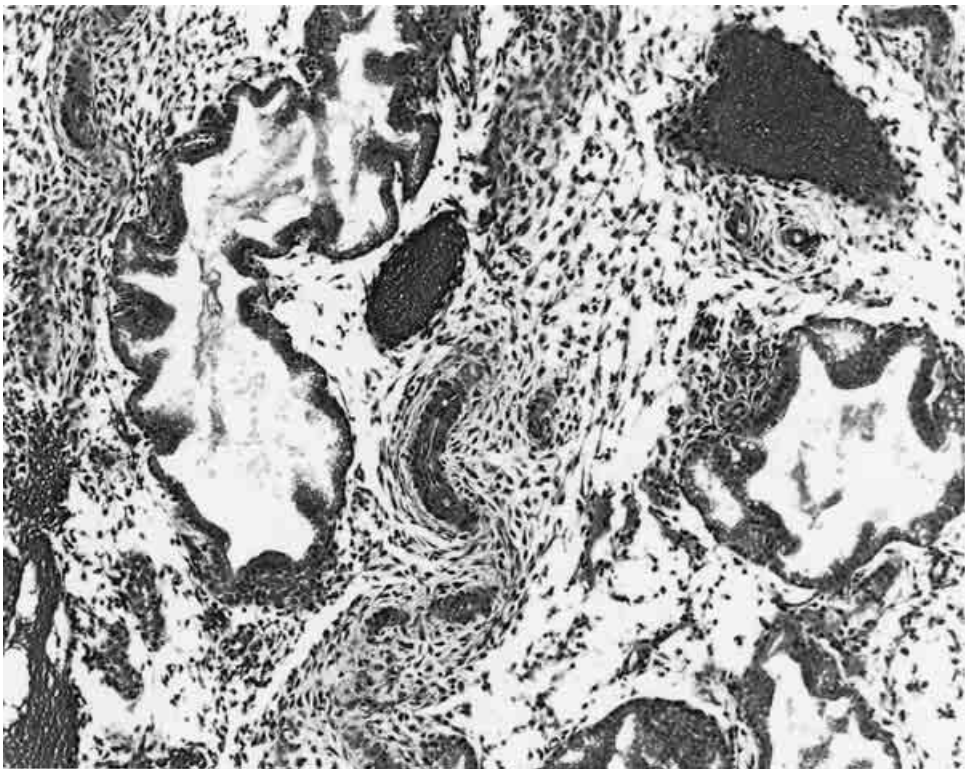


FIGURE 3.1. Early gestational endometrium, cycle of conception. Inadvertent endometrial biopsy in the cycle of conception shows distended, coiled glands and engorged vessels. Early decidual reaction is present around thickened spiral arteries. In the

absence of trophoblast or chorionic villi, these features are too subtle to be diagnostic of early pregnancy until the stroma shows more advanced decidual change.

TABLE 3.2. Histologic changes of the endometrium in pregnancy.<sup>a</sup>

Duration of pregnancy <sup>b</sup>	Stroma	Glands	Vessels
1–3 weeks	Edema, then progressive decidual change	Hypersecretory with cytoplasmic vacuoles, luminal secretions Saw-toothed, tortuous, distended Rare Arias-Stella reaction	Spiral arteries begin to thicken Superficial venules congested, dilated
4 or more weeks	Marked decidual change	Irregular with marked atrophy Variable Arias-Stella reaction, clear cytoplasm, optically clear nuclei	Spiral arteries thickened Superficial venules dilated

<sup>a</sup> Changes of endometrial glands, and stroma and vessels only.

<sup>b</sup> Duration from time of fertilization (day 15–16 of menstrual cycle). Add 2 weeks for time from last menstrual period.

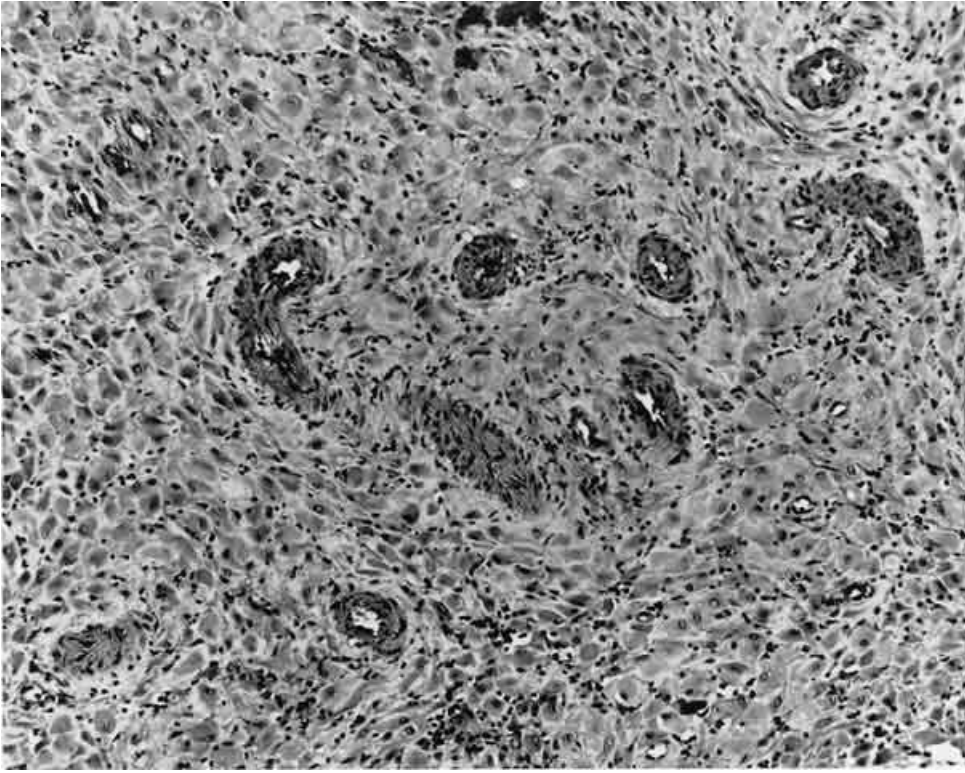


FIGURE 3.2. Early gestational endometrium with decidualized stroma. Endometrial stroma from a first-trimester abortion shows prominent decidual transformation. The decidualized cells have abun-

dant, pale cytoplasm, distinct cell borders, and uniform round to oval nuclei. Granular lymphocytes are numerous. Spiral artery walls are thicker than in nongestational endometrium.

Along with progressive decidual transformation of the stromal cells, the glands and the vessels undergo pronounced alterations. Secretory changes in the glands become more prominent with increased cytoplasmic vacuolization and augmented luminal secretions that distend the glands (Fig. 3.4). In addition to this hypersecretory activity, the glands become highly coiled with prominent serrations and papillary folds of epithelium projecting into the lumen. The epithelial cells become stratified. Concurrently, spiral arteries are more prominent (Fig. 3.2).

### Endometrium in Later Pregnancy (4 or More Weeks Postfertilization)

With advancing gestational age, pregnancy-related patterns become more pronounced and distinctive (Table 3.2). The decidualized

stromal cells are widespread and prominent, especially as the cell borders become better defined, and they develop an epithelioid appearance. Decidual cell nuclei become somewhat larger and may appear vesicular, but they maintain their uniform contours. The decidua shows small foci of physiologic necrosis during pregnancy, as it remodels during growth of the fetus and placenta and as the decidua capsularis fuses with the decidua parietalis. These small foci of necrosis, with a localized neutrophilic response, are physiologic. They do not reflect an infectious or septic process and do not indicate a significant abnormality. The decidua continues to contain a sprinkling of granular lymphocytes that remain throughout gestation. The hypersecretory pattern of the glands begins to regress early in pregnancy, and with increasing decidualization the glands become atrophic (Fig. 3.5) Conversely, in areas where the glands



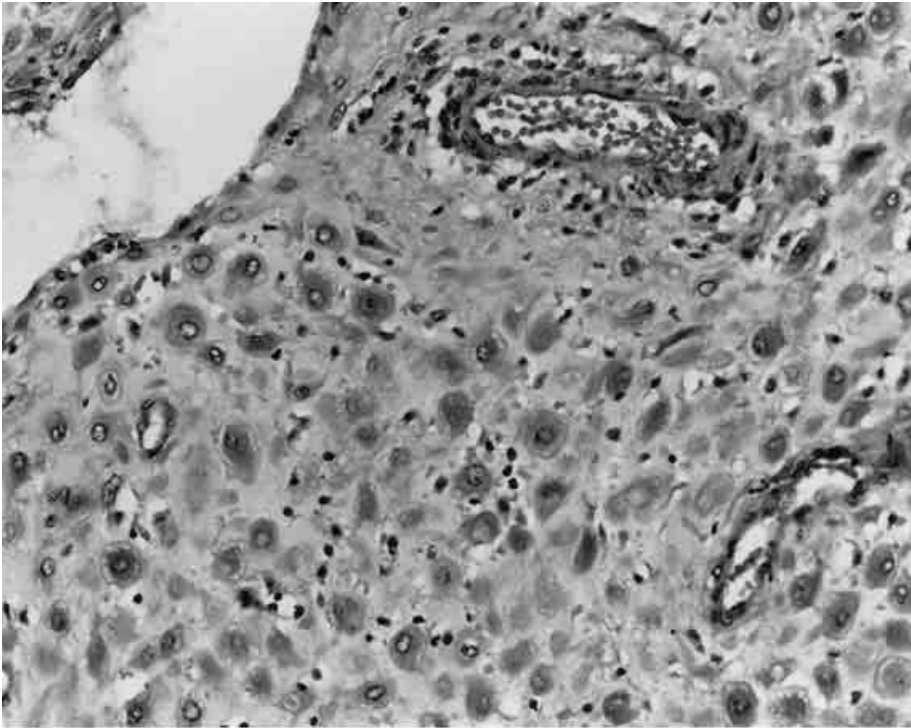


FIGURE 3.3. Decidualized stroma. Decidual cells have prominent cell borders and uniform, round to oval nuclei. Their cytoplasm has small vacuoles. A portion of an atrophic gland is present in the left upper corner.

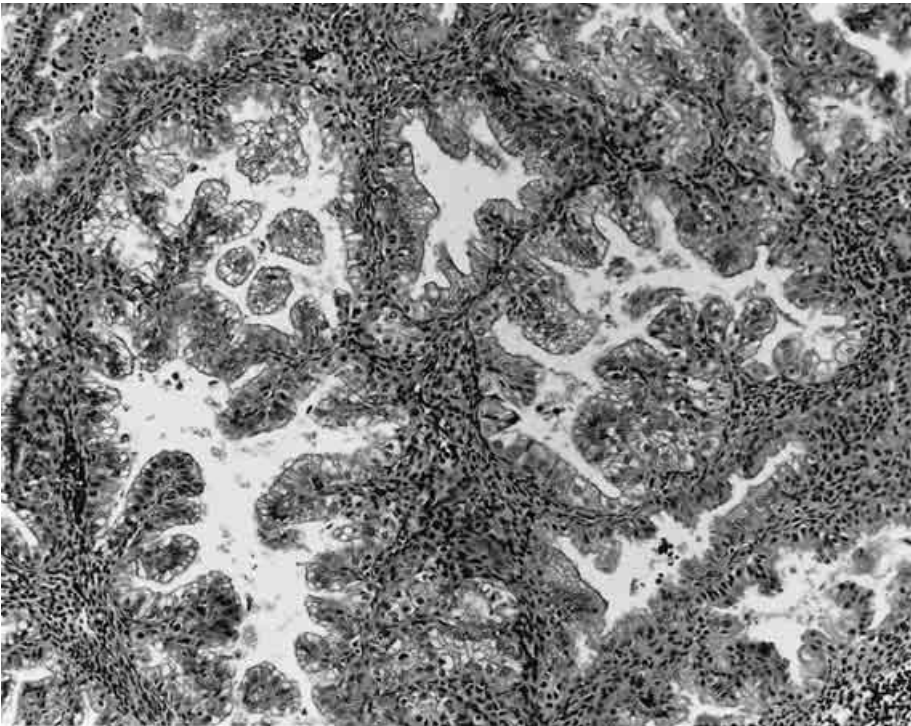


FIGURE 3.4. Gestational endometrium. Hypersecretory pattern of endometrial glands in early pregnancy with extensive cytoplasmic vacuolization. Decidualized stroma was present in other areas of the sections.

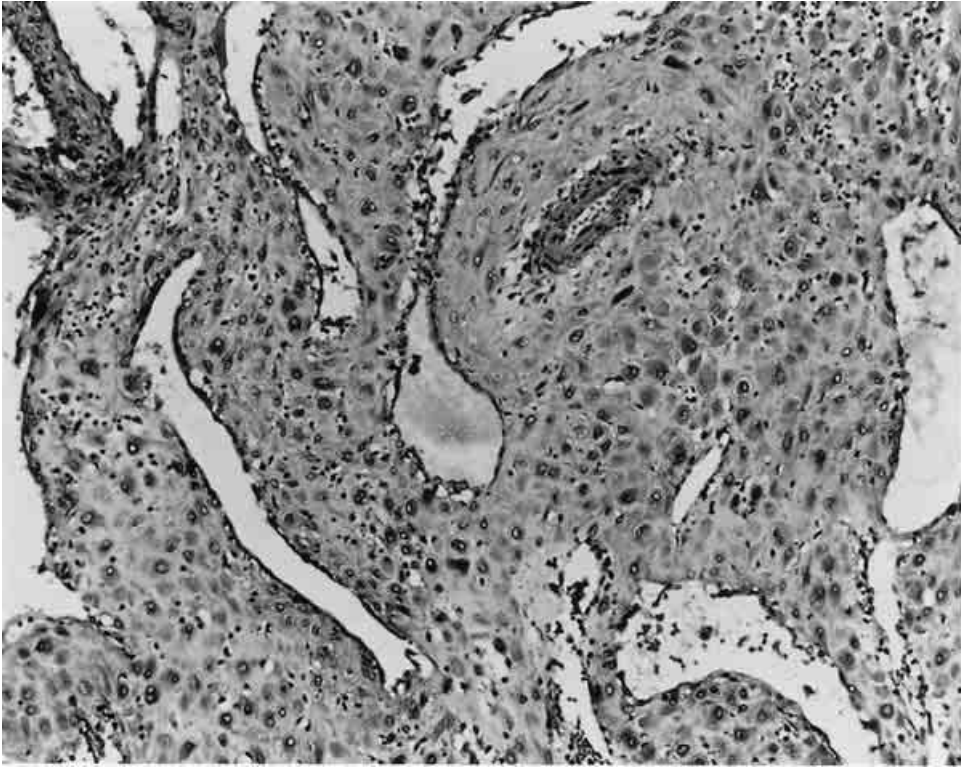


FIGURE 3.5. Gestational endometrium. Endometrium from spontaneous abortion shows diffuse decidual reaction of stroma. The glands are dilated

and lined by atrophic, indistinct epithelial cells. Therapy with high-dose progestins could induce a similar pattern.

appear hypersecretory, the stroma often is not decidualized (Fig. 3.4). Usually a mixture of hypersecretory and atrophic glands is present. By the end of the first trimester, the glands for the most part are atrophic and have lost their luminal secretions. In fact, as they form irregular, dilated spaces with indistinct epithelium, they may be difficult to distinguish from vascular channels.

As pregnancy advances, the spiral arteries maintain thick walls, a feature that persists to term and is helpful in recognizing gestational changes. Some authors suggest that in the first trimester the arteries develop a characteristic atherosclerosis-like change when an intrauterine pregnancy is present, characterized by subintimal proliferation of myofibroblasts with foam cells.<sup>15</sup> In addition, the venules beneath the surface epithelium dilate. Dilated superficial venules are not a specific change of preg-

nancy, however, as they may also be observed as a result of progestin stimulation, hyperplasia, and occasionally in polyps when the endometrium grows but does not undergo cyclical shedding.

### Arias–Stella Reaction

At 4 to 8 weeks after blastocyst implantation, the endometrium often shows at least a focal Arias–Stella reaction in the glands.<sup>16–20</sup> This glandular change is a physiologic response to the presence of chorionic tissue either in the uterus or at an ectopic site. The morphologic features of the Arias–Stella reaction include nuclear enlargement up to three times normal size and nuclear hyperchromasia, often accompanied by abundant vacuolated cytoplasm (Figs. 3.6 and 3.7). The cells typically are stratified and the nuclei hobnail-shaped, bulging



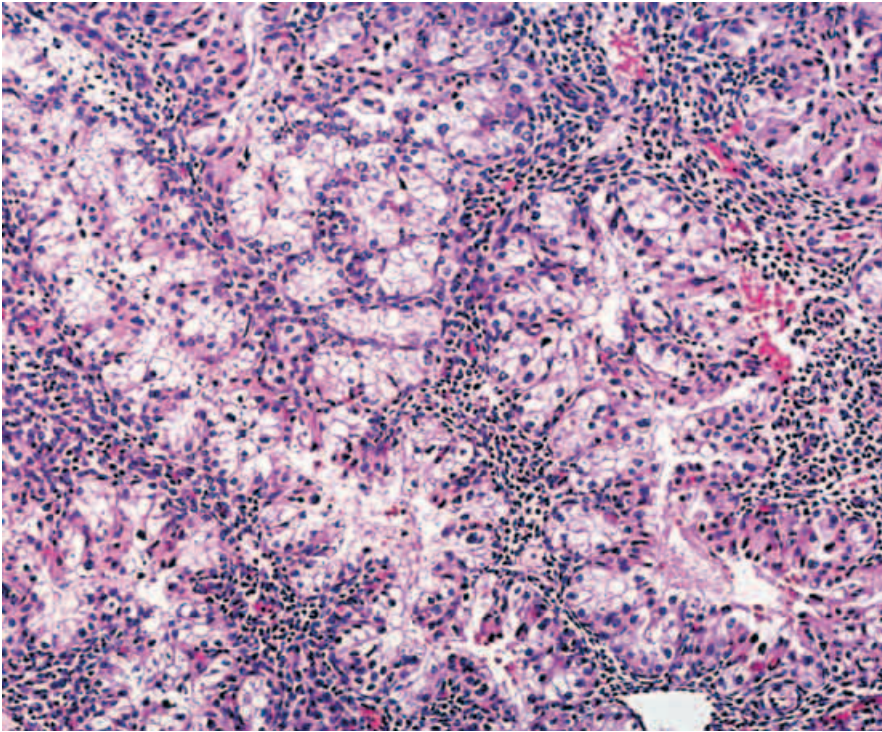


FIGURE 3.6. Arias-Stella reaction. Glands from an abortion specimen show prominent Arias-Stella reaction with hyperchromatic nuclei that bulge into

the glandular lumen. The glands also show marked cytoplasmic vacuolization. Identical changes can be seen in an ectopic pregnancy.

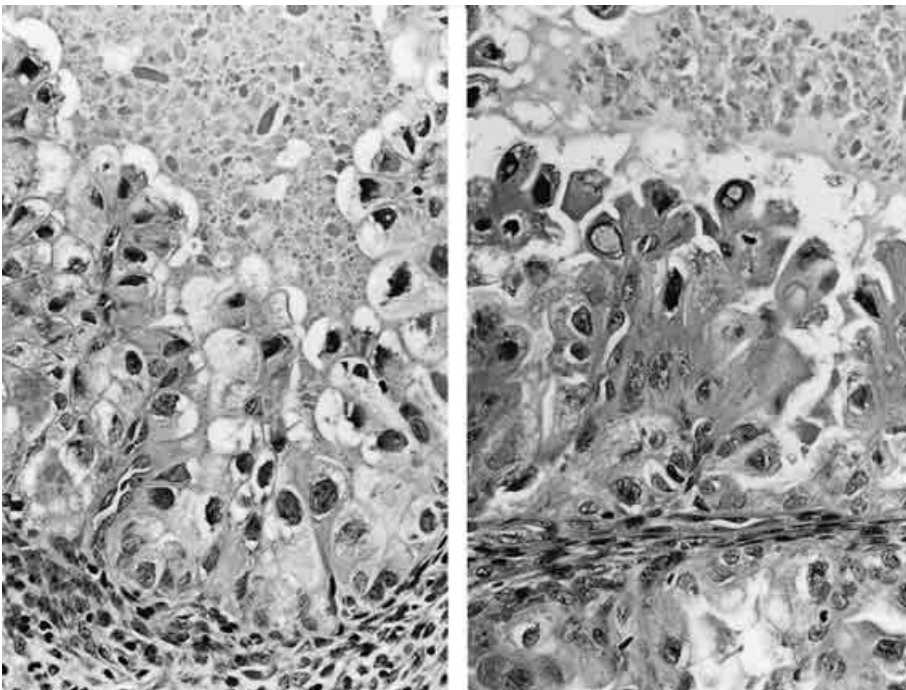


FIGURE 3.7. Arias-Stella reaction. *Left.* Arias-Stella reaction with a “hypersecretory” pattern shows stratified nuclei and vacuolated cytoplasm. *Right.* Arias-

Stella reaction with “regenerative” pattern shows hobnail cells with dense cytoplasm. Several nuclei show prominent cytoplasmic invaginations.

into the gland lumen. These large nuclei may contain prominent cytoplasmic invaginations.<sup>21</sup> Mitotic figures are rarely present, and Ki-67 immunostains demonstrate a very low proliferative index. This process may be extensive, involving many glands, or the reaction can be focal, involving only a few glands (Fig. 3.8). The change can even be limited to part of a gland, leaving the remaining nuclei unaffected.

The Arias-Stella reaction has two histologic patterns (Fig. 3.7).<sup>18</sup> One is a “hypersecretory” change characterized by highly convoluted glands lined by cells with stratified nuclei and abundant clear to foamy cytoplasm. The other pattern has been termed “regenerative,” although this hypothesized etiology for the change remains unsubstantiated. This pattern is characterized by glands lined by enlarged hobnail cells with little cytoplasmic secretory activity. In fact, the two patterns are not very distinct and there is frequent overlap between them.

The degree and extent of the Arias-Stella reaction are highly variable in normal and abnormal intrauterine gestation, in ectopic pregnancy, and in gestational trophoblastic disease.<sup>18;22–25</sup> This change occurs as early as 4 days after implantation,<sup>17</sup> although it generally is seen after about 14 days.<sup>18</sup> The Arias-Stella reaction persists up to at least 8 weeks following delivery. There is no apparent relationship between the presence and extent of the Arias-Stella reaction and the status of the fetus. The Arias-Stella reaction is almost unique to pregnancy or gestational trophoblastic disease. Similar phenomena are rarely produced by administration of exogenous progestins.<sup>26</sup>

### Other Glandular Changes in Pregnancy

Besides the Arias-Stella reaction, the endometrial gland cells may undergo other specific

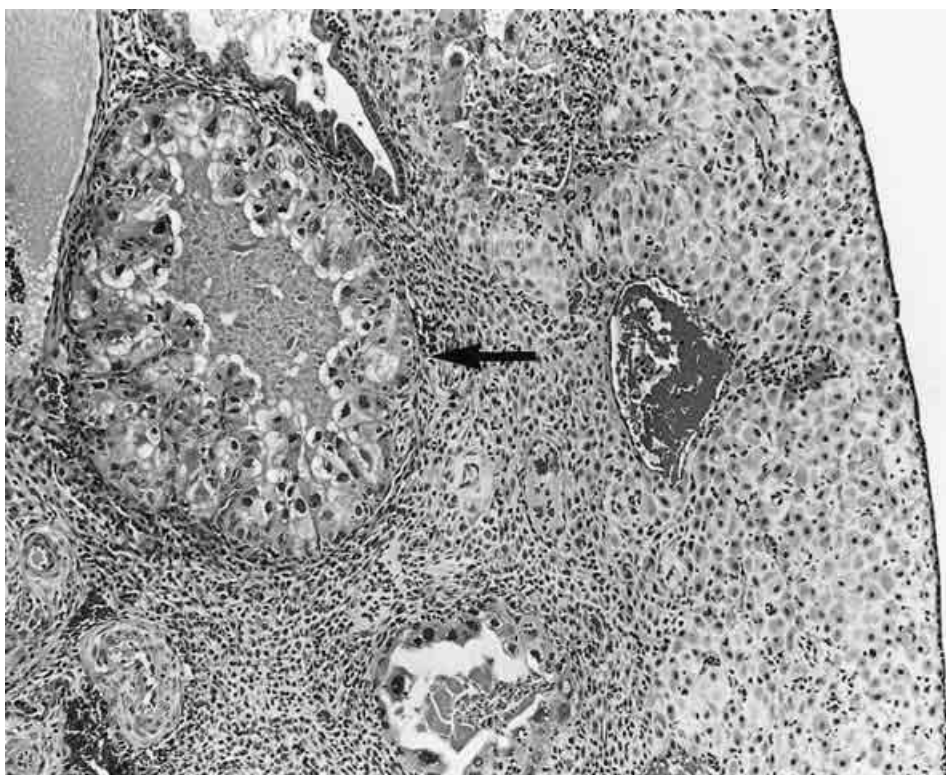


FIGURE 3.8. Gestational endometrium with Arias-Stella reaction. A dilated gland in decidualized stroma shows Arias-Stella reaction with stratified, enlarged, and hyperchromatic nuclei (arrow). A

gland in the upper portion of the field does not show Arias-Stella change. A dilated venule is present beneath surface epithelium on the right.



changes in the presence of trophoblastic tissue. One such change is abundant clear cytoplasm.<sup>16</sup> This phenomenon overlaps with the Arias–Stella reaction yet does not show the nuclear enlargement of the latter. With this change the gland cells accumulate abundant amounts of clear, glycogen-rich cytoplasm (Fig. 3.9). The nuclei in areas of clear cell change can become stratified, which, combined with the abundant clear cytoplasm, can result in apparent obliteration of the gland lumens.

Another pregnancy-related change is optically clear nuclei of gland cells (Fig. 3.10).<sup>27,28</sup> This alteration is also often associated with the Arias–Stella reaction but can occur independently. Optically clear nuclei usually are focal. They have a clear to glassy appearance that is caused by accumulation of a filamentous material in the nuclei. A recent study indicates that the change is related to the intranuclear accu-

mulation of biotin.<sup>27</sup> Clear nuclei can mimic the changes seen in herpesvirus infection, although the optically clear nuclei associated with pregnancy lack the Cowdry type A eosinophilic nuclear inclusions, nuclear molding, and associated necrosis seen in the virus infection. This alteration is infrequent, occurring in fewer than 10% of first-trimester abortion specimens. These changes may persist until term, however. As in the Arias–Stella reaction, optically clear nuclei simply reflect the presence of chorionic tissue.

Localized atypical-appearing endometrial glandular proliferations rarely may be found during gestation.<sup>29</sup> These focal abnormalities show glandular expansion with nuclear stratification and cribriform change. Mitotic activity is present, but nuclear cytology is bland. Intraglandular calcifications frequently are present. The few lesions studied have been

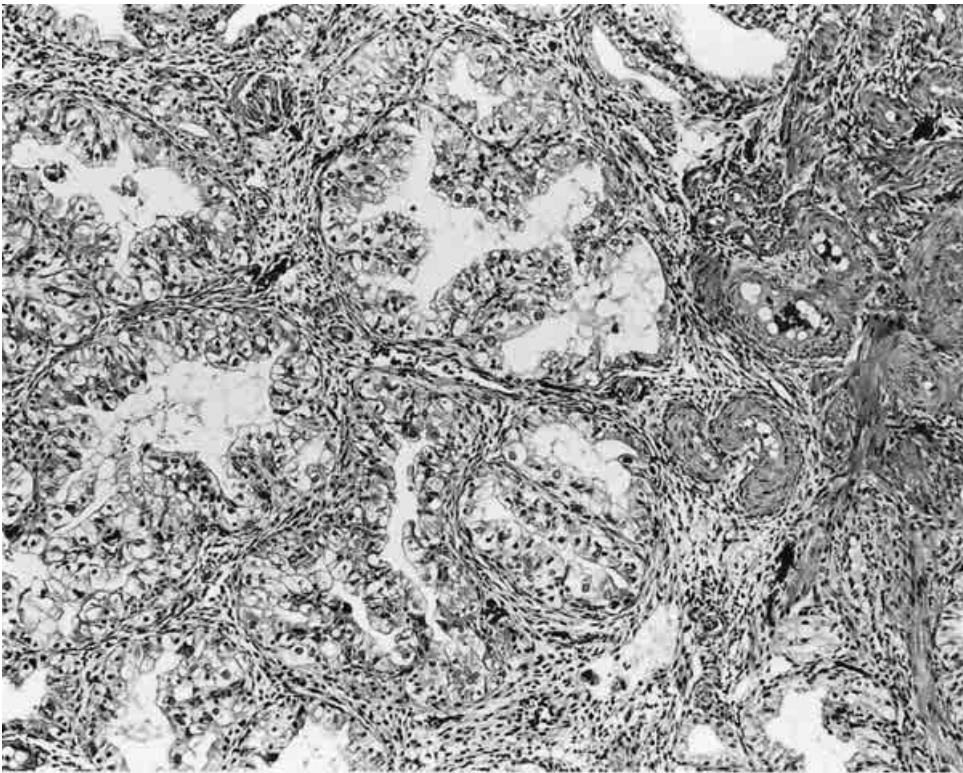


FIGURE 3.9. Gestational endometrium with clear cell change. Glands in early gestational endometrium are lined by cells with abundant clear cytoplasm. The

cells lack the nuclear enlargement of the Arias–Stella reaction.

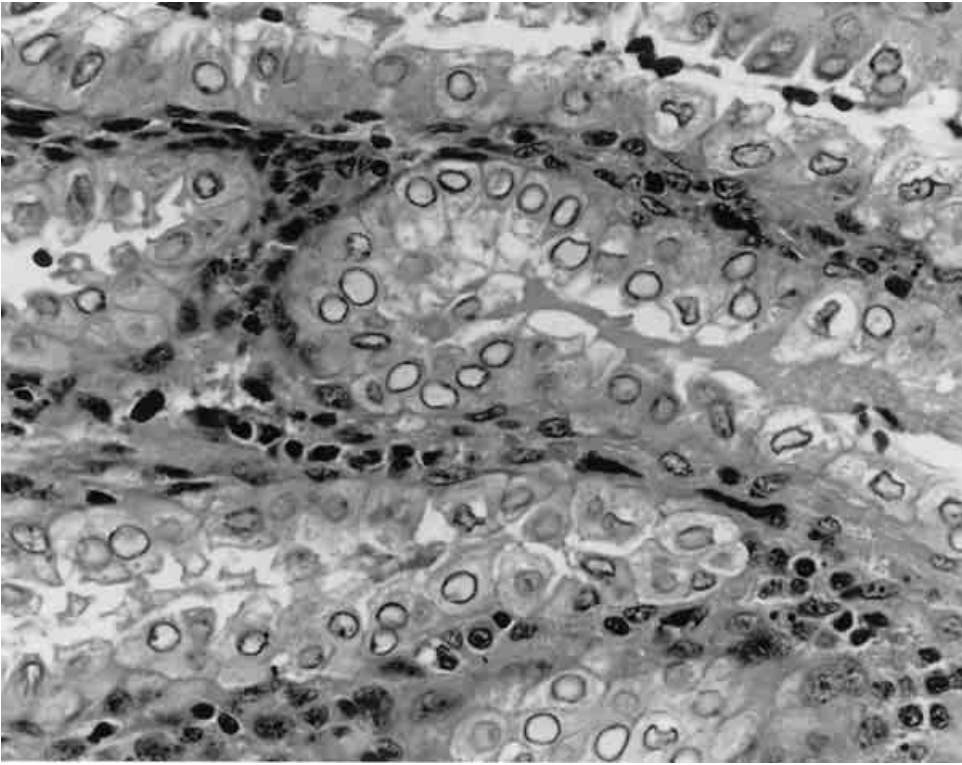


FIGURE 3.10. Gestational endometrium with optically clear nuclei. Crowded glands show prominent optically clear nuclei. This gland cell change is

infrequent and usually is focal. It may be seen throughout pregnancy, however.

benign, and some patients have had subsequent pregnancies, suggesting these proliferative foci represent another unusual gland response to a concurrent pregnancy.<sup>29</sup> Rarely, frank endometrial adenocarcinoma also may be associated with intrauterine gestation.<sup>30;31</sup>

In early pregnancy, endometrial glands become strongly immunoreactive for S-100 protein.<sup>32;33</sup> This immunoreactivity rapidly disappears after the 12th week of gestation. Normal proliferative and secretory endometrium, as well as glands in patients with hyperplasia and neoplasia, do not stain for S-100 protein. There are no other markers of the glands that are generally practical for identifying pregnancy-related changes except for the low Ki-67 index of the Arias-Stella reaction, which helps to indicate a benign glandular change.

## Trophoblast and Villi

In early pregnancy trophoblastic proliferation begins with the development of the blastocyst, the outer layer of which is termed the trophoblastic shell. Villous formation does not begin until about 7 days after implantation of the blastocyst (13 days following conception).<sup>4</sup> For morphologic identification, the products of conception are divided into three components: (1) the villi and their trophoblast ("villous" trophoblast), (2) the implantation site ("extravillous" trophoblast), and (3) fetal tissues. Usually these tissues are easy to recognize.

Identifying trophoblast and villi is essential for confirming the diagnosis of an abortion. Also, the presence of placental and fetal tissue in curettage samples, for all practical purposes, rules out an ectopic pregnancy. The morpho-

logic features of these abortion specimens can be highly varied. Occasionally the diagnostic features of the products of conception are difficult to identify, especially in early pregnancy, when the placental component is very small and often missed in small biopsy specimens, or if most of the products of conception were expelled prior to the curettage. When villi and fetal tissue are not present in curettage samples, trophoblastic cells should be searched for to confirm the diagnosis of intrauterine pregnancy. Recognizing the full morphologic spectrum of normal trophoblastic cells is important, not only for establishing the presence of an intrauterine pregnancy, but also for distinguishing exaggerated but physiologic changes from gestational trophoblastic disease.

Trophoblastic Cells

The trophoblast is extraembryonic but fetal in origin, growing in intimate association with host maternal tissues. Very early in pregnancy trophoblastic cells differentiate and invade decidua, even before villi form.<sup>4</sup> At this stage of early gestation, implanting trophoblast is the predominant component of placental tissue. The trophoblast continues to grow along this

interface of maternal and placental tissue throughout pregnancy. The decidua basalis where trophoblast interfaces with the endometrium and myometrium becomes the placental implantation site. The trophoblastic cells are the epithelial component of the placenta and are divided into three cytologically and functionally distinct populations: cytotrophoblastic (CT) cells, syncytiotrophoblastic (ST) cells, and intermediate trophoblastic (IT) cells (Table 3.3).<sup>34–38</sup> Trophoblastic cells can also be classified according to their anatomic location as “villous” and “extravillous” trophoblast.<sup>39</sup>

CT cells are the germinative cells from which other trophoblastic cells differentiate. Accordingly, they are mitotically active. They are uniform cells about the size of a decidualized stroma cell, with a single nucleus, one or two nucleoli, pale to faintly granular cytoplasm, and prominent cell borders (Fig. 3.11). ST cells, in contrast, are larger and multinucleate with dense amphophilic to basophilic cytoplasm. The nuclei of ST cells are dark and often appear pyknotic; they do not contain mitoses. The cytoplasm also typically contains small vacuoles and larger lacunae in which maternal erythrocytes can be identified. A microvillous brush border

TABLE 3.3. Morphologic and immunohistochemical features of intermediate trophoblastic cells in the first trimester.

	Villous IT	Implantation site IT	Chorionic-type IT
Morphology	Polyhedral; abundant, eosinophilic to clear cytoplasm; prominent cell borders	Pleomorphic and large; abundant, eosinophilic cytoplasm; occasional multinucleated cells	Round to polyhedral, regular abundant eosinophilic and clear cytoplasm
Immunostaining			
Cytokeratin <sup>a</sup>	++++ <sup>b</sup>	++++	++++
hCG	–	–; + in multinucleated IT	–
hPL	–/+	++++	++
Mel-CAM	–/++++ <sup>c</sup>	++++	++
PLAP	–	–	+++
EMA	–	–	+++
Inhibin-α	–	+/-	++
Ki-67 index	>90% <sup>d</sup>	0	3%–10%

hCG, Human chorionic gonadotropin; hPL, human placental lactogen; Mel-CAM, melanoma cell adhesion molecule (CD 146); EMA, epithelial membrane antigen; PLAP, placental alkaline phosphatase.

<sup>a</sup> Positive for cytokeratins 7, 8, 18, 19 and AE1/AE3; variable for cytokeratin 20; and negative for high molecular weight keratin.

<sup>b</sup> Semiquantitative scoring of proportion of cells positive.

<sup>c</sup> Mel-CAM staining increases from the base to the tip of the trophoblastic column.

<sup>d</sup> Ki-67 staining decreases from the base to the tip of the trophoblastic column.



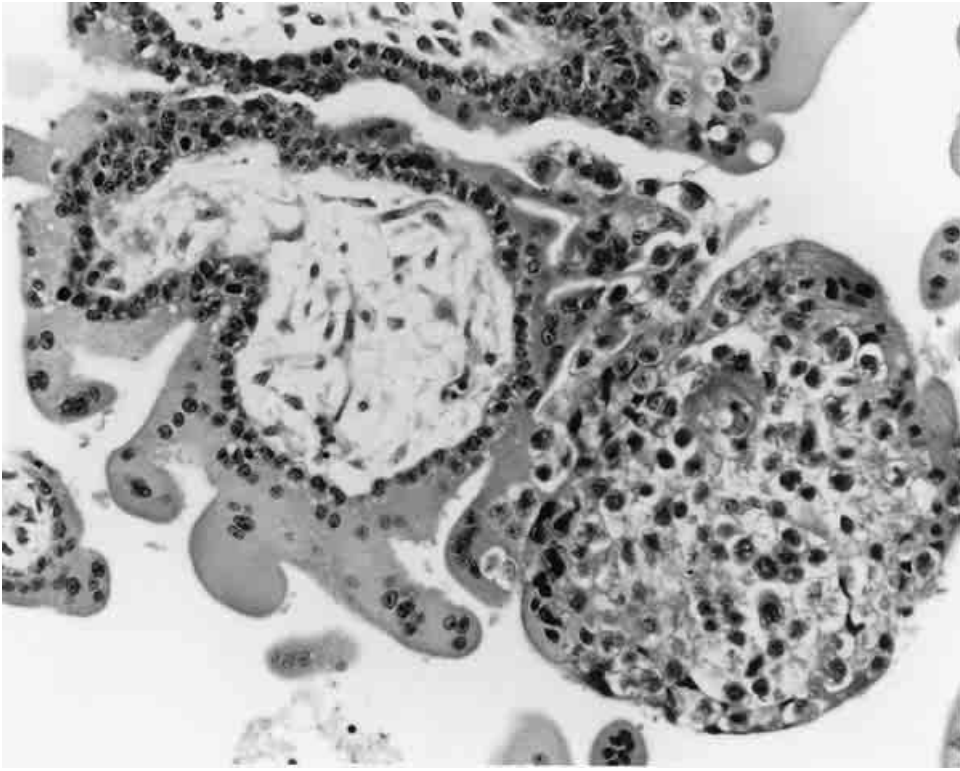


FIGURE 3.11. Immature chorionic villi with trophoblast. Syncytiotrophoblast and cytotrophoblast grow from the surface of immature first-trimester villi. The villi are lined by an inner layer of mononu-

cleated CT cells capped by ST cells. To the right of the villus a dimorphic mixture of ST and villous IT cells proliferates toward the implanting margin of the placental tissue.

sometimes lines the lacunae of the ST cells. CT and ST cells typically display a dimorphic growth pattern, with the two cell types growing in close proximity. In early abortions, the CT and ST cells are quite prominent compared with the amount of villi present. In very early, unanticipated abortions, the entire products of conception consist of previllous trophoblast that can be easily confused with choriocarcinoma (Fig. 3.12) (see Chapter 4). In curettage for suspected abortions, sometimes the only evidence of an intrauterine pregnancy is the presence of a few isolated trophoblastic cells mixed with blood, and these may be necrotic (Fig. 3.13). Careful scrutiny may be necessary to identify these diagnostic cells.

The intermediate trophoblast develops from cytotrophoblast on the villous surface, and in early pregnancy is manifested as sprouts and columns that extend to and extensively infil-

trate the underlying decidua at the implantation site (see later). In fact, the predominant location of the IT is at the implantation site, which explains why it is often called “extravillous cytotrophoblast.”<sup>39</sup> This latter term is less precise, however, as these cells also occur in association with villi (Fig. 3.11), and they are immunohistochemically and physiologically different from cytotrophoblast. Another older term for IT is “X cells.”<sup>4</sup> The IT actually represent a heterogeneous population of trophoblastic cells: the villous IT, the implantation site IT, and the chorionic-type IT.<sup>34;40</sup> The morphologic and immunohistochemical features of these IT subtypes depend on their differentiation status and their anatomic location.

The IT that extends from the trophoblastic column of the anchoring villi is designated “villous” IT.<sup>40</sup> These cells are mononucleate and

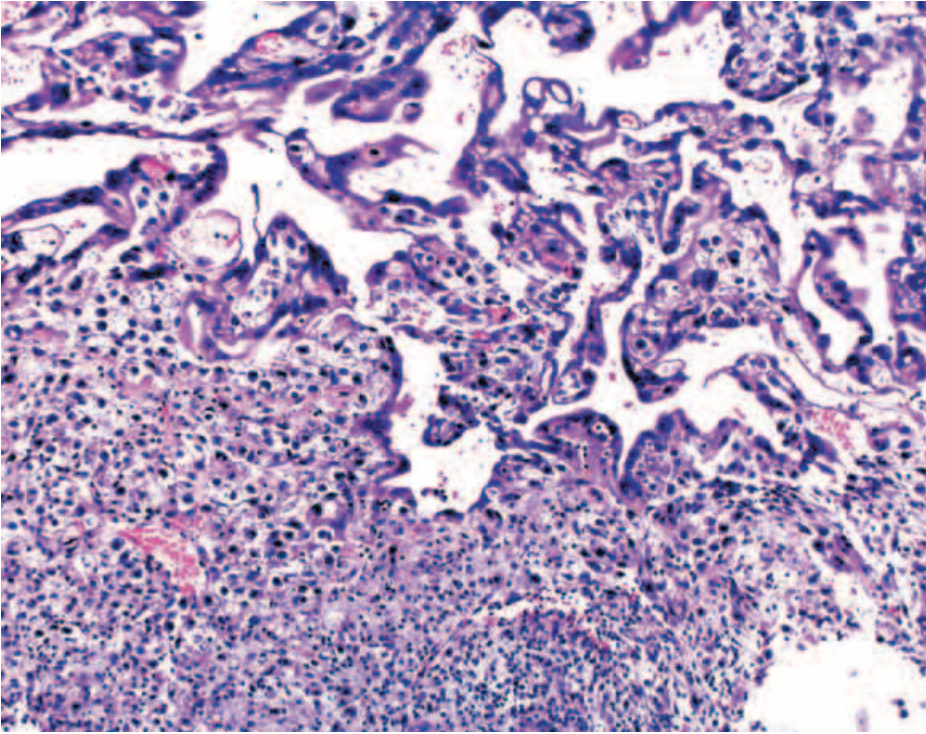


FIGURE 3.12. Trophoblast of early pregnancy. A prominent network of ST and CT encountered in inadvertent endometrial biopsy during early pregnancy. The cells with pleomorphic, hyperchromatic nuclei in the lower left part of the field are IT cells that are infiltrating the decidua. No villi are present.

Despite the biopsy, the pregnancy continued to term and uneventful delivery. In the absence of villi, this pattern resembles choriocarcinoma, and clinical history may be required to determine the significance of the finding.

larger than CT cells. They have pale cytoplasm and large, round nuclei. The implantation site IT cells infiltrate the decidua and the myometrium and have a heterogeneous appearance, as discussed in the following paragraphs. The chorionic-type IT constitute the cells of the chorion laeve where they form a cohesive layer of epithelium. These latter IT are composed of relatively uniform cells with eosinophilic to clear (glycogen-rich) cytoplasm. These cells are smaller than implantation site IT although an occasional cell is multinucleated (Table 3.3).

The villous and the implantation site IT constitute the two forms of IT usually seen in biopsy specimens from early pregnancy. The villous IT cells are readily recognized because they are associated with anchoring villi, but the implantation site IT may pose a greater chal-

lenge in recognition because the implantation site may be seen with no associated villi or the implantation site can appear prominent or “exaggerated” (see later). Implantation site IT also are the primary cell type of the placental site trophoblastic tumor discussed in Chapter 4. The chorionic-type IT constitute the cell population seen in the placental site nodule discussed later in this chapter and in the epithelioid trophoblastic tumor discussed in Chapter 4.

### Immunohistochemistry of Trophoblastic Cells

Trophoblastic cells express a number of proteins. The  $\beta$ -subunit of human chorionic gonadotropin (hCG), human placental lactogen (hPL), placental alkaline phosphatase (PLAP),

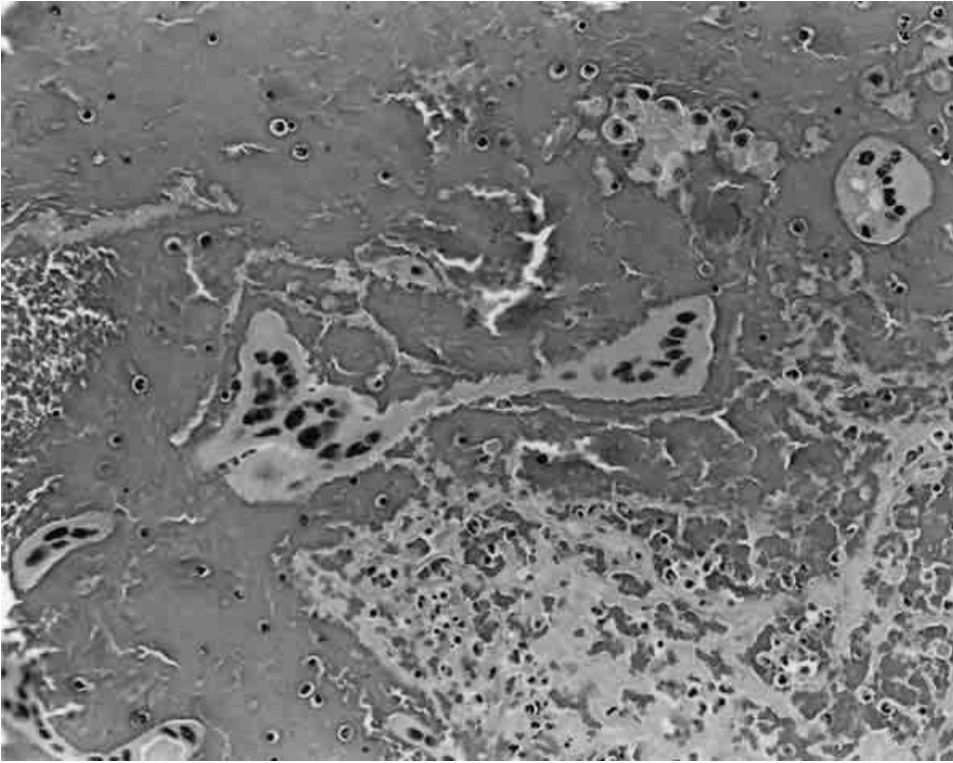


FIGURE 3.13. Isolated ST cells in abortion specimen. A few ST cells mixed with fibrin and blood are the only evidence of intrauterine pregnancy in this curet-

tage specimen from a patient with a spontaneous abortion. Isolated ST cells such as this are often found in areas of hemorrhage.

and cytokeratin all react with trophoblastic cells, but the degree of reactivity varies among the cell types. Cytokeratin is the most ubiquitous cell product.<sup>34</sup> Broad-spectrum antibodies such as AE1/AE3 diffusely stain all trophoblastic cells. Trophoblast also is reactive for simple epithelium-type cytokeratins, and cytokeratins 7 and 18 are especially notable for their reactivity in trophoblast. Cytokeratin 20, in contrast, is variably reactive in trophoblast, and high molecular weight cytokeratin is negative in trophoblastic cells. Other than cytokeratin, CT cells show limited immunoreactivity to commonly available antibodies. The CT cells do not stain for hCG, hPL, PLAP, and other antigens associated with specialized trophoblast such as Mel-CAM (melanoma cell adhesion molecule [CD 146]) and inhibin- $\alpha$ . The ST cells stain for the common trophoblastic markers

including hCG, hPL, PLAP, and inhibin- $\alpha$  as well as cytokeratin.<sup>41</sup> The ST do not react with antibodies to Mel-CAM.<sup>42</sup>

The IT cells vary in their staining pattern depending on the subtype (Table 3.3).<sup>40</sup> All IT cells react strongly for cytokeratin. Mel-CAM (CD 146) also is seen in all types of IT, although in the villous IT the staining increases from the base to the tip of the trophoblastic columns. The implantation site IT and chorionic-type IT are reactive for hPL and PLAP but the villous IT cells generally are not. Inhibin- $\alpha$  is seen only in chorionic-type IT. Chorionic-type IT cells also stain well for epithelial membrane antigen (EMA); it is the only type of trophoblastic cell that is EMA reactive. Ki-67 immunostaining also shows a variable proliferation index. CT shows a Ki-67 index of 25% to 50%, which is consistent with its role as the germinative tro-



phoblastic cell. The Ki-67 proliferation index in villous trophoblast is high at the junction with the CT at the base of the villus but decreases progressively toward the tip (distal end) of the trophoblastic column. The Ki-67 proliferation index is zero at the junction of the column with the decidua of the basal plate and is zero in the implantation-type IT cells as they “drop off” the column and infiltrate the endomyometrium. The Ki-67 proliferation index is low (<5%) in chorionic type IT. The Ki-67 index in ST cells is zero, which is consistent with that of terminally differentiated cells.

### Placental Implantation Site

The placental implantation site is composed largely of IT cells that infiltrate the decidua basalis, mixing with decidualized stromal cells, glands, and vessels.<sup>4;34;36;39;43–45</sup> This site begins as

a microscopic focus where the blastocyst implants into secretory endometrium, and it expands with the growing placenta to cover the entire area of decidua and superficial myometrium to which the placenta is attached. It can be diffuse or focal in endometrial biopsy specimens. Previous terminology for the trophoblastic infiltrate in decidual and myometrial tissue included “syncytial endometritis” and “syncytial endomyometritis” or “placental giant cell reaction.” None of these terms is correct, however, because the process is physiologic, not inflammatory; the majority of the cells are not giant cells; and the change is not confined to the endometrium but also involves the myometrium.

Placental site intermediate trophoblast characteristically diffusely permeates the decidua and implantation site (Figs. 3.14 to 3.18). Because they closely resemble decidual

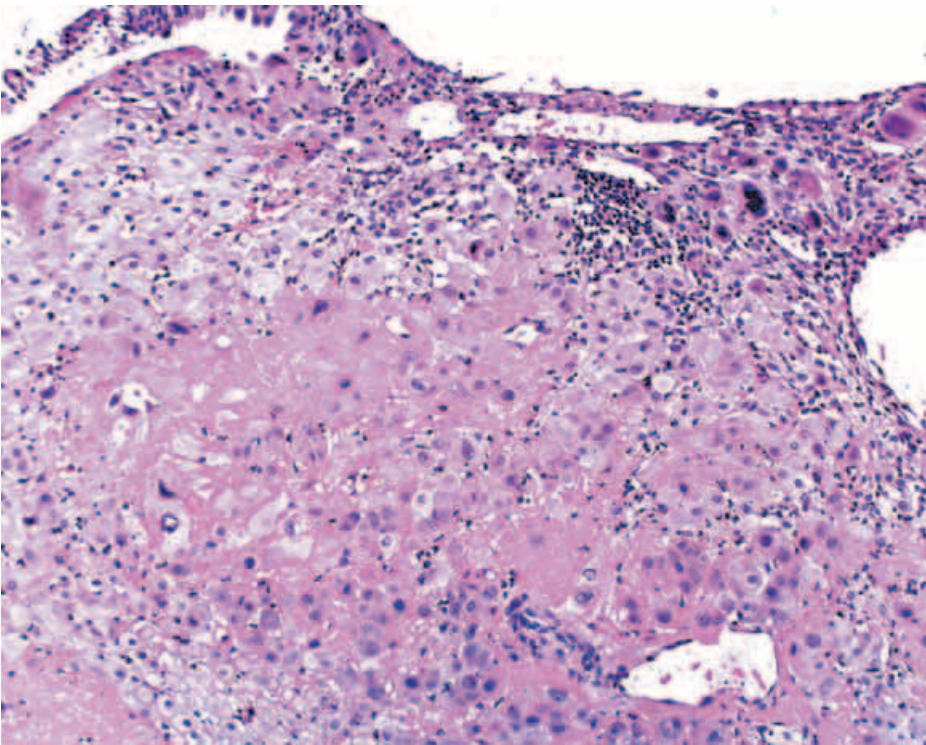


FIGURE 3.14. Placental implantation site. Fibrin and implantation site IT with irregular, hyperchromatic nuclei and cytoplasmic vacuoles are interspersed among decidual cells. In the right lower corner the

IT cells are partially replacing the endothelial cells of a blood vessel. Chorionic villi are not seen, but the presence of intermediate trophoblast in decidua establishes the diagnosis of intrauterine pregnancy.

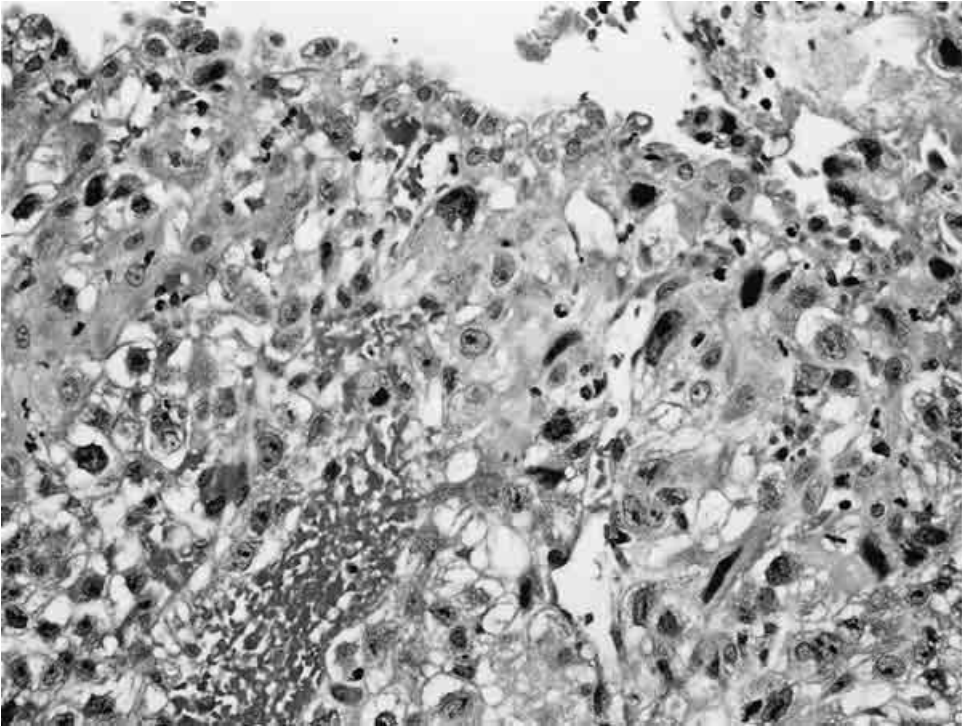


FIGURE 3.15. IT cells and decidua. Placental implantation site in an abortion specimen contains numerous implantation site IT that infiltrate the decidua.

IT have characteristic large, irregular, hyperchromatic nuclei. Some of the IT cells have prominent nucleoli.

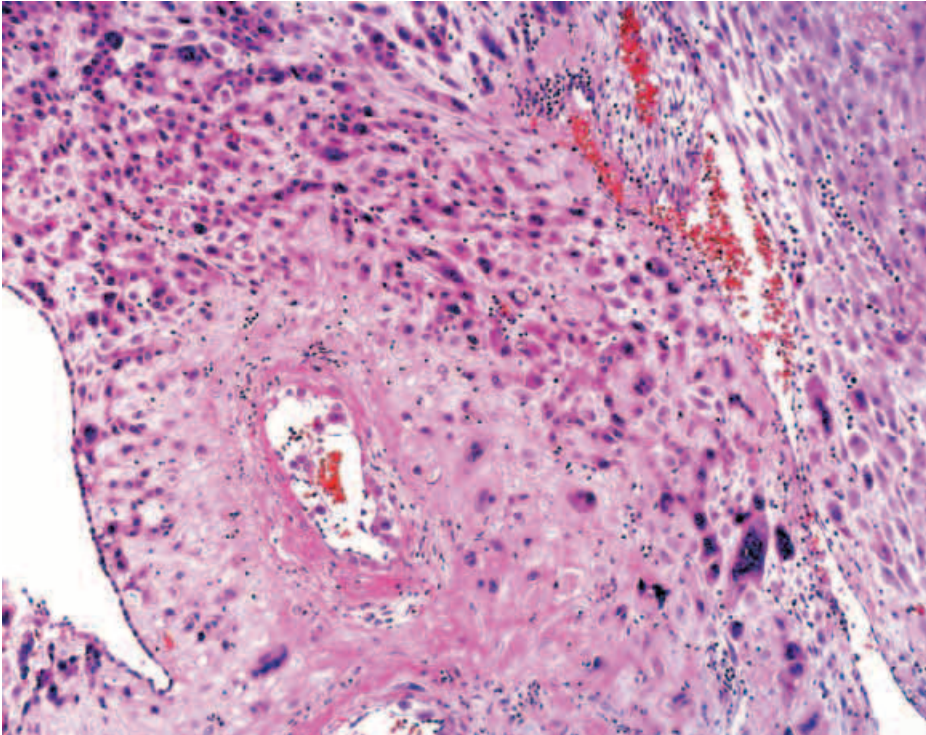


FIGURE 3.16. IT cells and decidua. Implantation site IT in decidua are prominent and hyperchromatic compared to the decidual cells on the right side of

the figure. A spiral artery in the center shows the wall replaced by IT and fibrinoid material.



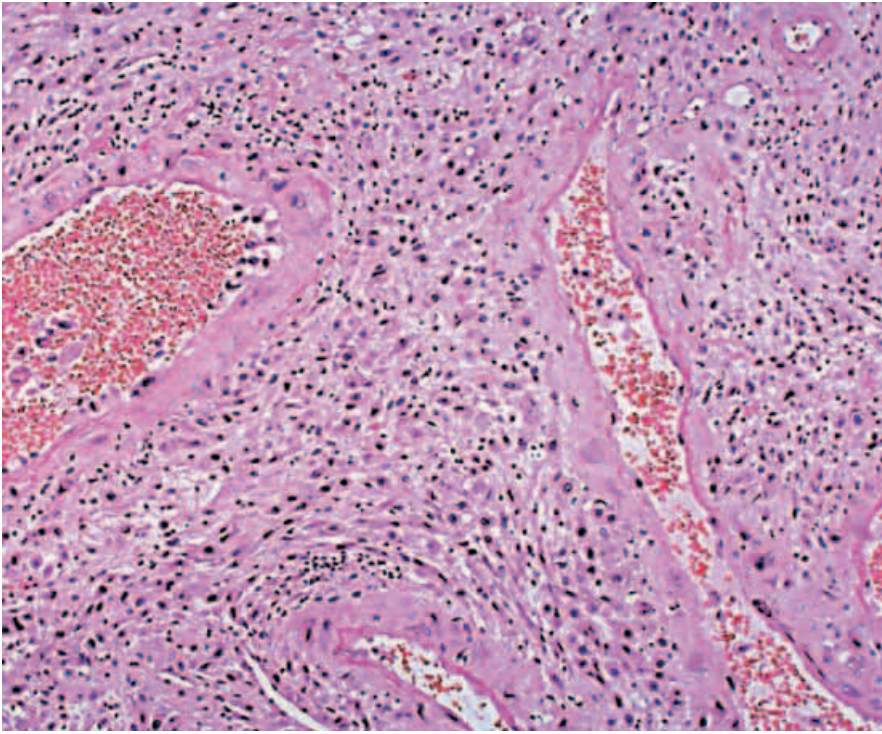


FIGURE 3.17. IT cells and decidua. Implantation site IT with enlarged, hyperchromatic nuclei infiltrate decidua in an abortion specimen. Several dilated

spiral arteries are infiltrated by the IT, replacing the endothelium.

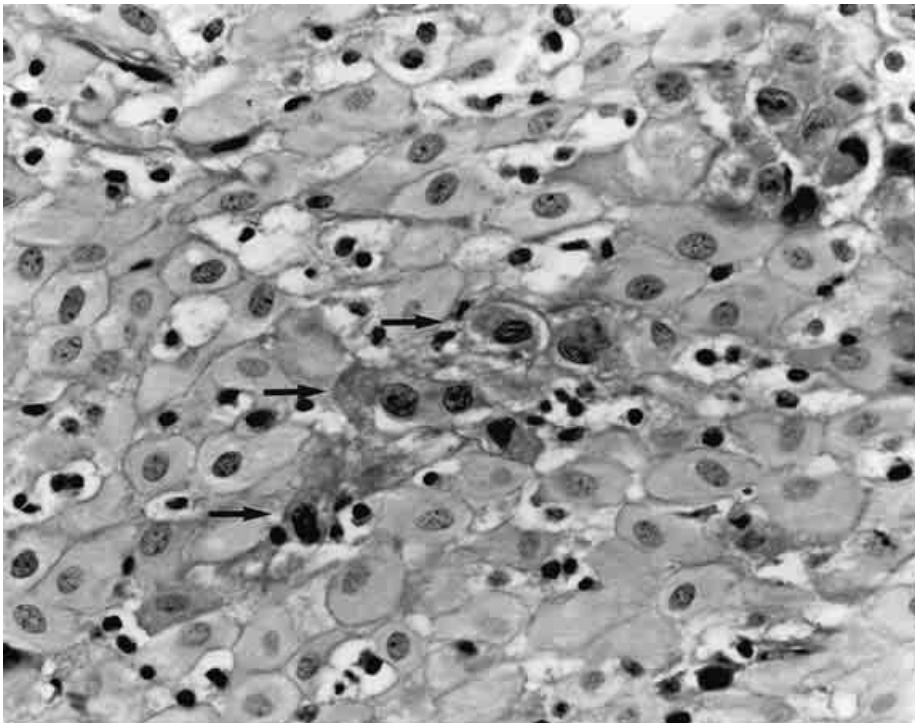


FIGURE 3.18. IT cells and decidua. The implantation site IT (*arrows*) have irregular, hyperchromatic nuclei that contrast with the round to oval, uniform nuclei of the surrounding decidualized stromal cells.



cells, they are often difficult to recognize. In fact, these IT cells have been misinterpreted as degenerating decidual cells because of their intimate association with the latter (Figs. 3.16 and 3.18). The implantation site IT cells have variable size and shape ranging from polygonal to round to spindle-shaped, with a moderate amount of eosinophilic to amphophilic cytoplasm.<sup>44</sup> They are larger than decidualized stromal cells, with which they are intimately admixed. They may have sharply outlined cytoplasmic vacuoles. The nuclear morphology of implantation site IT, however, is the most important feature that distinguishes these cells from decidua. They are enlarged, lobated, and hyperchromatic with irregular nuclear membranes. Sometimes they have deep clefts, and some nuclei appear smudged.<sup>46</sup> Most of these IT cells contain a single nucleus, but bi- or multinucleate cells with similar nuclear and cytoplasmic features occur as well. The dark and irregular implantation site IT nuclei, which

often contain a prominent nucleolus, contrast with the nuclei of decidualized stromal cells, which are uniform and round to oval with an even, delicate chromatin distribution. Immunohistochemical stains for keratin and human placental lactogen (hPL) help identify intermediate trophoblast cells and distinguish them from decidual cells which are negative (see later).<sup>35;47</sup>

At the implantation site intermediate trophoblastic cells also infiltrate into myometrium, where they often have a spindled appearance (Fig. 3.19). The implantation site IT cells are often more conspicuous here, especially when some of them become multinucleated. In the myometrium they infiltrate between muscle bundles and fibers, often with no evidence of a tissue reaction. Many are spindle shaped and can closely resemble smooth muscle cells. It is very common to see fragments of myometrium infiltrated by intermediate trophoblast in curettage samples from abortions.

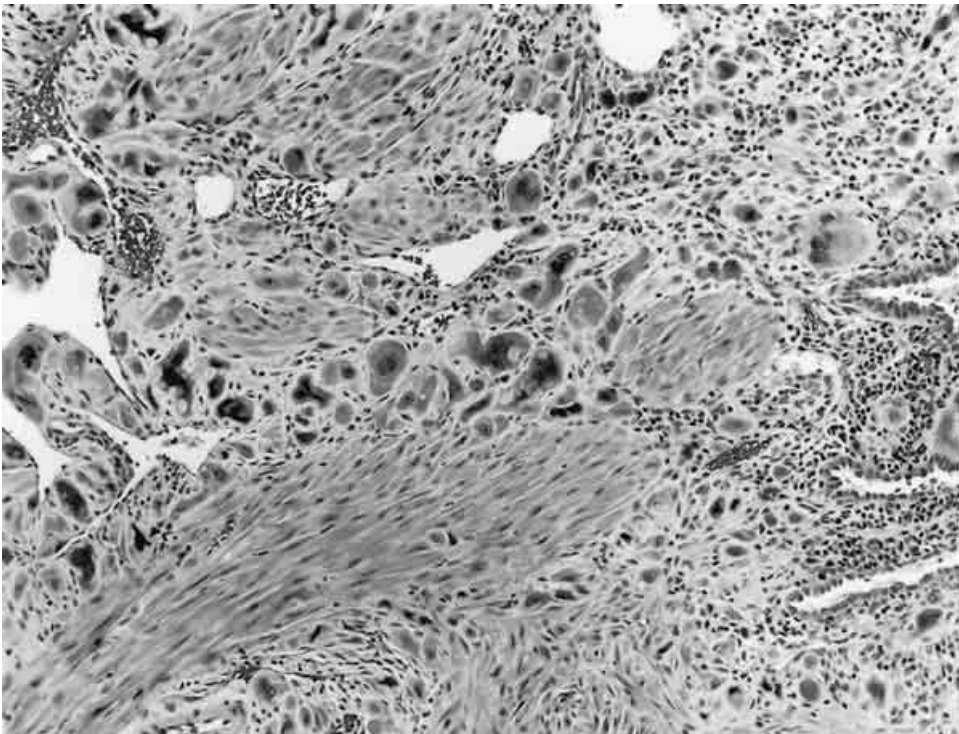


FIGURE 3.19. IT cells in myometrium. Curetted placental site from an abortion includes a fragment of myometrial smooth muscle infiltrated by large

implantation site IT. These cells often become multinucleated when they invade the myometrium.

In addition to infiltrating the decidua and myometrium, the implantation site IT cells invade spiral arteries, extensively replacing the wall and endothelium while maintaining the integrity of the lumen (Figs. 3.16, 3.17, and 3.20). When vascular infiltration is extensive, the IT cells may partially fill the lumen of the vessel. This infiltration of vessels contributes to the enlargement of the spiral arteries.

Besides their characteristic growth pattern and cytologic features, implantation site IT cells can be recognized because they typically are associated with patches of extracellular eosinophilic fibrinoid material (Fig. 3.21). This fibrinoid matrix in the placental bed eventually becomes the so-called Nitabuch's layer. When this fibrinoid material becomes disrupted in abortions, it forms hyaline, eosinophilic strands termed Rohr's stria. The origin of this fibrinoid, hyaline material is not fully understood, although it appears to be partly composed of

fibronectin, laminen, type IV collagen, and a small amount of fibrin. In any event, fibrinoid is a distinctive part of the implantation site.

Placental site fibrinoid can resemble fibrin thrombi that occur as a result of chronic bleeding from a variety of causes. Also, endometrial stroma can become hyalinized and fibrotic in areas of continued breakdown such as the surface of polyps, and this change, too, can mimic the fibrinoid deposition of the implantation site. Fibrin thrombi and hyalinized endometrial stroma are distinguished from fibrinoid by the absence of interspersed IT cells and the lack of the linear deposits of eosinophilic implantation site fibrinoid.

Changes in the spiral arteries of the placental site are significant. The presence of enlarged, hyalinized spiral arteries in the decidua of curettage specimens is a valuable adjunct in diagnosing intrauterine gestation.<sup>47</sup> These vessels have thickened hyalinized walls that are

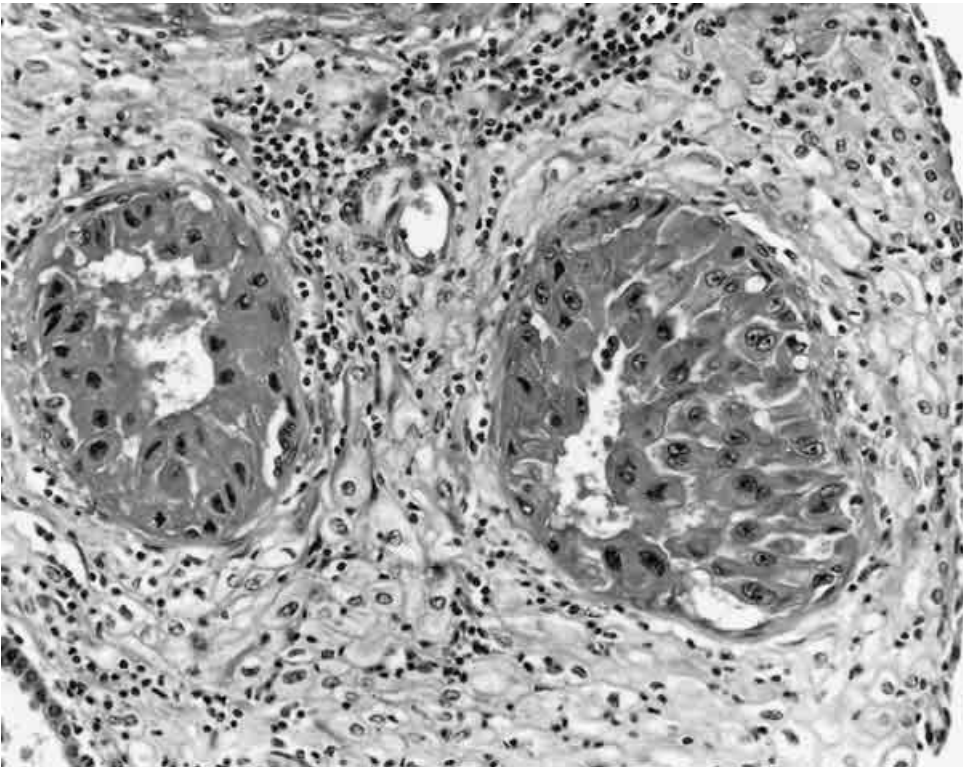


FIGURE 3.20. IT cells. Prominent infiltration of blood vessels in the decidua by implantation site IT in an abortion specimen. The cells infiltrate and replace the wall but preserve the lumen.

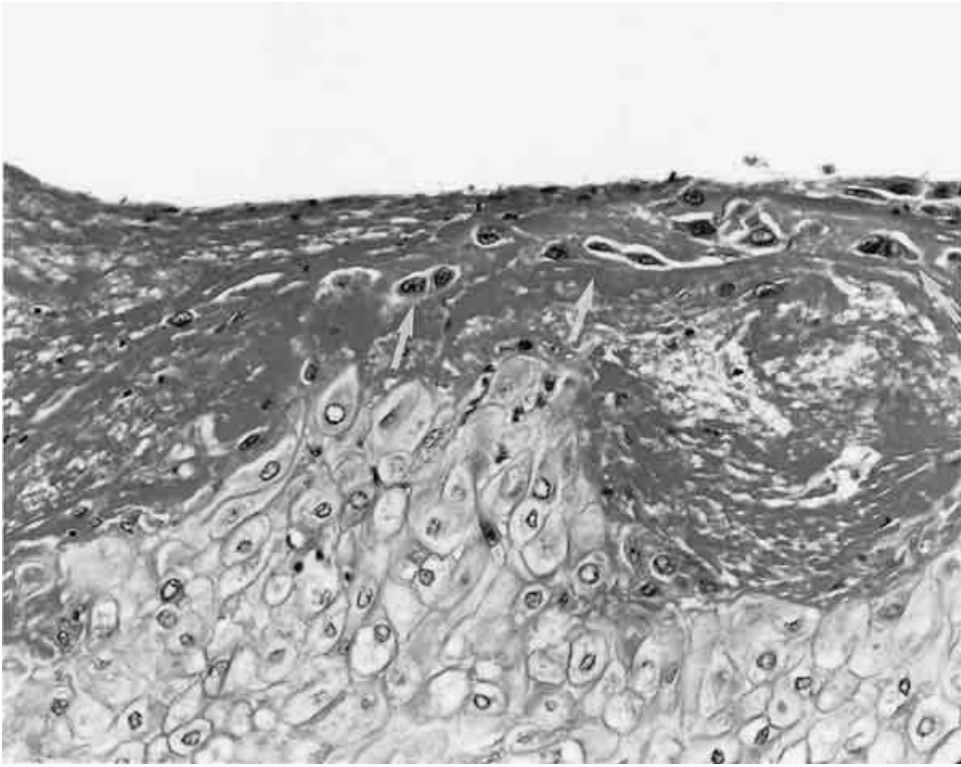


FIGURE 3.21. Fibrinoid (Rohr's stria). A strand of densely eosinophilic fibrinoid material of the placental implantation site overlies the decidua in curet-

tings from an abortion specimen. A few IT are enmeshed in the fibrinoid (*arrows*).

partially infiltrated by IT and show an increased luminal diameter (Figs. 3.16, 3.17, and 3.20). Often several implantation site vessels are seen in cross section forming a prominent cluster. These vascular changes, like the presence of IT in the decidua, are characteristic of the implantation site and are not found in endometrium associated with ectopic pregnancy.

Histologic recognition of the placental implantation site usually is straightforward. Sometimes IT cells are indistinct or are difficult to distinguish from degenerating decidual cells that develop dark nuclei. In these instances, ancillary immunohistochemical techniques are useful for the detection of IT. Broad-spectrum keratin antibodies are very useful for demonstrating IT.<sup>35;47-49</sup> Endometrial glands also stain with keratin, however, and therefore all keratin-positive cells do not represent IT cells.

It is the growth pattern along with immunoreactivity for keratin that identifies IT cells. With the keratin immunostain, the IT cells appear as intensely staining single cells or irregular clusters of cells with intervening decidua or smooth muscle that is nonreactive for keratin (Fig. 3.22). The IT cells, unlike decidual cells, also express hPL, Mel-CAM (CD 146), and, to a lesser degree, hCG.<sup>34</sup> Immunostains, especially hPL, are useful for detecting IT cells including the multinucleated IT in the myometrium, as smooth muscle cells do not express hPL.<sup>35;47-49</sup> The implantation site IT shows no proliferative activity and should not be reactive with Ki-67.<sup>50</sup>

### Exaggerated Placental Implantation Site

An exaggerated placental site represents one end of the spectrum of the morphologic fea-



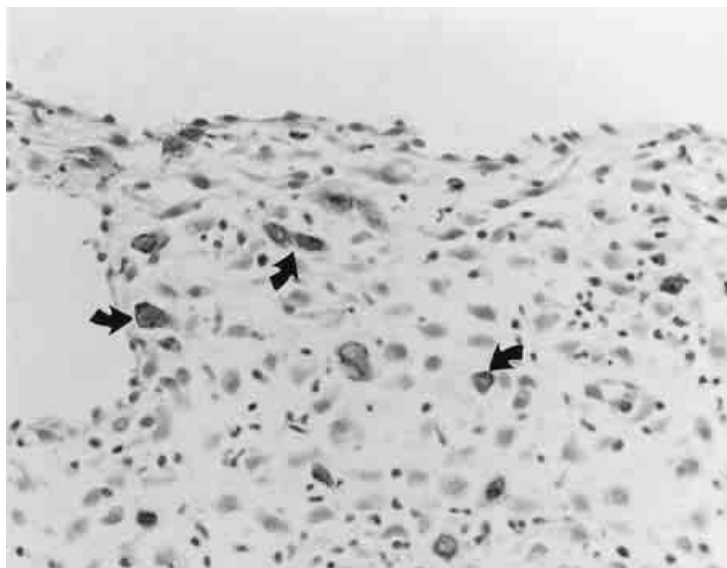


FIGURE 3.22. Keratin immunoreactivity of intermediate trophoblast. Scattered IT in decidua show cytoplasmic staining for keratin (arrows).

tures of the normal implantation site.<sup>43;44</sup> It is not a tumor. It is an unusually prominent but physiologic placental site that may be difficult to distinguish from a placental site trophoblastic tumor (PSTT) (see Chapter 4). In complete molar pregnancy the placental site is typically exaggerated, but exaggerated placental site can occur in association with a normal gestation as well. The exaggerated placental site is characterized by an increase in the number and size of individual IT cells. In addition, widely dispersed multinucleated IT cells are a component of the trophoblastic infiltrate. Often several fragments of tissue in curettage samples contain portions of the lesion, and this process can extensively infiltrate fragments of myometrium. A few chorionic villi may be present. In the exaggerated placental site, IT cells appear larger and more hyperchromatic than normal. Despite their apparent prominence, these IT cells show no mitotic activity, and Ki-67 immunostaining is zero when the exaggerated implantation site is associated with an abortus.<sup>50</sup> The Ki-67 index can be slightly elevated in exaggerated implantation sites associated with a complete mole. It is important to note that lymphocytes that typically are present in the implantation site often express Ki-67. These lymphocytes should not be misinter-

preted as IT cells. Double staining with Mel-CAM and Ki-67 can be very helpful in localizing Ki-67 to Mel-CAM-positive IT cells. Necrosis is not a feature of the exaggerated placental site, although the surrounding decidua often shows degeneration and necrosis typical of spontaneous abortions. PSTT is an important consideration in the differential diagnosis of this lesion. The distinction is largely a matter of degree, as discussed in Chapter 4.

### Placental Site Nodules

Placental site nodules are small, circumscribed foci of hyalinized implantation site with IT cells that occasionally present in an endometrial biopsy or curettage.<sup>40;43;44;51–53</sup> These benign lesions occur in women of reproductive age, although often the pregnancy history is remote.<sup>51;54</sup> Usually they are incidental findings, although they may be associated with abnormal uterine bleeding. The nodules may be present in biopsies taken several years after tubal ligation, suggesting that they are retained in the endometrium for extended periods of time.<sup>40;51;54</sup> The known antecedent pregnancy dates back 2 to 108 months, demonstrating the long duration of some lesions. They show a propensity for the lower uterine segment and

cervix. The surrounding endometrium often is proliferative or secretory, and usually is not decidualized.

Generally these lesions are microscopic, although hysterectomies may yield gross lesions as large as 1 or 2 cm in diameter. Occasionally, multiple nodules are present. In the past these nodules and plaques were considered hyalinized decidua, but they are now recognized as a distinctive benign lesion of IT. The lesion itself is circumscribed, nodular, or plaque-like with densely eosinophilic, hyalinized stroma containing aggregates of IT cells (Fig. 3.23). Often focal chronic inflammation including plasma cells surrounds the nodule, while the rest of the endometrium shows no inflammation. The trophoblastic cells in these nodules resemble chorionic-type IT. In the placental site nodule the cells vary in size; many have small,

uniform nuclei and some larger cells show irregular, hyperchromatic nuclei. Occasional multinucleated cells are present. (Fig. 3.24). Mitoses are rare or absent, and the cells show a low Ki-67 labeling index of <10%.

The IT of the placental site nodule demonstrate immunoreactivity that is similar to that seen in chorionic-type IT. The cells are strongly reactive for keratin and epithelial membrane antigen as well as PLAP, inhibin- $\alpha$ , and pregnancy-specific SP-1 (Fig. 3.25).<sup>51;54;55</sup> Other trophoblastic markers such as hPL and Mel-CAM (CD 146) may be positive but only in a few cells, and hCG reactivity is usually absent. The small size, circumscription, and extensive hyalinization are consistent features of the lesions that help to separate them from the placental site trophoblastic tumor and epithelioid trophoblastic tumor discussed in Chapter 4.

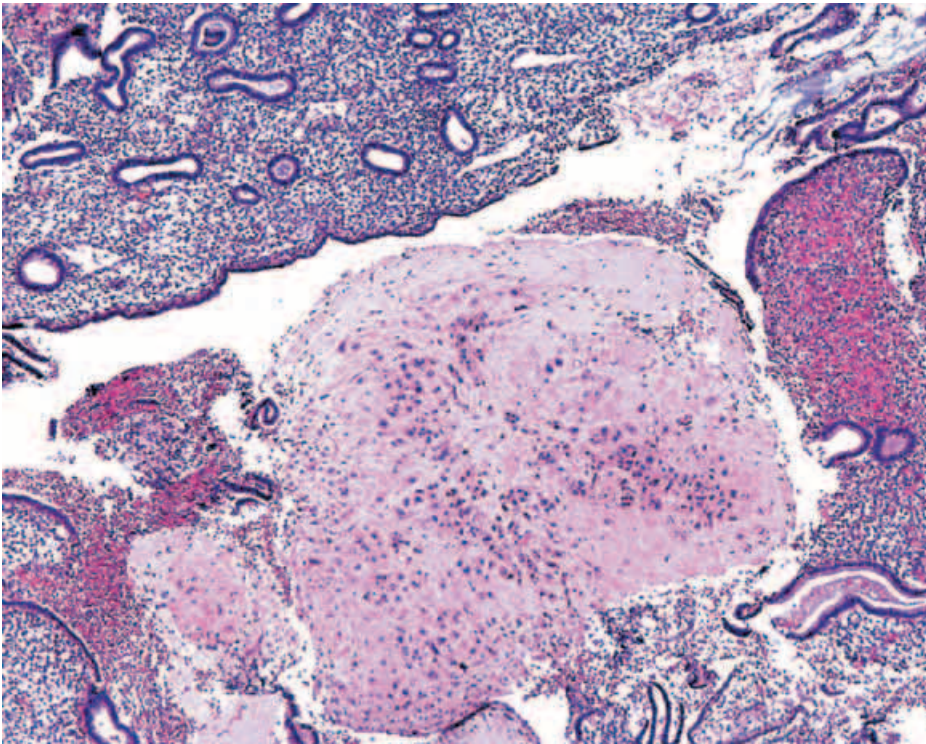


FIGURE 3.23. Placental site nodule. Well-circumscribed fragment of placental site nodule is present in endometrial curettings. This microscopic focus is

composed of hyaline material with entrapped, degenerate IT cells.

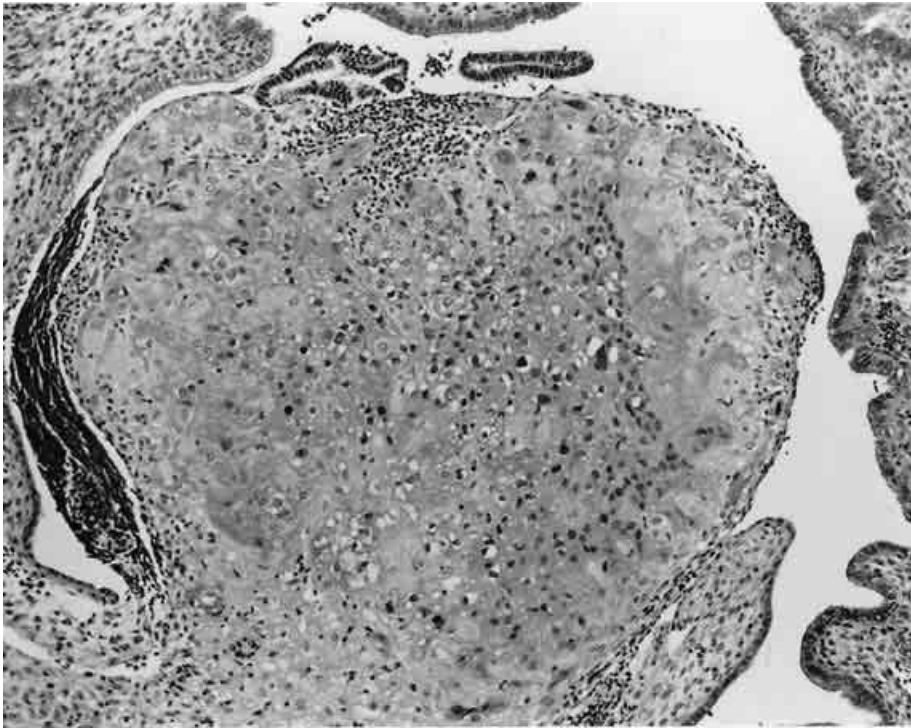


FIGURE 3.24. Placental site nodule. Placental site nodule shows degenerate, vacuolated IT cells with smudged nuclear chromatin surrounded by dense, hyaline stroma. A chronic inflammatory infiltrate is present at the periphery of the lesion.

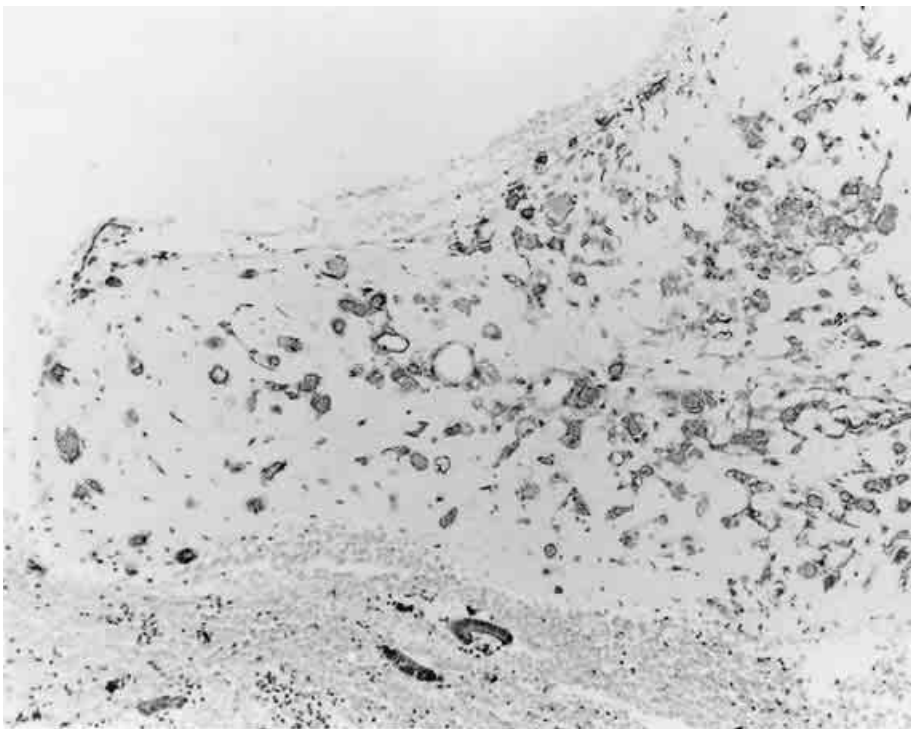


FIGURE 3.25. Placental site nodule. Immunohistochemical stain for keratin shows strong reactivity of the trophoblast.



## Chorionic Villi and Villous Trophoblast in the First Trimester

Villus formation in very early pregnancy depends on the existence of the embryonic disc. Villi begin to develop on the 12th to 13th day postfertilization, and by days 12 to 15 the placenta can develop for a while independently, without the presence of an embryo.<sup>4,56</sup> In fact, in spontaneous abortions the placenta can persist for several weeks after the death of the embryo. In the early stages of pregnancy, villi have a loose, edematous stroma with few well-developed capillaries (Figs. 3.11 and 3.26). Once the yolk sac and embryo develop, vascular circulation is established in the villous stroma and these vessels contain nucleated red blood cells. During this early period of placental development, the trophoblastic covering of the villi

consists of an inner layer of CT cells and an outer layer of ST cells. The CT and IT cells also proliferate at the implanting end of the anchoring villi that grow along the basal plate of the developing placenta.

A few histologic changes in the placenta help to determine the age of the developing conceptus (Table 3.4), although the length of gestation is an infrequent clinical question. These developmental intervals are stated in relation to the time of fertilization, also known as the postcoital or postconception date. Taking into account the time from the last known menstrual period adds 2 weeks to these figures. The conceptus is traditionally called an embryo in the first 2 months of development; thereafter it is called a fetus.

As placental development proceeds, the presence of nucleated erythrocytes produced in the yolk sac helps determine the approximate

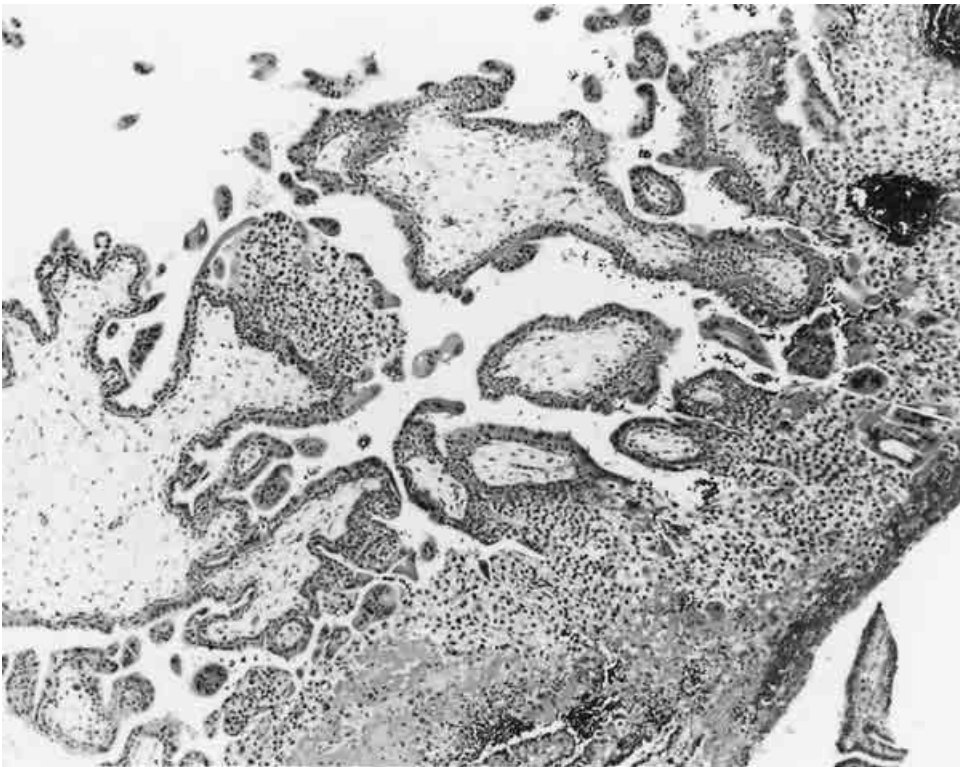


FIGURE 3.26. Immature chorionic villi. Immature villi from an abortion specimen show loose, edematous stroma containing a few capillaries with nucle-

ated erythrocytes. Trophoblast emanates from one pole of several villi, which is the implanting portion of the anchoring villi.

TABLE 3.4. Events in first trimester placental development.<sup>a</sup>

Development of placenta	Time after fertilization
Blastocyst implantation	6–7 days
Villus formation begins <sup>b</sup>	12 days
Nucleated RBCs from yolk sac appear in villi	4.5 weeks
Non-nucleated RBCs from liver appear in villi	5–6 weeks
Proportion of nucleated RBCs decreases from 100% to 10% in villi	4.5–9 weeks
Decrease in prominence of inner cytotrophoblast layer	16–18 weeks

RBCs, Red blood cells.

<sup>a</sup> From time of ovulation. For menstrual age add 2 weeks.

<sup>b</sup> After 12–15 days, placental development proceeds even if embryo dies.

gestational age.<sup>56</sup> The nucleated erythrocytes from the yolk sac appear in the villous circulation at 4.5 weeks. By 5 to 6 weeks, non-nucleated erythrocytes from the embryonic liver also begin to appear in the villi, and from this point on there is a shift in the proportion of nucleated to non-nucleated erythrocytes. By 9 weeks postfertilization the percentage of nucleated erythrocytes in the villi decreases from 100% to only 10%. Consequently, if the embryo dies before 4.5 weeks postfertilization, the villi contain no red blood cells. Death of the embryo between 4.5 and 10 weeks leaves a mixture of nucleated and non-nucleated erythrocytes in villous capillaries, and later death of the embryo usually leaves non-nucleated red cells in the stroma.

Other features also help to determine the relative length of gestation. For example, normally developing immature villi are relatively larger than those of later pregnancy. They have a loose, myxoid stroma with widely spaced capillaries. As pregnancy progresses, the villi become smaller but more vascular and their stroma loses its edematous appearance. The morphologic features of the trophoblast covering the villi change along with growth of the placenta. The bilayered CT and ST covering of the villi persists to some extent throughout gestation, but a visible inner layer of CT cells starts to disappear at about 14 weeks of gestation. Between week 14 and week 18, the

percentage of villi showing an inner layer of CT cells decreases from 80% to 60%.<sup>4</sup> From that point on there is a continuing gradual decrease in the CT layer. The large decrease in identifiable CT cells by week 18 is especially useful for determining the relative duration of early pregnancy.

### Hydropic Change and Other Pathologic Changes in Abortions

The microscopic features of the decidua and the products of conception in curettage samples vary depending on the type of abortion.<sup>4;57;58</sup> Villi are usually normal in therapeutic abortions, whereas they tend to reflect early death of the embryo in spontaneous or missed abortions. Therapeutic abortion specimens may show pathologic changes in the villi, however.<sup>59</sup> In spontaneous or missed abortions, placental morphology is influenced by gestational age, karyotype, and regressive changes.<sup>4;57;60–63</sup> With the death of the embryo, the villi often show hydropic change because of loss of the villous vascular supply, especially if embryonic death occurs very early, often before 4.5 weeks postfertilization age.<sup>56</sup> The avascular villi are mildly distended with fluid and the curettage samples do not contain fetal tissue giving the changes of the so-called blighted ovum (Fig. 3.27). This pattern of mild villous edema and no evidence of fetal development indicates that the embryo either never developed or ceased development at a very early stage of gestation. Microscopically, villous edema in a hydropic abortion can appear especially prominent at first glance. Hydropic change affects most villi but is minimal and microscopic; cistern formation in the villi is rare but does occur (Fig. 3.28). There is no associated trophoblastic hyperplasia except the normal growth at one pole of the anchoring villi. Usually these microscopic abnormalities are less impressive when the gross, quantitative aspects are considered also. Hydropic abortions usually consist of one or two cassettes of tissue with villi whereas moles typically yield multiple cassettes. It is important to recognize the changes of the blighted ovum in order to separate an abortion with hydropic changes from a hydatidiform mole (see Chapter 4). Hydropic change also may be

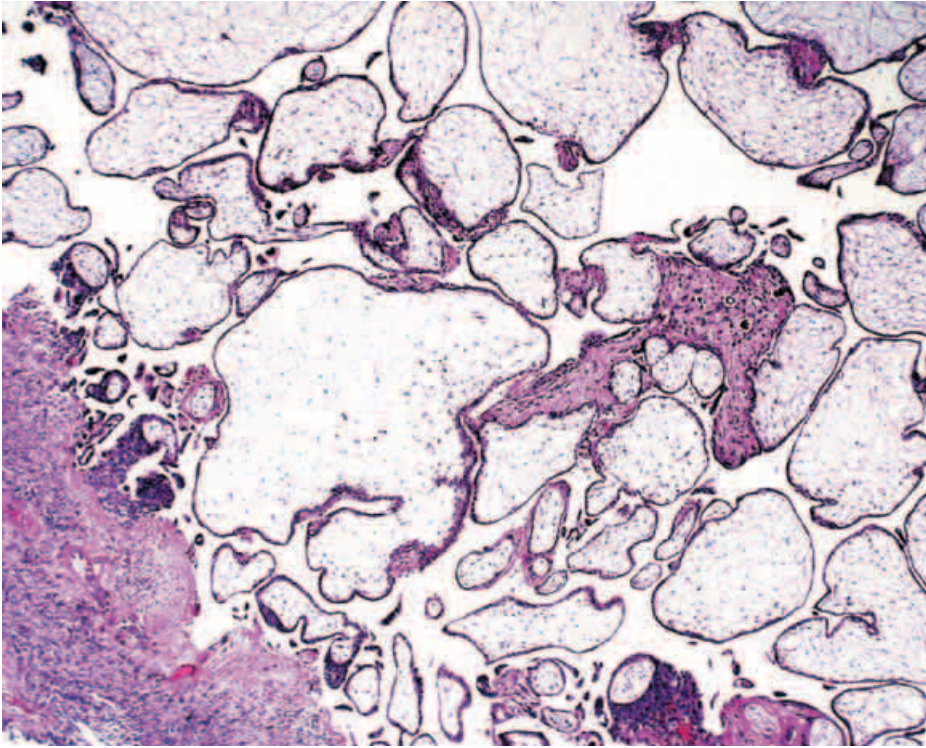


FIGURE 3.27. Immature chorionic villi with hydropic change. Abortion specimen shows avascular, edematous chorionic villi. This change is associated with the so-called blighted ovum and usually indicates very early demise of the embryo. Although the villi are edematous, the change is microscopic and not asso-

ciated with hyperplasia of trophoblast. Furthermore, there is a polar distribution of the trophoblast toward the placental implantation site at the bottom of the field. These features distinguish this hydropic abortus from a partial mole.

focally present in therapeutic abortions,<sup>59;64</sup> especially if the tissue blocks sample villi of the chorion leave, where the villi normally degenerate, and mild hydropic change often is difficult to distinguish from the loose, myxoid stroma of the normal early placenta.

Other morphologic changes in chorionic villi from first-trimester abortion specimens may be found.<sup>4</sup> Irregular outlines of villi yielding a scalloped appearance and trophoblastic invagination into the villous stroma forming pseudoinclusions often are associated with abnormal karyotypes of the conceptus, particularly triploidy, but the findings are not sufficiently specific by themselves to be diagnostic of a chromosomal abnormality. Karyotyping is necessary to determine whether a chromosomal abnormality is present.<sup>60;61;65</sup>

In incomplete abortions, the amount of villous tissue may be greatly reduced or even

absent if portions of the placenta spontaneously pass before curettage. The implantation site, however, with its characteristic features, usually is present. In missed abortions the villi often are necrotic or hyalinized and the decidua is necrotic. Another change in villi associated with death of the embryo is loss of villous vascularity and fibrosis of the villous stroma (Fig. 3.29).<sup>62;66;67</sup> This change occurs more frequently in missed abortions. Some or many villi may be necrotic. These villous changes have little if any clinical significance.

### Chorionic Villi and Villous Trophoblast After the First Trimester

After the first trimester or early second trimester, the placenta is sufficiently large that it is delivered spontaneously or by induction, and curettage specimens are rare. The villi are





FIGURE 3.28. Immature chorionic villi with hydropic change. This hydropic abortus shows scattered cisterns. Despite the edema, this is a microscopic

finding. There is no associated hyperplasia of the trophoblast, and this does not represent a hydatidiform mole.

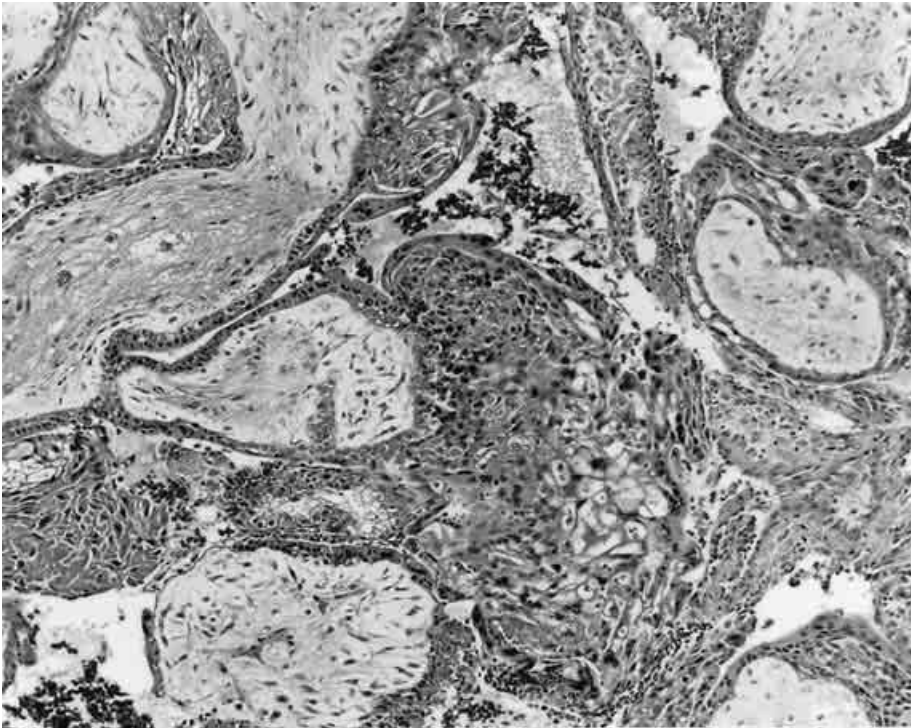


FIGURE 3.29. Immature chorionic villi with villous fibrosis. Abortion specimen showing immature villi with absence of vessels and stromal fibrosis. Hyper-

plastic trophoblast remains confined to one pole of the villi.

more numerous and become more complex. By this time there is a mixture of larger stem villi with prominent vessels and central stromal fibrosis, and many smaller tertiary villi containing numerous capillaries.<sup>4</sup> By late in the second trimester, the inner CT cells are indistinct over most villi and the trophoblastic proliferation along the anchoring villi has largely ceased. Some abortion specimens present early in the second trimester following intrauterine fetal death. In these cases the villous stroma often is fibrotic and hypovascular, with either no residual erythrocytes or a few residual degenerating red blood cells present.

Following delivery of the term or near-term placenta, abnormal bleeding may require curettage. The histologic findings in the postpartum endometrium vary. Failure of the implantation site to resolve quickly is called subinvolution. With subinvolution the uterus contains remnants of necrotic decidua and the placental site with eosinophilic fibrinoid, trophoblastic cells

and enlarged vessels that often are infiltrated by the intermediate trophoblast. Retained placental site also serves as a nidus for inflammation, yielding inflamed and necrotic endometrium and implantation site. Immunohistochemical stains for keratin help to demonstrate the residual intermediate trophoblastic cells.

### Placental Polyps

Placental polyps are a form of retained product of conception that represent polypoid portions of chorionic villi from an incomplete abortion or a term gestation retained in the uterine cavity.<sup>4</sup> The villi may be necrotic, hyalinized, or partially calcified (Fig. 3.30). These polyps are not tumors, but they do form a nidus for inflammation and bleeding. Often these pedunculated masses of villi are found within days to weeks following abortion or delivery of a term placenta. Rarely, they persist for months or years after pregnancy.

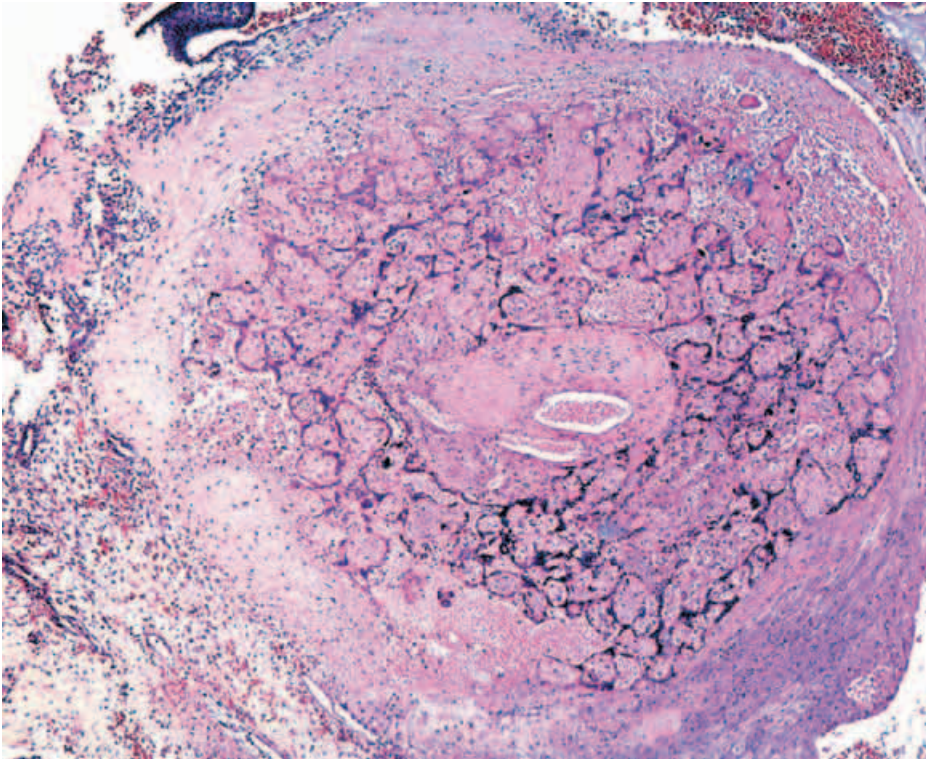


FIGURE 3.30. Placental polyp. Polypoid fragment of retained placental tissue removed by curettage several weeks after term delivery. The mature villi are degenerate and hyalinized.



## Placenta Accreta

Placenta accreta is a form of abnormal implantation in which the placenta implants directly onto the myometrium with no intervening decidua; it may grow into or through the myometrium (placenta increta and percreta, respectively).<sup>4;62</sup> Usually placenta accreta presents immediately following delivery of a term pregnancy when the placenta or portions of the placenta cannot be delivered. The placental tissue fails to detach from the implantation site in the myometrium and cannot be manually removed. The usual management of extensive placenta accreta is hysterectomy, but on occasion focal placenta accreta is encountered in curettage for postpartum hemorrhage. The diagnostic feature is villi in direct apposition to myometrium without intervening decidua (Fig. 3.31). Hyaline fibrinoid material with scattered IT cells is interposed between the villi and myometrium but decidual cells are absent.

Some placental polyps may represent focal placenta accreta, although the latter are diagnosed only when villi are contiguous with myometrium. Scattered IT cells without villi in the myometrium are a physiologic phenomenon and not placenta accreta.

## Endometrium Associated with Ectopic Pregnancy

In most circumstances, the endometrium associated with an ectopic pregnancy shows the typical features of early gestation, yet trophoblastic tissue is not present. A decidualized stroma, hypersecretory to atrophic glands, and thick-walled spiral arterioles usually are present.<sup>18;19;24;68;69</sup> Often the Arias-Stella reaction is present, at least focally. The endometrium associated with ectopic gestation can be highly variable, however, depending on

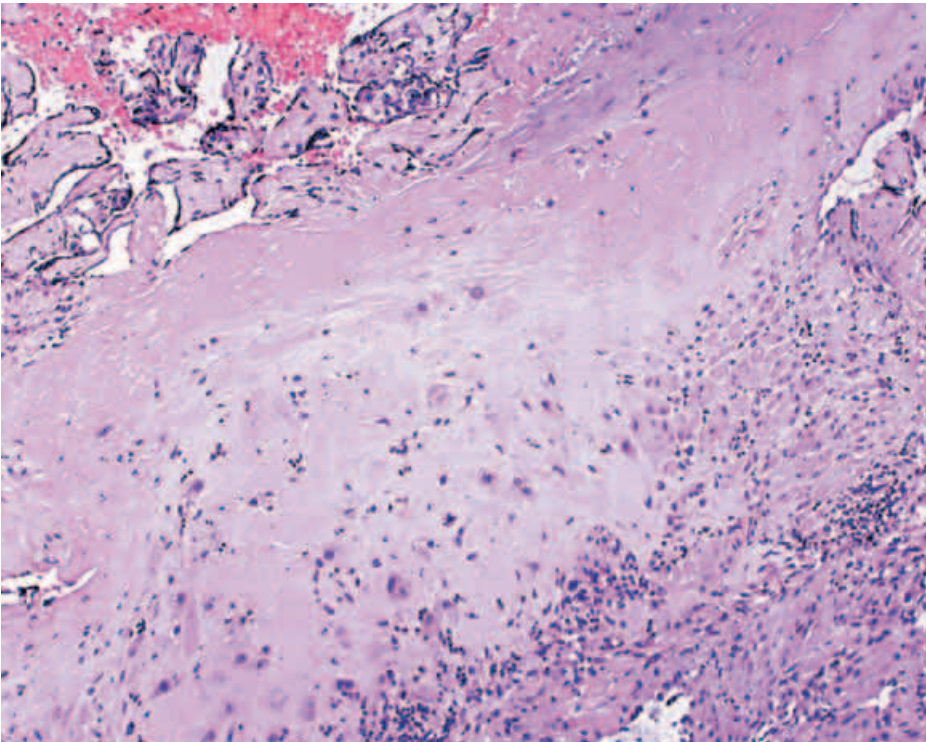


FIGURE 3.31. Placenta accreta. Curetting for bleeding following delivery of a term gestation shows mature chorionic villi at the top of the field. Implantation site

IT and fibrinoid material but no intervening decidua are all that separate the villi from the myometrial smooth muscle at the lower portion of the figure.



the status of the trophoblastic tissue. If ectopic trophoblast is actively proliferating, the endometrium continues to show the changes of pregnancy. If the trophoblast begins to regress, the endometrium can display a variety of patterns ranging from proliferative to secretory changes. The endometrium can show features seen in dysfunctional bleeding, including anovulatory bleeding patterns, abnormal secretory patterns, or progesterin effects. Subtle clues, such as a focal Arias-Stella reaction or a small aggregate of gland cells with clear cytoplasm, can suggest an ectopic pregnancy.

Establishing the presence of an intrauterine pregnancy effectively rules out an ectopic pregnancy. Evidence of an intrauterine pregnancy includes chorionic villi, trophoblastic cells, or the placental implantation site. Occasionally individual ST giant cells may be detected enmeshed in blood or fibrin. In cases where there are no villi or ST cells, an attempt should be made to identify IT cells scattered in partially necrotic decidua, often around spiral arterioles. Identification of IT cells of the placental site is crucial, and in such cases immunostaining for keratin can help show scattered trophoblast, usually IT cells in the decidua. Immunostains for hPL, hCG, inhibin- $\alpha$ , and Mel-CAM specifically identify trophoblast, but the reactivity is less sensitive than that seen with keratin antibodies. A panel using several of these latter immunostains can be helpful for identifying trophoblastic tissue if the keratin immunostain is inconclusive.

Clearly, adequate sampling of endometrial tissue is important to ensure recognition of chorionic tissue. We have empirically found that three cassettes from abortion specimens are usually sufficient to establish the presence of chorionic tissue. If no trophoblast or villi are present in the first three tissue blocks, all of the residual tissue should be processed.

## Clinical Queries and Reporting

For most endometrial biopsies or curettings related to pregnancy, three clinical questions need to be answered by pathologic examina-

tion: (1) Does the endometrium show features of pregnancy? (2) If the changes indicate pregnancy, are chorionic villi and/or trophoblast present? (3) If villi and/or trophoblast are present, do they appear normal? For example, endometrial changes of pregnancy without the presence of chorionic villi or trophoblast suggest the possibility of an ectopic pregnancy. In spontaneous abortions the villi may reflect pathologic development of the embryo, a feature that helps explain the occurrence of the abortion. In other cases, edematous villi or proliferative trophoblast can raise the question of a hydatidiform mole, choriocarcinoma, or placental site trophoblastic tumor (see Chapter 4).

The pathology report should consider the clinical questions asked regarding pregnancy as well as the pathologic findings. Most cases require only documentation of the presence of placental or fetal tissue. The most urgent question is that of an ectopic pregnancy. If pregnancy is suspected, or if the morphology shows pregnancy-induced endometrial patterns but there is no evidence of chorionic villi, placental site trophoblast, or fetal tissue, then an ectopic pregnancy must be considered. Occasionally the entire placenta with implantation site is expelled before the curettage, so lack of identifiable products of conception does not unequivocally indicate ectopic pregnancy. Nonetheless, an ectopic pregnancy can result in sudden, life-threatening intra-abdominal hemorrhage, so immediate notification of the clinician managing the patient is imperative. Also, all the residual tissue should be processed. The clinician should be informed if immunohistochemical stains to identify trophoblast are pending or if residual tissue is being processed. Another call should follow as soon as the results are available.

Occasional spontaneous abortion specimens show only a small amount of early placental site with intermediate trophoblast and no chorionic villi. This finding is sufficient to establish the diagnosis of an intrauterine pregnancy. The specimen represents products of conception, and a descriptive diagnosis such as "implantation site and decidua" or "intermediate trophoblast" serves to verify the presence of an intrauterine gestation.

When villi are present in first-trimester specimens, some morphologic findings may be clinically relevant. In spontaneous abortions, for example, mild villous edema (hydropic change) and absence of fetal tissues including erythrocytes in villous vessels indicates that the gestation was abnormal and may help the clinician in the counseling of a patient. Although the microscopic findings can help indicate early death of the embryo, cytogenetic analysis of tissue has more value for assessing significant abnormalities that may lead to recurrent abortion. Sometimes the term “hydropic villi” raises the specter of hydatidiform mole, so this term should be used cautiously unless the clinician fully understands the significance. If hydropic change is diagnosed, it may be useful to add a comment to indicate that this does not represent a mole.

Because pregnancy can be complicated by gestational trophoblastic disease, the status of the trophoblast, especially any abnormal proliferative activity, deserves comment. A specimen containing more than a small amount of trophoblast without villi, or an exaggerated placental site without villi or unusually hydropic villi that are not clearly molar (see Chapter 4) should be reported. In such cases, a comment regarding the uncertainty of the finding and recommendation for follow-up with serum hCG titers helps in the management of the patient.

The placental site nodule can be a confusing diagnosis to the gynecologist. The terminology for this lesion is relatively new. Although these lesions are almost always microscopic and incidental, confusion with PSTT may arise. It is therefore important to indicate clearly the small and benign nature of the lesion. This diagnosis of placental site nodule may be perplexing to the gynecologist because the patient often has no recent history of pregnancy and may even have had a tubal ligation, so a comment regarding the fact that the gestation may have been remote helps the clinician understand the lesion.

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