Chapter 8

Extravillous Trophoblast, Trophoblastic Invasion, and Fibrinoid

General Considerations

The nonvillous parts of the placenta include the **chorionic plate, cell islands, cell columns, placental septa, basal plate, marginal zone**, and **fibrinoid deposits** (Fig. 8.1). These structures do not participate in maternofetal exchange, but have mechanical and metabolic functions. Irrespective of their location and structure, the nonvillous parts of the placenta have the same three basic components, which structurally and functionally do not vary from one area to the next:

- **Extravillous trophoblast**,
- **Fibrinoid**, and
- **Decidua**

Extravillous Trophoblast

Among placental biologists, the term **extravillous trophoblast** is in general use, whereas among gynecologic pathologists the term **intermediate trophoblast** is widely applied. Unfortunately, this latter term is misleading. It had originally been used to designate villous trophoblastic

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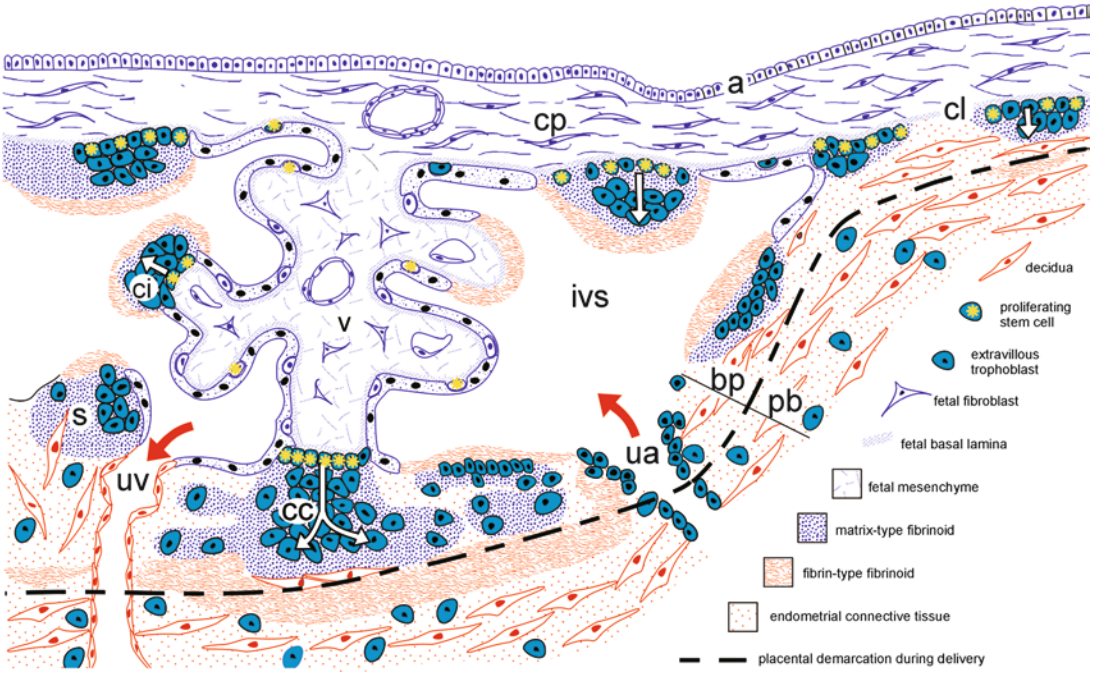

Figure 8.1. Schematic drawing of the distribution of the various trophoblast populations (*blue*) of the human placenta. Trophoblastic cells that rest on the trophoblastic basal lamina of the membranes, chorionic plate, villi, cell columns, and cell islands represent the proliferating trophoblastic stem cells (Langhans' cells). Those close to the intervillous space (ivs) differentiate and fuse to form the syncytiotrophoblast, which usually takes place in the placental villi (v). Without contact to the intervillous space, the daughter cells of the proliferating stem cells (marked by *asterisks*) do not fuse syncytially but rather differentiate and become extravillous trophoblastic cells. Their routes of invasion or migration are symbolized by *arrows*. Extravillous trophoblastic cells can be found in cell columns (c), cell islands (ci), chorionic plate (cp), chorion laeve (cl), septa (s), basal plate (bp), and uteroplacental arteries (ua). Fibrinoid (matrix-type fibrinoid) is *point-shaded*; fibrin (fibrin-type fibrinoid) is *line-shaded*.

cells that were *transitional* between villous cytotrophoblast and syncytiotrophoblast, cells that were in the process of donating their nuclei to the syncytium. The implication was that "intermediate trophoblast" was intermediate between cytotrophoblast and syncytiotrophoblast and therefore a type of *villous trophoblast*. However, the term "intermediate trophoblast" is currently used by many pathologists to indicate those cells in extravillous sites such as the implantation site, chorion laeve, chorionic plate, and so on, roughly equivalent to the traditional term **extravillous trophoblast.** However, the term "villous intermediate trophoblast," has also been used, and implies an "extravillous," "villous" trophoblast, which is essentially meaningless and its use should be discouraged. These distinctions are important in understanding the derivation and differentiation of trophoblastic tumors (see Chap. 25).

Although extravillous trophoblast is present in a variety of locations, its general structure and function are surprisingly homogeneous. Histologically, extravillous trophoblastic cells are *round to polygonal cells* that are present singly or in groups. They are usually associated with

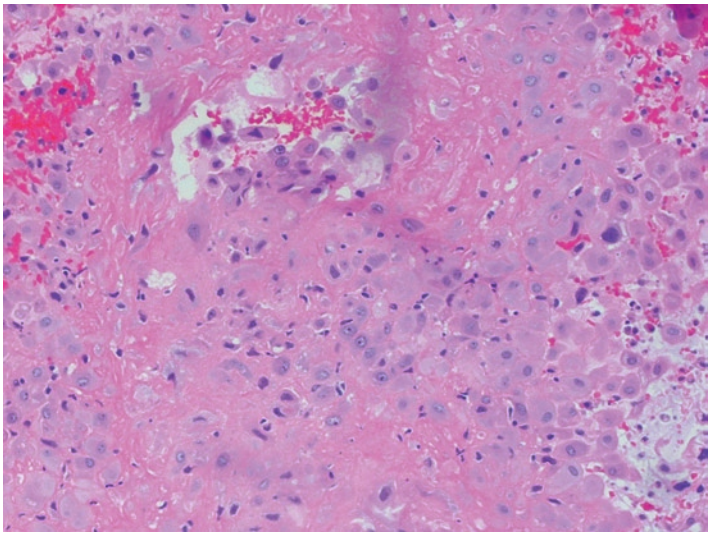

Figure 8.2. Implantation site with extravillous trophoblastic cells intermixed with decidual cells. Note that the trophoblast have hyperchromatic, irregular nuclei and the decidual cells have regular, rounded nuclei with fine chromatin and well defined cell border. H&E ×200.

fibrinoid, a type of extracellular matrix material (see below). They tend to have *pleomorphic, hyperchromatic, or irregular nuclei* (Fig. 8.2) and cytoplasm, which is usually *amphophilic* but occasionally eosinophilic. They are predominantly mononuclear, but binucleate, trinucleate, and multinucleate cells are also seen. Extravillous trophoblast in the chorionic plate and chorion laeve is often smaller and less pleomorphic than that present in the implantation site but has the same general characteristics.

Trophoblastic Stem Cells

Populations of **trophoblastic stem cells** include the *villous cytotrophoblast, the basal layers of the cell columns, the cell islands, the chorionic plate, and the chorion laeve*. It can be seen that, although these cells are in different sites, they all are in contact with the basal lamina of the fetoplacental stroma. The future fate of these stem cells, whether they acquire a villous phenotype or an extravillous phenotype, depends on the surrounding environment, that is, contact with extracellular matrix molecules (Fig. 8.1). *Transformation to extravillous trophoblast occurs on exposure to maternal blood or maternal extracellular matrix. Transformation to villous trophoblast occurs with contact to the syncytiotrophoblast*. Accordingly, the stem cells of the cell columns have a double function, contributing trophoblast for subsequent invasion *and* acting as a growth zone for villous trophoblast of the anchoring villi. Other populations of stem cells have the capacity to differentiate along both pathways but primarily contribute to either the villous or extravillous pathway.

Proliferative Phenotype

Extravillous trophoblast in the proximal portion of the cell columns is **proliferative** and will stain positively with proliferation markers such as MIB-1 (Ki-67). These proximal **proliferating extravillous trophoblastic cells** are *either in immediate contact with the basal lamina* or *separated from it by other proliferating trophoblastic cells*. These cells represent the *stem cells of the extravillous pathway of differentiation* (Figs. 8.1 and 8.3) and are said to have a proliferative phenotype.

Invasive Phenotype

Further differentiation of extravillous trophoblast results in a switch from a proliferative to an **invasive phenotype** (Fig. 8.3). In normal placentation, proliferation and invasion do not coexist in one and the same cell. *Thus, temporal and spatial separation of proliferation and invasiveness limits the depth of trophoblastic invasion*. This separation is thought to embody the major difference between "normal" trophoblastic invasion in pregnancy as compared to "malignant" invasion in tumors,

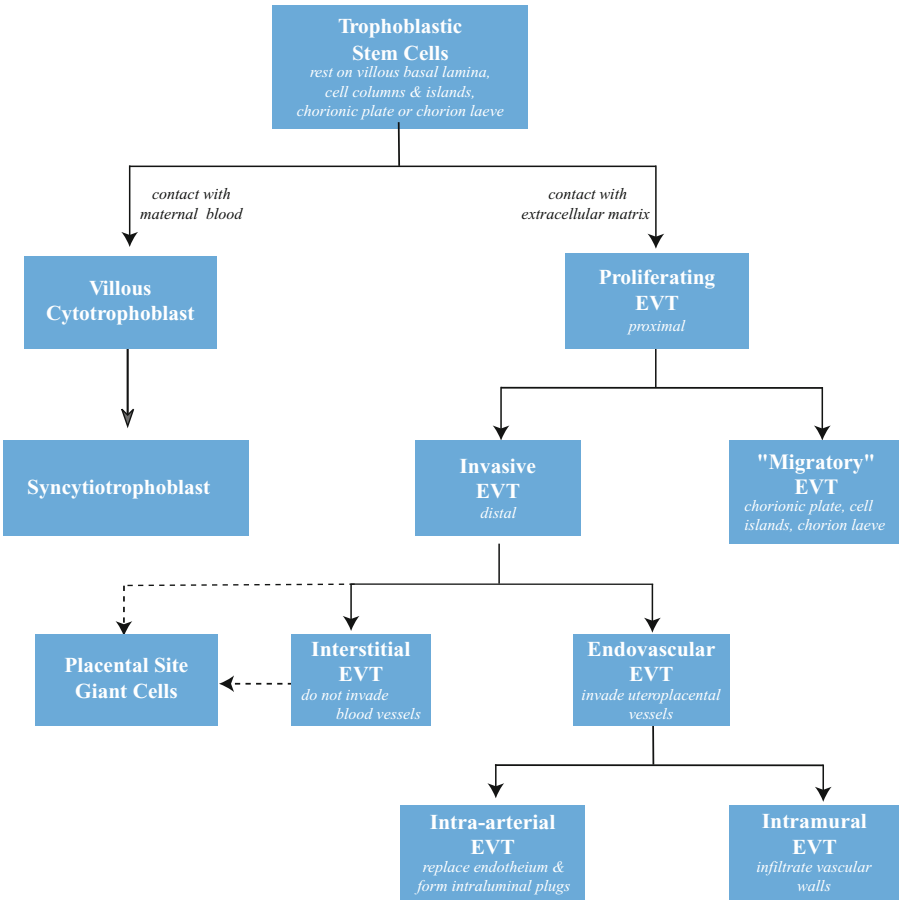

Figure 8.3. Diagram of trophoblastic differentiation. *Dotted lines* indicate possible routes. See text for discussion. *EVT* extravillous trophoblastic cells.

the latter being characterized by temporal and spatial coincidence of proliferation and invasion. Differences between the proliferative and invasive phenotypes are shown in Table 8.1.

A variant of the invasive type is the extravillous trophoblast of the chorion laeve chorionic plate and cell islands, which do not show true invasive behavior. This phenotype is often called "**migratory**." This is likely a quantitative rather than a qualitative difference as a result of downregulation by local factors in the normal intrauterine milieu. In an abnormal environment in which there is locally deficient decidualization, such as ectopic pregnancy and placenta accreta (see Chap. 12), abnormally invasive implantation occurs.

Interstitial Phenotype

The invasive extravillous trophoblast further differentiates into either an **interstitial phenotype** or **endovascular phenotype** (Fig. 8.3). *Interstitial trophoblast does not invade blood vessels, while endovascular trophoblast invades the walls and lumens of uteroplacental vessels* (Fig. 8.4). In contrast to normal epithelial cells, **interstitial extravillous trophoblast** secretes extracellular matrix in an **apolar** fashion, a feature usually only seen in mesenchymal cells. Matrix molecules accumulate extracellularly in large, three-dimensional patchy aggregates called fibrinoid, which completely embed the extravillous trophoblast (see below). Typically, this apolar matrix is secreted in the direct vicinity of maternal tissues, namely facing the maternal blood (e.g., cell islands, intervillous surface of the chorionic plate, placental septa) or maternal decidua (basal plate with cell columns, chorion laeve). As a consequence, fibrin from

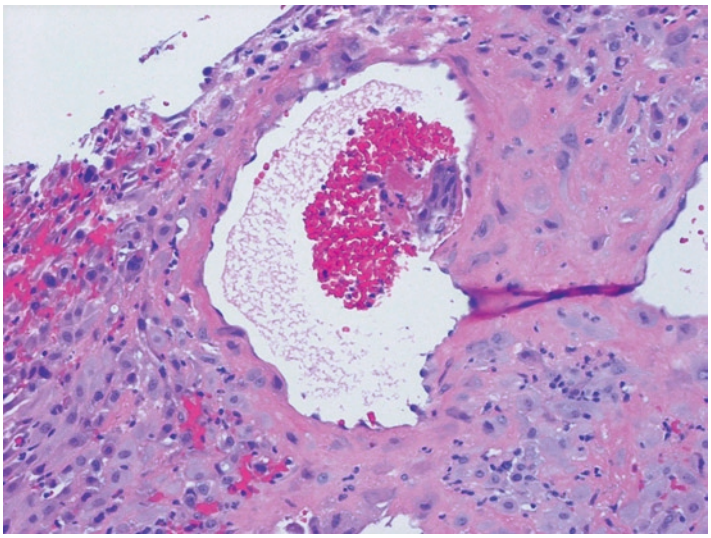

Figure 8.4. Physiologic conversion of the decidual vessel into a uteroplacental vessel by invading extravillous trophoblast. Note the fibrin in the wall, whose muscular coat is destroyed. The paler cells are decidual stromal cells, while those with dark, hyperchromatic nuclei are extravillous trophoblast. H&E ×200.

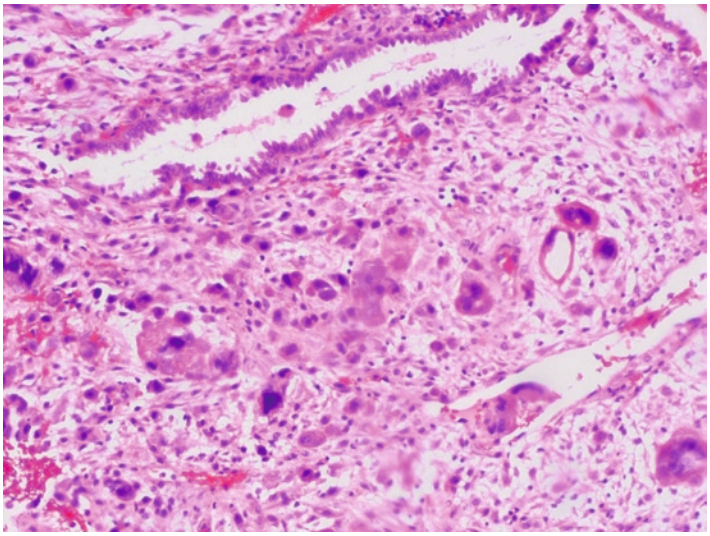

Figure 8.5. Multinucleated placental site giant cells present in the implantation site. H&E ×200.

maternal blood and decidual secretory products are added to the extracellular matrix.

The endovascular extravillous trophoblast further differentiates into **intramural extravillous trophoblast** and **intraarterial extravillous trophoblast**. The intramural trophoblast infiltrates the walls of uteroplacental vessels and therefore is essential to the conversion of decidual vessels into uteroplacental vessels. The intraarterial trophoblasts replace the endothelium, and as they do, they undergo "pseudovasculogenesis," in which they achieve an endothelial phenotype. Early in gestation, intraluminal plugs of these cells are present. However, later in pregnancy, they are an abnormal finding, often associated with other abnormalities of implantation and the decidual vessels (see Chap. 18).

Multinucleated Extravillous Trophoblast

Giant multinucleated extravillous trophoblastic cells in the implantation site and superficial myometrium are called **placental site giant cells**. Placental site giant cells tend to be *vacuolated and degenerative* (Fig. 8.5) and are occasionally found in association with fibrinoid deposits. They are thought to be highly differentiated extravillous trophoblastic cells that have *reached the end of the differentiation pathway*. Because surprisingly few invasive trophoblasts undergo apoptosis, local syncytial fusion at the end of the invasive pathway is an alternative mechanism for reducing the number of invasive trophoblast.

Decidua

The changes that occur in the human endometrium in response to the physiologic stimuli of pregnancy and implantation of the blastocyst are called *decidualization*. If the stimulus is a physiologic one, the resulting

tissue is the **decidua**, but if the stimulus is experimental or artificial, the tissue is called **pseudodecidua**. Decidualization is characterized by the enlargement of endometrial stromal cells, which eventually assume an epithelioid appearance. They become *round to polygonal, with sharply defined cell borders and a single round nucleus containing a small but prominent nucleolus* (Fig. 8.6a). The nuclei undergo endomitosis, become polyploid, and are sometimes atypical, acquiring the morphologic features known as the **Arias-Stella change** (Fig. 8.6b). Most of the glands atrophy but occasional remnants may be found in the basal plate or decidua capsularis. Within the decidual tissue are considerable numbers of hematopoietic cells including **macrophages,**

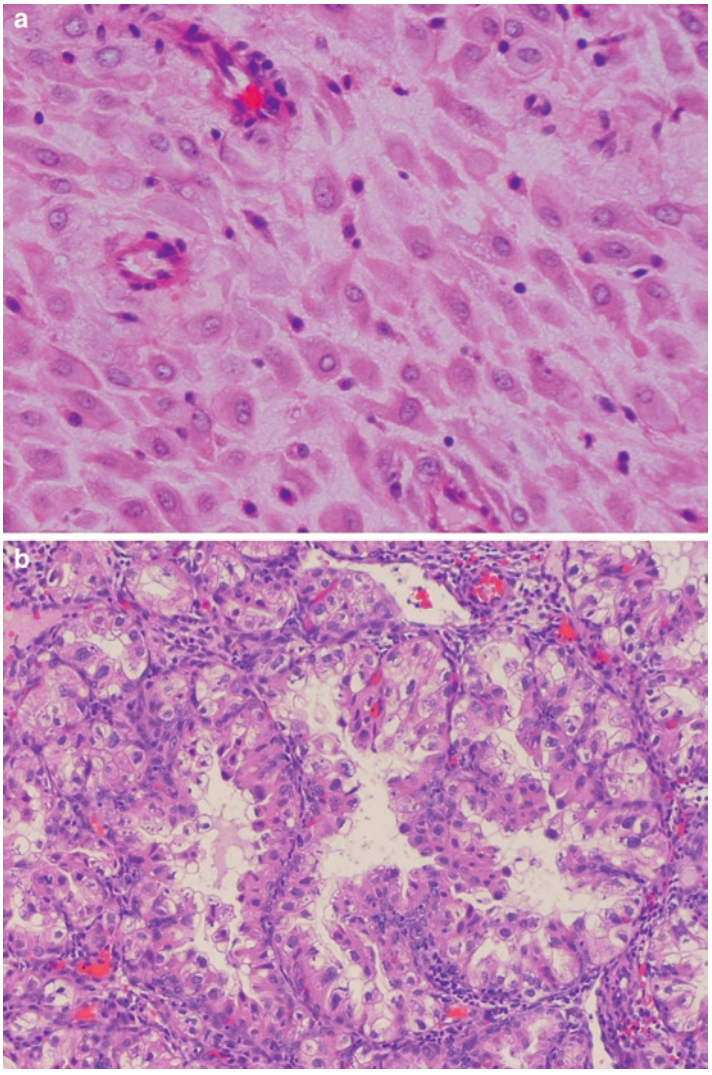

Figure 8.6. (**a**) Decidualized endometrial stromal cells showing abundant cytoplasm and vesicular nuclei H&E ×200. (**b**) Arias-Stella reaction of the decidua. Note the marked nuclear atypia and pleomorphism. H&E ×200.

T lymphocytes, granulocytes, and **large granular lymphocytes** (endometrial natural killer [NK] cells, endometrial NK cells, or "endometrial granular cells").

Fibrinoid

Fibrinoid is one of the most prominent components of the human placenta. It is a nonfibrous, acellular, relatively homogeneous material *derived from cellular secretion, cellular degeneration*, and other sources as yet unknown. Its light microscopic appearance varies from *glossy and homogeneous to lamellar, fibrous, or reticular* (Fig. 8.7). In routine sections, the color of fibrinoid varies from slightly pink to intense red. When Mallory's trichrome stain is used, the color is a light blue but may vary from dark blue to lilac or even red. *Because fibrin, blood clot, and secretory products are usually deposited in proximity and cannot be easily discriminated, the general term fibrinoid, rather than fibrin, is used*.

Fibrinoid is found throughout the placenta including the **subchorionic region** (Langhans' stria) (Figs. 8.1 and 8.7), **intervillous space** (perivillous), **chorionic villi** (intravillous), **placental septa**, **cell islands**, **cell columns**, **superficial basal plate** facing the intervillous space (Rohr's stria), **deep basal plate** (Nitabuch's stria), **uteroplacental arteries and veins** (intramural), and **fetal membranes** (chorion laeve) (see also Figs. 7.1, 7.2, and 7.4 in Chap. 7). Detailed histochemical, biochemical, immunohistochemical, ultrastructural, and experimental studies

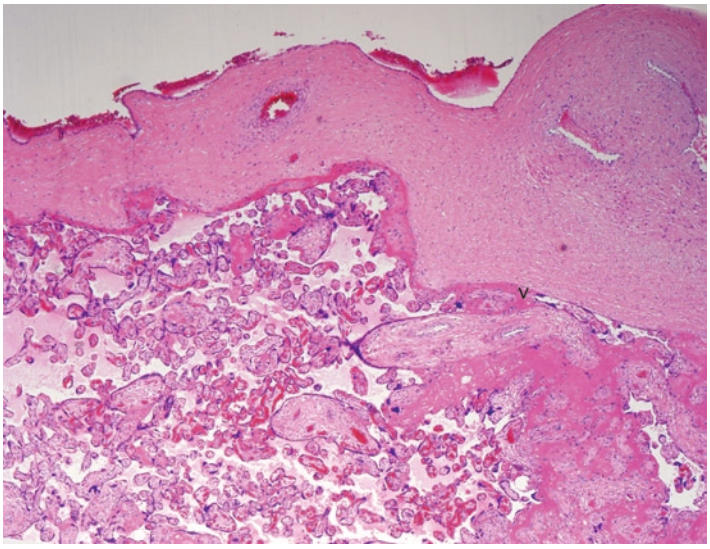

Figure 8.7. Section of the chorionic plate at the 40th week postmenstruation. There is deposition of Langhans' fibrinoid below the chorionic plate, particularly near the stem villi, near term. Clusters of extravillous trophoblast cells and residues of buried villi (V) are typically incorporated into mature Langhans' fibrinoid. ×85.

have revealed that fibrinoid is composed of two histologically similar types that differ in their origin and composition. **Fibrin-type fibrinoid** is derived from the coagulation cascade and is mainly composed of fibrin, likely derived from maternal blood and fetal plasma. **Matrix-type fibrinoid** is a secretory product of extravillous trophoblastic cells and decidual cells and is mainly composed of collagen IV and glycoproteins of the extracellular matrix. These two types are indistinguishable on H&E sections. As a general rule, **fibrin** *lines the intervillous space in all those locations where the syncytiotrophoblast layer is interrupted and is always interposed between fibrinoid and maternal blood*. **Fibrinoid** *embeds the extravillous trophoblastic cells and is found where trophoblastic migration or invasion takes place*.

Uteroplacental Vessels and Physiologic Conversion

The **uteroplacental arteries** derive from the distal segments of the uterine spiral arterioles. Trophoblastic invasion of these vessels and the subsequent alterations have been designated **physiologic conversion.** Physiologic conversion is characterized by a *loss of elastic fibers and smooth muscle cells* due to proteolytic activities of the invasive endovascular trophoblastic cells, replacement of the vessel walls by *intramural fibrin and fibrinoid*, and a considerable *increase in the luminal diameter* (see Fig. 8.4). These changes transform the originally flexible vessels into rigid channels, which are incapable of constricting. Thus the nutrient supply to the placenta will not be reduced despite changes in blood pressure in the mother. **Intraarterial trophoblastic cells** invade the spiral arterioles and *achieve an endothelial phenotype* and thus become difficult to distinguish from maternal endothelial. The majority of cells lining the lumens of uteroplacental arteries in the endometrium and inner myometrium are intraarterial trophoblast.

Table 8.1 Differences between the proliferative and invasive phenotype of extravillous trophoblast.

	Proliferative phenotype	**Invasive phenotype**
Invasion	–	+
Proliferation	+	–
Contact on or near fetal stromal basal lamina	+	–
Expression of proliferation markers	MIB-1, EGFR (c-erbB-1)	c-erbB-2
Integrin expression	Epithelial types (α6β4, α3β1)	Interstitial types (α5β1, α1β1, αvβ3, αvβ5)
Secretion of extracellular matrix	Polar	Apolar

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