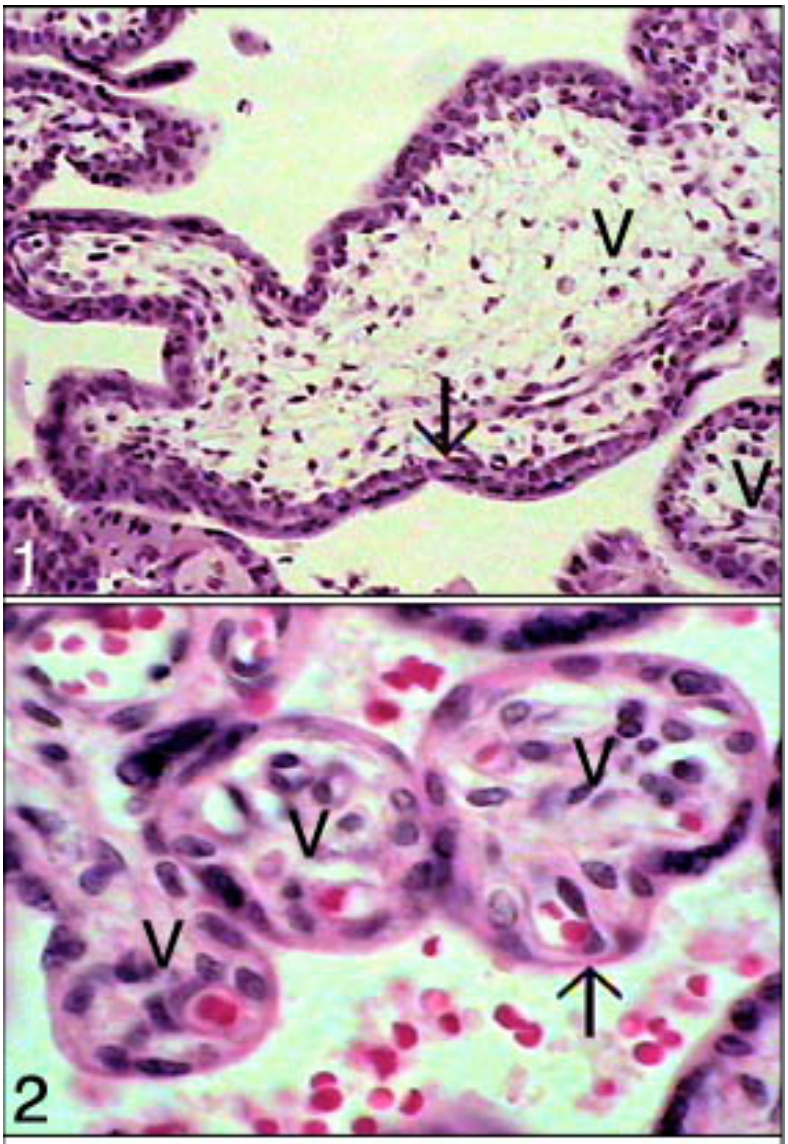
Pregnancy



1. Early placental villi (V). Note the syntrophoblast covering a single layer of cells, the cytotrophoblast (arrow).
2. Late placental villi (V). Note that the placental blood barrier (arrow) now consists only of a thin syntrophoblast, endothelial cells within villi, and a scant intervening connective tissue.

Pregnancy involves implantation of a blastocyst into a prepared uterine endometrium and subsequent formation of a placenta to nourish and maintain the developing embryo. Prior to implantation, fertilization of the ovum and cleavage of the resulting zygote usually occurs in the ampulla of the oviduct.

Fertilization

Before an ovum can be fertilized, it must undergo maturational changes, chief of which is reduction of the chromosome complement to the haploid number. The oocyte passes through the early stages of the first meiotic division during fetal life, and it is only just before ovulation that the division is completed and the first polar body is given off. The resulting secondary oocyte immediately enters the second meiotic division, which, however, proceeds only to metaphase and is not completed until fertilization occurs. At the time of ovulation, the oviduct shows active movements that bring the infundibulum and fimbria close to the ovary. Cilia on the surface of the fimbria sweep the ovum into the ampulla of the oviduct where fertilization, if it is to occur, takes place. The human ovum remains fertile for between 24 and 48 hours, after which it degenerates if fertilization does not occur. Approximately 300 million sperm are released into the vaginal lumen during coitus but it is estimated that only 300-500 spermatozoa reach the site of fertilization. These remain viable for about 72 hours. Muscular contractions within the walls of the uterus and oviduct propel the spermatozoa to the proximal region (ampulla) of the oviduct where fertilization takes place. The smooth muscle cells are thought to contract in response to prostaglandins and/or oxytocin released during sexual intercourse.
Of the millions of sperm initially deposited in the female tract, only one penetrates the ovum. There is no evidence for chemotactic attraction, and random movement brings sperm and ovum together. The zona pellucida is important in fertilization as it provides sperm recognition sites for sperm binding and is the most efficient trigger of the sperm acrosome reaction. Both sperm binding and induction of the acrosome reaction are ligand-receptor interactions, the ligands of which are located in the ZP3 glycoprotein of the zona pellucida. The acrosome reaction results in the release of acrosomal enzymes (acrosin and trypsin-like enzymes) needed to digest a hole in the zona pellucida. At the time of fertilization, when a spermatozoon pushes through the hole in the zona pellucida to enter the ovum, a period of hyperactivity of flagellar beat occurs, propelling the spermatozoon into the ovum. The entire spermatozoon is engulfed by the cytoplasm of the ovum. Thus, flagellar beat appears to be more important at the moment of fertilization rather than getting to the site of fertilization. Electron micrographs suggest that the plasma membranes of the sperm and ovum fuse, that of the spermatozoon being left at the surface of the ovum. Penetration is followed by release of electron-dense cortical granules that underlie the plasmalemma of the ovum (cortical granule reaction) and by immediate changes in the permeability of the zona pellucida, which thereafter excludes entry by any additional competing sperm (polyspermy). The ovum now completes the second maturation division and extrudes the second polar body. The remaining chromosomes (23) reconstitute and form the female pronucleus. The nucleus (head) of the spermatozoon swells and forms the male pronucleus, and the sperm body and tail are resorbed. The two pronuclei move to the center of the cell, and two centrioles, supplied by the anterior centriole of the spermatozoon, appear. The chromatin of each pronucleus resolves into a set of chromosomes that align themselves on a spindle to undergo a normal mitotic division of the first cleavage. Each cell resulting from this division receives a full diploid set of chromosomes.

Cleavage

The zygote undergoes a series of rapid divisions called cleavage that result in a large number of cells, the blastomeres. The cells are bounded by the zona pellucida, and a mulberry-like body, the morula, is formed. Cleavage is a fractionating process: no new cytoplasm is formed, and at each division the cells become smaller until a normal, predetermined, cytoplasmic-

nuclear ratio is reached. Thus, the total size of the morula is not increased. Cleavage occurs as the morula slowly is moved along the oviduct by the waves of peristaltic contractions in the muscle coat. When the morula reaches the uterine cavity, it is at the 12- to 16-cell stage.
At about this time, fluid penetrates the zona pellucida and diffuses between the cells of the morula. The fluid increases in amount, the intercellular spaces become confluent, and a single cavity, the blastocele, is formed. The morula has now become a blastocyst that forms a hollow sphere containing, at one pole, a mass of cells called the inner cell mass that will form the embryo proper. The capsule-like wall of the blastocyst consists of a single layer of cells, the trophoblast. After reaching a critical mass, the blastocyst breaks through the surrounding zona pellucida and remains free within the uterine cavity for about a day; then it attaches to the endometrium, which is in the secretory phase. Encasement within the zona pellucida protects the forming blastocyst from the possible damaging effects of oviductal movements, possible adverse effects of oviductal and uterine secretions, and/or destruction by maternal tissues until it reaches a critical mass for survival. During cleavage, the zona pellucida progressively thins and coupled with the expansion of the blastocoele, the blastocyst hatches and crawls through and out of the surrounding zona pellucida. The hatched blastocyst makes contact with the maternal endometrial surface through apposition of its trophectoderm to the uterine lining epithelial cells. The initial contact is mediated by cell surface oligosaccharides that play an important role in recognition, adhesion and attachment to the uterine epithelium. Following these events, trophoblast cells penetrate between surface uterine epithelial cells and establish direct contact with underlying decidual cells.

Implantation

At the time of implantation, the endometrium is in the secretory phase and, having been under the influence of progesterone from the corpus luteum for several days, has reached its greatest thickness and development. Implantation is initiated by close approximation of the trophoblast to the microvilli and surface projections of the uterine epithelial cells. At the points of contact, the cytoplasm of the trophoblast contains clusters of coated vesicles and numerous lysosomes. The microvilli shorten and disappear, and the trophoblast extends finger-like processes between the uterine epithelial cells, and the two layers become closely locked by numerous tight junctions that develop between them. The uterine epithelial cells degenerate and are engulfed by the trophoblast, the cellular debris appearing in phagosomes within the trophoblast cytoplasm. Where it is fixed to the endothelium, the trophoblast proliferates to form a cellular mass between the blastocyst and maternal tissues. No cell boundaries can be made out in this cell mass, which is called the syncytial trophoblast. The syncytium continues to erode the endometrium at the point of contact, creating a ragged cavity into which the blastocyst sinks, gradually becoming more deeply embedded until it lies entirely within the endometrial stroma. A fibrin plug closes the surface defect in the endometrium temporarily. Later, proliferation of surrounding cells restores the surface continuity of the endometrial lining. As the blastocyst sinks into the endometrium, the syncytial trophoblast rapidly increases in thickness at the original site of attachment and progressively extends to cover the remainder of the blastocyst. When completely embedded, the entire wall of the blastocyst consists of a thick outer syncytial trophoblast and an inner cytotrophoblast, which is composed of a single layer of cells with well-defined boundaries. The cytotrophoblast shows active mitosis and contributes cells to the syncytial trophoblast, where they fuse with and become part of that layer. The syncytial trophoblast continues to erode the uterine tissues, opening up the walls of maternal blood vessels. Spaces appear in the syncytial trophoblast and these lacunae expand, become

confluent, and form a labyrinth of spaces. Many of the spaces contain blood from eroded maternal blood vessels; this blood supplies nourishment for the embryo and represents the first step in the development of uteroplacental circulation.

Placenta

As the lacunae enlarge, intervening strands of trophoblast form the primary villi that cover the entire periphery of the blastocyst. Each villus consists of a core of cytotrophoblast covered by a layer of syncytial trophoblast. Trophoblastic cells at the tips of the villi apply themselves to the endometrium and form a lining for the cavity in which the blastocyst lies. When the embryonic germ layers have been established, mesoderm grows out from the embryo as the chorion and forms a lining for the trophoblast that surrounds the blastocyst. Mesoderm extends into the primary villi to form a core of connective tissue and convert the primary villi to secondary villi. The deeply embedded portion of the chorion constitutes the chorionic plate from which numerous villi project to form the chorion frondosum. Villi on that part of the chorion facing the uterine cavity grow more slowly and are less numerous; ultimately, these villi disappear; leaving a smooth surface that forms the chorion laeve. Blood vessels develop in the mesenchymal cores of the secondary villi and soon make connection with the fetal circulation. With vascularization, the secondary villi become the definitive or tertiary placental villi.
At parturition, all but the deepest layers of the endometrium are shed; thus the superficial part of the endometrium is called the decidua. A feature of the stroma is the alteration of its cells to form enlarged, decidual cells that contain much glycogen. According to the relationship with the implantation site, three areas of the decidua are recognized. The decidua capsularis is the part that lies over the surface of the blastocyst, while the decidua basalis underlies the implantation site and forms the maternal component of the placenta. The endometrium lining the remainder of the pregnant uterus is the decidua parietalis. As the embryo grows, the decidua capsularis becomes increasingly attenuated. Eventually, the decidua capsularis makes contact with decidua parietalis on the opposite surface of the uterus, and the uterine cavity is obliterated. The mature placenta consists of maternal and fetal components. The maternal part is decidua basalis; the fetal portion consists of the chorionic plate and the villi arising from it. Maternal blood circulates through the intervillous spaces and bathes the villi, of which there are two types. Some pass from the chorionic plate to decidua basalis as anchoring villi from which secondary and tertiary branches float in the intervillous spaces as the floating villi. Both types of villi consist of a core of loose connective tissue in which lie fetal capillaries. Covering each villus is an inner layer of cytotrophoblast cells, which have large nuclei and lightly basophilic cytoplasm containing considerable glycogen. External to the cytotrophoblast is a layer of syncytial trophoblast of variable thickness. The cells of the cytotrophoblast decrease in number in the latter half of pregnancy, and only a very few are present at term. The syncytial trophoblast also thins out to form a narrow layer. The placenta transfers oxygen and nutrients from the maternal to the fetal circulation and waste products from the fetal to the maternal circulation. Although maternal and fetal circulations are closely apposed, they remain separated by the syncytial trophoblast (and early in pregnancy by the cytotrophoblast also), a basement membrane, the connective tissue of the villi, and the wall of the fetal blood vessels. Transport of material between fetal and maternal blood appears to be regulated by the syncytial trophoblast. Being without cell boundaries and intercellular spaces, any materials passing into or out of the fetal blood must pass through the cell membranes and cytoplasm of the syncytium. Electrolytes, steroids, fatty acids, oxygen, and carbon dioxide traverse the syncytial trophoblast by passive diffusion. Other substances, such as glucose, cross this

barrier by carrier molecules. In addition, the syncytial trophoblast plasmalemma contains receptors for macromolecules such as transferrin, insulin, and immunoglobulins that are taken in by receptor-mediated endocytosis and cross the epithelial barrier in transport vesicles. The cytotrophoblast continues to serve as the source of cells for the syncytial trophoblast. The placenta also is a multipotential endocrine organ essential for maintaining pregnancy. The trophoblast secretes a glycoprotein, human chorionic gonadotrophin (hCG) that can be detected by the end of the first week after fertilization. It increases in amount to the fifth week of pregnancy and maintains and stimulates the corpus luteum to secrete estrogens and progesterone during early pregnancy. The placenta also secretes estrogens and progesterone that aid in maintaining the uterine environment for continued fetal development. At about 9 weeks' gestation the placenta takes over the production of progesterone. A variety of other factors, similar to releasing hormones of the hypothalamus as well as pituitary-like hormones, are synthesized and released by the placenta into the maternal blood. One of these, human chorionic somatomammotropin or hCS (also referred to as human placental lactogen) is important not only in breast development and lactation but also in making glucose available from the maternal circulation for both the placenta and fetus. Human chorionic somatomammotropin imparts a condition of insulin resistance to the mother so that glucose rather than being rapidly removed from the circulation by maternal tissues is available for the developing fetus.