Fetal Membranes and Placenta

As the fetus grows, its demands for nutritional and other factors increase causing major changes in the placenta. Foremost among these is an increase in surface area between maternal and fetal components to facilitate exchange. The disposition of fetal membranes is also altered as production of amniotic fluid increases.

Changes in the Trophoblast

By the beginning of the second month, the trophoblast is characterized by a great number of secondary and tertiary villi that give it a radial appearance. The villi are anchored in the mesoderm of the chorionic plate and are attached peripherally to the maternal decidua by way of the outer cytotrophoblast shell. The surface of the villi is formed by the syncytium, resting on a layer of cytotrophoblastic cells that in turn cover a core of vascular mesoderm. The capillary system developing in the core of the villous stems soon comes in contact with capillaries of the chorionic plate and connecting stalk, thus giving rise to the extraembryonic vascular system. During the following months, numerous small extensions sprout from existing villous stems into the surrounding lacunar or intervillous spaces. Initially these newly formed villi are primitive, but by the beginning of the fourth month, cytotrophoblastic cells and some connective tissue cells disappear. The syncytium and endothelial wall of the blood vessels are then the only layers that separate the maternal and fetal circulations. Frequently the syncytium becomes very thin, and large pieces containing several nuclei may break off and drop into the intervillous blood lakes. These pieces, known as syncytial knots, enter the maternal circulation and usually degenerate without causing any symptoms. Disappearance of cytotrophoblastic cells progresses from the smaller to larger villi, and although some always persist in large villi, they do not participate in the exchange between the two circulations.

ChorionFrondosum and Decidua Basalis

In the early weeks of development, villi cover the entire surface of the chorion. As pregnancy advances, villi on the embryonic pole continue to growand expand, giving rise to the chorionfrondosum (bushy chorion). Villi on the abembryonic pole degenerate and by the third month this side of the chorion,now known as the chorionlaeve, is smooth. The difference between the embryonic and abembryonic poles of the chorion is also reflected in the structure of the decidua, the functional layerof the endometrium, which is shed during parturition. The decidua over the chorionfrondosum, the decidua basalis, consists of a compact layer of large cells, decidual cells, with abundant amounts of lipids and glycogen. This layer, the decidual plate, is tightly connected to the chorion. The decidual layer overthe abembryonic pole is the decidua capsularis. With growth of the chorionic vesicle, this layer becomes stretched and degenerates. Subsequently,the chorionlaeve comes into contact with the uterine wall (decidua parietalis) on the opposite side of the

uterus and the two fuse, obliteratingthe uterine lumen. Hence the only portion of the chorion participating in the exchange process is the chorion frondosum, which, together with the deciduasbasalis, makes up the placenta. Similarly, fusion of the amnion and choriontо form the amniochorionic membrane obliterates the chorionic cavity. It is this membrane that ruptures during labor (breakingof the water).

Structure of the Placenta

By the beginning of the fourth month, the placenta has two components:
(a) afetal portion, formed by the ***chorionfrondosum***; and
(b) a maternal portion,formed by the ***decidua basalis***.

On the fetal side, the placenta is borderedby the chorionic plate; on its maternal side, it is bordered by the decidua basalis, of which the decidual plate is most intimately incorporated into the placenta. In the junctional zone, trophoblastand decidua cells intermingle. This zone, characterized by decidual and syncytial giant cells, is rich in amorphous extracellular material. By this time most cytotrophoblast cells have degenerated. Between the chorionic and decidual plates are the intervillous spaces, which are filled with maternal blood. They are derived from lacunae inthe syncytiotrophoblast and are lined with syncytium of fetal origin. The villoustrees grow into the intervillousblood lakes. During the fourth and fifth months the decidua forms a number of decidual septa, which project into intervillous spaces but do not reach the chorionic plate. These septa have a core of maternal tissue, but their surface is covered by a layer of syncytial cells, so that at all times a syncytial layer separates maternal blood in intervillous lakes fromfetal tissue of the villi. As a result of this septum formation, the placenta is divided into a number of compartments, or cotyledons. Since the decidual septa do not reach the chorionic plate, contact between intervillous spaces in the various cotyledons is maintained. As a result of the continuous growth of the fetus and expansion of the uterus, the placenta also enlarges. Its increase in surface area roughly parallel sthat of the expanding uterus and throughout pregnancy it covers approximately15 to 30% of the internal surface of the uterus. The increase in thickness of the placenta results from arborization of existing villi and is not caused by further penetration into maternal tissues.

Full-Term Placenta

At full term, the placenta is discoid with a diameter of 15 to 25 cm, is approximately3 cm thick, and weighs about 500 to 600 g. At birth, it is torn from the uterine wall and, approximately 30 minutes after birth of the child, is expelled from the uterine cavity. After birth, when the placenta is viewed from the maternal side, 15 to 20 slightly bulging areas, the cotyledons, covered by a thin layer of decidua basalis, are clearly recognizable. Grooves between the cotyledons are formed by decidual septa. The fetal surface of the placenta is covered entirely by the chorionic plate. A number of large arteries and veins, the chorionic vessels, converge toward

the umbilical cord. The chorion, in turn, is covered by the amnion. Attachment of the umbilical cord is usually eccentric and occasionally even marginal. Rarely, however, does it insert into the chorionic membranes outsidethe placenta.

Circulation of the Placenta

Cotyledons receive their blood through 80 to 100 spiral arteries that piercethe decidual plate and enter the intervillous spaces at more or less regular intervals. The lumen of the spiral artery is narrow, so blood pressurein the intervillous space is high. This pressure forces the blood deep intothe intervillous spaces and bathes the numerous small villi of the villous treein oxygenated blood. As the pressure decreases, blood flows back from thechorionic plate toward the decidua, where it enters the endometrial veins. Hence, blood from the intervillous lakes drains back into the maternalcirculation through the endometrial veins. Collectively, the intervillous spaces of a mature placenta contain approximately150 ml of blood, which is replenished about 3 or 4 times per minute. This blood moves along the chorionic villi, which have a surface area of 4 to 14 m2.However, placental exchange does not take place in all villi, only in those whosefetal vessels are in intimate contact with the covering syncytial membrane.In these villi, the syncytium often has a brush border consisting of numerousmicrovilli, which greatly increases the surface area and consequently the exchangerate between maternal and fetal circulations. The placentalmembrane, which separates maternal and fetal blood, is initially composedof four layers:

(a) the endothelial lining of fetal vessels;
(b) the connective tissue in the villus core;
(c) the cytotrophoblastic layer; and
(d) the syncytium.

From the fourth month on, however, the placental membranethins, since the endothelial lining of the vessels comes in intimate contact withthe syncytial membrane, greatly increasing the rate of exchange.Sometimes called the placental barrier, the placental membrane is not a truebarrier, since many substances pass through it freely. Because the maternalblood in the intervillous spaces is separated from the fetal blood by a chorionicderivative, the human placenta is considered to be of the hemochorial type.

Functions of the Placenta

The Main functions of the placenta are

(a) **exchange of metabolic and gaseous** products between maternal and fetal bloodstreams and

-Exchange of gases, such as oxygen, carbon dioxide,

-Exchange of Nutrients and Electrolytes, such as amino acids, free fatty acids,carbohydrates, and vitamins, is rapid and increases as pregnancy advances.

-**Transmission of Maternal Antibodies** Immunological competence begins to develop late in the first trimester, by which time the fetus makes all of the components of complement. Immunoglobulins consist almost entirely of maternal immunoglobulin G (IgG)that begins to be transported from mother to fetus at approximately 14 weeks. In this manner, the fetus gains passive immunity against various infectiousdiseases. Newborns begin to produce their own IgG, but adult levels are notattained until the age of 3 years.

(b) **production of hormones.**

By the end of the fourth month the placenta produces ***progesterone*** in sufficientamounts to maintain pregnancy if the corpus luteum is removed or fails to function properly. In all probability, all hormones are synthesized in the syncytialtrophoblast. In addition to progesterone, the placenta produces increasingamounts of ***estrogenic hormones, predominantly estriol,*** until just before theend of pregnancy, when a maximum level is reached. These high levels ofestrogens stimulate uterine growth and development of the mammary glands. During the first two months of pregnancy, the syncytiotrophoblast alsoproduces ***human chorionic gonadotropin (hCG),***which maintains the corpusluteum. This hormone is excreted by the mother in the urine, and in theearlstages of gestation, its presence is used as an indicator of pregnancy. Anotherhormone produced by the placenta is somatomammotropin (formerly placentallactogen). It is a growth hormone-like substance that gives the fetus priorityon maternal blood glucose and makes the mother somewhat diabetogenic. Italso promotes breast development for milk production.

Amnion and Umbilical Cord

The oval line of reflection between the amnion and embryonic ectoderm(amnio-ectodermal junction) is the primitive umbilical ring. ***At the fifth week of development, the following structures pass through the ring:***

(a) the connecting stalk, containing the allantois and the umbilical vessels, consisting of two arteries and one vein;

(b) the yolk stalk (vitelline duct), accompanied by the vitelline vessels; and

(c) the canal connecting the intraembryonic and extraembryonic cavities.

The yolk sac properoccupies a space in the chorionic cavity, that is, the space between the amnion and chorionic plate. During further development, the amniotic cavity enlarges rapidly at the expenseof the chorionic cavity, and the amnion begins to envelop the connectingand yolk sac stalks, crowding them together and giving rise to the primitive umbilical cord. Distally the cord contains the yolk sac stalk andumbilical vessels. More proximally it contains some intestinal loops and theremnant of the allantois. The yolk sac, found in the chorioniccavity, is connected to the umbilical cord by its stalk. At the end of the thirdmonth, the amnion has

expanded so that it comes in contact with the chorion,obliterating the chorionic cavity. The yolk sac then usually shrinksand is gradually obliterated.

The abdominal cavity is temporarily too small for the rapidly developing intestinal loops and some of them are pushed into the extraembryonic spacein the umbilical cord. These extruding intestinal loops form a physiologicalumbilical hernia. At approximately the end of the third month, the loops are withdrawn into the body of the embryo and the cavityin the cord is obliterated. When the allantois and the vitelline duct and its vessels are also obliterated, all that remains in the cord are the umbilicalvessels surrounded by the jelly of Wharton. This tissue, which is rich in proteoglycans,functions as a protective layer for the blood vessels. The walls of the arteries are muscular and contain many elastic fibers, which contribute toa rapid constriction and contraction of the umbilical vessels after the cord istied off.

Placental Changes at the End of Pregnancy

At the end of pregnancy, a number of changes that occur in the placentamay indicate reduced exchange between the two circulations. These changes138 Part One: General Embryologyinclude

(a) an increase in fibrous tissue in the core of the villus,
(b) thickening of basement membranes in fetal capillaries,
(c) obliterative changes in small capillaries of the villi, and
(d) deposition of fibrinoid on the surface of the villi in the junctional zone and in the chorionic plate.

Excessivefibrinoid formation frequently causes infarction of an intervillous lakeor sometimes of an entire cotyledon. The cotyledon then assumes a whitishappearance.

Amniotic Fluid

The amniotic cavity is filled with a clear, watery fluid that is produced in part by amniotic cells but is derived primarily from maternal blood. The amount of fluid increases from approximately 30 ml at 10 weeks of gestation to 450 ml at 20 weeks to 800 to 1000 ml at 37 weeks. During the early months of pregnancy,the embryo is suspended by its umbilical cord in this fluid, which serves as aprotective cushion. The fluid:

(a) absorbs jolts,
(b) prevents adherence of the embryo to the amnion, and
(c) allows for fetal movements.

The volume of amniotic fluid is replaced every 3 hours. From the beginning of the fifth month, the fetus swallows its own amniotic fluid and it is estimated that it drinks about 400 ml a day, about half of the total amount. Fetal urine is added daily to the amniotic fluid in the fifth month, but this urine is mostly water, since the placenta is functioning as an exchange for metabolic wastes. During childbirth,the

amnio-chorionic membrane forms a hydrostatic wedge that helps to dilatethe cervical canal.

Fetal Membranes in Twins

Arrangement of fetal membranes in twins varies considerably, depending onthe type of twins and on the time of separation of monozygotic twins.

DIZYGOTIC TWINS

Approximately two-thirds of twins are dizygotic, or fraternal, and their incidenceof 7 to 11 per 1000 births increases with maternal age. They result from simultaneous shedding of two oocytes and fertilization by different spermatozoa. Since the two zygotes have totally different genetic constitutions, the twinshave no more resemblance than any other brothers or sisters. Theymay or maynot be of different sex. The zygotes implant individually in the uterus, and usuallyeach develops its own placenta, amnion, and chorionic sac.Sometimes, however, the two placentas are so close together that they fuse.Similarly, the walls of the chorionic sacs may also come into close apposition and fuse. Occasionally, each dizygotic twin possesses red bloodcells of two different types (erythrocyte mosaicism), indicating that fusion ofthe two placentas was so intimate that red cells were exchanged.

MONOZYGOTIC TWINS

The second type of twins, which develops from a single fertilized ovum, ismonozygotic, or identical, twins. The rate for monozygotic twins is 3 to 4 per1000. They result from splitting of the zygote at various stages of development.The earliest separation is believed to occur at the two-cell stage, in which casetwo separate zygotes develop. The blastocysts implant separately, and eachembryo has its own placenta and chorionic sac. Although thearrangement of the membranes of these twins resembles that of dizygotictwins, the two can be recognized as partners of a monozygotic pair by theirstrong resemblance in blood groups, fingerprints, sex, and external appearance,such as eye and hair color.Splitting of the zygote usually occurs at the early blastocyst stage. The innercell mass splits into two separate groups of cells within the same blastocyst cavity. The two embryos have a common placenta and a common chorionic cavity, but separate amniotic cavities. In rare cases theseparation occurs at the bilaminar germ disc stage, just before the appearanceof the primitive streak. This method of splitting results in formationof two partners with a single placenta and a common chorionic and amnioticsac. Although the twins have a common placenta, blood supply is usually wellbalanced.Although triplets are rare (about 1/7600 pregnancies), birth of quadruplets,quintuplets, and so forth is rarer. In recent years multiple births have occurredmore frequently in mothers given gonadotropins (fertility drugs) for ovulatoryfailure.

Clinical correlates with Placenta

ErythroblastosisFetalis and Fetal Hydrops

Over 400 red blood cell antigens have been identified, and although most do not cause problems during pregnancy, some can stimulate a maternal antibody response against fetal blood cells. This process is an example of **isoimmunozation,** and if the maternal response is sufficient, the antibodies will attack and hemolyze fetal red blood cells resulting in **hemolytic diseaseof the newborn (erythroblastosisfetalis)**. The anemia may become so severe that **fetal hydrops**(edema and effusions into the body cavities) occurs, leading to fetal death. Most severe cases are caused by antigens from the **CDE(Rhesus)** blood group system.*The D or **Rh antigen** is the most dangerous, since immunization can result from a single exposure and occurs earlier and with greater severity with each succeeding pregnancy. The antibody response occurs in cases where the fetus is D(Rh) positive and the mother is D(Rh) negative and is elicited when fetal red blood cells enter the maternal system due to small areas of bleeding at the surface of placental villi or at birth.* Analysis of amniotic fluid for bilirubin, a breakdown product of hemoglobin, serves as a measure of the degree of red cell hemolysis. Treatment for the affected
fetus involves intrauterine or postnatal transfusions. However, the disease is prevented by identifying women at risk using an antibody screen and treating them with anti-D-immunoglobulin. Antigens from the **ABO blood group** can also elicit an antibody response, but the effects are much milder than those produced by the CDE group. About 20% of all infants have an ABO maternal incompatibility, but only 5% will be clinically affected. These can be effectively treated postnatally.

The Placental Barrier

Most maternal hormones do not cross the placenta. The hormones that do cross, such as thyroxine, do so only at a slow rate. Some synthetic progestinsrapidly cross the placenta and may masculinize female fetuses. Even more dangerous was the use of the synthetic estrogen **diethylstilbestrol,** which easily crosses the placenta. ***This compound produced carcinoma of the vagina and abnormalities of the testes in individuals who were exposed to it during their intrauterine life.***Although the placental barrier is frequently considered to act as a protective mechanism against damaging factors, many viruses, such as rubella, cytomegalovirus, Coxsackie, variola, varicella, measles, and poliomyelitis virus, traverse the placenta without difficulty. Once in the fetus, some viruses cause infections, which may result in cell death and birth defects.
Unfortunately, most drugs and drug metabolites traverse the placenta without difficulty, and many cause serious damage to the embryo. In addition, maternal use of heroin and cocaine can cause habituation in the fetus.

Umbilical Cord Abnormalities

At birth, the umbilical cord is approximately 2 cmin diameter and 50 to 60 cm

long. It is tortuous, causing **false knots.** An extremely long cord may encirclethe neck of the fetus, usually without increased risk, whereas a short one maycause difficulties during delivery by pulling the placenta from its attachment in the uterus. Normally there are two arteries and one vein in the umbilical cord. ***In 1 in 200 newborns, however, only one artery is present, and these babies have approximately a 20% chance of having cardiac and other vascular defects.***The missing artery either fails to form (agenesis) or degenerates early in development.

Amniotic Bands

Occasionally, tears in the amnion result in **amniotic bands** that may encircle part of the fetus, particularly the limbs and digits. Amputations, **ring constrictions,** and other abnormalities, including craniofacial deformations, mayresult. Origin of the bands is probably frominfection or toxic insultsthat involve either the fetus, fetal membranes, or both. Bands then form fromthe amnion, like scar tissue, constricting fetal structures.

Amniotic Fluid

Hydramniosor **polyhydramnios**is the term used to describe an excess of amniotic fluid (1500–2000 ml), whereas **oligohydramnios**refers to a decreased amount (less than 400 ml). Both conditions are associated with an increase in the incidence of birth defects. Primary causes of hydramnios include idiopathic causes (35%), maternal diabetes (25%), and congenital malformations, including central nervous system disorders (e.g., anencephaly) and gastrointestinal defects (atresias, e.g., esophageal) that prevent the infant from swallowing the fluid. Oligohydramnios is a rare occurrence that may result from renal agenesis. Premature rupture of the amnion, the most common cause of preterm labor, occurs in 10% of pregnancies. Furthermore, clubfoot and lung hypoplasia may be caused by **oligohydramnios**following amnion rupture. Causes of rupture are largely unknown, but in some cases trauma plays a role.

Twin Defects

Twin pregnancies have a high incidence of perinatal mortality and morbidity and a tendency toward preterm delivery. Approximately 12% of premature infants are twins and twins are usually small at birth. Low birth weight and prematurity place infants of twin pregnancies at great risk, and approximately 10 to 20% of them die, compared with only 2% of infants from single pregnancies. The incidence of twinning may be much higher, since twins are conceived more often than they are born. Many twins die before birth and some studies indicate that only 29% of women pregnant with twins actually give birth to two infants. The term **vanishing twin** refers to the death of one fetus. This disappearance, which occurs in the first trimester or early second trimester, may result from resorption or formation of a **fetus papyraceus**.

Another problem leading to increased mortality among twins is the ***twin transfusion syndrome, which occurs in 5 to 15% of monochorionicmonozygotic pregnancies.*** In this condition, placental vascular anastomoses, which occur in a balanced arrangement in most monochorionic placentas, are formed so that one twin receives most of the blood flow and flow to the other is compromised. As a result, one twin is larger than the other. The outcome is poor, with the death of both twins occurring in 60 to 100% of cases. At later stages of development, partial splitting of the primitive node and streak may result in formation of **conjoined (Siamese) twins.** These twins are classified according to the nature and degree of union as **thoracopagus**(*pagos*, fastened); **pygopagus;** and **craniopagus**. Occasionally, monozygotic twins are connected only by a common skin bridge or by a common liver bridge. The type of twins formed depends upon when and to what extent abnormalities of the node and streak occurred.

Preterm Birth

Factors initiating labor are not known and may involve: **"retreat from maintenance of pregnancy"** in which pregnancy supporting factors (e.g., hormones,etc.) are withdrawn; or **active induction** caused by stimulatory factors targetingthe uterus. Probably, components of both phenomena are involved.Unfortunately, a lack of knowledge about these factors has restricted progressin preventing **preterm birth.** Preterm birth (delivery before 34 weeks) of premature infants is the second leading cause of infant mortality in the UnitedStates and also contributes significantly to morbidity. ***It is due to premature rupture of the membranes, premature onset of labor, or pregnancy complicationsrequiring premature delivery.*** Maternal hypertension and diabetes aswell as abruptio placenta are risk factors. Maternal infections, including bacterialvaginosis, are also associated with an increased risk.