Chapter 11

Abortion and the Placenta in Chromosomal Anomalies

General Considerations

For purposes of the present discussion, an abortion will be defined as a conceptus expelled, removed or delivered before the 20th week of gestation. Local statutes and regulations, particularly state regulations, vary in the definition of what constitutes an abortion and thus viability, but 20 weeks is most commonly used. Furthermore, the definitions of abortion and the age of viability are vastly different from country to country, even reaching the level of 28 weeks in some countries, rendering the statistics on abortions, pregnancy loss, and neonatal and infant morbidity and mortality completely useless in comparing populations worldwide.

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The pathogenesis of pregnancy loss varies considerably depending on gestational age. Failure at less than 12 weeks is most commonly due to chromosomal or immune mediated phenomena. Loss between 12 and 20 weeks is uncommon and the etiology varies. Loss between 20 and 30 weeks is usually secondary to ascending infection and acute chorioamnionitis.

Abortions may be of several types, which are defined clinically as follows:

- **Induced** or voluntary, which include
  - **therapeutic –** electively terminated
  - **criminal –** illegally instrumented
- **Spontaneous** or involuntary, which include
  - **threatened –** uterine bleeding without cervical dilatation
  - **inevitable –** uterine bleeding with cervical dilatation or effacement
  - **incomplete –** all tissue has not yet passed
  - **missed –** intrauterine retention after embryonic death
- **Habitual/recurrent –** three or more consecutive spontaneous miscarriages

Induced, spontaneous and habitual abortion specimens are approached slightly differently, and each of these is discussed below. However, there are several goals in examination that should be addressed in all abortion specimens, and these are

- To document the presence of a **pregnancy**
- To rule out an **ectopic pregnancy**
- To identify suspected or unsuspected **abnormalities of the placenta or fetus**
- To rule out **gestational trophoblastic disease**

Induced Abortions

Clinical Features and Implications

Pregnancies may be terminated legally or illegally and both are termed **induced abortions.** There is little difference between the two from a pathologist's point of view, except that the latter type is more frequently followed by complications such as uterine infection and perforation. Induced abortions are performed by *dilatation and curettage, vacuum extraction, prostaglandin induction* (*with or without cervical laminaria*), *intraamnionic injection of hypertonic saline or urea solutions, and other means, although injection is rarely used*. Some induced abortions are performed because of the prenatal diagnosis of fetal anomalies, while others are presumably normal but "unwanted" pregnancies. Although in the latter case, the likelihood of anomalies is slight, occasionally abnormalities are identified on examination.

Complications of abortions, particularly "criminal" abortions, are rare but can include *uterine bleeding or hemorrhage, uterine perforation, infections, septic abortions, pulmonary embolism, disseminated*

intravascular coagulation, and other minor complications. These occur in up to 13% of induced abortions. In **septic abortions**, microscopic examination often reveals *acute villitis, acute intervillositis, and bacterial colonies filling the fetal villous capillaries*. Depending on the organism, some cases may show little inflammatory reaction (see Chap. 16). With the exception of infections, the various complications do not usually reveal specific pathologic lesions in tissue submitted to pathology.

Pathologic Features

To document the presence of an intrauterine pregnancy, and thus rule out an ectopic pregnancy, one must identify *implantation site, trophoblastic cells, or chorionic villi*. Occasionally, no chorionic villi may be found. In this case, the presence of *decidua with infiltration by extravillous trophoblast and physiologic conversion of decidual arterioles, i.e., the implantation site*, is definitive proof of an intrauterine pregnancy (see Fig. 1.7 in Chap. 1). A few chorionic villi may be present without an identifiable implantation site. In these cases, caution is advised since, under rare conditions, a few chorionic villi may be transported from the fallopian tube in an ectopic pregnancy. Thus, the presence of chorionic villi alone does not always document an **intrauterine** pregnancy. The same can be said for the presence of scattered trophoblastic cells without chorionic villi or implantation site. If there are abundant chorionic villi, they are usually associated with the implantation site, and so the diagnosis of intrauterine pregnancy is straightforward. For cases without definitive implantation site and in which there are few chorionic villi, a cautionary comment in the report and communication with the clinician is suggested.

At times, it may be difficult to differentiate decidual cells from extravillous trophoblast, a necessary task if one wants to identify the implantation site. *Decidual cells have distinct cell membranes with lightly eosinophilic cytoplasm containing oval nuclei with dispersed chromatin*. In contrast, *extravillous trophoblasts are polygonal cells without distinct cell borders, which contain abundant amphophilic cytoplasm, and irregular, mildly pleomorphic, hyperchromatic nuclei* (Fig. 11.1). Another clue to the presence of extravillous trophoblast and the implantation site is the characteristic *fibrinoid deposition*, typically seen in the vicinity of extravillous trophoblast. If after histologic examination doubt still remains, immunohistochemistry may be used. Since trophoblast is epithelial in origin, *all trophoblastic cells stain strongly positive for cytokeratins, while decidual cells are always negative* (Fig. 11.2). Similarly, *decidual cells will stain for vimentin and trophoblast will be negative*. Cytokeratin staining is very sensitive for trophoblast but not specific, and so care should be taken when using this stain for other purposes such as the differential diagnosis of trophoblastic disease in which other stains are more appropriate (see Chaps. 23–25).

Although most tissue is normal in induced abortions, occasionally some abnormalities may be found. For instance, fetal death has been reported in approximately 2% of induced abortions, macroscopic anomalies in approximately 1%, and chromosomal abnormalities in

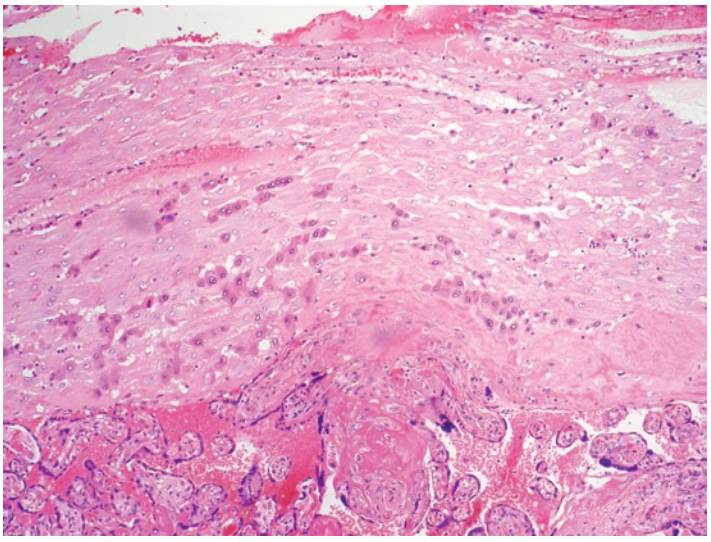

Figure 11.1. Implantation site showing extravillous trophoblast intermixed with decidual cells. The decidual cells have a more vesicular nucleus with pale eosinophilic cytoplasm and well-defined cell borders. The trophoblasts have more amphophilic cytoplasm and irregular, somewhat hyperchromatic nuclei. H&E ×200.

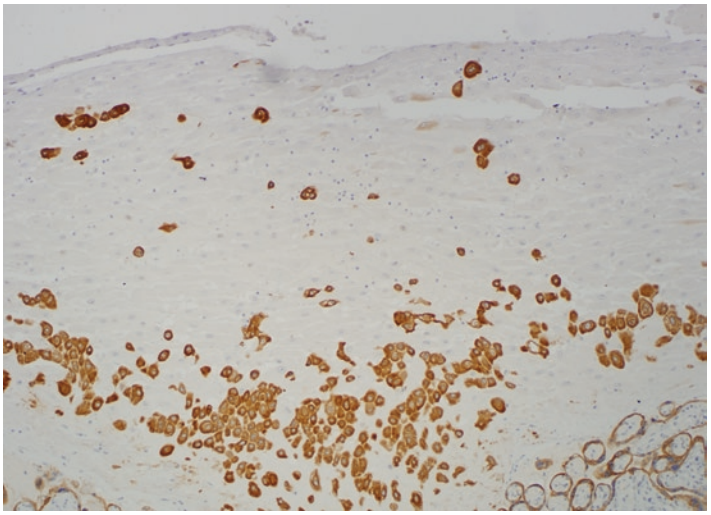

Figure 11.2. Cytokeratin stain of implantation site showing strong staining of the epithelial trophoblast and negative staining of decidual cells. Immunohistochemistry, cytokeratin 7. ×200.

5–6%. Rarely, unsuspected gestational trophoblastic disease may be diagnosed in an induced abortion (see Chap. 23). Normal implantation is often associated with *mild decidual necrosis and inflammation*. However, extensive inflammation or necrosis is an abnormal finding

that should be reported as it may be associated with abnormalities of implantation and pregnancy loss. Although these findings may indicate an imminent pregnancy loss or an underlying problem, they are relatively nonspecific. Finally, abnormalities in the decidual vessels and the implantation site may be present in early abortion specimens. These include *lack of normal physiologic conversion, thrombosis, and marked vascular inflammation*. They are often associated with disorders of placental malperfusion (see Chap. 18).

When dilation and curettage (D&C) or suction curettage is performed, instrumentation of the cervix and uterus has occasionally led to misplacement of fetal tissues. Paracervical or endometrial masses consisting of **fetal skeletal parts** have been identified months to many years after the last preceding pregnancy. Incompletely removed fetal tissues may cause unexplained bleeding and have been incriminated in *causing infertility* because they may act similar to an intrauterine contraceptive device.

When abortions are induced by introduction of different substances into the amniotic cavity, certain pathologic changes may occur. Injection of **hypertonic saline** solution results in extensive fetal ion fluxes. This results in *hemorrhage and necrosis under the chorionic plate, intervillous thrombosis, amnion necrosis*, and occasional chorionic vascular obliteration. In addition, the villous tissue is often pale secondary to hemolysis. This type of abortion is now rarely performed. Introduction of hypertonic urea gives similar changes, although not so severe.

Spontaneous Abortions

A **spontaneous abortion,** a "miscarriage," is essentially the *spontaneous delivery of a fetus prior to viability*. This is important to state at the outset, as the pathologic features of failed pregnancies differ markedly from those specimens obtained later in gestation, which are considered **preterm** deliveries. In addition, the result of a pregnancy of less than about 20 weeks' gestation is usually considered an "embryo" and treated as a surgical specimen. At later than 20 weeks it is considered a "fetus," whose examination constitutes an autopsy.

As stated previously, statutes vary from state to state on the gestational age of viability and what constitutes a surgical specimen versus human remains. The definition is legal in this context and does not take into account cultural or religious beliefs about when "life" begins. Therefore, the pathologist may be confronted with complicated circumstances in which the desires of the patient and family are at odds with the legal definition. Frequently, although the law considers a fetus a "specimen" that may be examined without permission and disposed of with other surgical waste, the family may have objections to autopsy examination and may desire burial of the remains. Clearly, it is vital that the patient's wishes be communicated to the pathologist. Unfortunately, this does not always occur, leading to not only difficulties, but at times considerable angst on the part of the patient. There are many ways of handling this; at our institution, any fetus of 12 weeks'

gestation or greater is not examined without autopsy consent, even though legally autopsy consent is not required. This ensures that no fetus will be examined when the patient objects. If the patient did want an autopsy, and the clinician did not obtain written permission, the fetal specimens are saved for a longer period than the routine surgical specimens so that the fetus can be later examined. Keeping the fetal specimens longer also ensures examination and proper disposal in the event the patient changes her mind. If private burial is requested at the time of examination or later, the fetus can be transported to the morgue for release to the funeral home. We request that the clinicians indicate on the surgical pathology requisition whether or not private burial is requested and whether autopsy is permitted in addition to requiring written consent. Although the clinicians may be unhappy with these extra steps, they ensure the patient's wishes are honored.

Pathogenesis

Most spontaneous abortions occur before 12 weeks of gestation and many are due to **chromosomal errors**. Chromosomal anomalies are present in 50% of all spontaneous abortions and in 70% of those occurring during the first 6 weeks. Increasing maternal age considerably increases the risk of spontaneous abortion, especially after the age of 35, and this correlates with an enhanced risk of fetal trisomies. However, the exact mechanism of the abortion in this situation is still disputed. Other less well-delineated *genetic defects* also make up a proportion of spontaneous abortions.

Endocrine disorders are a cause of a certain percentage of spontaneous abortions, and these include *luteal phase defects, polycystic ovary syndrome*, and *poorly controlled maternal diabetes*. Numerous physical factors have been associated with an increased incidence of abortions. *Uterine anomalies*, particularly *septate uteri*, have been implicated, and in the latter case, abortion likely ensues when implantation occurs on the septum. *Submucosal leiomyomas* and *trauma* have also been reported to increase spontaneous abortion as well. *Cervical incompetence* (see Chap. 16) is associated with preterm labor, preterm delivery and pregnancy loss. Other causes of spontaneous abortion are *multiple gestation* (see Chaps. 9 and 10), *antiphospholipid antibodies* (see Chap. 18), *drugs* (see Chap. 17), and *congenital malformations*. Relatively few spontaneous abortions occur in the period from 12 to 20 weeks' gestation. Between 20 and 30 weeks, spontaneous termination is primarily due to **ascending infection** (see Chap. 16). *Placental and fetal infections* that may lead to fetal infection and death in the first trimester are less common, but the causative organisms can include *Listeria, Cytomegalovirus, Toxoplasma, herpes simplex virus*, and *Coxsackie virus*.

Clinical Features and Implications

The incidence of spontaneous abortions is actually quite high. When prospective studies of complete populations are done on all pregnancies, including those that give few or no clinical symptoms of pregnancy, nearly 50% of conceptions terminate in abortion spontaneously. Some studies have quoted a higher figure of up to 65%.

There are also conceptuses that vanish even before implantation. Clinically recognized gestations end in abortion in approximately 15% of cases. Spontaneous abortions are usually accompanied by uterine bleeding and cramping with subsequent spontaneous passage of tissue. Often the embryo or fetus will pass first, followed by the placenta. Therefore, curettages done on women who have previously passed tissue often contain only decidualized endometrium and fragments of involuting implantation site.

Pathologic Features

Specimens will consist of embryonic tissue, decidua, and placental tissue, and each should be examined in turn. Specimens may have a *complete or incomplete embryo, have no embryo, or may contain an intact gestational sac*. If the embryo is present, it may be *grossly disorganized*, presenting as a nodular, cylindrical, stunted, or barely recognizable embryo (Fig. 11.3; see Chap. 2); it may show *focal, specific defects* such as spina bifida, cleft palate, etc., or it may be *without gross abnormalities*. The embryo may be macerated to a variable extent, and noting this may be helpful in assigning an estimation of intrauterine retention. Examination of abnormal fetuses is beyond the scope of this text; however, it is understood that with an abnormal embryo, as complete an examination as possible should be done.

Pathologic changes in the villous tissue may also be present. Unfortunately, in early abortion specimens, these changes often do not provide information on the cause of the pregnancy loss but rather

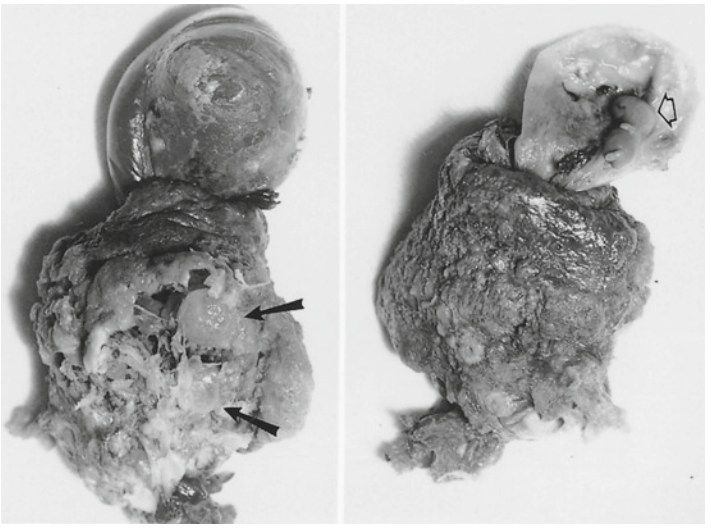

Figure 11.3. Spontaneous abortus at approximately 8 weeks' gestation. Note the opened sac at *right* with the nodular embryo at the *open arrow*. The hypoplastic placenta with hydropic degeneration is seen at the *arrows* (*left*). The decidua basalis is hemorrhagic.

on the presence of embryonic death. The few exceptions noted above include abnormalities of the implantation site vessels and excessive inflammation and necrosis. The pathologic changes in abortion specimens *are more often related to the timing of embryonic death and the age of the conceptus at the time of death than to the cause of the pregnancy failure*. The following is a list of the changes that generally occur after embryonic death:

- Early embryonic death – menstrual age less than 7 weeks (Fig. 11.4)
  - Hydropic villi
  - Thinned trophoblastic cover
  - Lack of red blood cells and villous capillaries
- Embryonic death – menstrual age approximately 7–8 weeks (Fig. 11.5)
  - Focal villous hydrops
  - Focal villous stromal sclerosis
  - Villous capillaries with varying degrees of vascular obliteration
  - Nucleated red blood cells, which may be "naked" in the stroma
  - Increased syncytial knots
  - Thickened trophoblastic basement membrane
- Embryonic death – menstrual age approximately 8–12 weeks (Fig. 11.6)
  - Increasing villous fibrosis with collagenous stroma
  - Obliteration of villous vessels
  - Ratio of nucleated to nonnucleated red blood cells changes from 100 to 10%
  - Fine mineralization of trophoblastic basement membrane and villous stroma
  - Perivillous fibrinoid deposition

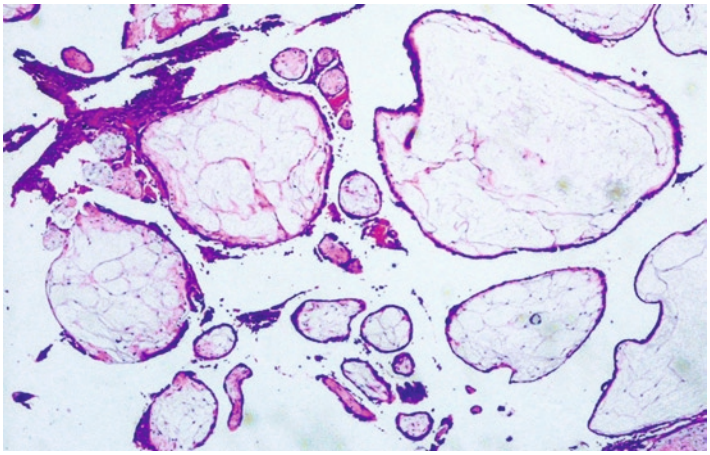

Figure 11.4. Early spontaneous abortion at about 6 weeks with prominent hydropic villi and no fetal capillaries or red blood cells. H&E ×40.

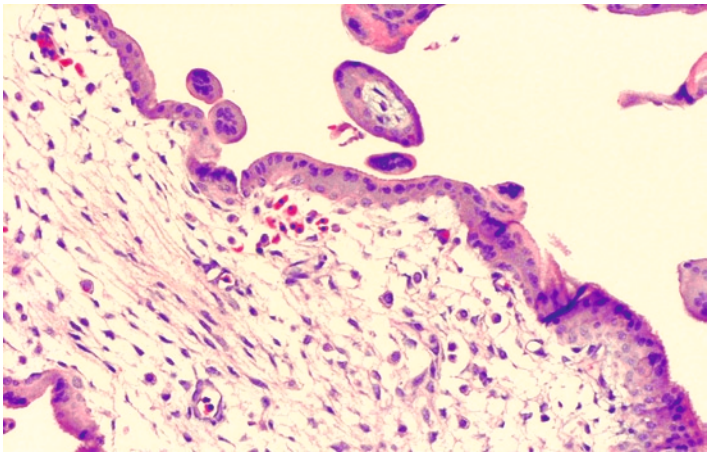

Figure 11.5. Early spontaneous abortion at about 7–8 weeks. This villus shows edema at the periphery and early fibrosis in the central region (*at the left*). Nucleated red blood cells are present "naked" in the villous stroma. H&E ×200.

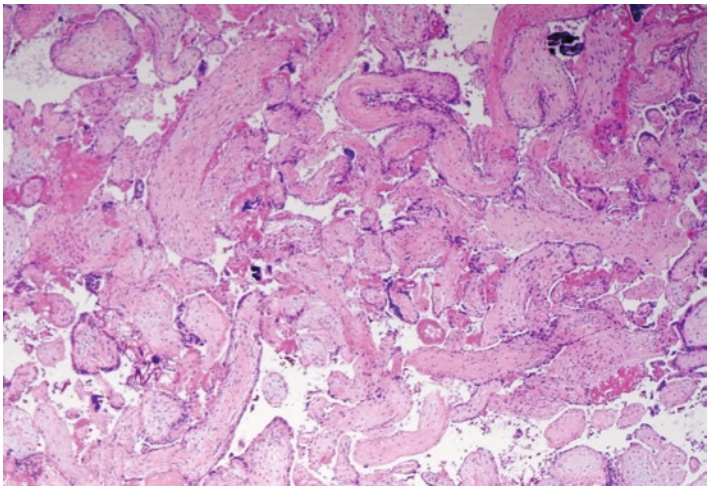

Figure 11.6. Spontaneous abortion with collagenous stroma and obliteration of blood vessels, at about 9 weeks. H&E ×20.

The reason for the preponderance of hydropic change in aborted specimens is not fully understood. It is generally believed that, following fetal death, the trophoblast continues to transport water from the intervillous space into the villi, where it cannot be removed by an absent fetal circulation; hence, the villi enlarge. Villous vascularization occurs at about 6.5 weeks menstrual age and so conceptuses reaching that age will show the presence of villous capillaries and nucleated red blood cells and will show less hydropic change.

Recurrent or Habitual Abortion

Habitual abortion is usually defined as a condition in which a woman has had *three or more consecutive spontaneous abortions*. Three consecutive losses is the preferred definition because after two consecutive spontaneous abortions, the chance of successful pregnancy is 80%. Known etiologies vary widely. There are many infectious causes (see Chap. 16) and a number of chronic maternal diseases such as *lupus erythematosus, maternal heart disease, thrombophilias, antiphospholipid antibody syndrome, and endocrine disorders* (see Chap. 17). *Recurrent villitis of unknown etiology, massive repetitive chronic intervillositis* (see Chap. 16), and *maternal floor infarction* (see Chap. 19) constitute another group of disorders that primarily placental in origin. The relation of *substance abuse* to spontaneous abortion and to abruptio placentae is difficult to evaluate, and the contribution of *maternal smoking* is also unclear. Many patients who smoke or use various toxic substances additionally consume alcohol, have various infections, and are prone to suffer misuse and trauma (see Chap. 17).

Parental chromosome aberrations and some *immunologic errors associated with placentation* are other well-studied causes of recurrent abortion. Some recurrent abortions are due to increasing maternal age with its increased chance of aneuploidy. Rarely, *balanced chromosomal translocations* of one parent have been the cause of habitual abortion. Therefore, it is suggested that in couples with recurrent abortions, the mother *and* the father be examined cytogenetically. The pathologist can contribute to a better understanding of the etiology by requesting cytogenetic evaluation of aborted specimens from recurrent aborters.

Chromosomal Anomalies

Some investigators have gone so far as to suggest that pathologic changes in chromosomally abnormal abortions are so characteristic that they enable chromosomal diagnosis from the morphologic findings of the villous tissue alone. When tested, experts and diagnostic pathologists are consistently unable to specifically label a given microscopic appearance with confidence. In general, *karyotyping is necessary to confirm the diagnosis*. The exception is the karyotypic abnormalities associated with hydatidiform moles (see Chap. 23). That being said, there are certain pathologic features that are commonly seen in aneuploid conceptuses as a group. One of the hallmarks of a **chromosomal anomaly** is the presence of *growth restriction of the fetus* and *an abnormally small and thin placenta*. Other histologic features that are often associated with chromosomal defects in general are *increased villous size, villous edema, trophoblastic inclusions or invaginations, irregular villous contour, and cytotrophoblastic giant cells*.

Trisomies

There are few specific findings that characterize a placenta with **trisomy**, but many abnormalities have been found sporadically. First, the

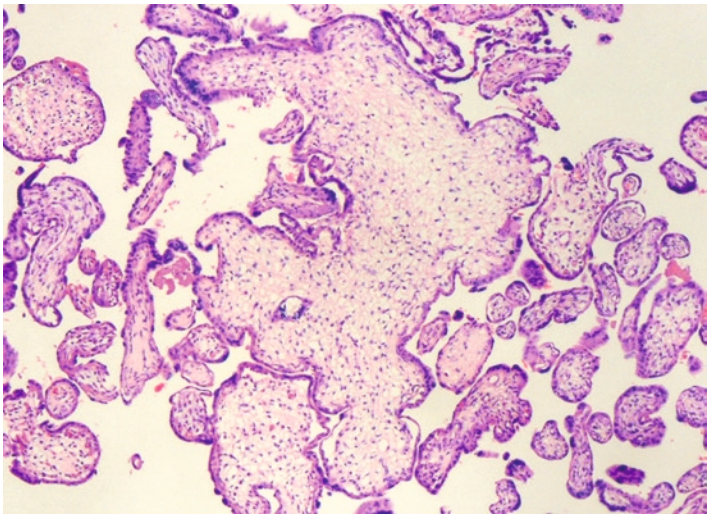

Figure 11.7. Spontaneous abortus with trisomy 13. There is scalloping of villi and trophoblastic "inclusions," most visible in the large villus in the center of the figure. H&E ×40.

incidence of *single umbilical artery* (SUA) is higher. Second, placentas tend to show *deficient vascularization* with a reduction in the number of small muscular arteries, decreased small muscular artery/villus ratio, and decreased numbers of capillaries. The villi are frequently *dysmature* with *trophoblastic inclusions or invaginations* (Fig. 11.7). Occasionally, *increased syncytial knots* and *increased cellularity of the villous stroma* are also found.

Trisomy 16 is one of the *commonest cytogenetic anomalies found in spontaneous abortion material*. The embryo is generally absent with a small, empty chorionic cavity. Histologically, the *villi and trophoblast are hypoplastic with decreased vascularization*. Some villi may be *hydropic*. Enlarged *cytotrophoblastic giant cells* are found in the stroma of up to 30% of villi (Fig. 11.8). The origin of these cells is unclear but they may be edematous stromal cells, enlarged Hofbauer cells, or cells derived from delaminating cytotrophoblast. In **trisomy 18**, *the chorionic villi are cystic and dilated, showing typical hydropic change*. Cysts may be large enough to be identified grossly (Fig. 11.9). There may also be *increased syncytial knots* (Fig. 11.10) or *increased cellularity of the villous stroma* (Fig. 11.11).

The abortions of **trisomies 6–12** have a variable morphology. The placenta is *less mature* than expected for gestational age. *Giant cytotrophoblastic cells* are found in 40% of villi (Fig. 11.8). In **trisomies 13–15** there is *variable placental maturation, decreased villous vascularity, and giant cytotrophoblast* in 50% of villi. Occasionally, *hydropic villi, scalloping, and trophoblastic inclusions may occur*. **Trisomy 21** is not accompanied by characteristic placental changes. Increased placental weight and size, however, have frequently been observed. There are even fewer characteristic patterns of the placentas of other trisomies, but *hydropic change is common and there is occasional atypical trophoblastic proliferation*.

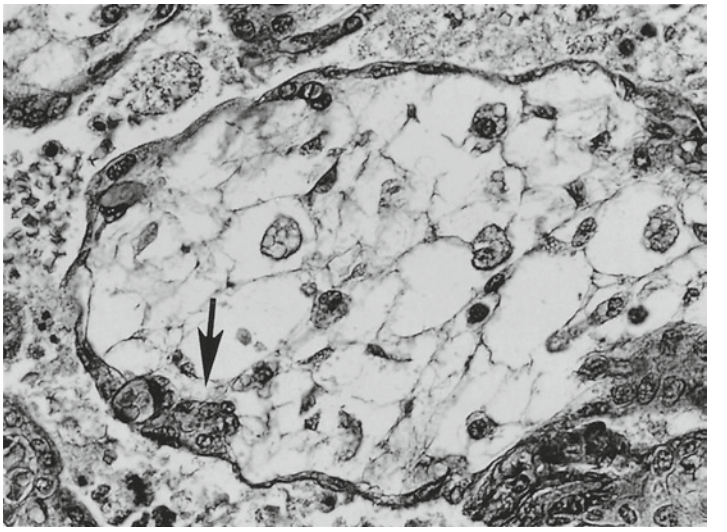

Figure 11.8. Villus with cytotrophoblastic giant cells in a spontaneous abortion. The much-enlarged cells in the villous core represent enlarged Hofbauer cells. Cystic lacunae are developing in the villus. H&E ×400.

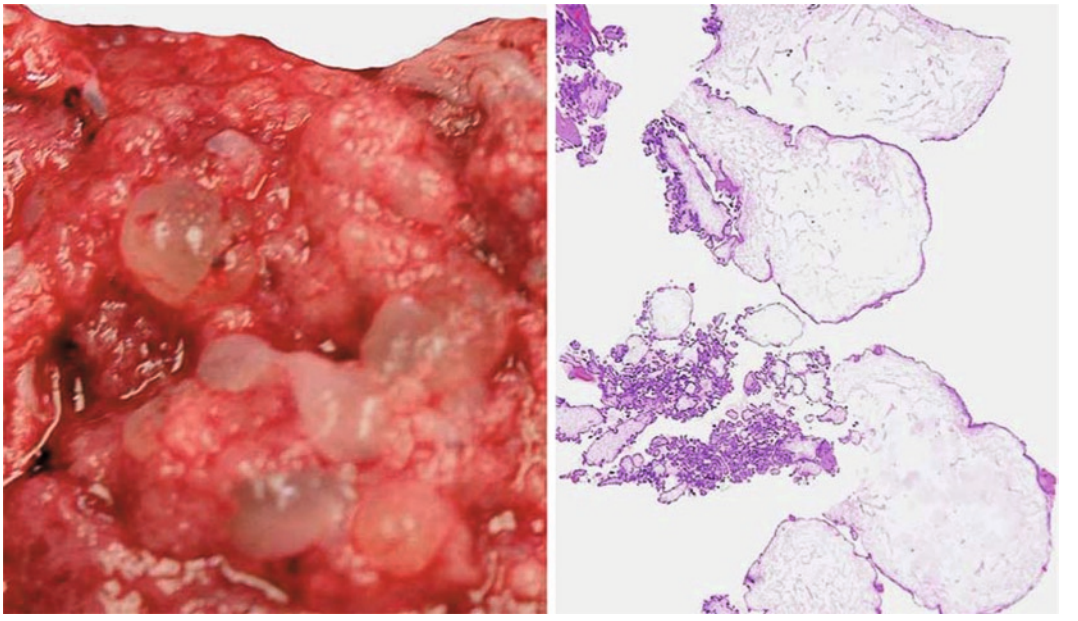

Figure 11.9. Premature trisomy 18 placenta. On the *left* is a gross picture of the hydropically enlarged villi. The *right* shows the histologic picture of hydropic villi and increased trophoblast, which may cause confusion with molar pregnancy. H&E ×160.

Other Chromosomal Anomalies

Triploid conceptuses may be either *dygynic* or *diandric*, with the extra chromosome set deriving from the mother and father respectively. Diandry results in partial hydatidiform moles. Triploidy due to dygyny

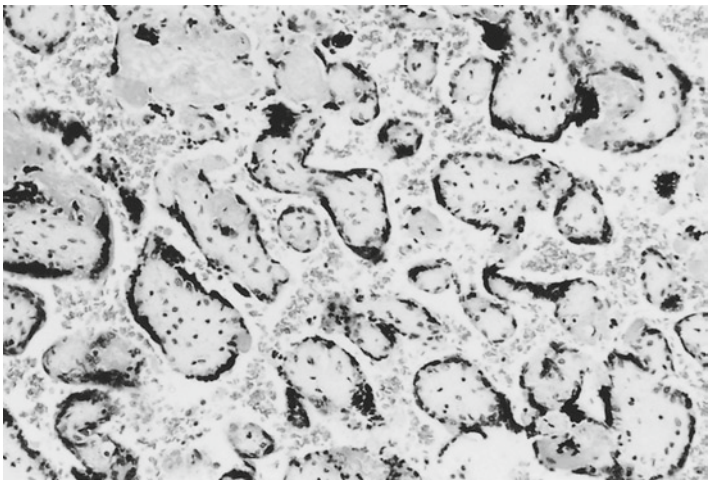

Figure 11.10. Villi of immature placenta (28 weeks' gestation) of a stillborn fetus with trisomy 18. There is increased syncytial knotting despite the absence of preeclampsia. Villi lack fetal vessels because of fetal demise, but many have hyalinized centers. H&E ×64.

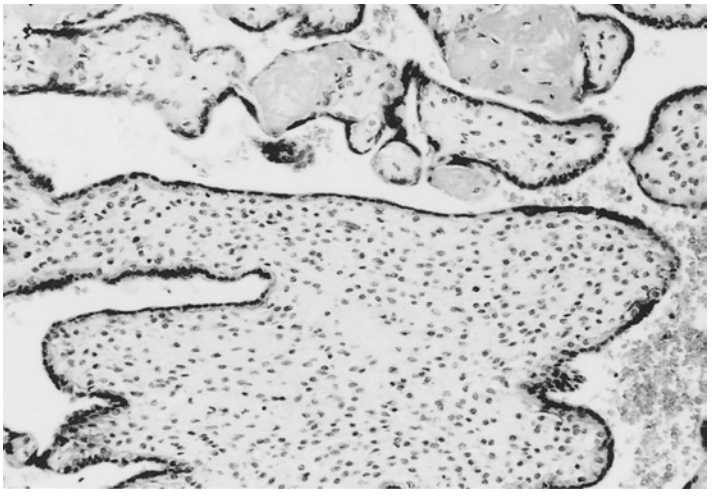

Figure 11.11. Trisomy 18 placenta with a marked increase in villous stromal cells. H&E ×160.

is much more common in older women in whom nondisjunction of chromosomes occurs more commonly. The fetus is usually *small for the expected age* and often has characteristic anomalous features such as *digital fusion; frequently the embryos are nodular and degenerating*. *SUA* is also common. Macroscopically, the placentas of triploids frequently show some degree of *hydropic change*, though not so prominent as seen with partial moles. Microscopically, some villi have *cavities or lacunae*

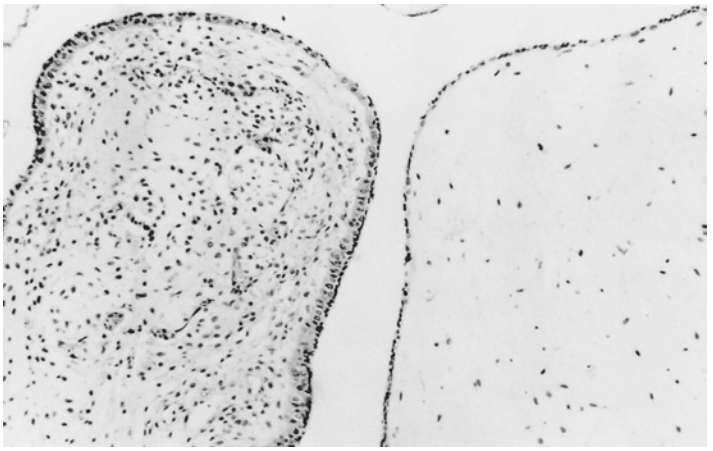

Figure 11.12. Two enlarged villi in a triploid abortus. One (*left*) is hypercellular, with faintly visible remnants of former fetal vessels; the other is hydropic. H&E ×160.

within the villi, which are smaller than the cisterns seen in molar pregnancies (see Fig. 23.4 in Chap. 23). Other villi may be disrupted or *compacted with increased cellularity* (Fig. 11.12), *and the trophoblast is variably hypoplastic*. There is characteristic *infolding or scalloping of trophoblast* into the villi, with trophoblastic nests occurring seemingly isolated in the villous stroma. A Breus' mole is occasionally found with triploid abortuses as well, although this is more common in monosomy X.

Tetraploid abortuses usually have an *empty cavity and voluminous, poorly vascularized villi*. They frequently have *severe decidual and villous hemorrhages*, and their villi are invariably somewhat cystic. Occasionally, massive hydropic change may be seen. The embryos and placentas of **monosomy X** often appear relatively normal with only *villous fibrosis* present. Frequently, only a cord remnant is found in a cavity that is small for gestational age. In some cases there are *intervillous thrombi* of the so-called Breus' mole type (see Chap. 14). The embryo may have nuchal hygroma and severe hydrops.

Ancillary Testing

In abortion specimens, the chromosomal errors are composed of trisomy in 50–60%, triploidy in 18%, monosomy X in 15%, and the remainder are double trisomies, tetraploidies, and individual chromosomal errors, such as rings, translocations, and mosaicism. The pathologist is occasionally asked to provide material for **cytogenetic study**. This is best done from embryonic tissue or from the chorionic surface when an embryo is not available or macerated. In some cases,

due to lack of viable embryonic tissue, placental tissue may be the only tissue able to grow in culture. Caution is advised when only placental tissue is obtained due to confined placental mosaicism (CPM) (see below). Therefore, *if possible it is optimal to obtain both embryonic and placental tissue*. When sampling the placenta, it is best to cleanse the fetal surface, peel the amnion away, and then obtain chorionic tissue with sterile instruments.

Chorionic villus sampling (CVS) is the procedure by which a *small sample of villous tissue is obtained early in gestation for the purpose of chromosomal or DNA testing*. CVS is usually done at about 11 weeks' gestation. It has been suggested that CVS is a significant cause of fetal loss and limb reduction defects. However, only a 0.8% increase of fetal loss in CVS patients has been documented. The relationship between limb defects and CVS exists principally in the gestationally earlier CVS and not when CVS is done after 9 weeks.

Because hydropic villi are such a frequent finding in many placentas of spontaneous abortions, the differentiation from moles and partial moles may present difficulty. Therefore, use of **flow cytometry** is advocated as a *rapid means for the delineation of diploidy and triploidy.* Thus, triploid partial moles may be differentiated from complete diploid hydatidiform moles, and diploid abortuses may be distinguished from triploid partial moles (see Chap. 23).

The sera of pregnant women are often tested with the **triple screen** and more recently the **quadruple screen** or **quad test.** The triple screen includes measurements of *β-human chorionic gonadotropin (β-hCG), unconjugated estriol*, and *α-fetoprotein* in the maternal serum. The quadruple screen adds *dimeric inhibin A*. Abnormalities in one or more of these markers are associated with increased risk of neural tube defects and chromosomal anomalies, particularly trisomy 21 and 18. The abnormalities and their associated test results are summarized in Table 11.1.

New methodology is evolving that will make it feasible to describe the genetic defects more accurately, such as various **DNA studies,** the **polymerase chain reaction (PCR), fluorescence in situ hybridization (FISH)** of whole cells, and delineation of translocations by spectral color staining of chromosomes. Some of these tests are feasible even using fixed tissue and individual, selected cells from paraffin-embedded tissues. Ploidy analysis and routine karyotyping also are essential tools in diagnosis. Placental material also lends itself for *paternity diagnosis*.

In assisted reproductive technology, germinal vesicles of oocytes from older women may be implanted into enucleated eggs of younger women due to the increase in chromosomal errors in older patients. This is one of the reasons for the recently more widely practiced "preimplantation genetics," which seeks to avoid implanting chromosomally abnormal embryos or those afflicted with single gene mutations. In addition, prenatal diagnosis of X-linked diseases has been achieved by the study of male cells from maternal blood, and this is currently under active study.

Suggestions for Examination and Report
(Abortions)

Gross Examination: If villi are grossly identified, one section in an induced abortion is sufficient, while two to three sections should be submitted in a spontaneous abortion. It is also suggested to submit a fragment of decidual tissue in addition to villous tissue as it often contains a portion of the implantation site. If villi are not grossly seen, consideration should be given to submission of the entire specimen, particularly if an ectopic pregnancy is suspected. If the clinical history indicates a habitual abortion, tissue should be sent for chromosome analysis if this has not already been completed. Embryonic tissue should be submitted to document its presence and to further clarify gross abnormalities.

Comment: The tissues that are present including implantation site, decidua and chorionic villi, should be listed in the diagnosis if all are normal. Abnormalities such as lack of physiologic conversion, excessive inflammation should be listed separately. If features of chromosomal abnormalities are present, those should be listed and a comment may be made that the findings are suggestive of a chromosomal anomaly or, if clinical history is given, that the findings are consistent with the clinical history of a chromosomal anomaly.

Confined Placental Mosaicism, Uniparental Disomy, and Imprinting

In order to understand the concepts of confined placental mosaicism (CPM) and uniparental disomy (UPD), a few definitions are necessary:

- **Mosaicism** is when an organism has two genetically distinct cells lines derived from a single fertilization product or genotype.
- **Chimerism** is present when an organism has two genetically distinct cells derived from two different fertilization products or genotypes.
- **CPM** is present when the placenta has a different cell line than the fetus, both deriving from the same fertilization product or genotype.
- **UPD** is the presence of two chromosomes from one parent.
- **Imprinting** is the transcriptional silencing of a portion (paternal or maternal) of one parental genome.

The presence of CPM, UPD, mosaicism, and chimerism has caused discrepancies in chromosomal findings between results obtained via CVS, amniocentesis, and fetal lymphocyte culture. Although some of the discrepancy may be due to contamination with maternal tissue, other discrepancies may be due to the above conditions. The finding of mosaic cell lines may also reflect the differing origin of cells from the **inner cell mass (fetus),** its **shell (placental trophoblast),** the **amnion,**

chorion, or **connective tissue of the villi.** One must know which cells are found to be chromosomally abnormal in order to infer probable fetal genotype.

Confined Placental Mosaicism

CPM may manifest in different ways. An abnormal karyotype such as trisomy 18 might be found in the placenta while the fetus has a normal karyotype. The placenta will often be *grossly and histologically normal* (*although sometimes small*), while the fetus is *growth restricted*. It is postulated that an *aneuploid placenta functions less efficiently than a normal organ* and therefore produces fetal growth restriction. The genotypically normal fetus is thus small but shows no anomalies. CPM may also present as a trisomic fetus with a euploid placenta. *Fetuses with trisomy 13 and 18 who survive turn out to have placental karyotype mosaicism*. In these cases, the mosaicism appears to be confined to cytotrophoblast and not found in villous stroma, chorion, or amnion. The suggestion is that *trisomics with mosaic* (*aneuploid/diploid*) *placentas have a better chance of reaching maturity than those with truly trisomic placentas*.

CPM is also found more frequently in *unexplained stillbirths and unexplained growth restriction*. It is found three times more commonly in placentas with intrauterine growth restriction (IUGR) fetuses than normal fetuses. Moreover, 10% of gestations with CPM have fetal cytogenetic abnormalities. Regrettably, there is not yet much direct correlation with placental pathologic features in CPM. For the pathologist, it is important to realize that CPM occurs in the setting of unexplained fetal growth restriction or demise, and that *in order to document CPM, samples from multiple placental sites are necessary to make the diagnosis*. If resources allow, the placenta may be evaluated for CPM in cases of IUGR that have no other apparent cause.

Uniparental Disomy

In **UPD** there are *two chromosomes from one parent* rather than one from each parent. It is an occasional finding in *growth restricted newborns* and *stillborns* and appears to be linked to CPM. It is postulated to take its origin from a trisomic conceptus with the loss of one *trisomic chromosome leaving the fetus with a normal chromosome complement*. Depending on which chromosome is lost, the fetus may end up with two chromosomes from the same parent, resulting in UPD. There are several ways in which UPD may complicate CPM. A trisomic fetus that loses its extra chromosome becomes diploid and may have UPD. If the corresponding placenta remains trisomic, CPM results. On the other hand, the placenta may lose the extra chromosome and develop UPD.

Imprinting

A final aspect of this complex array of potential genetic events is the concept of **imprinting.** It is a reality affecting fetal and placental tissues as well as many disease states and is presumably accomplished via DNA methylation of specific genes. There is good evidence that some *pater-*

nal genes are silenced during embryonic development (*maternal imprinting*), *while some maternal genes are silenced during placental development* (*paternal imprinting*). Imprinting is important in understanding how different types of triploidy may result in the development of partial hydatidiform moles. Partial moles are generally triploid with one set of maternal genes and two sets of paternal genes. The excess of paternal genes acts similar to silence of maternal genes and leads to preferential development of trophoblastic tissues over fetal tissues. On the other hand, triploidy with two sets of maternal genes and one set of paternal genes does not lead to a molar pregnancy but results in a small placenta and a fetus, often with typical anomalies such as syndactyly.

Table 11.1. Maternal serum markers and risk of anomalies.

Abnormality	AFP	hCG	UE3	DIA
NTD	↑	–	–	–
Trisomy 21	↓	↑	↓	↑
Trisomy 18	↓	↓	↓	–

Note: Arrows indicate increase or decrease compared to normal results at that gestational age, results are reported as multiples of the median.
AFP α-fetoprotein, *hCG* human chorionic gonadotropin, *UE3* unconjugated estriol, *DIA* dimeric alpha inhibin, *NTD* neural tube defect.

Selected References

PHP5, pages 762–796 (Abortions, Placentas of Trisomies and Immunologic Considerations of Recurrent Reproductive Failure).

Bennett P, Vaughan J, Henderson D, et al. Association between confined placental trisomy, fetal uniparental disomy, and early intrauterine growth retardation. Lancet 1992;340:1284–1285.

Cohen J. Coming to term. Uncovering the truth about miscarriage. Boston and New York: Houghton Mifflin, 2005.

Cohen J. Sorting out chromosomal errors. Science 2001;296:2164–2166.

Jauniaux E, Burton GJ. Pathophysiology of histological changes in early pregnancy loss. Placenta 2005;26:116–123.

Kalousek DK, Barrett, I. Confined placental mosaicism and stillbirth. Pediatr Pathol 1994;14:151–159.

Kalousek DK, Barrett IJ, McGillivray BC. Placental mosaicism and intrauterine survival of trisomies 13 and 18. Am J Hum Genet 1989;44:338–343.

Moore GE, Ali Z, Khan RU, et al. The incidence of uniparental disomy associated with intrauterine growth retardation in a cohort of thirty-five severely affected babies. Am J Obstet Gynecol 1997;176:294–299.

Redline RW, Hassold T, Zaragoza M. Determinants of villous trophoblastic hyperplasia in spontaneous abortions. Mod Pathol 1998;11:762–768.

Rushton S. Examination of products of conception from previable human pregnancies. J Clin Pathol 1981;34:819–835.

Salafia CM, Burns JP. The correlation of placental and decidual histology with karyotype and fetal viability. Teratology 1989;39:478(P37).
Sermon K, Steirteghem A, van Liebars I. Preimplantation genetic diagnosis. Lancet 2004;363:1633–1641.
Stirrat GM. Recurrent miscarriage I: definition and epidemiology. Lancet 1990;336:673–675.
Stirrat GM. Recurrent miscarriage II: clinical associations, causes, and management. Lancet 1990;336:728–733.
Tycko B. Genomic imprinting: mechanism and role in human pathology. Am J Pathol 1994;144:431–443.
Warburton D, Stein Z, Kline J, et al. Chromosomal abnormalities in spontaneous abortions: data from the New York City study. In: Porter IH, Hook EB (eds) Human embryonic and fetal death. New York: Academic Press, 1980:261–287.