APMIS JOURNAL OF PATHOLOGY, MICROBIOLOGY AND IMMUNOLOGY

APMIS 126: 544–550

DOI 10.1111/apm.12830

REVIEW ARTICLE

Indications for submission and macroscopic examination of the placenta

REBECCA N. BAERGEN

Weill Cornell Medicine, New York-Presbyterian Hospital, New York, NY, USA

Baergen RN. Indications for submission and macroscopic examination of the placenta. APMIS 2018; 126: 544–550.

The placenta is a fetal organ, composed of fetal DNA and as such reflects the fetal phenotype. The placenta consists of an umbilical cord, fetal membranes (amnion and chorion), and the placental disc which in turn is comprised of villous tissue. Both maternal and fetal disorders have placental sequelae and placental abnormalities can affect both maternal and fetal well-being. As such, placentas are often helpful in future maternal and neonatal healthcare. Thus, examination of the placenta is important for both mother and infant. On this basis, a list of indications for placental examinations has been created by a multidisciplinary group of pathologists, maternal-fetal-medicine specialists, and neonatologists that, if followed, will ensure that the vast majority of placentas that ultimately show any significant pathology will be examined (Arch Pathol Lab Med, 121, 1997, 449–76). This list include fetal, maternal, and placental indications. This chapter will discuss those indications as well as give a brief overview of macroscopic placental examination and procedure.

Key words: Placenta; macroscopic examination; indications for examination.

Rebecca Baergen, Weill Cornell Medicine, New York-Presbyterian Hospital, Surgical Pathology Starr-1002, 520 East 70th Street, New York, NY 10065, USA. e-mail: rbaergen@med.cornell.edu

INDICATIONS FOR SUBMISSION

As many placentas are normal, examination of all placentas may not be warranted, and may be impractical due to constraints on time and resources, especially in hospitals with large numbers of deliveries. Nonetheless, gross and microscopic examination of many placentas is necessary to provide a good base knowledge of what constitutes "normal" and "abnormal" and so examination of even normal placentas is encouraged particularly in teaching institutions. Furthermore, in today's litigious climate, study of placentas is highly valuable, particularly in the defense of hospitals, obstetricians, and other healthcare workers.

Tissue removed or spontaneously passed from the body is usually sent for pathologic examination, and indeed, local regulations may require submission. Placentas appear to be the notable exception. The Joint Commission on the Accreditation of Healthcare Organizations in the United States asserts that "normal placentas" from "normal deliveries" are not required to be examined nor submitted to pathology, despite the fact that a definition of what is "normal" is not forthcoming. In many institutions, this decision is left in the hands of healthcare workers involved in the delivery who may or may not have sufficient expertise to make such a determination. Although this may not be the optimal mechanism, if a set of specific criteria or at least guidelines are provided to caregivers, the submission of the most important placentas should be ensured.

To this end, the College of American Pathologists coordinated a multidisciplinary working group on pathologic examination of the placenta who then developed indications for submission of placentas included placental, fetal, and maternal indications (1). An adapted version is shown in Table 1. When healthcare workers involved in deliveries are responsible for the selection of placentas, it is recommended that these indications be adopted for their routine use. If these indications are followed, the likelihood that a placenta with any significant pathology will not be examined is very small.

Received 14 November 2017. Accepted 12 February 2018

Table 1. Indications for placental examination

Maternal indications:
History of reproductive failure – spontaneous abortions, stillbirths, neonatal deaths, or premature births
Maternal diseases:
Coagulopathy
Hypertension (preeclampsia, pregnancy induced or chronic)
Diabetes mellitus
Antenatal indications:
Prematurity (<32 weeks)
Postmaturity (>42 weeks)
Oligohydramnios
Polyhydramnios
Fever or Infection
Repetitive bleeding
Abruptio placentae
Fetal and neonatal indications:
Stillbirth or perinatal death
Fetal growth restriction (IUGR)
Hydrops
Severe neonatal central nervous system depression, neonatal encephalopathy or neurologic problems such as seizures
Apgar score of 3 or less at 5 min
Suspected infection
Congenital anomalies
Thick meconium
Placental indications:
Any gross abnormality of the placenta, membranes or umbilical cord such as masses, thrombi, excessively long, short or twisted umbilical cord, etc.
Optional recommendations:
Prematurity between 32 and 36 weeks
Low one minute Apgar score
Fetal distress or non-reassuring Fetal status
Multiple birth

Adapted from the College of American Pathologists (1).

As previously stated, the indications fall into three categories: maternal, fetal, and placental. Maternal factors fall generally into several subgroups. The first is reproductive history and this includes a previous history of reproductive loss such as preterm birth, spontaneous abortion, stillbirth or neonatal death. Second, is maternal medical history such as a personal history of hypertension, coagulopathy, or diabetes, and the final group of indications are those involving the current pregnancy. This includes essentially any complication of the pregnancy or delivery such as prematurity, oligohydramnios, infection, or bleeding. Fetal and neonatal indications are straightforward in that they include any problem with the infant such as stillbirth, growth restriction, low Apgar scores, anomalies, evidence of fetal distress, and so on. Placental indications include any abnormality noted in the delivered placenta.

In some institutions, placentas are initially selected for examination and the remaining placentas are stored (in a refrigerator at 4°C). This approach is particularly desirable as a number of neonatal problems do not become apparent until several days of life (2, 3). Furthermore, it provides a way to submit those placentas that should have been submitted but for some reason or another, were not. One week is sufficient time for these purposes, and placentas are extremely well-preserved for meaningful examination when refrigerated for this time period. During that week of storage, neonatologists, obstetricians, or other personnel may request placental examination based on development of neonatal or postpartum problems.

An alternative to this scheme is one in which all placentas are examined macroscopically and then, based on gross examination and clinical history, cases are selected to submit for microscopic examination. Those with no significant gross abnormalities and normal pregnancy and delivery history would only be examined macroscopically. This approach is somewhat dependent on the skill and experience of the examiner as well as the availability of clinical history. A variation in this method is macroscopic examination along with submission of tissue for processing into blocks on all placentas. Tissue sections are cut only on selected cases based on macroscopic examination and clinical history as above. If problems occur in the future, particularly in the case of litigation, the blocks may then be cut. These types of approach require more

resources, personnel and storage and thus may not be practical in many institutions.

STORAGE

The entire placental examination should ideally be done in the fresh state or at least prior to fixation. Formalin fixation prior to examination obscures many macroscopic features, makes examination more difficult, and causes difficulties in the submission of specimens for molecular studies, cytogenetics, and bacteriologic examination. Although a few lesions are better visualized after fixation, examination of unfixed placentas affords the opportunity to view lesions in both fresh and fixed states. As it is difficult to section fresh placental tissue, we recommend either fixing small portions overnight or briefly in Bouin's solution before doing the final trimming of sections. If storage is needed, placentas should be stored in tightly sealed containers in a refrigerator at 4°C.

During storage, the placenta loses some weight predominantly due to leakage of blood and serum and thus the fresh placenta will be softer, bloodier, and thicker than one that has been stored. Weight loss is most significant in hydropic or edematous placentas. Formalin fixation will add weight and it is estimated that the placenta will gain approximately 5% in weight after fixation.

EXAMINATION

As with examination of any specimen, it is wise to follow a routine protocol (2–4). This provides a systematic approach so that nothing will be omitted. The instruments needed are basic to gross examination and consist of a ruler or tape measure, a long, sharp knife, forceps with teeth, scissors, and a scale. An adjacent sink is optimal as this facilitates gentle rinsing of the placenta for removal of blood. The placenta should never be wiped off, as this will damage the epithelium and other surfaces. It should be noted in the gross description whether the placenta was received fixed, unfixed, or fresh.

It is most efficient to begin examining the umbilical cord, then the membranes and lastly the placental disc. The cord length should be measured including all pieces that have come detached and this can be given as a single number. Cord diameter should also be measured. Cord insertion should be noted – central, eccentric, marginal, velamentous, etc. and some advocate measuring the distance of the cord insertion from the margin. The twist or coiling of the cord should be noted as left or right. The direction of twist is usually to the left and is identified as the left side of the letter "V", while a right twist is identified as the right side of the "V" (Fig. 1) (2). It should also be noted if there is hypocoiling, hypercoiling, or an area of constriction (Fig. 2). True knots should also be described. Next, the number of umbilical vessels should be recorded which is generally three. Then any discoloration, hemorrhage, cysts, thrombosis, surface nodules, or masses should be identified and described if present. The cord should then be removed from the placenta at the insertion site. Two sections of cord should be submitted for microscopic examination, one near the placental insertion and one near the fetal end.

Attention should then be turned to the extraplacental membranes. To check for completeness, there should be sufficient membranes present to enclose the fetus. The membrane rupture site should be measured. This is the distance from the placental edge to the nearest rupture site. If it is greater than zero in a vaginally delivered specimen, a placenta previa is ruled out. The membranes are normally translucent and shiny, but may be opaque or discolored yellow, green, brown, or red-brown. Next, it should be noted whether the insertion of the membranes occurs normally at the margin or

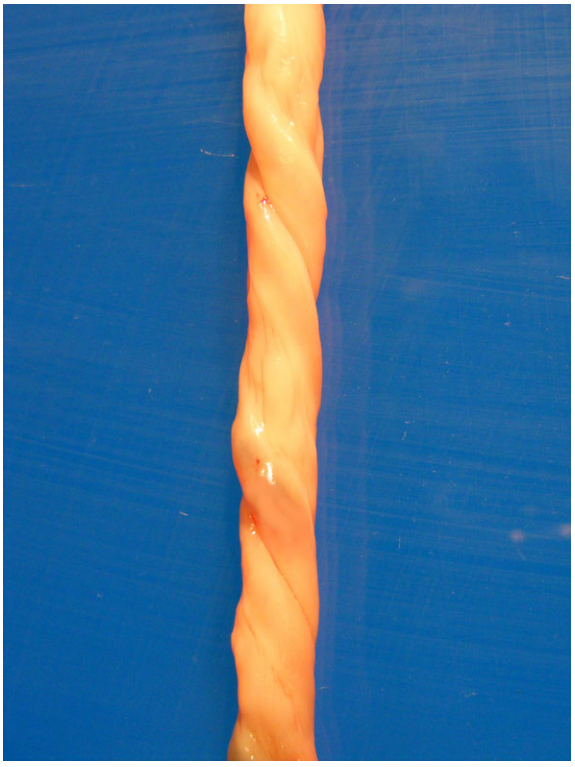

Fig. 1. A left twisted cord with normal coiling. Note that the spirals seen on the surface correspond to the left side of the letter "V".

Fig. 2. An umbilical cord with marked twisting or hypercoiling.

further inward as would be the case with circumvallate and circummarginate membrane insertion. The membranes should then be removed from the placental disc using sharp scissors and keeping the orientation to rupture site. A "membrane roll" should be made by taking a strip approximately 10 cm wide, and with forceps grasp the portion representing the rupture site (furthest from the placental margin). Roll the membranes with the rupture site in the center and with the amnion inward (Fig. 3). This roll can be briefly fixed and then cross-sections taken (preferably two) and submitted for microscopic examination in the same cassette as the umbilical cord (Fig. 4).

Examination of the fetal surface includes noting any discoloration or opacity, identification of any nodules, masses, cysts, and so on (Fig. 5). It should be kept in mind that some subchorionic fibrin is normal in most placentas. Then the fetal surface or chorionic vessels should be inspected specifically for gross evidence of thrombosis, hemorrhage, or disruption. Keep in mind that arteries cross over veins.

Now that the membranes and cord have been removed from the placenta, attention can be given to the placental disc. The disc should be measured in three dimensions and weighted (trimmed weight). The shape of the placental disc should be noted, most commonly discoid but it can be irregular or may consist of multiple lobes (bilobed placenta, or succenturiate lobes). The maternal surface should be checked for completeness, presence of adherent blood clots or other lesions (Fig. 6). Retroplacental hematomas occur in the setting of a placental abruption and in these cases there may be adherent blood clot, compression of villous tissue, and/or underlying infarction of villous tissue. The placental disc should then be serially sectioned at 5 mm intervals. The color of villous tissue should be evaluated as pale, congested, or normal (Fig. 7). Any villous lesions should be described noting color,

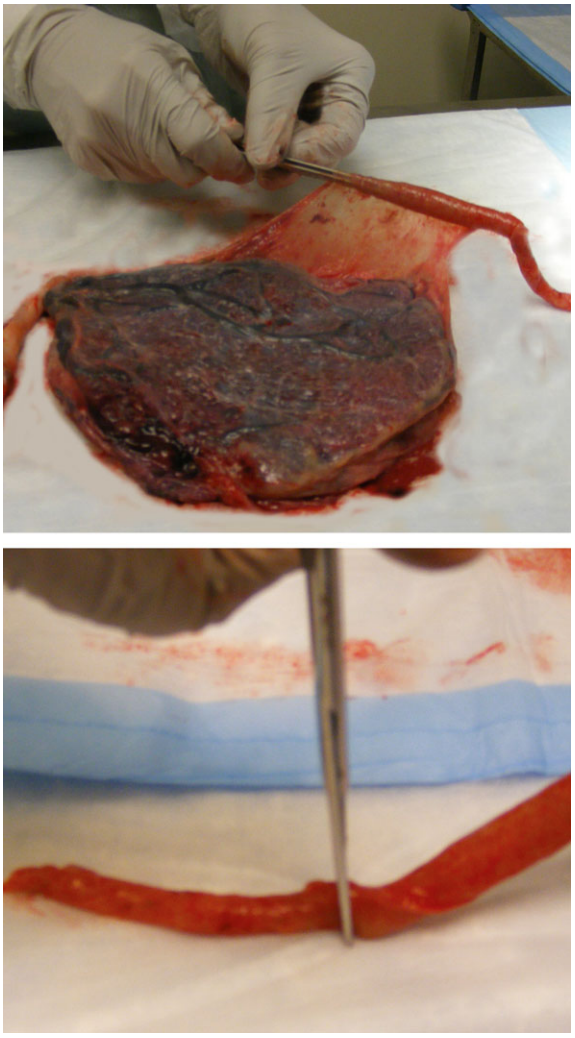

Fig. 3. Demonstration of how to start a membrane roll, taking a strip from the ruptured site and rolling it inward to the placental margin. The membrane roll is briefly fixed to facilitate cutting and two cross-sections are placed in a cassette for processing.

consistency, measurements, location (fetal vs maternal surface; peripheral vs central), whether single or multiple and percentage of the villous tissue involved. Then three full thickness sections should be submitted for microscopic examination, avoiding the peripheral portions of the placental disc. If there are any lesions or abnormalities identified, additional representative sections of those areas should be submitted.

NORMAL MACROSCOPIC APPEARANCE

In 90% of the cases, the placenta is disc-like, flat and round to oval. Abnormalities of shape occur in

Fig. 4. Cassette showing two membrane rolls and two sections of umbilical cord

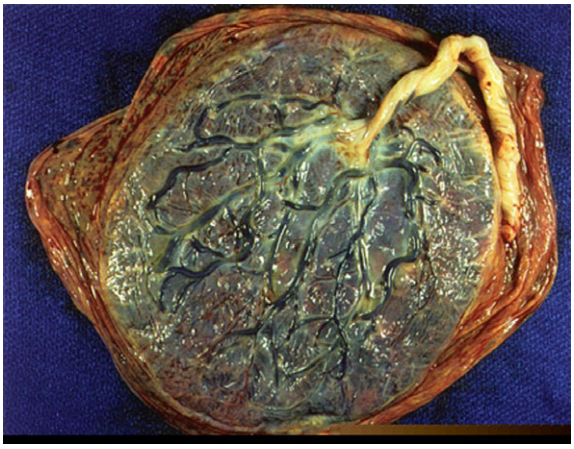

Fig. 5. Fetal surface of a normal placenta.

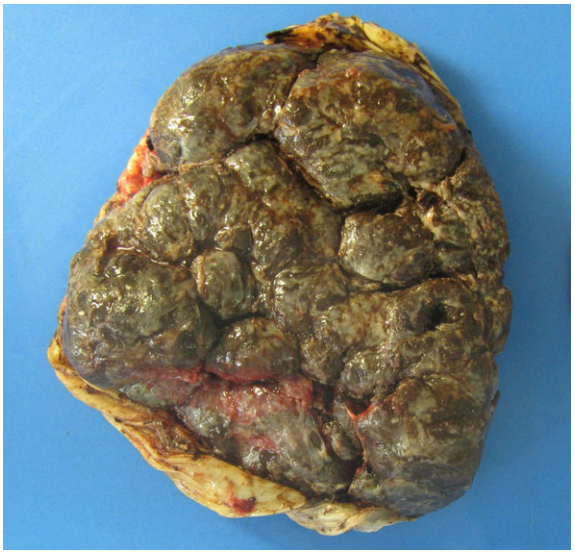

Fig. 6. Maternal surface of a normal placenta. Note white streaks on the surface which represent calcifications, a normal finding.

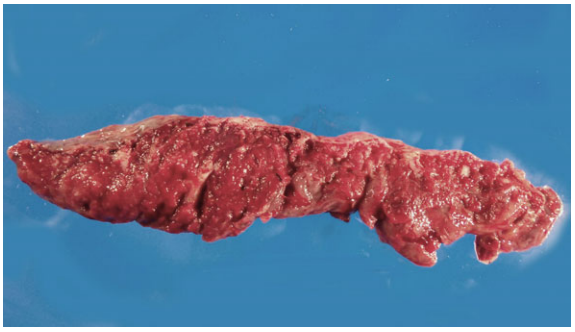

Fig. 7. Cross-section of placental disc showing red, beefy villous tissue.

about 10% of cases and include a bilobed placenta, succenturiate lobes, fenestrated, ring (zonary), and placenta membranacea (2, 3). At term, the average diameter is 22 cm, thickness is up to 2.5 cm and the average weight is 470 grams. The umbilical cord is normally pearly white and measures an average of 55–60 cm in length and 1.0–1.5 cm in diameter at term. It most commonly inserts eccentrically and usually contains three vessels, two arteries and one vein. In marginal insertions, the cord inserts at the edge of the placental disc. In velamentous insertions, the cord inserts into the membranes away from the placental margin and membranous (velamentous) vessels run in the membranes without the protection of Wharton's jelly. Interpositional insertions occur when the cord inserts into the membranes and runs in the membranes without branching of the vessels. A furcate insertion occurs when the cord divides, usually into two, prior to insertion onto the fetal surface. Occasionally a single artery or a persistent second vein occurs leading to 2 or 4 vessels respectively. Care must be taken when evaluating the cord for the presence of a single umbilical artery as the arteries commonly anastomose close to their insertion on the placental surface (Hyrtl's anastomoses) (5). The cord is left twisted in about 70% of cases, but occasionally cords are twisted in both directions. The coiling index may be used to evaluate the amount of twisting. A normal coiling index is 0.2 ± 0.1 coils/cm, i.e. one coil for every 5 cm (Fig. 2).

The fetal membranes are usually translucent but in pathologic conditions may be opaque or discolored and this includes the membranes over the fetal surface. Opacity is most commonly caused by ascending infection (acute chorioamnionitis) or

meconium. The chorionic vessels run underneath the amnion and branch centrifugally from the cord insertion with arteries crossing over veins. Around the larger vessels, the chorionic plate is more opaque due to increased numbers of collagen fibers and normally white fibrin plaques are seen representing subchorionic fibrinoid.

An incomplete system of "lobules" subdivides the basal surface into 10–40 lobes or cotyledons which correspond to the septae seen microscopically (Fig. 6). Often white streaks are present on the maternal surface. These represent calcifications which are normal in mature placentas (Fig. 6). On cut section, the villous tissue is red-brown, and spongy on cut section. Its color is almost wholly determined by its content of fetal blood and thus the fetal hemoglobin/hematocrit (Fig. 7). Within the villous tissue of many delivered placentas are so-called "lakes," which were filled with blood in utero; they are of no consequence. At the periphery of many term placentas, the villous tissue may show areas of tan-white and firmer tissue and thus may appear "infarcted." These are not true infarcts but rather, villous atrophy due to poor circulation at the periphery.

PLACENTAS OF MULTIPLE BIRTHS

In examination of placentas of multiple births, a recording of the membrane relation between the twins, triplets, and so on is mandatory. Second, in the case of monochorionic placentation, the vascular anastomoses should also be noted. Dizygotic twins essentially always have diamnionic/dichorionic (DiDi) placentas but their placentas may be fused. Monozygotic twins may have DiDi placentas separate or fused, diamnionic-monochorionic (DiMo) placentas or even, rarely monoamnionic-monochorionic placentas. The latter have no dividing membranes and may suffer from entanglements of the two umbilical cords (Fig. 8). The dividing membranes in DiDi placentas is thick and relatively opaque due to the presence of two amnions and two chorions, the latter showing streaks representative of atrophied vessels. In addition, there is always a fibrin ridge on the fetal surface where the dividing membranes insert (Fig. 9). This ridge is not present in DiMo placentas but rather the fetal surface is flat and the dividing membranes are thin and transparent consisting only of two amnions (Fig. 10). DiMo placentas virtually always have anastomoses which may be artery to vein, vein to artery, vein to vein, or artery to artery. As arteries cross over veins, most superficial anastomoses can be identified by visual inspection of the vascular equator and identification of a vessel connecting

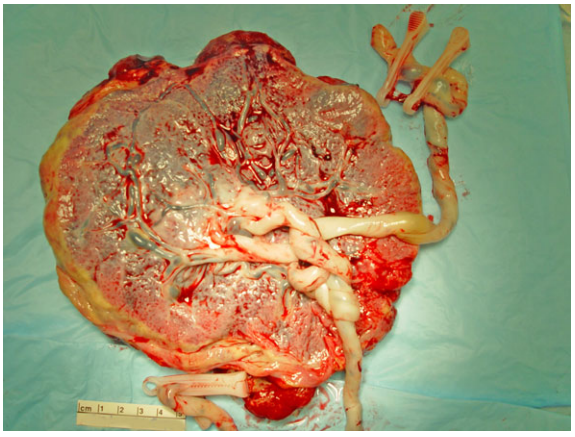

Fig. 8. Monoamnionic-monochorionic placenta with cord entanglement.

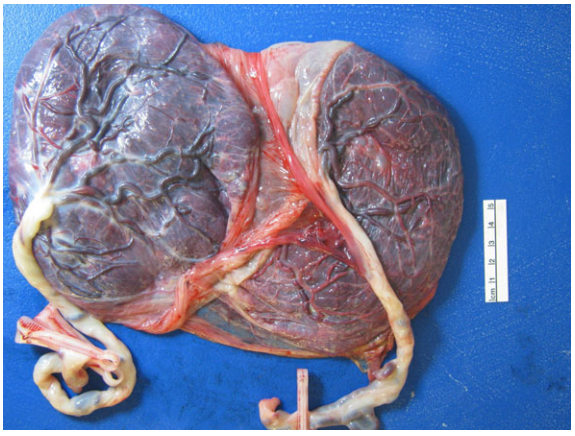

Fig. 9. Diamnionic-dichorionic placenta showing fibrin ridge on the fetal surface at the site of the dividing membranes.

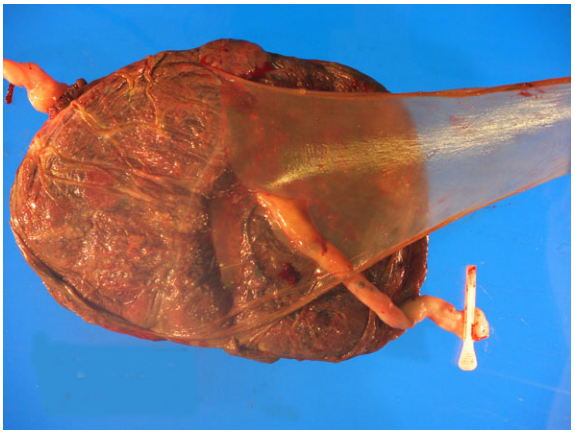

Fig. 10. Diamnionic-monochorionic placenta showing thin, transparent dividing membranes and no fibrin ridge.

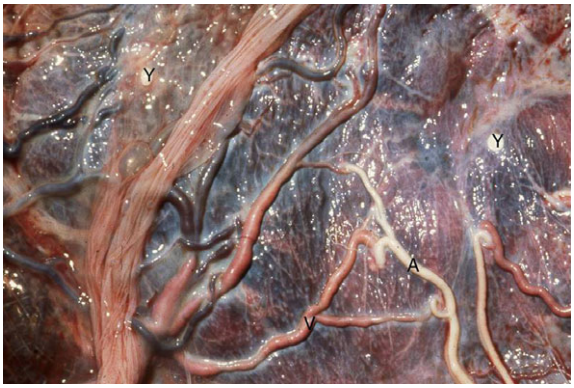

Fig. 11. Diamnionic-monochorionic placenta demonstrating anastomoses between two placentas. One side has been injected with opaque material and shows an artery to vein anastomosis (arteries cross over veins). A=artery, Y=yolk sacs of both twins.

the two circulations (Fig. 11). Usually a paired artery and vein extend from the branching umbilical vessels. Anastomoses can also be identified by identification of an unpaired vessel extending from one twin's placenta to an unpaired vessel of the other twin's placenta. After noting the type of placentation and anastomoses, sections should be taken of any dividing membranes. The placentas then should be separated along the vascular equator (which in fused twin placentas is generally NOT where the dividing membranes are present) and separate examination performed for each placenta as detailed above (2, 3).

SPECIAL STUDIES

Studies of gene expression have been used to investigate the pathophysiology of various placental disorders. The advent of commercially available microarray platforms allows thousands of transcripts to be analyzed at once, and for gene networks to be identified. When doing these types of studies, one must be cognizant that placentas from women who have undergone labor display higher levels of oxidative stress compared to those not in labor delivered by cesarean section. This is associated with changes in the endocrine and cytokine profiles (6). In addition, mRNA degrades rapidly following delivery, and tissue samples need to be frozen immediately, within 10 min. Multiple samples should be taken in a systematic uniform fashion as studies have shown that there is large intraplacental variability in gene expression (7, 8). The samples should be washed in buffered saline, frozen rapidly in liquid nitrogen, and then stored in a minus 80°C freezer for subsequent analysis.

The placenta can also serve as a good source of tissue for chromosome analysis, particularly in fetal demise when the fetus may be quite macerated. The fetal surface should be disinfected, usually with alcohol, then the amnion stripped from the surface. Then tissue can be obtained sterilely from the underlying chorion. Care should be taken in interpretation as confined placental mosaicism may result in abnormalities in placental tissue not present in the fetus.

REFERENCES

1. Langston C, Kaplan C, Macpherson T, Manci E, Peevy K, Clark B, et al. Practice guidelines for examination of the placenta. Developed by the placental pathology practice guideline development task force of the College of American Pathologists. Arch Pathol Lab Med 1997;121:449–76.
2. Benirschke K, Burton G, Baergen RN. Pathology of the Human Placenta, 6th ed. New York: Springer, 2013.
3. Kaplan CG. Color Atlas Of Gross Placental Pathology, 2nd ed. New York: Springer, 2007.
4. Khong YT, Mooney EE, Ariel I, Balmus NC, Boyd TK, Brundler MA, et al. Sampling and definitions of placental lesions: Amsterdam placental working group consensus statement. Arch Pathol Lab Med 2016;140:698–713.
5. Priman J. A note on the anastomosis of the umbilical arteries. Anat Rec 1959;134:1–5.
6. Cindrova-Davies T, Yung HW, Johns J, Spasic-Boskovic O, Korolchuk S, Jauniaux E, et al. Oxidative stress, gene expression, and protein changes induced in the human placenta during labor. Am J Pathol 2007;171:1168–79.
7. Mayhew TM. Taking tissue samples from the placenta: an illustration of principles and strategies. Placenta 2008;29:1–14.
8. Avila L, Yuen RK, Diego-Alvarez D, Penaherrera MS, Jiang R, Robinson WP. Evaluating DNA methylation and gene expression variability in the human term placenta. Placenta 2010;31:1070–7.