Late Fetal Stage (Previable) Placenta (Second Trimester, 12–22 Weeks Post LMP)

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Adverse Outcomes/Clinical Presentations

- Early stillbirth
- Late miscarriage/previable preterm birth
  - Vaginal bleeding/abruption
  - Preterm premature rupture of membranes
  - Cervical insufficiency
- Indicated termination for fetal anomalies or severe maternal disease
- Recurrent late miscarriage

Approach to the Gross Specimen

Gross specimens from this stage of pregnancy show the most heterogeneity ranging from "completely fragmented" in earlier cases to an intact fetus and placenta in later cases. Restricting this discussion to the placenta, it is important to weigh placental tissue trimmed of umbilical cord and membranes for comparison to normal reference values (Table 1); attempt to ascertain the location and nature of the umbilical cord insertion site; describe any cystic, solid, or hemorrhagic lesions; and note any alterations in the color and consistency of the parenchyma, umbilical cord, and fetal surface. Despite the fragmented nature of some specimens, the general rules of sampling membranes, umbilical cord, full thickness parenchyma, and lesions with adjacent normal parenchyma apply (described in detail below for later specimens). In grossly unremarkable cases, three sections of placental tissue are usually sufficient.

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Table 1 Means and standard deviations for placental and fetal weights by gestational age (UH Cleveland Medical Center, 2006–2015, unpublished data)

Gestational Age range (weeks))		Placental Weight (g)		Birth Weight (g)
12–12.9	Mean	39		18
$N = 9$	(SD)	−42	$N = 12$	−5
13–13.9	Mean	44		28
$N = 35$	(SD)	−15	$N = 41$	−6
14–14.9	Mean	52		46
$N = 54$	(SD)	−22	$N = 57$	−11
15–15.9	Mean	63		69
$N = 33$	(SD)	−17	$N = 32$	−13
16–16.9	Mean	74		99
$N = 25$	(SD)	−18	$N = 25$	−12
17–17.9	Mean	81		125
$N = 20$	(SD)	−24	$N = 15$	−18
18–18.9	Mean	92		172
$N = 11$	(SD)	−17	$N = 11$	−25
19–19.9	Mean	121		229
$N = 6$	(SD)	−30	$N = 6$	−43
20–20.9	Mean	116		307
$N = 4$	(SD)	−23	$N = 4$	−27

Specific Important Histopathologic Sequences

1. *Marginal abruption, acute and/or chronic*

   The preponderance of large remodeled spiral arteries in the central 2/3 of the placenta biases venous drainage to the placental margins. Although earlier descriptions of a continuous draining venous sinus are erroneous, decidual veins at the placental margin (where the chorionic and basal plates come together to form the placental membranes) are typically dilated and poorly supported by surrounding connective tissue. This places them at high risk for rupture in cases of decidual inflammation, increased maternal venous pressure, or abrupt changes in intrauterine geometry after rupture of membranes [1]. Acute marginal abruption is a common cause of both second and early third trimester premature loss, often occurring in combination with rupture of membranes and acute chorioamnionitis. Chronic marginal abruption often begins in the first trimester with vaginal bleeding and sonographic evidence of so-called "subchorionic hemorrhage" [2]. These early subchorionic hemorrhages may either resolve spontaneously or progress. With progression, persistent vaginal bleeding and oligohydramnios (chronic abruption/oligohydramnios sequence), and a constellation of placental findings including circumvallate membrane insertion, green (biliverdin) discoloration, organizing marginal blood clots, and diffuse chorioamnionic hemosiderosis may be observed [3–5](Fig. 1a). Diffuse chorioamnionic hemosiderosis

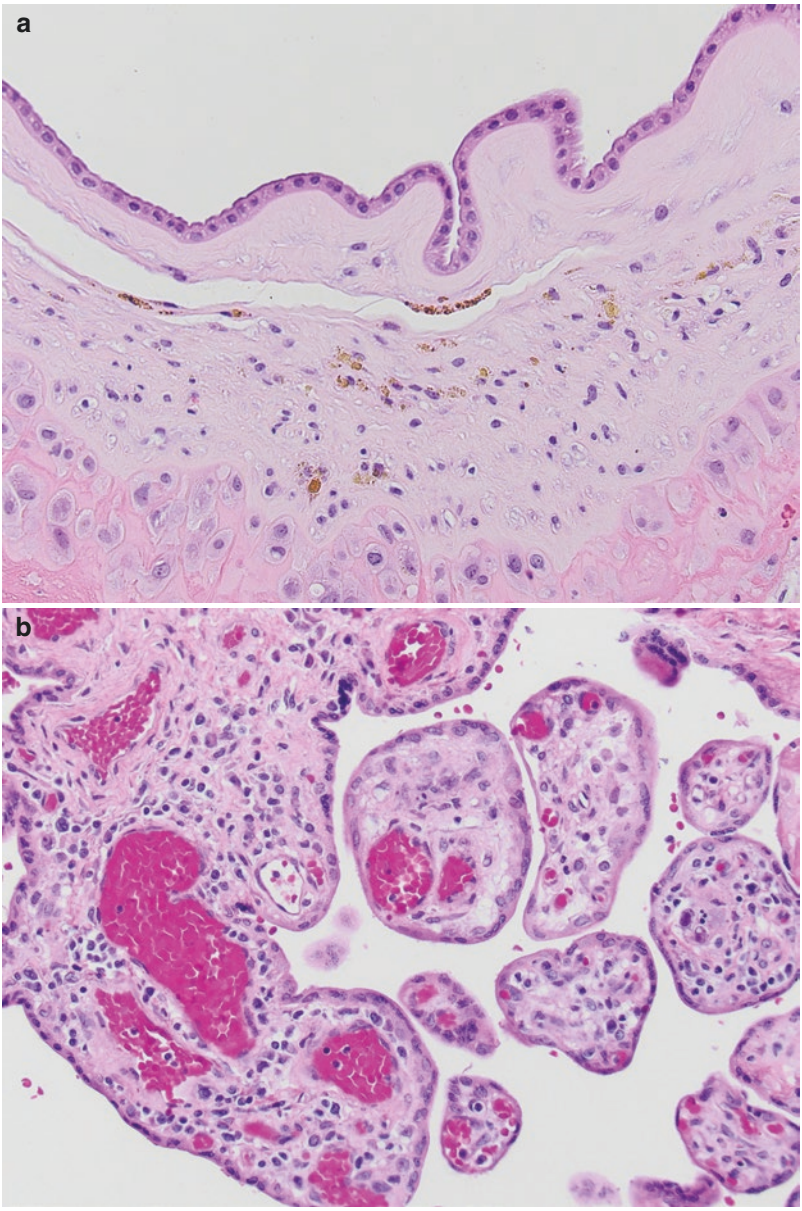

Fig. 1 Second trimester placental pathology: (**a**) Diffuse chorioamnionic hemosiderosis with numerous golden brown refractile hemosiderin crystals within the connective tissue of the chorion and amnion (200×). (**b**) Cytomegalovirus (CMV) villitis with villous stromal plasma cells on the left and large CMV nuclear inclusions on the right (200×). (**c**) Amnion Disruption Anterior Malformation (ADAM) sequence with absent umbilical cord, amnion disruption, and amnionic adhesions fusing the placenta to a fetus with an anterior wall defect. (**d**) Massive subchorial thrombohematoma with a large expansile hemorrhage elevating the chorionic plate above the underlying villous parenchyma

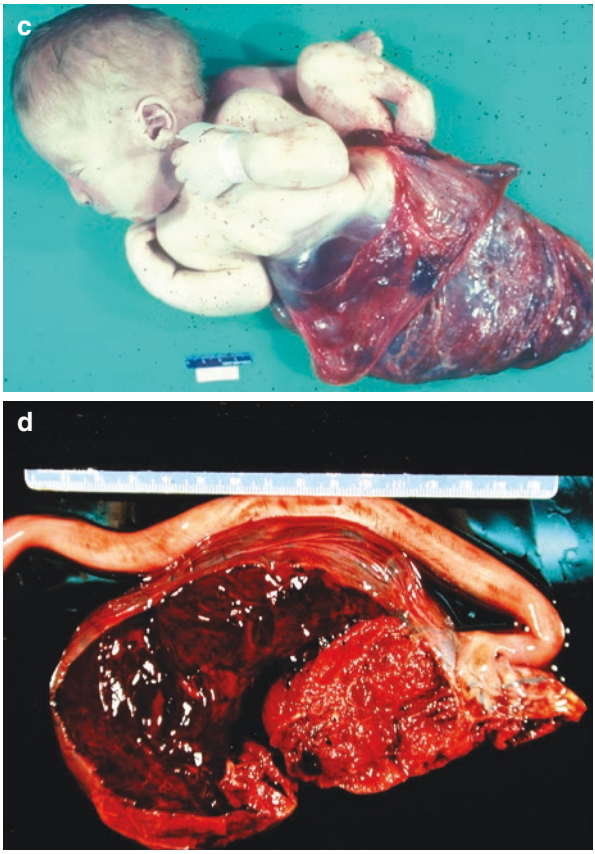

Fig. 1 (continued)

has been associated with preterm delivery, fetal growth restriction (FGR), and a distinct pattern of neonatal lung disease (so-called "dry" bronchopulmonary dysplasia or Mikity–Wilson disease) [6].

2. *Placental hydrops*

Hydrops fetalis is most commonly caused by fetal congestive heart failure due to either severe anemia (isoimmune, Parvovirus B19-related, or genetically determined) or fetal structural anomalies (arteriovenous shunts, impaired venous return, or right sided heart malformations) [7]. Less commonly, edema occurs due to decreased oncotic pressure (liver protein synthetic failure) or lymphatic malformations. Common gross and histologic findings in the placenta include increased weight for GA, pallor, villous edema, delayed villous maturation, and abnormalities at the villous trophoblast-stromal interface (artifactual cleavage and/or basement membrane calcification). The placenta plays a limited role in the differential diagnosis of hydrops. Presence or absence of increased circulating NRBC can broadly distinguish cases due to fetal anemia from other etiolo-

gies. In occasional cases, specific findings such as AV shunting in a large placental chorangioma, viral inclusions in Parvovirus B19 infection, and findings suggestive of TORCH infection or metabolic storage disease (see below) may be diagnostic.

3. *Chronic villitis, infectious ("TORCH infection")*

   Hematogenous infections of the placenta by specific bacteria (*Treponema pallidum*), protozoa (*Toxoplasma gondii, Trypanosoma cruzi*), and viruses (Zika virus and Herpes viridiae: cytomegalovirus (CMV), Varicella-Zoster, herpes simplex, Epstein Barr) typically evoke a lymphohistiocytic inflammatory response in the placental villi known as chronic villitis [8, 9]. These infections, together with some no longer seen in the developed world (Rubella, Vaccinia, Variola), are grouped under the acronym TORCH (Toxoplasmosis, Other, Rubella, CMV, and Herpes simplex). The most common of these infections in Europe and North America is CMV. Typical features of infectious villitis that distinguish it from the much more common, and later occurring, noninfectious villitis (see below) include diffuse but variable involvement of most villi, a predominance of histiocytes over lymphocytes, fetal endothelial damage with stromal hemosiderin, villous stromal and endovascular fibrosis, calcification, delayed villous maturation, and, in some cases, villous plasma cells and/or viral inclusions (both most commonly seen in CMV) (Fig. 1b). Typical histopathology, immunohistochemical staining, and evidence of fetal infection allow for definitive diagnosis in most cases. Prognosis for the pregnancy and fetus vary according to the causative organism but early miscarriage, FGR, stillbirth, and organ-specific malformations, deformations, and disruptions are all possible sequelae. Extent and severity of placental involvement generally parallel the severity of fetal disease.

4. *Amnion adhesions/premature amnion rupture*

   Defects in the formation and integrity of the amnion straddle the boundaries of malformation, deformation, and disruption. In the earliest presentation, the amniotic deformities, adhesions, and mutilation (ADAM) sequence are thought to be secondary to dysmorphogenesis of the body stalk with associated short umbilical cord, failure of abdominal wall closure, and amnionic adhesions fusing the placenta to the developing fetus [10, 11] (Fig. 1c). Later, isolated amnion rupture can lead to the formation of amnionic bands that can encircle and amputate fetal body parts or encircle and constrict the umbilical cord (disruptions) [12]. In the placenta, amnion rupture may be diagnosed grossly by string-like amnion bands connecting the surface of the chorionic plate to the UC or histologically as separation of the amnion from the chorion with degenerating and/or calcified amniotic epithelial cells between the two membrane layers. Finally, amnion and chorion can rupture together without triggering labor (prolonged preterm rupture of membranes) leading to loss of amniotic fluid and an increased risk for the fetal oligohydramnios deformation sequence (Potter syndrome) and ascending bacterial/fungal infections (discussed below). Amnion nodosum, defined by organized nodules of degenerating fetal squamous cells incorporated

into the amnionic epithelium, is a specific placental lesion associated with prolonged rupture of membranes, longstanding oligohydramnios, and lethal pulmonary hypoplasia.

5. *Massive subchorial thrombohematoma*

   Large, expansile subchorionic hemorrhages that distort and elevate the chorionic plate (Fig. 1d) are rare lesions with a very high rate of associated stillbirth [13]. At one time they were thought to be a consequence of fetal death, but case reports of liveborns disproved this hypothesis. Pathogenesis is unknown. Parallels with diffuse intervillous hemorrhage (Breus' mole, see above), subchorionic intervillous thrombi, and excessive subchorionic fibrin have all been drawn, but are not entirely satisfactory. Three possible scenarios are (1) overexpansion of the intervillous space due to inadequate villous support related to distal villous hypoplasia and a thick "jelly-like" placenta by ultrasound, (2) early intraplacental abruptions analogous to the recently described infarction-hematoma (discussed below), and (3) hemorrhage due to stem villous rupture with both fetal hemorrhage and secondary maternal thrombosis.

Pathology Report

The pathology report from a second trimester loss should separately address the fetus and placenta. In most cases of sporadic loss related to placental disease, the fetus lacks specific abnormalities aside from fragmentation due to the method of evacuation, involutional changes caused by antenatal fetal death, and growth abnormalities related to maternal-placental dysfunction. Accordingly, the first line of a typical diagnostic report can be outlined as follows (Fig. 2): *fragmented/intact, autolyzed/well preserved, (male/female) fetus/fetal fragments; small for/large for/appropriate for ___ weeks gestation by measurements; no congenital anomalies*. In most cases, the placental findings can be summarized in a second diagnostic line outlined as: *markedly fragmented/(complete/incomplete)/(relatively small/relatively*

Representative pathology report: second trimester fetus and placenta

FETUS AND PLACENTA:
--AUTOLYZED 125 G MALE FETUS; SMALL FOR 18 WEEKS GESTATIONAL AGE
--NO CONGENITAL ANOMALIES

--FRAGMENTED (?INCOMPLETE) SECOND TRIMESTER PLACENTA; 80 G IN AGGREGATE
--MASSIVE SUBCHORIAL THROMBO-HEMATOMA

NOTE: Massive subchorial thrombo-hematoma is a rare idiopathic expansile intraplacental hemorrhage often associated with fetal death. Recurrence risk is unknown.

Fig. 2 Second trimester placental pathology report

*large) intact second trimester placenta, __ g (in aggregate), with…*Any specific placental diagnoses are then listed in order of importance followed by a note correlating the antenatal history and the fetal and placental findings with pathogenesis, risk of recurrence, and any suggestions for further diagnostic evaluation.

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