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The Placenta in Toxicology. Part III: Pathologic Assessment of the Placenta

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Abstract

This short review is derived from the peer-reviewed literature and the experience and case materials of the authors. Brief illustrated summaries are presented on the gross and histologic normal anatomy of rodent and macaque placentas, including typical organ weights, with comments on differences from the human placenta. Common incidental findings, background lesions, and induced toxic lesions are addressed, and a recommended strategy for pathologic evaluation of placentas is provided.

Keywords: macaca; mus; rodent pathology; primate pathology; placenta; toxicology.

Introduction

This article offers a brief review of the gross and histologic anatomy of the rodent and nonhuman primate placenta, a discussion of common lesions and published toxic effects, and guidance regarding appropriate strategy for pathologic assessment of the organ. The placenta of eutherian mammals consists of the yolk sac, amnion, and chorioallantoic membranes. The chorioallantoic membranes are the major placental structures at term in most species, although the yolk sac provides an important hematopoietic and growth factor producing function in early embryogenesis, and persists in rodents until term. For additional information on the rodent placenta, the reader is referred to several excellent detailed recent reviews, addressing the development of the normal rat placenta (de Rijk, van Esch, and Flik 2002), the comparative anatomy of mouse placenta (Georgiades, Ferguson-Smith, and Burton 2002), toxic injury to the rat placenta (Furukawa et al. 2011), and pathologic evaluation of the mouse fetoplacental unit (Ward, Elmore, and Foley 2012). The development and anatomy of the macaque placenta has also recently been described in detail (de Rijk and van Esch 2008; Enders 2007). Comparative placental anatomy is best explored through the works of Dr. Kurt Benirschke, particularly his textbook on the pathology of the human placenta (Benirschke, Kaufmann, and Baergen 2006), and his web site at the University of California at San Diego, devoted to comparative placentation (http://placentation.ucsd.edu/homefs.html).

Rodents

Gross Anatomy

Mice and rats have hemochorial, discoid placentas. The weight of the placenta at term is approximately one-tenth of the fetal body weight (BW); during the development of the fetus and placenta, placental growth precedes fetal development, and in the last few days of gestation, the placental weight (PW) is unchanged, while the fetal weight increases exponentially. Normal values for CD-1 outbred mice have been published based on an ultrasound validation study (Mu et al. 2008; Figure 1). Figure 2 assembles data from several sources to illustrate a similar pattern in Sprague-Dawley and Wistar rats (Bartholomeuz and Bruce 1976; Bruce and Cabral 1975;

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Abbreviations: BW, body weight; EGF, epidermal growth factor; GD, gestational day; NK, Natural Killer; PW, placental weight; VEGF, vascular endothelial growth factor.

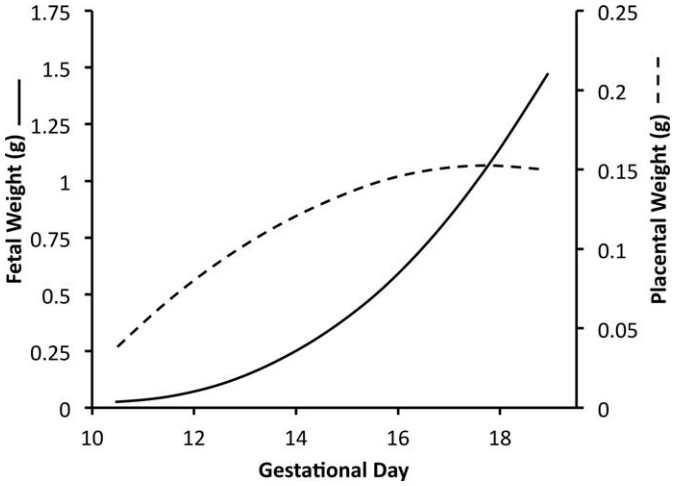

FIGURE 1.—Pattern of fetal and placental growth during gestation in CD-1 mice (redrawn from Mu et al. 2008).

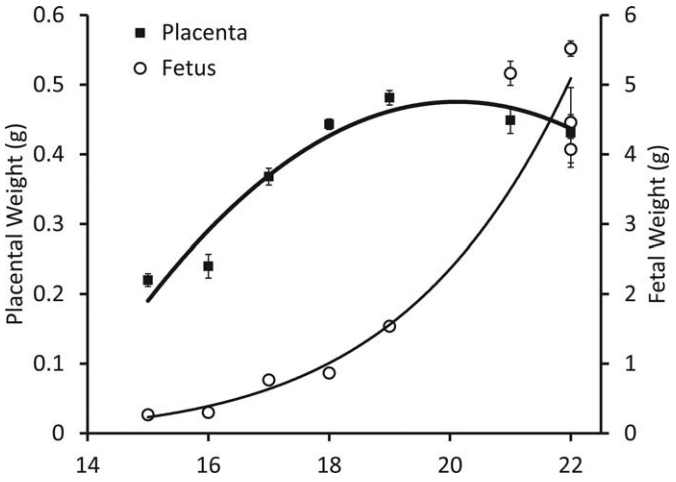

FIGURE 2.—Fetal and placental growth in Wistar and Sprague-Dawley rats (Bartholomeuz and Bruce 1976; Bruce and Cabral 1975; Furukawa et al. 2008; Jones et al. 2010; Zambrana and Greenwald 1971). Error bars indicate standard error of the mean; multiple symbols on the same gestational day indicate different data sets.

Furukawa et al. 2008; Jones et al. 2010; Zambrana and Greenwald 1971).

Histologic Anatomy

The cellular components of the rodent placenta are similar to those of the human, but with some important distinctions; major structures are shown in Figures 3 and 4. Proceeding outward from the fetus, the layers include the amnion, the yolk sac, Reichert's membrane, the placental labyrinth, the basal zone (trophospongium), decidua basalis, and metrial gland. Within the labyrinth, the fetal blood is separated from maternal blood by fetal endothelium, perivascular cells, fetal mesenchymal cells, and 3 thin layers of trophoblastic cells (cytotrophoblasts and two layers of syncitiotrophoblasts), thus the term

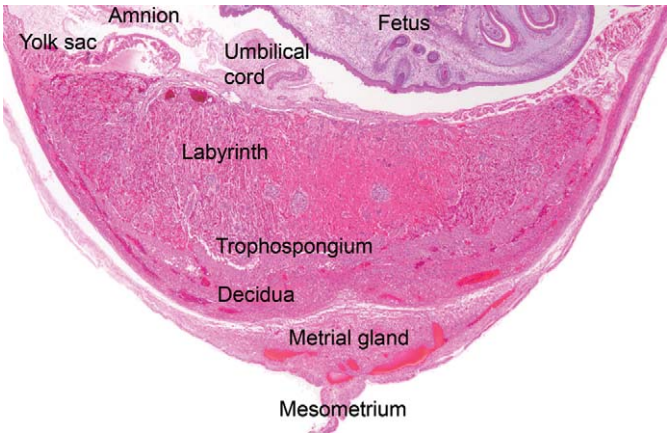

FIGURE 3.—Subgross histologic anatomy of the rat placenta.

hemotrichorial is applied to the rodent placenta. The next layer, the trophospongium, consists of spongiotrophoblasts, and a deeper layer of giant cell trophoblasts. Islands of glycogen-rich cells are admixed with the labyrinth and trophospongium. The decidua basalis consists of modified maternal endometrial stromal cells. The outermost layer of the maternofetal interface is the metrial gland, which is not glandular but consists of intermixed decidual cells, specialized natural killer (NK) cells, and vessel-associated trophoblasts. This structure spans the myometrium, extending into the mesometrium. In contrast, the term human placenta lacks a yolk sac, is villous rather than labyrinthine, has fewer trophoblastic layers, and with the exception of low numbers of vessel-associated trophoblasts does not cross the myometrium.

Lesions of the Chorioallantoic Placenta in Rats and Mice

Among mouse strains, placental size varies by strain, and some specific strain crosses are known to result in fetal loss by degeneration and resorption of fetoplacental units. For example, the CBA × DBA cross results in spontaneous abortion mediated by immunologic incompatibility (Duclos, Pomerantz, and Baines 1994). A wide variety of genetically altered mouse strains have impaired implantation and chorioallantoic organizational and growth deficiencies, most notably involving the fibroblast growth factor (FGF), Wnt, epithelial growth factor (EGF), and Hox pathways (Cross 2005; Lim and Wang 2010). Infectious diseases of the gravid uterus are relatively uncommon in laboratory rodents, consisting generally of ascending bacterial infections near term. Placental neoplasms are rare. Yolk sac carcinomas can be induced by fetectomy in rats (Sobis, Verstuyf, and Vandeputt 1993). Reactive hyperplasia of the metrial glands is common in rats, producing the so-called deciduoma, which properly speaking is not a neoplasm, nor does it involve the placenta; however, because it is a common lesion of the uterus mimicking an implantation site, it is important to recognize; for further discussion of this lesion, see Picut et al. (2009).

Toxic lesions of the placenta in rats and mice have been reported by many investigators, and some stereotypic patterns

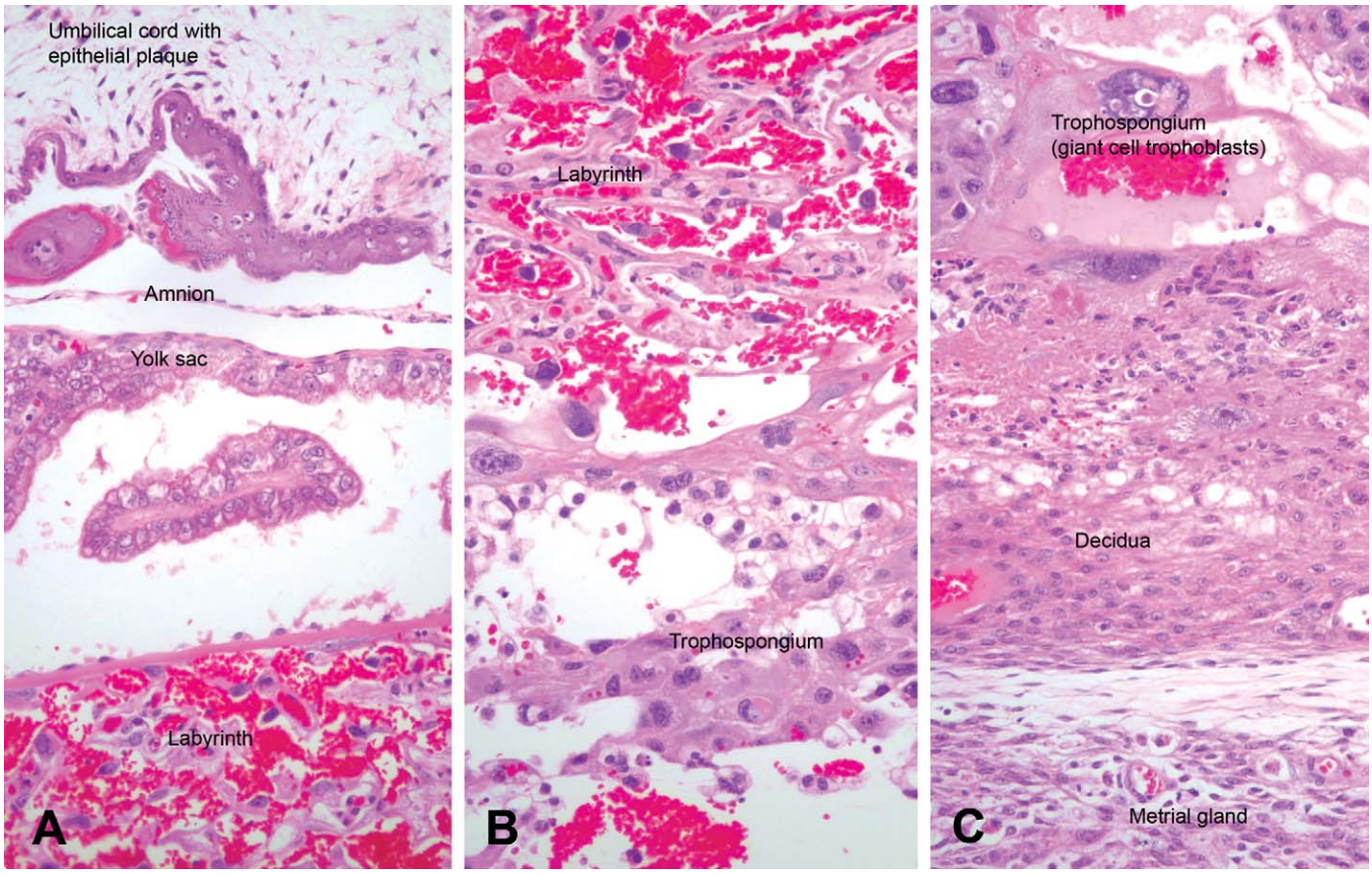

FIGURE 4.—Higher magnification figures showing cellular components of the rat placenta. (A) umbilicus (bearing an focally keratinized plaque), amnion, yolk sac, Reichert's membrane, and placental labyrinth; (B) placental labyrinth to trophospongium; (C) trophospongium to metrial gland.

of response have been identified. Corticosteroid exposure of rats causes a reduction in placental size and reduced expression of vascular endothelial growth factor (VEGF) (Hewitt, Mark, and Waddell 2006). A detailed review of reported toxicologic lesions in the rat placenta is provided by Furukawa et al. (2011). Examples include ketoconazole-induced placental hypertrophy; placental necrosis secondary to cadmium administration; cystic degeneration of glycogen cells induced by 6-mercaptopurine; busulfan-induced apoptosis of placenta trophoblasts and endothelial cells; and metrial gland hypoplasia as a result of tamoxifen treatment (Furukawa et al. 2011).

NONHUMAN PRIMATES

Gross Anatomy

The macaque placenta resembles the human placenta grossly, with the exception that most macaque pregnancies result in the formation of two placental disks. The fetal surface of the placental disk is smooth and bears a radial array of large blood vessels. The maternal surface is dark red, friable, and irregularly divided into lobules by septae of maternal tissue.

The most definitive report of PW in macques included assessment of 490 term placentae of rhesus macaques, obtained by cesarean section (and therefore known to be complete). In this collection, 75% of the placentas were bidiscoid, and 25% had a single disk. The mean PW was 135 $\pm$ 32 g, and the mean fetal weight was 480 $\pm$ 78 g. Formulae were derived from this collection for the calculation of expected PW when either gestational day (GD) or fetal BW were known. These were PW = 1.3 (GD) − 65.9, or PW = 0.29 (BW) − 0.12, respectively (Digiacomo, Shaughnessy, and Tomlin 1978).

Histologic Anatomy

The histology of the macaque placenta is nearly identical to that of the human placenta (de Rijk and van Esch 2008; Figure 5). The fetus is enclosed in an amniotic sac, which is closely apposed to the chorionic membrane. The yolk sac in primates regresses by the end of the first trimester. The fetal surface of the placental disk is identifiable by its smooth surface bearing large vessels. The chorion is sparsely populated by mesenchymal cells within a loose fibrous connective tissue matrix, and penetrated by paired arteries and veins at intervals. These vessel pairs arborize into a complex lobulated branching villous network, which is anchored both on the fetal side (the chorionic plate) and on the maternal side (the trophoblastic shell and decidua). The villi consist of fetal blood vessels, perivascular mesenchymal cells, cytotrophoblastic

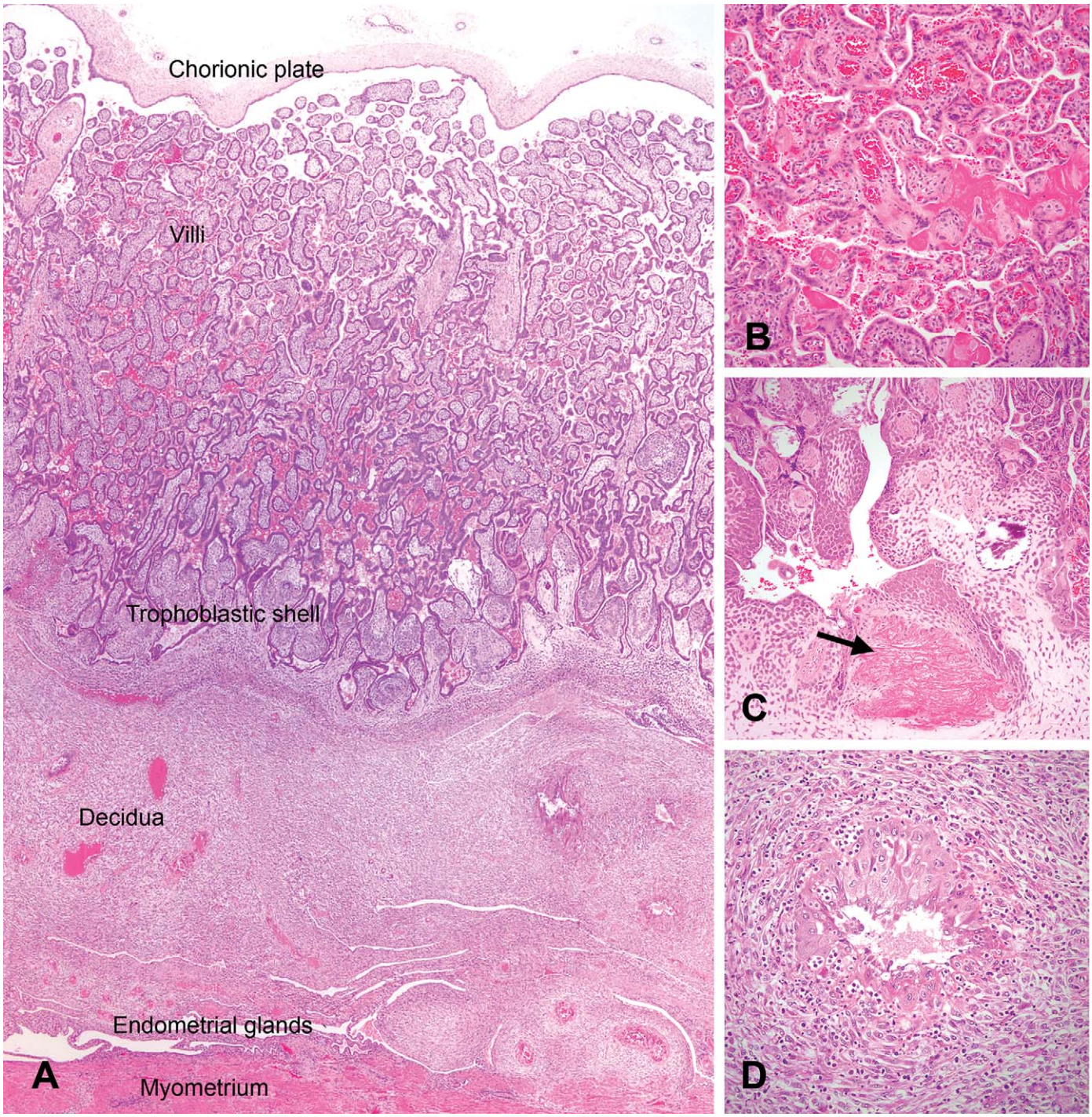

FIGURE 5.—Histology of the normal macaque placenta. (A) Full-thickness section of a mid-gestation placenta; (B) the villous portion of the placental disk; (C) near-term placenta sectioned near the trophoblastic shell, showing normal mineralization (white arrows) and placental fibrinoid (black arrow); (D) endometrium, consisting of decidual cells surrounding an endometrial vessel with a wall largely replaced by fetal trophoblasts.

epithelial cells, and large multinucleate syncitiotrophoblasts. The deep margin of the placental disk proper is demarcated by a layer of trophoblasts termed the trophoblastic shell. Fetal trophoblastic cells also invade the endometrium, surrounding and infiltrating the wall of maternal endometrial vessels; these are termed extravillous trophoblasts. Where the fetal villi contact the endometrium, they "root" and at these sites the mesenchymal cores contain some maternal decidual cells. With the exception of the maternal blood and this decidual cell invasion, nearly all cells comprising the placental disk are of fetal origin. Maternal blood vessels open into and drain from the intervillous space.

TABLE 1.—Common background findings in the placenta of macaques.

Finding	Comments	Reference
Mineralization	Present multifocally within villi of normal placentas	De Rijk and van Esch (2008)
Fibrin deposits	Present normally within and around villi of normal placentas	De Rijk and van Esch (2008)
Marginal coagulative necrosis	Present normally in term placentas	De Rijk and van Esch (2008)
Epithelial plaque response	A pseudo-placental epithelial lesion occurring during the luteal phase	Cline et al. (2008)
Circumvallation	A constrictive fibrotic malformation of the placental margin, usually asymptomatic	Bunton (2006)
Variation in disk number and lobulation	~70% of placentas are bidiskoid	Digiacomo, Shaughnessy, and Tomlin (1978)
Infarction	Marginal infarction is normal at term	Bunton et al. (2012)
Suppurative placentitis	Most often caused by *Listeria monocytogenes*	Cline, Brignolo, and Ford (2012)
Retained placenta	A medical emergency, usually fatal if untreated	Cline, Brignolo, and Ford (2012)
Neoplasia	Choriocarcinomas and trophoblastic neoplasms; most commonly ovarian	Cline et al. (2008)

The non-discoid, membranous portions of the placenta lack villi and are covered by a single layer of trophoblastic epithelium. Normal noncellular elements of the placental disk include inter- and intra-villous deposits of placental fibrinoid, which consists of fibrin, laminin, and other extracellular matrix molecules (Kaufmann, Huppertz, and Frank 1996); and multifocal mineralization of the placental villi. Coagulative necrosis of the margin of the placental disk is normal near term.

Beneath the placental disk, endometrial glands are dilated and sparse; beneath the membranous portions of the placenta, the endometrial glands are dilated by fluid and are lined by a simple cuboidal epithelium and surrounded by plump decidual cells. Throughout the gravid endometrium, stroma-derived decidual cells are abundant, as are granulated endometrial lymphocytes.

Placental Lesions in Macaques

Toxic lesions of the placenta are not well described in macaques; common background findings in the placenta of macaques are listed in Table 1.

RECOMMENDED STRATEGY FOR PATHOLOGIC ASSESSMENT OF THE PLACENTA

The placenta is remarkable in that it is a temporary vital organ. Because it forms, functions, and becomes senescent within the course of a single pregnancy, it is a dynamic structure, which should be evaluated in the context of gestational age.

Elements of a complete examination are:

- Maternal health status
- Known or estimated gestational age
- Fetal health and morphology
- Placental weight
- Fetal weight
- Documentation of gross findings, including photography
- Careful trimming of placenta and uterus
- Rodents: Centered sections, inclusion of the metrial gland
- Primates: Multiple sections, including center, margin, and non-disk regions
- Examination for presence and proportions of all cell types

Quantitative histology may be of value, because injury to the placenta may produce changes in overall placental size or the relative proportions of specific cellular regions, without overt necrosis at the time of examination. The distinct compartmentalization of the rodent placenta makes quantification of regional thicknesses or areas relatively simple (Furukawa et al. 2011), and detailed stereologic methods have been reported for evaluation of the mouse placenta (Coan, Ferguson-Smith, and Burton 2004). Strategies for quantification of injury to the macaque placenta have been published (e.g., Davison et al. 2000), and stereologic methods may also be adopted from the human literature (e.g., Mayhew 2009).

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