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The Frequency and Type of Placental Histologic Findings in Term Pregnancies with Normal Outcome

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Abstract

Objective: To determine the frequency and type of histopathologic lesions in placentas delivered by women with a normal pregnancy outcome.

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Methods: This retrospective cohort study included placental samples from 944 women with a singleton gestation who delivered at term without obstetrical complications. Placental lesions were classified into the following four categories as defined by the Society for Pediatric Pathology and by our Unit: 1) acute placental inflammation, 2) chronic placental inflammation, 3) maternal vascular malperfusion, and 4) fetal vascular malperfusion.

Results: 1) 78% of placentas had lesions consistent with inflammatory or vascular lesions; 2) acute placental inflammatory lesions were the most prevalent, observed in 42.3% of the placentas, but only 1.0% of the lesions were severe; 3) acute inflammatory lesions were more common in the placentas of women with labor than in those without labor; 4) chronic inflammatory lesions of the placenta were present in 29.9%; and 5) maternal and fetal vascular lesions of malperfusion were detected in 35.7% and 19.7%, respectively. Two or more lesions of maternal or fetal vascular features consistent with malperfusion (high-burden lesions) were present in 7.4% and 0.7%, respectively.

Conclusion: Most placentas had lesions consistent with inflammatory or vascular lesions, but severe and/or high-burden lesions were infrequent. Mild placental lesions may be interpreted as either acute changes associated with parturition or representative of a subclinical pathological process that did not affect the course of pregnancy.

Keywords

acute histologic chorioamnionitis; amniotic fluid infection; chronic chorioamnionitis; chronic deciduitis; chronic placental inflammation; fetal vascular malperfusion; funisitis; maternal vascular malperfusion; normal or uncomplicated pregnancy; villitis of unknown etiology

INTRODUCTION

In the evaluation of pregnancy complications, neglect of the placenta in developed countries has become a thing of the past. In 1997, the American College of Pathologists published guidelines for examining placentas in high-risk pregnancies (1); subsequently, the Perinatal Section of the Society for Pediatric Pathology in the United States published a series of reports led by Redline et al. about the classification and reproducibility of the diagnosis of placental lesions (2–9). Such lesions were broadly categorized as those consistent with 1) amniotic fluid infection (2, 9), 2) maternal vascular underperfusion (2, 8), and 3) fetal vascular underperfusion (2, 7), to which was added a fourth category—chronic placental inflammation (5, 10–20). During a workshop organized in Amsterdam in 2014, the recommendations for sampling and the definitions of placental lesions were updated (21).

However, to date, there is very little information on how frequently histologic inflammatory or vascular lesions are found in placentas of patients with normal pregnancy outcomes (22–24), and this information is required to interpret the significance of placental histopathologic findings in patients who have obstetrical complications. Moreover, this information may also be useful in counseling patients about the outcome of the index pregnancy (25–40), the prognosis for subsequent pregnancies (41–47), and in a medicolegal context (48–56). Often, the placenta has been considered a “witness” in litigation (57).

Therefore, the objective of this study was to determine the frequency with which different pathological lesions can be detected histologically in the placenta in a large cohort of women who had a singleton pregnancy, no obstetrical complications, and who delivered appropriate-for-gestational-age neonates at term without perinatal complications.

METHODS

Study Design

This report is based on a retrospective analysis of the placental histological lesions diagnosed by pediatric pathologists experienced in the assessment of placental lesions (CJK, JSK, YMK, SMJ, and FQ). Subjects recruited into a cohort study between January 11, 2006, and June 11, 2014, had no medical or obstetrical complications and delivered a singleton, term (37–42 weeks) neonate with a 5-minute Apgar score ≥ 7 and a birthweight between the 10th and 90th percentiles of a United States' reference population (58). Patients provided written informed consent before the collection of placentas. The collection and use of clinical data and specimens were approved by the Human Investigation Committee of Wayne State University (WSU) and the Institutional Review Board of the National Institute of Child Health and Human Development (NICHD). Pathologic examination of the placentas was undertaken for research purposes.

Placental Pathology Examination

Placentas were collected in the Labor and Delivery Unit or Operating Room at Hutzel Women's Hospital of the Detroit Medical Center (DMC) and transferred to the Perinatology Research Branch (PRB) laboratory. For all placentas, the maternal surface (basal plate), fetal surface (chorionic plate), and the umbilical cord were photographed prior to dissection. The gross morphologic description and placental measurements were documented, and the placental weight was recorded before and after the trimming of the chorioamniotic membranes and umbilical cord. Sampling of the placentas was conducted according to protocols of the PRB and the Department of Pathology of the WSU School of Medicine and the DMC.

Samples from the placenta were obtained using two approaches:

1) Systematic random sampling at the PRB and 2) targeted sampling in the laboratory of the WSU/DMC Department of Pathology.

A) Systematic random sampling at the PRB

1) Sampling of chorioamniotic membranes and the umbilical cord: Samples were taken from the extraplacental membranes in the form of membrane rolls (n=3), and the umbilical cord (n=3). The chorioamniotic membrane roll was dissected into a 30-mm piece and placed into a labeled specimen cup containing ~20 mL of 10% formalin. The umbilical cord was bisected at 3 cm from the point of insertion into the chorionic plate, followed by the collection of three samples from the umbilical cord at these locations: 1) the distal end attached to the placenta, 2) the middle portion, and 3) the proximal end closest to the fetus.

2) Sampling of the placental disc: Systematic random sampling of the placental disc was performed using a random sequence generator designed for this purpose, known as the PRB DICE software (Supplementary Material and Figures). A minimum of six blocks of the placental disc were obtained using random sampling; then, three of the six blocks were embedded in paraffin and stained with hematoxylin and eosin (H&E), while the remaining three blocks were stored for further research. Additional samples were obtained at the discretion of the pathologist. The placenta was then transferred to the WSU/DMC Department of Pathology where targeted sampling was performed, according to standard clinical protocols (1).

B) Targeted sampling in the laboratory of the WSU/DMC Department of Pathology—This processing technique entailed taking representative sections of the selected non-randomized predefined areas from the placenta. A minimum of one section from the membrane roll and two sections of umbilical cord were placed together in one cassette. The sections taken from the villous parenchyma included the entire thickness of the placenta, extending from the chorionic plate (fetal surface) to the basal plate (maternal surface), and both the amnion and decidua. A thick placenta necessitated bisecting the section to fit the cassette. The margins of the placenta were not sampled as they are often non-representative. Therefore, only appropriate sections from the central region were targeted. For those placentas that appeared grossly normal, a minimum of three full-thickness sections from the central portion of the placenta and three slivers from the basal plate were processed for histologic examination and stained with H&E, whereas for placentas with gross lesions, additional sections were taken at the discretion of the pathologist.

After sampling (both systematic random and targeted), tissues were fixed with 10% neutral buffered formalin (NBF) at a minimum 1:20 ratio (tissue: NBF) for at least 12 hours, but not more than 48 hours, before further processing. After an NBF fixation, the samples were trimmed, processed, and paraffin-embedded. A 5- μ m-thick section was taken from each paraffin block and stained with H&E for microscopic evaluation.

All H&E-stained slides of the chorioamniotic membrane roll, umbilical cord, and placental disc (minimum of seven: at least three by systematic random sampling and four by targeted sampling) were examined by pediatric pathologists who are specialists in the assessment of placental lesions (CJK, JSK, YMK, SMJ, FQ). Tables 1A and 1B show the terminology used in this study, which was based mainly on the criteria established by the Perinatal Section of the Society for Pediatric Pathology (2). Subsequently, the terminology was revised by the Amsterdam Placental Workshop Group Consensus (2, 21) and we used this for the purpose of this study. The grading and staging of chronic chorioamnionitis were scored following the publication of diagnostic criteria by our group (14).

Statistical Analysis

All data analyses were performed in R (59). For continuous data, comparisons between the groups were done using the Kruskal-Wallis test without making any distributional assumptions. For categorical data, proportions were compared between groups using exact

tests for contingency tables. Generalized linear models were used to examine the associations between covariates, such as ethnicity (African-American or others), nulliparity (nulliparous or multiparous), labor (yes or no), gestational age at delivery (continuous variable), duration of membrane rupture (continuous variable), and frequency of histopathologic lesions. Associations among the four major categories of histologic lesions (acute inflammatory, chronic inflammatory, maternal vascular malperfusion, and fetal vascular malperfusion) were studied by fitting hierarchically nested log linear models for multiway contingency tables. A p-value of 0.05 was considered significant.

RESULTS

Demographic and clinical characteristics of the study population

The placentas from 946 women were examined. The demographic and clinical characteristics of the study population are shown in Table 2. The majority of subjects were multiparous (66.2%; 626/946), of self-identified African-American origin (81.1%; 766/945), and delivered vaginally (73.9%; 699/946) (Table 2).

Of the 247 women who underwent a cesarean delivery, 63.6% (157/247) had the procedure performed before the onset of labor. Women who underwent cesarean delivery without labor had a statistically significant higher rate of advanced maternal age, multiparity, tobacco use during pregnancy, obesity (body mass index [BMI] > 30 kg/m²), lower median gestational age at delivery, and higher median birthweight than those in the other study groups (Table 2).

The indications for cesarean delivery were as follows: previous cesarean section, 64.8% (160/247); non-reassuring fetal heart tracing, 15.4% (38/247); malpresentation, 8.9% (22/247); failure to progress, 8.5% (21/247); failed induction, 0.8% (2/247); suspected macrosomia, 0.8% (2/247); a previous uterine surgical scar, 0.4% (1/247); and maternal request, 0.4% (1/247).

Placental histopathologic findings

The frequency of single and combined histopathological placental lesions is displayed in Supplementary Table A. Placental histologic inflammatory or vascular lesions were present in 77.8% (736/946) of the cases. Twenty-two percent (210/946) of the cases had neither inflammatory nor vascular lesions and 16.6% (157/946) of the cases had no placental histopathologic lesion. Figure 1 shows the frequency of the histological placental lesions.

The frequency of lesions classified as other than inflammatory or vascular was as follows: meconium-laden macrophages in fetal membranes, 12.9% (122/943); laminar necrosis of the decidua capsularis, 5.5% (52/944); basal plate myometrial fibers, 3.0% (28/944); hemosiderin-laden macrophages in the fetal membranes, 0.3% (3/944); massive perivillous fibrin deposition, 0.2% (2/944); intervillous thrombus, 10.3% (97/944); hypervascularity of the chorionic villi, 3.5% (33/940); and villous edema, 0.1% (1/944). These findings did not alter the classification of inflammatory or vascular lesions.

A. Acute placental inflammation—The frequency of all acute placental inflammatory lesions was 42.3% (400/946) (Table 3), but severe lesions (defined as stage 3 and/or grade 2 maternal and/or fetal inflammatory responses) were present in only 1.0% (9/946) of the cases. The distribution of acute placental inflammatory lesions according to the mode of delivery is shown in Figure 2.

The rate of acute placental inflammation was significantly higher in women who underwent labor than for those without labor: 46.9% (370/789) versus 19.1% (30/157), $p < 0.0001$. Among women with labor, African-American ethnicity, nulliparity, and duration of membrane rupture were independently associated with an increased frequency of acute placental histologic lesions [African American versus Other: prevalence ratio = 1.3, $p = 0.02$; nulliparity versus multiparity: prevalence ratio = 1.3, $p < 0.01$; and a two-hour duration of labor: prevalence ratio = 1.02, $p = 0.01$].

Maternal inflammatory response: The frequency of acute maternal inflammatory lesions ($n=342$) according to grading and staging were as follows: 1) stage 1 (early acute subchorionitis/chorionitis) in 64.3% (220/342) of the cases; 2) stage 2 (acute chorioamnionitis) in 33.6% (115/342); 3) the frequency of stage 3 (necrotizing chorioamnionitis) and/or grade 2 maternal acute placental inflammatory lesions was 2.0% (7/342); of note, these lesions were only observed in patients who delivered vaginally (Table 3). The frequency of lesions consistent with a maternal inflammatory response was associated with the presence of labor ($p < 0.0001$), African-American ethnicity ($p < 0.01$), gestational age ($p < 0.0001$), and nulliparity ($p < 0.001$) (Supplementary Table B).

Fetal inflammatory response: The frequency of acute fetal inflammatory lesions ($n=220$) according to grading and staging were as follows: 1) stage 1 (chorionic vasculitis/umbilical phlebitis) in 80.5% (177/220) of the cases; 2) stage 2 (umbilical arteritis) in 19.1% (42/220); 3) the frequency of stage 3 (necrotizing funisitis) and/or grade 2 fetal acute placental inflammatory lesions was 0.9% (2/220) (Table 3). A fetal inflammatory response was associated with labor ($p < 0.001$), and gestational age ($p < 0.0001$), adjusting for ethnicity and nulliparity (Supplementary Table B).

B. Chronic placental inflammation—The overall frequency of chronic inflammatory lesions was 29.9% (283/946), however, severe lesions (defined as high-grade lesions of chronic villitis of unknown etiology or grade 2 chronic chorioamnionitis) were present in only 2.5% (23/923) of chronic inflammatory lesions. Table 4 shows the frequency of the specific lesions. The most common lesion was chronic deciduitis in 19.2% (182/946) of the cases, followed by chronic villitis of unknown etiology present in 18.6% (176/946), and chronic chorioamnionitis present in 12.7% (120/946) of the cases. Nulliparity was negatively associated with chronic inflammatory lesions ($p < 0.001$), adjusting for the presence of labor, ethnicity, and gestational age (Supplementary Table B).

C. Maternal vascular malperfusion—The overall rate of lesions consistent with maternal vascular malperfusion was 35.6% (337/946). The frequency of specific lesion groups were as follows: 1) villous changes, 18.6% (176/946); 2) vascular lesions, 20.5%

(194/946); and 3) a high burden of lesions (defined as two or more lesions of maternal vascular malperfusion) were present in only 7.4% (70/946) of the cases (Table 5).

D. Fetal vascular malperfusion—The prevalence of lesions consistent with fetal vascular malperfusion was 19.7% (186/946). The frequency of specific lesion groups were as follows: 1) villous changes, 11.3% (107/946); 2) vascular lesions, 9.0% (85/946); and 3) a high burden of lesions (defined as two or more lesions of fetal vascular malperfusion) were present in only 0.7% (7/946) of the cases (Table 5).

Neither maternal nor fetal vascular malperfusion lesions were significantly associated with the presence of labor, gestational age at delivery, African-American ethnicity, and nulliparity (Supplementary Table B).

Associations among placental histologic lesions

While almost 40 percent of placentas in normal pregnancies showed multiple histological lesions, we investigated whether they co-occur in the same placenta purely by chance. A four-level contingency table was constructed by cross-classifying acute and chronic inflammatory lesions, and fetal and maternal vascular malperfusion lesions, and examined with log-linear models to determine whether the associations between different types of lesions could have occurred by chance. Only the association between chronic inflammatory and fetal malperfusion lesions of the villous type was significant ($p < 0.01$), and only chronic villitis of unknown etiology was associated with fetal malperfusion lesions of the villous type ($p < 0.01$).

DISCUSSION

Principal findings of the study:

1) 78% of placentas had lesions consistent with acute or chronic inflammation or maternal or fetal vascular malperfusion; 2) acute placental inflammatory lesions were the most prevalent, observed in 42.3% of the placentas – however, only 1.0% had severe acute inflammatory lesions; 3) acute inflammatory lesions were more common in the placentas of women with labor than in those without labor; 4) chronic inflammatory lesions of the placenta were present in 29.9%; and 5) multiple histologic lesions consistent with acute or chronic inflammation or maternal or fetal vascular malperfusion were present in 38.6% of the cases.

Why was this study performed?

Original research, review articles (60–79), monographs (80–82), and textbooks of placental pathology (83–96) have described the morphologic features of this organ. *Placenta*, a Journal dedicated specifically to the biology of the organ, reports regularly on histologic findings of human placentas (97).

Recent studies suggest that placental examination provides information that may be helpful in understanding the mechanisms of disease responsible for adverse pregnancy outcome (98–104) as well as in assessing the risk for adult disease (105–124). The importance of

placentology is increasingly recognized as evidenced, in part, by the launching of the Human Placenta Project by the *Eunice Kennedy Shriver* NICHD, National Institutes of Health, U. S. Department of Health and Human Services (125).

However, to date, there is very little information available about the frequency and type of histologic lesions in the placentas from uncomplicated pregnancies with normal outcome (22–24). Therefore, we sought to address this question to assist in the interpretation of the results of placental pathology reports.

Maternal and fetal acute inflammatory lesions of the placenta are more frequent in placentas delivered after labor

The reported prevalence of acute placental inflammation in uncomplicated term pregnancies ranges from 3.8% to 54.0% (18, 23, 24, 126–131). This broad range may be due to 1) the lack of uniformity of placental pathologic diagnostic and reporting criteria, e.g., different definitions of inflammation (23, 132) and inclusion of decidual inflammation (22); 2) variations in the methods of placental sampling (23, 127, 129, 132); 3) socioeconomic status and ethnicity (133); 4) the presence of spontaneous labor (130, 134–136); and 5) the duration of labor (130, 136, 137).

In our study, the frequency of acute placental inflammatory lesions increased with the presence of labor. Among women in labor, African-American ethnicity, nulliparity, and duration of membrane rupture were independently associated with the increased frequency of these lesions. Our findings are consistent with previous reports that the frequency of acute histologic chorioamnionitis in women with spontaneous labor was significantly higher than in those without labor (24, 130, 134, 136, 138). Specifically, Lee et al (136), in a seminal study, reported that the risk of intra-amniotic infection or intra-amniotic inflammation (defined by analysis of amniotic fluid) increased with cervical dilatation in a group of patients who underwent cesarean delivery during labor at term (136). In addition, the current study found that the frequency of the early stages (stages 1 and 2) of the maternal inflammatory response was associated with the presence of labor (Figure 2).

Acute placental inflammation at term most often represents the inflammatory process related to parturition rather than acute infection

The presence of early stage acute inflammatory lesions in the placenta may represent the inflammatory process associated with labor *per se*, and not necessarily infection (135, 139–141). Whether some forms of acute chorioamnionitis reflect mild forms of microbial invasion of the amniotic cavity during spontaneous labor or sterile intra-amniotic inflammation generated by the presence of danger signals is not known. While microbial invasion of the amniotic cavity has been reported in 13% to 19% of women in spontaneous labor at term with intact membranes (140, 142, 143), intra-amniotic inflammation (defined as an elevated interleukin (IL)-6, IL-8, or other inflammatory mediators) is also more common in patients with spontaneous labor at term than in those without labor (129, 144–156). Spontaneous labor at term is considered prototypical of a sterile inflammatory phenomenon accompanied by an activation of the inflammasome (157–162). Therefore, the

presence of acute inflammatory lesions of the placenta should not be construed as indicators of the presence of intra-amniotic infection.

Acute histologic chorioamnionitis represents a maternal host response, as neutrophils infiltrating the chorion and amnion are of maternal origin (163) that, in some cases, can reach the amniotic cavity (139, 164).

By contrast, funisitis and chorionic vasculitis represent a fetal inflammatory response, and these lesions are considered the histologic counterpart of the fetal inflammatory response syndrome (139, 165–169). Although the Society of Pediatric Pathologists and the Amsterdam group categorized these lesions under the label “amniotic fluid infection,” it is now clear that such lesions can also be present in the context of sterile intra-amniotic inflammation (139, 170–176). Therefore, we recommend that, when referring to acute placental inflammatory lesions, the term “amniotic fluid infection” be abandoned (139). Our interpretation is consistent with the results of Roberts et al. (177) who reported, based on placental cultures and molecular microbiologic studies for the identification of microbial footprints, that among nulliparous women who delivered at term following an uneventful pregnancy, the overall rate of histological chorioamnionitis at term was 34% (67/195). However, in 96% (64/67) of the cases, microorganisms could not be identified by either cultivation or molecular techniques (177). Indeed, using cultures and molecular techniques for the identification of viruses and bacteria, our group has shown that a subset of women with clinical or mild histologic chorioamnionitis at term do not have an intra-amniotic infection (169, 174). Collectively, these findings suggest that mild histologic acute placental inflammation represents the inflammatory process related to parturition or the aging of a placenta (178–180) rather than to acute infection.

Chronic placental inflammatory lesions in normal term gestation

Chronic inflammatory lesions are of maternal origin and are either caused by viruses (181–185), bacteria (185, 186), and/or parasites (183) or are a reaction to the foreign antigens of the fetus (19). Such lesions can also be of fetal origin, e.g., eosinophilic T-cell vasculitis (20, 187).

The rate of chronic placental inflammation in our study population was 29.9%, and the most frequent lesion was chronic deciduitis (19.2%), followed by chronic villitis of unknown etiology (18.6%) and chronic chorioamnionitis (12.7%).

There are few reports on the frequency of chronic placental inflammatory lesions in normal term pregnancy, and of these, most have been case-control studies that reported solely on individual lesions and in which normal pregnancies served as the control (18, 24, 131). The frequency of chronic villitis of unknown etiology ranged between 5% and 33.8% (5, 12, 14, 19, 129, 188–192) and that of chronic chorioamnionitis between 10% and 19% (18, 19), which agree with our findings, but the current study is the first report on the entire spectrum of chronic inflammatory lesions in normal pregnancy.

We doubt that nearly 30% of women with a normal pregnancy would have an infectious agent as an explanation of chronic placental inflammatory lesions, and therefore, favor an

immunological mechanism of disease to support these findings. It is very likely that an immunological stand-off between the mother and fetus occurs at the maternal-fetal interface throughout normal pregnancy, but if maternal lymphocyte infiltration of the fetal tissues is not associated with substantial damage of the chorioamniotic membranes, villous tree, or decidua basalis, a pregnancy without clinical complications is possible. Then, the presence of maternal lymphocytes infiltrating the chorioamniotic membranes would represent evidence of maternal-fetal cellular interaction without necessarily indicating a pathologic process.

Maternal and fetal placental vascular lesions in normal pregnancy at term

The frequencies of placental lesions consistent with maternal vascular malperfusion and fetal vascular malperfusion in the current study were 35.6% and 19.7%, respectively. Bar et al. (24) reported that the frequency of placental lesions consistent with maternal and fetal vascular malperfusion in an Israeli population was 24.5% and 7.9%, respectively. In contrast, Lee et al. reported that placental lesions with maternal and fetal vascular malperfusion were 1.3% and 2.7 %, respectively, in an Asian population (18). The high frequency of maternal and/or fetal vascular malperfusion lesions found in the current study may be attributed to a larger number of placentas studied, or the use of systematic random sampling and targeted sampling, leading to a higher number of sections evaluated and a meticulous adherence to the placental sampling protocol.

It has been proposed that some lesions consistent with fetal vascular malperfusion may be related to vascular stasis, and tissue damage that may occur in the placenta at the end of gestation (193). Alternatively, these lesions may reflect placental senescence as gestational age advances toward term (178–180).

Co-occurrence of placental lesions

We did not find significant correlation among the placental histological lesions with the exception of the co-occurrence patterns between chronic inflammatory lesions (i.e., villitis of unknown etiology) and fetal vascular malperfusion lesions of the villous type. This finding is consistent with previous reports indicating that avascular villi may be part of the spectrum of villitis of unknown etiology (5, 7, 181). The association of villitis of unknown etiology with villous lesions of fetal vascular malperfusion is most likely a reflection of villous injury caused by inflammation that can lead to luminal obliteration and resulting in downstream regions of avascular villi (5, 7). In general, if villitis of unknown etiology is present in the proximal villi, the distal changes of avascular villi should not be considered as fetal vascular malperfusion (5). Current terminology for occasional avascular villi seen in a placenta with villitis should be reported as “chronic villitis with associated avascular villi” (21). Therefore, we do not interpret this association as a true co-occurrence.

The placenta has a large functional reserve

Severe compromise of placental anatomy and function must occur before clinical disease becomes evident. There is a substantial body of clinical and experimental evidence in support of this view (89, 194–199).

Embolization of the umbilical artery in pregnant sheep can result in a decrease in blood flow, an increase in umbilical artery resistance and the systolic/diastolic ratio, and a progression of the diastolic waveform from normal to absent and, subsequently, the reversal of end-diastolic flow (200, 201). Substantial embolization of the placental cotyledons must occur before Doppler abnormalities are observed. Giles et al. (202) reported that placental microvascular anatomy was dramatically changed in patients with abnormal Doppler velocimetry findings. Specifically, the modal small-artery count in tertiary stem villi was significantly lower in patients with abnormal umbilical artery Doppler velocimetry than in those with normal Doppler indices (202). Such findings have been confirmed by the observation that absent end-diastolic flow in the umbilical artery of growth-restricted fetuses is demonstrated after there is an approximate 50% reduction of the vessel area in the placental terminal villi (203). Moreover, mathematical modeling of the placental circulation has shown that obliteration of 80% of the vascular tree is required before dramatic changes in the pulsatility index occur (204). Similarly, a substantial proportion of the placenta affected by perivillous fibrinoid deposition is required before an adverse pregnancy event will occur, such as severe fetal growth restriction or fetal death (205).

Strengths and Limitations

The strengths of this study include the following: 1) numerous term placentas from women without any obstetrical complications; 2) extensive examination of the placental sections; 3) comprehensive description of histologic placental pathology and its correlation to demographic and clinical parameters; and 4) the use of standardized protocols for histopathologic examination of the placenta. The limitations of the study included 1) the non-consecutive enrollment of patients over an extended time period and 2) the lack of follow-up beyond the neonatal period.

Conclusion

We report the frequency and type of histologic lesions from a large series of placentas of women with a normal pregnancy outcome. Most placentas had some type of lesion (either inflammatory or vascular), but most were mild. The results of this study can be used as a reference when interpreting the results of placental pathology in patients with perinatal complications. Placental histopathological lesions and the extent to which they can cause obstetrical complications needs to be rigorously evaluated and quantified.

Current pathologic examination of the placenta relies on limited sampling of a large organ and taxonomy based on morphologic criteria that are largely qualitative. The application of advances in molecular pathology that address sampling (206–213), the identification of cellular markers of pathological processes, and the computational methods utilized to summarize and analyze data can be utilized in placental pathology to improve the characterization of this important organ.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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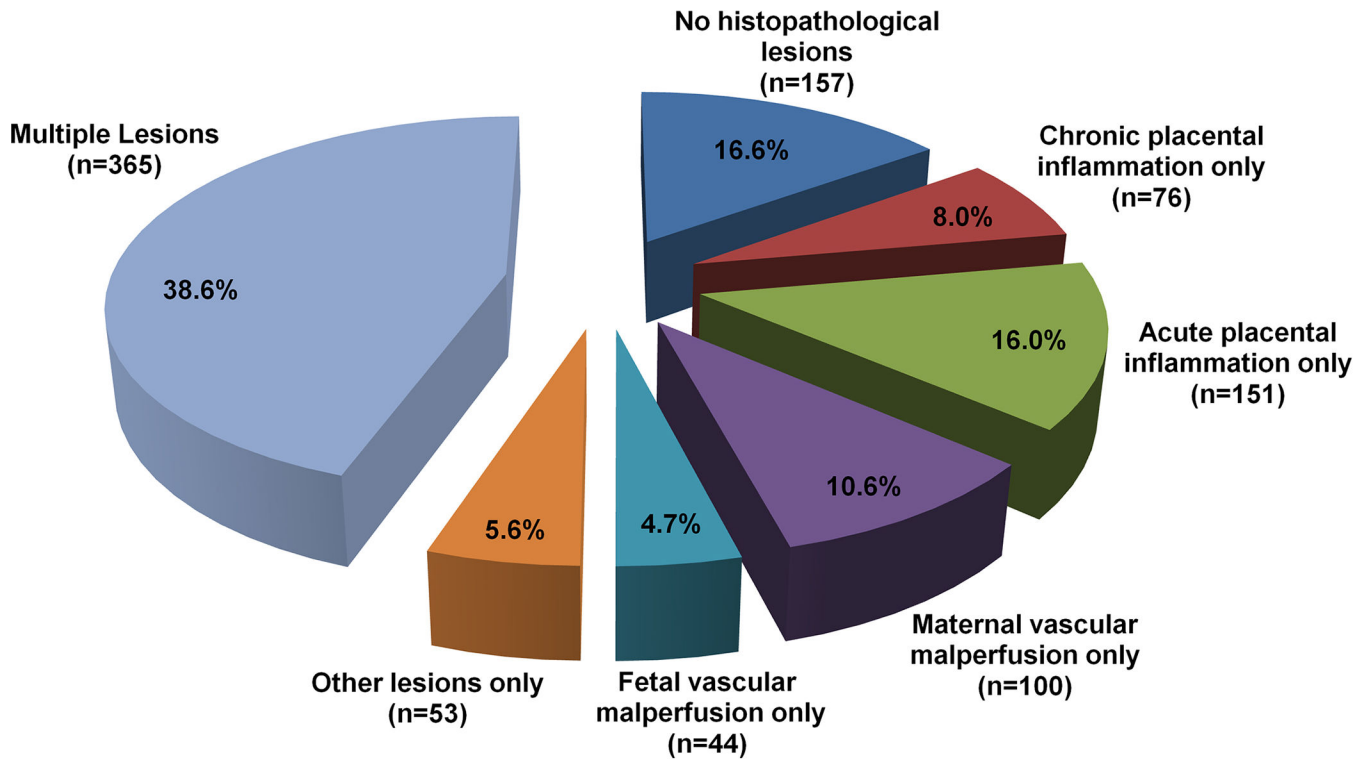


Figure 1 –. Distribution of placental lesions in term pregnancies with normal outcome

The distribution of histopathologic placental lesions in women with normal pregnancies indicates that the majority of cases had multiple lesions (consistent with more than one type of histopathologic lesion). Among women with isolated placental lesions the most frequent were acute placental inflammation, followed by maternal vascular malperfusion, chronic placental inflammation and fetal vascular malperfusion.

Other lesions include: Laminar Necrosis Decidua Capsularis; Meconium laden macrophages in fetal membranes; Hemosiderin laden macrophages in fetal membranes; Nucleated Red Blood cells; Massive Perivillous Fibrin Deposition; Basal plate myometrial fibers;and Hypervascularity of chorionic villi

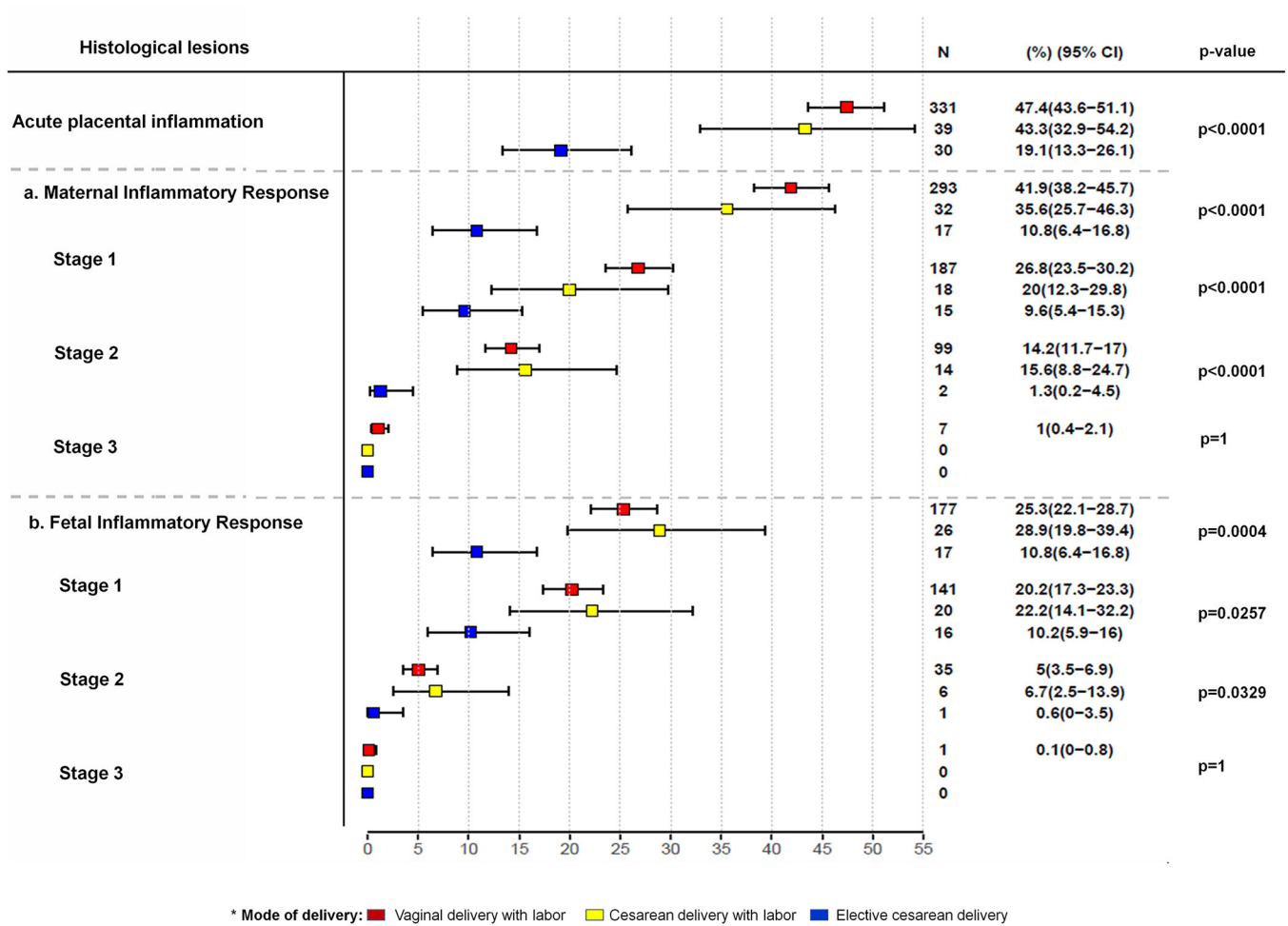


Figure 2 - The distribution of acute placental inflammatory lesions according to the mode of delivery

2a - The distribution of lesions consistent with a maternal inflammatory response according to mode of delivery

2b - The distribution of lesions consistent with a fetal inflammatory response, according to mode of delivery

Red box: vaginal delivery with labor

Yellow box: cesarean delivery with labor

Blue box: elective cesarean delivery

Table 1A.

Histopathology of placental inflammatory lesions.

Histologic Lesions
I. Acute inflammatory lesions
A. Maternal inflammatory response
Staging (location of neutrophil infiltration)
Stage 1: early acute subchorionitis or chorionitis
Stage 2: acute chorioamnionitis
Stage 3: necrotizing chorioamnionitis
Grading (intensity)
Grade 1 (not-severe)
Grade 2 (severe): subchorionic microabscess
B. Fetal inflammatory response
Staging (location of neutrophil infiltration)
Stage 1: chorionic vasculitis or umbilical phlebitis
Stage 2: umbilical arteritis
Stage 3: necrotizing funisitis
Grading (intensity)
Grade 1 (not-severe)
Grade 2 (severe): intense chorionic and/or umbilical vasculitis
II. Chronic inflammatory lesions
A. Maternal inflammatory response
Chronic deciduitis
Lymphocytic (without plasma cells)
Lymphoplasmacytic
Chronic villitis of unknown etiology
Low-grade lesions: < 10 contiguous villi in any one focus
High-grade lesions: 10 contiguous villi in at least one focus
Chronic chorioamnionitis
Staging (location of lymphocyte infiltration)
Stage 1: lymphocytic infiltration limited to the chorionic trophoblast layer
Stage 2: lymphocytic infiltration into the chorioamniotic connective tissue
Grading (Intensity)
Grade 1: <2 foci of inflammation or patchy inflammation
Grade 2: diffuse inflammation
Chronic histiocytic intervillitis
Villitis of infectious origin
B. Fetal inflammatory response
Eosinophilic T-cell vasculitis

Table 1B.

Placental histopathology of maternal and fetal vascular malperfusion.

Histologic Lesions
I. Findings consistent with maternal vascular malperfusion
A. Villous changes
Villous infarct(s)
Increased syncytial knots
Villous agglutination
Increased intervillous fibrin deposition
Distal villous hypoplasia
B. Vascular lesions
Persistent muscularization of basal plate arteries
Mural hypertrophy of decidual arterioles
Acute atherosclerosis of basal plate arteries and/or decidual arterioles
Spiral artery fibrinoid necrosis
Decidual vascular thrombosis
Persistence endovascular trophoblast
Retroplacental hemorrhage
II. Findings consistent with fetal vascular malperfusion
A. Villous changes
Early
Villous stromal-vascular karyorrhexis
Late
Hyalinized avascular villi, small foci
Hyalinized avascular villi, variable sized foci
Severe
Fetal thrombotic vasculopathy
B. Vascular lesions
Thrombi in large fetal vessels
Intimal fibrin deposition, large fetal vessels
Fibromuscular sclerosis, intermediate-sized fetal vessels

Table 2.

Demographic and clinical characteristics of 946 singleton normal pregnant women at term.

Characteristics	Vaginal Delivery with Labor (n=699)	Cesarean Delivery (n=247)		p-value ^a
		Cesarean Delivery with Labor (n=90)	Elective Cesarean Delivery (n=157)	
Maternal age (years)	23 (20–28)	24 (20–28.75)	28 (23–31)	<0.0001
Nulliparous	37.2% (260/699)	54.4% (49/90)	7% (11/157)	<0.0001
African American ethnicity ^b	82.4% (575/698)	80% (72/90)	75.8% (119/157)	0.1588
Tobacco use during pregnancy ^c	10.6% (74/696)	10% (9/90)	17.9% (28/156)	0.0399
Alcohol use during pregnancy ^d	0.7% (5/695)	0% (0/90)	1.3% (2/156)	0.6640
History of preterm births	6.7% (47/699)	7.8% (7/90)	8.9% (14/157)	0.5730
Obesity ^{e,f}	24.7% (164/663)	33.7% (28/83)	45.8% (65/142)	<0.0001
Gestational age at delivery (weeks)	39.6 (38.7–40.4)	40 (38.9–40.9)	39.1 (39–39.4)	<0.0001
Birth weight (grams)	3300 (3100–3565)	3330 (3145–3630)	3430 (3160–3620)	<0.01
Male sex neonate ^c	50.3% (350/696)	59.6% (53/89)	53.5% (84/157)	0.2309

Data are presented as median (interquartile range) or % (n/N).

^aThe p-values come from the Kruskal-Wallis test in the case of continuous variables and exact test for 2 by 3 contingency tables in the case of categorical variables.

Due to missing demographic data, total number of each case was

^bn=945,^cn=942,^dn=941,^en=888.^fObesity was defined as pre-pregnancy body mass index (BMI) >30 kg/m².

Table 3.

Frequency of acute inflammatory placental lesions of normal singleton pregnant women at term.

Histologic Lesions ^a	% (n/N)
Acute inflammatory lesions	42.3% (400/946)
A. Maternal inflammatory response	36.2% (342/946)
Stage 1: early acute subchorionitis or chorionitis	23.3% (220/946)
Grade 1	23.3% (220/946)
Grade 2	0% (0/946)
Stage 2: acute chorioamnionitis	12.2% (115/946)
Grade 1	12.2% (115/946)
Grade 2	0% (0/946)
Stage 3: necrotizing chorioamnionitis	0.7% (7/946)
Grade 1	0.6% (6/946)
Grade 2	0.1% (1/946)
B. Fetal inflammatory response	23.3% (220/946)
Stage 1: chorionic vasculitis or umbilical phlebitis	18.7% (177/946)
Grade 1	18.6% (176/946)
Grade 2	0.1% (1/946)
Stage 2: umbilical arteritis	4.4% (42/946)
Grade 1	4.4% (42/946)
Grade 2	0% (0/946)
Stage 3: necrotizing funisitis	0.1% (1/946)
Grade 1	0.1% (1/946)
Grade 2	0% (0/946)

^aPlacentas may have more than one type of acute placental inflammatory lesions.

Table 4.

Frequency of chronic inflammatory placental lesions of normal singleton pregnant women at term.

Histologic Lesions^a	% (n/N)
Chronic inflammatory lesions	29.9% (283/946)
A. Maternal inflammatory response	29.8% (282/946)
Chronic deciduitis	19.2% (182/946)
Lymphocytic (without plasma cells)	10.3% (97/946)
Lymphoplasmacytic	9.0% (85/946)
Chronic villitis of unknown etiology	18.6% (176/946)
Low-grade lesions	13.2% (122/927)
High-grade lesions	1.2% (11/927)
Chronic chorioamnionitis	12.7% (120/946)
Stage 1	3.8% (36/942)
Grade 1	3.6% (34/942)
Grade 2	0.2% (2/942)
Stage 2	7.6% (72/942)
Grade 1	6.6% (62/942)
Grade 2	1.1% (10/942)
Chronic histiocytic intervillitis	0.4% (4/944)
Villitis of infectious origin	0% (0/944)
B. Fetal inflammatory response	
Eosinophilic T-cell vasculitis	0.4% (4/944)

^aPlacentas may have more than one type of chronic placental inflammatory lesions.

Table 5.

Frequency of placental maternal and fetal vascular malperfusion lesions of normal singleton pregnant women at term.

Histologic Lesions ^a	% (n/N)
Maternal vascular malperfusion	35.6% (337/946)
A. Villous Changes	18.6% (176/946)
Villous infarct(s)	5.6% (53/945)
Increased syncytial knots	8.5% (80/946)
Villous agglutination	2.0% (19/946)
Increased intervillous fibrin deposition	6.3% (60/946)
Distal villous hypoplasia	0.1% (1/946)
B. Vascular Lesions	20.5% (194/946)
Persistent muscularization of basal plate arteries	16.3% (154/946)
Mural hypertrophy of decidual arterioles	1.8% (17/946)
Acute atherosclerosis of basal plate arteries and/or decidual arterioles	0.8% (8/946)
Spiral artery fibrinoid necrosis	0.3% (3/944)
Decidual vascular thrombosis	1.7% (16/944)
Persistence of endovascular trophoblast	0.3% (3/944)
Retroplacental hemorrhage	0.8% (8/944)
2 lesions of maternal vascular malperfusion	7.4% (70/946)
3 lesions of maternal vascular malperfusion	1.2% (11/946)
Fetal vascular malperfusion	19.7% (186/946)
A. Villous Changes	11.3% (107/946)
Early	
Villous stromal-vascular karyorrhexis	2.5% (24/946)
Late	
Hyalinized avascular villi, small foci	6.6% (62/946)
Hyalinized avascular villi, variable sized foci	2.0% (19/946)
Severe	
Fetal thrombotic vasculopathy	0.2% (2/946)
B. Vascular Lesions	9% (85/946)
Thrombi in large fetal vessels	2.6% (25/946)
Intimal fibrin deposition, large fetal vessels	6.4% (61/946)
Fibromuscular sclerosis, intermediate-sized fetal vessels	0% (0/946)
2 lesions of fetal vascular malperfusion	0.7% (7/946)

^aPlacentas may have more than one type of maternal and fetal vascular malperfusion lesions.