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PLACENTA
Placenta 29 (2008) 639–645

Pathophysiology of Placenta Creta: The Role of Decidua and Extravillous Trophoblast

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Accepted 19 April 2008

Abstract

Placenta creta is associated with massive postpartum hemorrhage and commonly leads to emergency hysterectomy. While the exact pathogenesis of placenta creta is unknown, proposed hypotheses include a primary deficiency of decidua, abnormal maternal vascular remodeling, excessive trophoblastic invasion, or a combination thereof. To assess these changes in placenta creta, we retrospectively reviewed 49 cases of gravid hysterectomy, 38 with and 11 without the diagnosis of creta, gathered clinical data, and evaluated histopathology of extravillous trophoblast. Specifically, we evaluated maternal vessels for remodeling by endovascular trophoblast, as well as the morphology and depth of invasion of interstitial trophoblast at the implantation site. Compared to controls, cases with creta had decreased proportion of remodeled vessels, with many vessels displaying partial physiologic change. Cases with creta also demonstrated vascular remodeling deeper in the myometrium; however, vascular remodeling of large outer myometrial vessels was only demonstrated in increta and percreta cases, and was absent in both non-creta and accreta. As previously reported, interstitial trophoblast invaded the uterine wall to a significantly greater depth in placenta creta; however, there was no significant difference between creta subtypes. Finally, Ki-67 staining was rarely observed in extravillous trophoblast, except in the trophoblast columns of first trimester creta cases. We, therefore, conclude that the pathogenesis of placenta creta is multi-dimensional, involving increased, but incomplete trophoblast invasion in a background of absent decidua. We further propose that placenta increta and percreta are not due to a further invasion of extravillous trophoblast in the uterine wall, rather they likely arise secondary to dehiscence of a scar, leading to the presence of chorionic villi deep within the uterine wall, and thus give extravillous trophoblast greater access to the deep myometrium.

Keywords: Placenta creta; Gravid hysterectomy; Remodeled vessels; Extravillous trophoblast

1. Introduction

Placenta creta is a severe pregnancy complication, associated with massive immediate postpartum hemorrhage, which often necessitates hysterectomy. It can be further subdivided into accreta, increta, and percreta based on the depth of placental villous tissue in the uterine wall [1]. Histologically, creta is characterized by the lack of intervening decidua and direct contact of villous tissue with the underlying myometrium [2]. In normal pregnancy, decidualized endometrial stroma is the site of placental separation from the uterine wall by the shearing action between the contracting myometrium and the non-contracting placenta. In placenta creta, the absence of decidua prevents separation, thus leading to a clinically adherent placenta and subsequent bleeding.

In addition to decidual deficiency, several studies have suggested excessive trophoblast invasion may contribute to the pathogenesis of placenta creta [3–5]. Normal implantation involves invasion of the uterine wall by two subgroups of extravillous trophoblast: the interstitial trophoblast invades through the endometrium and the superficial one-third of the myometrium, while the endovascular trophoblast invades and remodels the maternal spiral arterioles [2]. The latter process

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0143-4004/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.placenta.2008.04.008

involves loss of the smooth muscle in the arterial wall, resulting in vessels with dilated lumina with a hyalinized wall containing endovascular trophoblast [2]. Previous studies have suggested various abnormalities in both trophoblastic subtypes, including both defective and excessively deep vascular remodeling [1,2,6,7]. It is believed that in placenta creta, there is defective interaction between maternal tissues and migratory trophoblast in the early stages of placentation, coupled with the development of an abnormal uteroplacental circulation, resulting in deep trophoblast penetration into the uterus and thus adherence of the placenta [2,6].

Some authors have suggested absent decidua to be the primary factor in placenta creta, and the etiology of excessive trophoblast invasion [8,9]. Comparison has been made to tubal gestation, where absence of decidua is associated with deep invasion of trophoblast into adjacent vessels [2]. However, work of Ramsey and others in various primate species has shown a more complex, non-linear relationship between decidualization and trophoblast invasion [10,11]. In addition, some authors have suggested that decidua is present at the start of gestation and atrophies as the pregnancy proceeds, although no supportive data was presented [6,8]. While the lack of decidua remains etiologically unexplained, the strong association of placenta creta with a history of prior c-sections and endometrial curettage suggests a role for uterine scarring [1,2,6,8,9,12].

Given the controversies and conflicting data regarding the role of decidual deficiency and trophoblast invasion in pathophysiology of creta, this study was undertaken to systematically review the histology of placenta creta and evaluate the extent of decidualization and trophoblast invasion in this disease, compared to a control group. Based on a comprehensive histologic analysis of gravid hysterectomy specimens from all three trimesters, we conclude that placenta creta is primarily a maternal disease rooted in decidual deficiency, at least partially due to uterine scarring, and with secondary defects in trophoblast invasion and function.

2. Material and methods

2.1. Tissue samples

Following IRB approval, cases of gravid hysterectomy were retrieved from surgical pathology files of the Women's and Perinatal Pathology Division, at Brigham and Women's Hospital, from 2002–2007. Only patients who had available clinical data and paraffin-embedded tissue specimens were included in this study. The cases consisted of 16 cases of accreta, 17 increta, and 5 percreta (total of 38 cases). Accreta was diagnosed when chorionic villi were implanted on the myometrium without intervening decidua; increta, when the myometrium was invaded by villous tissue; and percreta, when the villi penetrated the uterine serosa [1]. Control (non-creta) cases consisted of gravid hysterectomies for the following diagnoses: uterine atony (5), uterine rupture (2), myomatous uterus (1), torn vessel at c-section (1), cervical pregnancy (1), or suspected gestational trophoblastic disease (1). Uterine scarring was defined as the presence, on H&E-stained sections, of hyalinized, acellular area in the myometrium, not associated with large vessels, consistent with replacement of myometrial fibers with extracellular matrix deposits.

From a retrospective review of medical records, the patient's demographic and surgical data were collected. A prior history of caesarean (c-) section, other uterine surgery, terminations of pregnancy, or miscarriages with dilatation and curettage was specifically sought.

All specimens were processed at the Women's and Perinatal Pathology Division of Brigham and Women's Hospital, according to a standard protocol, which emphasizes examination of the placental implantation site. On average, per case, six H&E-stained sections from the implantation site were reviewed to confirm the histological diagnosis and assess features of extravillous (implantation site or IS) trophoblast. Both subgroups of IS trophoblast were evaluated: (1) interstitial trophoblast (IT), which normally invade the decidua and myometrium, were evaluated for maximal depth of invasion and percent multinucleation, and (2) endovascular trophoblast (VT), which normally invade and remodel the spiral arterioles, were evaluated for both maximal depth of invasion and degree of completion of vascular remodeling. For the purposes of this study, the myometrium was divided into superficial and deep halves, and the depth of invasion of both IT and VT was measured from the villi-myometrium interface. Percent multinucleation was determined by counting 100 contiguous IT per case and scoring those with >2 nuclei as multinucleated. For evaluation of vascular remodeling, vessels with less than circumferential replacement of arteriolar smooth muscle wall by VT in hyalinized stroma were considered to be incompletely remodeled. Representative paraffin blocks of implantation site from each case were selected for cytokeratin immunostaining. In addition, representative cases from each subgroup (creta and non-creta), with prominent interstitial trophoblasts in the implantation site, were also stained for Ki-67.

2.2. Immunohistochemistry

Cytokeratin immunohistochemistry was used to complement H&E analysis, by highlighting extravillous trophoblasts. Ki-67 (mib1) was used to evaluate the proliferative index of IT. Briefly, sections of 4–5 micron thick were deparaffinized and rehydrated, followed by antigen retrieval by protease for 10 min. After being treated with 3% hydrogen peroxide to block endogenous peroxidase activity, the slides were incubated with mouse monoclonal anti-human cytokeratin antibody (clone AE1/AE3, Dako, CA, USA; 1:200 dilution) or Ki-67 (Dako, CA, USA; 1:200 dilution). Visualization of immunoreactivity was by chain polymer-conjugated techniques (Envision+ System-HRP, Mouse Envision, Dako, CA, USA), and diaminobenzidine (DAB) as the chromogen. Counterstaining was performed with Meyer's hematoxylin. For negative control, the primary antibody was substituted with nonimmune sera. We used skin and colonic tissue for positive control.

2.3. Statistical analysis

Statistical analyses were performed with the SPSS for Windows software (version 13; SPSS Inc., Chicago, IL, USA). The statistical significance of differences between the study groups was assessed with the Chi-square or Fisher's exact tests where appropriate. Results were considered significant for $P \leq 0.05$.

3. Results

3.1. Clinicopathologic features

There were 53 cases of gravid hysterectomy during the study period. Forty cases (75.4%) were histopathologically diagnosed as placenta creta. Four cases (two placenta creta and two non-creta) were excluded because of lack of information or unavailable paraffin blocks. The clinical data of the remaining 49 cases of gravid hysterectomy included in our study are presented in Table 1. Most cases were in the second and third trimester. Four cases of placenta creta were in the first trimester, consisting of two cases with percreta and two cases with accreta. Both percreta cases were prenatally diagnosed from ultrasound and magnetic resonance imaging (MRI), while accreta cases were undetected until curettage was performed.