A Retrospective Study of Placenta Creta: A Six Year Experience and Histopathological Insights

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Abstract
Objectives: The aims of this study were to describe the histopathological findings of placenta creta samples obtained over a six year period and to report the obstetric conditions related to the histopathologic findings.

Materials and Methods: Pathology records from gravid hysterectomies performed due to placenta creta from 2006 to 2012 were reviewed. We evaluated the decidual layer, percent of multinucleation, and depth of invasion of Interstitial Trophoblasts (ITs) at the implantation site. Spiral arteries were also assessed to determine the degree of remodeling.

Results: During the study period, 20 cases of placenta creta occurred: 3 (15%) were placenta accreta, 7 (35%) were placenta increta, and 10 (50%) were placenta percreta. In 25% of cases, vessels had no remodeling at all, whereas 45% had partially remodeled vessels, and 30% completely remodeled vessels. The proportion of incomplete or complete physiological changes in the vascular wall did not significantly differ between the different subtypes of creta (P=0.68). Depth of IT invasion varied significantly between the groups (accreta 1.3±0.17 mm, increta 3.56±1.12 mm, and percreta 2.00±1.31 mm, P=0.011). The number of multinucleated trophoblasts in the placenta accreta and increta were higher than those in placenta percreta cases. A history of Cesarean Section (CS) was present in 80% of the patients. All cases with placenta percreta (N=10) had undergone more than two previous CSs. Placenta previa was identified in four cases (20%).

Conclusion: Uterine damage caused by CSs results in poor decidualization, abnormal trophoblastic invasion, incomplete vascular remodeling, fewer multinuclei trophoblasts and deep infiltrative pathology.

Keywords: Placenta Accreta, Placenta Increta, Placenta Percreta, Cesarean Section

Introduction
In the English literature, the term “placenta accreta” or “abnormal placentation” may be used to refer to any degree of placental invasion, but we prefer to use the term defined by Tantbirojn et al. “placenta creta” (1). The classification of placenta creta (accreta, increta, or percreta) depends upon the degree of uterine invasion by villous tissue. Placenta accreta is characterized by direct attachment of the villous tissue to the underlying myometrium without intervening decidua. If placental villus invades the myometrium, it is termed placenta increta. If the placental villus extends to the uterine serosa or into the neighboring viscera, it is termed placenta percreta (2,3). The reported incidence of placenta creta ranges widely – from one in 100 to one in 100,000 pregnancies (4). The probable cause of these discrepancies is the variation in definition – some reports are based on clinical diagnoses, whereas others required histopathological confirmation. In particular, not obtaining pathologic confirmation in conservatively managed cases of placenta accreta with a preserved uterus may have led researchers to report a low incidence of placenta creta in their patients.

Although the risk factors for placenta creta are well established, the exact etiology of the condition remains unknown. Placenta creta has been attributed to a defect in or damage to the decidua basalis. This is usually caused by prior uterine surgery, Cesarean Section (CS) in particular (1,3). The increasing cesarean delivery rate has become a major public health concern worldwide, eg. Turkey has a 48% cesarean delivery rate (24.6% primary CS rate) (5). The scarred endometrium may heal incompletely after CS and leave a defect, facilitating villous penetration in the subsequent pregnancy. In addition to the lack of decidua, excessive invasion by Extravillous Trophoblasts (EVTs) may also contribute to the pathogenesis of placenta creta (6). Tseng and Chou found that factors stimulating growth, angiogenesis, and invasion were highly expressed in trophoblasts of the placenta creta; these may play an important role in its pathogenesis (7).

In normal pregnancies, EVT, which are derived from the basal plate and tips of the anchoring villi, invade through decidua, uteroplacental vessels, and myometrium; thereby anchoring the placenta to the uterine wall (6,8,9). A subtype of EVT, termed “Interstitial Trophoblast” (IT),
invades into the innermost third (inner sheet) of the myometrium, penetrating just a few millimeters (9). As pregnancy advances, most of the ITs convert to syncytial placental bed giant cells by symplasmic fusion (9). Another form of invasive trophoblast is an endovascular Trophoblast (VT) which serve in the transformation of spiral arteries. This essential physiological change in uteroplacental arteries is usually confined to the smaller spiral arteries (1,8,9). The vascular transformation known as “remodeling” is characterized by replacement of the uterine fibromuscular layer by EVTMs and loss of the smooth muscle in the arterial wall, resulting in vessels with dilated lumens with a hyalinized wall containing endovascular trophoblasts. This transformation is regarded as complete when the entire circumference has been thus affected. Incomplete remodeling is present when less than half of the hyalinized stromal tissue of the uterine wall is replaced by EVTMs (1,9). Abnormal vascular remodeling is also associated with placenta creta (1). The underlying mechanism of placenta creta remains unknown. Does the condition result primarily from a deficiency of decidualization, or from excessive invasion by extravillous trophoblasts? Most likely, several different pathophysiological processes play a role in its development. Histopathological diagnosis of placenta creta requires careful macroscopic examination, in particular, evaluation of uterine scars (if present) and appropriate sampling of invasive areas (1,3). The primary aim of this study was to compare the histopathological findings among the subsets of placenta creta (accreta, increta, and percreta) by presenting a case series obtained over a six-year period. The secondary aim was to report which obstetric conditions are related to the particular histopathologic findings.

Materials and Methods
Our University Ethics Committee approved the study (number 2012/04). The surgical pathology files of patients undergoing gravid hysterectomy due to placenta creta between 2006 and 2012 at our tertiary care University Hospital (Kahramanmaraş Şüitçi İmam University in Kahramanmaraş, Turkey) were reviewed and history regarding prior CS, demographic, surgical, and pathological data were recorded. In each case, an average of four to six Hematoxylin and Eosin (H&E) stained sections from the implantation site were reviewed to confirm the histological diagnosis. Placenta accreta was diagnosed when direct attachment of the villous tissue to the underlying myometrium without intervening decidua was seen. If placental villus invaded the myometrium but did not extend to the serosa, placenta increta was diagnosed. If the placental villus extended to the uterine serosa or into the neighboring viscera, placenta percreta was diagnosed. Features of EVTMs, and the presence of ITs and VTs were recorded. Maximal depth of the IT layer was measured in micrometers from the myometrium-chorial villi border to the terminal edge of cytotrophoblastic invasion into the myometrium. The percent of multinucleation was recorded at the implantation site by counting multinuclear trophoblasts that contained more than two nuclei among 100 contiguous cytotrophoblasts. Remodeling was recorded as complete if the smooth muscle layer converted to VT embedded hyalinized stroma in the whole circumference of the vascular wall. Remodeling was recorded as incomplete if this differentiation was not circumferential. Cytokeratin 7 (CK7) immunostaining, used to better delineate the infiltration of ITs and vascular trophoblasts into the myometrium, was performed to complement the microscopic analysis. Representative paraffin blocks of implantation site specimens from each case were selected for CK7 immunostaining. Specimens were sectioned (4 μm thick), mounted onto polylysine-coated glass slides, deparaffinized, and rehydrated. Then they were exposed to antigen retrieval via protease for 10 min and then were microwaved in citrate buffer (pH 6.0). Slides were then immersed in 0.3% hydrogen peroxide for 20 min to block endogenous peroxidase activity, and were then incubated with monoclonal mouse anti-human CK 7 antibody (clone RN7; Novocastra Laboratories, Newcastle, UK). After subsequent staining with chromogen AEC (Thermo Scientific, Fremont, USA), slides were counterstained with Mayer’s hematoxylin, and then they were dehydrated and mounted.

Statistical analysis
All statistical analyses were performed using SPSS 12.0 for Windows® (SPSS, Inc., Chicago, USA). The Chi-squared test and Kruskal–Wallis variance analysis test were used to compare among-group data. To detect statistically significant differences, the Mann-Whitney U test was used after the Bonferroni correction was applied. P values less than 0.05 were considered to be statistically significant. Data are given as mean±standard deviation.

Results
From 2006 to 2012, among 8,502 deliveries at our institution, 20 placenta creta patients were found with intact clinical data and paraffin-embedded tissue specimens (Table 1): 3 (15%) placenta accreta, 7 (35%) placenta increta, and 10 (50%) placenta percreta. A history of a previous CS was present in 80% of cases: one in 10%, two in 45%, and more than two in 25%. All cases with placenta percreta (N=10) had undergone more than two previous CSs. None of the cases were associated with uterine rupture. Placenta previa was identified in four cases (20%). Of these, only one patient was over 35 years of age. Advanced maternal age (≥35 years) was observed in 55% of all creta cases. Birth rates among the various placenta creta subgroups were not significantly different from each other. We encountered no maternal deaths. Five cases (25%) of placenta creta completely lacked remodeled vessels, whereas an additional nine cases (45%)
had partially remodeled vessels, and six (30%) had completely remodeled vessels. The proportion of cases with incomplete or complete physiological changes in the vascular wall did not significantly differ between the subtypes of creta (P=0.682).

ITs were principally uninucleated or binucleated; a few scattered and multinucleated cells were also seen (Figure 1A). The percent of multinucleated trophoblasts was significantly lower in placenta percreta (2.6±1.9%) than in accreta (5.5±1.9%) and increta (5.5±2.5%, P<0.017). Infiltration into the placenta-uterine junction and myometrium by ITs can be seen in Figure 1B. Infiltration of ITs and vascular trophoblasts can be clearly seen in CK7-stained samples (Figures 1C and 1D). In accreta cases, ITs were present, if at all, in only the inner half of the myometrium. In increta cases, ITs were present in all depths of the myometrium, but did not extend to the serosa. In percreta cases, the myometrium was very thin and was completely invaded by trophoblasts (Figure 1E). The maximal depth of the IT layer was significantly different between groups: accreta 1.3±0.2 mm, increta 3.6±1.1 mm, and percreta 2.0±1.3 mm (P=0.011). The maximal depth of the IT layer in the increta group was significantly greater than in the accreta and percreta groups (P=0.017). No decidual layer was observed in 85% of cases. In placenta accreta cases, sites of focal adhesion of the placenta to the focal decidua basalis were occasionally seen.

**Discussion**

Placenta creta, often associated with massive postpartum hemorrhage and carrying significant maternal morbidity, is one of the leading indications for gravid hysterectomies (2). In a study by Forna et al., only 12 cases were diagnosed from 1990 to 2002 in their series of 70,449 births (10). In the present study, among 8,502 deliveries over a six-year period, 20 gravid hysterectomies were performed due to placenta creta. The incidence of placenta creta seems to be increasing, possibly due to an increase in CS rates over the past decades (11). Placenta accreta and increta constitute the majority of creta cases, with placenta percreta occurring in only 5-7% of all creta cases. Miller et al. reported 62 cases of placenta creta identified on peripartum hysterectomy specimens over a 10-year period: 75% placenta accreta, 18% placenta increta, and 7% placenta percreta (12). Similarly, Wu et al. noted that the histopathological diagnosis of placenta accreta, increta, and percreta was made in 68.5% of 111 creta cases: 55.9% accreta, 8.1% increta, and 4.5% percreta (13). In contrast, a higher proportion of our cases exhibited deep infiltrative pathology: 35% with placenta increta, and 50% with placenta percreta. This difference may possibly be explained by the higher CS rates in our country, by a variation in primary CS rates with or without labor, or by the trend to prefer conservative management in minimally adhesive cases. In previous reports,
authors stated that CS performed electively, without a trial of labor, increased the risk of placenta creta (1, 14). In such cases, placenta creta may be attributed to the thicker myometrium in the area of the incision scar.

The most widely-known risk factors for placenta creta are previous CS and placenta previa in the current pregnancy (14). Additionally, nearly all invasive procedures that were thought to be minor in nature, such as uterine curettage, hysteroscopic surgery, myomectomy, endometrial ablation, and uterine artery embolization, have been associated with a higher incidence of placenta creta (2). The relative contributions of these risk factors remain unknown (1).

In our patients, the risk factors were advanced maternal age, previous CS, and placenta previa. Miller et al. reported an increased incidence of creta with age. The rates were 3, 6, 10, and 15% for women aged under 25, 25-29, 30-34, and over 35 years, respectively (12). Similarly, 55% of our cases were over 35 years of age. Kastner et al. found that the rates of placenta creta were 35, 56, 75, and 100% after zero, one, two, and more than two CSs, respectively (15). Chou et al. identified 14 patients with a histologically proven placenta accreta, of which seven (50%) had had a previous CS (16). In our smaller study, the incidence of placenta creta was 20, 10, and 70%, after zero, one, and two or more CSs, respectively.

In placenta previa, the placenta is implanted in an area of the lower uterine segment proximal to the cervical canal. This area is relatively poorly decidualized, which may result in abnormal or excessive trophoblastic invasion (2). The large prospective study of Silver et al. found that the risk of placenta accreta was 0.03% in a patient undergoing her first CS if placenta previa was absent. The risk increased slightly, to 1%, after five CSs, but to more than 4.7% after six or more CSs. In the same study, if placenta previa was present, the risk of creta was 3.3% at the first CS, but was 40% after the third CS (17). Forna et al. noted placenta previa in only 7% of their 55 placenta creta cases (10). In our series, placenta previa was present in 20% of creta cases.

Both the lack of decidua and excess invasion by EVTs likely play important roles in the pathophysiology of placenta creta, with the contribution of these factors varying in proportion from case to case (3). In our study, 85% percent of women lacked a decidual layer in the invaded area; in other words, the decidual layer was present in only 15 percent of cases. The decidual layer is usually present in the minority of placenta cretas, indicating that over-invasiveness of EVTs is a possible pathophysiologic mechanism. The ability of the decidua to block invasion of trophoblasts is well-known (18). Tantbirojn et al. reported that the maximal depth of IT invasion was not significantly different between subgroups of creta cases (1). However, we observed significantly deeper invasion by ITs in increta cases. This was found due to the thinning of the myometrial layer in percreta cases.

Primary ITs are mononuclear, and most of these cells later convert by symplasmic fusion to become multinucleated cells of the syncytiotrophoblastic bed. Because syncytial multinucleated trophoblastic cells represent the final stage of EVT differentiation, they exhibit a low potential for invasion (18,19). These cells constitute the syncytiotrophoblastic bed that covers the placental villous tree and are involved in the exchange of gases, nutrients, and waste across the maternal-fetal interface, as well as in the production of pregnancy-related hormones (18). Khong and colleagues found the number of multinucleated trophoblasts to be lower in creta patients compared to non-creta patients (9), which might be related to an intrinsic abnormality of the trophoblasts or to a defect in other regulating factors.

In normal placentation, smaller spiral arteries undergo physiologic remodeling. In placenta creta cases, remodeling of the larger radial and arcuate arteries is seen (3). In these arteries, the loss of muscular and elastic tissue renders them unresponsive to vasospasm because of their larger diameter and greater blood flow compared to the smaller diameter spiral arteries (3,9,16). Thus, when removal of the adherent placenta is attempted, heavy hemorrhage occurs. As seen in our cases, previous researchers also found partial remodeling of vessels in the uterine wall of placenta creta cases (2,9). In our study, the proportion of incomplete remodeling of the wall was similar among subtypes of cretas, which was also found in the recent study by Tantbirojn et al. (1). As Khong and Robertson observed in their creta cases, the defective interaction between migratory trophoblasts and decidua can be seen early in placentation, resulting in partial conversion of some vessels in the placental bed to uteroplacental arteries (9).

Conclusion

In this evaluation of placenta creta cases (defined histopathologically) over a six year period, we found higher proportions of increta and percreta cases compared to previous studies. The reported increase in the incidence of placenta creta is probably due to the higher rates of CS in recent decades. Placenta creta is likely to remain a prime cause of peripartum emergency hysterectomies in the near future, especially in areas which have high rates of CS.

Ethical issues
Approval from our “Kahramanmaras Sutcu Imam University Clinical Research Ethics Committee” was obtained before the study began.

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**Conflict of interests**
We declare that we have no conflict of interests.

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**References**


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