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The performance of hyperadherence markers in anterior *placenta praevia* overlying the Caesarean scar

CIPRIAN LAURENŢIU PĂTRU[1)], MARIUS CRISTIAN MARINAŞ[2)], ŞTEFANIA TUDORACHE[1)], RĂZVAN GRIGORAŞ CĂPITĂNESCU[1)], OVIDIU COSTINEL SÎRBU[1)], GEORGE LUCIAN ZORILĂ[1)], NICOLAE CERNEA[1)], ANCA-MARIA ISTRATE-OFIŢERU[1,3)], GABRIELA-CAMELIA ROŞU[3)], LARISA IOVAN[1,3)], DOMINIC GABRIEL ILIESCU[1)]

[1)]*Department of Obstetrics and Gynecology, University of Medicine and Pharmacy of Craiova, Romania*

[2)]*Department of Anatomy, University of Medicine and Pharmacy of Craiova, Romania*

[3)]*Department of Histology, University of Medicine and Pharmacy of Craiova, Romania*

Abstract

Objectives: To assess the ultrasound (US) impact in diagnosing *placenta accreta* (PA) in patients with anterior *placenta praevia* localization, overlying a Caesarean scar. *Patients, Materials and Methods*: This is a prospective study between January 2016 and December 2017 that included patients with Caesarean scar and *placenta praevia* in the third trimester of pregnancy. By means of two-dimensional (2D) grayscale and color Doppler, we investigated the presence of the following US markers for placental invasion: intraplacental lacunae, abnormal blood vessels at the myometrium–bladder interface, thinning of the hyperechogenic uterine serosa–bladder wall interface, loss of normal hypoechoic retroplacental myometrial space. Definitive diagnosis was made at delivery. The US findings were correlated with intraoperative and histopathological (HP) evaluations. *Results*: We found 46 cases with anterior *placenta praevia* overlying a Caesarean scar. Twelve patients presented US criteria for PA. The confirmation was obtained (by means of intraoperative and/or HP features) in 11 of them. The US evaluation with all markers yields a sensitivity of 100% for PA detection. Among the US markers, the association of abnormal blood vessels at the myometrium–bladder interface and the intraplacental lacunae had the highest statistical correlation in the antenatal diagnosis of PA. *Conclusions*: Our study suggests that the antenatal US is a useful tool in predicting PA in high-risk patients. Special attention should be given to the presence of intraplacental lacunae and abnormal myometrial vessels in cases where the placental insertion overlaps a uterine scar for best identification of PA high-risk cases.

Keywords: ultrasound, *placenta accreta*, *placenta praevia*, abnormal blood vessels, intraplacental lacunae.

Introduction

Placenta accreta (PA) defines an abnormal implantation into the uterine wall, where the placental villi adhere directly to the myometrium. The pathogenesis is multidimensional, involving increased, but incomplete trophoblast invasion in a background of absent decidua [1].

The incidence of PA has increased along with the rate of Caesarean sections [2]. Previous uterine surgery and *placenta praevia* are two major risk factors for PA [2, 3]. In such cases, the pregnancy outcome is associated with significant maternal morbidity due to intra- and postoperative complications [4].

Ultrasound (US) has become a useful tool used to diagnose PA and many diagnostic markers were proposed [5–10]. This included the presence of intraplacental lacunae, abnormal blood vessels at the myometrium–bladder interface, loss of the normal hypoechoic retroplacental myometrial zone and thinning of the hyperechogenic uterine serosa–bladder wall interface [11].

The antenatal diagnosis of PA is important to reduce the maternal complications, such as peripartum blood loss, need for blood transfusion and peripartum hysterectomy [12, 13].

The aim of this study was to investigate an optimal antenatal US approach to detect placental accretion in patients with anterior *placenta praevia* and Caesarean scar.

Purpose

The purpose of this study is to evaluate US and microscopic PA or *placenta praevia*. We marked immunohistochemically the blood vessels, myometrium myocytes and basal membranes to observe the placental interpenetration with the myometrium.

Patients, Materials and Methods

Our study included prospectively pregnancies, with prior Caesarean section (CS), who were diagnosed with *placenta praevia* located anteriorly and covering the entire internal cervical os. The patients delivered between January 1, 2016 and December 31, 2017 in the 1st Clinic of Obstetrics and Gynecology, Emergency County Hospital, Craiova, Romania.

Transabdominal and transvaginal US examinations were performed in each patient by at least two different operators using two-dimensional (2D) grayscale and color/

power Doppler. Examinations were performed using US machines equipped with curvilinear transabdominal 3–5 MHz and transvaginal 3–9 MHz transducers (Voluson 730, GE).

Intraplacental lacunae were diagnosed as hypoechoic irregular vascular spaces within the placental parenchyma. Loss of hypoechoic retroplacental space was detected as lack of *decidua basalis* and direct invasion of the trophoblastic tissue through the myometrium. On US, the *decidua basalis* is thought to be represented by the hypoechoic space between the placenta and underlying myometrium. The uterine hyperechogenic serosa–bladder interface was considered abnormal if found interrupted or thinned with myometrium measured less than 1 mm in the lower uterine segment between the bladder wall and the retroplacental vessels, as revealed by color Doppler. The vessels from the myometrium–bladder interface were considered abnormal in the cases with subjective increased vascularization in the uterine serosa–bladder wall interface, extending from the placenta. The combinations of the aforementioned US markers were considered specific for PA.

All pregnancies enrolled in this study delivered by CS. We correlated the US markers with intraoperative findings and histopathological (HP) examination. In the presence of heavy bleeding and impossibility of placental separation, a peripartum hysterectomy preserving the adnexa was performed.

For our microscopic study, we used the classical Hematoxylin–Eosin (HE) and Masson's trichrome (MT) stainings, and for the immunohistochemical (IHC) study, we used anti-cluster of differentiation 34 (CD34) antibodies to mark vascular endothelium, anti-alpha-smooth muscle actin (*α*-SMA) for highlighting smooth muscle actin and anti-collagen IV (Col. IV) for basal membrane labeling (Table 1).

Table 1 – ***Immunohistochemical panel of antibodies used by us***

Antibody	Manufacturer	Clone	Antigenic exposure	Secondary antibody	Dilution	Labeling
Anti-CD34	Dako	QBEnd 10	Citrate, pH 6	Monoclonal mouse anti-human CD34 Class II	1:50	Blood vessels of neoformation
Anti-α-SMA	Dako	1A4	Citrate, pH 6	Monoclonal mouse anti-human smooth muscle actin	1:100	Smooth muscle actin
Anti-Col. IV	Dako	CIV22	Citrate, pH 6	Monoclonal mouse anti-human collagen IV	1:50	Basal membranes

CD34: Cluster of differentiation 34; *α*-SMA: Alpha-smooth muscle actin; Col. IV: Collagen IV.

Statistical analysis of the collected data was made. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for the association of the US markers and separately for each involved parameter were calculated.

Results

We evaluated the presence of US markers associated with PA: intraplacental lacunae, loss of normal hypoechoic retroplacental myometrial space, thinning of the hyperechogenic uterine serosa–bladder wall interface and color Doppler abnormalities, such as abnormal blood vessels at the myometrium–bladder interface (Figure 1).

PA was defined based on the clinical evidence of placental invasion at the time of surgery (partial or complete impossibility of placental separation), and in the cases with postpartum hysterectomy, on the HP diagnosis of trophoblastic invasion through the myometrium (Figure 2).

During the study period, 46 patients with CS and anterior placenta were enrolled in the third trimester of pregnancy. We suspected placental invasion in 12 patients. In 11 of those patients, PA was confirmed postnatally, providing an overall sensitivity of 100%, a specificity of 97.14% and PPV and NPV of 91.67% and 100%, respectively (Table 2).

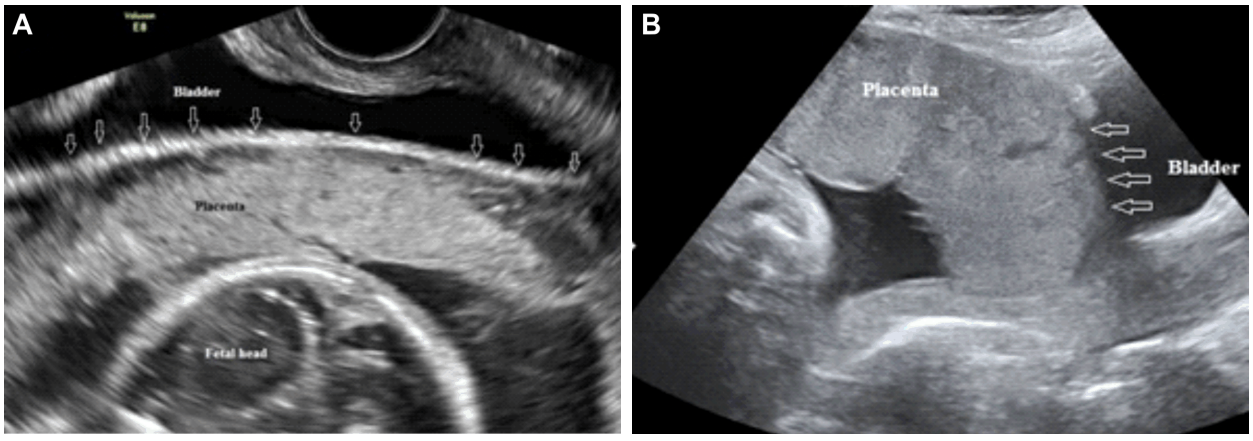

Figure 1 – ***2D/3D and power Doppler US images showing the US criteria for PA diagnosis: (A) Thinning of the uterine serosa–bladder interface (arrows); (B) Loss of the retroplacental clear space (absence of the myometrium – arrows). 2D: Two-dimensional; 3D: Three-dimensional; PA: Placenta accreta; US: Ultrasound.***

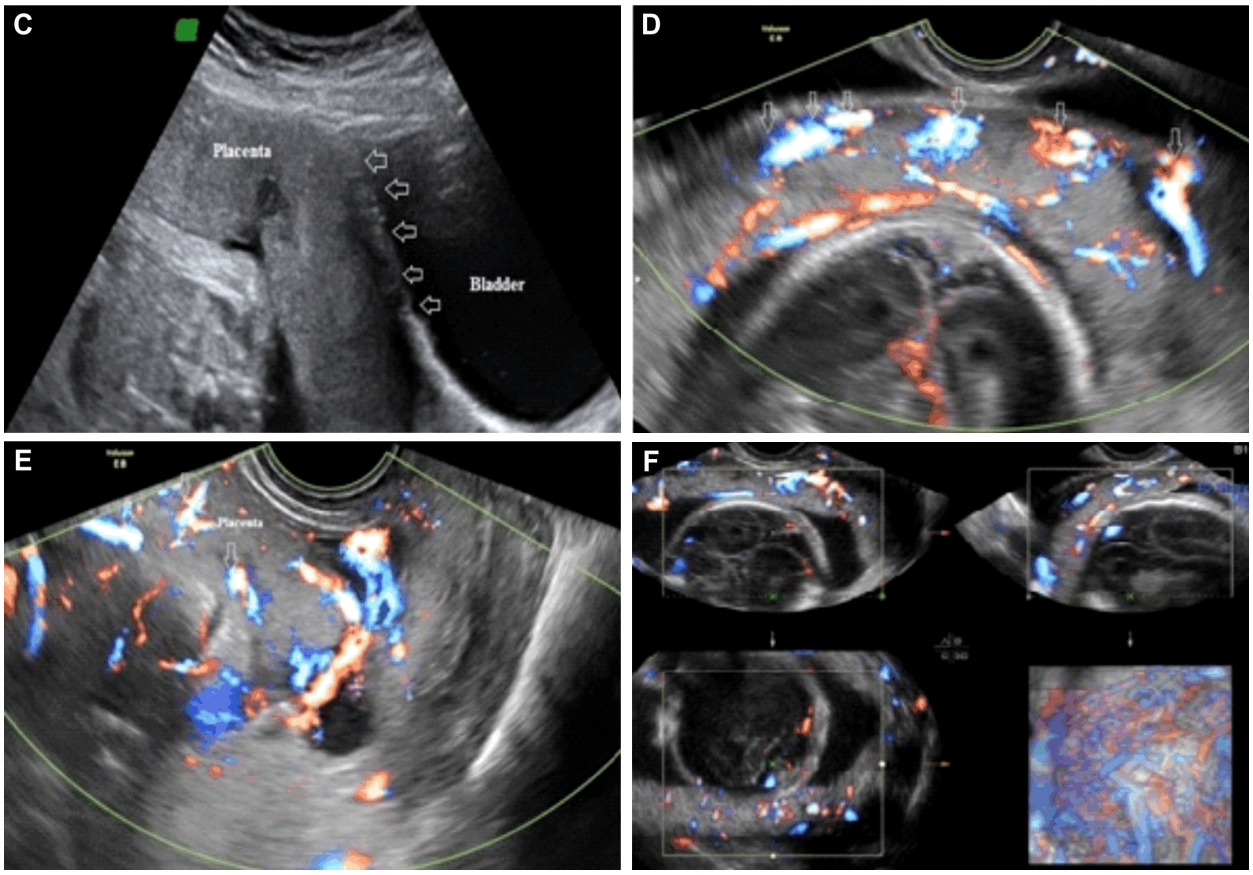

Figure 1 (continued) – ***2D/3D and power Doppler US images showing the US criteria for PA diagnosis: (C) Interruption of the uterine serosa–bladder interface (arrows); (D) Increased vascularity of the uterine serosa–bladder wall interface; (E) Turbulent placental lacunae; (F) 3D power Doppler US reconstruction of the increased vascularity of the uterine serosa–bladder wall interface. 2D: Two-dimensional; 3D: Three-dimensional; PA: Placenta accreta; US: Ultrasound.***

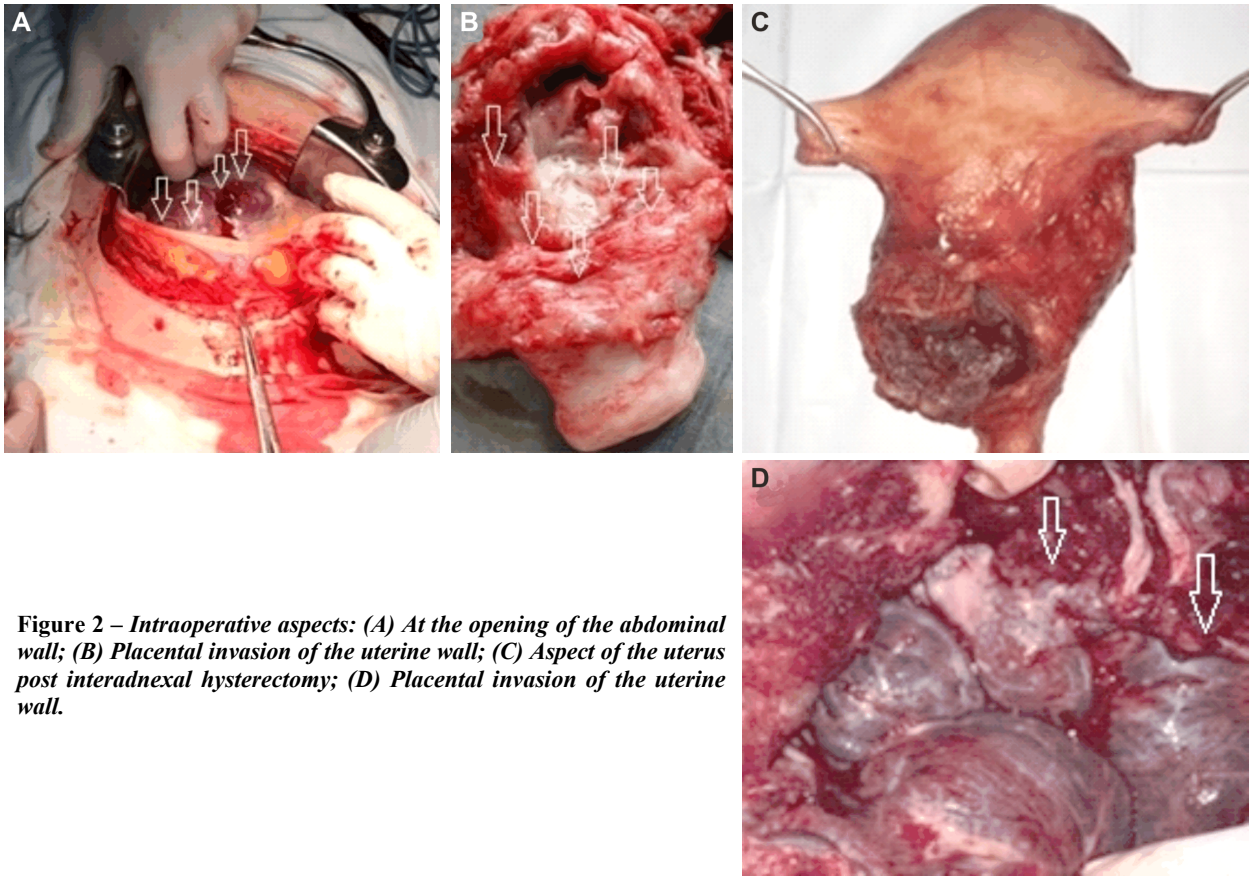

Figure 2 – ***Intraoperative aspects: (A) At the opening of the abdominal wall; (B) Placental invasion of the uterine wall; (C) Aspect of the uterus post interadnexal hysterectomy; (D) Placental invasion of the uterine wall.***

Table 2 – ***Performance of US markers***

US – overall assessment	***TP***	***TN***	***FP***	***FN***	***Sn***	***Sp***	***PPV***	***NPV***	***LR+***	***LR-***
	11	1	1	–	100%	97.14%	91.67%	100%	35	0
Association of US markers	***TP***	***TN***	***FP***	***FN***	***Sn***	***Sp***	***PPV***	***NPV***	***LR+***	***LR-***
	9	2	2	1	82.1%	98.9%	91.9%	97.4%	12.02	0.16
Thinning of the hyperechogenic uterine serosa–bladder wall interface	***TP***	***TN***	***FP***	***FN***	***Sn***	***Sp***	***PPV***	***NPV***	***LR+***	***LR-***
	6	4	3	3	45.45%	100%	100%	85.37%	∞	0.55
Loss of normal hypoechoic retroplacental myometrial space	***TP***	***TN***	***FP***	***FN***	***Sn***	***Sp***	***PPV***	***NPV***	***LR+***	***LR-***
	7	4	2	1	54.55%	97.14%	85.71%	87.18%	19.09	0.47
Intraplacental lacunae	***TP***	***TN***	***FP***	***FN***	***Sn***	***Sp***	***PPV***	***NPV***	***LR+***	***LR-***
	9	3	2	1	81.82%	97.14%	90%	94.44%	28.64	0.19
Abnormal blood vessels at the myometrium–bladder interface	***TP***	***TN***	***FP***	***FN***	***Sn***	***Sp***	***PPV***	***NPV***	***LR+***	***LR-***
	10	2	1	1	90.91%	97.14%	90.91%	97.14%	31.82	0.09

US: Ultrasound; TP: True positive; TN: True negative; FP: False positive; FN: False negative; Sn: Sensitivity; Sp: Specificity; PPV: Positive predictive value; NPV: Negative predictive value; LR+: Positive likelihood ratio; LR-: Negative likelihood ratio.

There was one false-positive case. This case was suspected based on the presence of small intraplacental lacunae, loss of normal hypoechoic retroplacental myometrial space and subjectively increased local vascularization, but intraoperative the placenta was easily removed without excessive bleeding.

We had no false negative results, meaning that all PA cases diagnosed at birth were highly suspected antenatally at the US investigation.

The best combinations of US markers with high performance in PA diagnosis were the abnormal blood vessels at the myometrium–bladder interface and the intraplacental lacunae.

Evaluation of the accuracy for each individual US marker demonstrated that the presence of abnormal blood vessels at the interface between the bladder and placenta on color Doppler was very sensitive (90.91%) and specific (97.14%), positive likelihood ratio (LR+) 31.82%, negative likelihood ratio (LR-) 0.09%. The intraplacental lacunae represented in our group a predictive US marker for PA diagnosis, with high sensitivity – 81.82% and specificity – 97.14%, LR+ 28.64%, LR- 0.19% (Table 2).

Our data show that both US markers (thinning of the uterine serosa–bladder wall interface and loss of normal hypoechoic retroplacental myometrial zone) can be considered specific – specificity of 100% and 97.14%, respectively, but not sensitive for PA diagnosis – sensitivity of 45.45% and 54.55%, respectively.

The study results confirmed a significant association between the US diagnosis, intraoperative findings and HP examination. From the 12 suspected cases, in 11 cases the antenatal PA prediction was confirmed by postnatal clinical and/or HP examination. Caesarean hysterectomy for severe hemorrhage was performed in seven PA. In four cases, a conservative treatment was possible and confirmation of PA was based on clinical evaluation the intraoperative findings (the placenta was very hard to separate from the uterus).

Using the classical HE staining, we observed decidual cells and syncytiotrophoblast interpenetrated with the myometrium, and with the help of MT staining, we highlighted the intervillous collagen areas and those distributed among the mometrium myocytes, stained in blue (Figures 3 and 4).

By IHC staining, using anti-CD34 antibody, we observed that decidual cells and syncytiotrophoblast that penetrated the myometrium are very well vascularized (Figure 5).

With the help of anti-α-SMA antibody, we visualized the myocytes present among decidual cells and invading syncytiotrophoblast (Figures 6–8), and with anti-Col. IV antibody, we marked the epithelial basement membranes (Figure 9).

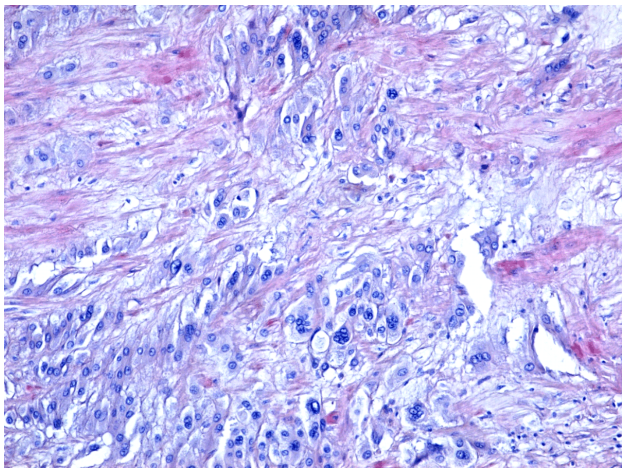

Figure 3 – ***Decidual cells and syncytiotrophoblast cells present among myometrium myocytes. Notice how it disorganizes and invades the uterine muscular layer. HE staining, × 100. HE: Hematoxylin and Eosin.***

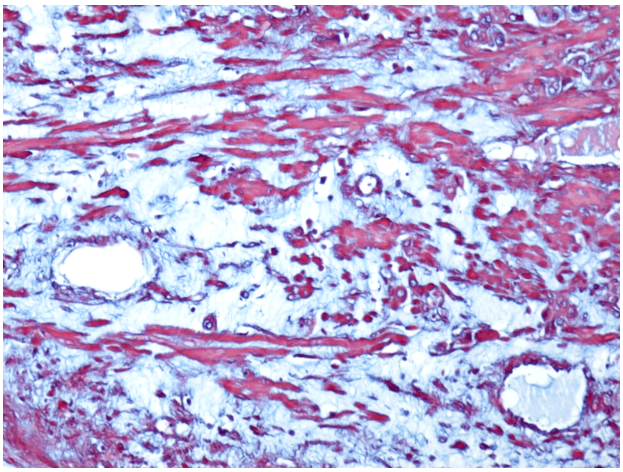

Figure 4 – ***Decidual cells and syncytiotrophoblast cells present among myometrium myocytes. We can observe how it disorganizes and invades the uterine muscular layer and determines the appearance of fibrosis areas (collagen), stained blue. MT staining, × 100. MT: Masson's trichrome.***

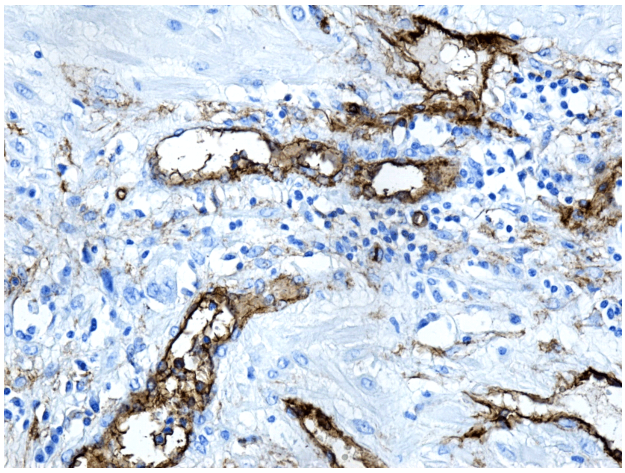

Figure 5 – ***Decidual cells and syncytiotrophoblast cells present among myometrium myocytes. Notice how they disorganize and invade the uterine muscular layer and receive blood through a well-developed vascularization. Immunostaining with anti-CD34 antibodies (marked in brown), × 200. CD34: Cluster of differentiation 34.***

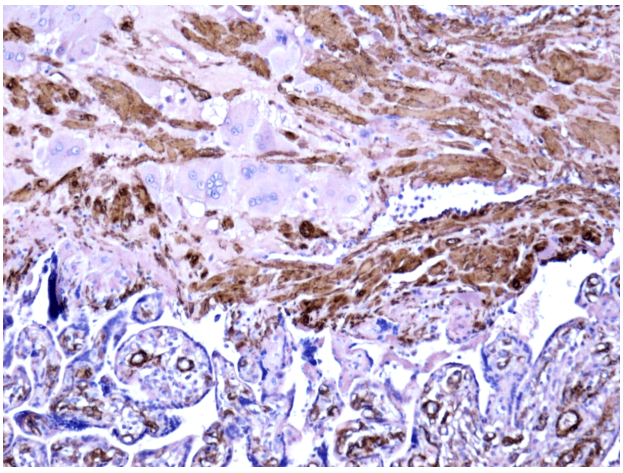

Figure 6 – ***At the bottom of the image, we can observe normal placental villi that began to penetrate the myometrium. The myocytes and muscular layer of the blood vessels are highlighted by immunostaining with anti-α-SMA antibody, and decidual cells and placental villi are histologically stained with MT, ×100. α-SMA: Alpha-smooth muscle actin; MT: Masson's trichrome.***

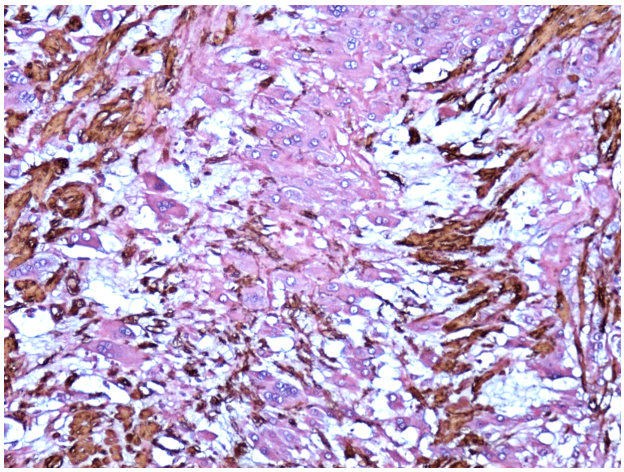

Figure 7 – ***Decidual cells and syncytiotrophoblast cells are observed as they penetrate the myometrium. The myocytes and muscular layer of the blood vessels are highlighted by immunostaining with anti-α-SMA antibody, and collagen fibers resulting from the disruption of the myometrium are stained blue by the histological staining with MT, ×100. α-SMA: Alpha-smooth muscle actin; MT: Masson's trichrome.***

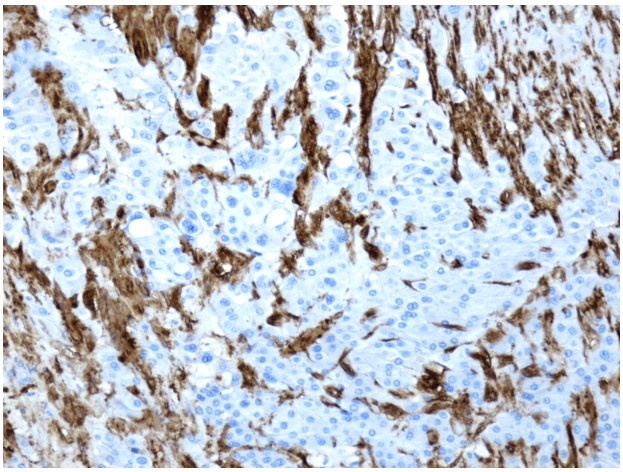

Figure 8 – ***We observe decidual cells and syncytiotrophoblast cells as they invade the myometrium. The myocytes and muscular layer of the blood vessels are highlighted by immunostaining with anti-α-SMA antibody, ×100. α-SMA: Alpha-smooth muscle actin.***

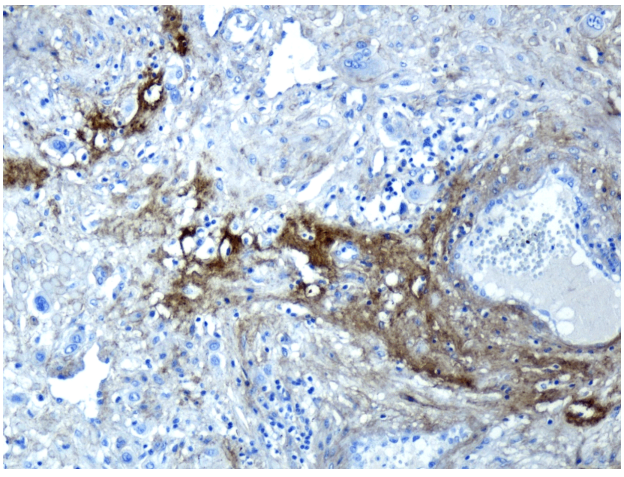

Figure 9 – ***Decidual cells and syncytiotrophoblast cells are observed as they invade the myometrium. The basement membranes (brown marking) are interrupted and the myometrium has a disorganized architecture. Immunolabeling with anti-Col. IV antibody, ×100. Col. IV: Collagen IV.***

Discussions

Our study data suggest that the use of an US protocol with several markers is an efficient tool to diagnose PA in high-risk patients, with anterior *placenta praevia* and history of Caesarean section, which is important, as the recognition of these cases and delivery in a tertiary center improve maternal and fetal outcome [14, 15].

In our study, we investigated the individual value of US markers proposed in previous studies, but we also searched for an optimal association of these parameters that can detect PA with minimal scanning. The highest detection was obtained with the association of abnormal blood vessels at the myometrium–bladder interface and the intraplacental lacunae. Other studies used only one criterion and obtained a higher sensitivity but a reduced specificity [16].

When the US markers were considered individually, they yielded a lower sensitivity. The aspect of abnormal blood vessels at the myometrium–bladder interface reached the highest sensitivity of them (90.91%), but with a lower PPV and specificity compared to markers' associations. Similarly, a recent meta-analysis showed that among the different US markers, the presence of abnormal vasculature on color Doppler imaging has the highest sensitivity and specificity [17].

The presence of intraplacental lacunae was also a high sensitive and specific marker. However, was a source of false positive results as presented before in literature [18].

Our data show that this US marker has a high specificity, as presented in previous studies [19], but with low sensitivity. The low sensitivity of this marker may be due to the fact that in the third trimester, the lower uterine segment appears as a thin line and evaluation of the interface between the myometrium and the placenta may be difficult. This aspect may be also misinterpreted in patients with prior CS at the scar site, because of the myometrium architectural changes.

Our study results show that the loss of the retro-placental clear space is associated with a low sensitivity and we suggest not using it alone for diagnosis. Our data support literature reports on the frequent pitfalls of this parameter in anterior low-lying placentas [20].

α-SMA is a protein actin that highlights the contractile microfilaments of smooth muscle cells. In humans, this is encoded by the actin, alpha 2, smooth muscle, aorta (*ACTA2*) gene, located on chromosome 10 (10q22-q24) [21]. Also, α-SMA is used for myofibroblast marking [22]. In our study, we observed by means of immunolabeling using the anti-α-SMA antibody how muscle myofilaments are stained, as well as the decidual mesenchymal stem cells [23].

Using the anti-CD34 antibody, we highlighted capillary endothelial cells. CD34 is a membrane phosphoglyco-protein found in both humans and animals [24, 25]. We observed the increased peri-decidual and myometrial vascularization in the areas with PA, which demonstrates the invasive potential of this pathology.

Placental and myometrial Col. IV was highlighted using anti-Col. IV antibody. This type of collagen is found in the basement membrane [26]. We observed that in the PA the epithelial basement membranes were disorganized, the syncytiotrophoblast and decidual cells anarchically penetrated among the myocytes and caused major structural and functional changes, both placental and myometrial.

The antenatal diagnosis allows for a multidisciplinary approach, special medical preparation and awareness of the couple regarding the risks and management of the pregnancy, which ultimately decrease the surgical compli-cations, blood loss, and prolonged intensive care unit admissions [27–29]. Our study results suggest that there is improvement in maternal outcome with an antenatal diagnosis of PA as grayscale and color Doppler US have good performance.

Conclusions

In high-risk patients with low anterior placenta and anterior Caesarean section, a third-trimester US protocol that considers the main PA markers is highly sensitive and specific in the antenatal diagnostic of PA. Among the various US markers for PA detection, color Doppler vascular abnormalities and intraplacental lacunae should be primarily used for screening. A correct antenatal diagnosis is the goal for a planned delivery that will decrease surgical complications and improve the perinatal outcome. From the microscopic point of view, decidual cells and syncytiotrophoblast cells that invaded and disorganized the myometrium were revealed.

Conflict of interests

The authors declare that they have no conflict of interests.

Acknowledgments

Microscopic images have been obtained in the Research Center for Microscopic Morphology and Immunology, University of Medicine and Pharmacy of Craiova, Romania (Manager: Professor Laurenţiu Mogoantă).

Authors' contribution

Ciprian Laurenţiu Pătru & Anca-Maria Istrate-Ofiţeru equally contributed to this article.

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Corresponding author
Marius Cristian Marinaş, MD, PhD, Department of Anatomy, University of Medicine and Pharmacy of Craiova, 66 1 May Avenue, 200628 Craiova, Romania; Phone/Fax +40251–599 228, e-mail: cristi_marinas84@yahoo.com

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