REVIEW

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Update on *placenta accreta* spectrum disorders by considering epidemiological factors, ultrasound diagnosis and pathological exam – literature review and authors' experience

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Abstract

The aim of this paper was to correlate the circumstances that could lead to an abnormal invasion of placenta with the updated requirements to perform screening by ultrasound for all pregnant women prone to develop this pathology. To screen in the middle trimester of gestation for *placenta accreta* spectrum (PAS) disorders sets up an in-time referral opportunity for pregnant women prenatally detected with this pathology to a medical center with elevated level of expertise in the management of PAS disorders, able to act permanently by a multidisciplinary team (MDT) and to have access at medical resources including blood bank available. The literature review reveals especially useful data for clinical practice as regards novel explanations related to the etiology and physiopathology of PAS disorders, the composition of the MDT and the relevance of an indispensable pathologist physician at the time of Cesarean hysterectomy involved in the selection of best samples with the purpose of avoiding the possibility of losing undiagnosed cases with litigation implications. Conclusions show that the prenatal diagnosis of PAS disorders is possible so decreasing the risk of mortality and morbidity of pregnant women. Screening in the second trimester of pregnancy for PAS disorders becomes mandatory as the number of births by Cesarean section is expected to rise past three-fold until 2030. The professional expertise of the pathologist physician could be enriched by immunohistochemical staining in all suspected cases of placental invasion in myometrium wall.

Keywords: *placenta accreta*, spectrum disorders, ultrasound screening, immunohistochemistry.

Introduction

Update of the epidemiological factors involved in abnormal invasive placenta (AIP) is necessary in situation when the incidence of these factors increase and generate local conditions favorable for intramyometrial invasion of placenta villi. Apart of these factors, the uterine scar post Cesarean delivery represents a higher level of incidence. Studies published in the last two decades shown that the risk of abnormal invasion in uterine wall by trophoblast villi increases progressively with the number of anterior Cesarean deliveries. Since 2006, Silver *et al.* showed in a published multicentric study that the incidence risk for PAS raises from 3% at the first Cesarean delivery to 11% at the second Cesarean delivery and this risk increases gradually to 40%, 61% and 67% for third, fourth and fifth delivery by Cesarean section (CS) [1]. The study published in 2021 by Betran *et al.* reveals that in 2018 on average 21.1% of women gave birth by CS worldwide and this percentage will be around to 28.5% for 2030 [2]. Over time, authors show that this rise of the rates concerning Cesarean deliveries is not uniform around the world, the lower rate

is attained in sub-Saharan Africa (on average 7.1%) and the highest rate is in place in Eastern Asia (on average 63.4%) [1, 3]. This is important since the CS stands for one of the most determinant factors in the etiopathology of *placenta accreta* spectrum (PAS) disorders. These realities and the causal chain are the source of our research which underlines the necessity to screen pregnancies with high risk factors for PAS with the purpose to estimate prenatally, with high level of accuracy, the diagnosis concerning AIP, which allows to compose an individual protocol concerning the elective moment of delivery, obstetrical way for delivery, access to an optimal multidisciplinary team (MDT) expertise within a high-level medical care center. Recent data emphasize the necessity to complete the MDT by a pathologist physician, which must act from the first moment of placental examination. The identification of these factors creates the opportunities to correct the medical decisions that generate conditions for myometrium invasion of placenta and at the same time to improve the medical methods able for an early diagnosis for all suspected cases of PAS disorders. To accomplish this requirement, it is necessary to identify all epidemiological specific factors for pregnancy cases with substantial risk for PAS disorders development and early referral of these cases to screening by ultrasound (US).

Aim

As concrete data reveal worldwide, there is an increased number of cases with PAS disorders, so the challenge is to search for ways to mitigate this obstetrical pathology. Towards this aim firstly we set out an analysis of the correspondence between the current scientific knowledge in the field of PAS disorders and the level of implementation in medical practice in some emergency hospitals in Romania. Then, we collect appropriate data from several reference hospitals and derive relevant statistics useful to identify the new epidemiological threat factors involved in PAS disorders incidence. To complete the scope, we look for how to detect risks, how to develop effective procedures for mother's pregnancy care surveillance, how to improve delivery management, and how to make progress in survival prognosis.

Materials and Methods

We began from the state of the art as regards the issue of PAS disorders as reflected in data published online in the last 15 years in reviews and guidelines and then we analyzed clinical data from three hospitals from Bucharest, Romania, between 2018 and 2021. The initial data were collected mainly from *PubMed*/*MEDLINE* databases, *Google Scholar*, *Science Direct* platforms. The data were analyzed in individual subchapters as concerns the terminology used, physiopathology, relevance of the immunostaining of trophoblast villi, grading of the AIP, epidemiological factors, ultrasonographic and magnetic resonance imaging (MRI) findings suggestive for PAS diagnosis, significance of the prenatal diagnosis of PAS disorders and its contribution to the management of this pathology. A special subchapter exhibits our experience in this field. The last subchapter contains discussions as regards the introduction of new notions in clinical practice and analyzes the data obtained in our study and authors' experience related to ultrasonographic findings suggestive for PAS disorders sustained by histopathological (HP) and immunohistopatological exams on investigated samples.

Results on literature review and authors' experience

Terminology and anatomopathological characteristics

The analysis of the published medical literature as regards the abnormal insertion of placenta shows that the terminology introduced in 1966 by Lucke *et al.* is available still nowadays with minor changes. PAS disorders incorporate three noteworthy features, such as degree of invasion of placental villi in myometrium, lateral extension of abnormal invasion of placenta and unevenness of invasion along placental bed. PAS disorders encompass three distinct types related to the depth of invasion of villi in the wall of uterus. From this point of view there are three types of placenta abnormalities: (*i*) *placenta accreta*, also known as *placenta creta*, *placenta vera* or adherent placenta characterized by direct attachment of the villi to the myometrium without invasion but associated with defect of decidua, (*ii*) *placenta increta* characterized by the deep expansion of villi in myometrium, (*iii*) *placenta percreta* differentiated by the deep penetration of villi till serosa of uterus or out serosa to neighborhood organs, such as bladder, colon and other pelvic organs [4, 5].

Macroscopic abnormalities

There are two different circumstances which could contribute to suspicion of PAS disorders diagnosis by gross exam, either by placenta exam immediately after vaginal delivery of fetus or by visual exam of uterus looking first to the external surface at time of Cesarean surgery before uterus section and then, secondary looking inside the cavity of the uterus at placental bed zone. In the last situation, the surgical pathologist should record the anatomic location of the placenta frequently placed in the low anterior uterus segment [6], and in cases which finished by hysterectomy, it is mandatory to describe the depth of invasion and the thickness of uninvolved myometrium [7]. In cases with invasive placenta, especially in cases with deep invasive placenta until the serosa uterine surface, the uterus presents a tumoral bulge corresponding to the invasive placenta, and also outside of uterus the surface is often congested, macroscopically uterus presents vessels with higher circumferences, radially and cranio-caudally distributed according to the grade of intramyometrial invasion. This macroscopic situation persists only for a brief time after fetus delivery. Macroscopically, the pathologist physician finds that the myometrium is often markedly thinned and in *placenta percreta* hemorrhagic zones could be seen after total invasion of myometrium [8]. *Placenta accreta* cannot be easily diagnosed from the delivered placenta because the deficiency of decidua that underlies *placenta accreta* is not obvious and most of time histological sections of such placentas will not highlight the deficiency of endometrium that triggers *placenta accreta*. However, if the focus of adherence is large, the abnormal implantation zone is often disrupted during delivery and there may be missing cotyledons on gross examination [8]. The visual exam performed by an expertise obstetrician could remark

the unequal bright and disruption of the cotyledon surface, features that could rise the doubt of an abnormal adherence of placenta, situation that requires specific management to avoid heavy *postpartum* hemorrhage and enhance mother's chances of survival. Occasionally, the retained cotyledons can be palpated by manual exploration in the *postpartum* uterus [9]. Any procedure of uterine curettage induces the danger to disseminated intravascular coagulation (DIC) and must be avoided. It is mandatory to emphasize that there is no advantage to get samples from these retained cotyledons pursuing to confirm the diagnosis of *placenta accreta*, because the probability to observe myometrial fibers attached to delivered placenta after manual removal is extremely low. Even nowadays the authors of a practical guide to placental examination for forensic pathologists again underline the significance of careful macroscopic assessment of maternal surface of the placenta at delivery because this offers visible aspects suggestive to highlight defects in the surface of placenta or adherent strands of muscle [10].

Microscopic features

Microscopic examination reveals villi in contact with or invading myometrial smooth muscle without intervening decidua [11]. Partial or complete absence of the *decidua basalis* is the most important feature in the diagnosis of *placenta accreta* [6]. Placental villi adhere directly to the myometrium, or invade into the myometrium, and often the villi do not adhere directly to the myometrium but rather are entrapped in fibrin and extravillous trophoblast [6, 7]. For better understanding of changes occurred in PAS disorder, it is very significant to underline that normal placenta is characterized by three major trophoblast subpopulations: the cytotrophoblast (CT), extravillous cytotrophoblast (EVCT), and syncytiotrophoblast (ST) [12]. In line with the name of location, there are two distinguished subtypes of EVCT known as interstitial subtype of EVCT and endovascular EVCT. While the interstitial subtype of EVCT has function to invade and implant into maternal *decidua*, with the goal to anchor and develop placenta, the endovascular subtype of EVCT is involved in the remodulating process of maternal spiral arteries that allows the control of blood perfusion and oxygenation in the developing placenta. The interstitial EVCT progress not further than one-third inner myometrium in a zone known under the name of the junctional zone (JZ). The terminal villi of EVCT fuse and develop multinucleated trophoblast giant cells (MTGCs). During the placental development, both interstitial and endovascular EVCTs suffer changes from epithelial cells to mesenchymal cells. PAS disorders offer anatomical conditions with pathological consequences due to the direct reach of terminal villi to radial and arcuate arterial vessels, accompanied at this level by the vascular remodeling mainly by vasodilatation of vascular diameter. The vascular changes could be easily observed such prenatally at US exam as postnatally at gross exam of the uterus immediately post-hysterectomy and at HP samples exam. All aforementioned data justify why it is necessary to stand up a correct diagnosis, envisaged by both obstetrician and pathologist physician, considering that in the same placental bed is possible to coexist both adherent and invasive placenta with different grades of invasion [13]. Unevenness of invasion limits the accuracy of microscopic examination in cases where whole uteroplacental interface is not available for HP exam. Unfortunately, this situation is rarely performed in medical practice and some cases miss the possibility to be correctly diagnosed [14].

Grade of the abnormal invasive placenta

Since 2015, Collins *et al.* have conceived a grading system as regards PAS disorders. The clinical aggressivity increases gradually from 1 to 6. While grades 1, 2 and 3 allow birth both by vaginal and Cesarean delivery, in cases with grades 4, 5 and 6 only Cesarean delivery is recommended followed up frequently by hysterectomy with best results in cases where placenta is not removed outside the uterus before surgical procedure [15] (Table 1).

Table 1 – *Relation between fetus and placenta delivery associated with PAS disorders grade*

Grade	Fetus delivery		Placenta delivery					
			Normal placenta	***Placenta accreta***		***Abnormal invasive placenta***		
	V	*CS*	*Total detachment*	*Focal adherence*	*Total adherence*	*Placenta increta*	*Placenta percreta*	
			Spontaneous	PD PMR	AD PHBMR	M Surgical plan	M + USe Without surgical plan	M + USe + Bladder ± Neighborhood organs Without surgical plan
1	Yes	Yes	Yes					
2A		Yes		Yes				
2B	Yes			Yes				
3A		Yes			Yes			
3B	Yes				Yes			
4		Yes				H		
5		Yes					H Bladder suture	
6		Yes						H Suture of pelvic organs injury

AD: Absent detachment under easy traction on umbilical cord and uterotonics; CS: Cesarean section; H: Hysterectomy; M: Myometrium; PAS: *Placenta accreta* spectrum; PD: Partial detachment under easy traction on umbilical cord and uterotonics; PHBMR: Possible heavy bleeding manual removal; PMR: Possible manual removal; USe: Uterus serosa; V: Vaginal delivery.

Pathophysiology in PAS disorders

From the year 1937, the hypothesis as regards the pathology of PAS disorders evolved. In the beginning, the first hypothesis sustained that the primary defect does exist within the trophoblast able to develop excessive attachment or invasion to the myometrium but afterwards the second hypothesis stated as first cause for PAS the failure of the decidualization under influence of more antenatal factors. Any defect inside the endometrium creates predispositions for abnormal invasion of the trophoblast to uterine wall in different grade of invasion extended from center to the periphery of the placental bed. More frequently, this pathology is correlated with a history of delivery by CS or any other factors that could determine uterine surgical scars or inflammatory injury of endometrium. The data show that the damage of endometrium, associated with myometrium scars does not heal by a normal process of regeneration. The heal process include new structures like collagen, increase of leukocyte recruitment inside endometrium after Cesarean delivery, changes in the surrounding uterine circulation [16]. The abnormal invasion of trophoblast induces permanent damage within myometrium and create the possibility that placental tissue to reach the deep uterine circulation [13]. The microscopical analysis of EVCT cells in PAS disorders shows an increase in size of these cells, a deep invasion in myometrium wall but a fewer number of MTGCs. The studies performed in cases with PAS disorders followed up by Cesarean delivery scar prove that the excessive EVCT occurred in the absence of the JZ [16]. The loss of reepithelization capacity within the uterine scar justifies the abnormal invasion of placenta at this level. As regards the endovascular EVCT cells, they are found both within and around spiral arteries, more in the central and less in periphery of placenta in the second trimester of gestation. Researchers have observed that the presence of chorionic villi in myometrial vascular spaces is frequently found in PAS disorders, 70.4% in *placenta accreta*, and increases for *placenta increta* and *placenta percreta* to 87.5% and 84%, respectively [17]. Other experts in domain confirmed in time this discovery on PAS disorders [13]. The PAS disorders are characterized by the lack of a plane of cleavage between the placental basal plate and the uterine wall that could allow spontaneous delivery of placenta. Obstetricians must become aware that in absence of this cleavage plan any attempt to detach by force the placenta led to high dangerous hemorrhage in placenta bed [4]. One of the US signs for PAS is the excessive dilatation of vessels and this situation is triggered by the EVCT cells, which directly infiltrate the tissue around both radial and arcuate arteries. The excessive vasculature and large vessels can be seen both at US as well as at gross examination immediately after Cesarean hysterectomy. All the data stand out that in cases with PAS disorders there is a correlation between the high numbers of EVCT cells and vascular remodeling process at level of the arcuate and radial arteries in myometrium [18]. The healing of Cesarean scar involves defect of reepithelization, remodeling of maternal vessels associated with neovascularization [15]. Nowadays, all data underline that the microscopical diagnosis of PAS disorders involve the absence of a decidual layer between the tip of anchoring villi and superficial myometrium. The accuracy of the diagnosis is influenced by the site of sampling because in the same specimen it is possible to coexist different degrees of invasion manifested by areas with *accreta*, *increta* or *percreta* invasion of trophoblast villi. This condition could be managed by more attention for the selection site of sampling by a pathological physician, expert member of the MDT. Another recommendation consists in gross exam of placenta by a specialist with the placenta inside the uterus immediately after Cesarean hysterectomy [19]. A recent explanation for the failure of placental detachment in accreta placentation is associated with excessive fibrinoid deposition at the utero–placental interface [20]. To avoid the possibilities to underdiagnosis cases with PAS disorders it is necessary to prepare a high number of samples and slides, and in cases where there is suspicion of myometrium villi to use immunostaining for markers able to highlight the existence of trophoblast villi cells [21]. The molecular biology in PAS disorders is not yet fully understood. In literature review, researchers underline many similarities between PAS and tumor behavior. They have agreed that in all cases with PAS disorders there are extensive neovascularization, downregulation of apoptosis, immunological dysfunction of decidua characterized by a suppressed T-cell response, persistent epithelial-to-mesenchymal transition (EMT) program after the first trimester of pregnancy, downregulation of tumor suppressor genes with lower expression of p53 [22, 23]. All these described aspects support the theory that PAS occurs in the conditions of disruption of the *decidua* integrity that creates opportunity to develop an invasive niche like a tumor behavior. There is a difference among vascular remodeling occurred in situation of great obstetrical syndrome like preeclampsia, intrauterine growth restriction and PAS disorders. While in the first circumstances spiral arteries are mainly involved, in the last situation vascular remodeling occurs in radial and arcuate uterine vessels [13]. This is a strong argument that differentiate the vascular changes between PAS disorders and preeclampsia. This truth explains the changes in uteroplacental vasculature represented by high peak systolic velocity (PSV) and low resistive index (RI) in Doppler spectrum. This reality could be used as a US marker able to identify pregnancies suspected to have PAS disorders [24]. In conclusion, PAS disorders are distinguished by absent *decidua*, deep invasion of trophoblast villi, increase in number of vessels, vascular remodeling that develop an excessive uteroplacental circulation and abnormal placental blood flow. All these changes have correspondent in US images, gross exam, HP exam and could be highlighted by immunomarkers on selected samples.

Immunostaining in PAS disorders

Various studies focused attention to the correlation between Hematoxylin–Eosin (HE) staining of villi and immunostaining expression visibility in PAS disorders. Immunostaining allows to better identify the trophoblast villi in the uterus wall, and it can identify trophoblast villi when standard staining could not detect this pathology. The results of this research revealed that researchers in PAS disorder domain found various levels of immunostaining according to villous trophoblast and EVCT. In PAS disorders, the immunostaining in ST shows lower expression for MTGCs [micro-ribonucleic acid (microRNA)-34a], transforming growth factor-beta (TGF-β), E-cadherin (E-CAD), epidermal growth factor (EGF), c-erbB-2,

vascular endothelial growth factor receptor-2 (VEGFR-2), and receptor tyrosine kinase (RTK), and a higher expression for epidermal growth factor receptor (EGFR) and tissue inhibitor of matrix metalloproteinase-1 (TIMP-1). As concerns the immunostaining expression in EVCT, this is lower for soluble fms-like tyrosine kinase-1 (sFLT-1) and higher for vascular endothelial growth factor (VEGF) and phosphotyrosine [16, 25]. One of available distinguishing marker for EVCTs is human leukocyte antigen-G (HLA-G) [26]. The studies performed to improve the information obtained by light microscopy on trophoblast at level of placental bed used the cytokeratin (CK) marker for better understanding the morphological features of trophoblast, not so visible before immunostaining [27]. CK immunostaining checks the efficiency of the HE examination as regards the identification of trophoblast villi. Especially CK7 is an immunomarker able to reveal the presence of the trophoblast villi so that to improve the accuracy of PAS diagnosis [28].

Update of epidemiological factors

Nowadays, news possibilities arise to approach the management of gynecological pathology, and this leads to new circumstances able to confirm the hypothesis that PAS disorders became an iatrogenic disease [4]. The epidemiological factors of PAS disorders are related to the history of surgical uterine scar after Cesarean delivery or other medical situations able to disturb the integrity of the endometrium. In this last situation, factors like uterine curettage, hysteroscopic investigation (associated or not with curative procedures), fertilization procedures (associated with non-surgical elements as endometritis generated by infections) and decubitus lesion of endometrium post-contraceptive device are involved. The incidence of PAS disorders boosts proportionally with the number of CS, and this situation requires more attention related to technical procedures and material used for suture of uterine section. The suture material recommended is the monofilament textile material. There is not a unique opinion as regards the type of suture procedure, so while some surgeons pronounced in favor of double-layer closure for uterine surgical section others recommend closing the uterus by a single layer continuous suture [29]. The incidence of PAS disorders increases proportionally with the age of pregnant women and occurs both in cases with or without obstetrical and gynecological uterus surgical history. The published data have disclosed that there is a strong correlation between incidence of *placenta praevia* associated with PAS disorders and this incidence progresses from 3% to 67% at the fifth pregnancy. The multifaceted analysis of this correlation highlights that the number of postpartum hysterectomies grows from 0.65% to 8.99% at the fifth Cesarean delivery in cases that associate these pathological circumstances [1]. The authors who conceived *International Federation of Gynecology and Obstetrics* (*Fédération Internationale de Gynécologie et d'Obstétrique* – FIGO) consensus guidelines on PAS disorders published in *International Journal of Gynecology & Obstetrics* in 2018 had mentioned the results of *UK Obstetric Surveillance System* (UKOSS) study, where it was shown that the prevalence of PAS disorders among pregnancies increased from 1.7 per 10 000 pregnancies to 577 cases per 10 000 pregnancies at women that had in the past a CS associated with *placenta praevia* [5]. Recent data underscore that the incidence of *placenta accreta* increased very much from one to 533 pregnancies in 2000s to one to 272 pregnancies in 2016s and the continuous increase of Cesarean deliveries number, main etiological factor involved in this pathology, is a dangerous cause leading to greater mortality and morbidity induced by PAS disorders [30]. Another study uncovers that the incidence of cases detected on US with *placenta praevia* proved to be diagnosed with *placenta praevia accreta* in 4.1% for cases, which recognized a history of CS and the incidence of *placenta accreta* was about three times higher at women with two or more CS in the past [31].

In line with this evolution of PAS disorders incidence, the work published in 2021 by Fonseca & Ayres de Campos reports contribution of PAS disorders to maternal morbidity becomes 18-fold greater [32].

The knowledge about the etiopathology factors and associated circumstances underline the need to introduce in clinical obstetrician's practice the necessity of screening for the PAS disorders and, at the same time, to also screen for the genetics syndromes in the second trimester of pregnancy.

Conditions for US assessment of placenta

The US description of placenta has two priorities related to localization of placenta in uterus and the description of the relationship between placenta and uterine wall. With the goal of assessing the placenta, the imagist physician must respect some conditions that allow to get the best image as regards the forehead mentioned situations. Evaluated cases by abdominal US must satisfy three mandatory criteria, such as selection of US transductor with high frequency 5–9 MHz, easy pression of transductor on the abdominal wall to avoid distortion of the clear retroplacental zone and full bladder with no less than 200–300 mL. Better images are observed by endovaginal scan with empty bladder, situation which allows a better assessment of the relationship between the inferior edge of placenta, internal cervical os, segment thickness and bladder wall [31].

Updates of ultrasonographic features expressive for PAS disorders diagnosis

The abnormal insertion of trophoblast villi inside the myometrium leads to high level of morbidity by heavy uterine hemorrhage and fast progress to DIC, especially in all situations when there is an attempt to remove placenta in unknown cases with PAS disorders followed up by uterine curettage. The lack of clinical experience in the situation characterized by impossibility to spontaneously detach placenta or by uterotonic medication directs to massive hemorrhage impossible to manage without availability of an MDT. Only a prenatal diagnosis performed by US and MRI could prevent this drama. The published studies shown that two thirds of cases with this pathology are unidentified before birth and become unwished medical surprise for physician, in fact a situation exceedingly difficult to control [33, 34]. This certainty constitutes a compelling argument to implement in current clinical practice US criteria that could allow to sustain an early suspicion of the presence of this dangerous obstetrical pathology. Since 1980, there is an ongoing attention on the discovery of US criteria for PAS disorders prenatal diagnosis by ultrasonography in gray scale, two-dimensional (2D) power Doppler color system or three-dimensional (3D) and

MRI. The literature review shows that ultrasonography has high sensitivity and a superior specificity for PAS disorders diagnosis [35]. The performance of the ultrasonography is directly correlated with the physician's ultrasonographical expertise, echography machine performance and age of pregnancy. A long time was required to agree a consensus as regards the imaging features able to characterize the presence of abnormal adherence or invasion of trophoblast villi. Towards this aim, in 2016, *European Working Group on Abnormally Invasive Placenta* proposed a particular description for each specific US image and attributed a properly image name [36]. This charge was accomplished by professors with elevated level of expertise in domain of PAS disorders, such as Jauniaux E, Collins SL, Bowman ZS, Bhide A, Finberg HJ, Ahmed M Hussein, which together have agreed about 10 suggestive images for US diagnosis of this pathology. The ultrasonographic images in 2D gray-scale system able to sustain prenatal diagnosis of PAS disorders are loss of anechogenous uteroplacental space, presence of abnormal placenta lacunae, interruption of the integrity of posterior vesical wall, myometrial thinning, focal exophytic mass, placental bulge. Other significant US signs observed with Doppler color system are length of uterovesical vascularization, hypervascularity of placental bed, bridging vessels between placenta and bladder serosa, placental lacunae feeder vessels, tortuous vascularity with "chaotic branching". Studies shown that the probability to diagnose an abnormal placenta invasion is higher when the US exam identifies more than four lacunae and myometrial thinning is less than 1 mm or the myometrial fibers are completely invisible [37, 38]. Researchers have displayed a correspondence between the depth of invasion and the incidence of specifical US facets. They show that in cases with *placenta accreta* the most frequently incidences are represented by US images with "bridging vessels" (71.4%) and loss of the clear zone (62.1%). US scan in *placenta increta* is characterized especially by the loss of anechogenous zone (84.6%). The US features most often encountered in *placenta percreta* cases are placenta lacunae (82.4%) and the subplacental hypervascularization (54.5%) [39].

After two years, in 2018, a large group of authors published the results of their research which encompasses 20 studies and have enrolled 3029 pregnancies targeting to analyze the accuracy of US for prenatal diagnosis of PAS disorders. The study discloses that the US exam offers a higher specificity *versus* sensitivity in all cases with abnormal invasion placenta [40]. We summarized the sensitivity and specificity for each US feature of PAS disorders assessed by the forehead mention group of researchers (Table 2). There are situations when US evaluation is limited by local conditions and these cases require MRI able to discriminate if there is or not invasion of trophoblast villi for cases with posterior *placenta praevia*, for parametrium invasion or for cases with obese pregnant women. The performance of MRI allows to better identify important explicit signs, such as placental bulge, focal exophytic mass, deformed like tenting bladder, and disorder of placental vascularization [41]. Even though MRI is a more expensive investigation compared to US exam the sensitivity and specificity are lower concerning AIP detection (75% and 65%, respectively) but the advantage of MRI is identification of this pathology before delivery time when US assessment is limited in obstetrical situations aforementioned [42].

Table 2 – ***Sensitivity and specificity of the most frequent signs detected by US in PAS disorders***

Sign	*Placenta accreta*		*Placenta increta*		*Placenta percreta*	
	Se	*Sp*	*Se*	*Sp*	*Se*	*Sp*
PL	74.8%	87.9%	88.6%	77.4%	76.3%	74.0%
LCZ	74.9%	92.0%	91.6%	76.9%	88.1%	71.1%
LF	81.2%	84.0%	84.3%	79.7%	45.2%	75.3%
UVH	12.3%	90.9%	94.4%	88.0%	86.2%	88.2%

Adapted using statistical data published by Pagani *et al.* (2018) [40]. LCZ: Loss of the clear zone; LF: Lacunar flow; PAS: *Placenta accreta* spectrum; PL: Placenta lacunae; Se: Sensitivity; Sp: Specificity; US: Ultrasound; UVH: Uterovesical hypervascularity.

Authors' results on PAS disorders

To enrich knowledge on PAS disorders, we performed an analysis in three clinical hospitals from Bucharest (St. Pantelimon Clinical Hospital, Prof. Dr. Panait Sîrbu Clinical Hospital, Polizu Clinical Hospital) collecting a high number of cases and shared experience on US diagnosis with Department of Obstetrics and Gynecology of Cuza Vodă Clinical Hospital from Iaşi, Romania.

The histopathological examination was made at the Department of Pathology from Filantropia Clinical Hospital and the expression of immunohistopathological markers was identified in Department of Cellular and Molecular Biology, and Histology, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania.

Our study was conducted from 2018 to 2021 and was focused on the total number of pregnant deliveries, way of delivery, incidence of PAS disorders, incidence of *placenta praevia* reported to their correlation with history of scar CS and on incidence of hysterectomies related to their relationship with the pathological factors above mentioned.

Our study comprises 32 540 deliveries, from which by vaginal spontaneous way 12 372 (38.1%) and by CS 20 168 (61.9%). Our statistical data reveal that *placenta praevia* was found in 589 cases corresponding to 1.81%. Among these a significant percentage (32.7%) pertains to 193 cases associated to an obstetrical history characterized by uterine scars after CS. The analysis underlines that PAS disorders were present in 22 cases corresponding to 1.09‰ of CS. Paying attention to the hysterectomy performed, we observe that this requirement was for 55 cases meaning 1.69‰ from all deliveries. Rigorous evidence shows that roughly one third of these hysterectomies (recognized as pathological cause of invasive placenta) proves a significant percentage 32.72%. The results are shown in Figures 1–5.

Pathological images from cases which proved to be diagnosed with AIP at HP exam are show in Figures 6–9.

To ascertain cases with unrevealed PAS disorders diagnosis in circumstances with unexplained cause for hemorrhage after delivery, immunohistochemical (IHC) staining on collected samples from uterus past hysterectomy is necessary. We can demonstrate, by IHC staining, the ability of cluster of differentiation 34 (CD34) immunomarker to immunoexpress abnormal invasion of placenta. This idea is supported by the fact that CD34 is a known marker for epithelial cells. In our research, CD34 immunostaining is showing vascular placental villi positivity (Figure 9).

We correlated the necessity to screen for PAS disorders by US early in pregnancy related to the incidence of the most frequent cause of this pathology in our clinical practice. An archive with US findings suggestive for PAS disorders is under construction.

Our clinical experience strongly recommends avoiding noteworthy catastrophic hemorrhage cases by abstinence to remove by force undetached placenta. We selected some US photos suggestive for PAS disorders diagnosis and associated some clinical data regarding their obstetric history to their description. The most frequent US images identified are shown in Figures 10–17.

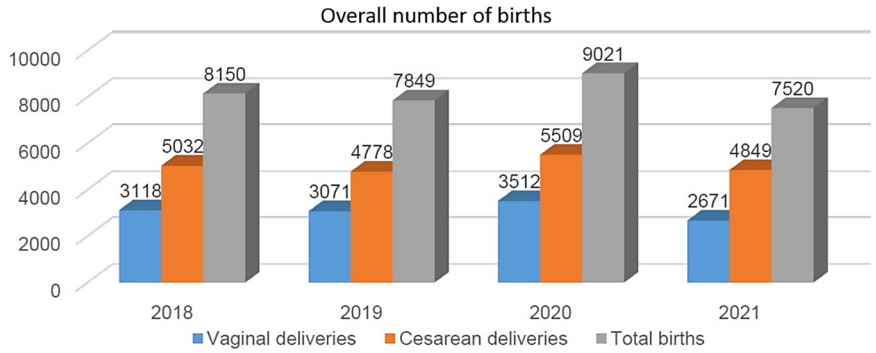


Figure 1 – *Pregnancies delivery way.*

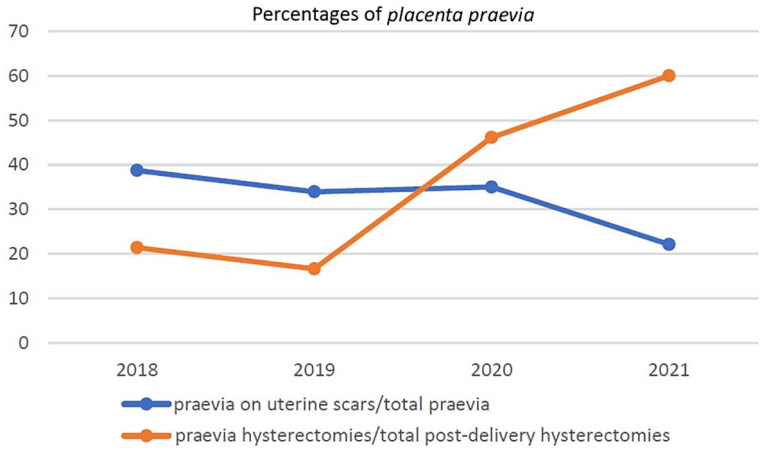


Figure 2 – *Incidence of placenta praevia.*

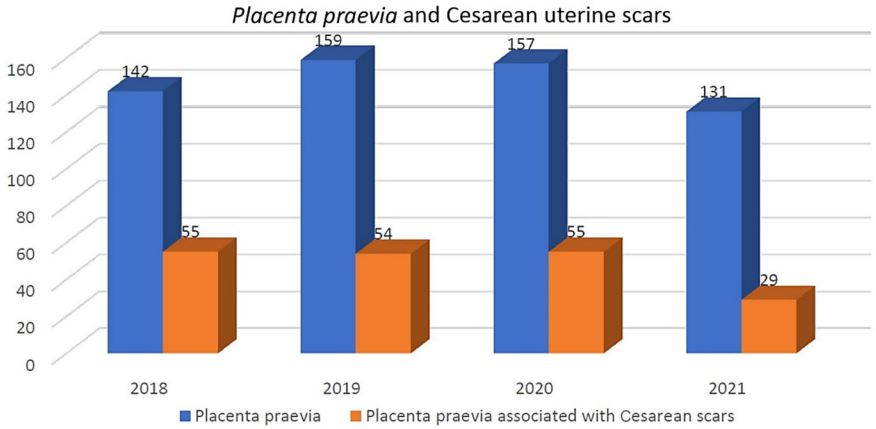


Figure 3 – *Correlation between placenta praevia and uterine scars.*

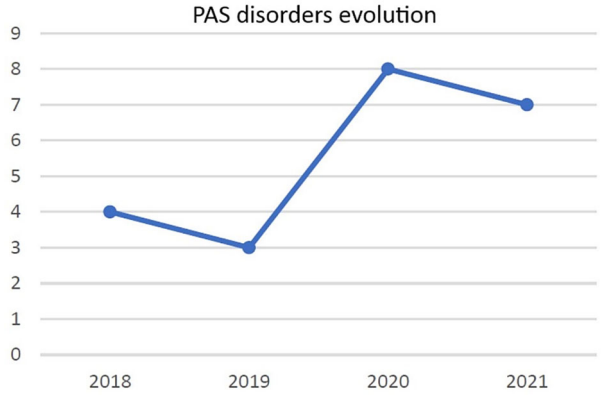


Figure 4 – *Incidence of PAS disorders between 2018–2021. PAS: Placenta accreta spectrum.*

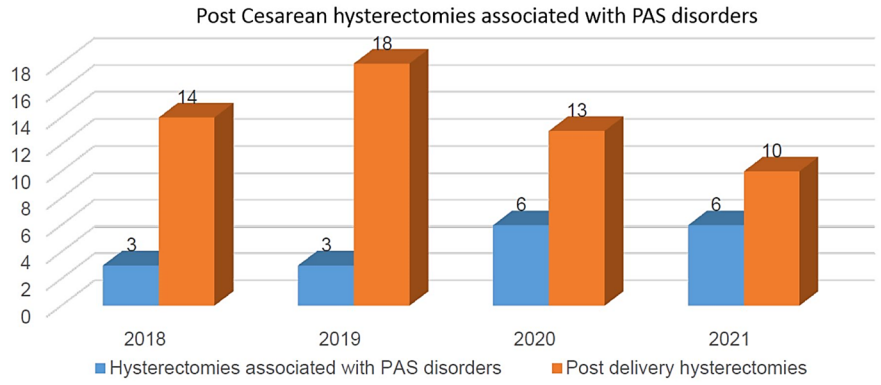


Figure 5 – ***Incidence of PAS disorders among post-deliveries hysterectomies. PAS: Placenta accreta spectrum.***

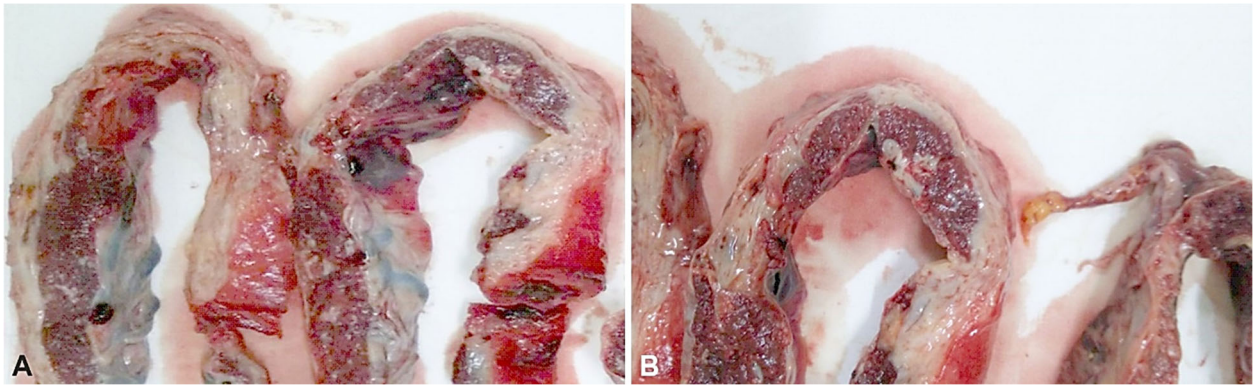


Figure 6 – ***(A and B) Placenta increta in a hysterectomy specimen. The myometrium is markedly thinned, or even absent.***

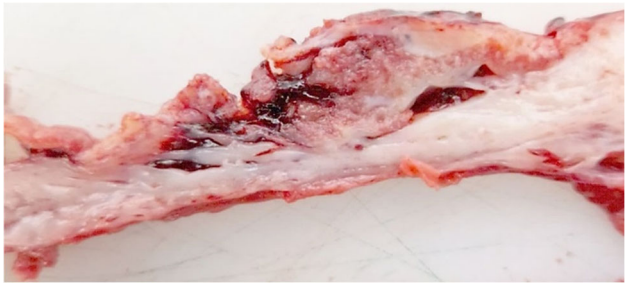


Figure 7 – ***Placenta detached before hysterectomy specimen. Placenta increta. Placental implantation site at the lower uterine segment – placenta penetrates through the myometrium.***

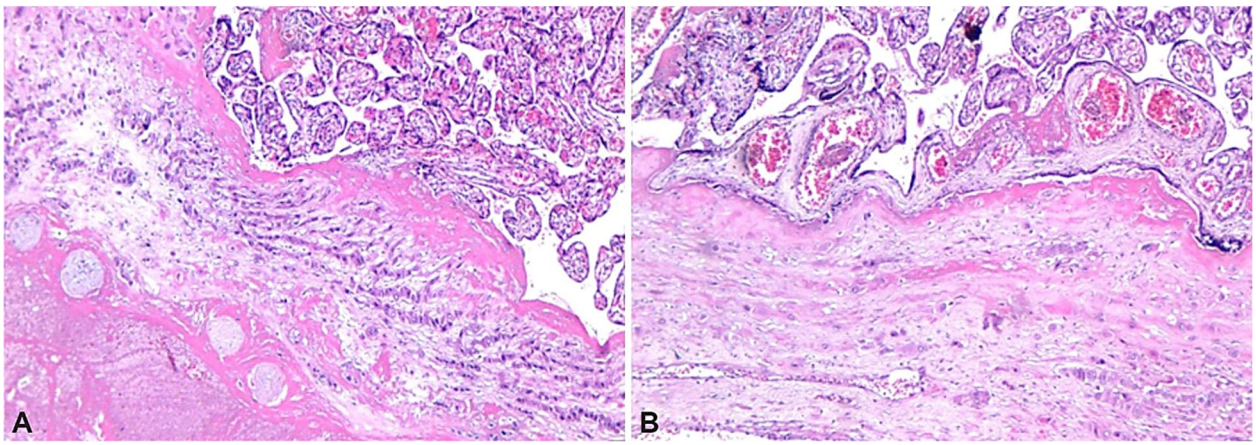


Figure 8 – ***(A and B) Placenta accreta. Villi can be seen directly adjacent to myometrium without intervening decidua. Hematoxylin–Eosin (HE): (A) ×100; (B) ×200.***

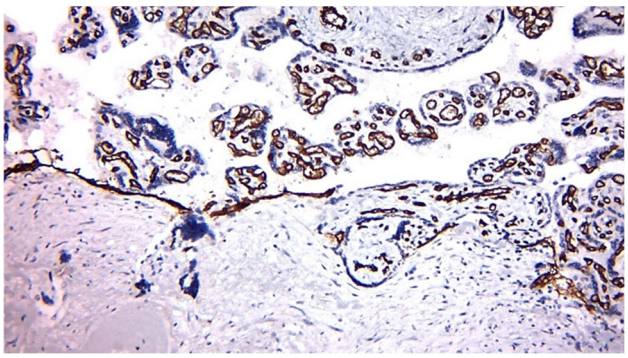


Figure 9 – ***CD34 immunostaining showing vascular placental villi positivity (×200). CD34 positive in small vessel of chorionic villi. Anti-CD34 monoclonal antibody, clone QBEnd/10 (Leica). CD34: Cluster of differentiation 34.***

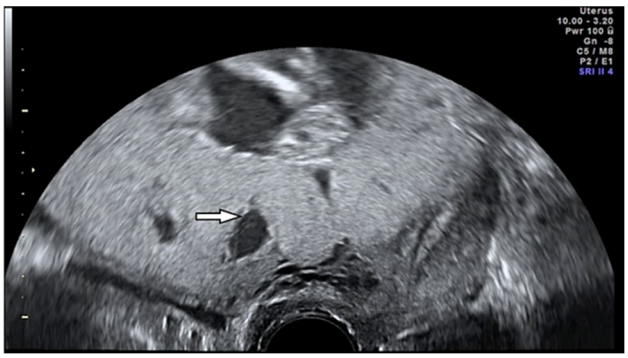


Figure 10 – ***Transvaginal sonogram: placenta lacunae (white arrow) in pregnant woman, 33 years old, 35 GW, no obstetrical history in the past, present delivery way by Cesarean section, placenta praevia associated with placenta increta. GW: Gestational weeks.***

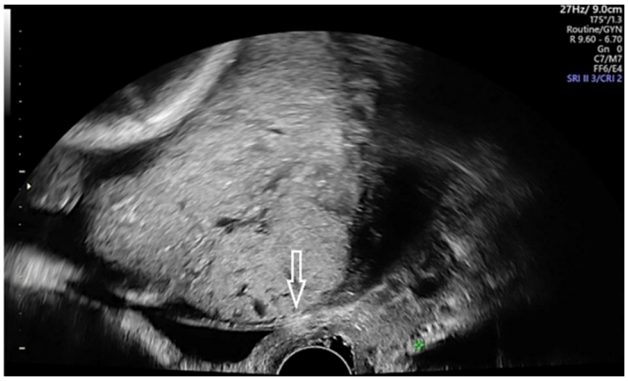


Figure 11 – ***Transvaginal sonogram: retroplacental clear zone (white arrow) in pregnant woman, 36 years old, 37 GW, obstetrical history: four uterine Cesarean scars, the last for placenta praevia associated with placenta increta. GW: Gestational weeks.***

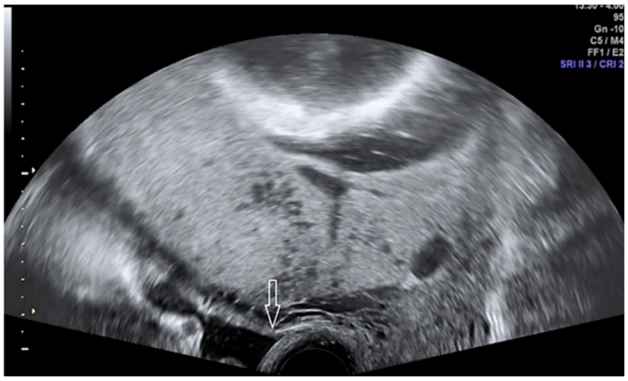
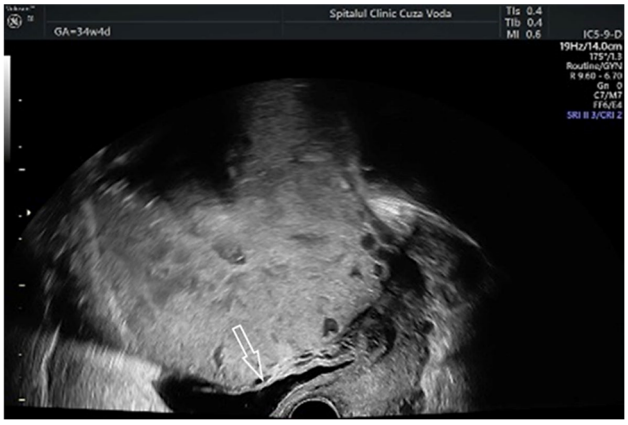


Figure 12 – ***Transvaginal sonogram: thinning of utero-vesical interface (white arrow) in pregnant woman, 31 years old, 34 GW, no obstetrical history in the past; present delivery by Cesarean section; placenta praevia associated with placenta increta. GW: Gestational weeks.***

Figure 13 – ***Transvaginal sonogram: thinning of retroplacental myometrium less than 1 mm (white arrow) in pregnant woman, 31 years old, 34 GW, no obstetrical history in the past; present delivery way by Cesarean section for placenta praevia associated with placenta increta. GW: Gestational weeks.***



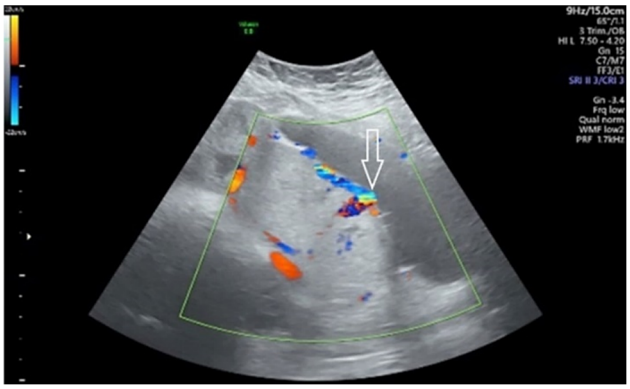


Figure 14 – ***Transabdominal sonogram: bridging vessels between placenta and bladder (white arrow) in pregnant woman, 39 years old, 34 GW, obstetrical history: two abortions, two Cesarean sections, the last for placenta praevia associated with placenta percreta. GW: Gestational weeks.***

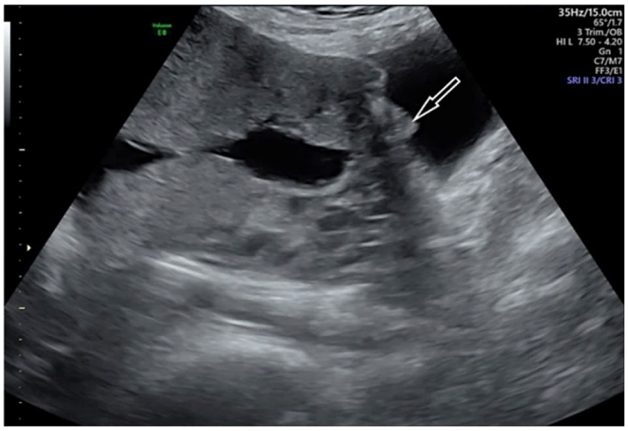


Figure 15 – ***Transabdominal sonogram: placental bulge (white arrow) in pregnant woman, 28 years old, 33 GW, obstetrical history: two uterine Cesarean scars; present delivery way by Cesarean section for placenta praevia increta. GW: Gestational weeks.***

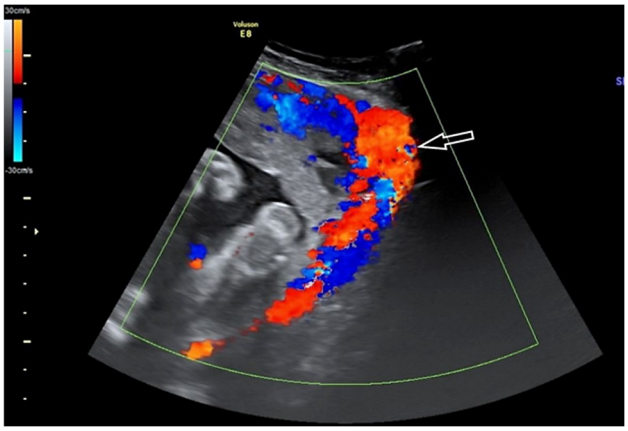


Figure 16 – ***Transabdominal sonogram: subplacental hypervascularity (white arrow) in pregnant woman, 33 years old, 28 GW, no obstetrical history in the past, present delivery way by Cesarean section, placenta praevia associated with placenta percreta. GW: Gestational weeks.***

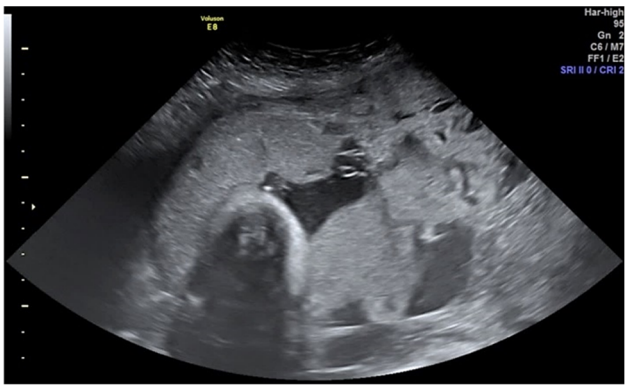


Figure 17 – ***Transabdominal sonogram: placental exophytic mass in pregnant woman, 33 years old, 28 GW, no obstetrical history in the past, present delivery way by Cesarean section for placenta praevia associated with placenta increta. GW: Gestational weeks.***

Comments as regards improvement of clinical practice experience according to new possibilities to prenatally detect of PAS disorders diagnosis – authors' experience

The knowledge of the state of the art as regards the consequences of existence of an abnormal insertion of placenta undiagnosed before delivery requests to insist upon the individual obstetrical and gynecological history of the pregnant women. To identify the risk factors for development of an invasive placenta, it is necessary to early screen the pregnant women concerning this obstetrical dangerous pathology, with the goal to obtain a prenatal diagnosis useful to decide on the best moment for delivery in the best conditions for mother and newborn. The growth of the number of deliveries by CS leads to higher number of uterine scars, main pathological factor that directs to abnormal invasion of placenta during next births. From this point of view, it is required to perform screening of PAS disorders in the middle trimester of pregnancy and to initiate in our clinical practice a register with these cases and their ultrasonographic and HP characteristics. Analysis of all registered cases offers the possibility to assess and check the probability of prenatally diagnosis of PAS disorders. An especially important aspect is related to physician's expertise able to detect by US the images specific for the diagnosis of PAS disorders. This expertise must be certified after attending training courses coordinated by *International Society for Abnormal Invasive Placenta* (IS–AIP). In the lack of this competence nothing could not stop physician to perform routine middle trimester US screening of PAS disorders and to gain US experience. The appraisal of placenta must simultaneously analyze localization and relationship between placenta and uterine wall. An abnormal localization of placenta inside the lower uterine segment has been demonstrated to be frequently associated with anomalous invasion of trophoblast villi in myometrium wall. Under this circumstance the possibility of hemorrhage during the pregnancy appears. Bleeding during pregnancy in cases identified as *placenta praevia* associated or not with AIP requires to finish the pregnancy at 34 weeks by programmed CS [43, 44]. To avoid heavy hemorrhage at delivery time in cases identified by US with PAS disorders, IS–AIP recommends finishing the pregnancy by programmed CS at 36–37 weeks in all cases without history of premature birth, premature rupture of membranes or CS [45]. All anatomical changes characteristic for PAS disorders inside placental bed, *decidua*, placenta, myometrium and organs around the uterus, mainly posterior wall of bladder, have correspondence in US images that could be prenatally discovered. Despite this achieved medical performance nowadays, in lack of mandatory screening for PAS disorders one-half to two-thirds of cases remain prenatally undiagnosed [46]. To prevent the risk of hemorrhage any attempt to remove placenta when it is no possible to be detached spontaneously or under uterotonics medication must not occur. Under these settings, placenta

must remain inside the uterus and hysterectomy after Cesarean delivery must be performed. A prenatal diagnosis of PAS disorders allows to send the pregnant woman to a center of excellence known such as a tertiary level hospital. This center must be able to ensure all the time, seven from seven days, an MDT composed by obstetricians, surgeons with skills in vascular surgery, hematologists, anesthetist, and specialists in intensive therapy care of mother and newborn. These physicians must prove a wide experience in managing all degrees of AIP. The researchers have agreed on the necessity to complete the MDT with an experienced pathologist physician that must be present at the time of hysterectomy with the goal to perform the best macroscopical description of uterus and placenta, and to select the most appropriate samples from wall of uterus and placenta before changes occur in the macroscopic uterine vasculature. Jauniaux *et al.* have underlined that immediately after hysterectomy, it is possible to analyze, for a brief time, at macroscopical exam with placenta left in uterus, the vascularization above placenta visible on the surface of the uterus. Cases with PAS disorders are characterized by a dense, tangled vessels or multiple vessels running laterally and cranio-caudally in the uterine serosa. This innovative approach increases the accuracy of the diagnosis as regards PAS disorders creating the possibility to differentiate focal *versus* large *increta* areas and between abnormal adherent placenta and invasive *placenta accreta*, frequently associated in the same case [19]. It is especially important to understand the dangerous pathological event happening under the circumstances when fetus delivery occurs by vaginal way in the condition of AIP inside uterine wall. When so, under the strong intensity of uterine contraction fetus presses upon placenta affecting the structural integrity with release of thromboplastin tissue from placenta directly to maternal vascular circulation. In this manner, the DIC disease is initiated. This trouble of coagulation progresses through two stages. First stage is characterized by an overactive clotting. The second stage is described by bleeding after consuming platelets and clotting factors. It is obvious that to successfully manage of DIC it is necessary to administrate primary anticoagulants, and secondary consumed coagulation factors, such as platelets and fibrinogen, in proportional ratio with coagulation status and with the weight of woman. Bleeding due to the second stage of DIC explains why uterine curettage is forbidden because it enhances the passage of thromboplastin tissue from the placental bed to maternal circulation and accentuates the consuming clotting factors. The progress of DIC manifests by systemic bleeding. Pregnancies with PAS grade 4 to 6, with myometrial invasive placenta, *increta* or *percreta* must be finished only by Cesarean way without any tentative/trial to remove placenta from uterus cavity. Our obtained data reveal a high percentage of deliveries by CS (61.9%), in line with the global world data published in 2021 by Betran *et al.*, with the mention that this percentage is past two times higher compared with the average percentage prognosed for 2030 and remarkably close to percentage forecasted for Eastern Asia (63.4%) [1]. The present study observes that the incidence of 32% *placenta praevia* cases associated with previous Cesarean scars is a real argument to expect for the next years an increase of this percentage moreover the percentage of delivery by CS reached 61.9% for 2021. In line with this disclosed data the percentage of PAS disorders cases will grow over 1.09‰ of CS. These results show a high compatibility with published international data. According to the data published in 2018 by Jauniaux *et al.*, also relying on Silver *et al.* published statistical data, the incidence of PAS disorders is increasing around the world from 0.24% to 6.74% corresponding to the rise of number of uterine scars from first to fifth after CS [1]. The same authors underline that the association between *placenta praevia* and *placenta accreta* simultaneously grow with the number of Cesarean deliveries from 3% for first Cesarean delivery to 67% for fifth Cesarean delivery [5]. Thinking like our approach other published data are underscoring that PAS disorders diagnosis must be thoroughly checked in circumstances such as need for manual removal of focal or total adherent placenta, suggestive US images for PAS disorders, expressive gross exam and finally confirmed by HP exam [47]. Published data reveal that in situation characterized by suspicion of PAS disorders that is not confirmed by HE microscopic exam, it is recommended to perform IHC exam with markers for trophoblast, such as CK7 and HLA-G, which are the most indicated immuno-markers to detect AIP. At the same time, we showed in the present work a strong significance of CD34 immunostaining to highlight the vascular placental villi positivity. All litigation cases of hysterectomy with non-detected cause for heavy *postpartum* hemorrhage at usual HP exam must be evaluated by immunomarkers for trophoblast able to identify real pathology. Related to the incidence of morbidity and mortality there are few information because there are not electronic data as regards the accuracy of prenatal diagnosis and, in many cases, they are missing a complete HP exam. Our study backs the idea that during next years the high number of deliveries by CS will rise and from this point of view the number of uterine scars, AIP and low-lying placenta will increase proportionally. The risk of a higher mortality and morbidity is expected. From this perspective, ensuring an improved medical care strongly requires paying more attention to this obstetrical issue.

Conclusions

There are more objective causes significantly affecting women's health due to PAS disorders like scars post CS deliveries, uterine curettage, surgical hysteroscopic procedures, fertilization procedures, infectious endometritis, and endometrial lesions due to intrauterine device. The statistical data prove that the highest weigh belongs to uterine scars after Cesarean deliveries. All above mentioned factors attest that during years to come it is awaited that, in line with the higher number of deliveries by Cesarean way, the number of cases with PAS disorders will increase. Immunostaining with markers for trophoblast in all suspected case of invasive placenta in uterus wall is a requirement in all litigated cases. The best immunomarkers able to draw without doubts conclusions on HP diagnosis were proved to be CK7, CD34 and HLA-G. The growing incidence of PAS disorders cases leads to a higher morbidity and mortality for mothers and newborns. To prevent this unwelcome situation, it is necessary to screen by US for PAS disorders in middle trimester of gestation all pregnancies with suggestive factors for PAS disorders, to record US

findings in a database targeting to analyze and improve the quality of prenatally diagnosis by US and to create all conditions able to choose for delivery the best age of gestation, to referral to a not less than a tertiary level hospital with adequate economic resources and a permanent large MDT having great expertise in management of PAS disorders. Meeting these requirements allows to improve the vital prognosis.

Conflict of interests

The authors declare that they have no conflict of interests.

Authors' contribution

The first and the last author had equal contribution to achievement of this paper.

References

[1] Silver RM, Landon MB, Rouse DJ, Leveno KJ, Spong CY, Thom EA, Moawad AH, Caritis SN, Harper M, Wapner RJ, Sorokin Y, Miodovnik M, Carpenter M, Peaceman AM, O'Sullivan MJ, Sibai B, Langer O, Thorp JM, Ramin SM, Mercer BM; National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network. Maternal morbidity associated with multiple repeat Cesarean deliveries. Obstet Gynecol, 2006, 107(6):1226–1232. https://doi.org/10.1097/01.AOG.0000219750.79480.84 PMID: 16738145

[2] Betran AP, Ye J, Moller AB, Souza JP, Zhang J. Trends and projections of Caesarean section rates: global and regional estimates. BMJ Glob Health, 2021, 6(6):e005671. https://doi.org/10.1136/bmjgh-2021-005671 PMID: 34130991 PMCID: PMC8208001

[3] Betrán AP, Ye J, Moller AB, Zhang J, Gülmezoglu AM, Torloni MR. The increasing trend in Caesarean section rates: global, regional and national estimates: 1990–2014. PLoS One, 2016, 11(2):e0148343. https://doi.org/10.1371/journal.pone.0148343 PMID: 26849801 PMCID: PMC4743929

[4] Jauniaux E, Jurkovic D. *Placenta accreta*: pathogenesis of a 20th century iatrogenic uterine disease. Placenta, 2012, 33(4):244–251. https://doi.org/10.1016/j.placenta.2011.11.010 PMID: 22284667

[5] Jauniaux E, Chantraine F, Silver RM, Langhoff-Roos J; FIGO *Placenta Accreta* Diagnosis and Management Expert Consensus Panel. FIGO Consensus Guidelines on *placenta accreta* spectrum disorders: epidemiology. Int J Gynaecol Obstet, 2018, 140(3):265–273. https://doi.org/10.1002/ijgo.12407 PMID: 29405321

[6] Baergen RN, Gersell DJ, Kraus FT. Diseases of the placenta. In: Kurman RJ, Ellenson LH, Ronnett BM (eds). Blaustein's pathology of the female genital tract. 7th edition, Springer, Cham, Switzerland, 2019, 1223–1305. https://doi.org/10.1007/978-3-319-46334-6_19 https://link.springer.com/referencework/10.1007/978-3-319-46334-6

[7] Schollenberg E, Lee AF, Terry J, Kinloch M. Placenta and pregnancy-related diseases. In: Zheng W, Fadare O, Quick C, Shen D, Guo D (eds). Gynecologic and obstetric pathology. Vol. 2, Springer, Singapore, 2019, 493–539. https://doi.org/10.1007/978-981-13-3019-3_15 https://link.springer.com/chapter/10.1007/978-981-13-3019-3_15

[8] Baergen RN. Postpartum hemorrhage, subinvolution of the placental site, and *placenta accreta*. In: Baergen RN. Manual of pathology of the human placenta. 2nd edition, Springer, New York, NY, USA, 2011, 185–202. https://doi.org/10.1007/978-1-4419-7494-5_12 https://link.springer.com/book/10.1007/978-1-4419-7494-5

[9] Frank HG, Kaufmann P. Nonvillous parts and trophoblast invasion. In: Benirschke K, Kaufmann P, Baergen R (eds). Pathology of the human placenta. 5th edition, Springer, New York, NY, USA, 2006, 191–312. https://doi.org/10.1007/0-387-26742-5_9 https://link.springer.com/book/10.1007/b137920

[10] Mittal N, Byard RW, Dahlstrom JE. A practical guide to placental examination for forensic pathologists. Forensic Sci Med Pathol, 2020, 16(2):295–312. https://doi.org/10.1007/s12024-019-00214-2 PMID: 31873913 PMCID: PMC8585837

[11] Clement PB, Young RH. Trophoblastic lesions, miscellaneous primary uterine neoplasms, hematopoietic neoplasms, and metastatic neoplasms to the uterus. In: Clement PB, Young RH. Atlas of gynecologic surgical pathology. 3rd edition, Elsevier–Saunders, London, UK, 2014, 285–286. https://www.worldcat.org/title/atlas-of-gynecologic-surgical-pathology/oclc/863173238?referer=di&ht=edition

[12] Bischof P, Irminger-Finger I. The human cytotrophoblastic cell, a mononuclear chameleon. Int J Biochem Cell Biol, 2005, 37(1):1–16. https://doi.org/10.1016/j.biocel.2004.05.014 PMID: 15381142

[13] Jauniaux E, Collins S, Burton GJ. *Placenta accreta* spectrum: pathophysiology and evidence-based anatomy for prenatal ultrasound imaging. Am J Obstet Gynecol, 2018, 218(1):75–87. https://doi.org/10.1016/j.ajog.2017.05.067 PMID: 28599899

[14] Luke RK, Sharpe JW, Greene RR. *Placenta accreta*: the adherent or invasive placenta. Am J Obstet Gynecol, 1966, 95(5):660–668. https://doi.org/10.1016/s0002-9378(16)34741-x PMID: 5942637

[15] Fitzpatrick KE, Sellers S, Spark P, Kurinczuk JJ, Brocklehurst P, Knight M. The management and outcomes of *placenta accreta*, *increta*, and *percreta* in the UK: a population-based descriptive study. BJOG, 2014, 121(1):62–70; discussion 70–71. https://doi.org/10.1111/1471-0528.12405 PMID: 23924326 PMCID: PMC3906842

[16] Jauniaux E, Bhide A, Burton GJ. Pathophysiology of accreta. In: Silver R (ed). *Placenta accreta* syndrome. 1st edition, CRC Press, 2017, 13–28. https://www.routledge.com/Placenta-Accreta-Syndrome/Silver/p/book/9781498745963#

[17] Parra-Herran C, Djordjevic B. Histopathology of *placenta creta*: chorionic villi intrusion into myometrial vascular spaces and extravillous trophoblast proliferation are frequent and specific findings with implications for diagnosis and pathogenesis. Int J Gynecol Pathol, 2016, 35(6):497–508. https://doi.org/10.1097/PGP.0000000000000250 PMID: 26630223

[18] Khong TY, Robertson WB. *Placenta creta* and *placenta praevia creta*. Placenta, 1987, 8(4):399–409. https://doi.org/10.1016/0143-4004(87)90067-1 PMID: 3684969

[19] Jauniaux E, Hussein AM, Zosmer N, Elbarmelgy RM, Elbarmelgy RA, Shaikh H, Burton GJ. A new methodologic approach for clinico-pathologic correlations in invasive *placenta previa accreta*. Am J Obstet Gynecol, 2020, 222(4):379.e1–379.e11. https://doi.org/10.1016/j.ajog.2019.11.1246 PMID: 31730756

[20] Jauniaux E, Hussein AM, Elbarmelgy RM, Elbarmelgy RA, Burton GJ. Failure of placental detachment in *accreta* placentation is associated with excessive fibrinoid deposition at the utero–placental interface. Am J Obstet Gynecol, 2022, 226(2):243.e1–243.e10. https://doi.org/10.1016/j.ajog.2021.08.026 PMID: 34461077

[21] Dannheim K, Shainker SA, Hecht JL. Hysterectomy for *placenta accreta*; methods for gross and microscopic pathology examination. Arch Gynecol Obstet, 2016, 293(5):951–958. https://doi.org/10.1007/s00404-015-4006-5 PMID: 26758078

[22] Goh W, Yamamoto SY, Thompson KS, Bryant-Greenwood GD. Relaxin, its receptor (RXFP1), and insulin-like peptide 4 expression through gestation and in *placenta accreta*. Reprod Sci, 2013, 20(8):968–980. https://doi.org/10.1177/1933719112472735 PMID: 23302396 PMCID: PMC3713646

[23] Bartels HC, Postle JD, Downey P, Brennan DJ. *Placenta accreta* spectrum: a review of pathology, molecular biology, and biomarkers. Dis Markers, 2018, 2018:1507674. https://doi.org/10.1155/2018/1507674 PMID: 30057649 PMCID: PMC6051104

[24] Zhang J, Li H, Wang F, Qin H, Qin Q. Prenatal diagnosis of abnormal invasive placenta by ultrasound: measurement of highest peak systolic velocity of subplacental blood flow. Ultrasound Med Biol, 2018, 44(8):1672–1678. https://doi.org/10.1016/j.ultrasmedbio.2018.04.004 PMID: 29747968

[25] Wehrum MJ, Buhimschi IA, Salafia C, Thung S, Bahtiyar MO, Werner EF, Campbell KH, Laky C, Sfakianaki AK, Zhao G, Funai EF, Buhimschi CS. *Accreta* complicating complete *placenta previa* is characterized by reduced systemic levels of vascular endothelial growth factor and by epithelial-to-mesenchymal transition of the invasive trophoblast. Am J Obstet Gynecol, 2011, 204(5):411.e1–411.e11. https://doi.org/10.1016/j.ajog.2010.12.027 PMID: 21316642 PMCID: PMC3136625

[26] Okae H, Toh H, Sato T, Hiura H, Takahashi S, Shirane K, Kabayama Y, Suyama M, Sasaki H, Arima T. Derivation of human trophoblast stem cells. Cell Stem Cell, 2018, 22(1):50–63.e6. https://doi.org/10.1016/j.stem.2017.11.004 PMID: 29249463

[27] Meekins WJ, Pijnenborg R, Hanssens M, McFadyen RI, Van Assche FA. Immunohistochemical identification of placental bed biopsies and the implications for the inclusion of specimens when studying the spiral artery response to pregnancy. Hypertens Pregnancy, 1994, 13(1):61–69. https://doi.org/10.3109/10641959409084172 https://www.tandfonline.com/doi/abs/10.3109/10641959409084172
[28] Konoplev SN, Dimashkieh HH, Stanek J. Cytokeratin immunohistochemistry: a procedure for exclusion of pregnancy in chorionic villi-negative specimen. Placenta, 2004, 25(2–3):146–152. https://doi.org/10.1016/S0143-4004(03)00188-7 PMID: 14972447
[29] Roberge S, Demers S, Berghella V, Chaillet N, Moore L, Bujold E. Impact of single- *vs* double-layer closure on adverse outcomes and uterine scar defect: a systematic review and metaanalysis. Am J Obstet Gynecol, 2014, 211(5):453–460. https://doi.org/10.1016/j.ajog.2014.06.014 PMID: 24912096
[30] Mogos MF, Salemi JL, Ashley M, Whiteman VE, Salihu HM. Recent trends in *placenta accreta* in the United States and its impact on maternal–fetal morbidity and healthcare-associated costs, 1998–2011. J Matern Fetal Neonatal Med, 2016, 29(7):1077–1082. https://doi.org/10.3109/14767058.2015.1034103 PMID: 25897639
[31] Jauniaux E, Bhide A. Prenatal ultrasound diagnosis and outcome of *placenta previa accreta* after Cesarean delivery: a systematic review and meta-analysis. Am J Obstet Gynecol, 2017, 217(1):27–36. https://doi.org/10.1016/j.ajog.2017.02.050 PMID: 28268196
[32] Fonseca A, Ayres de Campos D. Maternal morbidity and mortality due to *placenta accreta* spectrum disorders. Best Pract Res Clin Obstet Gynaecol, 2021, 72:84–91. https://doi.org/10.1016/j.bpobgyn.2020.07.011 PMID: 32778495
[33] Bailit JL, Grobman WA, Rice MM, Reddy UM, Wapner RJ, Varner MW, Leveno KJ, Iams JD, Tita ATN, Saade G, Rouse DJ, Blackwell SC; Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Maternal–Fetal Medicine Units (MFMU) Network. Morbidly adherent placenta treatments and outcomes. Obstet Gynecol, 2015, 125(3):683–689. https://doi.org/10.1097/AOG.0000000000000680 PMID: 25730233 PMCID: PMC4347990
[34] Thurn L, Lindqvist PG, Jakobsson M, Colmorn LB, Klungsoyr K, Bjarnadóttir RI, Tapper AM, Børdahl PE, Gottvall K, Petersen KB, Krebs L, Gissler M, Langhoff-Roos J, Källen K. Abnormally invasive placenta – prevalence, risk factors and antenatal suspicion: results from a large population-based pregnancy cohort study in the Nordic countries. BJOG, 2016, 123(8):1348–1355. https://doi.org/10.1111/1471-0528.13547 PMID: 26227006
[35] D'Antonio F, Iacovella C, Bhide A. Prenatal identification of invasive placentation using ultrasound: systematic review and meta-analysis. Ultrasound Obstet Gynecol, 2013, 42(5):509–517. https://doi.org/10.1002/uog.13194 PMID: 23943408
[36] Collins SL, Ashcroft A, Braun T, Calda P, Langhoff-Roos J, Morel O, Stefanovic V, Tutschek B, Chantraine F; European Working Group on Abnormally Invasive Placenta (EW-AIP). Proposal for standardized ultrasound descriptors of abnormally invasive placenta (AIP). Ultrasound Obstet Gynecol, 2016, 47(3):271–275. https://doi.org/10.1002/uog.14952 PMID: 26205041
[37] Hussein AM, Momtaz M, Elsheikhah A, Abdelbar A, Kamel A. The role of ultrasound in prediction of intra-operative blood loss in cases of *placenta accreta* spectrum disorders. Arch Gynecol Obstet, 2020, 302(5):1143–1150. https://doi.org/10.1007/s00404-020-05707-y PMID: 32740869
[38] Jha P, Põder L, Bourgioti C, Bharwani N, Lewis S, Kamath A, Nougaret S, Soyer P, Weston M, Castillo RP, Kido A, Forstner R, Masselli G. Society of Abdominal Radiology (SAR) and European Society of Urogenital Radiology (ESUR) Joint Consensus Statement for MR imaging of *placenta accreta* spectrum disorders. Eur Radiol, 2020, 30(5):2604–2615. https://doi.org/10.1007/s00330-019-06617-7 PMID: 32040730
[39] Jauniaux E, Collins SL, Jurkovic D, Burton GJ. *Accreta* placentation: a systematic review of prenatal ultrasound imaging and grading of villous invasiveness. Am J Obstet Gynecol, 2016, 215(6):712–721. https://doi.org/10.1016/j.ajog.2016.07.044 PMID: 27473003
[40] Pagani G, Cali G, Acharya G, Trisch IT, Palacios-Jaraquemada J, Familiari A, Buca D, Manzoli L, Flacco ME, Fanfani F, Liberati M, Scambia G, D'Antonio F. Diagnostic accuracy of ultrasound in detecting the severity of abnormally invasive placentation: a systematic review and meta-analysis. Acta Obstet Gynecol Scand, 2018, 97(1):25–37. https://doi.org/10.1111/aogs.13238 PMID: 28963728
[41] D'Antonio F, Iacovella C, Palacios-Jaraquemada J, Bruno CH, Manzoli L, Bhide A. Prenatal identification of invasive placentation using magnetic resonance imaging: systematic review and meta-analysis. Ultrasound Obstet Gynecol, 2014, 44(1):8–16. https://doi.org/10.1002/uog.13327 PMID: 24515654
[42] Budorick NE, Figueroa R, Vizcarra M, Shin J. Another look at ultrasound and magnetic resonance imaging for diagnosis of *placenta accreta*. J Matern Fetal Neonatal Med, 2017, 30(20):2422–2427. https://doi.org/10.1080/14767058.2016.1252744 PMID: 27806657
[43] Jung EJ, Cho HJ, Byun JM, Jeong DH, Lee KB, Sung MS, Kim KT, Kim YN. Placental pathologic changes and perinatal outcomes in *placenta previa*. Placenta, 2018, 63:15–20. https://doi.org/10.1016/j.placenta.2017.12.016 PMID: 29486851
[44] Robinson BK, Grobman WA. Effectiveness of timing strategies for delivery of individuals with *placenta previa* and *accreta*. Obstet Gynecol Surv, 2011, 66(1):4–6. https://doi.org/10.1097/OGX.0b013e3182021db5 https://journals.lww.com/obgynsurvey/Abstract/2011/01000/Effectiveness_of_Timing_Strategies_for_Delivery_of.3.aspx
[45] Collins SL, Alemdar B, van Beekhuizen HJ, Bertholdt C, Braun T, Calda P, Delorme P, Duvekot JJ, Gronbeck L, Kayem G, Langhoff-Roos J, Marcellin L, Martinelli P, Morel O, Mhallem M, Morlando M, Noergaard LN, Nonnenmacher A, Pateisky P, Petit P, Rijken MJ, Ropacka-Lesiak M, Schlembach D, Sentilhes L, Stefanovic V, Strindfors G, Tutschek B, Vangen S, Weichert A, Weizsäcker K, Chantraine F; International Society for Abnormally Invasive Placenta (IS-AIP). Evidence-based guidelines for the management of abnormally invasive placenta: recommendations from the International Society for Abnormally Invasive Placenta. Am J Obstet Gynecol, 2019, 220(6):511–526. https://doi.org/10.1016/j.ajog.2019.02.054 PMID: 30849356
[46] Ali H, Chandraharan E. Etiopathogenesis and risk factors for *placental accreta* spectrum disorders. Best Pract Res Clin Obstet Gynaecol, 2021, 72:4–12. https://doi.org/10.1016/j.bpobgyn.2020.07.006 PMID: 32753310
[47] Pegu B, Thiagaraju C, Nayak D, Subbaiah M. *Placenta accreta* spectrum – a catastrophic situation in obstetrics. Obstet Gynecol Sci, 2021, 64(3):239–247. https://doi.org/10.5468/ogs.20345 PMID: 33757280 PMCID: PMC8138076

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