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Catastrophic Morbidly Adherent Posterior Placenta: Case Reports, Literature Review Current Through at Long Time Since Cases Registration

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Abstract

There are analyzed the difficulties and accuracy of diagnosis, in conjunction to the moment technical opportunities at long interval after registration (2009, 2012) in two cases of posterior Morbidly Adherent Placenta/Placenta Accreta Spectrum (MAP/PAS), with deep myometrial invasion (grade 3B) and uterine serosa perforation (grade 3E), a contemporary serious disease generating severe maternal coagulation disorders, multiple organ failure and hemorrhagic shock up to death, after total hemostasis hysterectomy. Undiagnosed or suspicious second trimester posterior MAP/PAS, in low-lying placenta, morbid obesity (BMI>40), in an intact uterus, or in a scar uterus post cesarean delivery (CD) were followed by maternal death. In countries with low-to-middle income/ resources, and few centers of excellence, medical staff surgical qualities, and well trained interdisciplinary team must meet patients' and their families trust and cooperation, and timely available life-saving resources for complex therapies in critical care cases, and hospital infrastructure to benefit from actual expanded knowledge and guidelines.

Keywords: Posterior invasive placenta, Grade 3B (increta), Grade 3E (percreta), Morbid obesity, Cesarean section/delivery, Hemorrhage, Hysterectomy, Maternal death

1. Introduction

Morbidly adherent placenta (MAP) named in the last decade as Placenta. Accreta Spectrum (MAP/PAS) has an arising trend in the last 30-40 years, and it represents a great challenge for medical staff, even for those from excellence centers, mainly when posterior inserted [1]. MAP/PAS is a heterogeneous group of anomalies characterized by abnormal adhesion or invasion of chorionic villi through the myometrium (grade 3B), and uterine serosa (grade 3E), when absent or pathologic decidua basalis in non-scar, and more frequent in scar uterus, generating high financial costs, and maternal health jeopardize, with even life loss, as in two Romanian cases. MAP/PAS can be associated to pregnancy's previous conditions-also frequently actually described: obesity and previous cesarean section/delivery (CS/CD). The cases were registered in two tertiary maternities from Bucharest, capital of a low-to-middle income country and the cases are revised at long time since their registration (2009, 2012), after medical staff knowledge great expand, and after publication of many systematic reviews, meta-analysis, and guidelines, according to the burden of MAP/PAS, and the profound scientific worldwide interest on each pregnant women suffering from MAP/PAS. One analyses the diagnosis difficulties, and accuracy of ultrasound for posterior low-lying placenta with abnormal invasion and penetration, generating maternal death by antepartum severe disseminated intravascular coagulation, and secondary fibrinolysis, with multiple organ failure (Case 1), and by intraperitoneal massive/malignant hemorrhage, with shock, and severe anemia (Case 2), both cases treated with hemostasis hysterectomy. The forensic expertise proved severe comorbidities pregestationally unknown (heart, liver and kidneys) in Case 1. In both cases the new born babies survived, first being large for gestational age and preterm the second. One compares the knowledge and capabilities from the years of records to our days, when the prospective and retrospective clinical trials are trying to offer knowledge to existing gaps in low-lying and invasive posterior placenta, which induced the Romanian catastrophic MAP/PAS evolution, and worldwide medical staff must continue to improve outcomes,

to every case peculiarities. An invasive placenta, independently from its early accurate depiction preserves or increases its invasiveness with advancing gestation, according to its genes and their epigenetics, maternal uterine microenvironement at endometrium-myometrium interface, fetal capabilities to survive hypoxia aggression. Medical staff has actually data clarify on many persistent questions regarding diagnosis difficulties of posterior invasive placenta, and the management may be compared to that from preeclampsia, which is also a placental-vascular pathology, pregnancy termination before term, around 35 -37weeks' gestation, or even earlier 34-35 weeks' gestation without significant increase in neonatal morbidity [2,3], to avoid and/or reduce the amplitude of characteristic MAP/PAS life-threatening complications, with multidisciplinary well trained teams involvement, and to prevent a hysterectomy in almost 80% of cases using a resective–reconstructive technique [4].

2. Case Reports

2.1 Case 1

Maternal death nearly 3 days post hemostasis hysterectomy due to disseminated intravascular coagulation (IDC), triggered antepartum by undiagnosed placenta increta at a patient with morbid obesity (BMI >40, a BMI=41.23, at admission for delivery (height=1.67m, weight=115kg), hepatic, cardiac and renal chronic pathology followed by multiple organ failure. Patient was 30 years old, secundipara, beer consumer and cigarettes smoker, 3 abortions, 2 vaginal deliveries (the first 7 years ago, 3500g weight, Apgar score 10, and the second after a precipitate labor, finished 3 hours before hysterectomy, by delivery of a newborn, weight 4,500g, Apgar score 8, with brachial plexus paralysis, and facial ecchymosis), manual removal of a 800g weight placenta. Obstetrical history reveals 10kg in weight gain in the first 5 months' gestation and the weight of 115kg at term, after weight gaining 35kg along all pregnancy, no registered data as regards the blood pressure values. Laboratory analyses showed bacterial vaginosis–"clue cells" presence and vaginal positive cultures for Chlamydia Trachomatis, and Ureaplasma Hominis, no investigation for diabetus melitus. After delivery, in the labor fourth period, the postpartum hemorrhage that occured induced the treating obstetrician to try correction by 2 uterine curretages, uterotonics and bilateral cervico-vaginal arteries ligatures, intravascular cristaloid solutions administration. After 3 hours from delivery, uncontroled uterine tonus, and intermitent uterine hemorrhage, with hemodinamic instability requiered emergency histerectomy by a team only of obstericians, the duty team at that day. The intrasurgery clinical findings directed to uteroplacental apoplexy diagnosis with IDC, accordingly to the coagulation status at surgery beginning. When histerectomy procedure began, the clotting disorder revealed severe fibrinolysis:fibrinogen-50mg%, platelets-90.000/mmc, D-dimers- high level, and severe anemia-hemoglobin: 5.7g%. Hemotransfusional treatment for anemia and IDC was paralel to surgery, by administration of blood B (III), Rh negative, frosen fresh plasma (ffp), crioprecipitate, and NovoSeven®(INN eptacog alpha activate)-administreted because lack of hemoglobin and fibrinogen values correction. The anesthesiologist managed the hematologic treatment in Intensive Care Unit, were the patient was monitored during all postoperative period. Bleeding persistance through the Douglas drenaige with increasing flow after six hours from hysterectomy, induced a second laparotomy, confirming the continuing coagulation disorders- fibrinolysis, with no active source of hemorrhage, and necessity of Mikulicz pelvic swab. Patient's evolution was progressively deteriorating, under continuous medication for correction of anemia and hypofibrinogenemia (62 blood units, NovoSeven®70 viaIs), being depicted an acute kidney failure, requiring hemodyalysis in the third postoperative day, and patient died with irreversible cardiopulmonary arrest in this third postoperative day. The case was sent to "Mina Minovici" NationaI Forensic Institute, as Romanian legislation imposes. A turning point is that there are medical documents at "Mina Minovici" NationaI Forensic Institute, not included in the hospital file, and subsequently not available. The mentioned records reveal that at 22 weeks' gestation, the ultrasound assessment shows a low lying placenta. Even more, verification of placenta location at 34 weeks' gestation highlights the location of the placental edge to 15mm from internal cervical ostium (ICO), on posterior uterine wall. The forensic expertise depicted subepicardic lipomatosis continued to intramyocardic focal lipomatosis, considered a characteristic of beer consumers, as Virchow described many years ago, a sign of alchool induced liver pathology; recent thrombi in coronary vessels; recent intravascular thrombi in dilated kidneys'vessels of medularis and glomerularis structures, generating the conclusion of an acute infarct with ischemic tubulopathy, over an old chronic pielonephritis. Regarding the uterus the forensic pathologist described placenta increta, with intramyometrial trophoblast cells, having the characteristics of the third trimester pregnancy, and hemorrhages and intravascular decidual remnants, that were considered the source of antenatal intravascular disseminated coagulation.The microscopy confirmed a term placenta with signs of acutizated chronic hypoxia, with small villi, some with necrobiosis, or with placental infarcts. The pathologist described intervilosity fibrinoid on the examinated samples, abundant extravillous trophoblastic piles, important fibrinoid piles. The pathologist emphasizes that some recorded changes may be artefacts because of multiple uterine maneuvers (placental manual extraction, uterine curretages). Umbilical cord contained two arteries and one vein dilated by a large thrombus.

2.2 Case 2

Maternal death at 28 weeks' gestation, by irreversible cardiac arrest and maternal shock, at the end of hysterectomy imposed by a percerta posterior / lateral placenta, in a scar uterus from cesarean delivery (CD), with intraperitoneal massive hemorrhage from acute, torrential blood loss/ As regards patient's history: 33 years old, Caucasian, married, house-keeper, medium level of education, 1 cesarean CD in1999 for a negative trial of labor (a male fetus 4,400g weight, Apgar score=9; myometrial double layers suture, and peritoneal cover of uterine suture, with normal postoperative evolution), 3 abortions in first trimester after CD; pregnancy high risk registration from the first visit at 9-10 weeks' gestation, when the gynecologist who performed previous abortions refused a new one (fact hidden by patient, and

reason to demand medical assistance at the hospital where the first CD was done), bi-test with low risk. Bi-test was associated to echography to identify the correct pregnancy location, amid a non cesarean scar pregnancy, at 12 weeks'gestation. Laboratory analyses for hematology and biochemistry were normal. TTGO negative at 26 weeks' gestation. Repeated ultrasound examinations (by an obstetrician with high training in maternal-fetal medicine) at 20 weeks' gestation depicted a low-lying placenta, on anterior uterine wall, above the left side of the CD scar area, without signs of it's invasion (interruption of the posterior bladder wall-uterine interface, absence of retroplacental clear zone, and placental lacunae), and at 26 weeks' gestation it was visualized an increased vascularity on left uterine wall, at level of uterine artery at color Doppler evaluation, when patient was informed about her pregnancy high risk, and about a planned preterm second cesarean section. Regarding the fetus the sonography revealed normal morphology and growth, normal umbilical artery Doppler. At 28 weeks' gestation, after nearly 24 hours of low abdominal progressive in intensity pains, uncontrolled by usual antispastic medication, and after a strong abdominal pain with home lypothimia at 7.00 am on the 5th May 2012, the patient comes to hospital, at 9,10 am being admitted semiconscious, extremely pale, in haemodynamic instability (blood pressure=70/30mmHg, AV=120b/min, 24 breaths/min), abdominal over-distension, with organs difficult identification. Emergency ultrasound revealed an alive fetus, 170 beats/min, and intraperitoneal massive amount of blood, and images of low-lying placenta on anterior wall, lateral to previous CD scar, widened to left lateral and to posterior uterine walls, with placenta lacunae or retroplacentar hematoma suspicion. Ultrasound assessment was simultaneously with blood collection for analysis, and intravenous solutions administration-per 2 catheters (peripheral and central). The emergency surgery confirmed intraperitoneal red blood- fresh-fluid, and clots (3000 ml in aspiration collection recipient), anterior uterine wall being bluish-purple to pale colored, no adherence, no CD scar dehiscence or blood loss, with placental bulge on the uterine left side, and a 5-6 cm, anfractuous, irregular rupture on posterior wall, near left large ligament insertion, with an active "malignant" bleeding, as Arakaza A, et al, 2023 [5], or "torrential" hemorrhage as Palacios-Jaraquemada JM, D'Antonio F. 2021 [6] named this massive uterine bleeding. After a transverse low hysterotomy, and extraction from head presentation of an alive girl 1,000g weight, Apgar score: 4/1', 5/5', 6/10', one found placenta inserted anterior-above the previous CD scar, lateral and posterior uterine walls, over a large area, with uterine lateral wall myometrial invasion, and complete penetration in posterior wall and serosa. It was decided hemostasis total hysterectomy, done without surgical incidents, but with patient's status continuously altering, with hemodynamic deterioration, and during abdominal wall closure, at 50 minutes from surgery start, one registers cardiopulmonary arrest, irreversible at all resuscitation maneuvers.The macroscopic evaluation of the surgical specimen performed in the operating room, and at the end of the surgery confirmed the diagnosis of MAP/PAS grade 3 E by use of the diagnostic criteria for MAP/PAS endorsed by the International Federation of Gynecology and Obstetrics (FIGO) [7]. Deep invasion of the placenta with penetration through the serosa (placenta percreta), without any other section of uterine wall, as pathologists require for an optimum gross pathologic exam [8].

3. Discussion

3.1Romanian MAP/PAS Cases' Place in the last 30-40 Years Contemporary World

The last 30-40 years of modern obstetrics worldwide are shadowed every day by ascendant trend in the MAP/PAS prevalence, affecting 1 in 500 pregnancy in a twenty years analysis from year 2005 [9]. Rate that is markedly higher compared with the rate from 1980, with differences between developed and developing countries, and from country to country, as UK national case-control study [10], and New South Wales population-based record on births in Australia, between 2003 and 2012 has remarked [11]. The Australian population-based record on births has shown that the overall rate of abnormally invasive placenta was 24.8 per 10 000 deliveries, and 22.7 per 10 000 among primiparae, and the incidence increased by 30%, from 20.6 to 26.9 per 10 000, over the 10-year study period.

The meta-analysis and systematic review of Jauniaux E, et al. [12] presents a prevalence of over 60% for placenta accreta, 15% increta, and 20% percreta, with data from developed countries, being appreciated the insufficient data from medium-and low-income countries, as Romania when the reported cases were registered. When Romanian cases where recorded, the antenatal diagnosis was more frequent than intrapartum/postpartum diagnosed (62/47), as presented the study of University of California, San Diego Medical Center from January 1990 to April 2008 [2]. A retrospective analysis over 10 years (February 2006 to January 2016) at Flinders Medical Centre (FMC), South Australia [13] regarding multidisciplinary management revealed 64 MAP/PAS cases with an overall incidence of 2.3 per 1000 deliveries; 56 women were antenatally diagnosed, and all 64 cases were confirmed to be invasive at delivery; 28 accreta (superficial) and 32 increta/percreta (deep) cases The four cases with no invasion at delivery were suspected antenatally to have MAP/PAS.

As a national register for MAP/PAS disorders is lacking in Romania, a team of Stănculescu RV, et al. in 2022 [14] was involved in a systematic approach for cases with MAP/PAS encountered in physicians working hospitals during 2018-2021, by collecting data from three tertiary maternities from Bucharest, covering 32,540 deliveries.The statistical analysis showed: 12,372 (38.1%) spontaneous deliveries by vaginal route, and 20,168 (61.9%) by cesarean section; placenta praevia incidence was 1.81%, of which 32.7% pertains to cases with history of scars from CD, and 1.09‰ of CD were associated to MAP/PAS disorders. Hysterectomy without placenta inside the uterus was in 1.69‰ cases requiring emergency from all deliveries, and the pathologist confirmed MAP/PAS disorders in 32.72% cases.

One knows since long time, the high risks for maternal morbidity and mortality when placenta percreta, such as hysterectomy after vaginal spontaneous birth (very rare today when antenatal MAP/PAS diagnosis), during cesarean delivery, delayed hysterectomy, transfusion of ≥10 U of packed red blood cells for massive

hemorrhage, septic shock, acute kidney injury, cardiovascular failure, injury to neighboring structures, maternal transfer to intensive care, or even death, as a French retrospective study [15] is emphasizing, despite multidisciplinary planning, management in a referral center, and better antenatal confirmation of suspicion. The French study showed a composite maternal morbidity rate significantly much higher in the percreta than the accreta group (86.3% [44/51] vs 28/105 [26.7%], P < .001), and the secondary analysis restricted to cases with an abnormally invasive placentation diameter >6 cm showed similar results [86.0% (43/50) vs 48.7% [(19/38), P < .01]. The rate of hysterectomy during CD was significantly higher in the percreta than the accreta group [52.9% (27/51) vs 20.9% (22/105), P < .01], as was the total hysterectomy rate [84.3% (43/51) vs 23.8% (25/105), P < .01], and no maternal death. One may add the Australian remarks that deep invasion is significantly associated with increased bleeding, intensive care unit admission, surgical complications and an extended postpartum stay [13].

Maternal mortality rate has been reported to be 7% at the severe end of the spectrum, many years ago [16], reduced to 0.25% (USA analysis in 2021 for 2015-2017) [17], in high-income countries with an abundance of experienced surgeons, and readily available life-saving resources. In resource-limited settings it is likely that women with MAP/PAS have a much greater risk of death, although the exact comparative figure remains unknown, due to technical, logistic, and resourcing inadequacies, as one speaks in 2022 [18]. The report of Aryananda RA, et al. 2023[19] on 29 cases recorded in 2019 from poor-resources-settings [Columbia 2 cases, Indonesia 27 cases, with demographics: age 34 years (between 27–42) and obstetrical history approximately similar to Romanian cases] included in four groups of previously undiagnosed AIP [according to the initial type of management: (1) no cesarean delivery; (2) placenta left in situ after cesarean delivery; (3) partial removal of the placenta after cesarean delivery; and (4) post-cesarean hysterectomy] compared to the outcomes of women in hospitals that used the support of the placenta accreta spectrum center (telehelp) during the initial surgery revealed five maternal deaths (14%) in the group that did not receive telehelp, and 4 women died of irreversible shock because of uncontrolled bleeding different to cases predelivery diagnosed. The Romanian cases were treated in tertiary maternities; Bucharest has no excellence center special for MAP/PAS.

In front of rising rates of CD since 1996, reaching 32.9% in USA in 2009, followed by annual increased rates of placenta previa, placenta accreta, and maternal mortality, a team from the Department of Obstetrics, Gynecology, and Reproductive Sciences, of the University of California, San Francisco, CA, USA [20] estimated future annual incidence of placenta praevia, placenta accreta and maternal mortality using data of national birthing order trends, and cesarean and vaginal birth after cesarean rates. Using TreeAge Pro software the team predicted that if primary and secondary cesarean rates continue to rise as it was in the years around their analysis, by 2020 the cesarean delivery rate will be 56.2%, and there will be an additional 6236 placenta previa, 4504 placenta accreta, and 130 maternal deaths annually, and the rise in these complications will lag behind the rise in cesareans by approximately 6 years. Connected to these estimations for USA, Matsuzaki S, et al. 2021[17] have shown the raising trend of MAP/PAS to 2.1% every three months from October 2015 to December 2017: 8030 cases (0.29%) out of 2,727,477 births (placenta accreta (n=6205, 0.23%), placenta percreta (n=1060, 0.04%), and placenta increta (n=765, 0.03%)). MAP/PAS increasing prevalence is associated to high increasing CD's rate, being reported to range from 6% to 27,2%: for Europe CD's rate being 25% during 1990-2014 [21], interval including the Romanian cases report (2009; 2012). Eurostat (in Europe) has shown that Romania had the second high CD's rate (44.1%), after Cyprus (54.8 %), and Findland the lowest (16.5%) in 2017, with a Romanian reduction (-4.24%) in 2020 [22].

CD's association to placenta praevia is the most important risk factor in the cohort study from the Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden) [23], and in scar uterus (CD, hysteroscopy, septum and endometrial ablation) is recommended to be vigilant for placenta accreta suspicion, and depiction [24]. In many countries these unfavorable factors are associated to high rate in assisted reproductive technology (ART) [25] followed by MAP/PAS in obtained pregnancies. When using ART, one considers beside possible scars, there are microscopic endometrial defects from adenomyosis, submucous fibroids, or bicornuate uterus that affects the normal biological functions of the endometrium and thus allow abnormal placenta attachment [26,27]. One may consider that repeated abortions with cervical dilation, and uterine curettage (3 in each Romanian case) is an explanation for pathogenesis of MAP/PAS, with unknown recurrence of basal plate myofibers, with further development of an abnormally adherent and invasive placenta [28]. The Nordic countries cohort study on three years records, on 205 cases of AIP representing 3.4 per 10 000 deliveries [23]. 70% of all cases were not diagnosed antepartum, 39% had prior CD, and 33% had placenta praevia; the AIP risks increased seven-fold after one prior CD (as it was the second Romanian case) to 56-fold after 3 or more CD.

3.2 Low-lying Posterior Placenta Increta and Percreta/ Abnormal Spiral and Arcuate Uterine Vessels Remodeling, Intraplacental Hypervascularisation

The deficiency or the absence of decidua at the uterine interface between normal decidualized endometrium, and myometrial layers permits an abnormal anchoring of placental villous and extravillous trophoblasts (EVT), and the chameleonic cytotrophoblast cells as Bischof P, et al. 2005 [29] named them, are suffering epithelial-to-mesenchymal transition [30] or are developing transcriptomics, that can be depicted by microRNA [31,32]. The EVTs pathological changes were initially hypothetized by Tantbirojn P, et al. [33] and later by different scenarios of Illsley NP, et al., Park JY, et al. [34,35]. Recently it was proposed "pregnancy-specific beta-1-glycoprotein 6" as a novel biomarker present in the placenta genes changes in cases with abnormal adherence, invasiveness and penetration [36], earlier literature mentioning the complex gene families regulating maternal-fetal

interactions by pregnancy-specific glycoproteins [37] and their different actions in preeclampsia(PE), intrauterine fetal growth restriction(IUFGR) and MAP/PAS [38], and after the demonstration of trophoblast cell clusters in maternal circulation [39].

MAP/PAS and PE, IUFGR have different patterns of vascular changes/remodeling in their pathogenesis: large surface and hypervascularisation in placenta MAP/PAS vs small and low vascular net-work in PE, IUFGR placenta. Transcriptomics developed by EVTs' increase these cells capacity to deeply invade the myometrium, and to induce abnormal spiral and arcuate uterine vessels remodeling, transforming them in turbulent vessels from placental lacunae, with low-velocity lacunar blood flow sometimes, and to develop neovascularization limited to the basal layer (placenta increta) or to affect the entire remaining placental parenchyma (placenta percreta). These vascular changes induce an image of multiple linear irregular vascular spaces within the placenta, intraplacental vascularization with tortuous confluent vessels across the entire placental width, which are detected only on 3D power Doppler ultrasound, and magnetic resonance imaging (MRI) in cases of placenta percreta [40,41], as c, d images of Figure 1 show

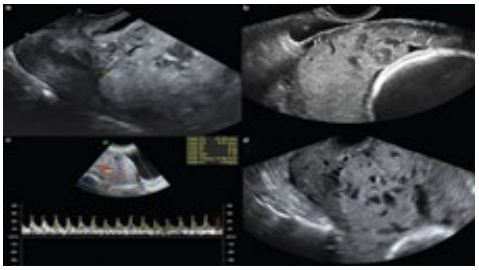

Figure 1: Signs in sonographic diagnostic criteria for morbidly adherent placenta, using Gray-scale and color Doppler images. (a) Clear space: loss/irregularity of echolucent area located between uterus and placenta (arrows). (b) Bladder line: thinning or interruption of hyperechoic interface between uterine serosa and bladder wall (arrows). (c,d) Placental lacunae with turbulent high-velocity flow (Adopted from Calì G et al. 2013[40]).

The dialog between maternal uterine wall, in fact between endometrial myometrial interface and implanting embryo is physiologic and mandatory for a normal pregnancy progression [42-44] and it may suffer many disturbances from prepregnancy, early and possible in late pregnancy.

In the description of the revisited Romanian Case 1 with PAS, it was a low-lying placenta (revealed at mid pregnancy' s sonography), proving that maternal uterine wall jeopardize could be from metabolic disorders induced by prepregnancy morbid obesity, and Chlamydia trachomatis plus Ureaplasma hominis acute undiagnosed and untreated cervicitis and endometritis, previous 3 uterine curettages for abortion. In the second case it was a 3 years previous cesarean delivery at 5-6 cm dilation, after a negative trial of labor, with double myometrial layers suture and peritoneal cover–proved in a Japan study to be without post CD interference to uterine wall healing [45], 3 uterine curettages for abortion after CD, and low-lying placenta above, and lateral to left side of the CD scar, as emergency surgery confirmed.

One may suppose that in both cases the eggs were opportunistic implanted in an area of reduced uterine wall capacities to defense/barrier to its trophoblast invasiveness, as it is the lower part of uterine corpus, which physiologic fraility (absence of protective Nitabuch fibrinoid layer)-is metabolically increased in obesity by increased duration of hypoxia- a physiologic characteristic only for early pregnancy [46], hypoxia becoming an inducer of cytotrophoblast cells autophagy and increased invasiveness [47]. Morbid obesity can increase the inflammatory potential of mentioned vaginal infections, the level of endothelial factors and receptors (as vascular endothelial growth factor (VEGF) and soluble fms-like tyrosine kinase-1(sFlt-1), considered with diagnostic value for placenta praevia without signs or pernicious (pernicious placenta praevia) and placenta accreta/increta), much analyzed when are suspicions on abnormal spiral and arcuate uterine vessels remodeling, and intraplacental hypervascularisation, associated to trophoblast invasiveness in increta placentation, in the three factors "proliferation, angiogenesis, and inflammation/invasion" similar to cancer's cells [48].

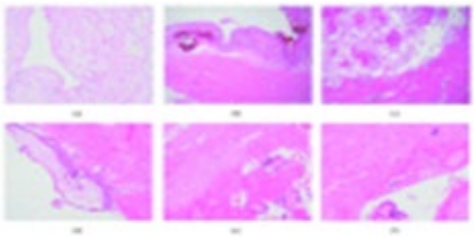

Figure 2: Histopathology of PAS. (a) High-power picture of decidualised endometrium as a result of pregnancy. Stromal cells are large, pale, and polygonal. (b) Low-power image of decidualised endometrium on the surface with underlying congested myometrial blood vessels and myometrium. (c) Low-power image of PAS showing chorionic villi in direct contact with myometrium (no intervening decidua). (d) Chorionic villus with polar trophoblast invading myometrial muscle. (e) Non-adherent area of the same placenta where decidua is seen between villi (bottom right) and myometrium (top left). (f) PAS-chorionic villi in direct contact with muscle; a multinucleated extravillous trophoblast is seen in the top right. Adopted from Bartels HC, et al. 2018 [48], an open access article distributed under the Creative Commons Attribution License,

It was registered a large and thick placenta, 800g weight in Case 1, covering a large uterine surface, with a rich endometrial-myometrial interface vascular net-work, profoundly changed in invasive MAP/PAS as previously mentioned.

Placental mass was prenatal diagnosed to be low-lying on posterior wall in both cases, and the thick myometrium offered for the first case more resistance to trophoblast invasiveness, pregnancy progressing up to term, and not for the second case. The unanticipated intractable postpartum hemorrhage after vaginal birth, with manual placental removal, not spontaneous placental separation (missing file's records on reasons for this procedure,

its risks of massive obstetric hemorrhage being well known to appear during/immediately after it, when one describes placenta increta [41], as the Romanian obstetricians had to correct), and after repeated uterine curettages, maneuvers which were more jeopardizing than curing, by accentuating the non-diagnosed antepartum disseminated intravascular coagulation, favored by early pregnancy fibrinoid deposition at the utero-placental interface with progressive distortion of the above cotyledonary architecture as Jauniaux E, et al described [49], and one can explain the progression to catastrophic end. The administration of utero-tonics is considered only in antenatal known abnormal invasive placenta, when the placenta has been mostly or even completely removed, or major bleeding has already occurred, and one desires a conservative management, possible only with well trained teams– obstetricians, anesthesiologists, pathologists, radiologists able to action immediately, when a severe incident may appear [25]. All these pathological changes have driven to hemostasis hysterectomy followed by multiple organ failure on the basis of organ chronic disorders, and unfortunately maternal death, being a continuum from severe maternal morbidity to maternal mortality as literature mentions in recent years [50-52].

Previous CD may be considered in the second Romanian case as the trigger for posterior low-lying placenta, according to the study on vaginal ultrasound in cases with CD vs non CD, assessed in London, at Imperial College Obstetrics and Gynecology [53] which depicted that implantation in early pregnancy (6-11 weeks' gestation) is most frequently posterior (53%) in the CD cases versus fundal in the non-CD cases (42%), and more than this fact, the gestation sac implantation was 8.7 mm lower in the CD group (95% CI 6.7-10.7, $P < 0.0001$).

3.3 Transabdominal and Transvaginal Ultrasonography Diagnosis of Posterior MAP/PAS

Pregnancy was catastrophic ended at 28 weeks' gestation in the second Romanian case from placenta complete penetration of posterior uterine wall, with uterine dissection, and serosa rupture generating malignant bleeding [5], and torrential hemorrhage [6], inducing maternal shock, and death.

We were and are sure that the prenatal ultrasound are primarily to make detection and risk stratification for MAP/PAS invasion grade, by transabdominal (with a 4.0–6.0-MHz curved transducer) and transvaginal (with a 5.0–7.0-MHz transducer-transvaginal imaging optimizes resolution and allows a detailed assessment of the lower uterine segment, posterior bladder wall, and cervix) routes of examination, and different types- 2D (grey sclae)/3D ultrasound color and power/pulsed Doppler, based on a standardized assessment for each case at risk, being considered that irrespective of the imaging modality, the sonography accuracy depends on operator's experience, which sometimes is limited by the rarity of the condition [54], a statement working in Case 1, but in Case 2, the obstetrician involved in sonography had a good training, depicting an abnormal vascular pattern. The systematic review and meta-analysis of prenatal ultrasound diagnosis and outcome of placenta accreta found no data on the ultrasound screening of placenta accreta at the routine midtrimester ultrasound examination from the nonexpert ultrasound units [55], The capacity of a software associated to ultrasound machines, and their work system (2D/3D) is very important, all new data are presenting their value in abnormaI placenta invasiveness detection. One presents some challenging imaging conditions as elevated body mass index (BMI) or posterior placentation, that may impede the sonographic detection of MAP/PAS markers, as many recent papers presents [56, 57]. One must recognize that advances in prenatal imaging have led to an increase in the detection rate of MAP/PAS, and so to improve the surgical and maternal outcome, and making possible to stratify the risk of adverse surgical outcome by the sonographic stages in the second/third trimester (MAP/PAS 0 to MAP/PAS 3 disorder, which are listed in Table 1) [58-60]. One must add the recommendation of Delphi consensus expert panel "Modified Delphi study of ultrasound signs associated with placenta accreta spectrum" (2023, April) [61] to assess the cervix beside lower uterine zone for CD scar appearance, and central placenta praevia, or for intracervical lakes as sonographic marker of MAP/PAS disorder similar to placenta lacunae from increta or percreta placentae [62] in patients with placenta praevia or low lying placenta. In the Delphi third round, the panelists reached a consensus that 7 of the 11 conventional signs of MAP/PAS should be included in the examination of high-risk patients, and in the routine mid-gestation scan report (Table 1).

Classical signs of MAP/PAS disorder for stratification on third-trimester (adapted from Collins SL, et al. 2016; Calí G, et al. 2019 [58.60])	Ultrasound conventional signs of MAP/PAS (adopted at Delphi consensus expert panel, April 2023 [61]).
MAP/PAS 0: presence of placenta previa with no ultrasound signs of invasion or placenta previa with placental lacunae but no evidence of abnormal uterine–bladder interface (loss of the clear zone and/or bladder wall interruption); **MAP/PAS 1:** presence of at least two of the next ultrasound signs: placental lacunae, loss of the clear anechoic zone of the myometrium or bladder-wall interruption ; **MAP/PAS 2:** MAP/PAS 1 plus uterovesical hypervascularity; **MAP/PAS 3:** MAP/PAS1 or MAP/PAS2 plus evidence of increased vascularity in the inferior part of the lower uterine segment extending into the parametrial region.	(1) loss of the "clear zone' (2) myometrial thinning (3) bladder-wall interruption (4) placental bulge (5)utero-vesical hypervascularity (6) placental lacunae and (7) bridging vessels.
The EW-AIP established a list of 11 PAS ultrasound markers (6 in 2D gray scale, 4 in 2D color Doppler, and 1 in 3D power Doppler).	

Table 1: Ultrasound classical signs for MAP/PAS stratificationon second/third-trimester (2016-2019) and conventional signs of MAP/PAS adopted at Delphi consensus expert panel (April 2023).

The experts participating at the third Delphi consensus expert panel were also asked to determine which MAP/PAS signs should be quantified, and consensus was reached only for the quantification of placental lacunae presence of turbulent placental lacunae with high-velocity flow (>15 cm/s).which are easier and better depicted by 3D power Doppler [41] (see Figure 1), using an existing score. For predicting surgical outcome in patients with a high probability of MAP/PAS at delivery, a consensus was obtained for loss of the clear zone, bladder-wall interruption, presence of placental lacunae and presence of placenta praevia involving the cervix.

Associated to that 7 signs adopted at Delphi consensus expert panel (2023) [61] it is an index, named Tovbin index [63], to predict MAP in cases with at least one previous CD, which assigned with 0, 1 or 2 points the next parameters: cesarean section number, the ultrasound changes in placenta structure (lacune- number, and; maximal size: ≤ or ≥ 2 cm, obliteration of utero-placenta demarcation; placenta location-anterior, praevia color Dopper flow in lacune, hypervascularity of placenta-bladder and/or uteroplacenta interface). The authors repeated the scan at every 2-3 weeks. The highest score for MAP probabiIity was 8-12 points, and these cases were referred to the highest level of muItidisciplinary teams, for CD around 36 weeks' gestation. Receiver-operating-characteristics curve (AUC) using the number of placenta lacune and obliteration of utero-placenta demarcation yielded an area under curve of 0.94 (95%,CI:0.86-1.09). A recent Mexican study [64] showed thatTovbin index as an ultrasonographic prenatal diagnosis of placenta accreta has a statistically significant association (p:0.04) with histopathology diagnosis.

When pregnancy was registered in Case 2, the appreciated high risk was induced by the previous CD; first trimester transvaginal sonography (2D gray-scale) was associated to bi-test, at 12 weeks'gestation (a low risk first trimester aneuploidy being revealed, aspect considered associated to low risk placenta accreta [65], but controverted [48]), and the check of the relationship between the gestational sac position, and the prior CD scar, showed presence of the gestational sac above it, so excluding cesarean scar pregnancy (CSP). Literature presents three sonographic markers for first-trimester (5-7 weeks' gestation) depiction of a CSP, which is an indication for termination being considered an initial phase, or a MAP precursor, through their common histology [66]. The reported markers are: (1) cross over sign (COS) by Calí G, et al. [67] (see Figure 3); (2) implantation of the gestational sac on the scar vs in the niche of the CD by Kaelin Agten A, et al. [68], and (3) position of the center of the gestational sac below vs above the midline of the uterus (i.e. the longitudinal line between the external cervical os and the fundus), by Timor-Tritsch IE, et al. [69] were analyzed in mentioned studies, and by the systematic review and meta-analysis of D'Antonio F, et al. 2018 [70] for their prediction of MAP/PAS in third trimester (Figures 3-5) .

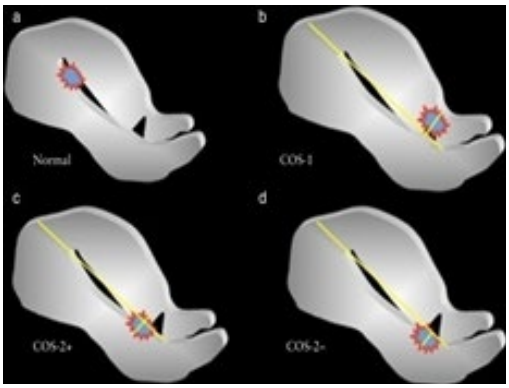

Figure 3: Diagrammatic representation of relationship between ectopic gestational sac, Cesarean scar (CS) and anterior uterine wall, defined as "crossover sign (COS)' in MAP. In sagittal view of uterus, a straight line is drawn connecting internal cervical os and uterine fundus through endometrium (endometrial line; long yellow line). Gestational sac is identified and superior–inferior (S–I) diameter perpendicular to endometrial line is traced (short yellow line). Pregnancies can be divided into groups according to relationship between endometrial line and S–I diameter of gestational sac: (a) normal pregnancy, gestational sac implanted away from CS, in close proximity to uterine fundus; (b) COS-1, gestational sac implanted within previous CS, and at least two thirds of S–I diameter of gestational sac is above endometrial line, towards anterior uterine wall; (c) COS-2+, gestational sac implanted within previous CS, and less than two thirds of S–I diameter of gestational sac is above endometrial line; and (d) COS-2–, gestational sac implanted within previous CS, and less than two thirds of S–I diameter of gestational sac is above endometrial line but there is no intersection between S–I diameter of ectopic sac and endometrial line.(Adopted from Calí G, et al. 2017 [67]).

The differentials between normal pregnancy location or IUP (intrauterine pregnancy, as the authors named it) in a scar uterus and CSP is very important; accordingly Timor-Tritsch IE, et al. 2016 [69] emphasized that location of the center of the gestational sac relative to the midpoint axis of the uterus can be used as an easy method for sonographic differentiation of IUP and CSP between 5-10 weeks of gestation.

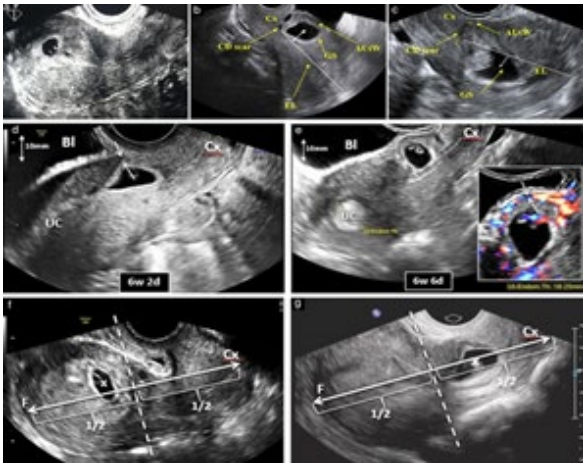

Figure 4: Evaluation of site of implantation of pregnancy following previous CD, based on three suggested sonographic markers (a–c) Ultrasound images showing different types of crossover sign (COS): (a) normal pregnancy, (b) COS-1, (c) COS-2. (d,e). Ultrasound images showing pregnancy implanted on top of well-healed Cesarean section scar (on-the-scar) (d) and into deficient or dehiscent Cesarean section scar (in-the-niche) (e). (f,g) Sagittal consecutive ultrasound images showing implantation of center of gestational sac (X) above (f) and below (g) midpoint of uterus along longitudinal line connecting external cervical os and fundus (F).AUtW, anterior uterine wall (Legend: Bl, bladder; Cx, cervix; EL, endometrial line; GS, gestational sac; UC, uterine cavity) (Adopted from Calí G, et al. 2020 [71]).

Diagnosis of COS-1, implantation of the gestational sac in the niche of the prior Cesarean scar and location of the sac below the uterine midline on first-trimester ultrasound should raise suspicion of a higher risk of severe MAP/PAS in the third trimester, and adverse surgical outcome, by using logistic regression analysis and area under the receiver-operating-characteristics curve (AUC) to analyze the data. The mentioned meta-analysis [70] included seven studies, involving 551 pregnancies before 11 weeks' gestation at high risk of AIP, and at least one ultrasound sign suggestive of AIP was detected in 91.4% (95% CI, 85.8-95.7%) of cases with confirmed AIP at histopathology.

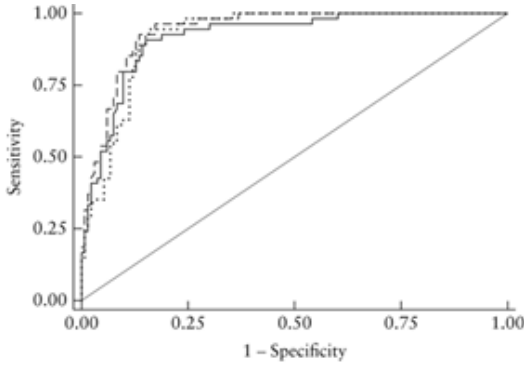

Figure 5: Value of first trimester ultrasound in prediction for third-trimester sonographic stage of placenta accreta spectrum disorder and surgical outcome. Receiver -operating-characteristics curves showing diagnostic performance of first-trimester diagnosis of crossover sign Type1 ( ), implantation of gestational sac in niche of prior Cesarean scar ( ) and location of center of gestational sac below uterine midline ( ) for prediction of placenta accreta spectrum disorder Stage 3 on third-trimester ultrasound in women with placenta previa. (Adopted from Calí G, et al. 2020 [71]).

The meta-analysis also showed that pregnancies with a gestational sac low implantation had a significantly higher risk of AIP [odds ratio, 19.6 (95% CI, 6.7-57.3)], with a sensitivity and specificity of 44.4% (95% CI, 21.5-69.2%) and 93.4% (95% CI, 90.5-95.7%), respectively. The authors concluded that although its individual predictive accuracy was not high, one must have in mind the knowledge on trophoblastic tissue that may start early in pregnancy, thus being theoretically detectable during the first-trimester scan, as an earlier systematic review and meta-analysis mentioned [72]. There were some other details such as anechoic spaces within the placental mass (lacunae) that were observed in 46.0% (95% CI, 10.9-83.7%) and a reduced myometrial thickness in 66.8% (95% CI, 45.2-85.2%) of cases affected by AIP, but these details are working for anterior implantation.

The Special Report of the Society for Maternal-Fetal Medicine Placenta Accreta Spectrum Ultrasound Marker Task Force [56] emphasizes that the prevalence and type of markers of PAS in the first trimester vary between the early first trimester of pregnancy (6–9 weeks' gestation) and the later first trimester of pregnancy (11–14 weeks' gestation) as Jauniaux E, et al. 2016 [73] were sustaining.

Usually one appreciates that 18 to 24 weeks' gestation are optimal for MAP/PAS ultrasound assessment, as the diagnosis of MAP/PAS can be confirmed or excluded up to 90% of cases [10,23], existing very limited evidences regarding the schedule for ultrasound examination among cases without specific risk factors [74], fact that was not the Romanian cases' status.

The Romanian interest for posterior placenta increta and percreta sonography on vascular architecture at placental-maternal interface, and the signs of "placental lacunae", plus "subplacental hypervascularity" is sustained by two papers of Belgian authors [75,76]. The first study from the Centre HospitalierUniversitaire, Hôpital la Citadelle, Liège, used computer-assisted image analysis of whole-slide CD31 immunolabeled sections for comparison of the vessel numbers and cross-section area density and spatial and area distributions in 13 placenta-increta placental beds versus 9 normal placental beds. Their results have shown that the total areas occupied by vessels in normal and placenta-increta placental beds were comparable, but vessels were significantly sparser and larger in the latter, plus in placenta increta the distributions (area and distance from the placental-myometrial junction) were more heterogeneous.

The second one is a retrospective cohort study case series of placenta percreta between January 1, 2002, and March 31, 2017, in a single-center (Saint Luc University Hospital, Brussels, Belgium) (19 pregnancies) vs a control groupof case series of non-accreta placenta previa. The study had shown that the most common sonographic signs in the study group were loss of the clear zone (14/17;82%), placental lacunae (17/17; 100%), and subplacental hypervascularity (11/14; 79%).

On the basis of experience obtained in the technique for 3D ultrasound measurement of placental volume [77], a previous study to the third Delphi consensus expert panel of Collins SL, et al. [54], evaluated the largest area of confluent 3D-power Doppler signal (Area of Confluence [Acon], cm), at the uteroplacental interface in cases of AIP (42 cases, 39 confirmed histo-pathologically).and in a control group (45 cases) with no abnormally invasive placenta.The obtained receiver operating characteristic curves were plotted for prediction of AIP, and AIP requiring cesarean hysterectomy. It was revealed a greater Acon for AIP [44.2 (31.4-61.7) cm] versus women in the control group [4.5 cm (2.9-6.6), P<.001], and even greater in the 36 cases requiring hysterectomy [46.6 cm (37.2-72.6), P<.001]. Acon rose with histopathologic diagnosis: focal accreta (32.2 cm (17.2-57.3), accreta [59.6 cm (40.1-89.9)], and percreta percreta [46.6 cm (37.5-71.5); P<.001 analysis of variance for linear trend. The receiver operating characteristic curves used for prediction of AIP revealed an Acon of 12.4 cm or greater, to have a 100% sensitivity (95% CI: 91.6-100) could be obtained with 92% specificity (95% CI: 79.6-97.6); area under the curve was 0.99 (95% CI: 0.94-1.0). For prediction of AIP requiring hysterectomy, 100% sensitivity (95% CI 90.3-100) can be obtained with an Acon of 17.4 cm or greater with 87% specificity [95% CI: 79.6-97.6); area under the curve was 0.99 (95% CI: 0.94-1.0)].

Prenatal diagnosis of MAP/PAS was and continues to be crucial, at 20 weeks'gestation, a moment very important for sonography diagnosis, the data in Case 2 did not detailed more signs for posterior MAP, as recent literature confirms [57]. This is fundamental, as accurate knowledge of specific risk factors for posterior MAP/PAS would allow the identification of a subset of women who should be referred for detailed imaging assessment in order to rule out these anomalies [57].

In Case 2 it was not perceived a myometrial wall thinner □1mm, as one usually describes in anterior invasive placenta when a scar uterus at 15 to 20 weeks' gestation [78], and the suspicion of placenta abnormal invasiveness was at 26 weeks' gestation by color Doppler assessment, and visualization of an intense vascular network on uterine lateral left wall, one of the most predictive factors associated to placenta lacunae and bridging vessels. More than these, at posterior wall has no sign of placenta invasiveness, fact that cannot be real/correct, thinking that placenta was invasive also at that area, at that moment at two weeks before the catastrophic uterine wall perforation. According to placenta invasiveness progression along pregnancy, that posterior area was a "trap/pitfall", which could be resolved by MRI associated to sonography with a score of invasiveness. penetration [79], which will be detailed further.

One cannot discuss the seven signs detailed in Delphi consensus from 2023 [61], in posterior low lying placenta in Romanian cases, because in the first case the sonographer was not experienced in the diagnosis of MAP/PAS, as actually one speaks in low resources sittings [81], fact concordant to other recent papers showing that posterior MAP/PAS is usually undetected until surgery, commonly presenting with bleeding before or at the time of CD [6], The systematic review of Tinari S et al. 2021 [57] of 20 published studies from MEDLINE, EMBASE and CINAHL, from countries of Europe, North and South America exploring prenatal imaging diagnostic performance in posterior MAP/PAS detection reported a detection rate around 52,4% (95% CI: 37.0–167.6) for ultrasound, and 73.5% with MRI, from technical limitation in assessing the posterior myometrium, and myometrium- placenta junction in the absence of bladder contrast, and so significant lower than those for anterior MAP/PAS [82]. Their analysis on the distribution of the conventional ultrasound signs of MAP/PAS, placental lacunae were present in 39.0% (12/30; seven studies), loss of the clear zone in 41.1% (13/30; seven studies) and bladder-wall interruption in 16.6% (4/30; seven studies) of women, while none of the included cases showed hypervascularization at the bladder-wall interface. Bridging vessels are considered the most useful in anterior MAP/PAS, because they occur only when there is a significant amount of neovascularity at the serosal surface, and this condition was not accomplished at 26 weeks' gestation on posterior serosal surface, because these only occur when there is a significant amount of neovascularity at the posterior serosal surface, and not within the myometrium; The previously used 2D ultrasound (gray scale) was not able to depict them. We are sure that if the CD would be done 24 hours earlier, immediately after pains onset, in the previous day to hospital admission, it could be possible to find such an intense vascularization on the uterine posterior wall, under the serosa as Figure 6 is showing, on anterior uterine wall.

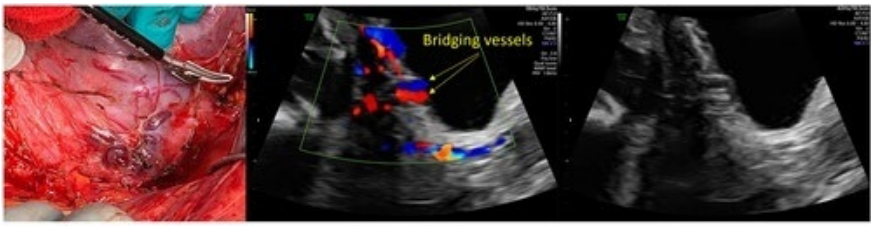

Figure 6: Demonstrating the neovascularity seen at laparotomy (a), bridging vessels with color Doppler ultrasound (b) and as bladder wall interruption (c). (a) Demonstrating the massive neovascularity seen at laparotomy between the anterior aspect of the uterus and the posterior bladder. (b) Demonstrating the same vessels as in (a) seen as 'bridging vessels' with color Doppler ultrasound. (c) Demonstrating the same vessels as in (a) seen as bladder wall interruption with gray-scale ultrasound. (Adopted from: Adu-Bredu TK, et al. 2023 [82]).

The Romanian authors appreciate that at hospital admission, during emergency ultrasound, the massive intraperitoneal blood from Douglas pouch was a good contrast for placenta lacunae visualization, as full bladder works for anterior invasive MAP/PAS to visualise lacunae, and bridging vessels at utero-bladder junction.

3.4 Magnetic resonance imaging for morbidly adherent posterior placenta

The medical staff involved in these 2 sad cases management did not have the opportunity to use magnetic resonance imaging (MRI). This result is concordant to the responses to questionnaires emailed to all members of the expert panel for the 2018 FIGO consensus guidelines on PAS (n=34), as well as international experts who had contributed to the content of these guidelines (n=16 [83]: transvaginal imaging used by 31 (86%) experts, and both ultrasonography and MRI used by 22 (61%).

The systematic review of Tinari S, et al. 2021[57] on published studies on accuracy in posterior placenta accreta spectrum disorders, had shown that in assessing posterior MAP/PAS, 73.5% (26/32; 11 studies) of cases were detected by prenatal MRI, while 26.5% (6/32; 11 studies) were discovered at the time of CS.

Pain F-A, et al. 2022 [79] proposed a nomogram in the first existing study regarding ultrasound (and Doppler for vessels), and MRI capabilities to accurate differentials between increta and percreta placenta, trying to reduce the persistency of inconsistencies [84],

and all images where compared to pathological examination. Among 82 patients, 29 (35%) had placenta accreta/increta and 53 (65%) had placenta percreta. The best features to discriminate between placenta accreta/increta and placenta percreta with ultrasound were increased vascularization at the uterine serosa–bladder wall interface [odds ratio (OR) 7.93; 95% CI: 2.78–24.99; p<0.01] and the number of lacunae without a hyperechogenic halo (OR 1.36; 95% CI: 1.14–1.67; p=0.012). Concerning MRI markers, heterogeneous placenta (OR 12.89; 95% CI 3.05–89.16; p=0.002), dark intraplacental bands (OR 12.89; 95% CI 3.05–89.16; p=0.002) and bladder wall interruption (OR 15.89; 95% CI 4.78–73.33; p<0.001) had a higher OR in discriminating placenta accreta/increta from placenta percreta. Myometrial thinning was excluded, because it appears in all MRI examinations. The nomogram yielded areas under the curve of 0.841 (95% CI 0.754–0.927) and 0.856 (95% CI 0.767–0.945), after bootstrap resampling, for the accurate prediction of placenta percreta.

3.5 Pathology/Histopathology assessment, gold standard in modern medicine

Medical staff respects this axiom, and so one had the final explanation of Case 1 unexpected sad evolution triggered by invasive placenta, with antepartum early onset of disseminated intravascular coagulation, followed by abundant hemorrhage after manual placenta remove-with no explanation for it's reason, two uterine curretages, haemostasis hysterectomy, which was not able to stop the systemic changes/disasters induced by invasive placenta, and mulTiorgan failure. These complications avoidance could be possible with 3-4 weeks before labor onset, by a planned cesarean section, with fetal preparation, according to its weight, and if posterior low lying placenta/marginal placenta praevia would be correctly assessed for invasiveness. The forensic expertise sustained the association of chronic liver and kidney disorders contributing to death, by the deleterious effects of IDC, and enormous amount of blood and derivates transfusion.

The missing microscopy in Case 2 is not changing the diagnosis, or maternal fate. In Romania the surgical specimens are gross evaluated in operative room, by senior obstetricians, the Romanians being since 40-50 years involved in placentology, and with good expertise.Table 2 presents the Clinical Grading System for PAS, used in UK, at hospitals of University of Oxford, and Universityof Cambridge [54], Case 2 is in cathegory 6 of PAS. The large uterine posterior dissection with massive hemorrhage was sonographic and intraoperative visualized, the microscopy could show the extension of implantation area, or the presence of focal area of PAS, the quality of cesarean scar and relationship to placenta, the inter utero-pIacentar fibrinoid depositions, which may be interpreted as a maternal defense mechanism to trophoblast invasion, when Nitabuch layer is missing in PAS. There were avoided more uterine sections beside those induced by PAS, and surgery, to offer the best conditions for pathologists [8]. If the case would suffer the examinations in the "Dr I Cantacuzino" Hospital, not in "Mina Minovici" National Forensic Institute, the obstetricians would participate at macroscopic assessment and more details could be possible. In low-income countries, in referral hospitals hospital with limited resources, one claims missing opportunities to confirm the results of the prenatal ultrasound diagnosis by uterine histological study after hysterectomy, which is done in all cases with prenatal PAS suspicion or at intraoperative PAS diagnosis [18].

Grade	Definition
1	At cesarean or vaginal delivery: complete placental separation at third stage; not abnormally invasive placenta.
2	At cesarean delivery or laparotomy: no placental tissue seen invaded through the serosal surface of the uterus; only partial separation with synthetic oxytocin and gentle controlled cord traction, manual removal of placenta required for remaining tissue AND parts of placenta thought to be abnormally adherent by a senior, experienced clinician. At vaginal delivery; manual removal of placenta required AND parts of placenta thought to be abnormally adherent by a senior, experienced clinician.
3	At cesarean delivery or laparotomy: no placental tissue seen invaded through the serosal surface of the uterus; no signs of any separation with synthetic oxytocin and gentle controlled cord traction, manual removal of placenta required AND the whole placental bed thought to be abnormally adherent by a senior, experienced clinician. At vaginal delivery: manual removal of placenta required AND the whole placental bed thought to be abnormally adherent by a senior, experienced clinician.
4	At cesarean delivery or laparotomy: placental tissue seen to have invaded through the serosal surface of the uterus but NOT passing into any surrounding structures (including the posterior wall of the urinary bladder); a clear surgical plane can be identified between the bladder and uterus to allow nontraumatic reflection of the urinary bladder at hysterectomy.
5	At cesarean delivery or laparotomy: placental tissue seen to have invaded through the serosal surface of the uterus AND invaded into the urinary bladder ONLY (consequently, a clear surgical plane cannot be identified between the bladder and uterus to allow nontraumatic reflection of the urinary bladder at hysterectomy).
6	At cesarean delivery or laparotomy: placental tissue seen to have invaded through the serosal surface of the uterus AND invaded into the pelvic side wall or any organ other than the urinary bladder, with or without invasion into the urinary bladder.

Table 2: Clinical Grading System Used to Assess the Severity of the Abnormally Invasive Placenta in United Kingdom, 2015 (adopted from Collins SL, et al. [54]).

4. Conclusion

Trophoblast invasiveness starts from early pregnancy and it is continuous progressing when favorable conditions. Contemporary medicine has a single possible attitude to stop the trophoblast invasiveness: pregnancy termination, in early pregnancy, when a cesarean scar pregnancy, or correct antenatal diagnosis and treatment of prepregnancy pathology and correct antenatal placenta accreta diagnosis by ultrasound plus MRI, when posterior invasive placenta with tremendous abnormal vascular remodeling difficult to accurate identify, and continuous monitoring associated to patient's compliance for pregnancy termination at 34-35 weeks' gestation, according to neonatal intensive care unit capacities for avoiding severe disseminated intravascular coagulation and massive/malignant hemorrhage, which were final causes for maternal deaths. Hysterectomy is life saving, if it not too late, when maternal complications amplitude are very advanced, irremediable by actual medicine, even for multidisciplinary well trained team or in low resources sittings.

Conflict of Interest

None.

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