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Eric Jauniaux, MD, PhD, Ahmed M. Hussein, MD, Rana M. Elbarmelgy, MsC, Rasha A. Elbarmelgy, MsC, Graham J. Burton, MD, DSc

PII: S0002-9378(21)00960-1

DOI: https://doi.org/10.1016/j.ajog.2021.08.026

Reference: YMOB 14019

To appear in: *American Journal of Obstetrics and Gynecology*

Received Date: 1 June 2021

Revised Date: 9 August 2021

Accepted Date: 23 August 2021

Please cite this article as: 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, *American Journal of Obstetrics and Gynecology* (2021), doi: https://doi.org/10.1016/j.ajog.2021.08.026.

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Eric Jauniaux, MD, PhD; Ahmed M Hussein, MD; Rana M Elbarmelgy; MsC; Rasha A Elbarmelgy; MsC; Graham J Burton, MD, DSc

From the EGA Institute for Women's Health, Faculty of Population Health Sciences, University College London (UCL), London, UK (Dr Jauniaux); the Department of Obstetrics and Gynecology, University of Cairo, Cairo, Egypt (Drs Hussein, RM Elbarmelgy and RA Elbarmelgy); The Centre for Trophoblast Research, Department of Physiology, Development and Neuroscience, University of Cambridge, Cambridge, UK (Dr Burton).

Corresponding author: *Eric Jauniaux, MD, PhD, FRCOG*
Institute for Women's Health, *University College London, 86-96 Chenies Mews, London WC1E 6HX, UK.*
e.jauniaux@ucl.ac.uk

No funding was obtained for this project.

The authors have no conflict of interest to declare.

Short title: Utero-placental interface fibrinoid deposition in accreta placentation.

Condensation

Accreta areas present a thick layer of fibrinoid deposition at the utero-placental interface which distorts the site of physiological placental detachment.

Key Words: Placenta previa accreta, placenta increta, abnormal adherence, villous invasion, fibrin deposition

Word count: 2999

Abstract

BACKGROUND: The main histopathologic diagnostic criteria for the diagnosis of placenta accreta has been for over 80 years the finding of a direct attachment of the villous tissue to the superficial myometrium or adjacent to myometrial fibres without interposing decidua. There have been very few detailed histopathologic studies in pregnancies complicated by placenta accreta spectrum (PAS) disorders and our understanding of the pathophysiology of the condition remains limited.

OBJECTIVE: To prospectively evaluate the microscopic changes used in grading and to identify changes that might explain the abnormal placental tissue attachment.

MATERIAL AND METHODS: Forty consecutive cesarean hysterectomy specimens for placenta previa accreta at 32-37 weeks of gestation with at least one histological slide showing deeply implanted villi were analysed. Prenatal ultrasound examination included placental location, myometrial thickness, subplacental vascularity and lacunae. Macroscopic changes of the lower segment were recorded during surgery and areas of abnormal placental adherence were sampled for histology. Seven hysterectomy specimens with placenta in-situ from the Boyd Collection at 20.5 – 32.5 weeks were used as controls.

RESULTS: All 40 patients had a history of at least two prior cesarean deliveries and presented with a mainly anterior placenta previa. Thirty-seven (92.5%) cases presented with increased subplacental vascularity, 31 (77.5%) cases with

myometrial thinning and all with lacunae. Twenty (50%) cases presented with subplacental hypervascularity, lacunae score 3+ and lacunae feeder vessels. Intraoperative findings included anterior lower segment wall increased vascularisation in 36 (90.0%) cases and extended area of dehiscence in 18 (45.0%) cases. Immediate gross examination of hysterectomy specimens showed an abnormally attached areas involving up to 30% of the basal plate, starting at < 2 cm from the dehiscence area in all cases. Histologic examination found deeply implanted villi in 86 (53.8%) samples with only 17 samples (10.6%) presenting with villous tissue reaching at least ½ the uterine wall thickness. There were no villi crossing the entire thickness of the uterine wall. There was microscopic evidence of myometrial scarification in all cases. Dense fibrinoid deposits, 0.5-2 mm thick, were found at the utero-placental interface in 119 (74.4%) of the 160 samples between the anchoring villi and the underlying uterine wall at the accreta areas and around all deeply implanted villi. In controls, the Nitabuch's stria and basal plate became discontinuous with advancing gestation and there was no evidence of fibrinoid deposition at these sites.

CONCLUSION: Samples from accreta areas at delivery present with a thick fibrinoid deposition at the utero-placental interface on microscopic examination independently of deeply implanted villous tissue in the sample. These changes are associated with distortion of the "Nitabuch's membrane" and might explain the loss of parts of the physiological site of detachment of the placenta from the uterine wall in PAS. These findings also indicate that accreta placentation is

82 more than direct attachment of the villous tissue to the superficial myometrium
83 and support the concept that accreta villous tissue is not truly invasive.

AJOG at a Glance

A. Why was the study conducted?

- To evaluate the microscopic changes used in the diagnosis of placenta accreta spectrum and identify changes that might explain the abnormal placental tissue attachment.

B. What are the key findings?

- Thick fibrinoid deposition between the tip of most anchoring villi and the underlying uterine wall and around all deeply implanted villi are found at delivery in most samples from accreta areas.

C. What does this study add to what is already known?

- Our data challenge the classical concept that placenta accreta is simply due to villous tissue sitting atop of the superficial myometrium without interposing decidua but rather suggest that the distortion of the "Nitabuch's membrane" by thick fibrinoid deposition is the main factor leading to abnormal placental attachment.

Introduction

When Irving and Hertig published the first cohort on placenta accreta in 1937, they defined the condition clinically as the abnormal adherence either in whole or in part of "the afterbirth" to the underlying uterine wall with placental villi directly attached to the myometrium underneath[1]. They hypothesized that the pathological basis for accreta placentation was the complete or partial absence of the decidua basalis allowing direct attachment of the villous tissue to the superficial myometrium. Only one of their patients had history of cesarean delivery (CD) and the main risk factors at the time were prior uterine curettage, placental manual removal and endometritis which can all lead to endometrial fibrosis and poor decidualisation[2]. Following the recent increase in CD rates, the epidemiology of PAS has considerably changed and now more than 90% of cases occur in women with a history of CD presenting with an anterior low-lying/placenta previa[2-5].

In 1966, Lukes et al[6] introduced the concept of placenta accreta spectrum (PAS) to accommodate the different grades of adherence/invasion and suggested that they may co-exist in the same specimen. There have been few detailed histopathologic series published since then, and most pathologists have used and continue to use the original finding of an absence of the decidua proposed by Irving and Hertig as the main criterion for the diagnosis of PAS[7-10]. Similarly, authors of clinical studies do not provide complete information on both clinical and histopathological findings at birth or simply refer to Irving and Hertig definitions[1]. Not surprisingly, the reported prevalence of PAS at delivery is highly

variable ranging between 0.01% and 1%[11]. Less than half of the published clinical cohorts on prenatal diagnosis or management of PAS lack histopathological confirmation of the diagnosis and/or grading[11,12] and thus our understanding of the pathophysiology of the different grades of PAS remains limited.

Raissa Nitabuch was the first to describe in 1887 the anatomy of the decidual layers and to identify the spiral arteries[13]. Although her findings were based on only one case, “Nitabuch’s membrane” is still known as a continuous fibrinoid layer or stria that is laid down between the trophoblastic cell columns of the anchoring villi and uterine decidual cells. In addition to Nitabuch’s layer, there is also Rohr’s layer of fibrinoid on the surface of the mature basal plate facing the intervillous space[14]. Towards the end of pregnancy, the basal plate is separated from the myometrium by only a thin layer of decidua basalis which contains an extensive venous vascular plexus and represents the plane of cleavage at the time of delivery. The basal plate is part of the utero-placental interface which also includes the superficial myometrium with its vascular network, i.e. spiral arteries and veins[14]. The objectives of the present study were to prospectively evaluate the microscopic changes used in the grading of PAS and to identify changes that might explain the abnormal attachment of the placental tissue in women with prior cesarean delivery scars.

Material and Methods

Patients and ultrasound examination

This is a prospective study of 40 consecutive cases of elective cesarean hysterectomy for placenta previa accreta at 32-37 weeks of gestation with at least one histological slide showing deeply implanted villi (increta). All patients presented with a singleton pregnancy and a history of two or more prior CDs and ultrasound signs of PAS between 20th March 2019 and 15th of Dec 2020 at the Department of Obstetrics and Gynecology, University of Cairo. Institutional Scientific and Research Ethical Committee approval (RSEC 021001) was obtained prior to the start of this study and all patients were consented for the use of the photographic images obtained before and during delivery.

All patients had detailed transabdominal and transvaginal sonographic (TVS) examinations, including colour doppler imaging (CDI) mapping of the placenta and utero-placental interface, within 48 hours before surgery (GE Voluson E10, GE Medical System, Zipf, Austria). The placenta was labeled previa when its lower edge reached the internal os (marginal) or was completely covering it[15]. Ultrasound signs of PAS were recorded using a standardized description[16]. The myometrial thickness was measured transabdominally with a full bladder in the middle area at the upper, middle and lower edges of the bladder-uterine wall junction. In addition, we used the score for placental lacunae (Fig. 1A&B), proposed by Finberg and Williams (0= none; 1+= 1-3; 2+= 4-6; 3+=>6)[17]. Birthweight percentiles were calculated using the intrauterine growth curves of the Fetal Medicine Foundation[18].

Histopathologic examination

Macroscopic features during surgery and gross examination of the hysterectomy specimens were recorded using an image capture digital photographic protocol as previously described[18]. In brief, anterior wall uterine dehiscence with placental tissue visible through the serosa was recorded according to the proportion of the lower segment surface as focal (spot < 10%), large (30- 50%) or extended (> 50%). Abnormally increased vascularity of the lower segment was defined when dense tangled bed of vessels and multiple vessels running cranio-caudally and laterally in the anterior perimetrium of the uterine serosa over the placental bed (Fig. 1C). Areas of abnormal placental attachment (accreta) that could not be digitally separated were identified during the gross examination of the hysterectomy specimen (Fig. 1D&E). They were recorded according to their surface area as focal or large when involving < 10% or 10-30% of the basal plate, respectively and distance from the dehiscence area.

Depending on the size of the accreta area, between 2-6 samples of the full thickness of the uterine wall and around a third of the placental thickness (Fig. 2A) were obtained from the area of abnormal attachment, processed for histologic examination and stained with hematoxylin and eosin (H&E). Microscopic lesions (Fig. 2B & C) were recorded using established criteria[14,20]. Deeply implanted villi were defined as the presence of villi beyond the placental basal plate reaching at least ½ the uterine wall thickness (Fig 2D).

The Boyd Collection is an archival collection of hysterectomy specimens with placenta in-situ assembled with ethical permission in the 1950's and 1960's when pregnant hysterectomy was a more common surgical procedure. The

Collection is held in the Centre for Trophoblast Research at the University of Cambridge. Scanned images of some of the slides are available at www.trophoblast.cam.ac.uk/Resources/boyd-collection on application to the Centre's Administrator. Seven specimens were studied, ranging in gestational age estimated from the crown-rump length of the fetus from 20.5 – 32.5 weeks.

Statistical analysis

StatGraphic-plus Version 3 data analysis and statistical software package (Manugistics, Rockville, MD) was used to analyse the data. A standard Kurtosis analysis indicated some values were not normally distributed and the data are therefore presented as median and interquartile range (IQR). The data were separated into subgroups according to the size of the accreta area. Categorical variables were compared between using the Pearson's Chi-square test. A *P* value <0.05 was considered significant.

Results

The study group clinical characteristics, main ultrasound features and intra-operative macroscopic features are presented in table 1. All patients had a history of at least two prior CDs and presented with a mainly anterior placenta previa including five marginal and 35 complete previa. Twenty (50%) women presented with increased subplacental vascularity, lacunae score 3+ and lacunae feeder vessels. Twelve of the 19 cases with extended area of dehiscence had a myometrial thickness < 1mm on ultrasound. Abnormally attached areas, involving

< 10% and 10-30% of the placenta basal plate were found in 22 (55.0%) and 18 (45.0%) cases respectively, all starting at < 2 cm from the dehiscence area. In nine case, it extended to the posterior uterine wall, covering the internal os of the cervix. Table 2 displays and compares the ultrasound features and intra-operative findings according to the size of the abnormally attached area. There were no significant differences between the subgroups.

A total of 160 tissue samples obtained from abnormally attached placental areas were examined microscopically (Fig. 2A). Evidence of myometrial scarification mainly thinning, myofibre disarray and tissue edema were found in all cases (Fig. 2B) and in a total of 141 (88.1%) samples. Eighty-six (53.8%) samples showed deeply implanted villi (Fig. 2C), with only 17 samples (10.6%) presenting with villous tissue reaching at least ½ the uterine wall thickness (Fig. 2D). There were no villi crossing the entire thickness of the uterine wall. Large recent intervillous thrombosis were found in 20 (50%) cases and three cases presented with a small infarct. Dense fibrinoid deposits, 0.5-2 mm thick were found at the utero-placental interface making a continuous layer between the anchoring villi and the underlying uterine wall in 119 (74.4%) samples (Fig. 2B) from 28 cases and around all the deeply implanted villi (Fig. 2C & D). These included 16 of the 20 cases that presented with subplacental hypervascularity, lacunae score 3+ and lacunae feeder vessels on ultrasound imaging. In the areas of thick fibrinoid deposits, the utero-placental interface appeared undulated. Thick fibrinoid deposition were also found around all deeply implanted villi (Fig. 2D) separating them from the surrounding scarred myometrium. There

were no villous microscopic morphological alterations of the villous architecture above the abnormally attached areas.

By 20 weeks of gestation the decidua basalis of Boyd collection specimens was approximately 0.5 mm thick, although the depth is variable across the placental bed. By that stage, most of the decidual cells were incorporated into the basal plate and were enmeshed in the fibrinoid of Nitabuch's stria, along with extravillous trophoblast cells derived from the anchoring villi. The bulk of the remaining decidua basalis consisted of an extensive plexus of thin-walled blood vessels and remnants of the endometrial glands. With advancing gestational age, the Nitabuch's stria and basal plate become discontinuous (Fig. 3A), and at these sites, placental villi appeared closely approximated to the myometrium (Fig. 3B). The villi were often only separated from the muscle fibres of the myometrium by a narrow space which *in vivo* must have been blood filled due to its continuity with the intervillous space (Fig. 3C). There was no evidence of fibrinoid deposition at these sites.

Comment

Principal findings of the study

PAS is a consequence of uterine remodelling following scarification with secondary increase in the subplacental and intervillous circulation leading to progressive fibrinoid deposition involving the entire thickness of the utero-placental interface in the scar area. This thick fibrinoid deposition distorts of the "Nitabuch membrane" and may explain the loss of parts of the physiological site of detachment of the placenta from the scarred uterine wall at delivery. These changes are independent of the presence of villous tissue implanted more deeply within the uterine wall under the accreta area.

Comparison with existing literature

Unlike, the present study, all previous histopathologic studies were retrospective[1,6-10,21] with the diagnosis of PAS obtained from histologic samples of hysterectomy specimens after fixation in formalin which makes it difficult to identify where these samples were collected from. Lukes et al[6], reported that most hysterectomy specimens arrive at the laboratory distorted by attempts to remove the placenta during delivery, limiting considerably the macroscopic examination and sampling. Recently, Einerson et al[22], highlighted that even in severe cases of PAS where the placenta abuts the uterine serosa, the villous tissue is almost always contained within the scar shell and that it is the surgical manipulation and dissection that leads to false diagnosis of placenta percreta. In the present study, only around half the 160 histologic samples from the

abnormally attached areas showed deeply implanted villous tissue inside the uterine wall underneath. In addition, the absence of villi crossing the entire thickness of the uterine wall within or around the scar area in any of our samples, supports the concept that the villous tissue in PAS is not truly invasive[2] and suggest that the depth of villous implantation is secondary to the remaining uterine wall thickness in the scar area.

Due to the surgical manipulation of the hysterectomy specimens, Lukes et al[6], were not able to evaluate if their cases of PAS were complete or partial. In the present study, we were able to map the lower uterine segment and accurately identify the abnormally attached areas, finding that they involve maximum a third of the total utero-placental interface. Thus, our data do not support the notion of “complete PAS” which derives from the intra-operative findings in case of large dehiscence where the uterine wall is replace by a translucid shell made of thin connective tissue and the epithelium of the serosa through which the placental tissue may be visible[19,22]. These changes are more pronounced in women with multiple prior CD presenting with an anterior low-lying/placenta previa[19]. In those cases, part of the placental basal plate can be visible at opening of the pelvis and is almost always damaged by the surgical procedure[22]. This can explain the variable rates of placenta percreta in modern clinical studies[11,12].

In 2016, Dannhein et al[23] proposed a protocol for the histopathologic examination and reporting of hysterectomy specimens to facilitate the retrospective correlation with prenatal imaging and surgical findings. We recently

showed that intra-operative and immediate post-operative gross examination provides detailed additional data on uterine dehiscence, vascular changes and allow accurate sampling of the abnormally attached area compared to gross examination after formalin fixation[19]. In the present study, almost 90% of the histological samples examined prospectively showed evidence of myometrial scarification. These findings confirm that the immediate post-operative sampling is efficient, and provides accurate data on the relationship between the abnormally attached placental tissue and the cesarean scar area.

Clinical implications

Remodelling of the lower segment after CD, changes the spatial relationship between the uterine wall and the anchoring villi implanted within and around the scar. Most women in our study presented with a myometrial thickness of less $\leq$ 1 mm on ultrasound (Fig. 1) and myofibre disarray and tissue edema on histologic examination (Fig. 2). The focal loss of normal myometrium structure including the junctional zone and the factors that control trophoblastic migration[21,25-28] brings part of the placental tissue in close proximity with the deep myometrial circulation. The transformation of these vessels leads to abnormally higher volume of high-velocity blood flows entering the intervillous space from the beginning of the second trimester of pregnancy[29] and secondary distortion of the cotyledon architecture in the area of the definitive placenta directly implanted into a cesarean scar[30]. This can explain the development of intra-placental lacunae which are a strong ultrasound marker of PAS[4,5,15,16].

In the present study, in 74.4% of the samples from abnormally attached areas, we found dense layer of fibrinoid deposition of 0.5-2 mm in thickness under most anchoring villi and the underlying uterine wall (Fig. 2B), including in samples where no deeply implanted villi were found. Thick fibrinoid deposits were also found around all the deeply implanted villous tissue (Fig 2C & D). By contrast, the examination of the specimens from the Boyd collection showed no similar fibrinoid deposition and found that with advancing gestational age Nitabuch's stria and the basal plate become discontinuous with areas of placental villi closely approximated to the myometrium but not directly attached to it. Boyd and Hamilton showed that placental fibrin and fibrinoid increase during the last 6 months of pregnancy[24]. In addition, the correlation of the ultrasound imaging features and histopathology data confirmed that scar placentation leads to increase perfusion of the intervillous space (Table 2). We therefore hypothesized that the abnormal attachment of the villous tissue to the uterine wall in PAS is secondary to high volume high-velocity blood flowing from the abnormally dilated deep arterial uterine circulation during the second half of pregnancy. The resulting accumulation of fibrinoid onto the basal plate at the level of Rohr's layer, where the villous population is denser, leads to the distortion of the "Nitabuch membrane" and the loss of parts of the physiological site of detachment of the placenta from the uterine wall.

We also found that the abnormally attached areas start within 2 cm of the ridge of the dehiscence area and can extend posteriorly in placenta previa accreta covering the cervix. These findings highlight the need for the use of

transvaginal ultrasound in all cases of placenta previa covering the cervix to identify possible PAS areas of the posterior uterine wall.

Strengths and limitation of the study

To our knowledge this the first prospective and second largest[8] histopathologic detailed study of PAS. Using a new protocol for the intraoperative and immediate gross examination, we were able in all cases to accurately identify and sample areas of abnormal placental attachment for microscopic examination. We acknowledge several limitations of this study. First, non-adherent areas were disrupted during the mapping of abnormal placental adherence and thus could not be sampled. Second, no clinical information is available for the hysterectomy specimens in the Boyd collection but these are unlikely to be due to PAS as CD rates were very low at that time. These specimens were processed without opening the uterus providing a unique view of the entire placental bed between the early first trimester and 32 weeks of gestation.

Conclusions

Guided sampling of the accreta areas show dense thick fibrinoid depositions between the anchoring villi of the basal plate and the scarred myometrium that could explain the abnormal placental attachment independently of the presence of deeply implanted villi in the sample. Our findings also indicate that there is more to the diagnosis of PAS than the absence of the decidua with the villi sitting atop of the superficial myometrium as described by Irving and Hertig[1] in 1937.

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Table 1. Patient clinical characteristics (median and IQR) and distribution of the ultrasound signs and intra-operative macroscopic features (n= 40).

Variables	
Maternal age (Years)	31.9 (29.0;35.0)
Gravidity	5.0 (3.5;6.0)
Parity	3.0 (2.0;4.0)
No of prior CD	3.0 (2.0;4.0)
Gestational age at delivery (weeks)	36.2 (36.0;36.8)
Fetal weight (g)	2850 (2600;3040)
ULTRASOUND	
Myometrial thickness	
- < 1mm	19 (47.5%)
- 1-2 mm	12 (30.0%)
- > 2 mm	9 (22.5%)
Subplacental vascularity	
- Normal	3 (7.5%)
- Increased (HV)	37 (92.5%)
Lacunae score	
- 1+ (1-3)	3 (7.5%)
- 2+ (4-6)	12 (30.0%)
- 3+ (> 6)	25 (62.5%)
Lacunae feeder vessels	
- Yes	23 (57.5%)
- No	17 (42.5%)
MACROSCOPY	
Anterior wall dehiscence	
- Focal	8 (20.0%)
- Large	13 (32.5%)
- Extended	19 (47.5%)
Anterior wall vascularisation	
- Normal	4 (10.0%)
- Increased	36 (90.0%)

CD= Cesarean delivery; HV= hypervascularity

Table 2. Comparison of ultrasound features and intra-operative findings according to the size of the accreta area.

Variables	**<10%** (n= 22)	**10-30%** (n= 18)	P (χ^2)
ULTRASOUND			
Myometrium thickness			
- < 1mm	10 (45.5%)	9 (50%)	
- 1-2 mm	5 (22.7%)	7 (38.9%)	0.247
- > 2 mm	7 (31.8%)	2 (11.1%)	
Lacunae score			
- 1+ (1-3)	3 (13.6%)	0 (0.0)	
- 2+ (4-6)	6 (27.3%)	8 (44.4%)	0.191
- 3+ (> 6)	13 (59.1)	10 (55.6%)	
Subplacental vascularity			
- Normal	3 (13.6%)	1 (5.6%)	0.397
- Increases (HV)	19 (86.4%)	17 (94.4%)	
Lacunae feeder vessels			
- Yes	13 (59.1%)	10 (55.6%)	0.822
- No	9 (40.9%)	8 (44.4%)	
MACROSCOPY			
Anterior wall dehiscence			
- Focal	4 (18.2%)	4 (22.2%)	
- Large	7 (31.8%)	6 (33.4%)	0.927
- Extended	11 (50%)	8 (44.4%)	
Anterior wall vascularisation			
- Normal	4 (18.2%)	0 (0%)	0.057
- Increased	18 (81.8%)	18 (100%)	

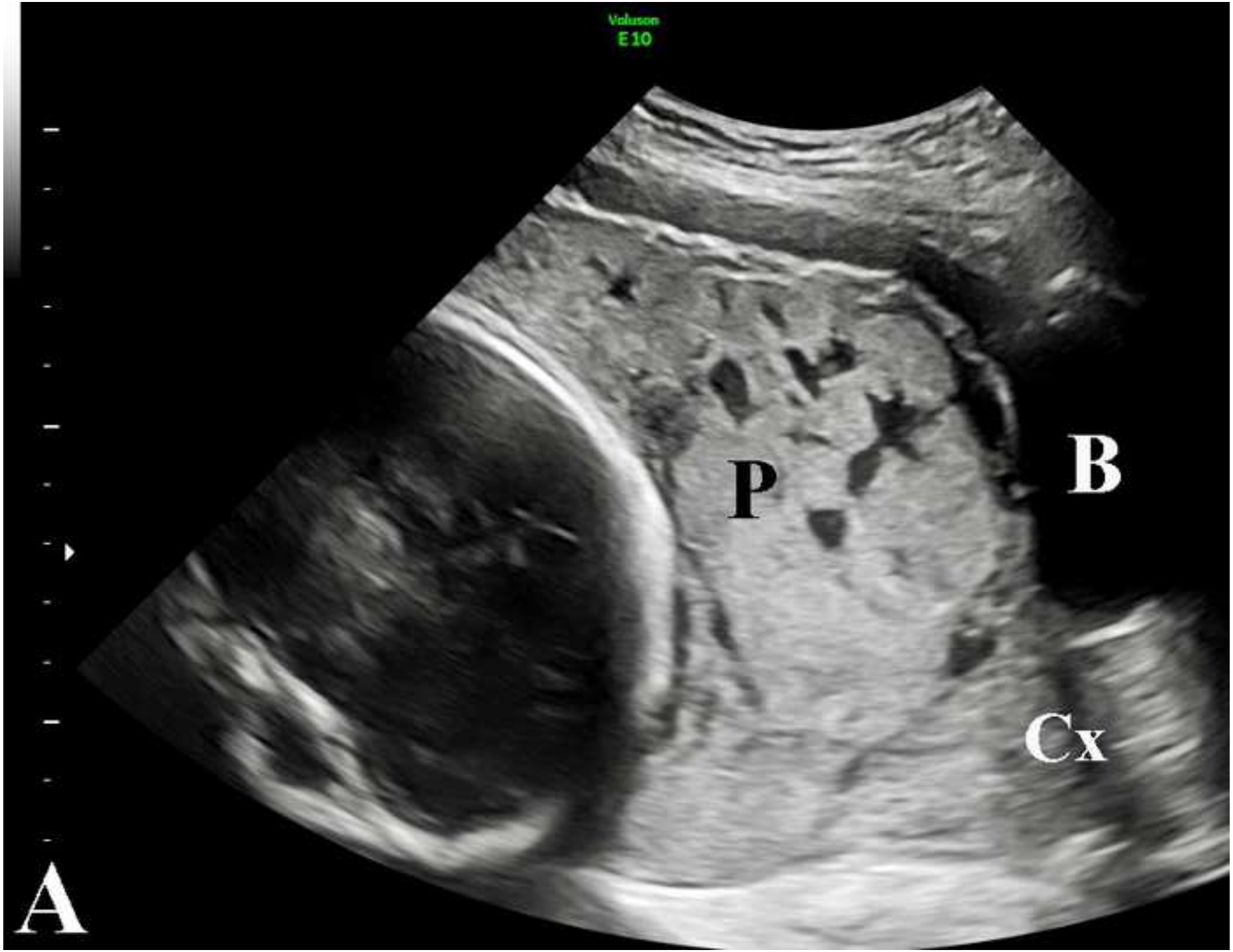
HV= hypervascularity

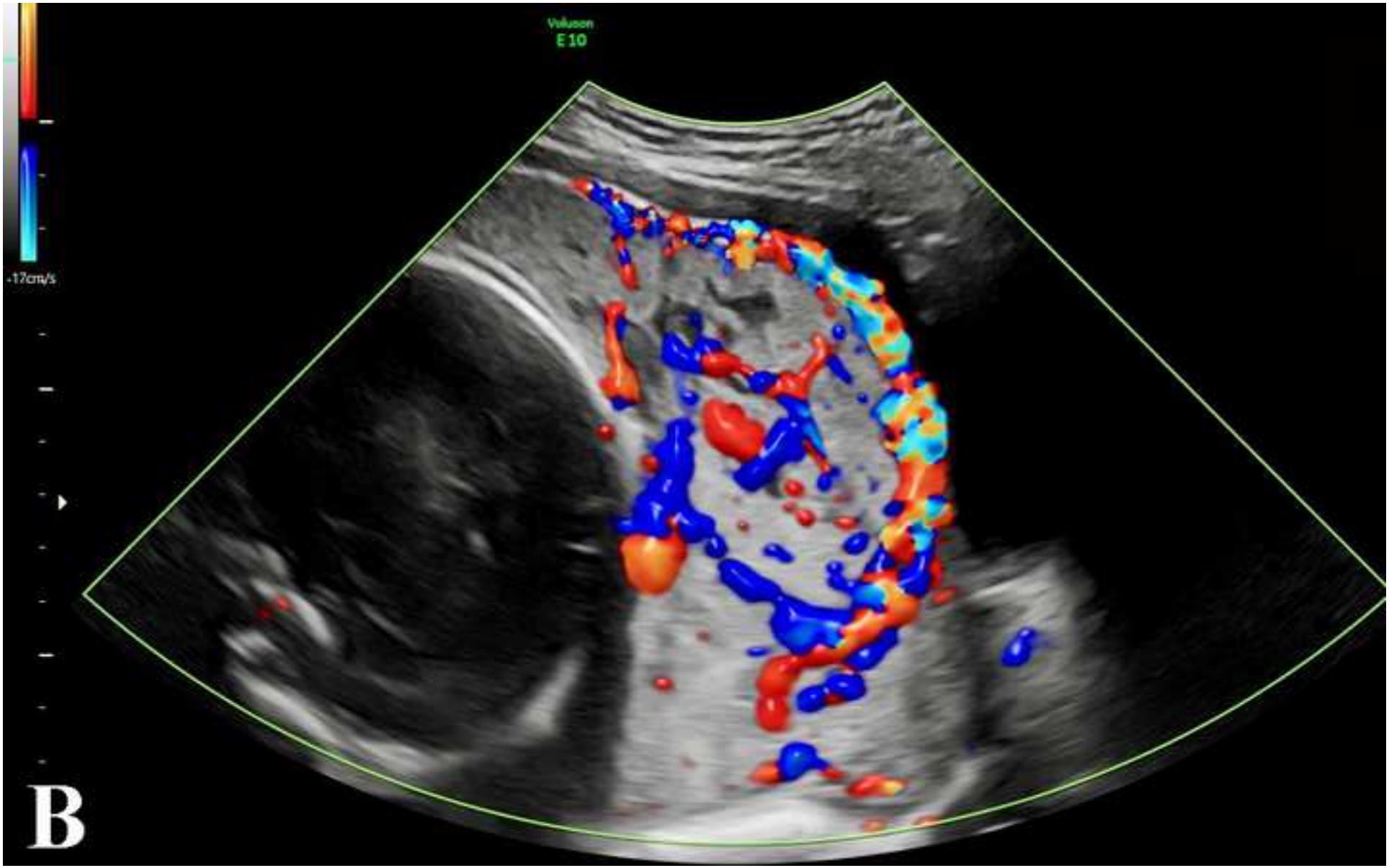
Figure legends

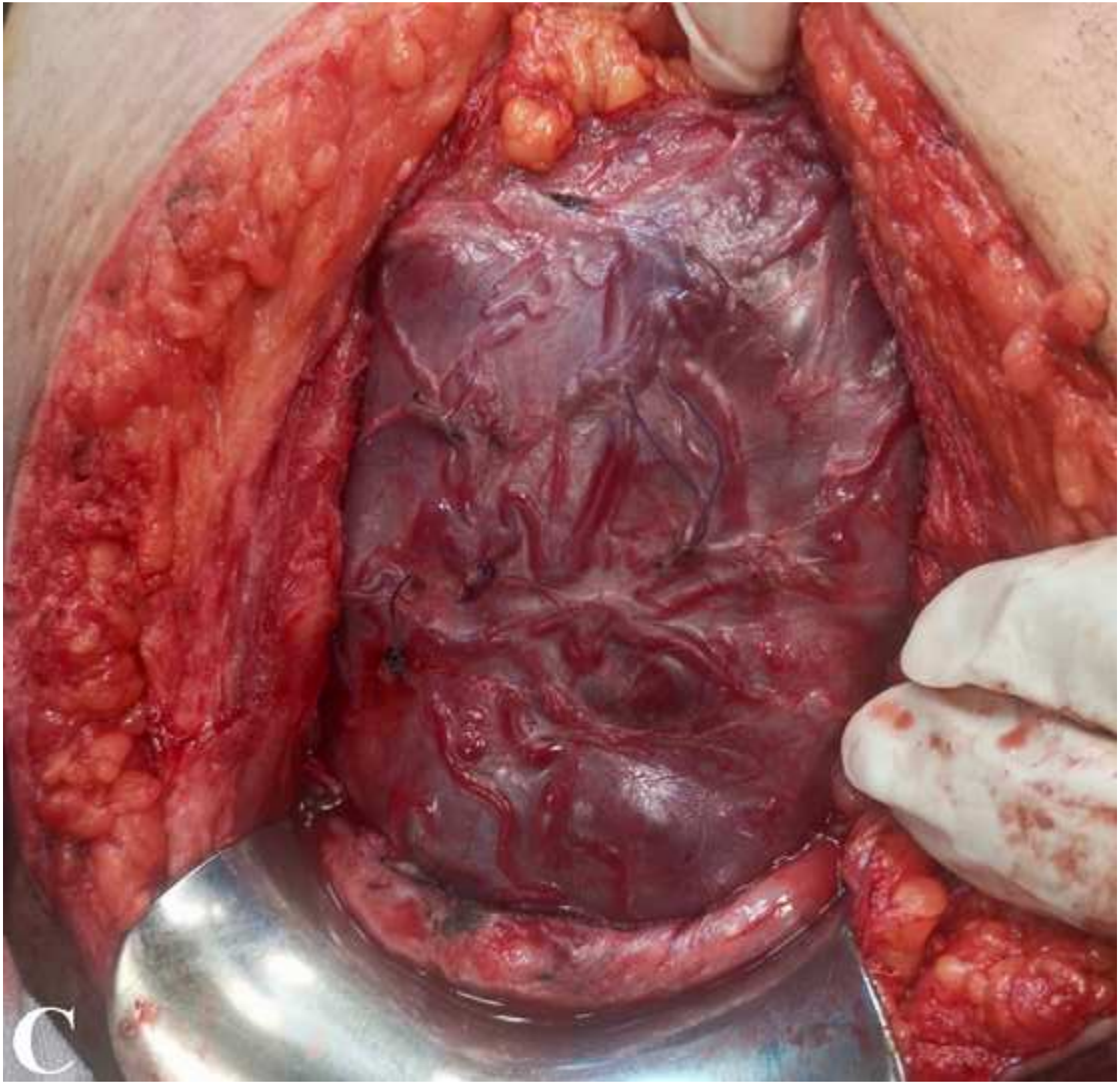
Fig 1. Transabdominal ultrasound and macroscopic views of in a case of placenta previa accreta at 36 weeks showing in **A**: The placenta (P) behind the bladder (B) containing numerous large lacunae (stage 3+) with the edge covering partially the cervix (Cx); **B**: increased sub-placental hypervascularity and intra-lacunar blood flow on CDI; **C**: Intraoperative view of the anterior uterine wall dense tangled bed of vessels and multiple vessels running cranio-caudally and laterally in the anterior perimetrium of the uterine serosa over the placental bed; **D**: Anterior view of the hysterectomy specimen showing the fundal cesarean section incision (top). On opening, the placenta was previa covering the entire lower segment (LS) of the uterus and the cervix confirming the ultrasound diagnosis; Note that the serosa is on the left of the image **E**: Central slice from the hysterectomy specimen showing the area of the placental (P) basal plate that could not be digitally separated (*) from the uterus (U) and which showed thick fibrinoid deposition on microscopic examination.

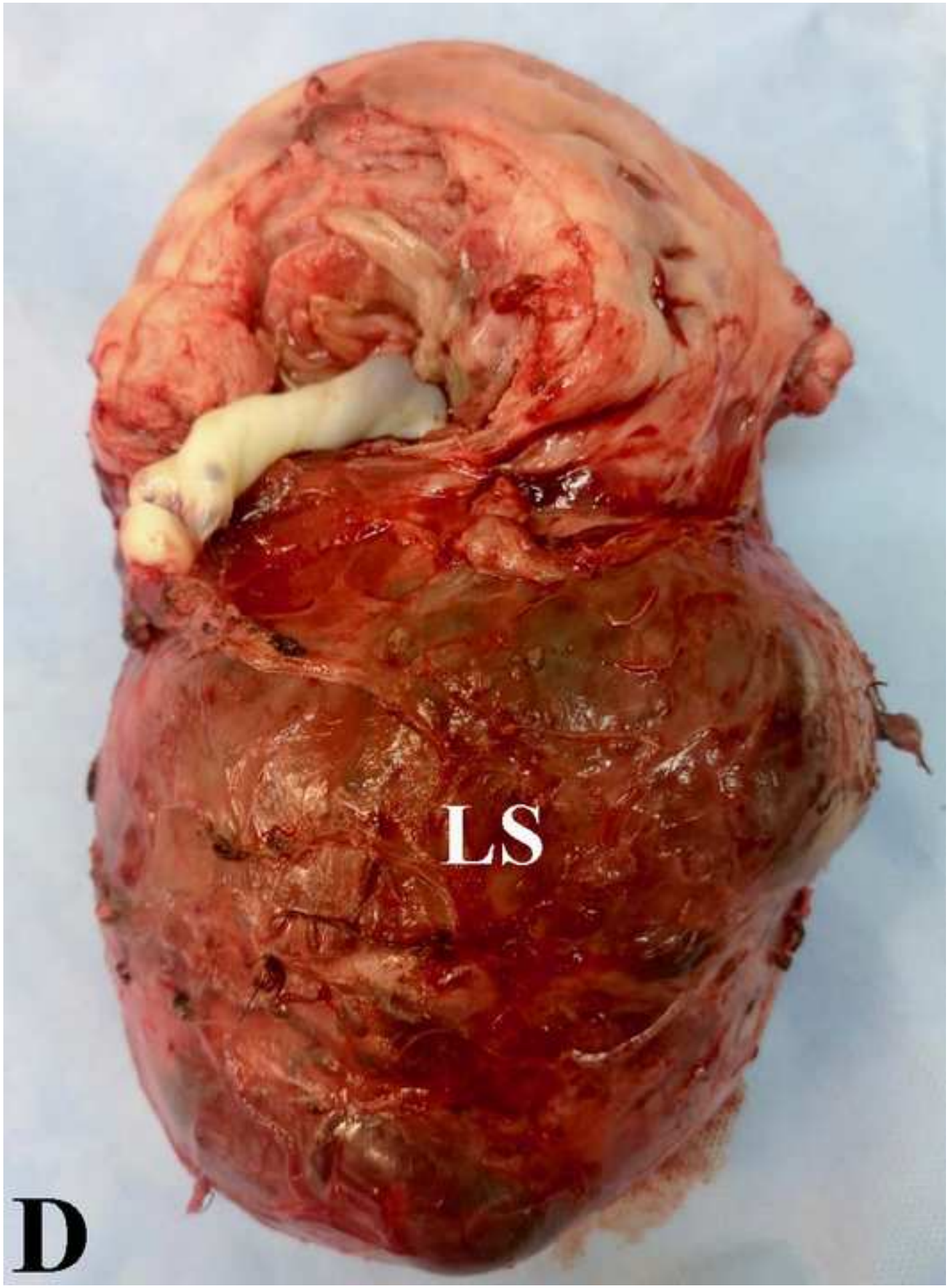
Fig 2. Histological sections of the myometrium (m) and placenta from abnormally attached areas of the placenta showing **A:** Full-thickness section of the uterine wall with attached villi to the basal plate (bp) without interposing decidua (H&E x 2.0). Note the myofiber disarray of the thin underlying myometrium (m); **B:** View of the myometrium under the utero-placental interface (H&E x 1.5). The placental villi are separated from the myometrium by thick fibrinoid deposition (fd). Note the utero-placental interface undulating appearance and the myofiber disarray and tissue edema of the underlying myometrium (m); **C:** Villi separated from the edematous myometrium (m) by thick fibrinoid deposition (fd) (H&E x 5.0); **D:** Deeply implanted villi (H&E x 2.5) separated from the myometrium (m) by thick fibrinoid deposition (fd).

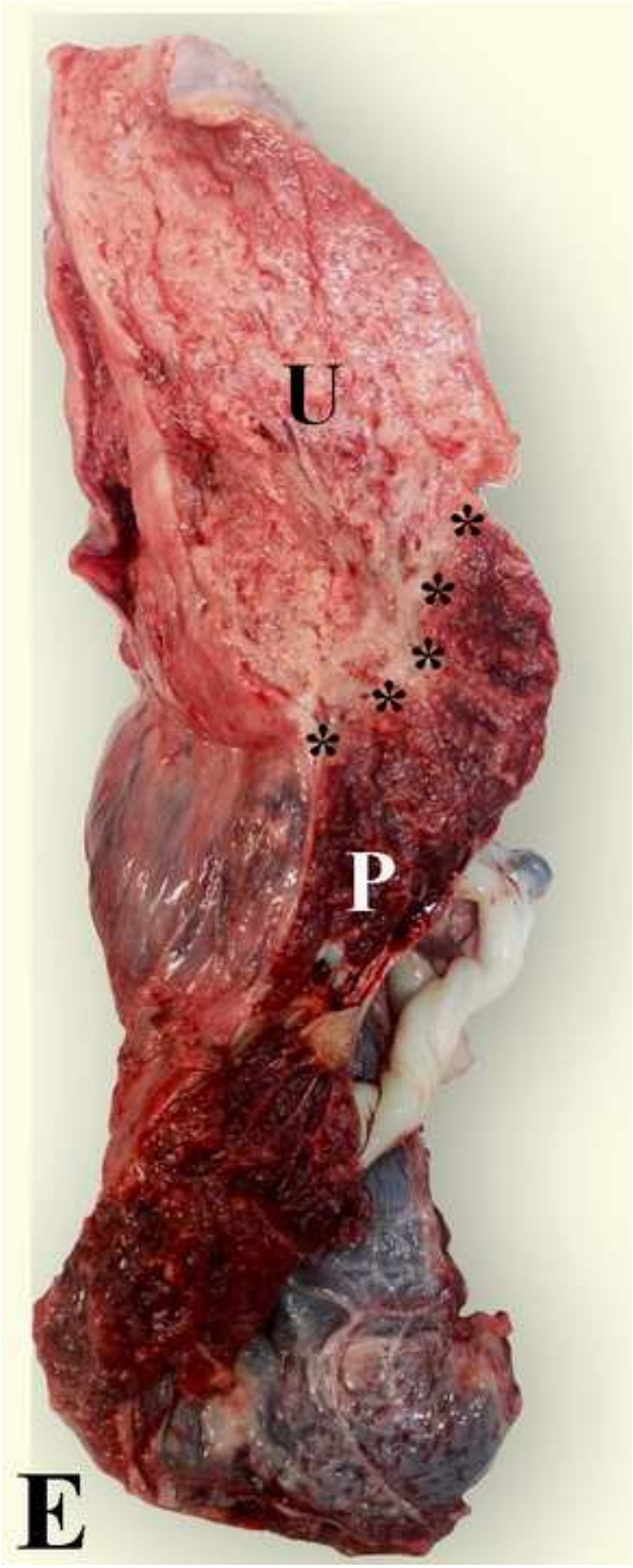
Fig 3. Photomicrographs showing discontinuities in the basal plate during the third trimester. **A**) Gestational age 27 weeks. An extensive discontinuity of the basal plate marked by arrows. The decidua is absent and the villi are separated from the myometrium (m) by a narrow vascular space. (Stain, hematoxylin & eosin). **B**) Gestational age 30 weeks. A gap in Nitabuch's stria stained in red (*), marked by arrows, allows the villi to be in close contact with, but not adherent to, the decidua basalis (db) (Stain, trichrome). **C**) Gestational age 32 weeks. Pale-staining decidual cells can be seen incorporated within the maternal surface of the basal plate (*). The decidual cells are absent in a discontinuity of the basal plate marked by arrows. The placental villi are separated from the myometrial fibres (m) by a narrow space, presumably blood filled as it is continuous with the intervillous space. (Stain, Masson's trichrome).

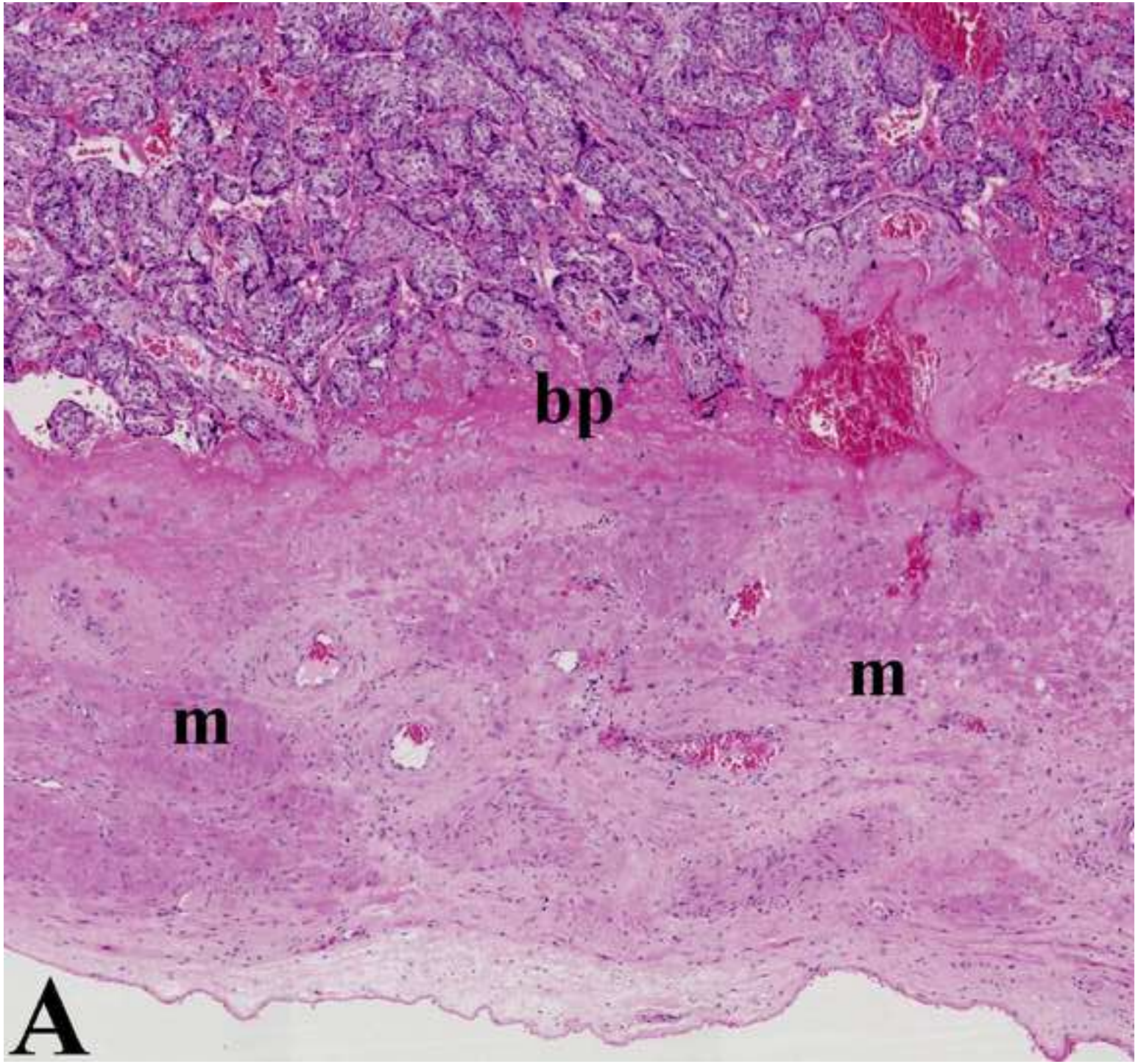

Voluson
E10
P
B
Cx
A

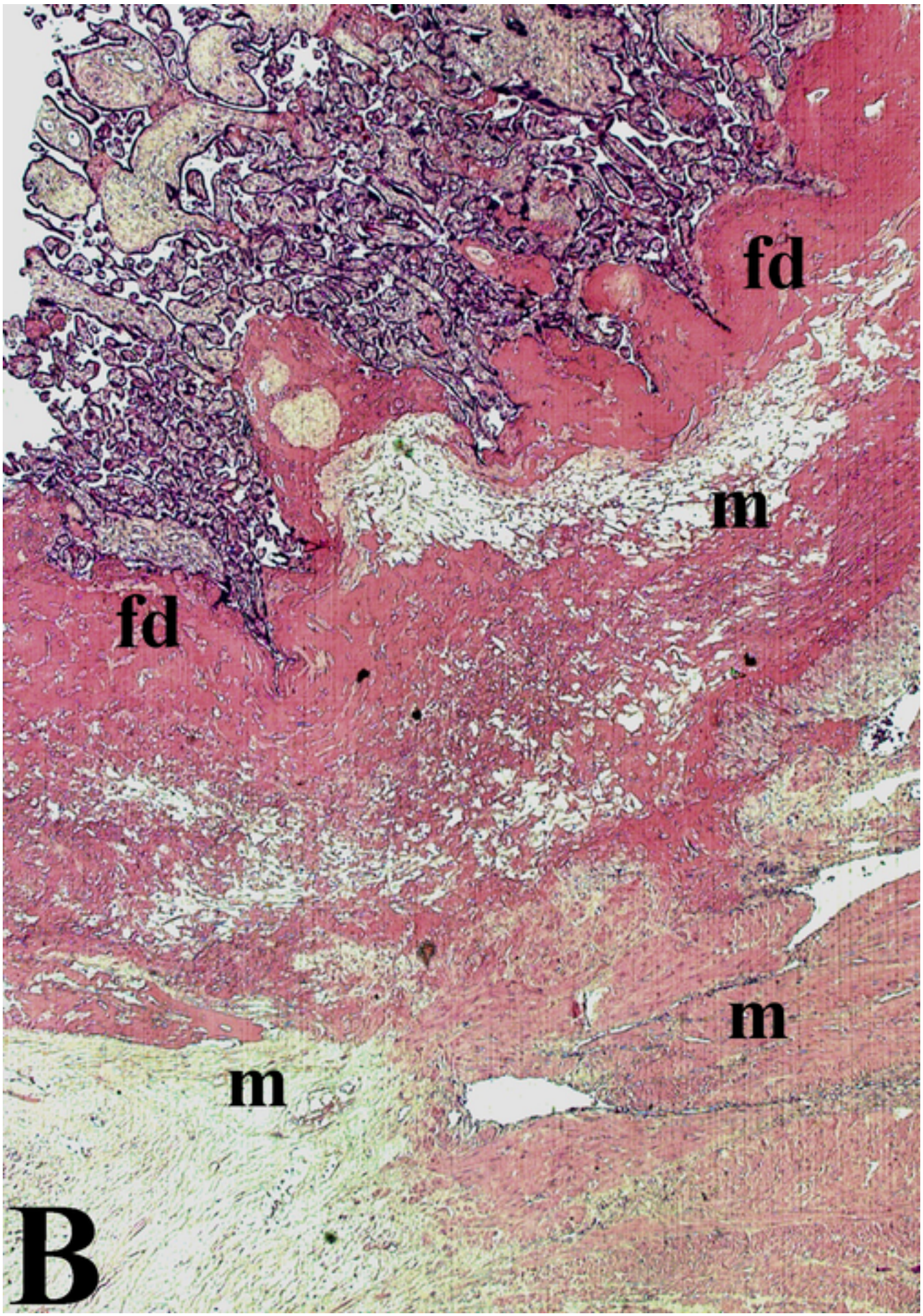

Voluson
E10
-17cm/s
B

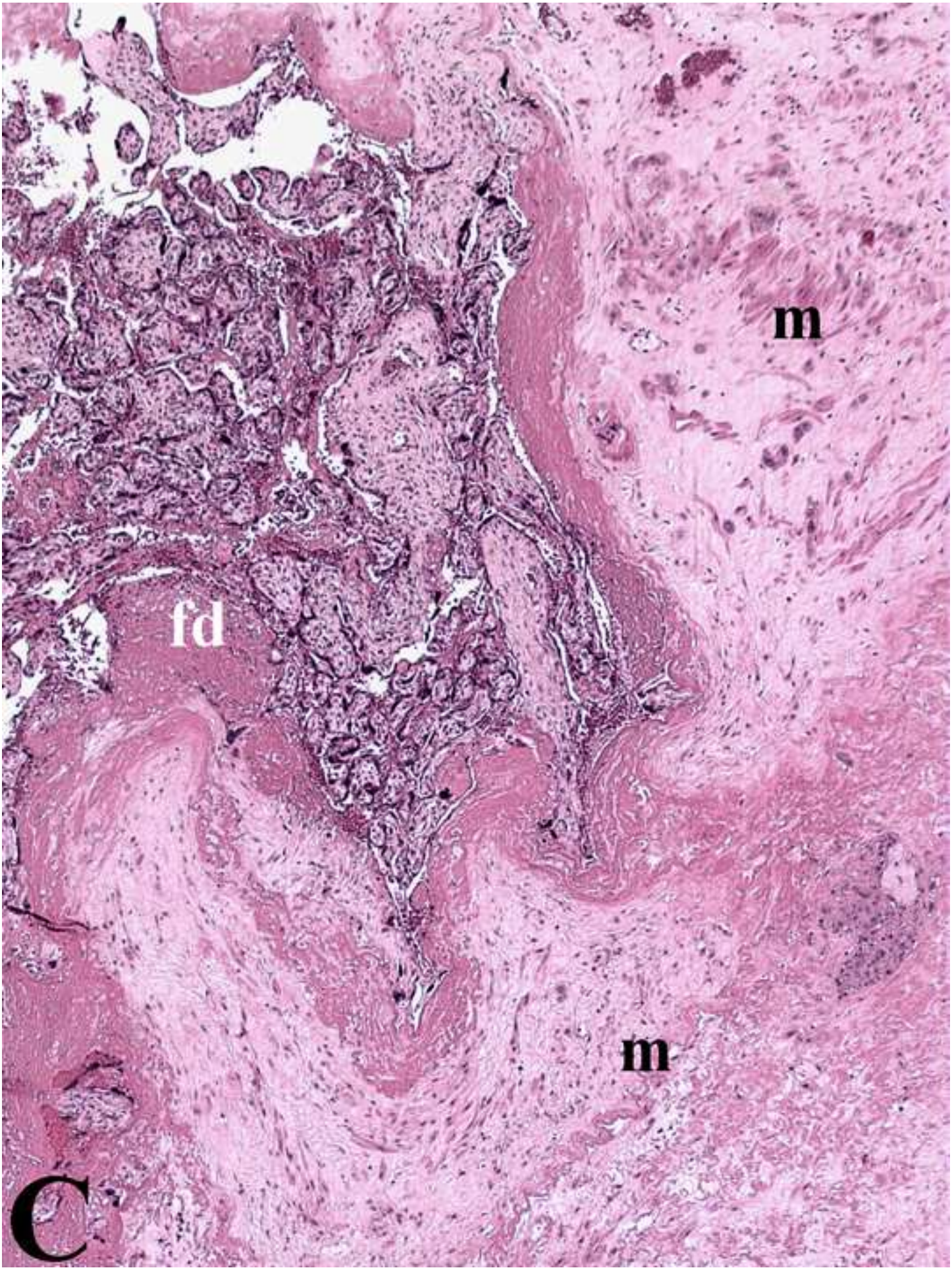

C

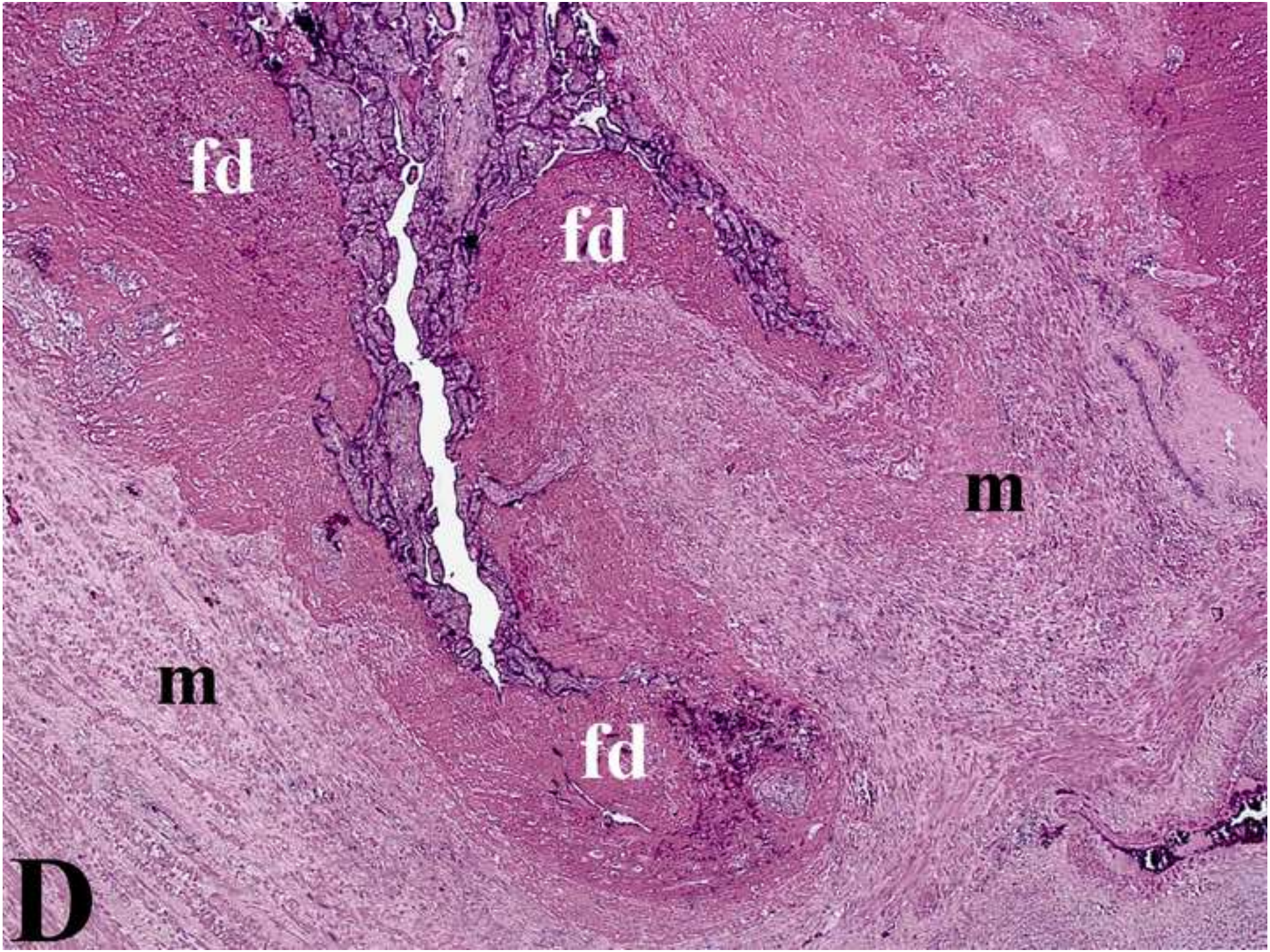

LS
D

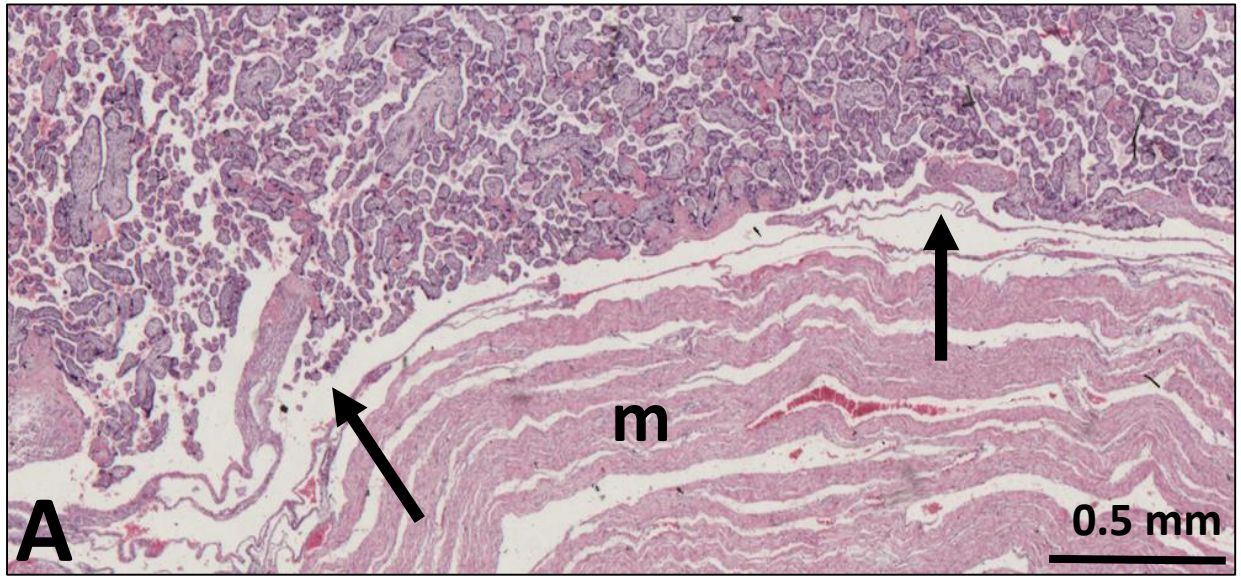

U
P
E

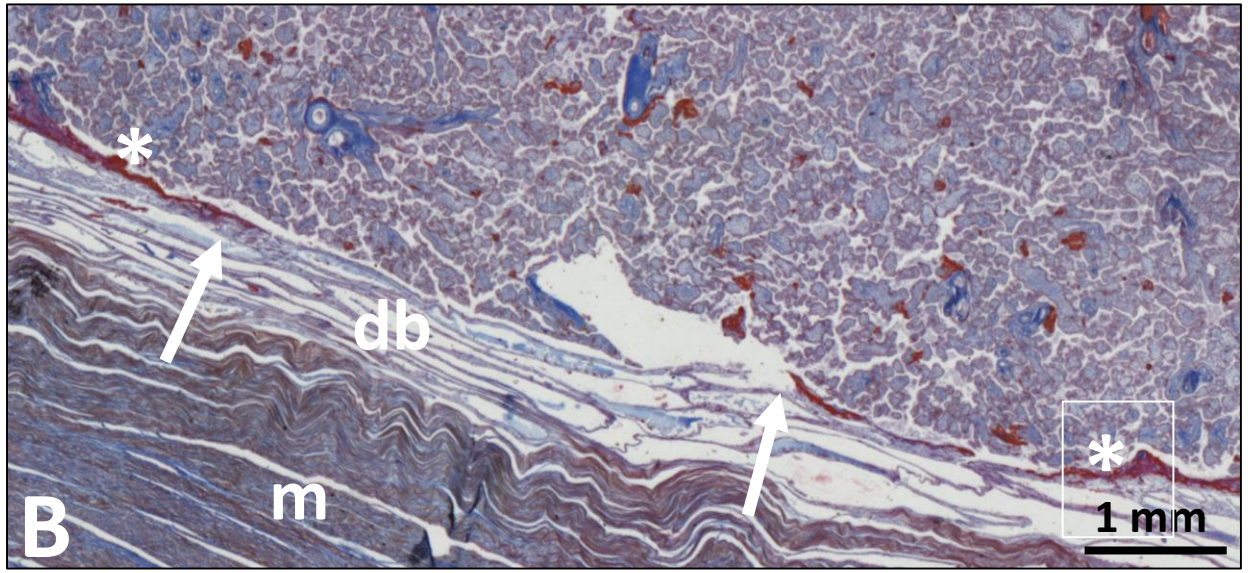

bp
m
m
A

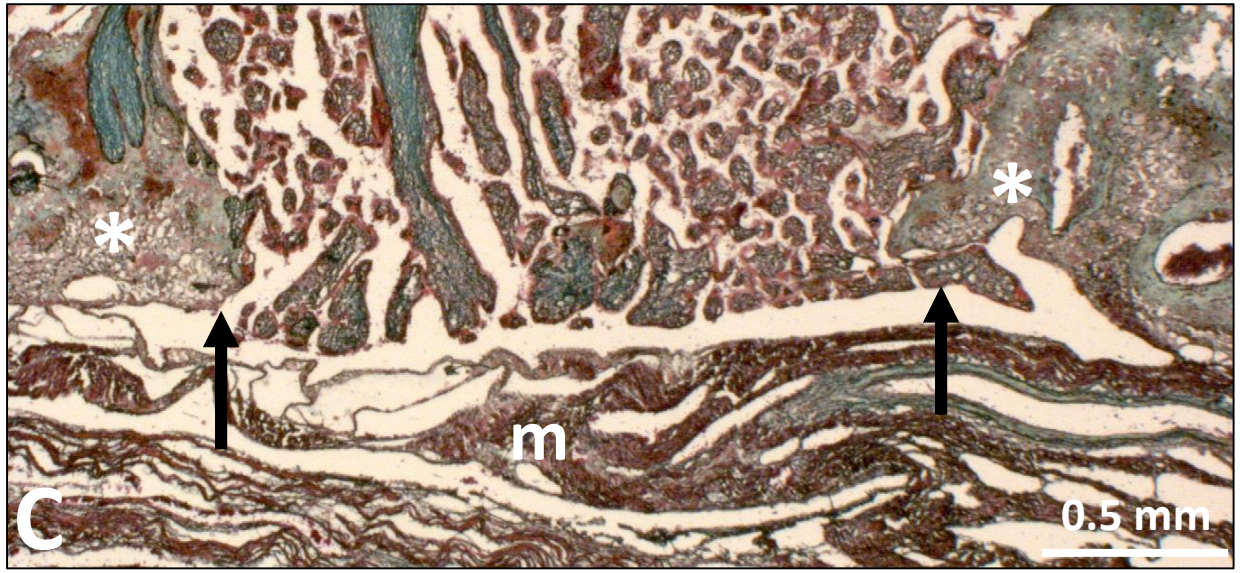

fd
m
fd
m
m
B


m
fd
m
C


fd
fd
m
m
fd
D


m
A
0.5 mm


*
db
m
B
*
1 mm


*
*
m
C
0.5 mm

Additional Table: Distribution of the histopathologic lesions in the 40 cases included in the study.

Case No	Dehiscence area	Anterior wall vascularisation	No of tissue samples (n= 160)	No of samples with increta villi (n= 86)	No of samples with scarification changes (n= 141)	No of samples with thick fibrinoid (n= 119)
1	Focal	Normal	3	2	3	2
2	Major	Increased	3	1	2	1
3	Large	Increased	4	1	2	4
4	Major	Normal	3	1	2	3
5	Major	Normal	4	2	4	2
6	Focal	Increased	2	1	1	2
7	Large	Increased	3	1	1	3
8	Large	Increased	4	4	3	4
9	Focal	Normal	4	1	2	1
10	Large	Increased	4	3	4	4
11	Large	Increased	4	3	3	4
12	Focal	Increased	5	3	4	4
13	Major	Increased	5	4	4	4
14	Large	Increased	4	3	4	3
15	Large	Increased	4	3	3	3
16	Large	Increased	5	2	4	2
17	Major	Increased	6	3	5	5
18	Major	Increased	4	2	3	2
19	Focal	Increased	2	1	2	3
20	Large	Increased	4	1	3	1
21	Major	Increased	4	1	4	1
22	Major	Increased	2	1	2	1
23	Major	Increased	4	1	4	1
24	Major	Increased	6	3	6	5
25	Major	Increased	6	3	6	3
26	Major	Increased	4	2	4	2
27	Focal	Increased	5	2	4	4

28	Major	Increased	5	3	5	5
29	Large	Increased	4	2	4	4
30	Major	Increased	5	3	5	5
31	Major	Increased	5	2	5	2
32	Major	Increased	6	3	6	6
33	Large	Increased	4	3	4	3
34	Focal	Increased	4	2	4	4
35	Major	Increased	3	2	3	2
36	Large	Increased	2	2	2	2
37	Large	Increased	4	3	4	4
38	Major	Increased	4	2	4	4
39	Focal	Increased	4	2	4	2
40	Major	Increased	2	2	2	2