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Condensation

The changes in utero-placental circulation during placentation in cesarean scar pregnancies vary according to the scar residual myometrial thickness of at the start of pregnancy

AJOG at a Glance

A. Why was the study conducted?

- To compare the development utero-placental circulation in pregnancies implanted in a cesarean scar with those implanted in the lower uterine segment.

B. What are the key findings?

- The utero-placental circulation in cesarean scar pregnancies develops in three phases: increased peri-gestational sac vascularization due to the proximity of the primitive placenta to the deep uterine arterial vasculature; subplacental vasculature physiological changes during the lateral development of the definitive placenta; a rapid increase in subplacental and intervillous circulations in those diagnosed as placenta accreta spectrum at birth.

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

- Cesarean scar pregnancies implanted in deficient scars with a residual myometrial thickness < 2mm at 6-10 weeks of gestation are at increased risk of both uterine rupture and accreta placentation.

Abstract

BACKGROUND: Cesarean scar pregnancies (CSP) are at high risk of pregnancy complications including placenta previa with antepartum hemorrhage, placenta accreta spectrum (PAS) and uterine rupture.

OBJECTIVE: To evaluate the development of the utero-placental circulation in the first half of pregnancy in ongoing CSP and compare it to pregnancies implanted in the lower uterine segment above a prior cesarean section scar with no evidence of PAS at delivery.

MATERIAL AND METHODS: This was a retrospective case-control study conducted in two tertiary referral centers. The study group included 27 women diagnosed with a live caesarean scar pregnancy in the first trimester of pregnancy who elected to conservative management. The control group included 27 women diagnosed with a low-lying/placenta previa at 19-22 weeks of gestation who had a first and an early second trimester ultrasound examinations. In both groups, the first ultrasound examination was carried out at 6-10 weeks to establish pregnancy location, viability and to confirm the gestational age. The utero-placental and intra-placental vasculatures were examined using color Doppler imaging (CDI) and described semi quantitatively using CDI score 1-4. The remaining myometrial thickness (RMT) was recorded in the study group whereas in the controls the ultrasound features of prior cesarean scar were noted including the presence of a niche. Both CSP and controls had also ultrasound examinations at 11-14 and 19-22 weeks of gestation.

RESULTS: The mean CDI vascularity score at the 6-10 weeks ultrasound examination was significantly (*P* <.001) higher in the CSP group than in the controls. The high vascularity scores 3 and 4 were recorded in 20/27 (74%) cases of the CSP group. There was no vascularity score of 4 and only 3/27 (11%) controls had vascularity score

of 3. In 15/27 (55.6%) CSPs the RMT was < 2 mm. At the 11-14 weeks ultrasound examination, there was no significant difference between the groups for the number of cases with increased subplacental vascularity but 12 CSPs (44%) presented with one or more placental lacunae whereas there was no case with lacunae in the controls. In the 18 CSP that progressed into the third trimester, ten were diagnosed with placenta previa creta at birth, including 4 creta and 6 increta. At the 19-22 weeks ultrasound examination, eight of the ten PAS presented with subplacental hypervascularity out of which, six showed also placental lacunae.

CONCLUSION: The vascular changes in the utero-placental and intervillous circulations in CSPs are due to the loss of the normal uterine structure in the scar area and the development of placental tissue in proximity of large diameter arteries of the outer uterine wall. The intensity of these vascular changes, development of PAS and risk of uterine rupture depend on the RMT of the cesarean scar defect at the start of pregnancy. A better understanding of the pathophysiology of the utero-placental vascular changes associated with CSP should help in identifying those cases that may develop major complications and thus contribute to counselling women about the risks associated with different management strategies.

Key Words: cesarean scar pregnancy; ectopic pregnancy; gestational sac size; ultrasound imaging

Introduction

A cesarean section pregnancy (CSP) describes a gestation sac developing inside the scar area of a prior low-segment cesarean delivery (CD)[1]. First diagnosed with ultrasound imaging by Rempen and Albert in 1990[2], the incidence of CSPs has increased due to the continuous rise in CD rates over the last three decades. A recent national cohort study has shown that the incidence of CSP is now 1.5 per 10 000[3]. In the last decade, there has been mounting evidence showing that at least half of CSP can evolve into placenta accreta spectrum (PAS)[4-7].

Histological studies have shown that myometrial scars areas often show myofibre disarray, tissue edema, inflammation, elastosis, apoptosis and decreased smooth muscle volume density[8,9]. The lower uterine segment contains less muscle fibers than the upper segment and their number decrease towards the cervix[10]. Thus, the anatomical impact of a surgical procedure is more pronounced in the lower than in the upper segment and the development of cesarean scar defect, also called a niche is now well documented[11-13]. A recent histopathologic study has shown that most uterine niches contain endocervical mucosa and are surrounded by thick walled vessels[14]. In large niches, there is often an absence of re-epithelialisation[15] and the remaining myometrial thickness is often < 2mm[11-13]. These findings suggest that in cesarean scar defects there is a permanent loss of most of the myometrial thickness including the spiral arteries and most of the length of the radial arteries.

In normal placentation, trophoblastic cells detached from the tips of anchoring villi and are found both within the wall and around the spiral arteries in the central area of the primitive placenta [16,17]. From 8 weeks of gestation, these extravillous trophoblastic cells migrate along the spiral arteries as far as the inner third of myometrial region or junctional zone. They gradually migrate laterally, reaching the periphery of the definitive placenta around mid-gestation which corresponds to the end the placentation process[17]. In hysterectomy specimens from cases complicated by PAS, extravillous trophoblastic cells are found near the uterine serosa and are associated with some degree of remodeling of the arteries in the deep myometrium[18]. This leads to major anatomical changes in the utero-placental circulation under the placental bed and inside the intervillous space[19], including subplacental hypervascularization and placental lacunae and the corresponding ultrasound signs are used for the prenatal diagnosis of PAS in the second half of pregnancy[20,21]. A recent systematic review and meta-analysis has identified 52 cases of expectantly managed live CSP in the literature[7] and thus there is limited information on the pattern of these changes during placentation in ongoing CSP and how they can impact pregnancy outcomes.

The aim of this study was to evaluate and compare the development of the utero-placental circulation in the first half of pregnancy in ongoing CSP with those of pregnancies implanted in the lower uterine segment above a prior cesarean section scar with no evidence of PAS at delivery.

Materials and Methods

Patients and ultrasound examination

We conducted a case-control study at the Early Pregnancy Assessment Units at University College London and King's College Hospitals, over a 7 year-period ending February 2021 were included in the study. The study group included all women diagnosed with a viable CSP, who declined termination and opted to continue with their pregnancy. The control group consisted of women with at least one prior cesarean delivery (CD) diagnosed during the same period of time with an anterior low-lying/placenta previa at the mid-trimester (19-22 weeks) anatomy scan. In both groups, all women had undergone detailed ultrasound examinations by experienced operators at 6-10 and 11-14 weeks and CSP were diagnosed using the same protocol[22].

All ultrasound examinations were carried out transvaginally and transabdominally with high-resolution ultrasound equipment (Voluson 730 and Voluson E8 Expert, GE Medical Systems, Milwaukee, WI, USA). In both groups, the placenta was recorded as "low lying" when the edge was 0.5-2 cm from the internal os of the uterine cervix after 16 weeks[23]. When the placenta was <0.5cm from the internal os or completely covering it, it was defined as placenta previa (marginal or complete)[23]. The final PAS grading at birth was recorded as previously described[18]. Demographic and outcome data from both groups were analysed retrospectively.

All pregnancies were dated according to the last menstrual period (LMP) and gestational age was confirmed by measurement of the fetal crown-rump length (CRL). At 6-10 weeks, the residual myometrial thickness (RMT) under the gestational sac was recorded and Color Doppler imaging (CDI) was used to map the vascularity around the gestational sac in both groups (default pulse repetition frequency of 0.9 kHz, gain of 0.8 and low wall motion filter (40 Hz). In controls, the myometrial scar of prior CD was noted and reported as intact or defective (niche). A semi-quantitative color score method with a scale from 1 to 4 is routinely used in our units in all complicated early pregnancies to record peri-gestational sac blood supply as previously described (1= no detectable blood flow; 2= minimal blood flow present; 3= moderate blood flow; 4= high vascularity)[24].

CDI was used at 11-14 and 19-22 weeks to map subplacental and intraplacental vascularity. Subplacental hypervascularity was defined as "striking amount of colour

Doppler signal seen in the placental bed and placental lacunae as large and irregular spaces often containing turbulent flow visible on greyscale imaging”[20]. In addition, at 19-22 weeks, we used the score, proposed by Finberg and Williams for reporting on placental lacunae in the second half of pregnancy (0= none; 1+= 1-3; 2+= 4-6; 3+=>6)[25]. Myometrial thinning at 19-22 weeks was recorded when the uterine wall thickness under the placental bad was < 1 mm or undetectable[20].

Ethical committee approval was obtained prior to the start of this study (NHS Health Research Authority 18/WM/0328). Retrospective patient consent was waived as all records were examined in the centre where it was undertaken and all data were fully anonymised.

Statistical analysis

StatGraphic-plus Version 3 statistical software package (Manugistics, Rockville, MD) was used to analyse the data. The standard Kurtosis analysis indicated that all values were normally distributed and the data are presented as mean and standard deviation (SD). Categorical variables of the study and control groups were compared using the Pearson’s chi-square test or Fisher’s exact test when samples sizes were small. Continuous variables were compared using a t-test at the 95% confidence interval (CI). A *P* value <0.05 was considered significant.

Results

During the study period, 227 women were diagnosed with a CSP out of which 111 (48.9%) had a fetus with evidence of cardiac activity. Thirty women opted to continue with their pregnancy including one with a twin heterotopic pregnancy combining a fundal intrauterine gestational sac and a cesarean scar sac. Three women had a miscarriage at 9-10 weeks of gestation leaving 27 pregnancies in the study group to be compared with the same number of controls. The maternal demographics and main ultrasound characteristics at 6-10 weeks and 11-14 weeks of the study and control groups are displayed and compared in Table 1. The groups were balanced in the mean maternal age, parity, number of prior cesarean deliveries, the distribution of the symptoms. The mean gestational age at the 6-10 weeks' and the 11-14 weeks' ultrasound examinations were also similar.

At the 6-10 weeks' ultrasound examination, the mean CDI vascularity score was significantly (*P* <.001) higher in the CSP group (Figs. 1-3) than in the controls (Figure 4). The vascularity scores were 4 (high blood flow) and 3 (moderate flow) in 12 and eight cases of the CSP group, respectively (Fig. 2). There was no vascularity score of 4 and only three cases with a vascularity score of 3 in the controls. In fifteen (55.6%) of the 27 CSPs the RMT was < 2 mm. In the control group, a scar was identified in 25 (92.6%) cases including 13 (48.1%) which classified as niche 13 (Fig. 5).

At the 11-14 weeks ultrasound examination, one or more placental lacunae were present in12 (44%) cases in the CSP group. There were no cases with lacunae among the controls but the definitive placenta of nine controls contained intervillous lakes (Fig. 5). There was no difference between the groups for the number of cases with increased subplacental vascularity at 11-14 weeks (Table 1). A niche was still visible on ultrasound after 10 weeks of gestation in two controls.

Six (22.2%) women in the study group opted for a pregnancy termination at 13-15 weeks of gestation, five following continuous heavy bleeding between their 6-10 weeks' and 11-14 weeks' ultrasound examinations, and one following the diagnosis of fetal anencephaly at 13 weeks of gestation. Two (7.4%) women presented with uterine rupture requiring laparotomy and hysterectomy at 13 weeks and 6 days' (twin pregnancy) and 15 weeks and 6 days', respectively, both with an RMT < 1mm at 6-10 weeks and one woman was diagnosed with a late miscarriage at 16 weeks and 1 day.

The ultrasound features at 19-22 weeks of gestation and outcome according to intraoperative and histopathologic findings of 18 ongoing CSPs are presented in Table 2. All pregnancies progressed into the third trimester and 14 (77.8%) were delivered before 37 weeks' due to antepartum hemorrhage. Sixteen (88.9%) had a placenta previa and two (11.1%) had a low-lying placenta. Ten (55.5%) cases were diagnosed with placenta previa accreta at birth including three cases of placenta creta and seven cases of placenta increta of which eight required a primary cesarean hysterectomy (Table 3). Eight of the ten PAS presented with subplacental hypervascularity out of which seven also presented with myometrial thinning and six with placental lacunae. Eight of the PAS had an RMT < 2mm at the 6-10 weeks scan. In the control group, there were eight (29.6%) cases of anterior placenta previa and 19 (70.4%) cases of low-lying placenta, with no case of abnormal placenta attachment at delivery. Sixteen controls presented with intervillous and/or marginal lakes at the 19-22 weeks ultrasound examination (Figure 5). Three were delivered by emergency cesarean section before 37 weeks due to antepartum hemorrhage. None required a hysterectomy.

Comment

Principal findings of the study

In CSP, the vascularity around the gestational sac increases within a few weeks after implantation due to the proximity of the developing villi of the primitive placenta and the large diameter vessels of the periphery of the uterine wall. These changes are independent of the subsequent diagnosis of accreta placentation but excessive amount of high velocity maternal blood around the gestational[26,27] can explain the high rate of pregnancy loss in CSP. During the lateral growth of the definitive placental development, the vascular changes are similar in CSP and controls and are mainly related to the normal development of utero-placental circulation. As pregnancy advances, the changes in both utero-placental and intervillous circulations become more pronounced in CSP diagnosed as PAS at birth.

Comparison with existing literature

The distribution of the first-trimester symptoms and obstetric complications of our cohort of ongoing CSP are similar to those reported by Cali et al[7]. Of particular interest are the cases complicated by uterine rupture and those diagnosed with PAS at birth. Both cases complicated by a second trimester uterine rupture, presented with an RMT < 2 mm at 6-10 weeks scan and the primary mechanism of the uterine rupture in CPS is probably the stretching of the very thin scar tissue at the bottom of the niche. An RMT < 2 mm at first trimester ultrasound examination has also been associated with PAS at delivery[28]. Out of the 18 CSP that progressed up to 28 weeks in the present study, ten had an RMT < 2mm at 6-10 weeks out of which nine were diagnosed as PAS at birth. This suggest that both the niche rupture and/or the development of accreta areas depends on the depth of the niche at the beginning of pregnancy and the amount of villous tissue developing inside it.

The increase in subplacental hypervascularity is the ultrasound marker with the strongest association with PAS[20,21,29]. This marker is mainly used in the second half of pregnancy for the prenatal screening of PAS but has also been described in the first trimester[26]. In the present study, using a semi-quantitative color score, we found an increase in vascularity around the gestational sac from as early as 6 weeks of gestation in most CSPs, with or without PAS at birth. Both the mean vascularity score (Table 1) and the incidence of high vascularity scores (Table 3) were more frequent in CSPs than in controls. This suggest that the loss of the normal structure of uterine wall in the scar area, including the spiral arteries and the junctional zone, brings the anchoring villi of the primitive placenta in CSP directly in contact with large diameter arteries of the outer uterine wall. This leads to the rapid increase in blood flow around the first-trimester gestational sac which is independent of the development of accreta placentation.

The definitive placenta expends rapidly laterally between 12 and 16 weeks of gestation, incorporating an increasing number of both spiral arteries and veins[30]. In CSP, most of the definitive placenta will grow outside the scar area. Our data show that the changes in the subplacental vasculature in the early second trimester are similar in CSPs and controls (Table 1) indicating that the increase in subplacental vascularity of definitive placenta is physiological and secondary to its lateral growth. By contrast, at 19-22 weeks, which correspond to the end of the placentation process, eight of the ten cases of CSP diagnosed as PAS at birth presented with subplacental hypervascularity (Table 2). A recent prospective study of the ultrasound signs of PAS at in women at low-risk of PAS has found evidence of subplacental hypervascularity in 37% of the cases at 18 to 24 weeks of gestation[31]. The definition of what constitutes subplacental or utero-vesical "hypervacularity" in the second half of pregnancy remains elusive and there is currently no vascularity score. These findings suggest that there is a need to develop standardised ultrasound protocols for the report of subplacental vascularity in the second trimester in women with a history of CD presenting with a low-lying/placenta previa.

Clinical implications

In the central area of the basal plate, destined to become the definitive placenta in normal intrauterine pregnancies, the extravillous trophoblast plugs block the tip of the spiral arteries until the end of the first trimester[32,33]. These trophoblastic plugs create a shell restricting inflow into the intervillous space and protecting the fetus and the villous tissue against the effect of excessive oxidative stress[32,33]. At the end of the first trimester the trophoblastic plugs are progressively dislocated, allowing maternal blood to flow freely and continuously within the intervillous space of the entire definitive placenta[32,33]. By contrast, in over 70% of miscarriages, there is reduced extravillous trophoblast invasion and a thinner and fragmented trophoblastic shell[32]. This allows premature and excessive entry of maternal blood inside the intervillous space with secondary villous degeneration and detachment of the placenta from the uterine wall[32,33]. Around 50% of the CSP in our population presented as a miscarriage and three in the study group had a miscarriage before 10 weeks. These early pregnancy failure rates are much higher than those observed in pregnancies sited normally within the uterine cavity[34,35]. These findings suggest that, in at least 50% of the CSP, the remodelling of the radial and arcuate arteries in the scar area allows high velocity maternal blood from reaching the trophoblastic shell of the early placenta preventing it from forming and/or dislocating it prematurely.

Lacunae have been commonly described as an ultrasound marker of PAS in the second half of pregnancy[19,21,29]. They are the result of distortion of the anatomy of one or more cotyledons including an inter-lobular septa[36] by high velocity from a feeding radial or arcuate artery[19]. Placental lacunae have been reported at 11-14 weeks in pregnancies with confirmed PAS at birth[37] but up to mid-gestation, difference between lacunae and placental lakes may not clear cut[19]. In the present study, placenta lacunae were found on ultrasound at 11-14 weeks in around 40% of the CSPs but not in any of the controls (Table 1). At 19-22 weeks, seven out of the ten ongoing CSP diagnosed as PAS at birth also contained lacunae (Table 2). In three cases, the lacunae grade[25] increased from a grade 2 to 3 on ultrasound examination between 11-14 weeks and 19-22 (Table 3). As pregnancy advances, with the continuous dilatation of the radial and arcuate arteries, lacunae will become more prominent, giving the placenta a "moth-eaten" appearance on ultrasound examination, independently of the size of the accreta area[38].

Strengths and limitation of the study

To our knowledge this the first study that has assessed the development of the utero-placental circulation in ongoing CSP. The comparison with controls implanted in the lower uterine segment immediately above the scar area allowed us to evaluate the impact of placentation within a cesarean scar at different gestational age on the uterine vasculature and intervillous circulation.

The primary limitation of our cohort study lies in its retrospective design. However, all the data of both the study cases and controls were collected according to a defined protocol and both clinical and ultrasound records were electronically stored in a dedicated database. In addition, the interpretation of the CDI score and diagnosis of hypervascularity are operator dependent.

Conclusions

CSP are high risk pregnancies due to the combined effect of major changes in the surrounding uterine vasculature, stretching of the prior cesarean scar and development of the placenta in the lower segment. The impact of a gestational sac developing inside and around a cesarean section scar on the surrounding uterine vasculature is immediate. The pattern of these utero-placental vascular changes may vary according to the depth the cesarean scar defect at the start of pregnancy. Further understanding of pathophysiology of these complications requires prospective investigations of the morphology of uterine niche before pregnancy.

References

1. Jurkovic D, Hillaby K, Woelfer B, Lawrence A, Salim R, Elson CJ. First trimester diagnosis and management of pregnancies implanted into the lower uterine segment cesarean section scar. Ultrasound Obstet Gynecol. 2003;21:220–7.
2. Rempen A, Albert P. Diagnosis and therapy of and therapy of an early pregnancy implanted in the cesarean section scar. Z Geburtshilfe Perinatol. 1990;194:46-8.
3. Harb HM, Knight M, Bottomley C, et al. Caesarean scar pregnancy in the UK: a national cohort study. BJOG. 2018;125:1663-1670.
4. Ben Nagi J, Ofili-Yebovi D, Marsh M, Jurkovic D. First-trimester cesarean scar pregnancy evolving into placenta previa/accreta at term. J Ultrasound Med. 2005;24:1569-73.
5. Timor-Tritsch IE, Monteagudo A, Cali G, et al. Cesarean scar pregnancy and early placenta accreta share common histology. Ultrasound Obstet Gynecol. 2014;43:383-95.
6. Zosmer N, Fuller J, Shaikh H, Johns J, Ross JA. Natural history of early first-trimester pregnancies implanted in cesarean scars. Ultrasound Obstet Gynecol 2015;46:367–75.
7. Calì G, Timor-Tritsch IE, Palacios-Jaraquemada J, et al. Outcome of cesarean scar pregnancy managed expectantly: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2018;51:169-175.
8. Roeder HA, Cramer SF, Leppert PC. A look at uterine wound healing through a histopathological study of uterine scars. Reprod Sci 2012; 19:463-473.

9. Wu C, Chen X, Mei Z, et al. A preliminary study of uterine scar tissue following cesarean section. J Perinat Med 2018; 46:379-386.
10. Schwalm H, Dubrauszky V. The structure of the musculature of the human uterus--muscles and connective tissue. Am J Obstet Gynecol. 1966;94:391-404.
11. Ofili-Yebovi D, Ben-Nagi J, Sawyer E, et al. Deficient lower-segment Cesarean section scars: prevalence and risk factors. Ultrasound Obstet Gynecol 2008; 31:72-77.
12. Bij de Vaate AJ, van der Voet LF, Naji O, et al. Prevalence, potential risk factors for development and symptoms related to the presence of uterine niches following Cesarean section: systematic review. Ultrasound Obstet Gynecol. 2014;43:372-382.
13. Antila-Langsjo RM, Maenpaa JU, Huhtala HS, Tomas EI, Staff SM. Cesarean scar defect: a prospective study on risk factors. Am J Obstet Gynecol 2018; 219:458.e1-458.e8.
14. Karpathiou G, Chauleur C, Dridi M, et al. Histologic findings of uterine niches. Am J Clin Pathol. 2020;154:645-655.
15. Ben-Nagi J, Walker A, Jurkovic D, Yazbek J, Aplin JD. Effect of cesarean delivery on the endometrium. Int J Gynaecol Obstet 2009;106:30-4.
16. Burton GJ, Woods AW, Jauniaux E, Kingdom JC. Rheological and physiological consequences of conversion of the maternal spiral arteries for uteroplacental blood flow during human pregnancy. Placenta. 2009;30:473-482.
17. Pijnenborg R, Dixon G, Robertson WB, Brosens I. Trophoblastic invasion of human decidua from 8 to 18 weeks of pregnancy. Placenta. 1980;1:3-19.

18. Jauniaux E, Zosmer N, Subramanian D, Shaikh H, Burton GJ. Ultrasound-histopathologic features of the utero-placental interface in placenta accreta spectrum. Placenta 2020;97:58-64.
19. Jauniaux E, Collins SL, Burton GJ. Placenta accreta spectrum: Pathophysiology and evidence-based anatomy for prenatal ultrasound imaging. Am J Obstet Gynecol 2018;218:75-87.
20. Collins SL, Ashcroft A, Braun T, et al; European Working Group on Abnormally Invasive Placenta (EW-AIP). Proposed for standardized ultrasound descriptions of abnormally invasive placenta (AIP). Ultrasound Obstet Gynecol 2016;47:271-275.
21. Jauniaux E, Collins SL, Jurkovic D, Burton GJ. Accreta placentation. A systematic review of prenatal ultrasound imaging and grading of villous invasiveness. Am J Obstet Gynecol 2016;215:712-721.
22. Jurkovic D, Hillaby K, Woelfer B, Lawrence A, Salim R, Elson CJ. First-trimester diagnosis and management of pregnancies implanted into the lower uterine segment Cesarean section scar. Ultrasound Obstet Gynecol. 2003;21:220-227.
23. Reddy UM, Abuhamad AZ, Levine D, Saade GR; Fetal Imaging Workshop Invited Participants. Fetal imaging: executive summary of a joint Eunice Kennedy Shriver National Institute of Child Health and Human Development, Society for Maternal-Fetal Medicine, American Institute of Ultrasound in Medicine, American College of Obstetricians and Gynecologists, American College of Radiology, Society for Pediatric Radiology, and Society of Radiologists in Ultrasound Fetal Imaging Workshop. J Ultrasound Med 2014;33:745-757.

24. Timmerman D, Valentin L, Bourne TH, et al. Terms, definitions and measurements to describe the sonographic features of adnexal tumors: a consensus opinion from the International Ovarian Tumor Analysis (IOTA) Group. Ultrasound Obstet Gynecol 2000;16:500-5.
25. Finberg HJ, Williams JW. Placenta accreta: prospective sonographic diagnosis in patients with placenta previa and prior cesarean section. J Ultrasound Med 1992;11:333-343.
26. Jauniaux E, Zaidi J, Jurkovic D, Campbell S, Hustin J. Comparison of colour Doppler features and pathological findings in complicated early pregnancy. Hum Reprod. 1994;9:2432-2437.
27. Jauniaux E, Greenwold N, Hempstock J, Burton GJ. Comparison of ultrasonographic and Doppler maping of the intervillous circulation in normal and abnormal early pregnancies. Fertil Steril. 2003;79:100-106.
28. Kaelin Agten A, Cali G, Monteagudo A, Oviedo J, Ramos J, Timor-Tritsch I. The clinical outcome of cesarean scar pregnancies implanted "on the scar" versus "in the niche". Am J Obstet Gynecol. 2017;216:510.e1-510.e6.
29. Shainker SA, Coleman B, Timor-Tritsch IE, et al. Special Report of the Society for Maternal-Fetal Medicine Placenta Accreta Spectrum Ultrasound Marker Task Force: Consensus on definition of markers and approach to the ultrasound examination in pregnancies at risk for placenta accreta spectrum. Am J Obstet Gynecol 2021;224:B2-B14.
30. Boyd JD and Hamilton WJ. The Human Placenta. Heffer and Sons, Cambridge, UK. 1970
31. Philips J, Gurganus M, DeShields S, et al. Prevalence of sonographic markers of placenta accreta spectrum in low-risk pregnancies. Am J Perinatol. 2019;36:733-780.

32. Jauniaux E, Watson AL, Hempstock J, Bao YP, Skepper JN, Burton GJ. Onset of maternal arterial blood flow and placental oxidative stress. A possible factor in human early pregnancy failure. Am J Pathol. 2000;157:2111-2122.

33. Jauniaux E, Hempstock J, Greenwold N, Burton GJ. Trophoblastic oxidative stress in relation to temporal and regional differences in maternal placental blood flow in normal and abnormal early pregnancies. Am J Pathol. 2003;162:115-125.

34. Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Schlatterer JP, Canfield RE, et al. Incidence of early loss of pregnancy. N Engl J Med 1988;319:189–94.

35. Zinaman MJ, Clegg ED, Brown CC, O'Connor J, Selevan SG. Estimates of human fertility and pregnancy loss. Fertil Steril 1996;65:503–9.

36. Fox H. Placenta accreta: 1945-1969. Obstet Gynecol Survey. 1972;27:475-490.

37. Panaiotova J, Tokunaka M, Krajewska K, Zosmer N, Nicolaides KH. Screening for morbidly adherent placenta in early pregnancy. Ultrasound Obstet Gynecol. 2019;53:101-106.

38. Jauniaux E, Hussein AM, Zosmer N, et al. A new methodologic approach for clinico-pathologic correlations in invasive placenta previa accreta. Am J Obstet Gynecol. 2020;222:379.e1-379.e11.

Table 1. Comparison of the maternal demographics and main ultrasound characteristics for the cesarean scar pregnancies (CSP) and controls.

Variables	**CSP (n= 27)**	**Controls (n=27)**	***P***
Mean maternal age (years)	35.7 (4.9)	37.0 (3.9)	.074[¶]
Mean parity	1.9 (1.2)	1.6 (1.0)	.162[¶]
Mean prior CDs	1.8 (1.1)	1.6 (0.8)	.203[¶]
Symptoms			
- Bleeding (%)	10 (37.0%)	3 (11.1%)	
- Pain (%)	2 (7.4%)	2 (7.4%)	
- Bleeding and pain (%)	2 (7.4%)	2 (7.4%)	.154*
6-10 weeks ultrasound examination			
Mean gestational age (weeks)	7.7 (0.9)	7.8 (1.0)	.859[¶]
Mean CRL (mm)	13.8 (6.9)	12.7 (7.9)	.761[¶]
Mean vascularity score	3.1 (0.8)	2.1 (0.3)	<.001[¶]
No of RMT < 2 mm	15 (55.6%)	0	<.001*
11-14 weeks ultrasound examination			
Mean gestational age (weeks)	12.2 (1.3)	12.5 (0.8)	.532[¶]
Subplacental hypervascularity (%)	14 (51.9%)	9 (33.3%)	.271*
Presence of lacunae (%)	11 (40.7%)	0	<.001

Numerical data are presented as mean (standard deviation) and categorical data as n (%). [¶]t-test; *Chi-square with Yates correction.

CRL: Crown-rump length; CD: Cesarean delivery

Table 2. Distribution of ultrasound examination findings at 19-22 weeks of gestation and outcome according to intraoperative findings and histopathology diagnosis at birth in 18 cases of ongoing cesarean scar pregnancies.

Findings	**PAS n =10**	**Normal placentation n=8**
Ultrasound imaging		
Low-lying placenta	0	2
Placenta previa	10	6
Myometrial thinning (< 1mm)	7	3
Subplacental hypervascularity	8	1
Lacunae	7	0
Outcome		
Elective CD $\geq$ 37 weeks	1	3
Emergency preterm CD (28-35 weeks)	1	4
Cesarean hysterectomy < 37 weeks	8	1

PAS: Placenta accreta spectrum; CD: Cesarean delivery

Table 3. Ultrasound features and outcomes in the ten CSP diagnosed with PAS at delivery.

Case No	6-10 wks	10-14 wks	19-22 wks	Outcome
1	RMT 1.1 mm V Score 4	Hypervascularity Lacunae 3+	Hypervascularity Lacunae 3+ MT < 1mm	Em CHT 29 wks for APH Placenta previa increta
2	RMT 1.3 mm V Score 4	Hypervascularity Lacunae 1+	Normal vascularity Lacunae 1+ MT 1-2mm	Em CHT 35 wks for APH Placenta previa creta
3	RMT 1.1 mm V Score 4	Hypervascularity Lacunae 2+	Hypervascularity Lacunae 3+ MT < 1mm	El CHT 36 wks Placenta previa increta
4	RMT 2.0 mm V Score 3	Hypervascularity No lacunae	Hypervascularity No lacunae MT <1 mm	Em CD & Partial myometrial resection 35 wks Placenta previa creta
5	RMT 0.3 mm V Score 3	Normal vascularity No lacunae	Hypervascularity No lacunae MT <1 mm	Em CHT 29 wks for APH Placenta previa increta
6	RMT 1.1 mm V Score 3	Hypervascularity Lacunae 2+	Hypervascularity Lacunae 2+ MT <1 mm	Em CHT 32 wks for APH Placenta previa increta
7	RMT 1.2 mm V Score 3	Hypervascularity Lacunae 2+	Hypervascularity Lacunae 3+ MT 1-2 mm	El CHT 35 wks Placenta previa creta
8	RMT 0.2 mm V Score 4	Normal vascularity No lacunae	Normal vascularity No lacunae MT 2.2 mm	El CD & Partial Myometrial resection 37 wks Placenta previa creta
9	RMT 3.1 mm V Score 3	Hypervascularity Lacunae 2+	Hypervascularity Lacunae 3+ MT <1 mm	Em CHT 31 wks for APH Placenta previa increta
10	RMT 0.5 mm V Score 3	Hypervascularity Lacunae 3+	Hypervascularity Lacunae 3+ MT < 1mm	Em CHT 28 wks for APH Placenta previa increta

RMT= Residual myometrial thickness; V Score= Vascularity score; MT= Myometrial thickness; El= elective; Em= Emergency; CHT= Cesarean hysterectomy; CD= cesarean delivery; APH= antepartum hemorrhage.

Figure legends

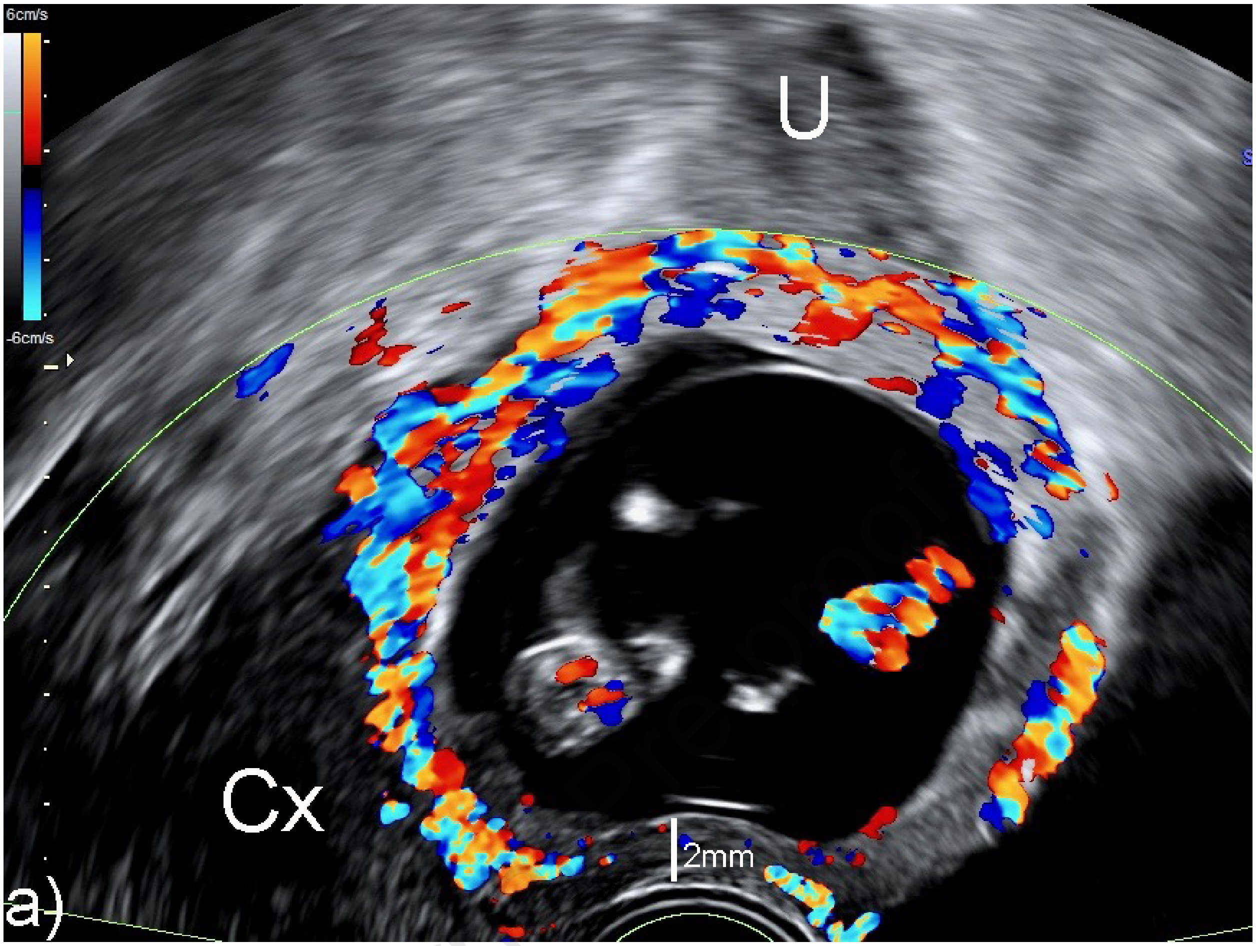
Fig 1. Transvaginal and transabdominal abdominal ultrasound views in case of CSP diagnosed as placenta previa accreta at 20 weeks and confirmed at birth as a placenta increta showing a): High vascularity around the gestational sac at 10 weeks of gestation; b) focal increased subplacental vascularity and lacunae at 14 weeks; c): Increased subplacental hypervascularity and intra-lacunar blood flow at 20 weeks; d) view of the lower placental edge containing numerous large lacunae (stage 3+) at 20 weeks. Bladder (B); Cervix (Cx); Placenta (P); Lacuna (L).

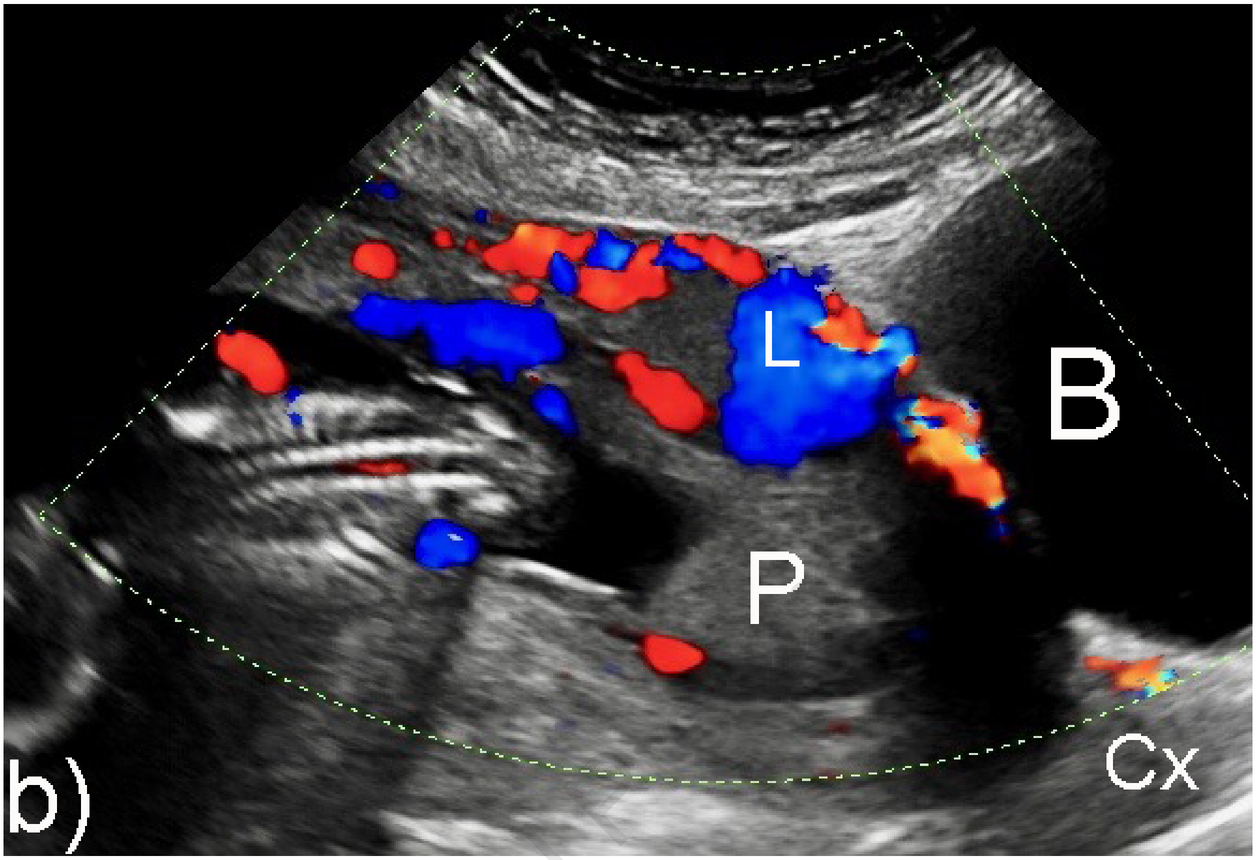
Fig 2. Transvaginal and transabdominal abdominal ultrasound views in case of CSP diagnosed as placenta previa at 20 weeks and confirmed at birth showing a): High vascularity around the gestational sac at 8 weeks of gestation; b) increased subplacental vascularity and lacunae at 12 weeks; c): Normal subplacental vascularity and appearance of the placenta at 20 weeks. Amniotic cavity (AC); Chorionic cavity (CC); Cervix (Cx); Placenta (P).

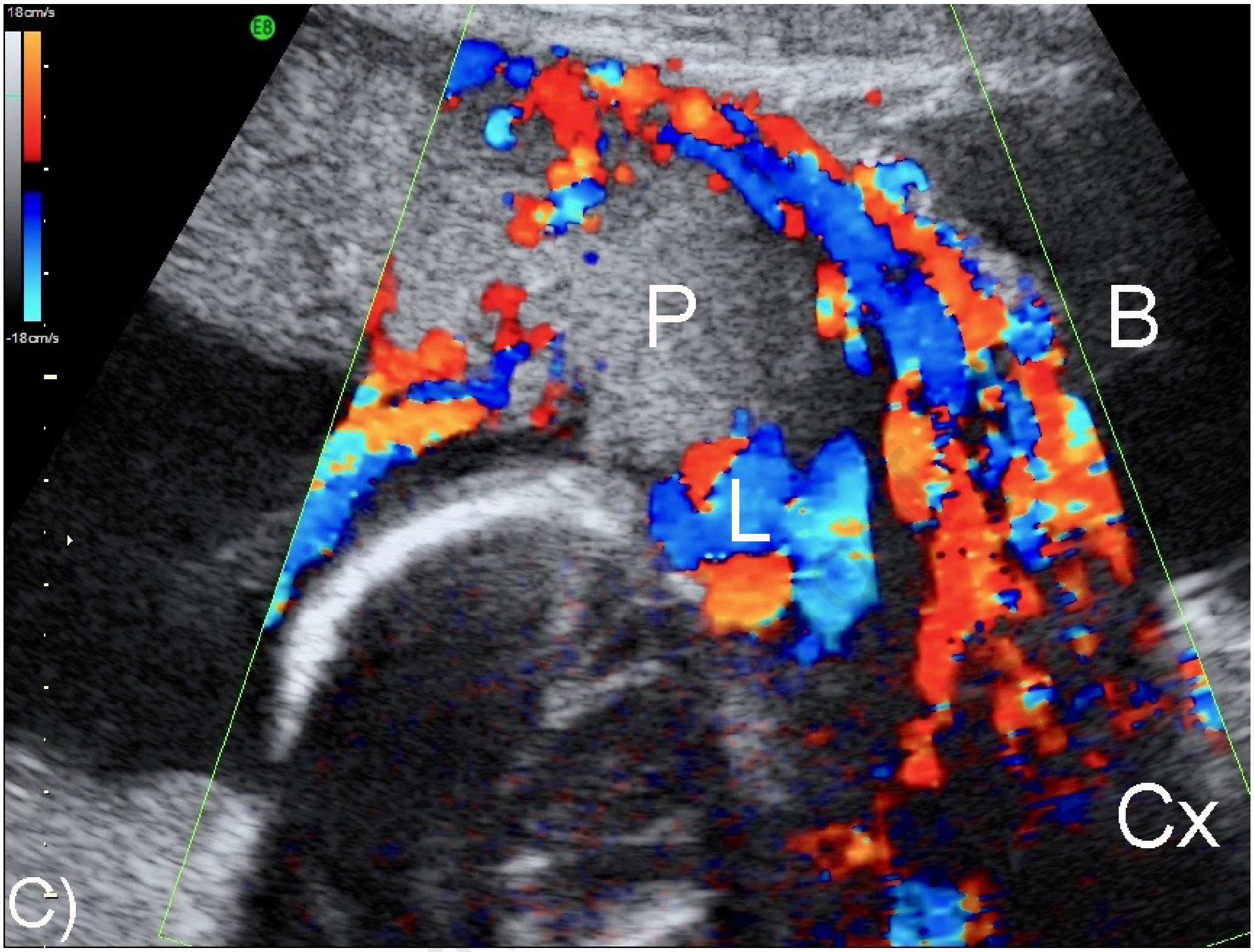
Fig 3. Transvaginal and transabdominal abdominal ultrasound views in case of CSP diagnosed as placenta previa at 20 weeks and confirmed at birth showing a): Moderate vascularity around the gestational sac at 8 weeks of gestation; b) Normal subplacental vascularity at 14 weeks; c): Normal subplacental vascularity at 20 weeks. Note the presence of marginal placental lakes (*). Amniotic cavity (AC); Cervix (Cx); Placenta (P).

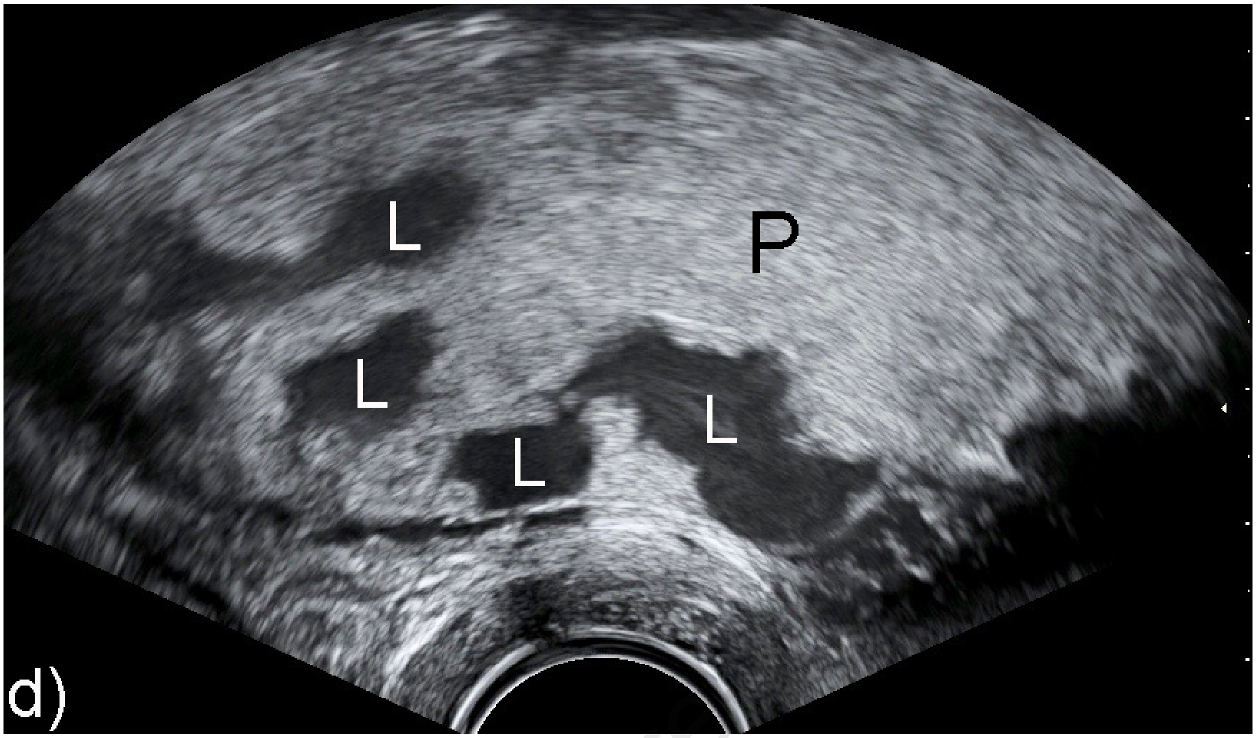
Fig 4. Transvaginal and transabdominal ultrasound views in control case diagnosed as placenta previa at 20 weeks and confirmed at birth showing a): Minimal vascularity around the scar area and lower part of gestational sac at 7 weeks of gestation; b) focal subplacental vascularity in the prior cesarean scar area at 13 weeks; c): Normal subplacental vascularity at 21 weeks. d) Focal subplacental vascularity between the placental bed and the cervix. Note the normal appearance of the placenta. Bladder (B); Gestational sac (GS); Amniotic cavity (AC); Cervix (Cx); Placenta (P).

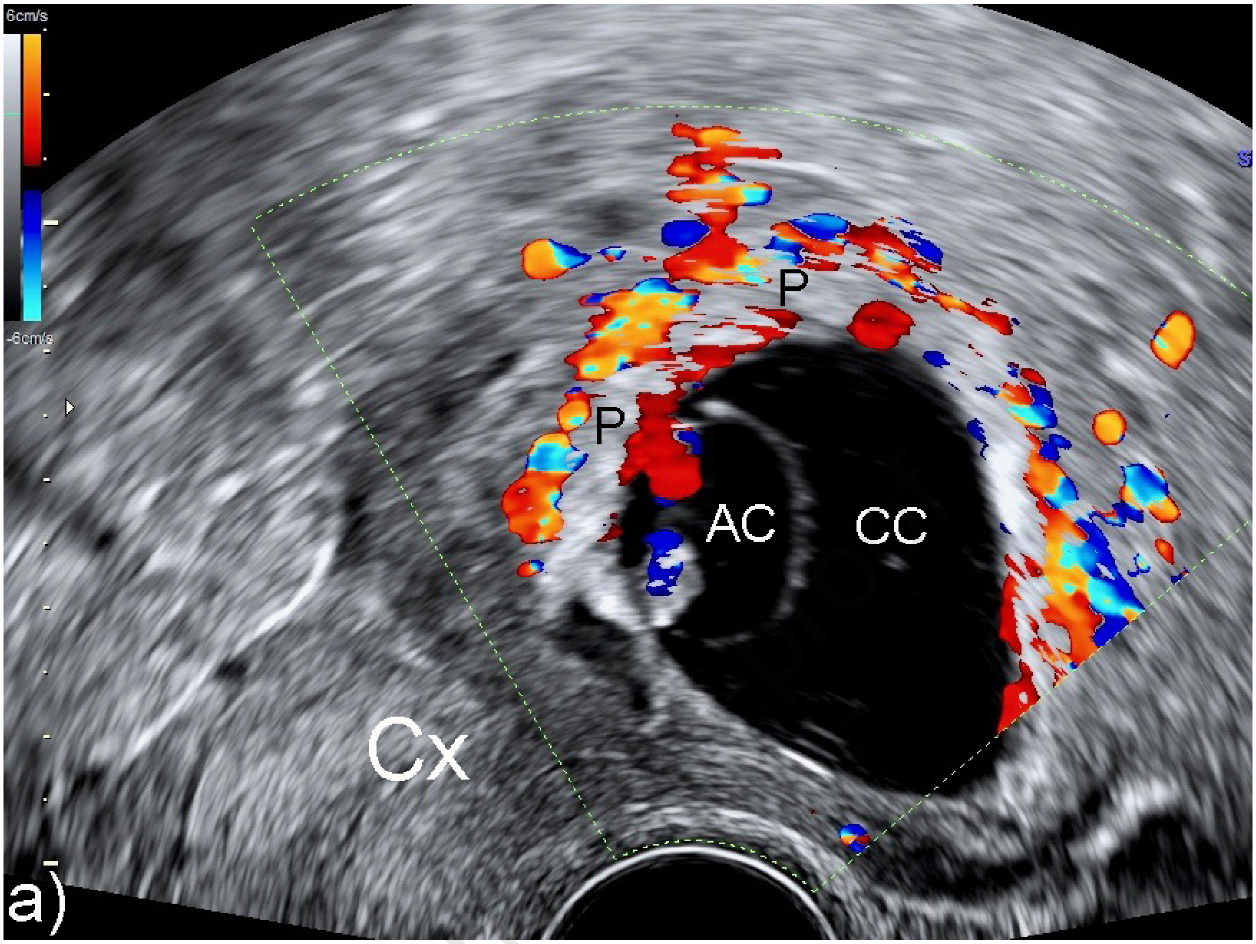
Fig 5. Transvaginal and transabdominal ultrasound views in control case diagnosed as low-lying placenta at 20 weeks showing a): a niche (N) at the junction between the cervix and the lower segment at 7 weeks of gestation; b) A lake with a feeder vessels in the prior cesarean scar area at 13 weeks. Bladder (B); Gestational sac (GS); Amniotic cavity (AC); Cervix (Cx); Placenta (P).

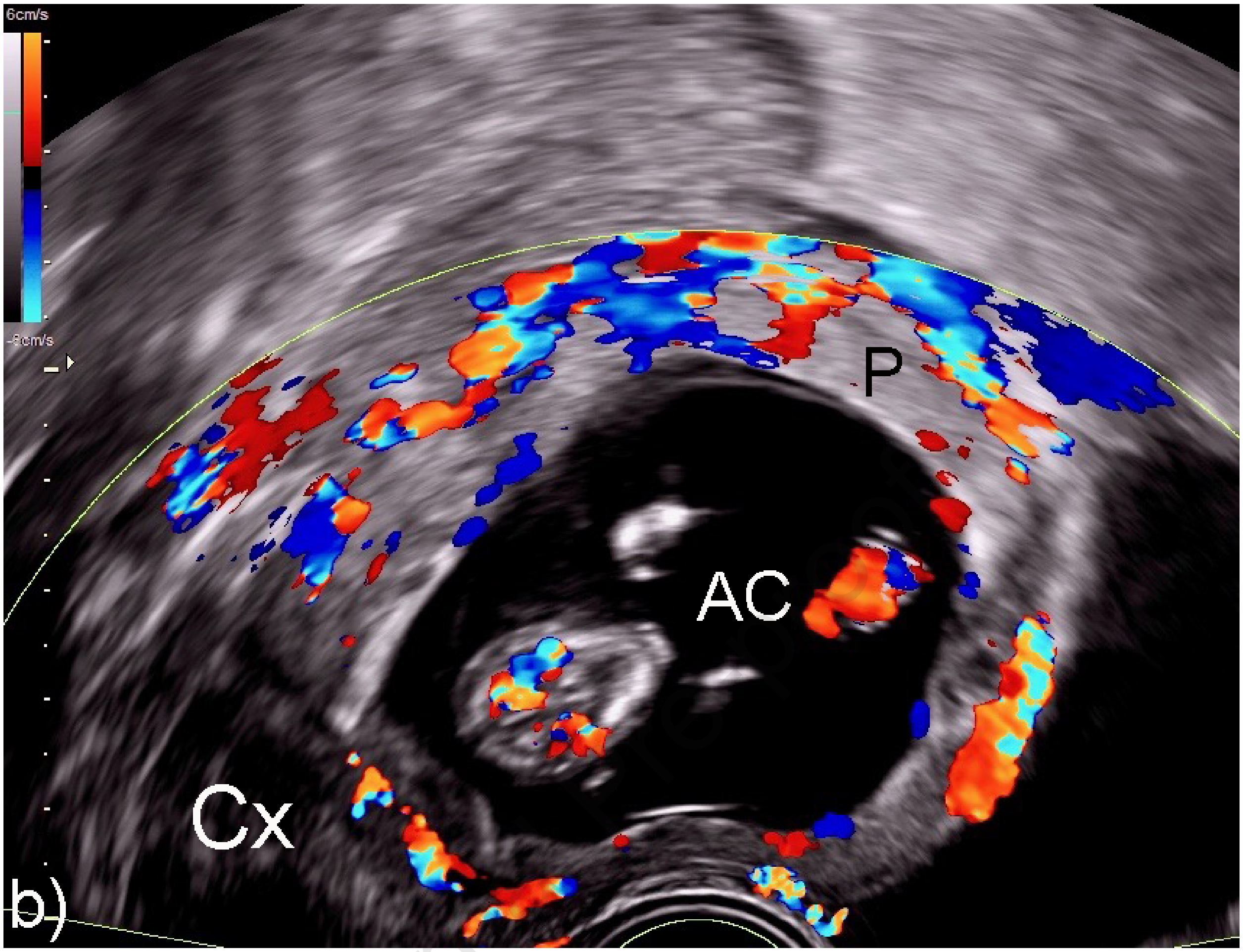

6cm/s
-6cm/s
U
Cx
2mm
a)

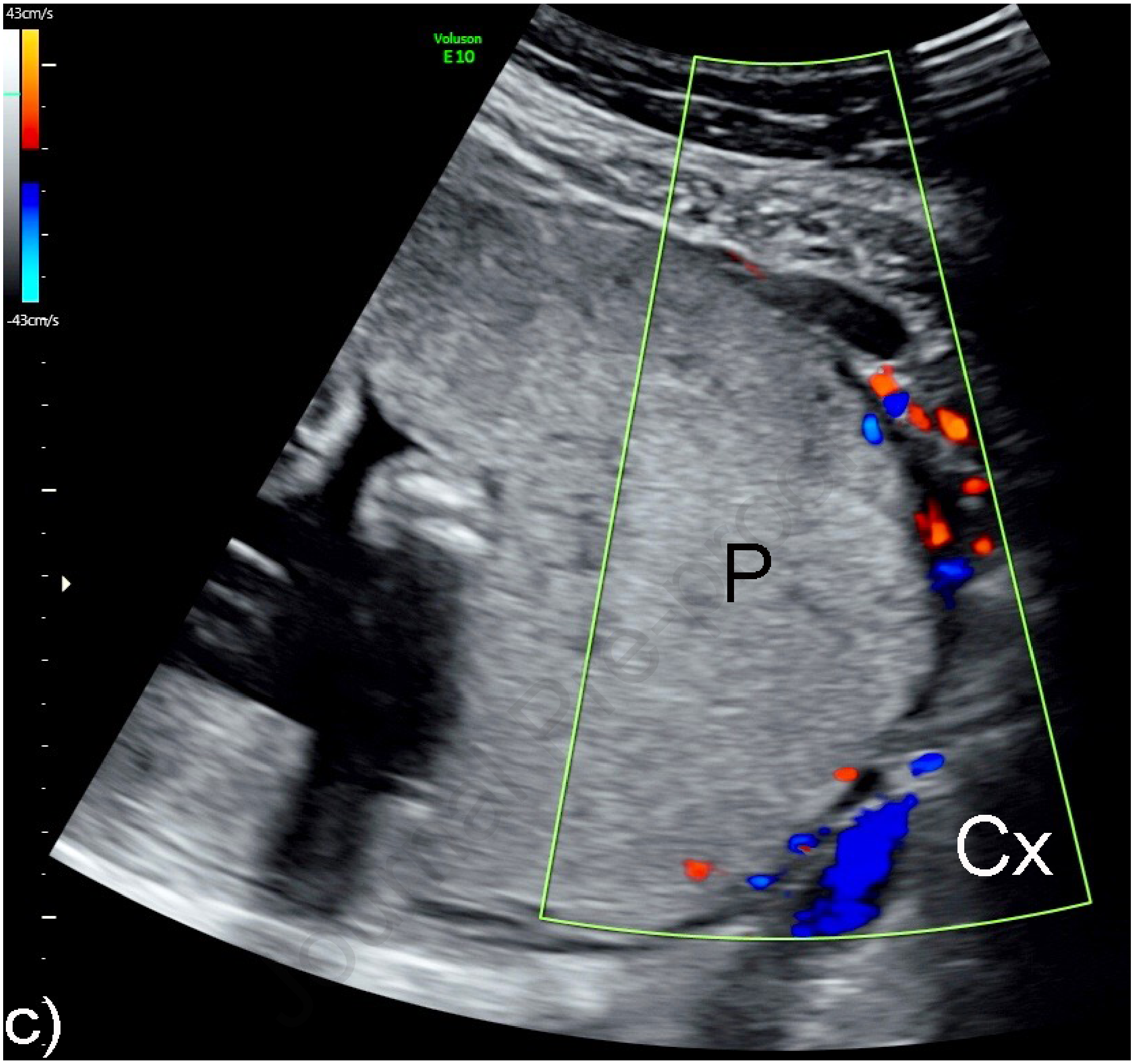

L
B
P
Cx
b)

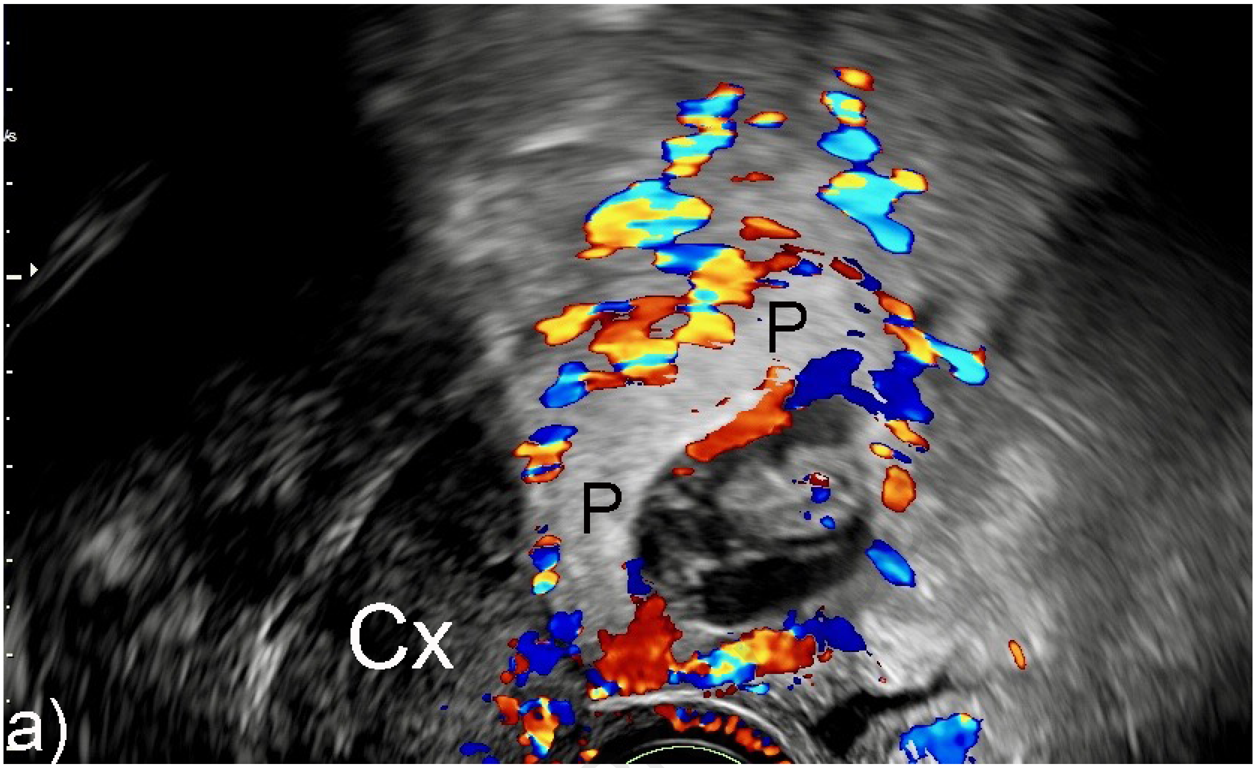

18cm/s
-18cm/s
P
B
L
Cx
C)

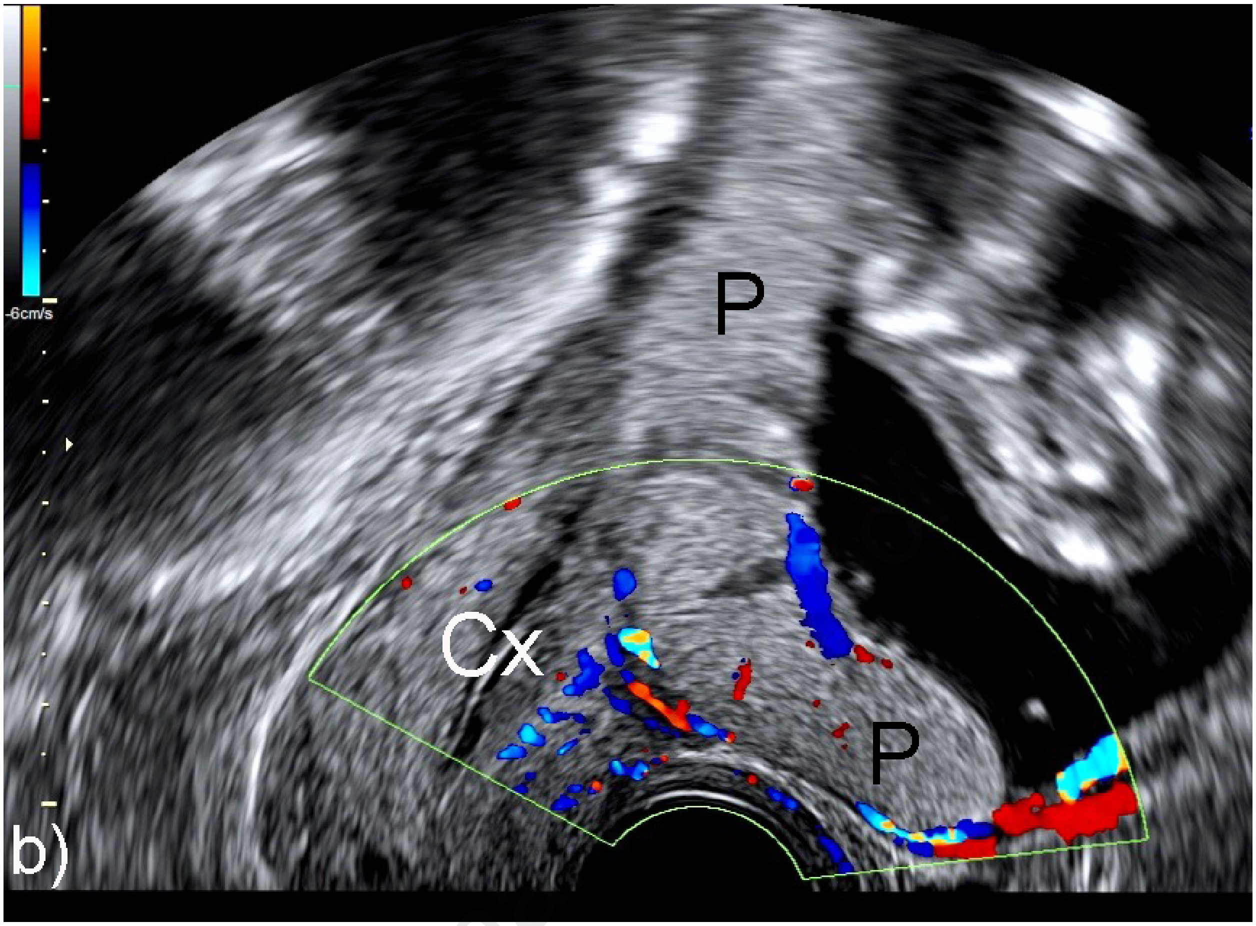

L
P
L
L
L
d)

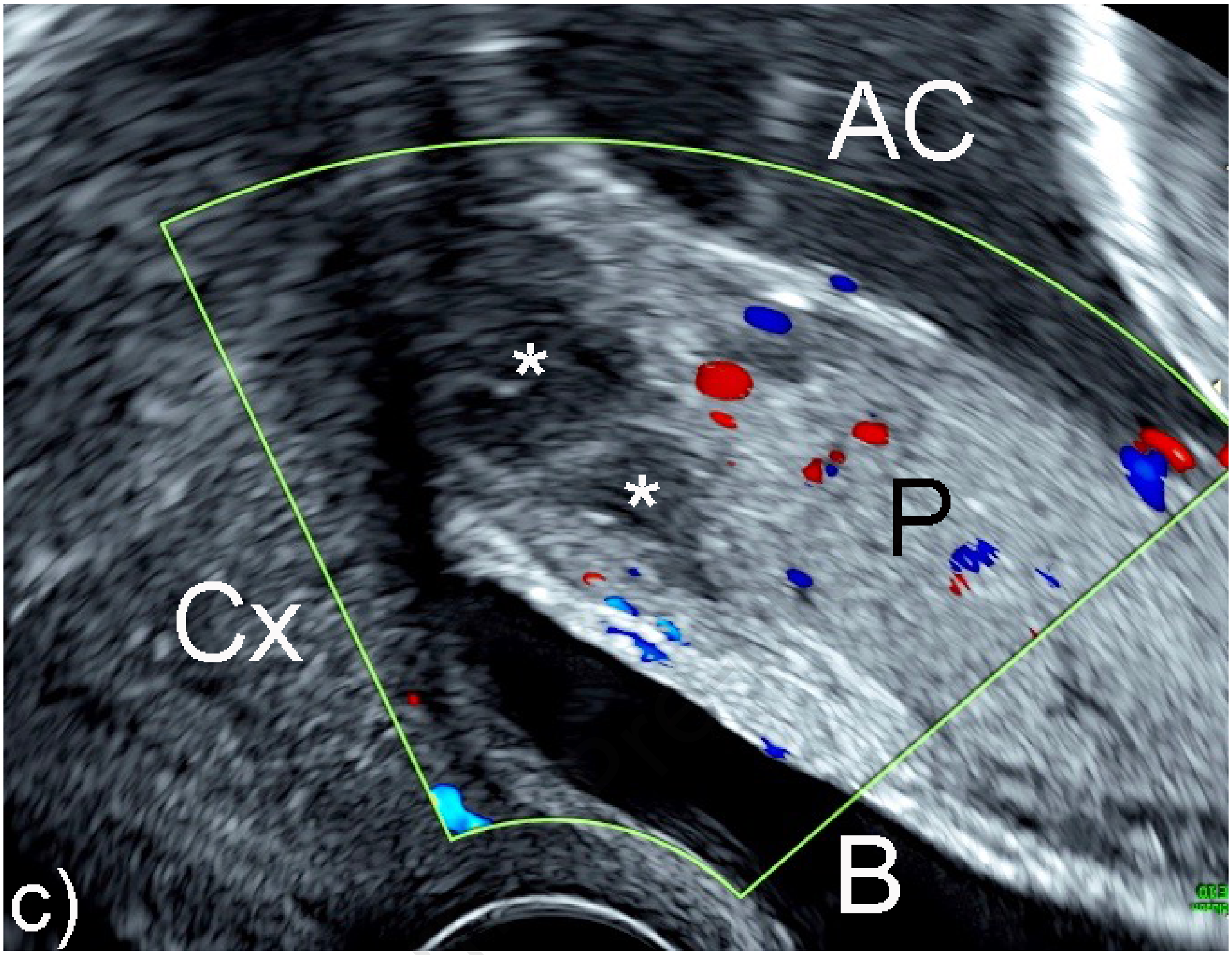

6cm/s
-6cm/s
P
P
AC
CC
Cx
a)

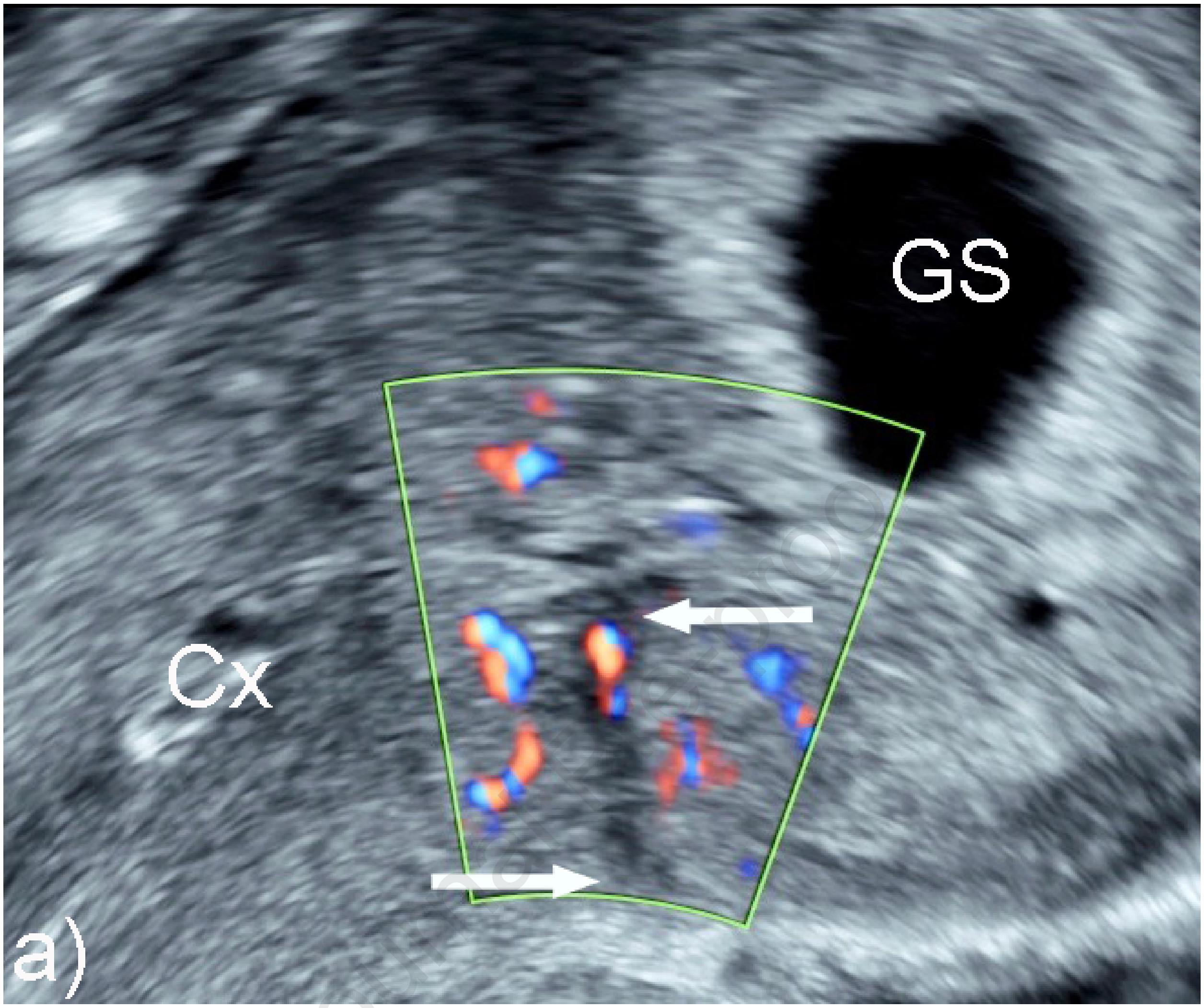

6cm/s
-6cm/s
P
AC
Cx
b)

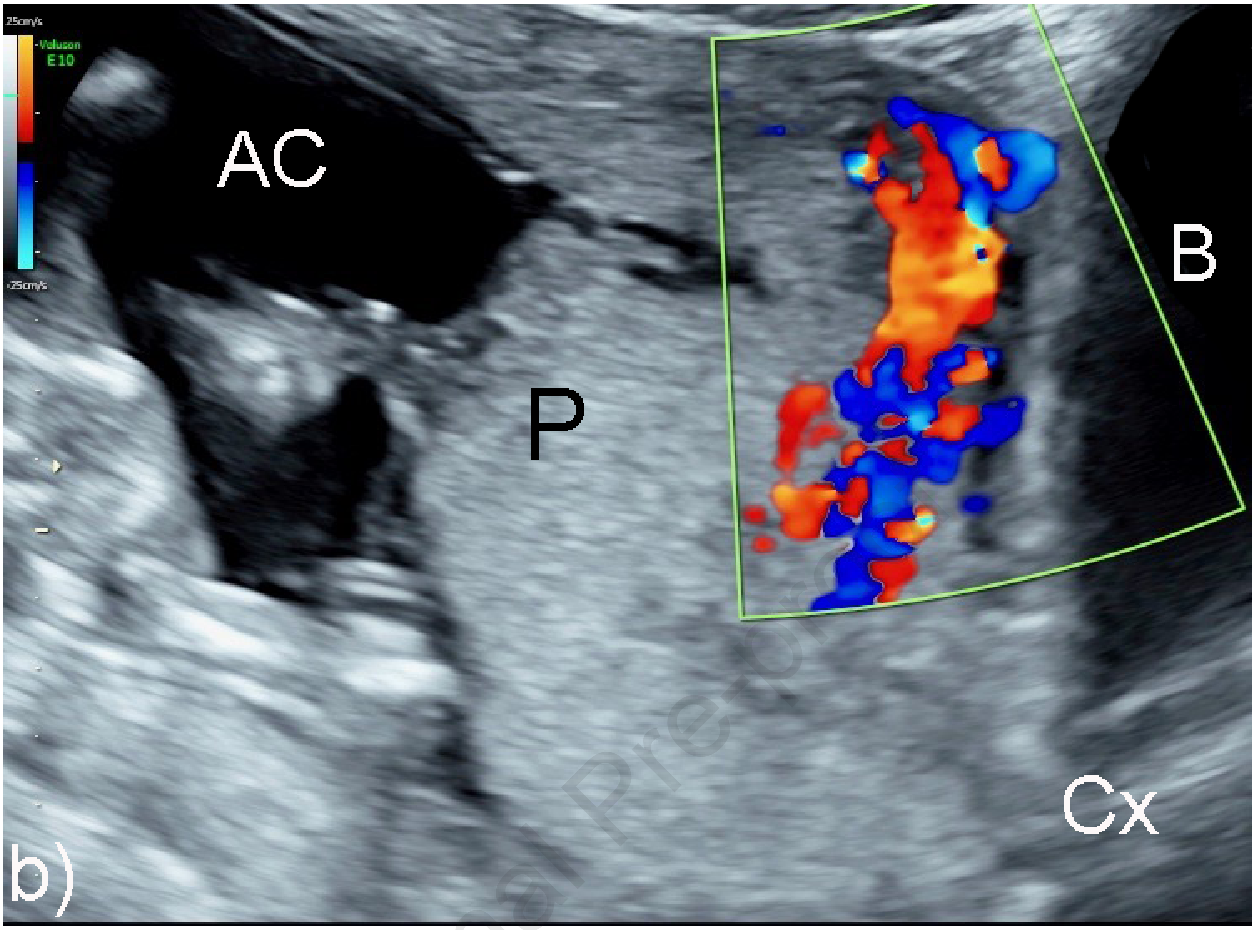

43cm/s
Voluson
E10
-43cm/s
P
Cx
c)


P
P
Cx
a)


-6cm/s
P
Cx
P
b)


AC
*
*
P
Cx
B
c)


GS
Cx
a)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P
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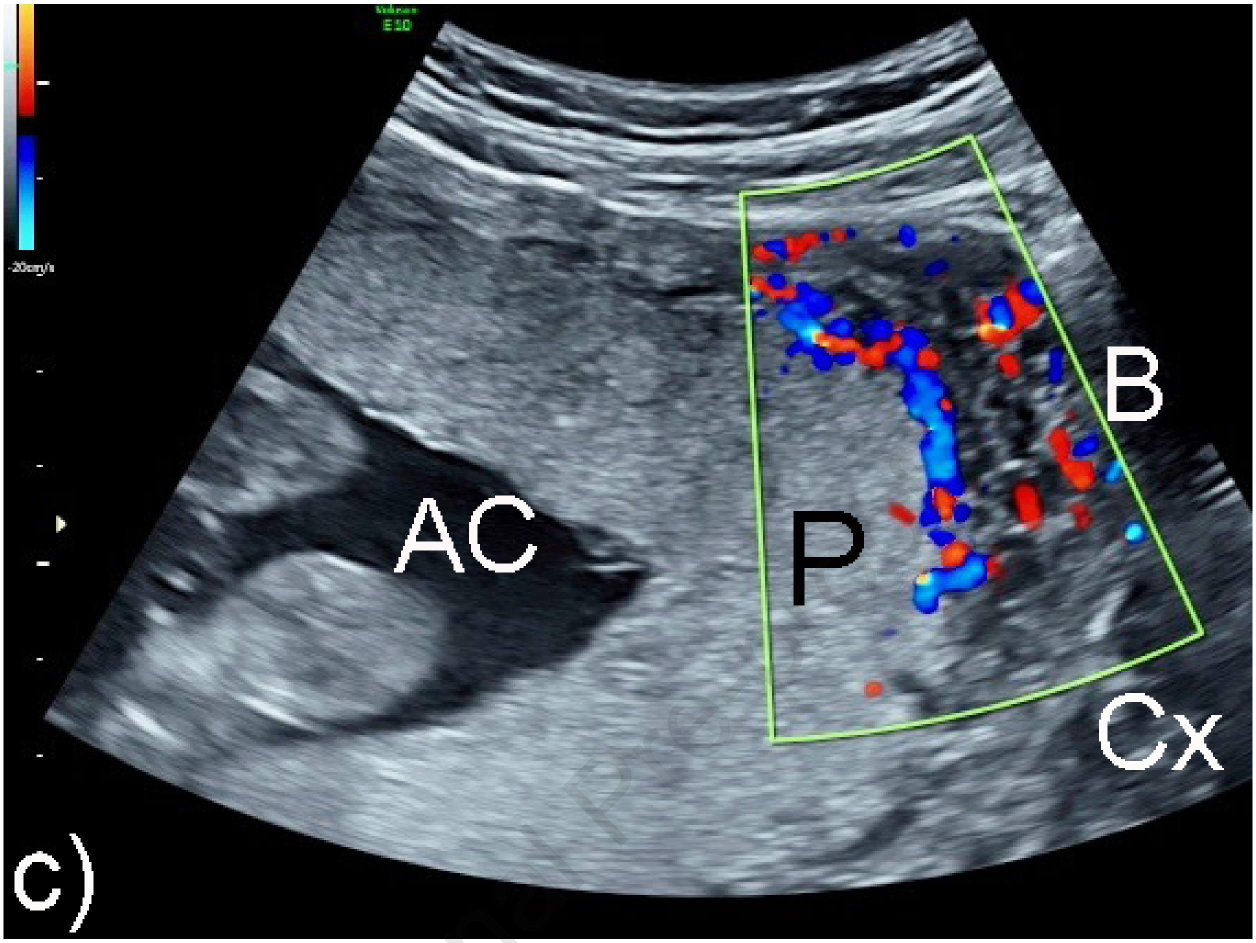
Cx
b)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P
B
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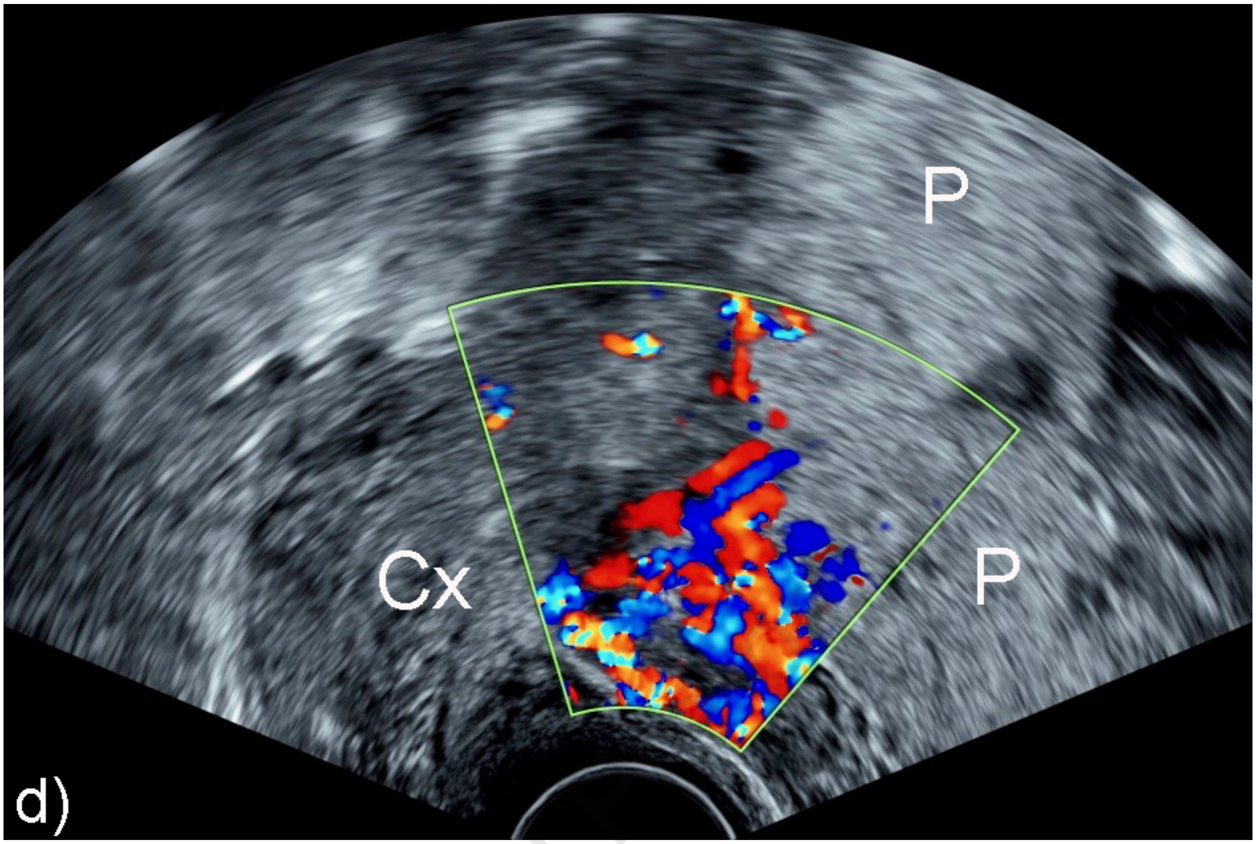
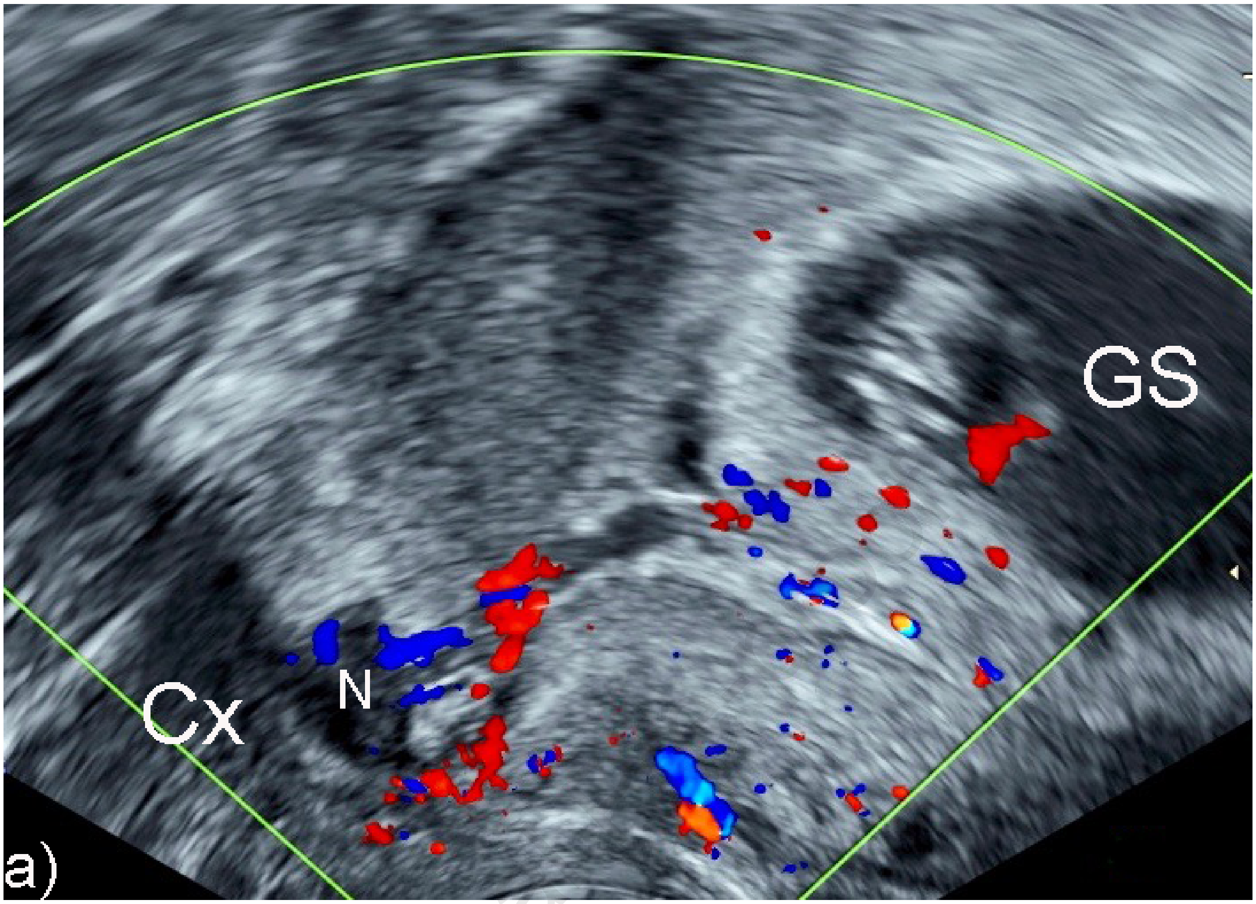
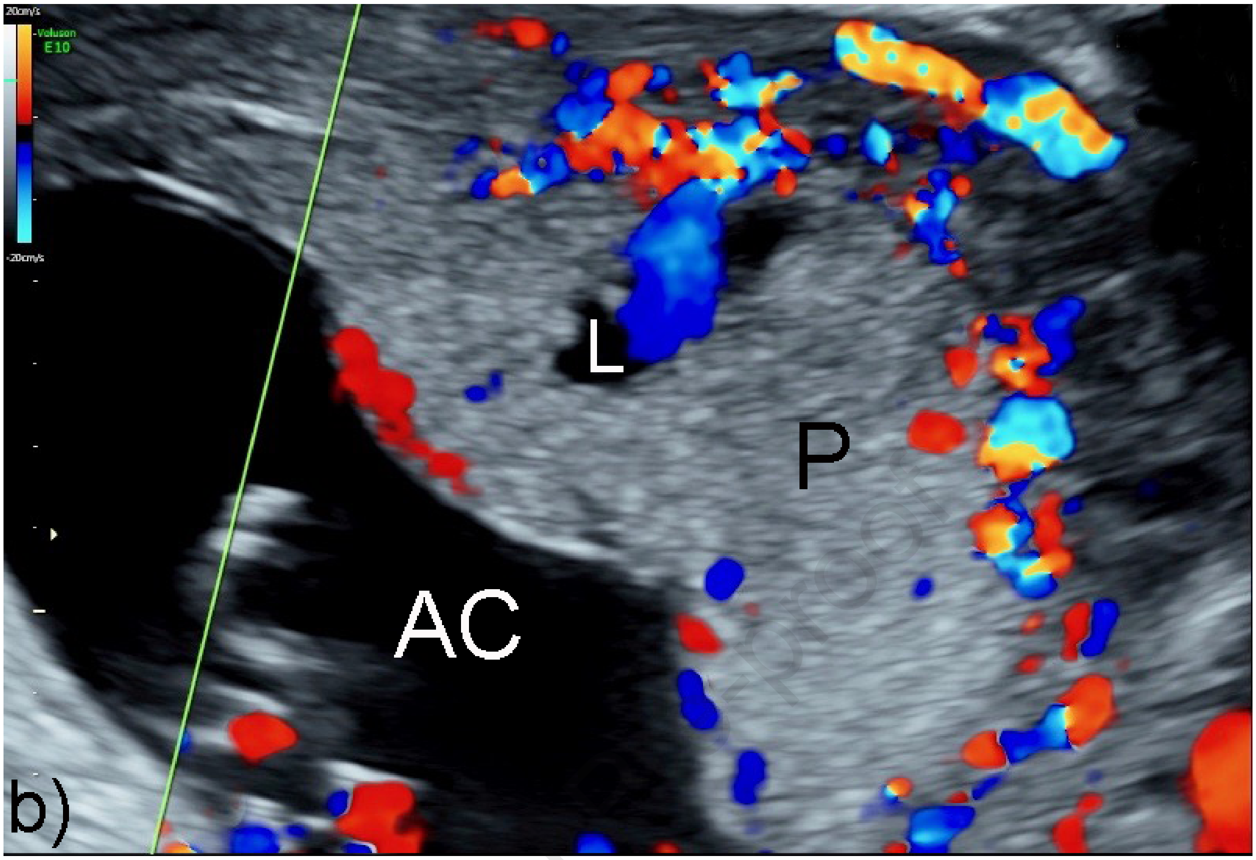
c)

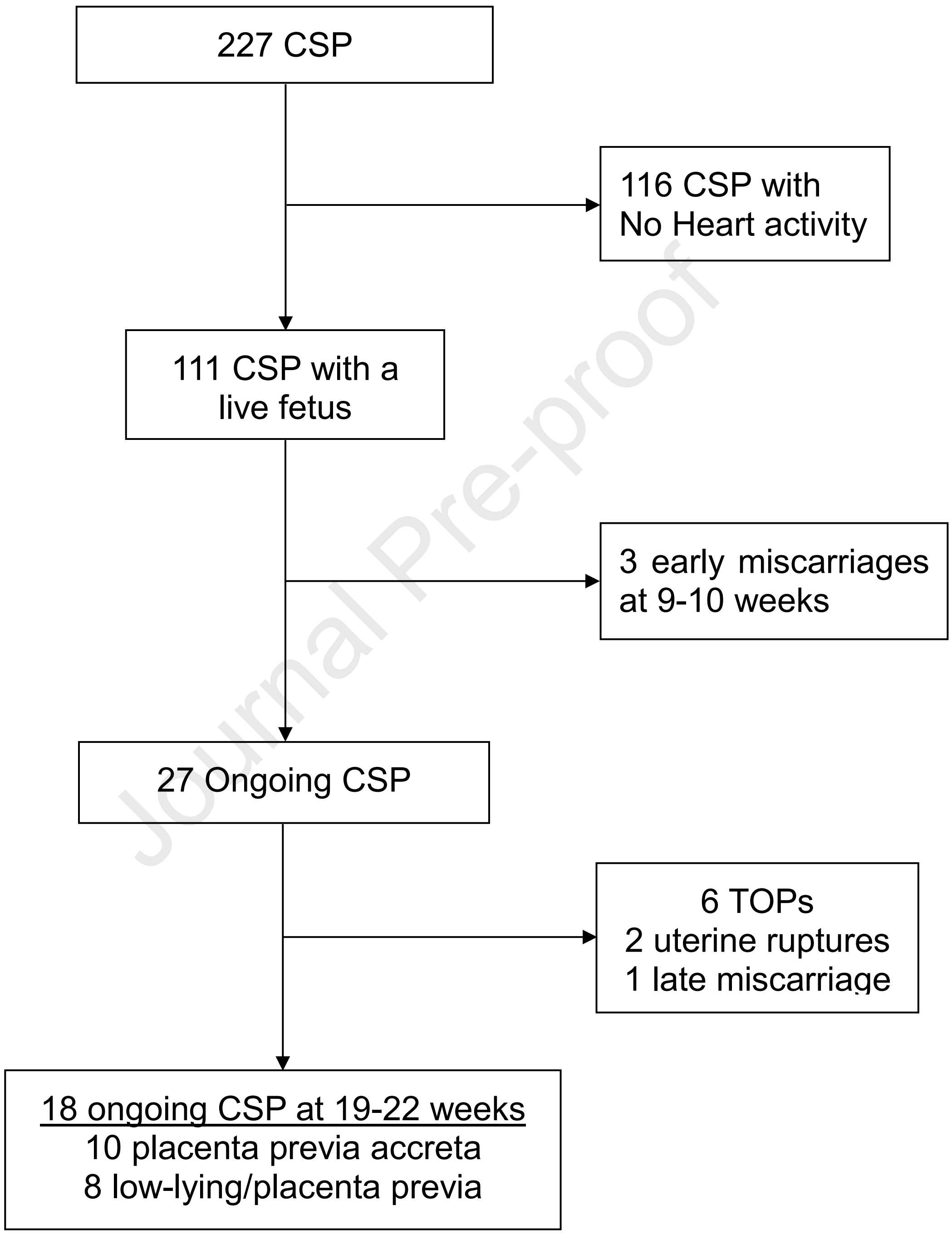

P
Cx
P
d)


GS
N
Cx
a)



L
P
AC
b)

Flow chart of the cases of cesarean section pregnancies (CSP) included in the study



TOP= Termination of pregnancy

Figure legends

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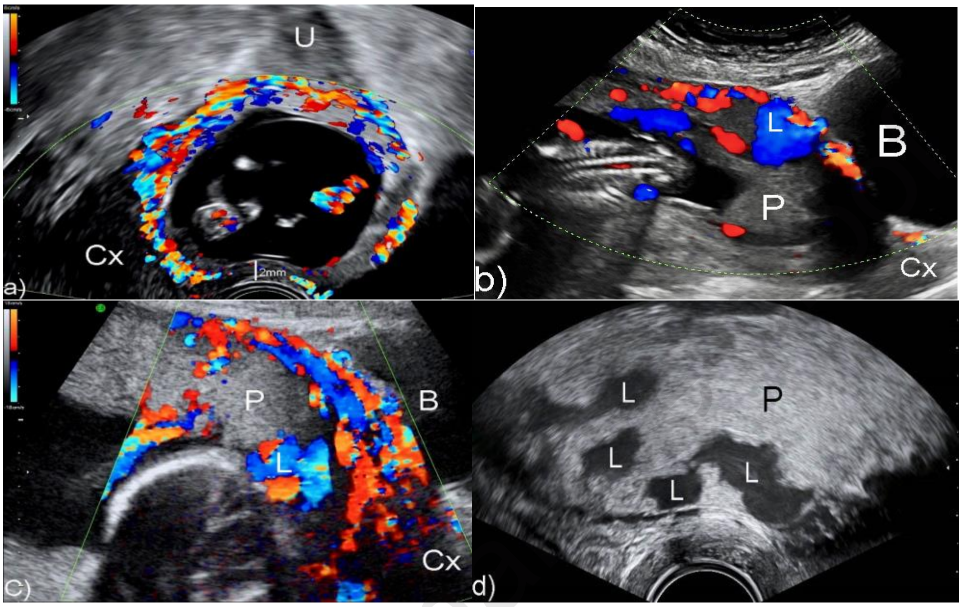

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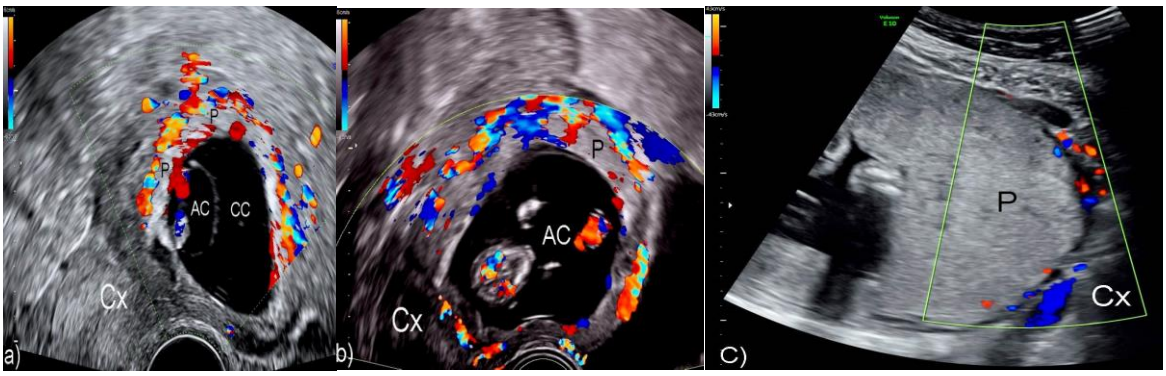

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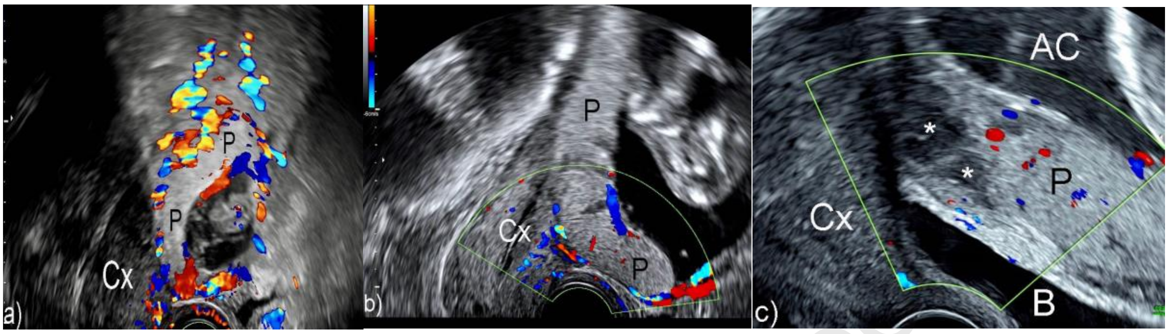

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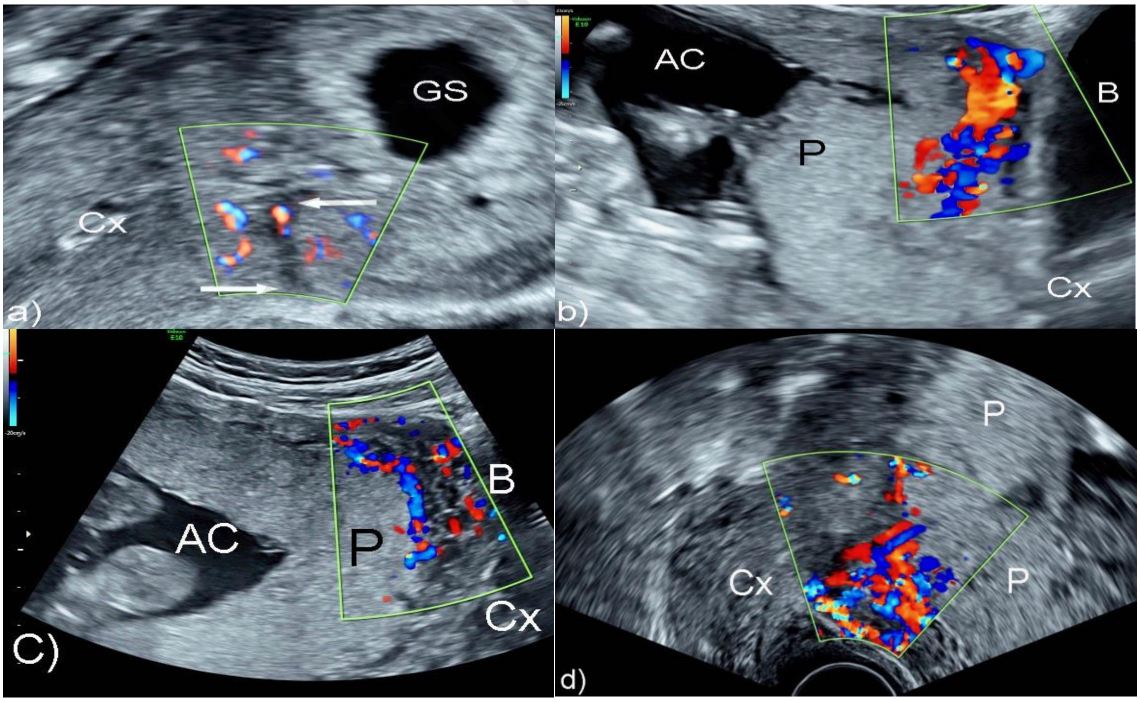

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