First trimester detection of abnormally invasive placenta in women at risk: a systematic review and meta-analysis

Francesco D'Antonio[1], Ilan E. Timor-Trisch[2], Josè Palacios-Jaraquemada[3], Ana Monteagudo[2], Danilo Buca[4], Francesco Forlani[5], Gabriella Minneci[5], Francesca Foti[5], Lamberto Manzoli[6], Marco Liberati[4], Ganesh Acharya[7], Giuseppe Calì[5]

1: Women´s Health and Perinatology Research Group, Department of Clinical Medicine, Faculty of Health Sciences, UiT-The Arctic University of Norway, Tromsø, Norway
2: Department of Obstetrics and Gynaecology, Division of Maternal-Fetal Medicine, New York University SOM, New York, NY, USA
3: Centre for Medical Education and Clinical Research (CEMIC), University Hospital, Buenos Aires, Argentina
4: Department of Obstetrics and Gynaecology, University of Chieti, Chieti, Italy
5: Department of Obstetrics and Gynaecology, Arnas Civico Hospital, Palermo, Italy
6: Department of Medical Sciences, University of Ferrara, Italy.
7: Department of Clinical Science, Intervention and Technology, Karolinska Institute, Stockholm, Sweden

Short Title: First trimester detection of AIP

Keywords: abnormally invasive placenta, first trimester diagnosis, ultrasound

Corresponding Author: Francesco D'Antonio, MD, PhD
Department of Clinical Medicine
Faculty of Health Sciences
UiT - The Arctic University of Norway
Hansine Hansens veg 18
9019 Tromsø, Norway
francesco.dantonio@uit.no

ABSTRACT

Objectives: The primary aim of this systematic review was to ascertain whether ultrasound (US) signs suggestive of abnormally invasive placenta (AIP) are present in the first trimester. The secondary aims were to ascertain the strength of association and the predictive accuracy of such signs in detecting AIP in the first trimester of pregnancy.

Methods: MEDLINE, EMBASE, CINAHL and Cochrane databases (2000-2016) were searched. Only studies reporting the first trimester diagnosis of AIP that was subsequently confirmed in the third trimester either during operative delivery or by pathology were included. Meta-analysis of proportion, random-effect meta-analysis and hierarchical summary receiver operating characteristic curve (HSROC) analysis were used to compute the data.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/uog.18840

Results: Seven studies (551 pregnancies at risk for AIP) were included. At least one ultrasound sign suggestive of AIP was detected in 91.4% (95% CI 85.8-95.7) of cases with confirmed AIP. The most common ultrasound feature in the first trimester of pregnancy was a low implantation of the gestational sac close to the previous uterine scar which was observed in 82.4% (95% CI 46.6-99.8) of the cases. Anechoic spaces within the placental mass (lacunae) 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) cases affected by AIP. Pregnancies with a low implantation of the gestational sac had a significantly higher risk of AIP, (OR:19.6, 95% CI 6.7-57.3), with a sensitivity and a specificity of 44.4% (95% CI 21.5-69.2) and 93.4% (95% CI 90.5-95.7) respectively.

Conclusions: Ultrasound signs of AIP are already present during the first trimester of pregnancy, especially before 11 weeks of gestation. Low anterior implantation of the placenta/sac close to or within the scar was the most common early US signs suggestive of AIP, although its individual predictive accuracy is not high.

INTRODUCTION

Abnormally invasive placenta (AIP) encompasses a spectrum of conditions characterized by an abnormal adherence of the placenta to the implantation site[1-4]. AIP is associated with the occurrence of several major maternal complications such as severe hemorrhage, need for blood transfusion, peri-partum hysterectomy, intra- and post-operative complications and an increased risk of adverse perinatal outcome.[1] Accurate prenatal diagnosis of AIP is desirable because it has been shown to reduce the burden of maternal and fetal morbidity associated with this condition, especially by allowing implementation of pre-planned management strategies[5-13].

The underlying mechanisms leading to AIP are not entirely understood yet. A defective development of the decidua basalis constitutes the anatomical prerequisite for the occurrence of AIP[14-16]. More recently, several studies have shown that caesarean scar pregnancy (CSP), a condition in which gestational sac implants on or in close proximity to the previous caesarean section (CS) scar, represents the precursor of AIP, although it is not entirely certain yet whether all the different sub-types of AIP share this pathophysiology[17].

Although prenatal diagnosis of AIP is commonly accomplished during the second or third trimester of pregnancy, there are reports suggesting that signs of AIP are already present in early pregnancy[18-20]. Furthermore, the recently proposed association between CSP and AIP suggests that the invasion of the uterine scar by trophoblastic tissue may start in early pregnancy, thus being theoretically detectable at the first trimester scan[17].

The primary aim of this systematic review was to ascertain whether ultrasound signs suggestive of AIP are present at the first trimester scan (<14 weeks of gestation); the secondary aims were to ascertain the strength of association and the predictive accuracy of such signs in detecting AIP in the first trimester of pregnancy.

MATERIALS AND METHOD

This review was performed according to an a-priori designed protocol and recommended for systematic reviews and meta-analysis.[21-23] MEDLINE, EMBASE, CINAHL and The Cochrane Library including The Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and The Cochrane Central Register of Controlled Trials (CENTRAL) were searched electronically on 23rd February 2017 and utilizing combinations of the relevant medical subject heading (MeSH) terms, key words, and word variants for "Abnormal invasive placenta" "morbidly adherent placenta" and "ultrasound" (Supplementary Table 1). The search and selection criteria were restricted to English language. Reference lists of relevant articles and reviews were hand searched for additional reports. Prisma and STARD guidelines were followed.[24,25] The study was registered with the PROSPERO database (Registration number: CRD42017060513).

Studies were assessed according to the following criteria: population, prenatal diagnosis of AIP during the first trimester of pregnancy and study design. AIP was defined based on clinical observation of abnormal placental adherence with evidence of gross placental invasion at the time of surgery and/or histopathological diagnosis of trophoblastic invasion through the myometrium with the absence of normal decidua at the basal plate.

Only studies reporting the first trimester diagnosis of AIP confirmed in the third trimester of pregnancy either at surgery or by pathological examination were included in the analysis. Studies reporting exclusively the prenatal diagnosis of AIP after first or second trimester abortion and those including only exclusively cases of CSP were excluded, on the basis that such anomalies may represent only the worst spectrum of invasive placental disorders.

Prospective and retrospective cohorts, case-control studies and case series were analyzed. Opinions and studies carried out only in the second and/or third trimester of pregnancy were excluded. Case reports were also excluded to avoid publication bias. Studies published before 2000 were excluded, as we considered that advances in prenatal imaging techniques, improvements in the diagnosis and definition of AIP make these less relevant.

First trimester US signs of AIP explored in the present systematic review were: location of gestational sac within the lower part of the uterus in the isthmic region in proximity to the scar of a previous CD, presence of intra-placental lacunae, reduced myometrial thickness between the placenta/gestation sac and the bladder and abnormal uterine bladder interface[16,17,20]. Gestational age at which the ultrasound was performed was also recorded.

Two reviewers (FD, DB) independently extracted data. Inconsistencies were discussed among the reviewers and consensus reached. For those articles in which targeted information was not reported but the methodology was such that the information might have been recorded initially, the authors were contacted requesting the data. Histopathological findings and/or surgical notes were used as a gold standard.

Quality of studies was assessed using the revised tool for the quality assessment of diagnostic accuracy studies (QUADAS-2.[26] Each item was scored a ''yes'', ''no'', or ''unclear'' if there was insufficient information to make an accurate judgment.

Funnel plots displaying the outcome rate from individual studies *vs* their precision (1/standard error) were carried out with an exploratory aim. Tests for funnel-plot asymmetry were not used when the total number of publications included for each outcome was less than ten. In this case, the power of the test is too low to distinguish chance from real asymmetry.

First, we explored the prevalence of the different US–signs suggestive of AIP at the first trimester scan; for the purpose of this analysis, meta-analysis of proportion was used to analyse the data. Then, we explored the strength of association between the different US signs reported in the published literature, and the occurrence of any type of AIP; we planned to use random-effect meta-analysis to compute a summary odd ratio (OR) of the likelihood of each US sign in fetuses with or without AIP.[26-28] A sensitivity analysis was performed in order to evaluate the occurrence of each explored US sign in cases scanned before 11 weeks of gestation.

Finally, we evaluated the diagnostic accuracy of first trimester ultrasound compared to intraoperative/histopathological diagnosis. We computed summary estimates of sensitivity, specificity, positive and negative likelihood ratios (LR+ and LR-) and diagnostic odds ratio (DOR) for the overall predictive accuracy of first trimester US in detecting AIP using the hierarchical summary receiver operating characteristic (HSROC) model.[30-33] Rutter and Gatsonis HSROC parameterization was used because it models functions of sensitivity and specificity to define a summary ROC curve, and its hierarchical modelling strategy can be used for comparisons of test accuracy when there is variability in threshold between studies.[30-33]

Statsdirect (StatsDirect Ltd. StatsDirect statistical software. http://www.statsdirect.com. England: StatsDirect Ltd. 2013) was used to analyze the data.

RESULTS

A total of 876 articles were identified. After screening the abstracts, 51 full text articles were assessed with respect to their eligibility for inclusion (Supplemental Table 2) and 7 studies were included in the systematic review (Table 1, Figure 1).[35-43] These 7 studies included 551 pregnancies at risk for AIP, out of these 117 (30.9%, 95% CI 19.4-48.9) had AIP. The occurrence of placenta accreta, increta and percreta was 45.3% (95% CI 36.7-54.3), 15.4% (95% CI 10.0-23.0) and 24.8% (95% CI 17.9-33.3), respectively.

General characteristics of the studies included in the present systematic review are reported in Table 1. Most of the included studies were retrospective series including only cases of AIP confirmed either at surgery or by histopathology, thus not allowing an objective assessment of specificity of ultrasound in ruling out AIP at the time of first trimester scan. Similarly, the evaluation of the diagnostic accuracy in term of specificity could not be assessed in view of the lack of false positive and true negative cases for the majority of the US signs explored. Quality assessment based on QUADAS-2 guidelines is shown in Figure 2.

Some of the included studies had high or unclear risk of bias regarding the patient selection and index test, especially because of the heterogeneity in gestational age at scan and definition of individual US signs, while there was an overall low risk of bias regarding the reference standard. However, it should be taken into account that such tests have a low statistical power where the overall number of publication is less than ten, such as in the present review.[28]

When considering all studies on first trimester diagnosis of AIP, at least one US sign suggestive of AIP was detected in 91.4% (95% CI 85.8-95.7) of cases with confirmed AIP at delivery. The most common US feature in the first trimester of pregnancy was a low implantation of the gestational sac close to the previous uterine scar which was observed in 82.4% (95% CI 46.6-99.8), of the cases, while anechoic spaces within the placental mass (lacunae) were observed in 46.0% (95% CI 10.9-83.7) (Table 2, Figures 3 and 4).

Myometrial thickness was assessed by four studies; Rac et al. reported several cut-offs of myometrial thickness although the ones which showed the optimal combination of sensitivity and specificity were 5 and 6 mm, while in the study by Comstock et al. the authors compared the anterior with posterior myometrium and defined reduced myometrial thickness as anterior myometrium thinner than the posterior[35,37,39,42]. Overall, a reduced myometrium thickness was present in 66.8% (95% CI 45.2-85.2) of cases of AIP scanned in the first trimester.

Finally, two studies, reported the assessment of an abnormal uterine bladder interface in the first trimester of pregnancy and reported an overall prevalence of this sign in 51.84% of cases affected by AIP (Figure 3) [37,40].

When considering only cases scanned before 11 weeks of gestation, the presence of at least one US signs suggestive of AIP was present in 95.1% (95% CI 75.3-99.5) of the cases, with a low implantation of the gestational sac within the CD scar being visible in all affected cases affected by AIP. However, it was not possible to perform a comprehensive pooled assessment on the prevalence of the other ultrasound signs explored in the present systematic review in view of the very small number of included cases.

A pooled risk assessment between different US signs and AIP could be performed only for the low implantation of the gestational sac and intra-placental lacunae. Two studies explored the strength of association between a low implantation of the gestational sac and the occurrence of AIP in a population at risk for these anomalies such as women with a previous CD[42,43]; the study by Stinnerman et al. included women scanned between 11 and 14, while that by Rahimi-Sharbaf et al. those assessed between 9 and 14 weeks of gestation. Overall, cases with a low implantation of the gestational sac had a significantly higher risk of AIP, with an OR of 19.6 (95% CI 6.7-57.3; I^2: 0%). Once translated this figure into predictive accuracy, a low implantation of the gestational sac had a sensitivity of 44.4% (95% CI 21.5-69.2), a specificity of 93.4% (95% CI 90.5-95.7), a LR+ of 7.5 (95% CI 3.8-14.9) a LR- of 0.6 (0.4-0.9) and a DOR of 11.0 (4.0-30.3) in the detection of AIP.

The presence of intra-placental lacunae in the first trimester of pregnancy did not carry an increased risk of AIP (OR: 1.03, 95% CI 0.2-4.8); likewise, the diagnostic accuracy was poor, with a sensitivity of 33.3% (95% CI 11.8-61.6), a specificity of 67.5% (50.9-81.4), a LR+ of 1.4 (95% CI 0.5-3.6), a LR- of 0.9 (0.6-1.3), and a DOR of 1.0 (95% CI 0.7-1.6).

DISCUSSION

Main findings

The findings from this systematic review showed that US signs suggestive of AIP can be detected since the first trimester of pregnancy. At least one US sign suggestive of AIP was detected in 91.4% (95% CI 85.8-95.7) of all cases and in 95.1% (95% CI 75.3-99.5) of those scanned before 11 weeks of gestation. Low anterior implantation of the placenta/sac close to or within the scar was the most common early US signs associated of AIP, although its individual predictive accuracy was not high.

Strengths and limitations

The very small number of cases per each included study represents the major limitation of the present systematic review. In such situations, the estimates of the variances of the random effects are subject to a high level of uncertainty, and caution is required when interpreting the results.

Heterogeneity in the inclusion criteria among the different studies and their retrospective design is another major limitation of this systematic review. The majority of the studies included exclusively cases with surgically or histologically confirmed AIP, thus making it impossible to extrapolate any information regarding the specificity of first trimester ultrasound in ruling out AIP. Furthermore, the included studies differ as regards to the gestational age at assessment, type of scan and population analyzed. The present systematic review, included mainly women at risk for AIP; however, such risk assessment differed among the included studies and was ascertained at the time of the second or third trimester scan (i.e. women with placenta previa or and previous CD), thus not being clinically applicable to women in the first trimester of pregnancy. AIP is still a relatively rare anomaly and the large majority of women with a CD scar would not have AIP, thus questioning about the need of such first trimester assessment. Finally, because of the small number of cases, it was not possible to perform any sub-analysis according to the severity of placental invasion.

Implications for clinical practice and research

Prenatal diagnosis of AIP is usually accomplished during the second and/or third trimester of pregnancy although there is no consensus yet on the optimal gestational age at scan to detect AIP and the number and type of imaging criteria which should be adopted in order to improve the overall diagnostic accuracy of ultrasound.[18,19,42]

The recently proposed association between CSP and AIP poses the dilemma of how women with a prenatal diagnosis of CSP should be counselled and whether termination of pregnancy should be the only therapeutic option offered to these women[17]. Several studies aiming at stratifying the risk of AIP in women with a previous CSP have been published in the recent past[35,36,45,46]. Kaelin Agten et al. showed that CSP implanted "on the scar", defined as a placenta implanted partially or fully on top of a well healed scar, had a substantially better outcome compared to cases in which the CSP implanted into the niche of a deficient or dehiscent scar. Myometrial thickness below 2mm in the first trimester US was associated with morbidly adherent placenta at delivery.[35] Cali et al. showed that the relationship between the gestational sac of the CSP, previous caesarean scar and the anterior uterine wall thickness can be used to predict not only the evolution of the CSP towards the most severe types of AIP, but also the clinical outcome of these women.[36,45]
Despite this, identification of CSPs that will have successful pregnancy outcome or are amenable to treatment without serious complications remains a challenge (Figures 5 and 6).

First trimester diagnosis of AIP has been rarely reported and there is still no consensus on which imaging sign should be looked for in order to diagnose AIP in early pregnancy. In the collective authors' experience low anterior implantation of the placenta/sac close to or within the scar, a reduced myometrial thickness and abnormal vascularity at the uterine/bladder interface are the most common early US signs suggestive of AIP, although there is no consensus yet on how to define such signs.

Several cut-offs of myometrial thickness have been reported to be associated with AIP in the first trimester. In the study by Rac et al. myometrial thickness ≤6 mm measured in a sagittal plane showed the optimal combination of sensitivity and specificity, although the authors did not stratify their analysis according to the depth of placental invasion.[37]. However, whether routine assessment of myometrial thickness in women with a prior CS and low implantation of the gestational sac improves the diagnostic accuracy of first trimester US has requires confirmation in large prospective studies.

Placental lacunae are among the most commonly detected US signs in pregnancies with AIP diagnosed in second and third trimester.[18] However, in the present systematic review that included only first trimester pregnancies, the prevalence of lacunae was about 46%, with a large heterogeneity among the included studies. Furthermore, the risk of AIP in women presenting with lacunae was not higher compared to those not showing such sign on US. Placental lacunae may be less common or difficult to identify in the early first trimester.

Prenatal diagnosis of AIP has been shown to be improved when a multiparametric prediction model including either ultrasound, maternal and pregnancy characteristics is applied to women at risk[47]. In this scenario, integrating first with second and third trimester scan, together with maternal and pregnancy characteristics might theoretically improve the diagnostic accuracy of ultrasound in detecting the presence and the severity of AIP.

In conclusion, ultrasound signs of AIP are already present during the first trimester of pregnancy. Further studies aiming at prospectively evaluating women at risk for AIP, such as those with a prior CD, since the first trimester of pregnancy are needed in order to ascertain whether first trimester ultrasound may help in stratifying such risk and whether it should be integrated with second and third trimester scan in order to improve the overall diagnostic accuracy of ultrasound in identifying AIP.

Acknowledgments

We would like to thank Dr. N Zosmer for the additional information provided.

REFERENCES

1. Belfort MA. Placenta accreta. *Am J Obstet Gynecol* 2010; **203**: 430-439.
2. Oyelese Y, Smulian JC. Placenta previa, placenta accreta, and vasa previa. *Obstet Gynecol* 2006; **107**: 927-941.
3. Miller DA, Chollet JA, Goodwin TM. Clinical risk factors for placenta previa-placenta accreta. *Am J Obstet Gynecol* 1997; **177**: 210-214.
4. Wu S, Kocherginsky M, Hibbard JU. Abnormal placentation: twenty-year analysis. *Am J Obstet Gynecol* 2005; **192**: 1458-1461.
5. Tikkanen M, Paavonen J, Loukovaara M, Stefanovic V. Antenatal diagnosis of placenta accreta leads to reduced blood loss. *Acta Obstet Gynecol Scand* 2011; **90**: 1140-1146.
6. Silver RM, Fox KA, Barton JR, Abuhamad AZ, Simhan H, Huls CK, Belfort MA, Wright JD. Center of excellence for placenta accreta. *Am J Obstet Gynecol* 2015; **212**: 561-568.
7. Shamshirsaz AA, Fox KA, Erfani H, Clark SL, Salmanian B, Baker BW, Coburn M, Shamshirsaz AA, Bateni ZH, Espinoza J, Nassr AA, Popek EJ, Hui SK, Teruya J, Tung CS, Jones JA, Rac M, Dildy GA, Belfort MA. Multidisciplinary team learning in the management of the morbidly adherent placenta: outcome improvements over time. *Am J Obstet Gynecol* 2017; **216**: 612.e1-612.e5
8. Shamshirsaz AA, Fox KA, Salmanian B, Diaz-Arrastia CR, Lee W, Baker BW, Ballas J, Chen Q, Van Veen TR, Javadian P, Sangi-Haghpeykar H, Zacharias N, Welty S, Cassady CI, Moaddab A, Popek EJ, Hui SK, Teruya J, Bandi V, Coburn M, Cunningham T, Martin SR, Belfort MA. Maternal morbidity in patients with morbidly adherent placenta treated with and without a standardized multidisciplinary approach. *Am J Obstet Gynecol* 2015; **212**: 218.e1-218.e9.
9. Fox KA, Shamshirsaz AA, Carusi D, Secord AA, Lee P, Turan OM, Huls C, Abuhamad A, Simhan H, Barton J, Wright J, Silver R, Belfort MA. Conservative management of morbidly adherent placenta: expert review. *Am J Obstet Gynecol* 2015; **213**: 755-760.
10. Flood KM, Said S, Geary M, Robson M, Fitzpatrick C, Malone FD. Changing trends in peripartum hysterectomy over the last 4 decades. *Am J Obstet Gynecol* 2009; **200**: 632.e1-632.e6.
11. Angstmann T, Gard G, Harrington T, Ward E, Thomson A, Giles W. Surgical management of placenta accreta: a cohort series and suggested approach. *Am J Obstet Gynecol* 2010; **202**: 38.e1-38.e9.
12. Ballas J, Hull AD, Saenz C, Warshak CR, Roberts AC, Resnik RR, Moore TR, Ramos GA. Preoperative intravascular balloon catheters and surgical outcomes in pregnancies

complicated by placenta accreta: a management paradox. *Am J Obstet Gynecol* 2012; **207**: 216.e1-216.e5.

13. Bowman ZS, Manuck TA, Eller AG, Simons M, Silver RM. Risk factors for unscheduled delivery in patients with placenta accreta. *Am J Obstet Gynecol* 2014; **210**: 241.e1-241.e6.
14. Jauniaux E, Jurkovic D. Placenta accreta: pathogenesis of a 20th century iatrogenic uterine disease. *Placenta* 2012; **33**: 244-251.
15. Timor-Tritsch IE, Monteagudo A. Unforeseen consequences of the increasing rate of cesarean deliveries: early placenta accreta and cesarean scar pregnancy. A review. *Am J Obstet Gynecol* 2012; **207**: 14-29.
16. Timor-Tritsch IE, Monteagudo A, Cali G, Vintzileos A, Viscarello R, Al-Khan A, Zamudio S, Mayberry P, Cordoba MM, Dar P. Cesarean scar pregnancy is a precursor of morbidly adherent placenta. *Ultrasound Obstet Gynecol* 2014; **44**: 346-353.
17. D'Antonio F, Iacovella C, Bhide A. Prenatal identification of invasive placentation using ultrasound: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2013; **42**: 509-517.
18. D'Antonio F, Iacovella C, Palacios-Jaraquemada J, Bruno CH, Manzoli L, Bhide A. Prenatal identification of invasive placentation using magnetic resonance imaging: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2014; **44**: 8-16.
19. Palacios-Jaraquemada JM, Bruno CH, Martín E. MRI in the diagnosis and surgical management of abnormal placentation. *Acta Obstet Gynecol Scand* 2013; **92**: 392-397.
20. Timor-Tritsch IE, Monteagudo A, Cali G, Palacios-Jaraquemada JM, Maymon R, Arslan AA, Patil N, Popiolek D, Mittal KR. Cesarean scar pregnancy and early placenta accreta share common histology. *Ultrasound Obstet Gynecol* 2014; **43**: 383-395.
21. Henderson LK, Craig JC, Willis NS, Tovey D, Webster AC. How to write a Cochrane systematic review. *Nephrology* (Carlton) 2010; **15**: 617-624.
22. NHS Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking reviews in health care. York (UK): University of York; 2009.
23. Leeflang MM, Deeks JJ, Gatsonis C, Bossuyt PM; Cochrane Diagnostic Test Accuracy Working Group. Systematic reviews of diagnostic test accuracy. *Ann Intern Med* 2008; **149**: 889-897.
24. Prisma statement. http://www.prisma-statement.org/ [accessed 10 March 2017]
25. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, Lijmer JG, Moher D, Rennie D, de Vet HC; Standards for Reporting of Diagnostic Accuracy. Towards complete

and accurate reporting of studies of diagnostic accuracy: the STARD Initiative. *Clin Chem* 2003; **49**: 1-6.

26. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MM, Sterne JA, Bossuyt PM; QUADAS-2 Group. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011; **155**: 529-536.
27. Hunter JP, Saratzis A, Sutton AJ, Boucher RH, Sayers RD, Bown MJ. In meta-analyses of proportion studies, funnel plots were found to be an inaccurate method of assessing publication bias. *J Clin Epidemiol* 2014; **67**: 897-903.
28. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 [updated September 2009]. The Cochrane Collaboration, 2009. at www.cochrane-handbook.org. Accessed 3 December 2016]
29. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315**: 629-634.
30. Rutter CM, Gatsonis CA. A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations. *Stat Med* 2001; **20**: 2865-2884.
31. Harbord RM, Whiting P. Metandi: meta-analysis of diagnostic accuracy using hierarchical logistic regression. *Stata Journal* 2009; **9**: 211-229.
32. Cochrane Handobook for Systematic Reviews of Diagnostic Test Accuracy, Chapter 10; http://srdta.cochrane.org/handbook-dta-reviews.
33. Glas AS, Lijmer JG, Prins MH, Bonsel GJ, Bossuyt PM. The diagnostic odds ratio: a single indicator of test performance. *J Clin Epidemiol* 2003; **56**: 1129-1135.
34. Zamora J, Abraira V, Muriel A, Khan K, Coomarasamy A. Meta-DiSc: a software for meta-analysis of test accuracy data. *BMC Med Res Methodol* 2006; **6** : 31.
35. 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.
36. Cali G, Forlani F, Timor-Trisch I, Palacios-Jaraquemada J, Minneci G, D'Antonio F. Natural history of caesarean scar pregnancy on prenatal ultrasound: the cross-over sign. *Ultrasound Obstet Gynecol* 2016. [Epub ahead of print]
37. Rac MW, Moschos E, Wells CE, McIntire DD, Dashe JS, Twickler DM. Sonographic findings of morbidly adherent placenta in the first trimester. *J Ultrasound Med* 2016; **35** : 263-269.
38. Baldassarre RL, Gabe M, Pretorius DH, Ramos GA, Romine LE, Hull AD, Ballas J, Pettit KE. Placental sonolucencies in the first trimester: incidence and clinical significance. Ultrasound Q 2016; **32**: 43-46.

39. 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**: 367-375.
40. Ballas J, Pretorius D, Hull AD, Resnik R, Ramos GA. Identifying sonographic markers for placenta accreta in the first trimester. *J Ultrasound Med* 2012; **31**: 1835-1841.
41. Stirnemann JJ, Mousty E, Chalouhi G, Salomon LJ, Bernard JP, Ville Y. Screening for placenta accreta at 11-14 weeks of gestation. *Am J Obstet Gynecol* 2011; **205**: 547.e1-547.e6.
42. Comstock CH, Lee W, Vettraino IM, Bronsteen RA. The early sonographic appearance of placenta accreta. *J Ultrasound Med* 2003; **22**: 19-23.
43. Rahimi-Sharbaf F, Jamal A, Mesdaghinia E, Abedzadeh-Kalahroudi M, Niroomanesh S, Atoof F. Ultrasound detection of placenta accreta in the first trimester of pregnancy. *Iran J Reprod Med* 2014; **12**: 42142-42146.
44. Moschos E, Wells CE, Twickler DM. Biometric sonographic findings of abnormally adherent trophoblastic implantations on cesarean delivery scars. J Ultrasound Med 2014; 33:475–481.
45. Cali G, Forlani F, Minneci G, Foti F, Di Liberto S, Familiari A, Scambia G, D'Antonio F. First trimester prediction of surgical outcome in abnormal invasive placenta using the cross-over sign. *Ultrasound Obstet Gynecol* 2017. [Epub ahead of print]
46. Timor-Tritsch IE, Monteagudo A, Cali G, El Refaey H, Kaelin Agten A, Arslan AA. Easy sonographic differential diagnosis between intrauterine pregnancy and cesarean delivery scar pregnancy in the early first trimester. *Am J Obstet Gynecol* 2016; **215**: 225.e1-225.e7.
47. Rac MW, Dashe JS, Wells CE, Moschos E, McIntire DD, Twickler DM. Ultrasound predictors of placental invasion: the Placenta Accreta Index. *Am J Obstet Gynecol* 2015; **212**: 343.e1-7.

Table 1. General characteristics of the included studies.

Author	Year	Country	Study design	Inclusion criteria	Reference standard	GA at scan (w)	Type of scan	US signs	Pregnancies (n)	AIP (n)
Cali	2016	Italy	Retrospective	Women with confirmed AIP	Surgery/pathology	6-8	TV	Gestational sac location	68	68
Rac	2016	United States	Retrospective	Women with placenta previa or low lying and previous LSCS	Surgery/pathology	9.25 (5.5-13.6)	TA/TV	Gestational sac location, location of the decidua basalis, intra-placental lacunae, uterine-bladder interface irregularity, myometrial thickness	39	14
Bladassarre	2016	United States	Retrospective	Women with placenta previa	NS	12.9±0.8	NS	Intra-placental lacunae	10	1
Ballas	2012	United States	Retrospective	Women with confirmed AIP	Surgery/pathology	$8+^{4}$-14^{+2}	TA/TV	Gestational sac location, anechoic areas, irregular placental myometrial interface	10	10
Stirnemann	2011	France	Prospective	Women with previous LSCS	Pathology	11^{+0}-13^{+6}	TA	Gestational sac location	95	1
Comstock	2003	United States	Retrospective	Women with confirmed AIP	Surgery/pathology	10,00	NS	Gestational sac location, myometrial thinning, retro-placental space	6	6

Table 2. Pooled proportions (PP) of the prevalence of the different first trimester ultrasound signs in women with AIP**.**

US sign	Studies (n)	Pregnancies (n/N)	Raw proportions (95% CI)	I^2 (%)	Pooled proportions (95% CI)
At least one sign	7	100/117	85.47 (77.8-91.3)	88.4	91.42 (85.8-95.7)
Low implantation of the gestational sac	5	90/102	88.24 (80.4-93.8)	89.7	82.42 (46.6-99.8)
Placental lacunae	3	12/25	48.0 (27.8-68.7)	71.0	46.03 (10.9-83.7)

Reduced myometrial thickness	2	13/19	68.42 (43.4-87.4)	0	66.79 (45.2-85.2)
Abnormal uterine-bladder interface	2	11/24	45.83 (25.6-67.2)	93.2	51.84 (0.2-100)

Figure legends

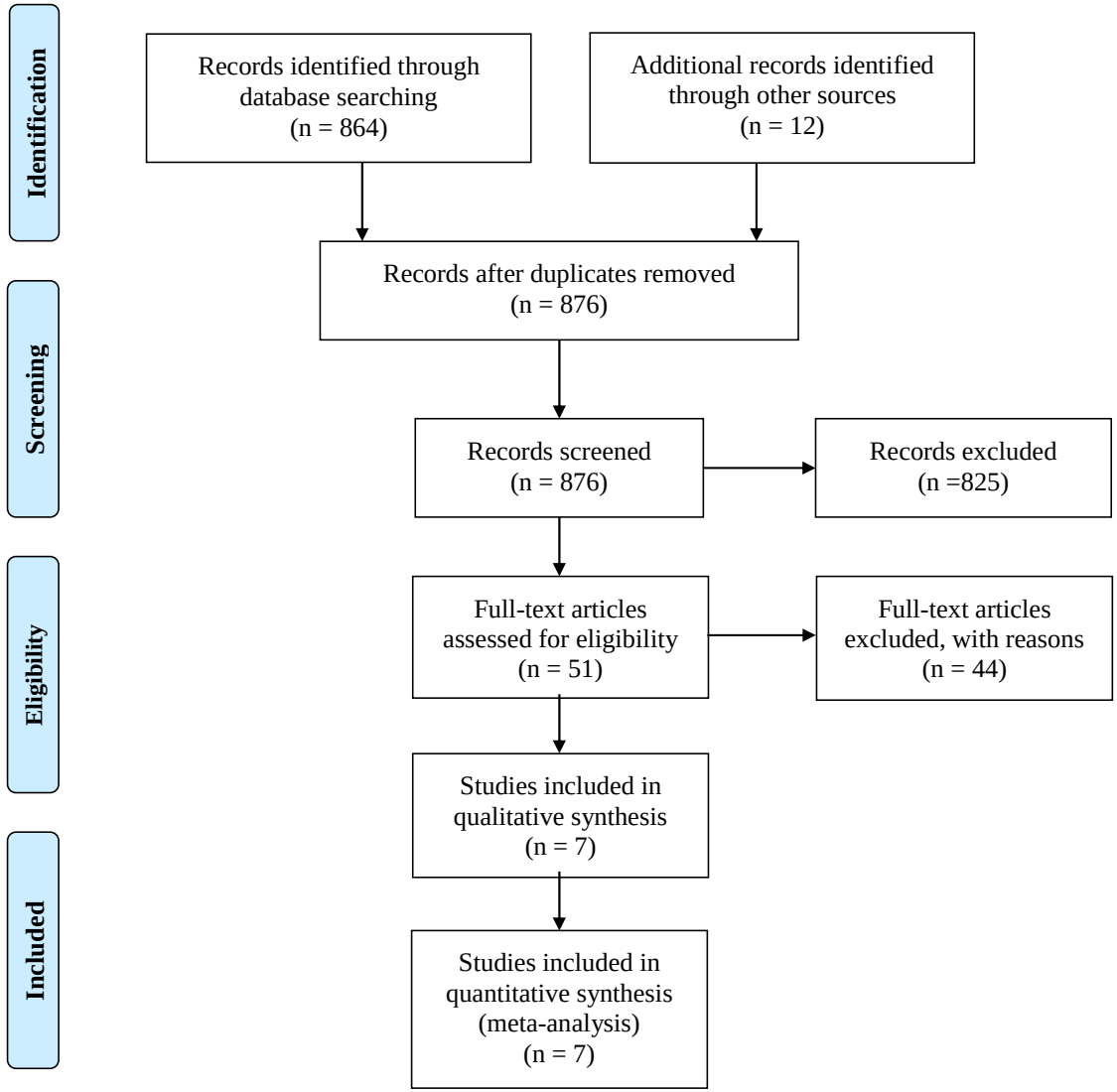
Figure 1. Systematic review flowchart.

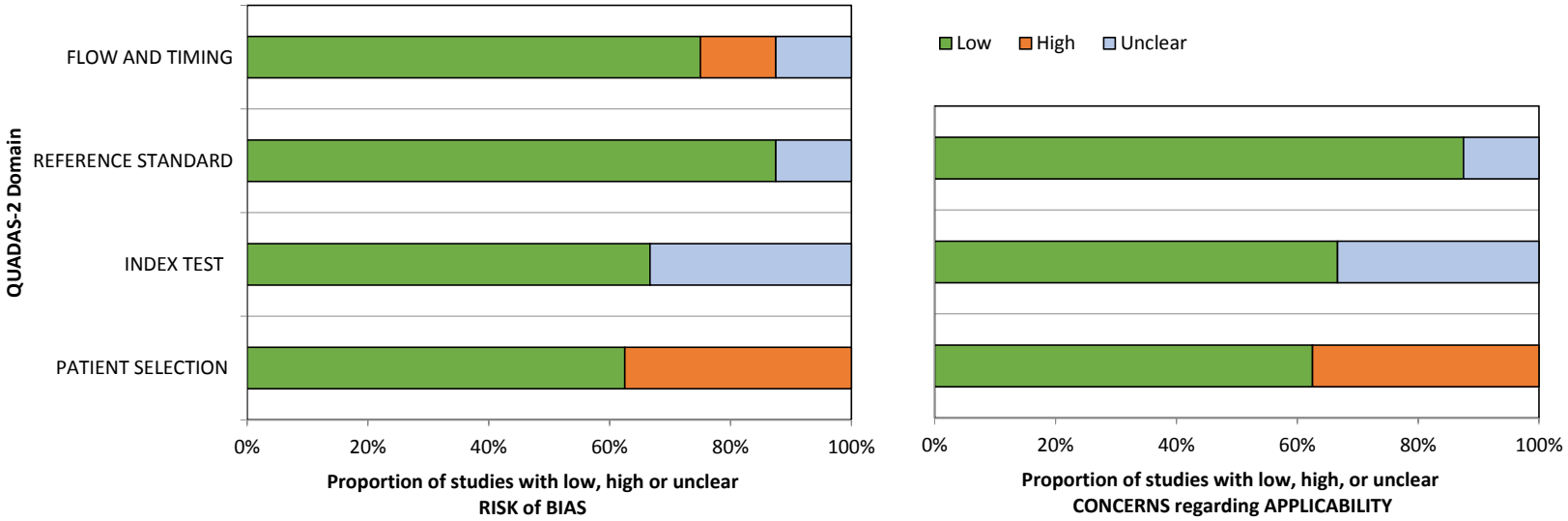
Figure 2: QUADAS-2 assessment of the studies included in the systematic review.

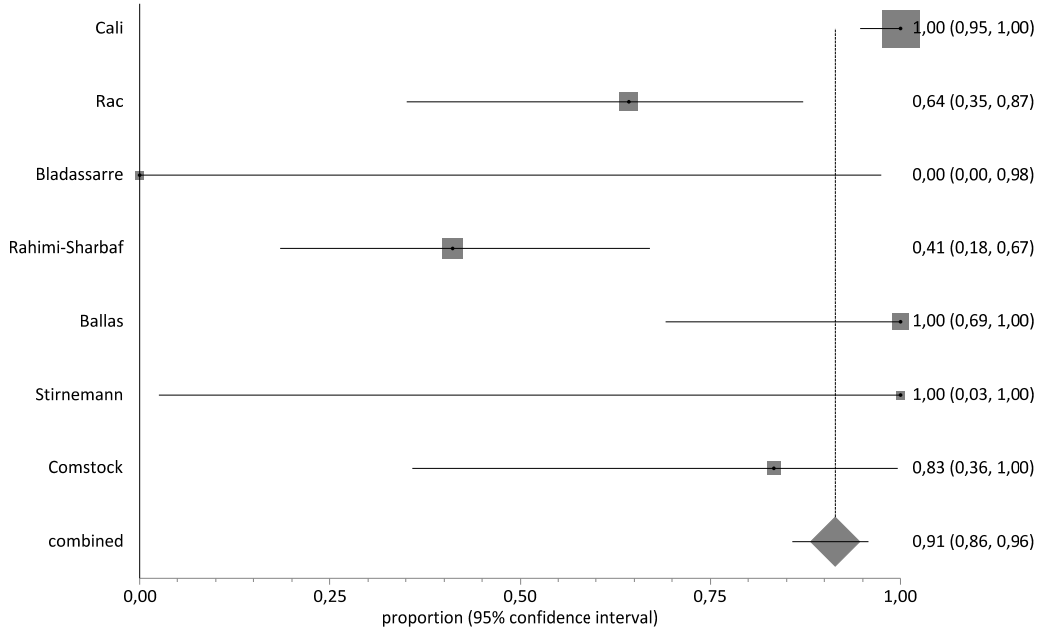
Figure 3. Pooled proportion showing the prevalence of at least one ultrasound sign suggestive of AIP in women with confirmed placental invasion scanned in the first trimester of pregnancy.

Figure 4. Pooled proportion showing the prevalence of the different ultrasound signs suggestive of AIP in women with confirmed placental invasion scanned in the first trimester of pregnancy.

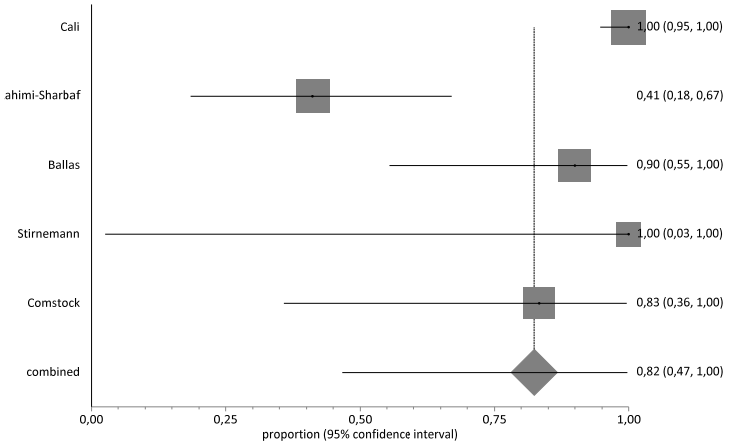
Figure 5. Ultrasound criteria to diagnose CSP and AIP during the first trimester of pregnancy. a) TV scan at 5 weeks + 5 days of gestation showing a low implantation of the gestational sac embedded eccentrically in the lower uterine segment and implanted in the location of the prior CS scar. b,c) assessment with Colour Doppler revealed the presence of a rich vascular pattern in the area between the CS scar and the placenta. The myometrium beneath the placental mass is irregular and scarcely visible in some points (arrows). No intra-placental lacunae can be detected. d,e) TA scan at 14 weeks of gestation. The abnormal location of the gestational sac is more difficult to be appreciated with advancing gestation. The myometrium beneath the placental is not entirely visible in some areas and there is also increase sub-placental vascularity (arrowheads); intra-placental lacunae can be seen at this stage as hypoechoic spaces within the parenchyma. (arrows). f) TA scan at 17 weeks of gestation showing the classical second trimester signs of AIP, such as intra-placental lacunae, abnormal uterine bladder interface with increased vascularity and absence of the retro-placental clear space.



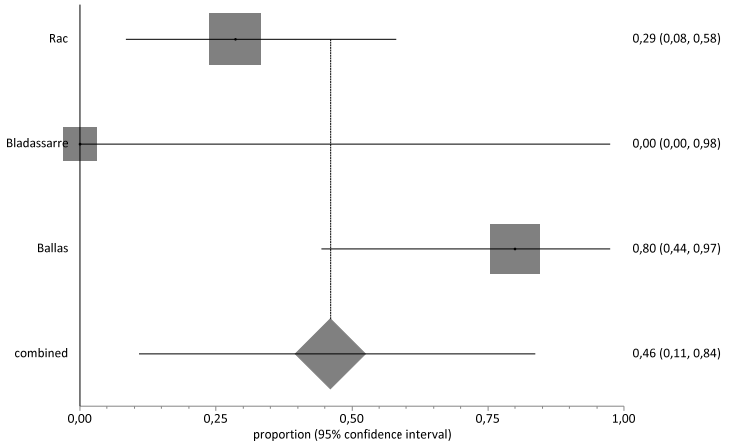




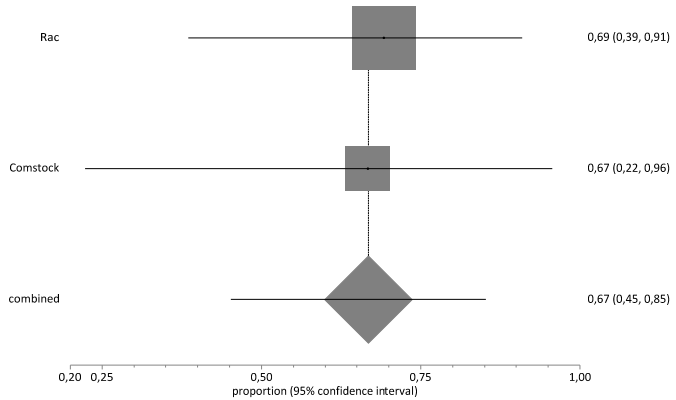
Abnormal gestational sac location



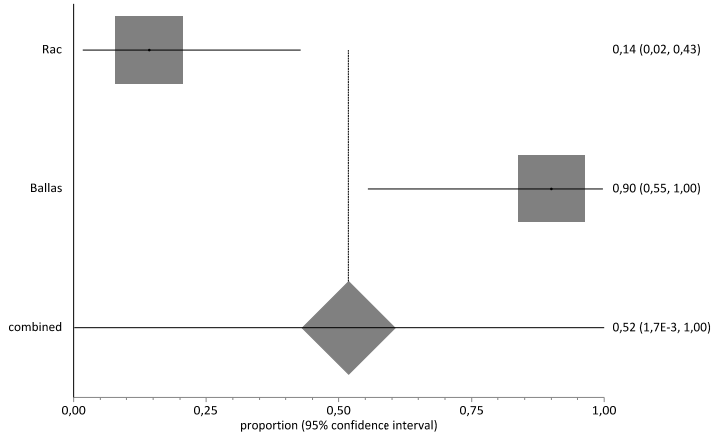
Intra-placental lacunae



Reduced myometrial tickness



Abnormal uterine-bladder interface



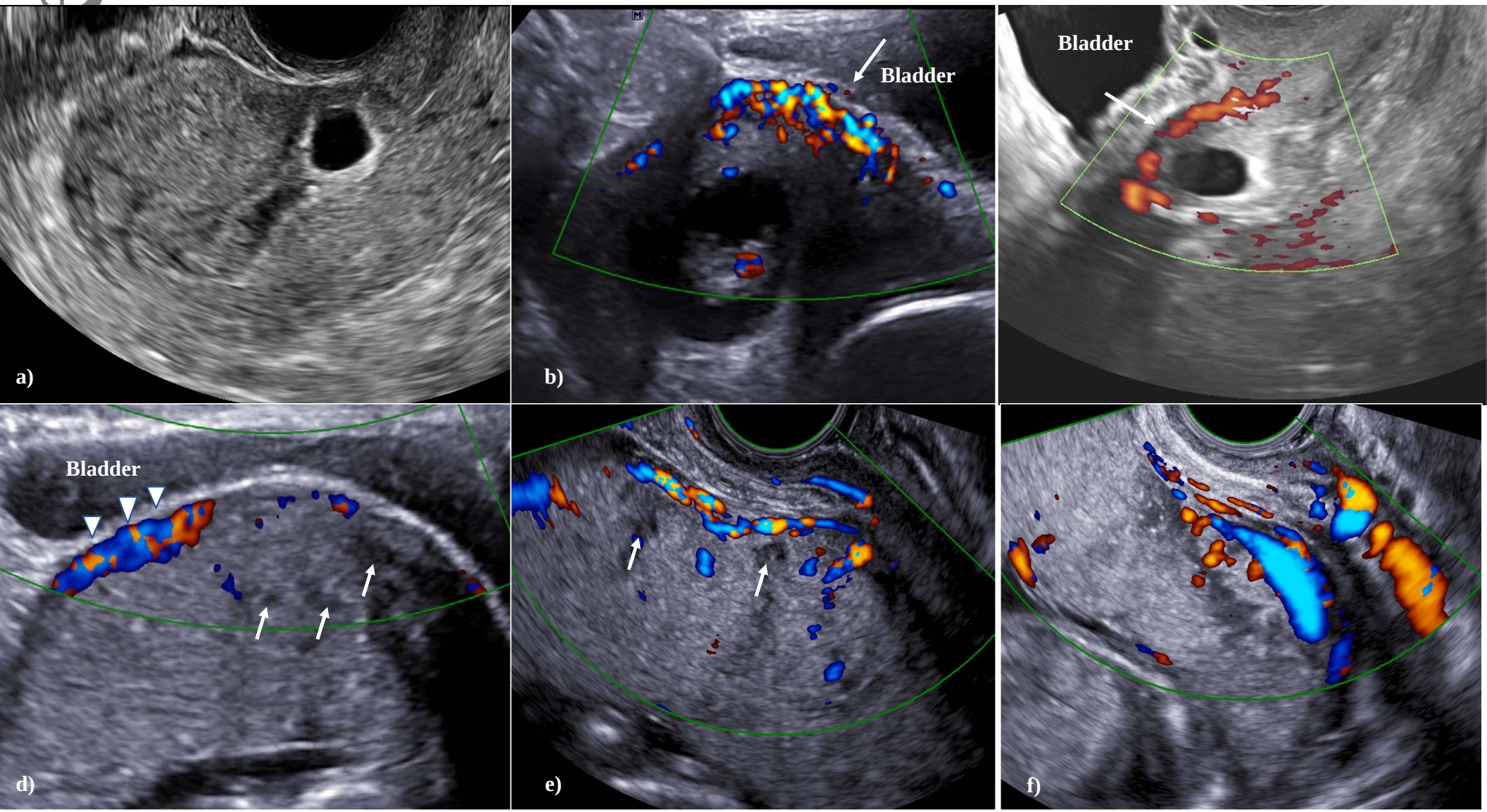


Figure 6. Clinical evolution of CSP towards AIP.