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Imaging of gynecological disease: clinical and ultrasound characteristics of serous cystadenofibromas in the adnexa

B.A. VIRGILIO[1,2], I. DE BLASIS[1], P. SLADKEVICIUS[3], F. MORO[4], G.F. ZANNONI[5], D. ARCIUOLO[6], F. MASCILINI[4], F. CICCARONE[4], D. TIMMERMAN[7], J. KAIJSER[7], R. FRUSCIO[8], C. VAN HOLSBEKE[9], D. FRANCHI[10], E. EPSTEIN[11], F.P.G. LEONE[12], S. GUERRIERO[13], A. CZEKIERDOWSKI [14], G. SCAMBIA[4], A. C. TESTA[1*], L. VALENTIN[3, 15*].

1 Istituto di Ginecologia ed Ostetricia, Università Cattolica del Sacro Cuore, Rome, Italy

2 *Department of Obstetrics and Gynecology, Policlinico Hospital, Abano Terme, Padua, Italy.*

3 *Department of Obstetrics and Gynecology, Skåne University Hospital, Malmö.*

4 Dipartimento Scienze della Salute della Donna e del Bambino, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy

5 Dipartimento Scienze della Salute della Donna e del Bambino, Unità di Ginecopatologia, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy

6 Dipartimento Scienze della Salute della Donna e del Bambino, Unità di Ginecopatologia, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy

7 *Department of Obstetrics and Gynecology, University Hospitals, Katholieke Universiteit Leuven, Leuven, Belgium.*

8 *Clinic of Obstetrics and Gynecology, Department of Medicine and Surgery, San Gerardo Hospital, University of Milan-Bicocca, Monza, Italy.*

9 *Department of Obstetrics and Gynecology, Ziekenhuis Oost-Limburg, Genk, Belgium.*

10 *Preventive Gynecology Unit, Division of Gynecology, European Institute of Oncology, Milan, Italy.*

11 *Department of Clinical Science and Education, Karolinska Institutet, and Department of Obstetrics and Gynecology, Södersjukhuset, Stockholm, Sweden.*

12 *Department of Obstetrics and Gynecology, Clinical Sciences Institute, L. Sacco, Milan, Italy.*

13 *Department of Obstetrics and Gynecology, University of Cagliari, Policlinico Universitario Duilio Casula, Monserrato, Cagliari, Italy.*

14 *First Department of Gynecological Oncology and Gynecology, Medical University of Lublin, Lublin, Poland.*

15 *Institution of Clinical Sciences Malmö, Lund University, Sweden*

* Contributed equally

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Corresponding author: Dr. B.A. Virgilio, Department of Obstetrics and Gynecology, Policlinico Hospital, Piazza Cristoforo Colombo, 1, 35031 Abano Terme (PD), Italy (e-mail: bruna81@tiscali.it)

ABSTRACT

Objectives

To describe the clinical and ultrasound characteristics of serous cystadenofibromas in the adnexa.

Methods

This is a retrospective study. From the International ovarian tumor analysis (IOTA) database we identified patients with a histological diagnosis of serous cystadenofibroma, who had undergone preoperative ultrasound examination by an experienced ultrasound examiner between 1999 and 2012. In the IOTA database containing prospectively collected data, the tumors were described using the terms and definitions of the International Ovarian Tumor Analysis (IOTA) group. In addition, three authors reviewed, first independently and then together, ultrasound images of serous cystadenofibromas and described them using pattern recognition.

Results

We identified 233 women with a histological diagnosis of serous cystadenofibroma. In the IOTA database, most (67.4%) were described as containing solid components (157/233) but 19.3% (45/233) were described as multilocular cysts and 13.3% (31/233) as unilocular cysts. Papillary projections were described in 52.4% (122/233) of the cystadenofibromas. In 79.5% (97/122) of the cysts with papillary projections color Doppler signals were absent in the papillary projections. Most cystadenofibromas (83.7%, 195/233) manifested no or minimal color Doppler signals. On retrospective analysis of 201 ultrasound images of serous cystadenofibromas using pattern recognition we identified 10 major types of ultrasound appearance. The most common pattern was a unilocular solid cyst with one or more papillary projections (25.9%, 52/201). The second most common pattern was a multilocular solid mass with small solid component(s) but no papillary projections (19.4%, 39/201). The third and fourth most common patterns were multilocular cyst (16.9%, 34/201) and unilocular cyst (11.9%, 24/201). Using pattern recognition, shadowing was identified in 39.8% (80/201) of the tumors, and microcystic appearance of the papillary projections was observed in 35 (39.8%) of the 88 tumors containing papillary projections.

Conclusions
The ultrasound features of serous cystadenofibromas vary. The most common pattern is a unilocular solid cyst with one or more papillary projections with absent color Doppler signals. Most serous cystadenofibromas are poorly vascularized on color Doppler and many manifest acoustic shadowing.

INTRODUCTION

Aim

To describe the clinical and sonographic characteristics of serous cystadenofibromas in the adnexa.

Background

Epidemiology

Cystadenofibromas are defined by the World Health Organization (WHO) as tumors composed predominantly of benign-appearing stroma derived from the ovarian stroma[1]. They contain dominant stromal proliferations that overshadow the epithelial element. When the stroma is highly cellular and fibrous and forms large solid areas containing scattered glands or thick papillary projections, the tumor is called adenofibroma. If there is a cystic component it is called cystadenofibroma[2].

Cystadenofibromas occur in women of all ages but most frequently between 40 and 60 years. The true prevalence of cystadenofibromas is uncertain[3]. Cystadenofibromas and adenofibromas, together with cystadenomas, comprise two thirds of all benign ovarian epithelial neoplasms[2]. Even though mucinos, endometrioid and clear cell cystadenofibromas exist they are very rare[2]. This work deals only with serous cystadenofibromas.

Microscopy

Serous cystadenofibromas display an epithelium lining lacking proliferation. The stroma can resemble normal ovarian stroma, but it is more fibrous or edematous[2]. The stromal component is essentially identical to that of ovarian fibromas. Seidman and colleagues have proposed an

interesting hypothesis on how serous cystadenofibromas arise. They hypothesize that serous cystadenofibromas are ovarian stromal neoplasms, i.e. fibromas that have encompassed glandular inclusions, adhesions or both[4]. The papillary projections of the cystadenofibromas have been described to be short, broad structures composed of fibrous tissue[5].

Macroscopy

Serous cystadenofibromas macroscopically are composed of cysts filled with clear watery fluid or thin mucoid material. Occasionally these cysts contain thicker mucus-like material, but this is more typical of mucinous cystadenofibromas. The external surface of serous cystadenofibromas is generally smooth and glistening, but occasionally there are papillary excrescences on the external surface of the lesion. The internal lining of the cysts is either flat or may have a varying number of coarse papillary projections. Tumors vary in size. They may have a diameter of up to 30 cm, with a mean of 5-8 cm.[2]

Clinical symptoms and prognosis

The symptoms and signs associated with serous cystadenofibromas are unspecific. The most common symptoms are pelvic pain and discomfort, but many cystadenofibromas are diagnosed in asymptomatic women, especially if they are small.[2] Serous cystadenofibromas are benign tumors but macroscopically and on medical imaging they may look malignant [6,7,8,9].

Methods

This is a retrospective study. From the International ovarian tumor analysis (IOTA) database we identified patients with a histological diagnosis of serous cystadenofibroma, who had undergone preoperative ultrasound examination by an experienced ultrasound examiner between 1999 and 2012 (IOTA phase 1, 1b, 2 and 3)[10-13]. Clinical and ultrasound information in the IOTA database is collected and entered into the database prospectively. All patients had been examined with transvaginal ultrasound (supplemented with a transabdominal scan, if necessary) using a standardized examination technique following a strict research protocol, all masses being described using the standardized IOTA terminology[14]. Most examinations had been carried out using high-end ultrasound equipment, the frequency of the vaginal probes varying between 5.0 and 9.0 MHz and that of the abdominal probes between 3.5 and 5.0 MHz. In case of bilateral masses, the mass representing the cystadenofibroma was included. If both masses were cystadenofibromas, the data from the dominant mass were used for statistical analysis. The dominant mass is the one with the most complex ultrasound appearance; if both masses manifest similar ultrasound morphology the dominant mass is the largest one or the one most easily accessible with ultrasound. Using IOTA terminology, a papillary projection is defined as a projection of solid tissue into a cyst cavity with a height of at least 3 mm [14]. Papillary projections differ from other solid components, in that they protrude into the cyst cavity while other solid components do not. The difference between a papillary projection and other solid components is illustrated in Figure 1. Results of Doppler examinations are reported in terms of a color score[14]. A color score of 1 means that no color or power Doppler signals are detected in the tumor, a score of 2 that a minimal amount of color Doppler signals is detected, a color score of 3 that a moderate amount is detected and a score of 4 that abundant color Doppler signals are detected.

In addition to using the prospectively collected clinical and ultrasound information in the IOTA database, we retrospectively assessed ultrasound images of serous cystadenofibromas using pattern recognition[15]. Ultrasound images were available for 135 serous cystadenofibromas in the IOTA database. We also assessed ultrasound images of 66 histologically confirmed serous cystadenofibromas examined outside the IOTA phase 1, 1b, 2 and 3 studies. These 66 cases were identified from the databases of the participating ultrasound centers, and six of them are also

included in the ongoing IOTA phase 5 study. Three authors (A.C.T., B.A.V. and L.V.) independently reviewed the 201 ultrasound images (most of them electronic). They used pattern recognition to identify possible typical ultrasound patterns. Finally, the three authors assessed all 201 ultrasound images together to reach consensus. Their agreed description was used for statistical calculations. Shadowing was noted as being present or absent, and the appearance of any solid components was classified as microcystic or not microcystic. Microcystic appearance of papillary projections is illustrated in Figure 2.

All clinical and ultrasound information was entered into a dedicated Excel file which was used for statistical analysis (Microsoft Office Excel 2003, Redmond, WA, USA).

Results

Clinical background data for the 233 patients in the IOTA database with histologically confirmed serous cystadenofibromas are shown in Table 1. Median age was 54 years (range, 14 to 89) and 63% of the patients were postmenopausal.

The sonographic characteristics of cystadenofibromas as reported in the IOTA database and the diagnosis suggested by the original ultrasound examiner are presented in Table 2. The median largest tumor diameter was 76 mm (range 21-350). Most tumors (67.4%) were described as containing solid components (157/233) but 19.3% (45/233) were described as multilocular cysts and 13.3% (31/233) as unilocular cysts. Papillary projections were described in 52.4% (122/233) of the cystadenofibromas and in 52.4% of these (64/122) only one papillary projection was present. In 79.5% (97/122) of the cysts with papillary projections color Doppler signals were absent in the papillary projections. Shadowing was described in 9.9% (23/233) of serous cystadenofibromas. Most cystadenofibromas (83.7%, 195/233) manifested no or minimal color Doppler signals. The original ultrasound examiner suspected malignancy in 21.4% (50/233) of the cystadenofibromas, and in most cases (34/50) a borderline tumor was suspected. Of the 50 cystadenofibromas suspected to be malignant, 39 (78%) were described on ultrasound as having papillary projections versus 83/183 (45%) of those judged to be benign.

When analyzing ultrasound images from 201 serous cystadenofibromas using pattern recognition, 10 major patterns were identified. These are shown together with their prevalence in Figure 3. The most common pattern was a unilocular solid cyst with one or more papillary projections (25.9%, 52/201). The second most common pattern was a multilocular solid mass with small solid component(s) but no papillary projections (19.4%, 39/201). The third and fourth most common patterns were multilocular cyst (16.9%, 34/201) and unilocular cyst (11.9%, 24/201). The patterns can be collapsed into five larger groups: unilocular or multilocular cysts with no solid components (58/201, 29%), cysts with papillary projections but no other solid components (72/201, 36%), cysts with solid components other than papillary projections (53/201, 26%), cysts with both papillary projections and other solid components (16/201, 8%), and purely solid tumors (2/201, 1%). Shadowing was identified in 39.8% (80/201) of the tumors. Microcystic appearance of papillary projections was observed in 34 (38.6%) of the 88 tumors containing papillary projections. Ultrasound images illustrating the ultrasound patterns are shown in Figures 4-10.

Discussion

In this retrospective study we identified ten ultrasound patterns of serous cystadenofibromas in the adnexa using pattern recognition. We found the most common pattern to be a unilocular solid cyst with papillary projections but no other solid components and the second most common to be a multilocular solid mass with small solid component(s) but no papillary projections. On retrospective assessment of ultrasound images, shadowing was found to be present in 40% (80/201) of the serous cystadenofibromas. Other typical features were microcystic appearance of the papillary projections (seen in almost 40% of all cystadenofibromas with papillary projections) and absence of color Doppler signals in the papillary projections (absent in 80% of the cystadenofibromas with papillary projections). The serous cystadenofibromas varied greatly in size and most of them were poorly vascularized on color Doppler.

To the best of our knowledge this is the largest series describing the ultrasound characteristics of histologically confirmed serous cystadenofibromas in the adnexa. A limitation is that the study is retrospective. Ultrasound images were not available for all cases, and this may have limited our possibility to detect typical ultrasound features. Moreover, we have information only from the largest or the most complex mass in case of bilateral ones, and this may have introduced bias. The reader might find it surprising that shadowing was recorded prospectively in the IOTA database in only about 10% of the cystadenofibromas but in almost 40% when images were assessed to reach consensus on the ultrasound pattern. This is likely to be explained by the original ultrasound examiners not paying much attention to shadowing in the earlier phases of the IOTA studies, while when reviewing the ultrasound images using pattern recognition in this study, shadowing was specifically searched for.

Our results agree well with the description of serous cystadenofibromas in textbooks of pathology with regard to patient age (variable), size (variable) and macroscopic appearance: cysts filled with clear fluid with smooth internal cyst walls or with a varying number of papillary projections[2,16].

Results similar to ours with regard to the ultrasound appearance of cystadenofibromas were reported in two small retrospective studies. Alcazar et al.[17] found papillary projections or solid nodules to be present in 56% of 23 serous cystadenofibromas. Goldstein et al. reported papillary projections in 69% of 32 cystadenofibromas (30 serous and 2 mucinous)[18]. They emphasized that

the absence of vascularization in papillary projections was a typical finding in cystadenofibromas. None of the cystadenofibromas in their series contained vascularized papillary projections or vascularized solid components. In our series vascularized papillary projections were found in 20% of those serous cystadenofibromas that contained papillary projections (Figure 11).

How can the differences in the ultrasound appearance of papillary projections in serous cystadenofibromas be explained histologically? Shadowing behind a papillary projection might be explained by dense fibrous tissue, while microcystic appearance might be explained by edematous areas in the papillary projection (Figures 12 and 13). Shadowing behind papillary projections in cystadenofibromas was first reported in an oral presentation by Ilan Timor-Tritsch at the 19th World Congress of the International Society of Ultrasound in Obstetrics and Gynecology in 2009, "Timor sign" (Goldstein S. R., Timor-Tritsch I., Monda S., Popliolek D., Monteagudo A. Ultrasound appearance of cystadenofibroma: can we reduce surgical intervention? Abstract OC25.03 *Ultrasound Obstet Gynecol* 2009; **34** (S1): 49).

An interesting feature that might be encountered in cystadenofibromas is papillary projections on the surface of the tumor, as reported in text books of pathology.[2] However, we have no information on how often this feature was seen on surgery or in the pathological specimens of our cystadenofibromas, and we do not know if it would be possible to detect surface papillary projections on ultrasound. Extensive papillary projections surrounding normal ovaries has been described in serous borderline tumors[23]. To recognize the typical ultrasound features of various adnexal pathologies is helpful when selecting treatment for women with adnexal masses. In this work we have described ultrasound features of serous cystadenofibromas. Because many cystadenofibromas contain papillary projections they may be confused with malignancies, in particular with borderline tumors[19-21]. In our study, 50 serous cystadenofibromas, i.e. approximately one in five, were suspected to be malignant (most often borderline tumors) by the original ultrasound examiner, and most (78%) of those suspected to be malignant contained papillary projections. A published retrospective analysis of 204 unilocular solid cysts with papillary projections but no other solid components showed that shadows behind papillary projections were more often present in benign than in borderline or malignant cysts, while papillary projections with anechoic spaces were more often present in borderline or malignant cysts than in benign cysts, i.e. in 60% vs in 24%[22]. The finding that anechoic spaces in papillary

projections was associated with malignancy is surprising in view of microcystic appearance of papillary projections being so common (38.6%) in the serous cystadenofibromas in our study. However, not all benign lesions in the study by Landolfo et al were serous cystadenofibromas, serous cystadenofibromas constituting only 29% of the benign lesions in that study[22]. Moreover, the study by Landolfo et al included only cysts with one cyst locule and no other solid components than papillary projections[22].

Absence of color Doppler signals inside papillary projections and the presence of shadowing seem to be common ultrasound features of benign serous cystadenofibromas with papillary projections, but the ability of these features to discriminate between serous cystadenofibromas and borderline tumors with papillary projections need to be investigated in a prospective study.

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Figure legends

Figure 1. Ultrasound images illustrating the International Ovarian Tumor Analysis (IOTA) definition of papillary projection as opposed to other types of solid components in an adnexal mass. (a) Ultrasound image of a serous cystadenofibroma in a 61-year-old patient appearing as a unilocular-solid cyst with a papillary projection but no other solid components. A papillary projection is defined as solid tissue that protrudes into the cyst lumen with a height of at least 3mm but with no upper limit of size. (b) Solid tissue that does not protrude into the cyst cavity is not a papillary projection. Ultrasound image of an endometrioid carcinoma stage I A in an 86-year-old patient appearing as a unilocular-solid cyst with a solid component that is not a papillary projection. From Landolfo et al, Ultrasound Obstet Gynecol 2018; 52:269-278.

Figure 2. Gray-scale ultrasound image of a unilocular solid serous cystadenofibroma with papillary projections in a 57-year old woman. The papillary projections manifest microcystic appearance.

Figure 3. Schematic drawing of ultrasound patterns of serous cystadenofibromas identified using pattern recognition and their prevalence. In multilocular solid tumors, the solid components were judged to be large if subjectively they constituted a large proportion of the lesion.

Figure 4. Ultrasound images of serous cystadenofibromas with no solid components.

a. Unilocular serous cystadenofibroma in a 53-year old woman.

b. Bilocular serous cystadenofibroma in a 45-year old woman.

c. Multilocular serous cystadenofibroma in a 49-year old woman.

Figure 5. Ultrasound images of unilocular solid serous cystadenofibromas with papillary projections but no other solid components.

a. Serous cystadenofibroma in a 19-year old woman. No shadowing is seen.

b. Serous cystadenofibroma in a 15-year old woman. Shadowing is seen.

c. Serous cystadenofibroma in a 61-year old woman. The papillary projection manifests a microcystic appearance and shadowing is seen behind it.

Figure 6. Gray-scale ultrasound images of multilocular solid serous cystadenofibromas with papillary projections but no other solid components.

a. Serous cystadenofibroma in a 48-year old woman. The papillary projection manifests microcystic appearance.

b. Serous cystadenofibroma in a 34-year old woman. Shadowing is seen behind one of the papillary projections.

Figure 7. Gray-scale ultrasound images of multilocular solid serous cystadenofibromas with solid components but no papillary projections.

a. Small solid components with shadowing but no papillary projections are seen in this serous cystadenofibroma in a 52-year old woman.

b. A large solid component with shadowing but no papillary projection is seen in this serous cystadenofibroma in a 77-year old woman.

Figure 8. Gray-scale ultrasound image of a multilocular solid serous cystadenofibroma with a large solid component and papillary projections in a 64-year old woman. Shadowing is seen.

Figure 9. Ultrasound images of solid serous cystadenofibroma.

a. Power Doppler ultrasound image from a 48-year old woman.

b. Color Doppler ultrasound image from a 48-year old woman. Shadowing is seen.

Figure 10. Gray-scale ultrasound image of a unilocular solid serous cystadenofibroma with both a solid component and a papillary projection in a 38-year old woman. Shadowing is seen.

Figure 11. Power Doppler ultrasound images of serous cystadenofibromas with vascularized papillary projections.

a. Serous cystadenofibroma in a 15-year old woman.

b. Serous cystadenofibroma in a 64-year old woman.

c. Serous cystadenofibroma in a 68-year old woman.

Figure 12. Ultrasound images and hematoxylin and eosin stained sections of an ovarian serous cystadenofibroma. On ultrasound the internal cyst wall shows a papillary projection measuring 7 x 6 x 6 mm (a), not vascularized on color Doppler (b), with smooth surface, shadowing (arrow). The histological image of this cystadenofibroma shows a papillary projection (see the dotted blue box) with rounded shape (c). A zoomed image of the papillary projection (d) shows fibromatous stroma constituting >95% of the papillary projection covered by serous monostratified epithelium without cytological atypia. Small edematous areas (constituting <5% of the papillary projection) are visible (dotted arrow).

Figure 13. Ultrasound images and hematoxylin and eosin stained sections of an ovarian serous cystadenofibroma. On ultrasound the internal cyst wall shows a papillary projection measuring 9 x11x10 mm (a), vascularized on color Doppler (b), with irregular surface, no shadowing and small cystic areas inside. The histological image of this cystadenofibroma (c) shows a papillary projection (outlined by a blue line) with large edematous areas within the stroma. A zoomed image of the edematous stroma of the papillary projection surrounded by a monostratified serous epithelium is shown in (d).

Table 1: Clinical background data for the patients with serous cystadenofibromas included in the International Ovarian Tumor Analysis (IOTA) study

Characteristic	n = 233
Family history of ovarian cancer	4 (1.7)
Personal history of ovarian cancer	0 (0)
Age (years)	54 (14-89)
Postmenopausal status	147 (63)
Nulliparous*	38/133 (28.6)
Tender mass when pressed upon with the vaginal probe†	4/100 (4)
CA 125 (U/mL) ‡	46 (2-1808)

Results are shown as median (range) or n (%).
*Results available for 133 patients (parity was not recorded in the IOTA phase 3 study).
†Results available for 100 patients (tenderness was recorded only in the IOTA phase 3 study).
‡Results available for 162 patients.

Table 2. Sonographic characteristics of serous cystadenofibromas included in the International Ovarian Tumor Analysis (IOTA) study and diagnosis suggested by the original ultrasound examiner

Characteristic	n = 233
Bilateral masses	37 (15.9)
Largest diameter of the lesion (mm)	76 (21-350)
Type of mass	
- unilocular	31 (13.3)
- multilocular	45 (19.3)
- unilocular-solid	67 (28.7)
- multilocular-solid	85 (36.5)
- solid	5 (2.1)
Echogenicity of cyst fluid	
- anechoic	148 (63.6)
- low level	61 (26.2)
- ground glass	5 (2.1)
- mixed	14 (6.0)
- no cyst fluid	5 (2.1)
Largest diameter of the largest solid component (mm)*	17 (3-93)
Presence of papillary projection	122 (52.4)
Number of papillary projections	
- 1	64/122 (52.4)
- 2	21/122 (17.2)
- 3	16/122 (13.1)
- 4 or more	21/122 (17.2)
Largest papillary projection, height (mm)	5 (3-44)
Presence of Flow in papillary projection when papillary projection present	25/122 (20.5)
Shadowing present	23 (9.9)
Ovarian crescent sign present†	25/64 (39)

Ascites	2 (0.9)
Fluid in the pouch of Douglas	35 (15)
Fluid in the pouch of Douglas, mm (if fluid present) ‡	16 (1-31)

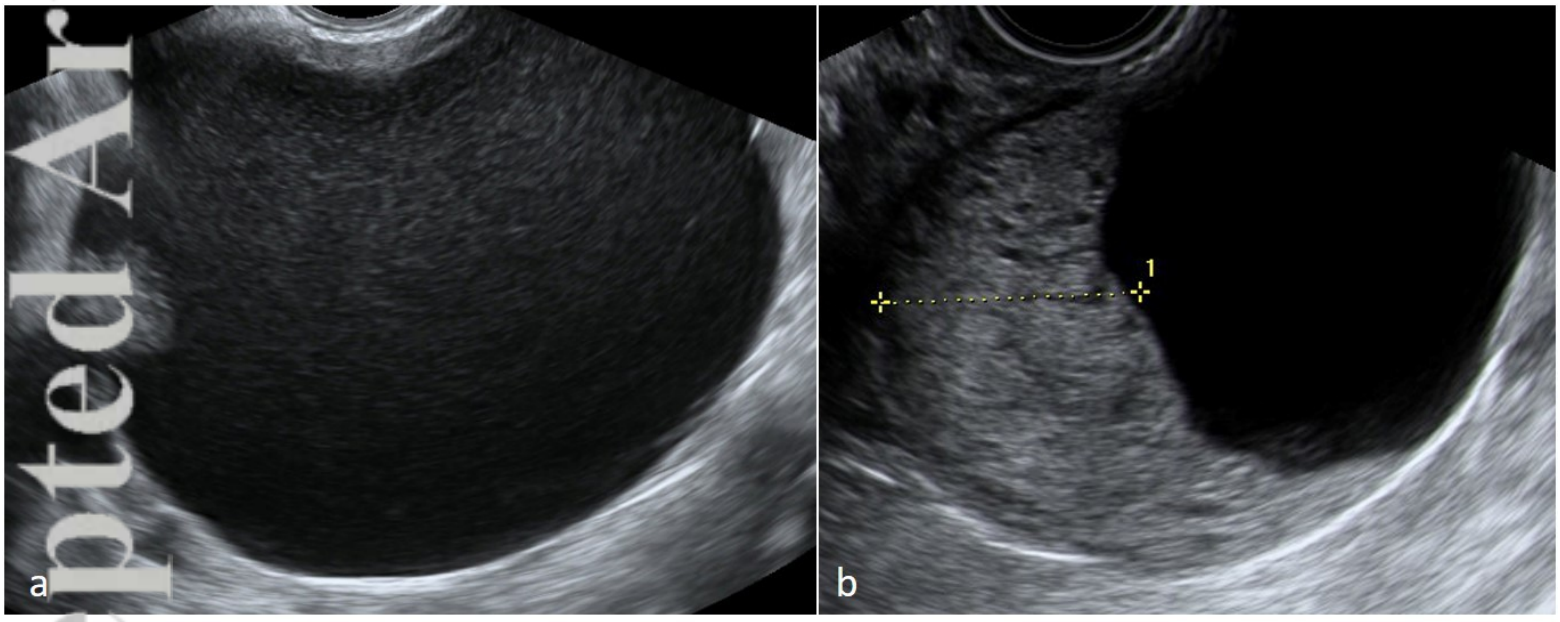
cont.

Table 2. (Continued) Sonographic characteristics of serous cystadenofibromas included in the International Ovarian Tumor Analysis (IOTA) study and diagnosis suggested by the original ultrasound examiner

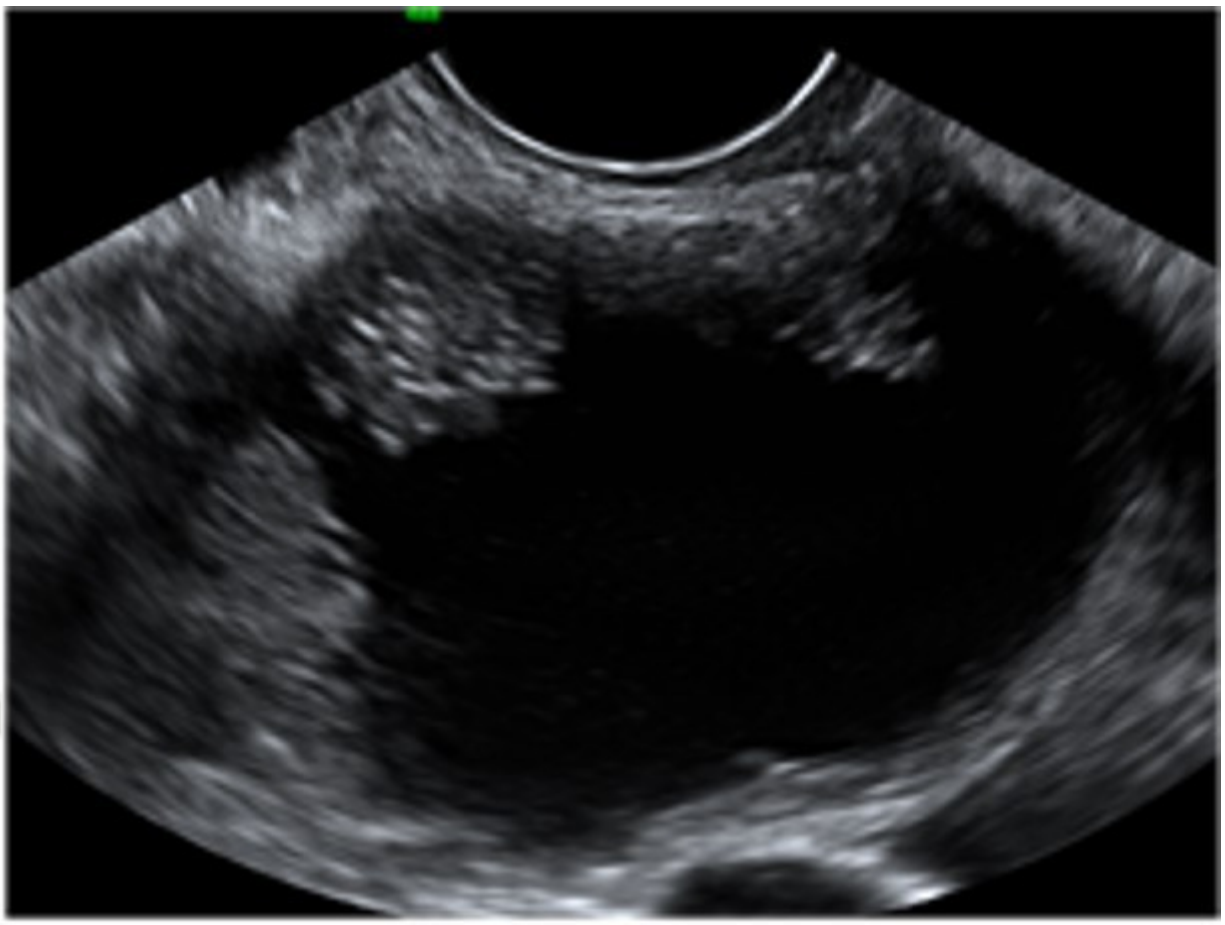
Color score	
- 1	96 (41.2)
- 2	99 (42.5)
- 3	37 (15.9)
- 4	1 (0.4)
Diagnosis on the basis of subjective assessment (original examiner)	
- benign	183 (78.6)
- borderline or malignant	50 (21.4)
Specific diagnosis suggested on the basis of subjective assessment§	
- Dermoid	6/211 (2.8)
- Simple cyst/paraovarian cyst	13/211 (6.2)
- Functional ovarian cyst	6/211 (2.8)
- Hydrosalpinx	5/211 (2.4)
- Peritoneal pseudocyst	2/211 (0.9)
- Abscess	1/211 (0.5)
- Fibroma/fibrothecoma	4/211 (1.9)
- Serous cystadenoma/ cystadenofibroma	87/211 (41.2)
- Mucinous cystadenoma/ cystadenofibroma	18/211 (8.5)
- Cystadenofibroma	1/211 (0.5)
- Cystadenoma	7/211 (3.3)
- Primary invasive tumor	7/211 (3.3)
- Borderline tumor	34/211 (16.1)
- Other malignant tumor	3/211 (1.4)
- Not possible	17/211 (8.1)

Results are shown as median (range) or number (%).
* Solid component was present in 157 masses.
† Data available for 64 cases (obligatory information only in IOTA phase 3).
‡ Information was available in all 35 cases with fluid in the pouch of Douglas.

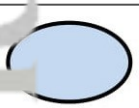
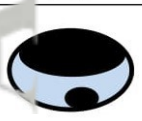
§ Data available for 211 cases (it was not obligatory to suggest a specific diagnosis in IOTA phase 1b).



UOG_20277_Figure 1.jpg

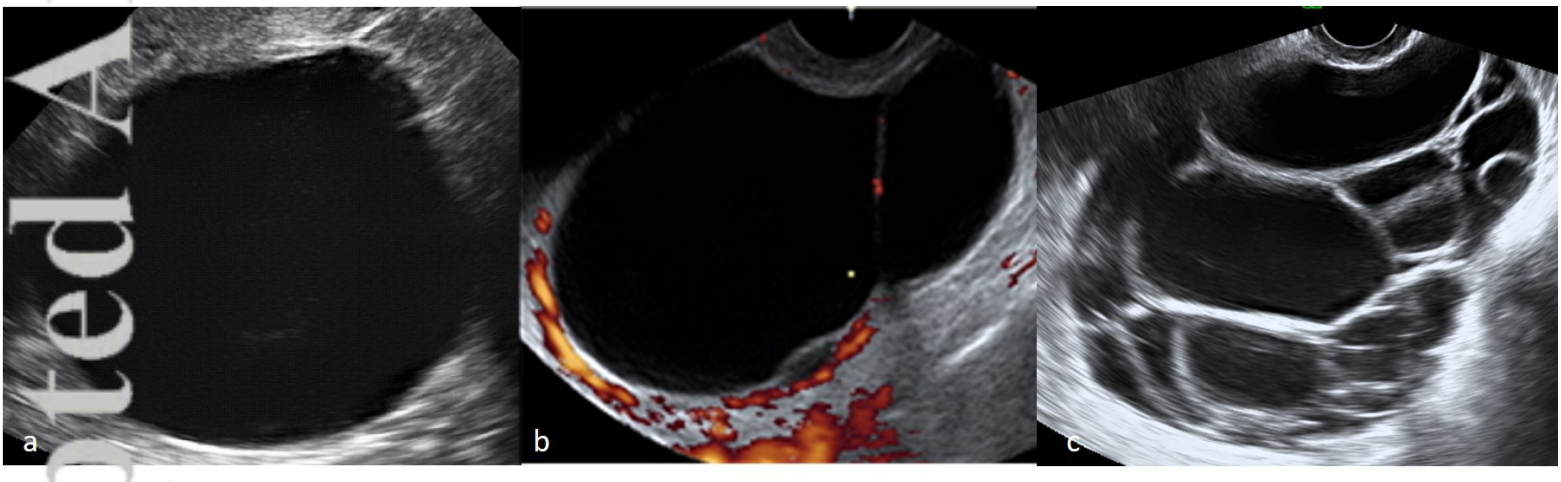


UOG_20277_Figure 2.jpg

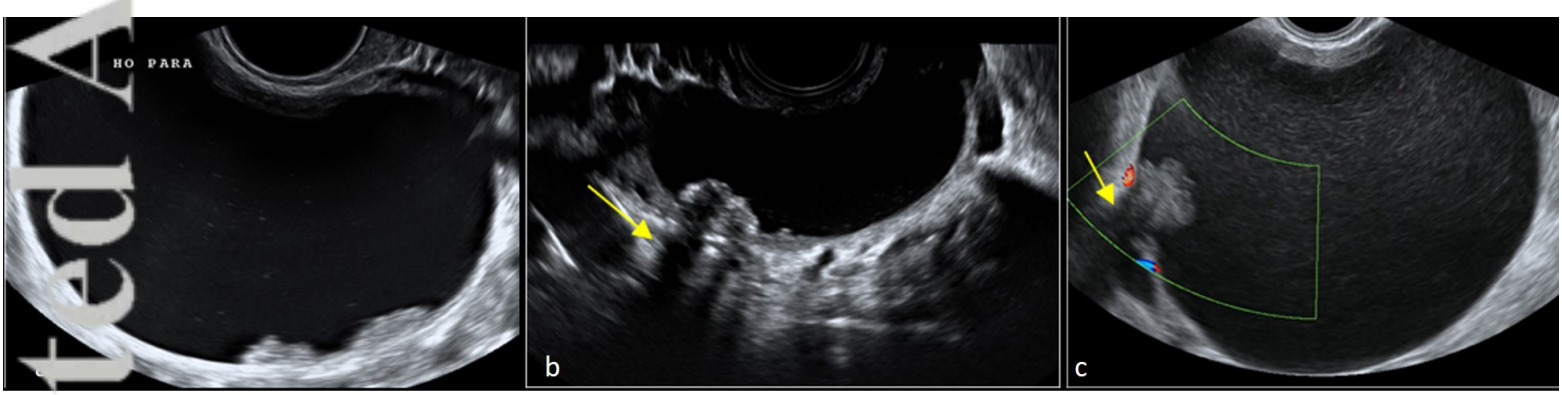
Pattern		Tumors of each type	Tumors of each type without shadowing*	Tumors of each type with shadowing*	Tumors of each type with microcystic appearance of papillary projections*
	Unilocular cyst	24 (11.9)	24 (11.9)	0	Not applicable
	Bilocular cyst	9 (4.5)	9 (4.5)	0	Not applicable
	Multilocular cyst	25 (12.4)	25 (12.4)	0	Not applicable
	Unilocular solid cyst with one or more papillary projections	52 (25.9)	30 (14.9)	22 (10.9)	22 (10.9)
	Multilocular solid cyst with papillary projection(s) but no other solid components	20 (10.0)	9 (4.5)	11 (5.5)	7 (3.5)
	Multilocular solid cyst with small solid component(s) but no papillary projections	39 (19.4)	14 (7.0)	25 (12.4)	Not applicable
	Multilocular solid cyst with large solid component(s) but no papillary projections	14 (7.0)	5 (2.5)	9 (4.5)	Not applicable
	Multilocular solid cyst with both papillary projection(s) and small or large other solid component(s)	15 (7.5)	4 (2.0)	11 (5.5)	4 (2.0)
	Solid mass	2 (1.0)	1 (0.5)	1 (0.5)	0 (0)
	Unilocular solid cyst with both papillary projection(s) and other solid component(s)	1 (0.5)	0 (0)	1 (0.5)	1 (0.5)
Total number		201	121	80	34

Results are shown as n (%). *Percentages are calculated per all 201 cystadenofibromas.

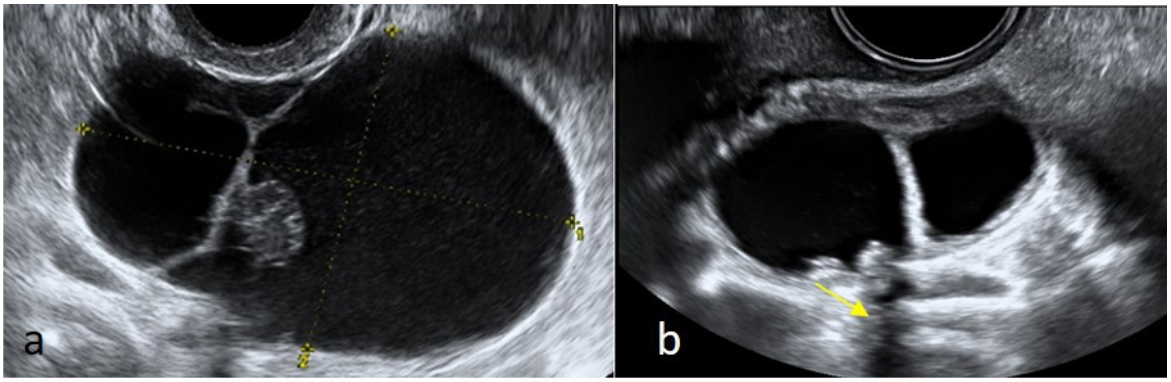
UOG_20277_Figure 3.jpg



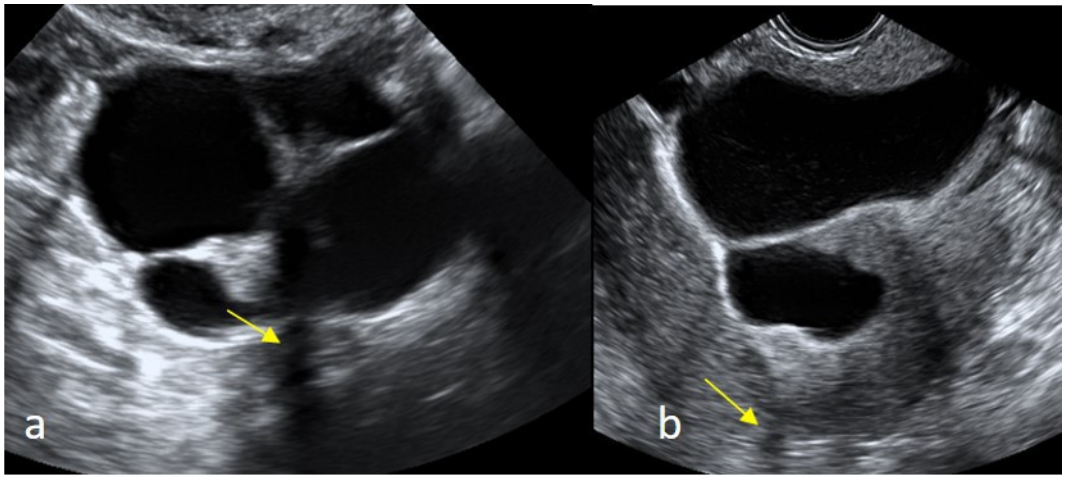
UOG_20277_Figure 4.jpg



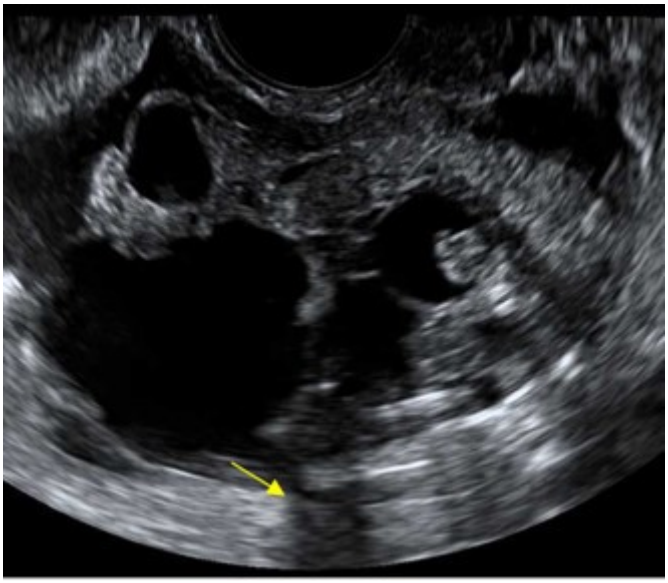
UOG_20277_Figure 5.jpg



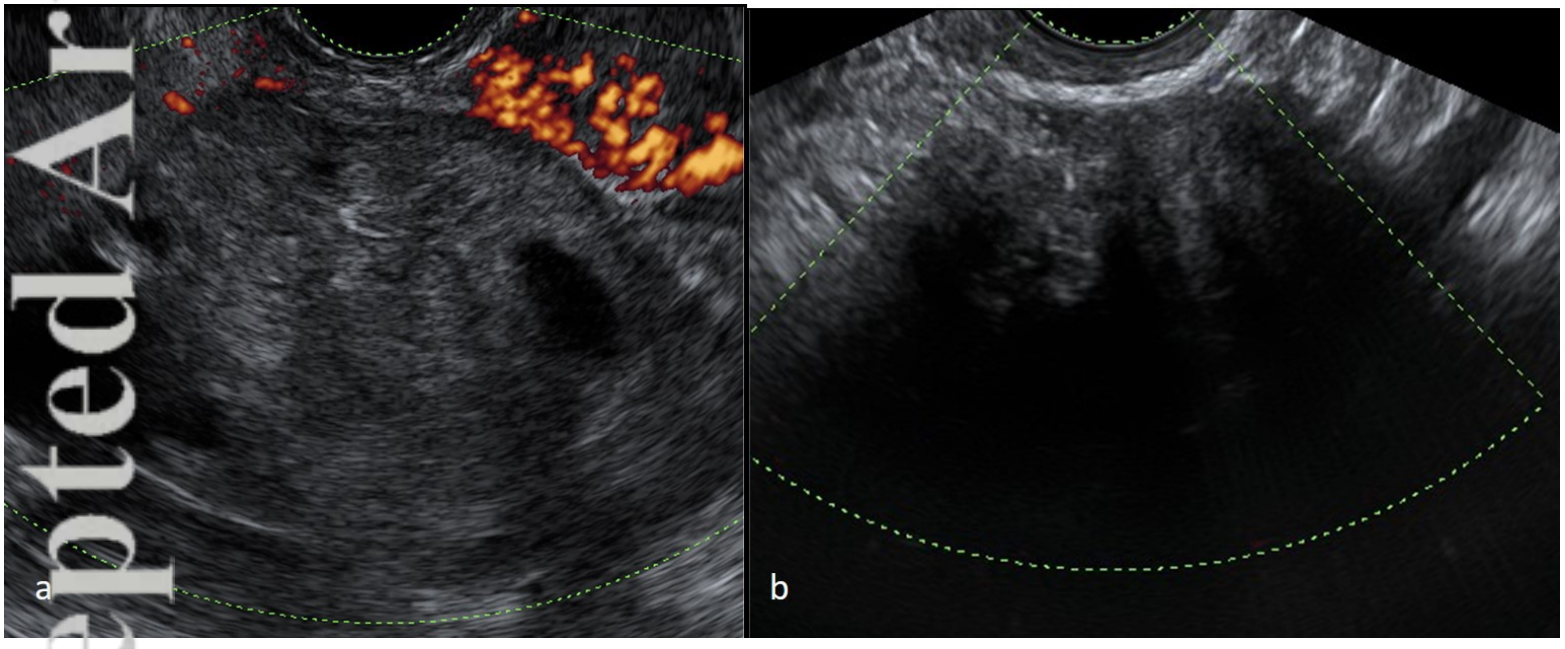
UOG_20277_Figure 6.jpg



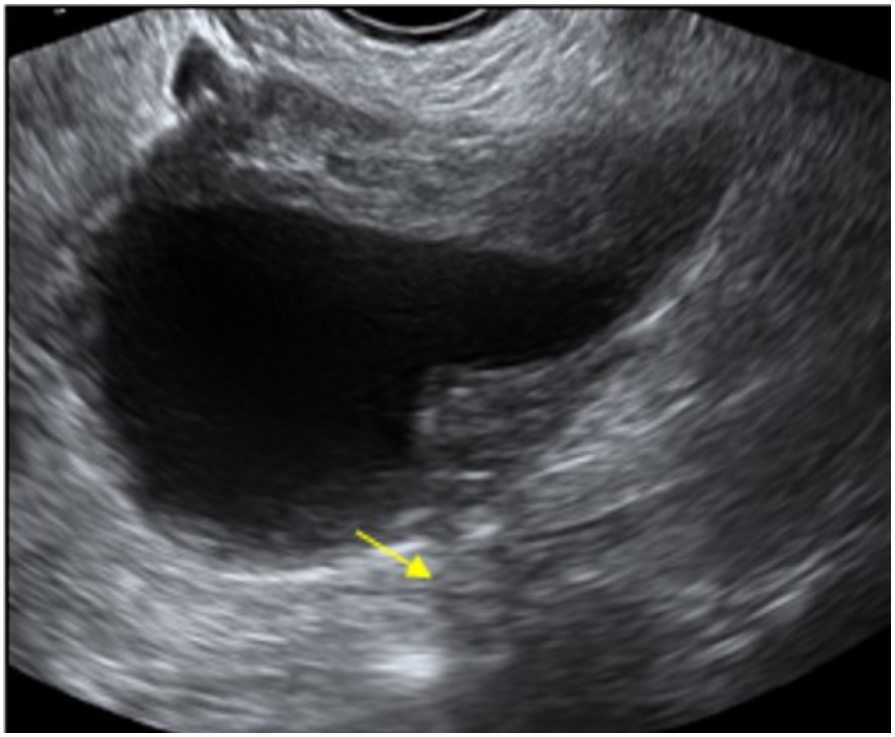
UOG_20277_Figure 7.jpg



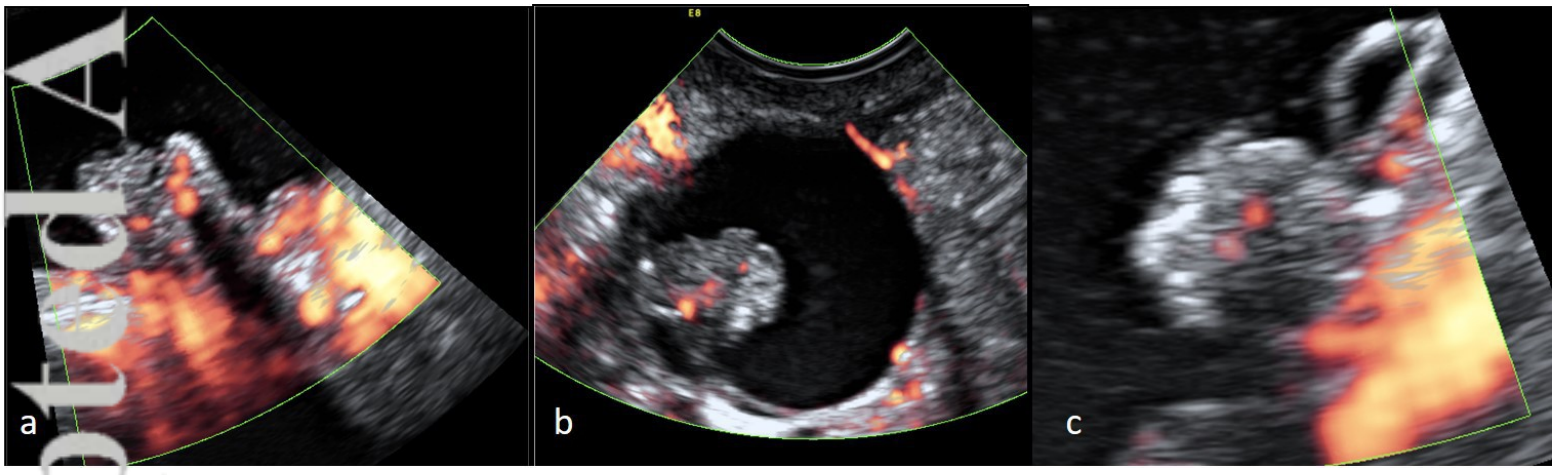
UOG_20277_Figure 8.jpg



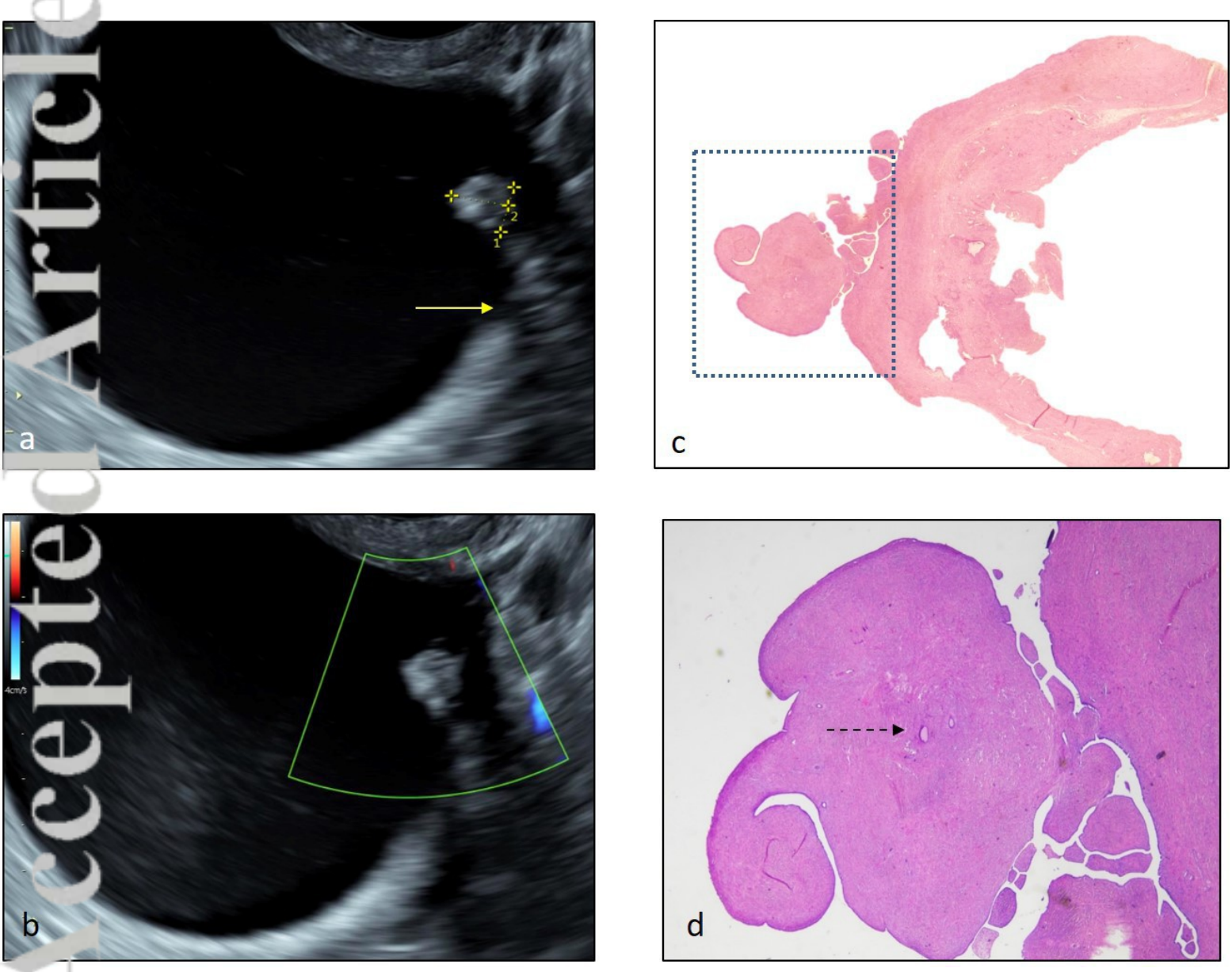
UOG_20277_Figure 9.jpg



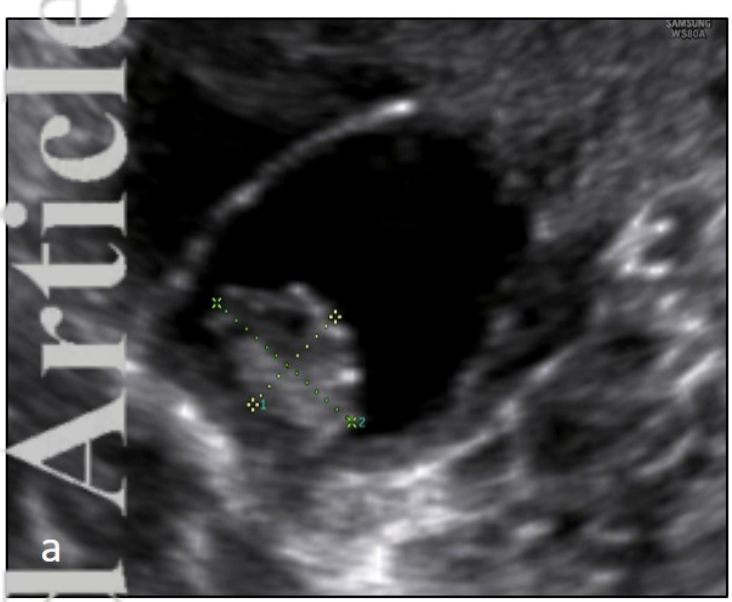
UOG_20277_Figure 10.jpg

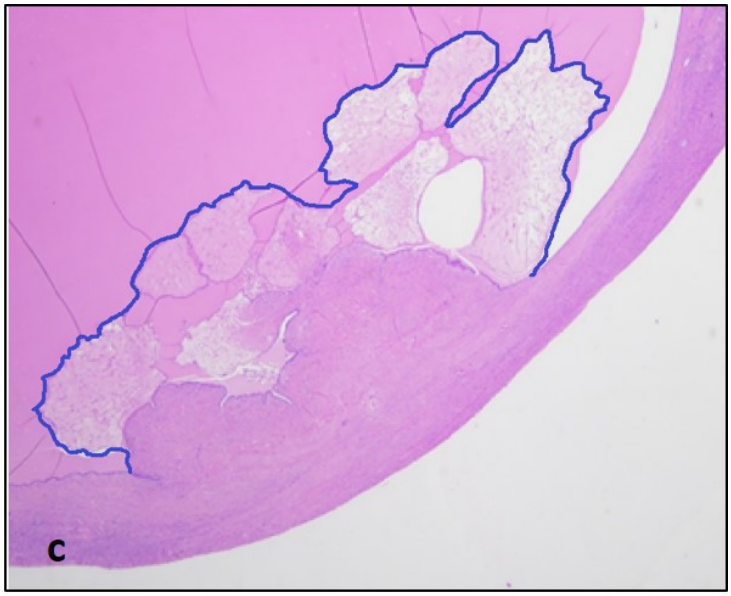


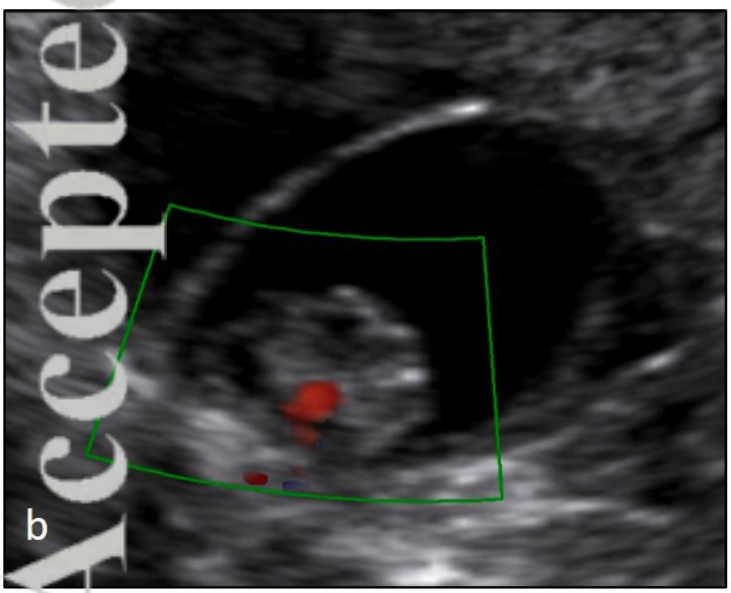
UOG_20277_Figure 11.jpg

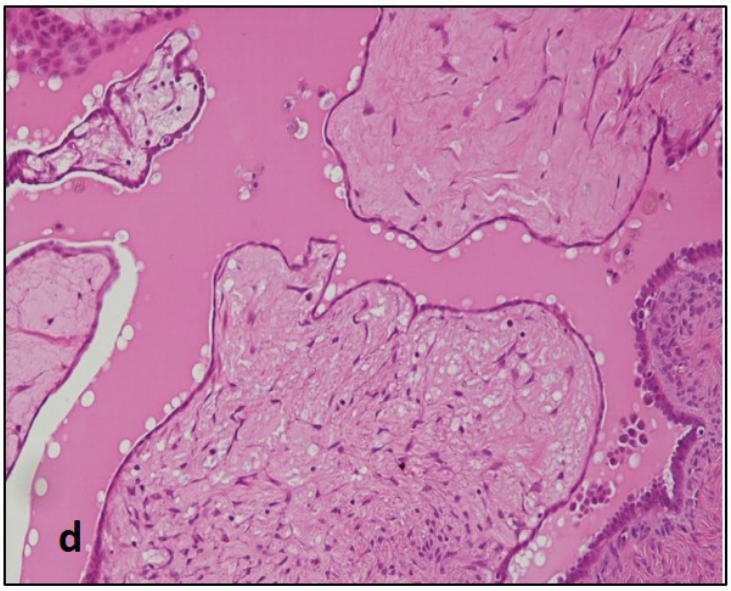


UOG_20277_Figure 12.jpg









UOG_20277_Figure 13.jpg