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Imaging in gynecological disease: clinical and ultrasound characteristics of accessory cavitated uterine malformations

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Running head: Ultrasound diagnosis of ACUM

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Contribution

What are the novel findings of this work?

ACUMs are a relatively rare abnormality of the uterus and there is little information about the criteria that should be used for diagnosis, either on imaging or during surgery. In this largest case series so far we provide a summary of ultrasound features which could be used to diagnose this condition with more confidence in the future

What are the clinical implications of this work?

This study should further clinician knowledge of this under recognised condition. It also describes a non-excisional interventional procedure, that has not been widely described as being used for this condition in the literature. Thus a greater number of women will receive a diagnosis and have a greater number of treatment options.

Abstract

Objective

To describe the clinical and ultrasound characteristics of accessory cavitated uterine malformations (ACUMs).

Methods

This was a single center observational case series of consecutive patients diagnosed with ACUMs who were retrospectively identified from medical records. We identified 20 patients with an ACUM after having undergone an ultrasound examination by an experienced ultrasound examiner between January 2013 and May 2019. ACUMs were diagnosed when a cavitated lesion with a myometrial mantle and echogenic contents was seen within the anterior lateral wall of the myometrium beneath the insertion of the round ligament. In all women, presenting symptoms and clinical histories were recorded along with detailed descriptions of the lesions and any concomitant pelvic abnormalities.

Results

The median age of the 20 women diagnosed with ACUMs was 29 (inter-quartile range: 25-36). None of the women were pre-menarchal or post-menopausal. Twelve of the ACUMs were in the right anterior lateral myometrium and eight were in the left anterior lateral myometrium. All of the women reported painful periods or pelvic pain and none of them reported subfertility. Surgical excision was carried out in eight cases and the diagnosis was confirmed on histopathological examination in all of them.

Conclusions

ACUMs are a uterine abnormality with a distinct ultrasound appearance, which are associated with dysmenorrhoea and chronic pelvic pain. Its typical appearance on ultrasound scan could facilitate early detection and treatment. There are several treatment options ranging from simple analgesia to complete excision. Further prospective and longitudinal studies are required to study the prevalence and natural history and of this condition.

Introduction

Accessory cavitated uterine malformations or masses (ACUM) are recently coined names for a previously described myometrial lesion considered to be a significant and treatable cause of pelvic and menstrual pain. We prefer the term malformation, which better reflects the nature of this abnormality, rather than mass, which is less specific and is more likely to have sinister connotations for women. This abnormality has been almost exclusively described in young women[1]. Possible early descriptions of these anomalies date back to the early 20th century[2] and up until as recently as 2012, they were termed 'juvenile cystic adenomyomas' (JCA) and were treated as a rare form of adenomyosis[3].
They are now considered to be a Mullerian uterine anomaly[1] and treatment, in the form of complete surgical excision, is thought to be curative[4]. Nevertheless, the condition is likely to be significantly under-diagnosed, in part due to lack of clinician knowledge of the lesion but also because of a lack of agreed diagnostic criteria. The aim of this study is to increase knowledge and facilitate better detection of ACUMs in the future by describing their clinical symptoms and ultrasound characteristics.

Epidemiology
The current literature on ACUMs is limited and there are currently no population-based studies looking at ACUMs, with the published literature consisting entirely of case reports and case series. The prevalence of ACUMs is unknown, but they are generally considered to be a rare abnormality.
One epidemiological feature of ACUMs is the age of women in which they have been diagnosed, with some authors stipulating that they could only be seen in women ≤30 years[4]. There have; however, been descriptions of ACUMs in women over the age of 30[1].

Microscopy
Microscopically, the cavity of the lesion is lined with functional endometrium consisting of glands and stroma[4,5] and blood may be seen within the cavitation (Figure 1a). The endometrial tissue within the ACUMs of all patients in two studies was positively stained for CD10, estrogen receptors (ER) and progesterone receptors (PR), which are markers of normal endometrium[4,5]. In the same study, the myometrial mantle of the ACUMs contained irregularly arranged smooth muscle cells that stained positive for desmin, ER, and PR[4]. The myometrium surrounding the cavitated lesion may be hypertrophic and will often contain foci of adenomyosis[6].

Macroscopy
Macroscopically, ACUMs are isolated cavitated lesions (Figures 1b & c) located within the lateral aspect of the myometrium, beneath the attachment

of the round ligament to the uterus. Their mean overall diameters have been reported as ranging from 25mm to 42mm and their mean inner cavity as ranging from 10mm to 23mm. In the same study, the weight of resected specimens ranged from 3.5g to 11.5g[4]. At surgery or on hysterectomy specimen, they often appear as a subtle bulge on the lateral surface of the uterus near the attachment of the round ligament (Figure 1d) and could easily be missed if not looked for. The cavities contain altered blood (Figure 1e).

Clinical symptoms

Severe pelvic pain or dysmenorrhoea, often ipsilateral to the side of the lesion is considered to be ubiquitous in most studies. There is no evidence suggesting ACUMs are associated with heavy menstrual bleeding or subfertility although there are no published studies that have attempted to look for such an association. There are several cases of ACUMs found in parous women[1,2,4,6].

Prognosis

There are no longitudinal or observational studies on ACUMs. All case series and most of the case reports describe surgical excision with alleviation of symptoms and so the natural history of ACUMs remains unknown. Studies describe an unsatisfactory response to conservative treatments in women with ACUMs. In Acien's case series, all four patients had inadequate pain relief with NSAIDs, the oral contraceptive pill or both, and all patients ultimately had surgical resection[6]. Takeuchi *et al* described NSAIDs as ineffective for symptom relief, the oral contraceptive pill or GnRH analogues as somewhat effective for pain relief and again, all patients ultimately ended up having surgical resection[4]. There are no reports of ACUM recurrence post-resection.

Methods

This was an observational case series of consecutive patients diagnosed with ACUMs who were retrospectively reviewed from medical records. Following the coining of the term ACUM in 2012[6], we started actively looking for cases of ACUMs in our general gynaecology clinic (University College London Hospitals, London). ACUMs were diagnosed if cavitated lesions with a myometrial mantle and echogenic contents, were seen in the anterior lateral wall of the myometrium beneath the insertion of the round ligament (Figures 2, 3 & 4). Ruling out obstructive congenital anomalies, such as communicating and non-communicating horns, was considered crucial to diagnosis. ACUMs can be differentiated from obstructive congenital anomalies by their absence of a connection to either the uterine cavity or to the Fallopian tubes. Therefore an uninterrupted endometrial echo and two normal interstitial portions of Fallopian tubes were always visualised to be certain of the diagnosis (Video 1). Twenty women were diagnosed with ACUMs between March 2013 and April 2019. In all cases, the diagnosis was confirmed by one of two level 3 expert ultrasound examiners (JN & DJ) [7], either by real-time scanning or offline assessment of stored images. All the women had demographic data recorded and a detailed clinical history was taken prior to undertaking the ultrasound scan. This included the history of the presenting complaint along with age, pregnancy history, smear history, surgical and medical history.

All the women then underwent a conventional clinical ultrasound examination by a gynaecologist with a special interest in gynaecological ultrasound, as part of a referral for diagnosis and/or management. All women were examined using either transvaginal (TVUS) or transrectal (TRUS) ultrasound, using a 4–9 MHz probe with three-dimensional facility (Voluson E8, GE Medical Systems, Milwaukee, WI, USA). The overall diameters of the ACUMs and their cavities were measured in three orthogonal planes and a 3D scan of the uterus was performed in order to classify the uterine morphology. Any concomitant pelvic abnormalities diagnosed on ultrasound were recorded.

Some of the women were referred for diagnosis only. In these cases we requested the subsequent treatment and outcomes from the referring clinicians. Where women were referred for diagnosis and management, their treatments and subsequent outcomes were recorded. All clinical and ultrasound information was entered into a dedicated Excel file (Microsoft Office Excel 2003, Redmond, WA, USA). IRB approval was not deemed necessary as there was no randomisation, no deviation from standard clinical care and the study was descriptive. As the study was retrospective, no written patient consent was deemed necessary.

Results

Morphology and diagnosis

During the study period 20 ACUMs were identified, all of which were found within uteri that were either normal or arcuate according to both CUME & ASRM[8]. All were isolated cavitated lesions located in the anterolateral aspects of the myometrium, beneath the insertion of the round ligament on the uterine horn. There were 12/20 (60%) lesions on the right and 8/20 (40%) on the left, which were all clearly delineated from the surrounding myometrium. Having both a myometrial mantle and a fluid–filled cavitation, were considered to be a defining features on ultrasound. The fluid contained within the cavitation was either echogenic with a 'ground glass' appearance, identical to the classical appearance of the altered blood seen within endometriotic cysts (Figure 5) or hyperechoic (Figure 6). They were all spherical in shape (Figure 7). The Doppler flow seen in the outer rim was not markedly different to that of the surrounding myometrium and the contents of the cavity, being fluid, were avascular on Doppler examination (Figure 8).

The mean outer cavity diameter of the ACUMs was 22.8mm (95%CI: 20.9mm-24.8mm) and the mean internal cavity diameter of the ACUMs was 14.1mm (95%CI: 12.2mm-16.1mm). In all cases, the interstitial portions of both Fallopian tubes were identified to exclude misclassification of an obstructive uterine anomaly as an ACUM. Table 1 outlines the other diagnoses made at the time of ultrasound scan, including three women diagnosed in early pregnancy having attended with bleeding in early pregnancy.

Two women, who had only had transabdominal (TAUS) scans at their first attendance, were diagnosed with ACUMs at their second attendance. In both women, the ACUM was diagnosed at their first TVUS or TRUS.

Symptoms

All 17 of the non-pregnant patients diagnosed with ACUMs had been referred for investigation of pelvic pain or painful periods. Eleven of them reported unilateral pain that was ipsilateral to the side where the ACUM was located and the remaining 6 patients reported more generalised pain. None of the patients were referred for heavy periods or subfertility.

Treatments

The three women who were pregnant at the time of diagnosis were managed expectantly. One woman was lost to follow up. Of the remaining sixteen women, six opted for hormonal treatments (3 progesterone-only pill, 2 combined hormonal contraceptive pill, and 1 Levonorgestrel-containing intrauterine contraceptive system). Four women opted for transvaginal

ultrasound-guided alcohol sclerotherapy. In all four cases, cytology confirmed that the ACUM contents were haemorrhagic.

Six women opted for primary surgical treatment. In addition, surgery was carried out in 1 woman with failed medical management and 1 in whom symptoms recurred six months after sclerotherapy. In all eight women who opted for surgical treatment, the excision was completed laparoscopically and in all cases, histopathology confirmed the preoperative diagnosis of ACUM.

Histopathology

All eight ACUMs that were excised were described on histopathological examination as cavitated smooth muscle lesions lined by functioning endometrium. The myometrial mantle comprised smooth muscle fibres with a well-ordered concentric orientation. This concentric orientation can help differentiate ACUMs from adenomyosis, which will tend to have a more disordered orientation of muscle fibres.

Differential diagnoses

Several women that were ultimately considered not to have ACUMs, were suspected of having ACUMs by clinicians who referred to us for a second opinion. Figures 9, 10 & 11 illustrate examples of this and detail the reasons why they were ultimately not diagnosed as ACUMs. In these cases, the lesions were thought to be focal adenomyosis, cystic adenomyomas or a lateral uterine fibroid.

Demographics

The median age of the women diagnosed with ACUMs was 29.2 (inter-quartile range: 25-35.8). None of the women were pre-menarchal or post-menopausal and in three cases the ACUMs were diagnosed in the first trimester of pregnancy. All of the women in whom ACUMs were diagnosed outside pregnancy had been referred for investigation of pelvic pain and all three of the women who were diagnosed during pregnancy described a history of painful periods or had previously been investigated or treated for pelvic pain. Of the 20 women in the study, 13 were nulligravid and 16 were nulliparous. Table 2 outlines the obstetric history of the 5 women who had had pregnancies prior to diagnosis.

Pregnancy

None of the patients who were pregnant at the time of diagnosis reported a history of difficulty conceiving, with one pregnancy being unplanned. The two women with ACUMs who had planned conceptions both had an

uncomplicated antenatal course and had vaginal deliveries at term. The patient with an unplanned pregnancy had a first trimester miscarriage.

Discussion

This study represents the largest case series of ACUMs in the literature to date. The morphological appearance of the ACUMs in this series are consistent with what is already described in the literature, in that they were all isolated cavitated lesions with a myometrial mantle and echogenic contents, located in the anterior lateral aspects of the myometrium, beneath the insertion of the round ligament. ACUMs appear to have a distinctive and consistent morphological appearance dating back to what appears to be their original description in 1912[2].

Terminology

ACUMs are also referred to in the literature as juvenile cystic adenomyomas (JCAs). As discussed by Acien *et al* in their 2010 paper, we would consider these names synonymous[1]. There are several reasons why we use ACUM instead of JCA. The word 'juvenile' to describe a lesion that can be found in adults could be a cause of confusion. While there is clear overlap between ACUMs and adenomyosis with both being myometrial pathologies where there are endometrial glands and stroma within the myometrium, there are also many features of ACUMs that make them distinct from adenomyosis. ACUMs have a very consistent appearance, in contrast to the highly variable morphological appearances of adenomyosis, and ACUMs appear to be present in a markedly different demographic to adenomyosis. While there is no irrefutable evidence to confirm Acien *et al*'s supposition that ACUMs represent a uterine malformation, we feel it has more in common with a malformation than it does with adenomyosis[6]. We favour the term malformation rather than mass because mass can take on a sinister meaning for patients and therefore we feel that Accessory Cavitated Uterine Malformation is a better term that describes what the lesion is, where it is and its likely aetiology.

Diagnosis

Our ultrasound findings mirror the descriptions of ACUMs seen in Magnetic resonance imaging (MRI) studies[5]. While MRI can of course be used to diagnose ACUMs, we did not use or require MRI to diagnose any of the ACUMs in our series. This may reflect our greater experience and confidence in using ultrasound, as gynecologists with a particular interest in ultrasound. Given that ACUMs tend to occur in younger women there is likely to be a proportion of patients with ACUMs who have never had penetrative vaginal intercourse and who therefore would not tolerate a TVUS. Transrectal ultrasound can offer equivalent views to TVUS in this circumstance but not all patients will consent to such an examination. Acien *et al* state that MRI and hysterosalpingography (HSG) are an essential part of the work-up for

ACUMs[6]. With regards to the use of HSG in the diagnosis of ACUMs, its role was to prevent the misdiagnosis of obstructive anomalies as ACUMs. We feel that these can be excluded on standard or 3D TVUS and they therefore have no role in the diagnosis of ACUMs.

Symptoms

All the patients in our series had a history of severe pelvic pain or painful periods, with many of the subjects having had multiple surgeries to either investigate or treat their pain. This is entirely consistent with the literature where pain symptoms are always present in women who have been diagnosed with ACUMs. The likely mechanism for this is the build-up of menstrual fluid and blood in a cavitated, and therefore enclosed space, causing substantially increased pressure and pain. This mechanism for causing pain is also seen in women and girls with obstructive anomalies. ACUMs do not appear to impact on the 'normal' uterine cavity or the Fallopian tubes. There is therefore no obvious reason they should cause heavy menstrual bleeding or subfertility. Consistent with this, none of the patients in our study reported heavy periods or subfertility alongside their pain symptoms.

Age

The mean age in our series was 29.2 years of age (inter-quartile range: 25-35.8). This is higher than the mean age reported in other studies with Takeuchi *et al* reporting a mean age of 25years[4]. Some authors have suggested diagnostic criteria should only include women up to the age of 30 years, but our findings do not support that as half of our patients were aged ≥30 years.

There may be a variety of reasons why the literature reports so few women being diagnosed with ACUMs after the age of 30 years. Women are more likely to develop other uterine pathologies as age increases such as uterine fibroids or adenomyosis[9,10]. The presence of these pathologies is likely to make diagnosis of ACUMs more challenging as they might obscure ACUMs or become of the focus of the ultrasound examination. Pregnancy may also change their appearance in a similar manner, although many case series contain parous women

Associated abnormalities

In contrast to other series who reported no major gynecological pathologies in their populations of women with ACUMs[5,6], many of the women in our series had concommitant pathologies, as previously detailed in Table 1. Only one woman in our study was diagnosed with endometriosis at the time of her ACUM diagnosis. Obstructive anomalies that cause increased retrograde menstruation are associated with a higher prevalence of endometriosis. In ACUMs however, the anomaly is cavitated and so the menstrual fluid is completely contained within the lesion. There is therefore no currently known reason why there should be an increased likelihood of endometriosis in women with ACUMs.

Treatment

In contrast to the published literature, where all women with ACUMs ultimately underwent surgical excision, only 8/20 (40%) of the patients in our series underwent surgical excision and subsequent histopathological analysis of the ACUM. Nevertheless, in the 8 patients who underwent surgical excision, the excised lesions were all confirmed to be ACUMs on histological examination. We used medical treatment more liberally than other authors. One fifth of the women in our study underwent alcohol sclerotherapy during the study period and none of them had intraoperative or postoperative complications. Alcohol sclerotherapy offers a low risk, day case intervention[11,12] that attempts to destroy the functioning endometrium within the ACUM, thereby reducing the monthly build-up of menstrual fluid within the ACUM cavity. All of the women reported a significant reduction in their pain symptoms although one of them subsequently opted for surgical excision as their pain returned to its pre-treatment levels 6 months after treatment. We found that the majority of patients were keen to avoid surgery in the first instance when given the option of conservative management.

In our series, all the women who underwent surgical excision had it completed laparoscopically and without complication. Some authors have expressed a preference for performing open excision, the logic being that it is easier to find the surgical planes of the ACUM at open surgery[6]. In our experience, finding the correct surgical planes laparoscopically can be a challenge and in a number of our cases, we used intraoperative transvaginal ultrasound to aid excision. None of the women in our study managed non-surgically nor those who had their ACUMs excised have subsequently conceived so we have no data on which we could base discussions about management of future pregnancy. Nevertheless, the procedure of ACUM excision, as mentioned above, is similar to resection of a moderately sized subserous or superficial

intramural fibroid and extrapolation from this group would not be unreasonable until ACUM-specific data becomes available.

Histology

While histopathological examination can confirm findings consistent with an ACUM, there are challenges to considering histopathology as definitive in the diagnosis of ACUMs. Firstly the location of ACUMs within the uterus is fundamental to their diagnosis but histopathological examination of an excised lesion is done without certain knowledge of where the lesion was excised from.

Secondly there is substantial overlap in histological appearance between ACUMs and cystic adenomyomas, which also represent a cavitated myometrial lesion that can be lined with endometrium. Pre-operative imaging therefore becomes crucial to the diagnosis of ACUMs as it can determine the exact location of the lesion within the uterus. Peyron *et al* report that cystic adenomyomas tend to involve or be in close proximity to the endometrial-myometrial junction, in contrast to ACUMs, which will be more distinct from the uterine cavity[5]. Cystic adenomyomas can be sagittal whereas ACUMs, as already mentioned, are always in the lateral aspect of the myometrium.

Conclusion

In this paper, we describe the unique morphological ultrasound appearance of an important but under recognised gynaecological condition. There appears to be strong correlation between the presence of these morphological features and symptoms of severe menstrual pain and pelvic pain. We also describe a variety of different treatments, which can lead to partial or complete resolution of symptoms. Increased recognition and understanding of the condition has the potential to help an enormous number of women of reproductive age worldwide who would otherwise suffer debilitating pelvic pain. Further work is needed to determine the prevalence and clinical impact of this condition and to determine the efficacy of current treatments.

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Figure legends

Figure 1a Microscopy of a histological slice through an ACUM showing smooth muscle mantle (pink) and the inner cavity lined with endometrium (purple). Blood is seen in the lateral aspect of the cavitation.

Figure 1b Macroscopy of an intact ACUM after laparoscopic excision

Figure 1c Macroscopy of serial histological slices through a laparoscopically resected ACUM

Figure 1d Laparoscopic image of the uterus before excision of an ACUM (yellow arrow). Note the ACUM bulging anterior to the right round ligament and its location inferior to the right Fallopian tube

Figure 1e Laparoscopic image of the uterus during excision of the ACUM, after opening of the round ligament. Note the presence of altered blood on the anterior surface of the ACUM

Figure 2 Transverse view of uterus on transvaginal ultrasound showing location of ACUM (thick yellow arrow) relative to uterine cavity (thin yellow arrow) and interstitial portion of the right Fallopian tube (thin white arrow)

Figure 3 3D rendered coronal view of uterus on transvaginal ultrasound showing location of ACUM (A) relative to uterine cavity (UC) and interstitial portion of the Fallopian tubes (I)

Figure 4 Hand drawn illustration of uterus and ACUM from original description published in the Lancet in 1912 by Oliver

Figure 5 Transverse transvaginal ultrasound image of a uterus and ACUM with echogenic contents of ‘groundglass’ appearance seen within the ACUM

Figure 6 Transverse transvaginal ultrasound image of a uterus and ACUM with hyperechoic contents seen within the ACUM

Figure 7 Measurement of an ACUM in three orthogonal planes illustrating a spherical shape

Figure 8 Transverse view of the uterus on transvaginal ultrasound showing Doppler examination of an ACUM, illustrating the presence of vascularity within the myometrial mantle but not within the cavitated part of the lesion

Figure 9 Sagittal view of a retroverted uterus on transvaginal ultrasound showing cystic adenomyosis at the fundus. Note central fundal location of lesion rather than the anterior lateral location typical of an ACUM.

Figure 10 Sagittal view of anteverted uterus on transvaginal ultrasound showing cystic adenomyoma in the anterior myometrium. Note lack of myometrial mantle, direct proximity to uterine cavity, location in central anterior aspect of uterus and anechoic contents of lesion

Figure 11 Transverse view of uterus on transvaginal ultrasound showing subserous fibroid at left posterior aspect of the uterus. Note lack of myometrial mantle and lack of cavitation within the fibroid

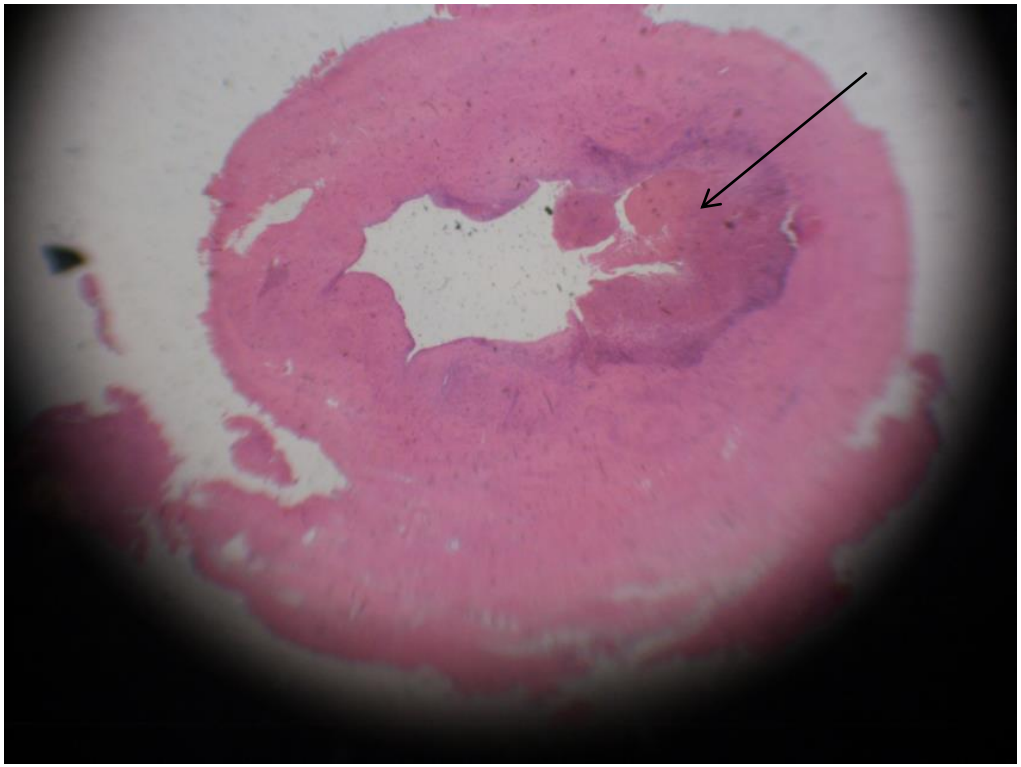
Supplementary videoclip: Video of 3D volume acquisition of a left sided ACUM and an otherwise morphologically normal uterus

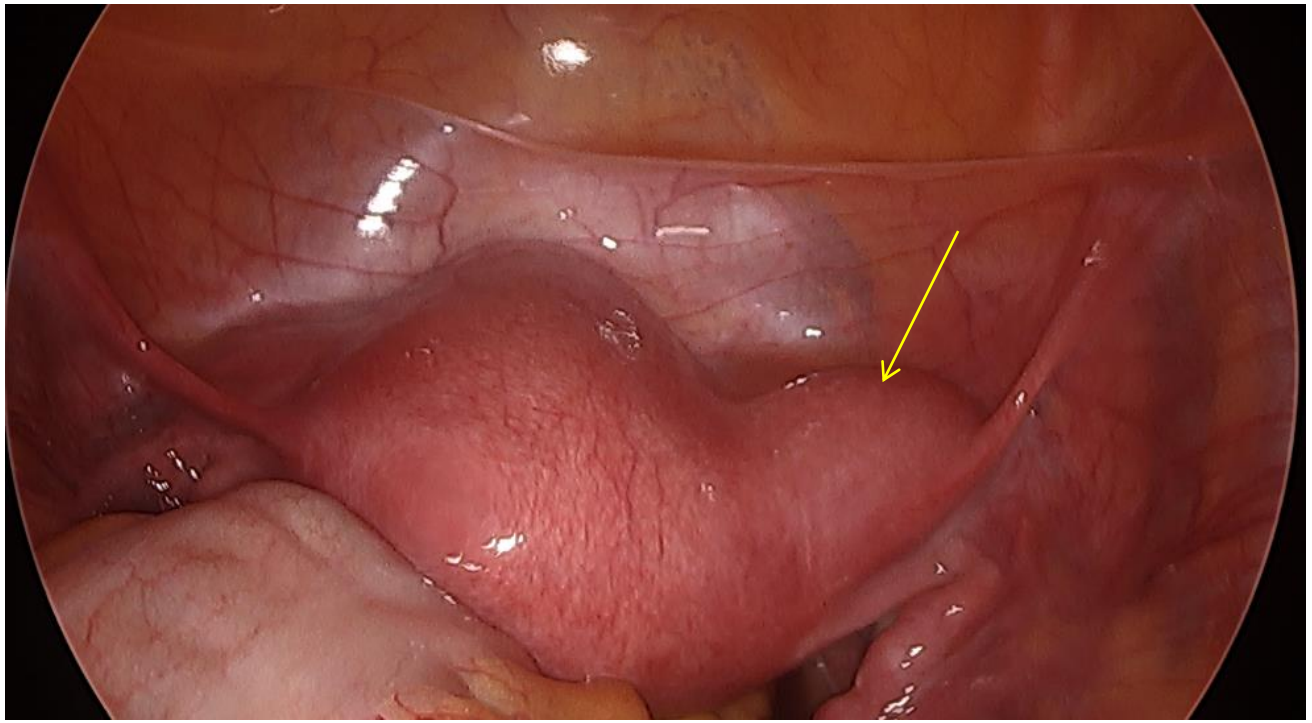
Table 1 Table detailing the concurrent ultrasound diagnoses made at the time of ACUM diagnosis

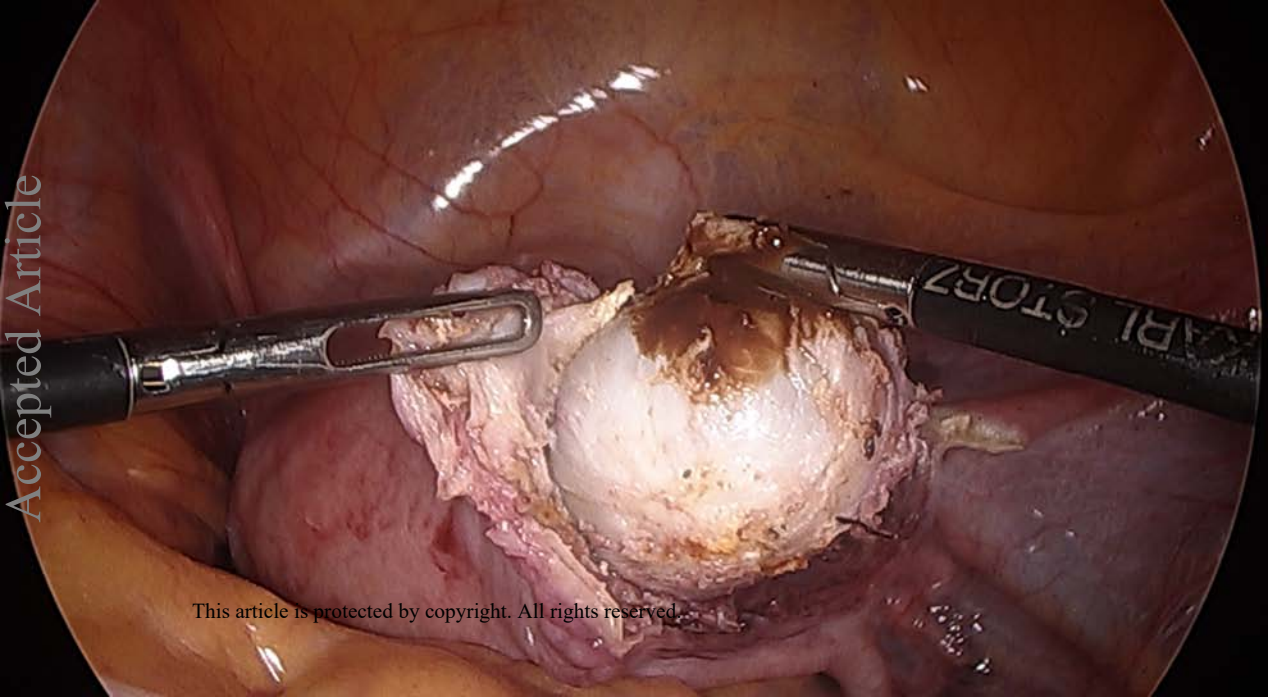
Ultrasound diagnoses at the time of ACUM diagnosis	Number
ACUM only	12
Intrauterine pregnancy	3
Uterine fibroids	2
Polycystic ovarian morphology	2
Deep infiltrating endometriosis	1

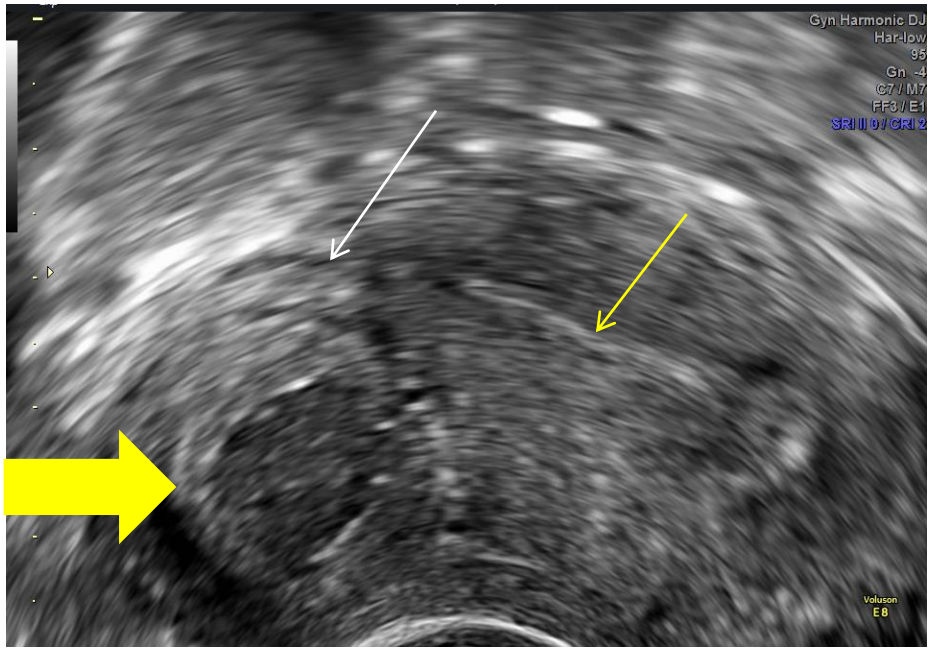
Table 2 Table detailing the obstetric history of the five parous women diagnosed with ACUMs

Study number	First pregnancy	Second pregnancy	Third pregnancy
1	Miscarriage	Miscarriage	Vaginal delivery
3	Caesarean section	Caesarean section	
9	Caesarean section		
13	Surgical termination of pregnancy	Vaginal delivery	Vaginal delivery
17	Miscarriage	Tubal pregnancy	









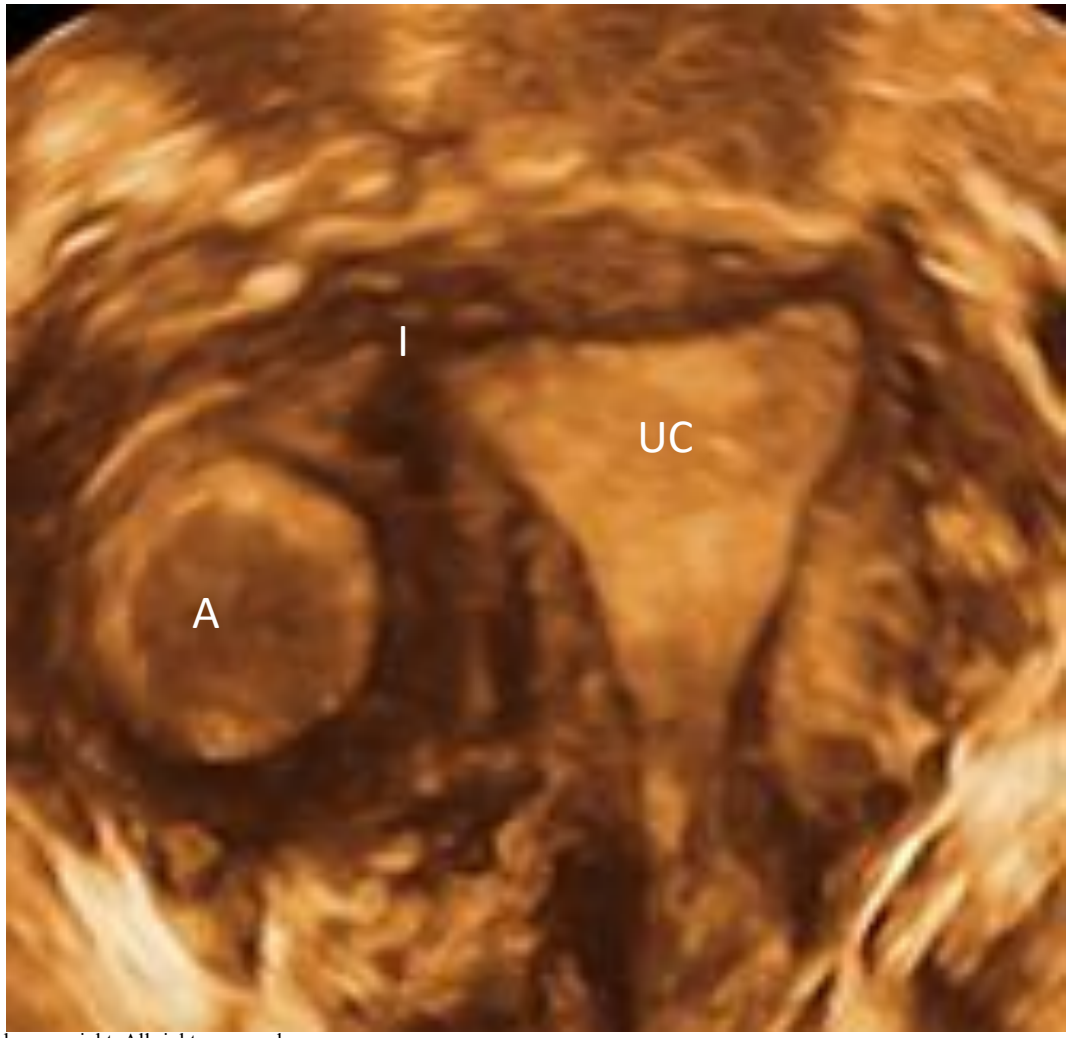
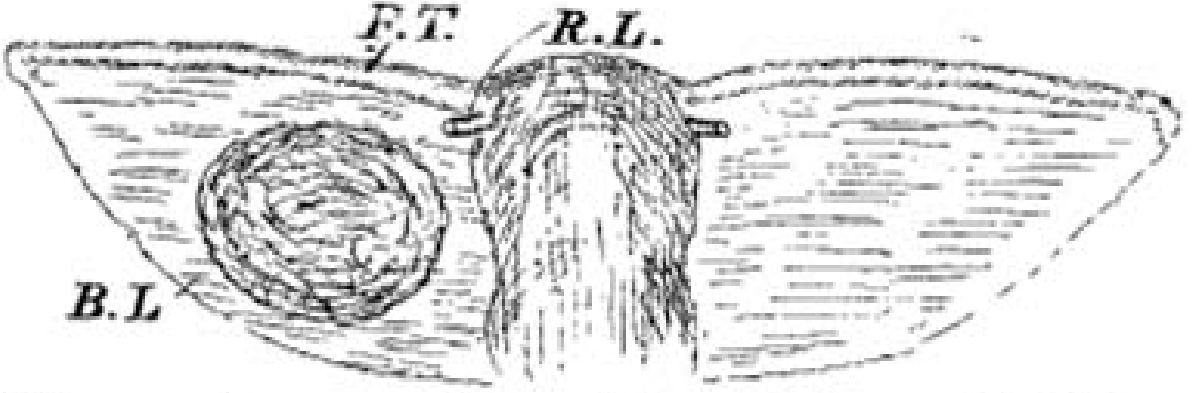


FIG. 1.



Diagrammatic representation of the anterior aspect of the tumour showing relative size and relationship to the uterus, which was normal. F.T., Fallopian tube. R.L., Round ligament. B.L., Broad ligament.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