Hemoperitoneum as a precursor of deep pelvic endometriosis: a cohort study

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Abstract

Objective

To determine whether significant hemoperitoneum could be a precursor of deep pelvic endometriosis

Methods

This was a prospective observational cohort study which was carried out in a dedicated gynecological diagnostic unit over a period of 18 months. We included consecutive pre-menopausal, non-pregnant women who attended with severe acute lower abdominal pain and underwent a pelvic ultrasound examination. Women were triaged for surgical or conservative management depending on the cause of pain and severity of their symptoms. Those who were selected for conservative management were invited for follow up ultrasound scans. The main outcome measure was evidence of newly developed deep endometriosis at follow up.

Results

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One hundred and eighteen non-pregnant women attended with severe acute lower abdominal pain, 20 of whom had emergency surgery. Seventeen women with past history of endometriosis or evidence of endometriosis on the initial scan were excluded from the study. Conservative management was employed in 81 women, eight of whom had evidence of significant hemoperitoneum at presentation. A total of 35 women attended for all their follow up ultrasound scans. At the completion of follow up 4/6 (67%, 95% CI 22-96)] women who initially presented with significant intra-abdominal bleeding had developed new evidence of DE compared to 1/29 (3%, 95% CI 0-18) of those without hemoperitoneum. (RR 19.3 (95% CI 3–144) (p=<0.001).

Conclusion

In some women, the presence of significant hemoperitoneum that is managed conservatively precedes the development of deep endometriosis (DE).

Introduction

Endometriosis is a benign condition affecting approximately 10% of women of reproductive age [1]. Endometriosis causes significant morbidity and often has severe adverse effects on women's quality of life[2]. The cause of deep endometriosis (DE) is unknown and there are currently no effective strategies to prevent its development. There are several theories attempting to explain the etiology of DE, including those of retrograde menstruation, celomic metaplasia, and Müllerian remnants. Several studies have described progression of endometriosis and its response to medical and surgical therapy; however, there is a paucity of data describing the natural history of DE[3,4].

No studies exist showing the development of endometriosis in a previously normal pelvis, nor are there any descriptions of morphological features which precede the formation of DE. Better understanding of the pathophysiology of DE could facilitate identification of women who are at risk, prior to disease formation. This could assist in the development of preventative and more effective treatment strategies.

Ultrasound and magnetic resonance imaging (MRI) are commonly used for non-invasive diagnosis of endometriosis and have been shown to provide a safe and accurate alternative to surgical diagnosis[5,6]. Morphological appearances of endometriosis on ultrasound have been extensively documented and transvaginal sonography (TVS) is increasingly used as the first-line technique for diagnosis of DE[7,8]. Overall, there is a good level of agreement between ultrasound and laparoscopy in assessing severity of DE[9].

Hemoperitoneum is often the result of rupture of a functional hemorrhagic ovarian cyst. If vital signs are normal and the woman is cardio-vascularly stable with no evidence of continuing active bleeding, hemoperitoneum can be managed conservatively. In our department, we observed several women who were referred with symptoms of chronic pelvic pain following conservative management of hemoperitoneum. At follow up, some of these women were found to have developed DE. Based on this observation, we postulated that persistent hemoperitoneum may result in a peritoneal reaction and precipitate the development of DE. The aim of this prospective study was to test the hypothesis

that the presence of significant hemoperitoneum is a precursor of DE in non-pregnant women presenting with severe acute lower abdominal pain.

Materials and methods

This was a prospective observational cohort study which was carried out in our dedicated gynecological diagnostic unit over a period of 18 months. We included consecutive women presenting with acute severe lower abdominal pain. Acute severe pain was defined as sudden onset pain which necessitated attendance to the emergency hospital department. All women were assessed clinically and they also underwent detailed transvaginal ultrasound scans. Examinations were performed by expert operators with extensive experience in ultrasound diagnosis of endometriosis. In our practice, we routinely record the indications for examination, demographic data, gynecological, obstetric and medical history which are stored on the ultrasound clinic database (PIA Fetal Database, version 2.23; Viewpoint Bildverarbeitung GmbH, Munich, Germany). All scans were performed using the same model of ultrasound equipment (Voluson E8, GE Medical Systems, Milwaukee, WI, USA).

Ultrasound examinations were carried out in a standardized fashion. The ovaries were identified in the transverse plane by following the broad ligament from the interstitial portion of the Fallopian tube. Ovarian cysts were diagnosed as fresh hemorrhagic cysts when they contained hyperechoic blood clots which were typically located at the inferior aspect as a result of gravitational pull. They could also be seen filling the cyst lumen creating the characteristic reticular 'spider's web' appearance[10]. Ovarian cysts were diagnosed as endometriomas when they appeared as well-circumscribed thick-walled cysts that contained homogeneous low-level internal echoes ('ground glass')[11]. The adnexa, anterior compartment and posterior compartment of the pelvis were then examined for the presence of endometriotic nodules. They were visualized as hypoechoic solid lesions with irregular outer margins, which were fixed to the surrounding pelvic structures. They were typically located in the rectovaginal septum, anterior wall of the recto-sigmoid colon and uterosacral ligaments. Endometriotic nodules located in the anterior wall of the recto-sigmoid colon appeared as hypoechoic thickenings of bowel muscularis propria. Bimanual palpation was used in the adnexa, anterior and posterior compartments of the pelvis to assess tenderness and identify pelvic adhesions. Obliteration of the pouch of Douglas (POD) with adhesions was assessed using the 'sliding sign'[12]. The absence of any sliding between the serosa on the posterior surface of the cervix or uterus and the bowel behind was defined as

complete obliteration of the POD (negative sliding sign). Partial obliteration was diagnosed in the presence of adhesions between the uterus and either the bowel or adnexal structures, whilst some free sliding was preserved[9].

The morphological features of a blood clot in the pelvis included the presence of a thick, hyperechoic, inhomogeneous substance, which was distinguishable from free fluid. The material was compressible on palpation by the ultrasound probe and it appeared avascular on Doppler examination.

Moderate hemoperitoneum was diagnosed on ultrasound examination when there were visible blood clots within the POD and severe when blood and clots were present both in the POD and in the vesicouterine space[13]. We used the term significant to describe hemoperitoneum which was severe enough to result in the formation of blood clots within the peritoneal cavity.

We created an electronic database (EXCEL™ spreadsheet, Microsoft Corporation, Seattle, USA) and for each patient that presented with severe acute lower abdominal pain we recorded demographics, past gynecological and obstetric history, previous history of endometriosis, past medical and surgical history. We also recorded all relevant ultrasound findings including the presence of clinically significant hemoperitoneum and ultrasound features of endometriosis.

We included all non-pregnant pre-menopausal women age ≥16 years presenting with severe acute lower abdominal pain who were managed conservatively. All women who reported a previous diagnosis of endometriosis were excluded from the study. We also excluded women with evidence of endometriotic lesions on the pelvic ultrasound scan at the time of initial visit. All women with significant hemoperitoneum were invited to follow up visits after a minimum of four weeks and were followed up prospectively until the blood clot had resolved or until DE had developed. Those without evidence of significant hemoperitoneum were invited back if they experienced persistent or recurrent pelvic pain.

Statistical analysis

Statistical analysis and exact 95% confidence intervals (CI) for proportions were calculated using SPSS, Inc. (Chicago, Illinois, USA, version 16.0 or 17.0). Non-normally distributed variables (age, parity, gravidity, number of endometriotic lesions and time for clot resolution) were expressed as

median and range. The size of endometriotic nodules was expressed as the mean diameter (mm). We used the Chi-square test to compare proportions.

Ethical approval

Ethical approval was sought from the local research ethics committee who deemed that full ethical approval was not required. Projects which do not alter standard clinical management do not require ethical review by an NHS or Social Care Research Ethics Committee or management permission through the NHS R&D office. Under these circumstances, there was no need to submit applications to the NHS Research Ethics Committee (REC) or NHS/HSC R&D office (www.hra.nhs.uk). All women in this series were managed conservatively. As no intervention was instigated, written consent was not obtained.

Results

Between June 2016 and November 2017, 118 non-pregnant pre-menopausal women attended the Gynecological Diagnostic and Treatment Unit at University College London hospital with severe acute lower abdominal pain. The study flow chart is presented in Fig. 1. Their median age was 30 years (range 16 – 52), parity 0 (range 0 - 6) and gravidity 0 (range 0 – 16). All of these women underwent a detailed ultrasound examination of the pelvis and the list of diagnoses at presentation are shown in Table I. 20/118 (17%) women had emergency surgery and the remaining 98 (83%) were managed conservatively. 17/98 were excluded from the study due to pre-existing endometriosis. Of these women, 8/17 had a previous surgical diagnosis, 7/17 had a previous ultrasound diagnosis and in 2/17 it was a new diagnosis at the time of attendance with acute pelvic pain.

In the remaining 81 women, eight (10%, 95% CI 3 - 16) had evidence of clinically significant hemoperitoneum on pelvic ultrasound examination. Seven of the eight women presented with ruptured hemorrhagic ovarian cysts and one was undergoing fertility treatment and presented with hemoperitoneum following egg collection. One of these women was unable to tolerate a transvaginal or transrectal ultrasound examination and another woman failed to attend for her follow up visits.

A total of 35 women attended for all their follow up visits. At the completion of follow up 5/35 (14%, 95% CI 3 - 26) women had developed DE. 4/6 (67%. 95% CI 22 - 96) who initially presented with significant intra-abdominal bleeding had developed new evidence of DE compared to 1/29 (3%, 95%CI 0 - 18) of those without hemoperitoneum. [RR 19.3 (95% CI 3 – 144) (p=<0.001)]. (Fig.2a-f)

The median number of follow up visits was 4 (range 3 - 6) in the hemoperitoneum group and 2 (range 1 - 4) in the non-hemoperitoneum group, with a median time interval from initial presentation until completion of follow up of 159 days (range 43 - 590) and 119 days (range 12 - 715) respectively. (Fig.4) The length of time between the initial visit and conclusive evidence of DE on follow up ultrasound scan is shown in Table II. In two women who did not develop DE, the pelvic blood clot had completely resolved by the time of their follow up visit, 43 and 58 days respectively after the initial presentation.

Two women developed severe endometriosis with a complete obliteration of the POD, whilst the remaining three women had evidence of moderate disease. The median number of nodules was 1 (range 1 - 3). They were located in the rectosigmoid colon (n = 2) rectovaginal septum (n = 3) and right uterosacral ligament (n = 2). (Table II)

All five women who developed DE reported symptoms of pain during follow up. Generalized pelvic pain was the most common symptom, followed by dysmenorrhea and dyspareunia. One woman described symptoms of dyschezia and had evidence of endometriotic nodules involving the rectosigmoid colon. One of the women with evidence of severe disease, involving the rectosigmoid colon and rectovaginal septum, opted for surgical management of endometriosis due to excessive pain symptoms that were intractable to conservative therapies. She underwent laparoscopic hysterectomy and excision of DE. The diagnosis of DE was confirmed on histological examination. The remaining four women were managed conservatively. Three of them were trying to conceive and they eventually fell pregnant. Two of them had an uneventful pregnancy and a vaginal delivery at term, whilst the latter pregnancy is still in progress. The fifth patient was planning to try for a pregnancy within 12 months, so opted to continue conservative management.

Discussion

Our findings indicate that significant hemoperitoneum, in the presence of functional hemorrhagic ovarian cysts, may precipitate development of DE. DE developed in two thirds of women with a hemoperitoneum that was managed conservatively, compared to 3% of women without evidence of intra-abdominal bleeding, although numbers were relatively small. We observed that in some women blood clots do not clear and become more organized. Organized clots appear solid and hypoechoic on ultrasound, which differs from fresh bleeding. At interval scans they remain in the same position, becoming progressively smaller, less echogenic and hyperdense. As the density increases and the lesion decreases in size due to contraction, the surrounding peritoneum adheres to the lesion. In some women, the rectum is pulled anteriorly towards the uterus and the POD becomes obliterated with adhesions. Finally, solid incompressible hypoechoic lesions are formed, which have typical appearances of endometriotic nodules. Figure 3 is a pictorial diagram of the evolution of a blood clot in the POD prior to the development of DE.

The pattern observed in these women suggests that blood clots in the pelvis are precursors for the development of endometriotic nodules. These findings also explain why endometriotic nodules are frequently found in dependent areas as a result of natural deposition of clots due to gravitational pull. Our observations could explain the distortion of normal anatomy and obliteration of the POD, that has a typical appearance observed in women with DE. The initial findings of a blood clot that behaves in a contractile manner, drawing neighbouring tissues towards it, results in 'dragging upwards' of the rectosigmoid colon and obliteration of the POD.

Intra-peritoneal blood clots consist of erythrocytes separated by strands or condensed masses of fibrin. This can cause development of fibrous bands of adhesions which are often covered by mesothelium, containing blood vessels and connective tissue fibres, including elastin[14]. Cines et al showed that clots develop a structured meshwork of fibrin and platelet aggregates on the exterior and close-packed polyhedral erythrocytes within[15]. The clot contracts due to forces exhibited by platelets and fibrin, resulting in an impermeable barrier important for hemostasis and wound healing.

Healing of the peritoneum differs from healing of the skin as the entire surface becomes epithelialized simultaneously and not gradually from the borders. Time required for regeneration of the mesothelial layer, despite the size of the damage, is seven days[16]. Kruitwagen et al have shown that endometrial epithelial cell colonies are identified in peritoneal fluid in approximately 79% of women[17]. They showed no significant distinction in incidence and number of cell colonies in women with minimal endometriosis or those without endometriosis.

We hypothesize that when peritoneal healing occurs over a blood clot, endometrial cells may be trapped under the peritoneal surface. Clot contracture and remodelling followed by cyclical proliferation of endometrial cells may result in the development of endometrial deposits on or under the peritoneal surface of the pelvis.

The main limitation of our study is the relatively small number of women who developed endometriosis. Hence, we were unable to explore further the reasons why some women are more susceptible. The condition is likely to be multifactorial and this requires investigation with further detailed prospective studies.

It was difficult to standardize follow up for women as the rate of clot resorption and development of DE was unknown when the study started. There were significant variations in the time interval between initial presentation and development of DE, which could be partly attributed to differences in frequency and number of follow up visits.

It is important to acknowledge that only a proportion of women without evidence of intra-abdominal bleeding attended for follow up. The rate of endometriosis in those not undergoing a follow up ultrasound is unknown and may differ from those that did attend. Although the relative risk has been reported, caution must be used in interpreting the absolute reliability.

In the majority of women, the diagnosis was based on ultrasound findings alone as only one woman had surgical confirmation. Although the operators were not blinded to the previous diagnosis of

hemoperitoneum, we are confident that our findings are accurate as women served as their own controls and all scans were performed by two expert operators. A previous study within our unit showed 94% accuracy for the diagnosis of moderate to severe endometriosis when comparing ultrasound to surgical findings[9]. Ultrasound diagnosis of endometriosis has been extensively described in the literature and defined in a recent consensus statement[7].

At initial assessment, we were unable to identify women with mild peritoneal endometriosis that is not visible on TVS. We are unable to hypothesize whether mild endometriosis is a factor for developing DE.

Although our findings present a plausible hypothesis for development of DE within the peritoneal cavity, the etiology behind endometriotic deposits at distant sites remains unclear e.g. thoracic endometriosis.

We considered that there may be difficulties examining women with acute pain during TVS. However, we found that the presence of blood in the pelvis facilitated assessment of the POD by delineating the peritoneal surface. This made it relatively easy to assess for the presence of adhesions without need for vigorous palpation.

This is the first study to demonstrate the development of endometriosis in a previously normal pelvis. We have shown evidence that hemorrhagic cysts in the presence of hemoperitoneum can precede the development of DE. We observed blood clots in the pelvis prior to the development of endometriotic nodules and that DE developed in dependent parts of the pelvis where clots settled due to gravitational pull. We provide a plausible explanation for typical distortion of pelvic anatomy in women with DE.

These findings could facilitate detection of women who are at risk of developing DE. This opens the possibility for further research into the pathophysiology of DE and targeted preventative strategies, such as ovulation prevention or surgical evacuation of significant hemoperitoneum. However, the number of participants in our study was relatively small and further larger prospective studies are needed to confirm our findings before any interventional studies could be planned.

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Figure captions

Figure 1: Flowchart of participants included in the study.

Figure 2a: A 33 year old woman presenting with acute post coital pain. A transverse view of the pouch of Douglas shows a thick hyperechoic, inhomogenous substance, which is distinguishable from free fluid and appears avascular on Doppler examination. The material is compressible on palpation with the ultrasound probe and separate from the surrounding peritoneal surface of the pelvis. These features are in keeping with the presence of a blood clot in the pouch of Douglas [C = blood clot, O = ovary].

Figure 2b: At follow up (day 58), the blood clot [C] has reduced in size and appears more hypoechoic and homogenous in echotexture. On palpation, the clot ('inhomogeneous conglomerate') is fixed to the surrounding peritoneum and the bowel posteriorly.

Figure 2c: On day 97 the clot [C] has contracted further in size and is adherent to the neighbouring bowel and ovary [O].

Figure 2d: On day 125, the clot [C] continues to contract and regress pulling the neighbouring bowel and ovary [O] with it.

Figure 2e: On day 194 the clot [C] has reduced further in size and appears more hypoechoic and homogenous in echotexture. The lesion was consistently tender on palpation with the ultrasound probe and adherent to the adjacent rectosigmoid colon and ovary [O].

Figure 2f: Finally (day 288), the development of a solid incompressible hypoechoic lesion develops, which is fixed to surrounding structures and tender on palpation. These features are typical of an endometriotic nodule in the rectovaginal septum [N].

Figure 3: Pictorial diagram of hemoperitoneum with blood clot in the pouch of Douglas evolving to develop DE. The active phase: Blood and blood clot collect in the pouch of Douglas as a result of gravitational pull (a). The intermediate phase: As the blood absorbs, the blood clot contracts and adheres to neighbouring bowel and the posterior aspect of the uterus (b). The chronic phase: As the clot resolves completely, a solid incompressible mass behind the uterus is noted. These features are

typical of an endometriotic nodule. Where the surrounding tissues are drawn in by the contractile nature of the blood clot, the pouch of Douglas becomes obliterated with adhesions (c).

Figure 4: A Kaplan Meier estimator demonstrating the proportion of women that remained free of endometriosis during following up. The estimator is inclusive of all women who presented with acute pain and had evidence of significant hemoperitoneum at initial scan, who were managed conservatively.

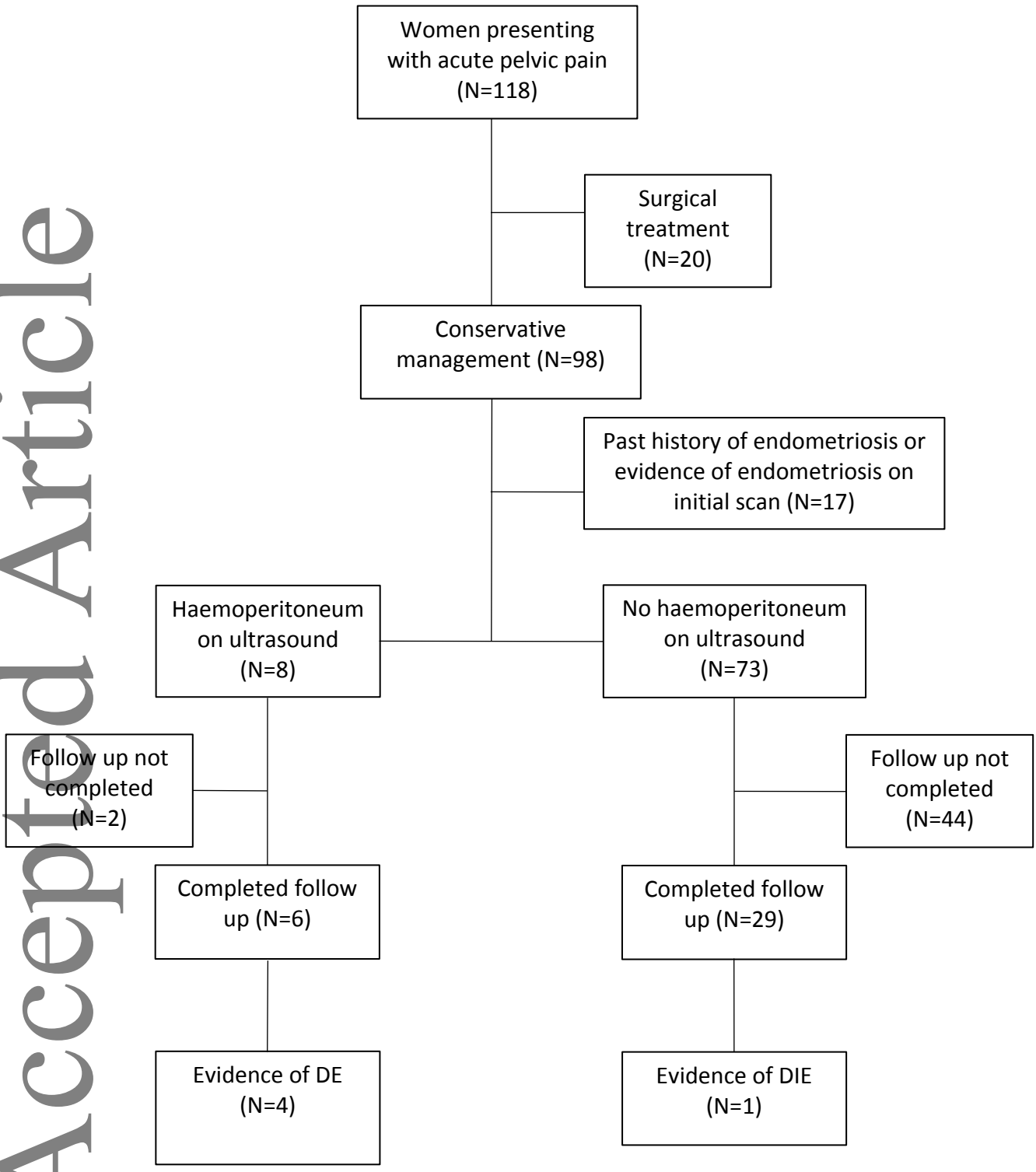
Table I: Ultrasound findings in women attending with acute pelvic pain

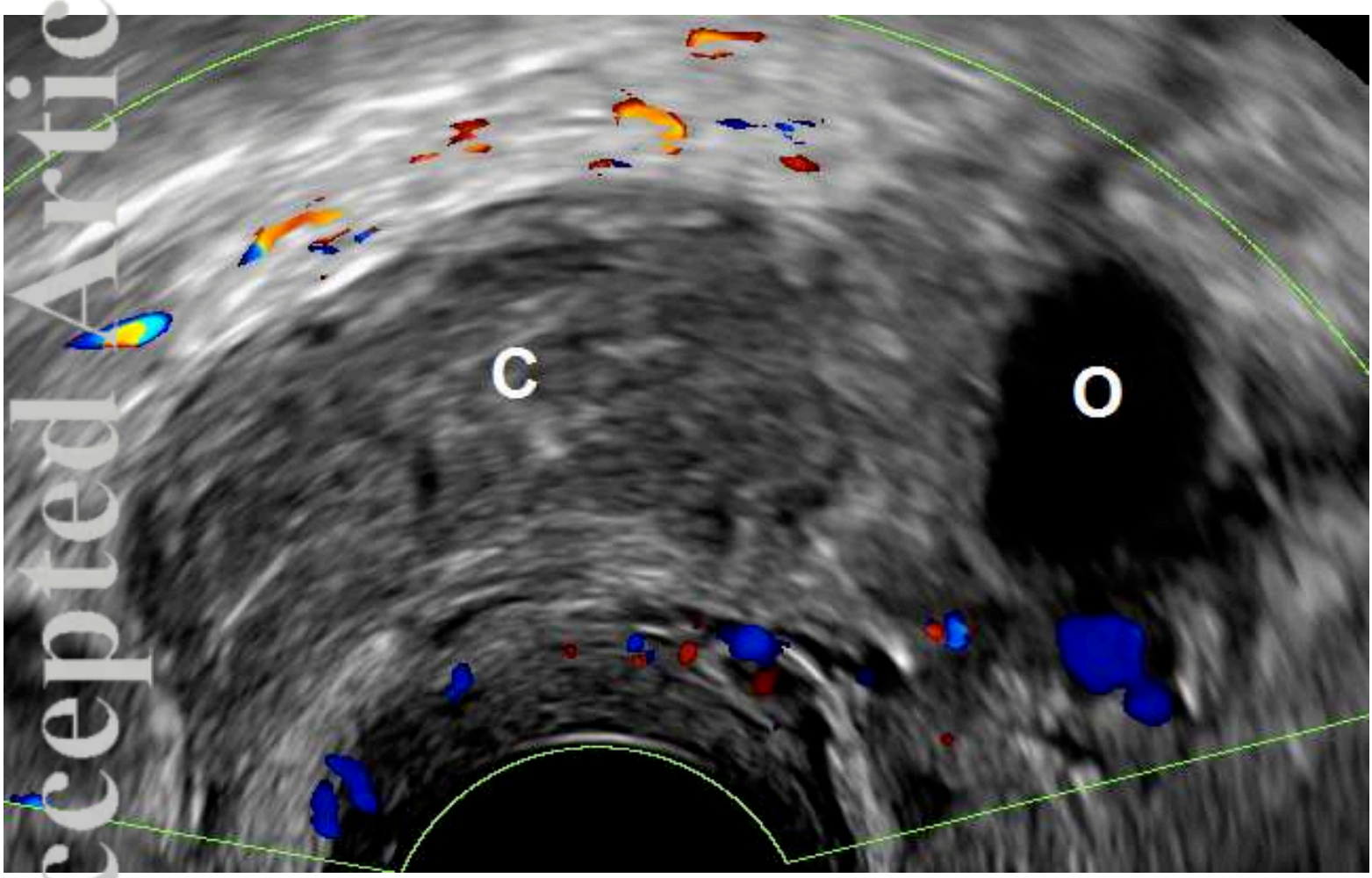
Diagnosis at presentation	n = 118	%
Unexplained pain	56	47.5
Endometriosis	16	13.6
Recent ovulation	12	10.2
Hemoperitoneum due to functional cyst rupture	8	6.8
Acute pelvic inflammatory disease	6	5.1
Ovarian torsion	5	4.2
Ureteric calculus	3	2.5
Hemoperitoneum following egg collection	2	1.7
Ovarian cancer	2	1.7
Fibroid degeneration	2	1.7
Ovarian hyperstimulation	2	1.7
Hematometra	1	0.8
Acute appendicitis	1	0.8
Post-operative hematoma	1	0.8
Urinary tract infection	1	0.8

Table II: Severity of hemoperitoneum, time interval from initial presentation to development of DE, assessment of sliding sign, location and size of DE lesions in women with new evidence of DE on follow up ultrasound (N=5)

(DE = Deep endometriosis, RVS = rectovaginal septum, RSC = rectosigmoid colon, USL = uterosacral ligament, POD = pouch of Douglas)

	Hemoperitoneum	Time from initial presentation to development of DE (days)	Sliding sign	Para-ovarian adhesions	Location of endometriotic lesions	Size of lesions (mean diameter, mm)	Symptoms at follow up
1	Moderate	227	Negative	Bilateral	RVS RSC RSC	16 13 8	Pelvic pain Dysmenorrhea Dyspareunia Dyschezia
2	None	413	Partial obliteration	Right	RVS	9	Pelvic pain
3	Severe	288	Partial obliteration	Bilateral	USL	9	Pelvic pain
4	Severe	242	Positive	None	RVS	6	Dyspareunia
5	Moderate	76	Negative	Right	USL	15	Pelvic pain Dysmenorrhea





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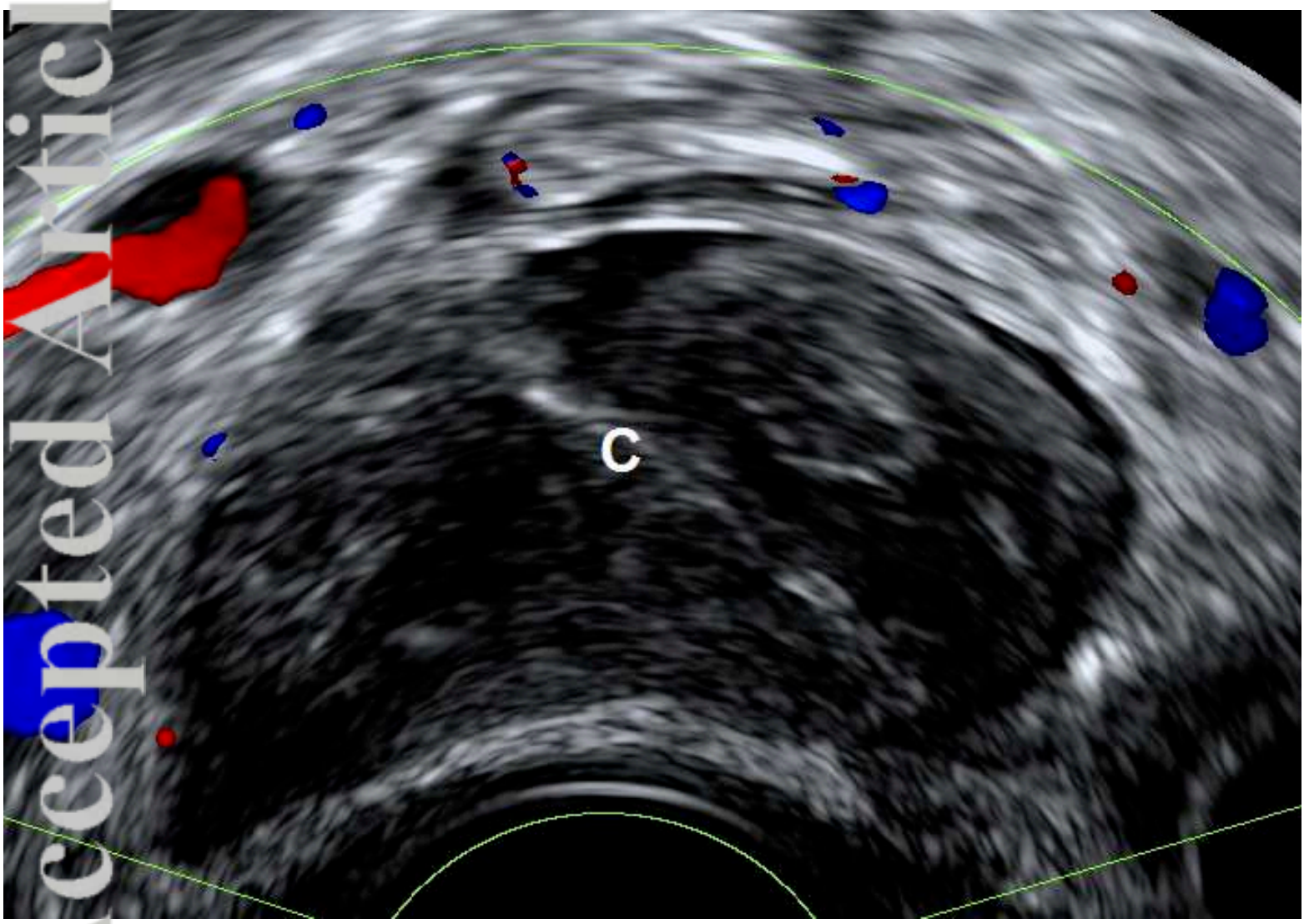

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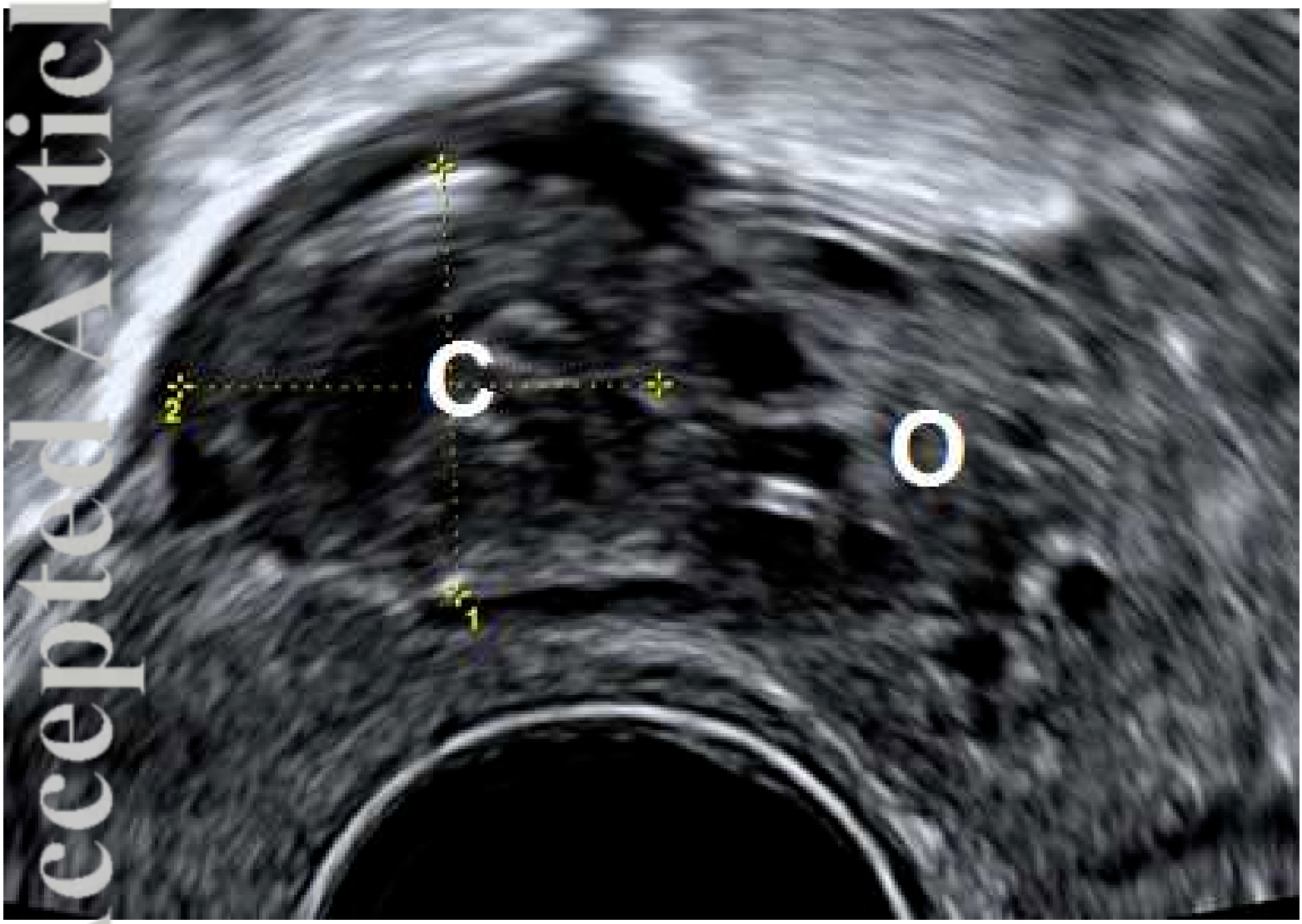

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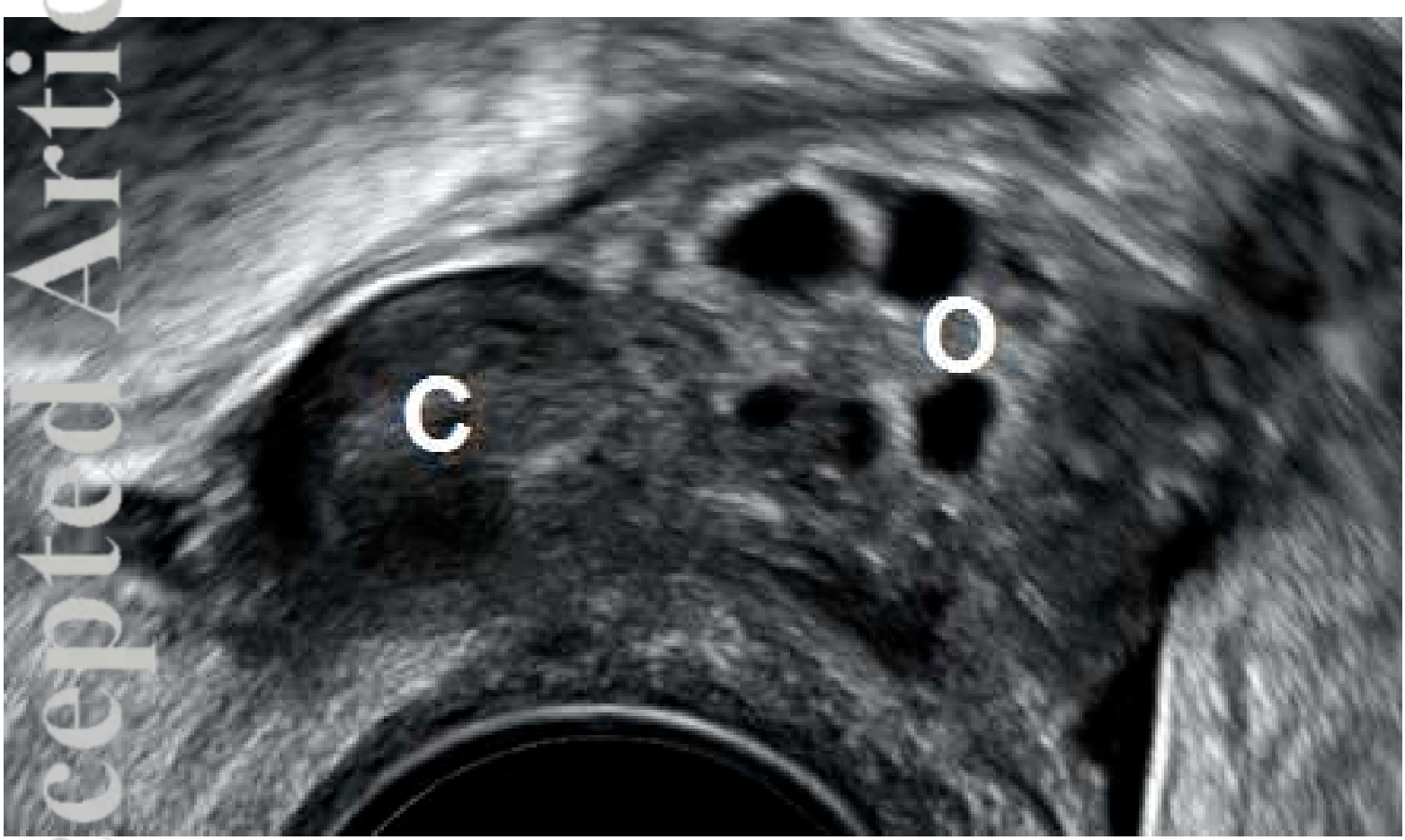

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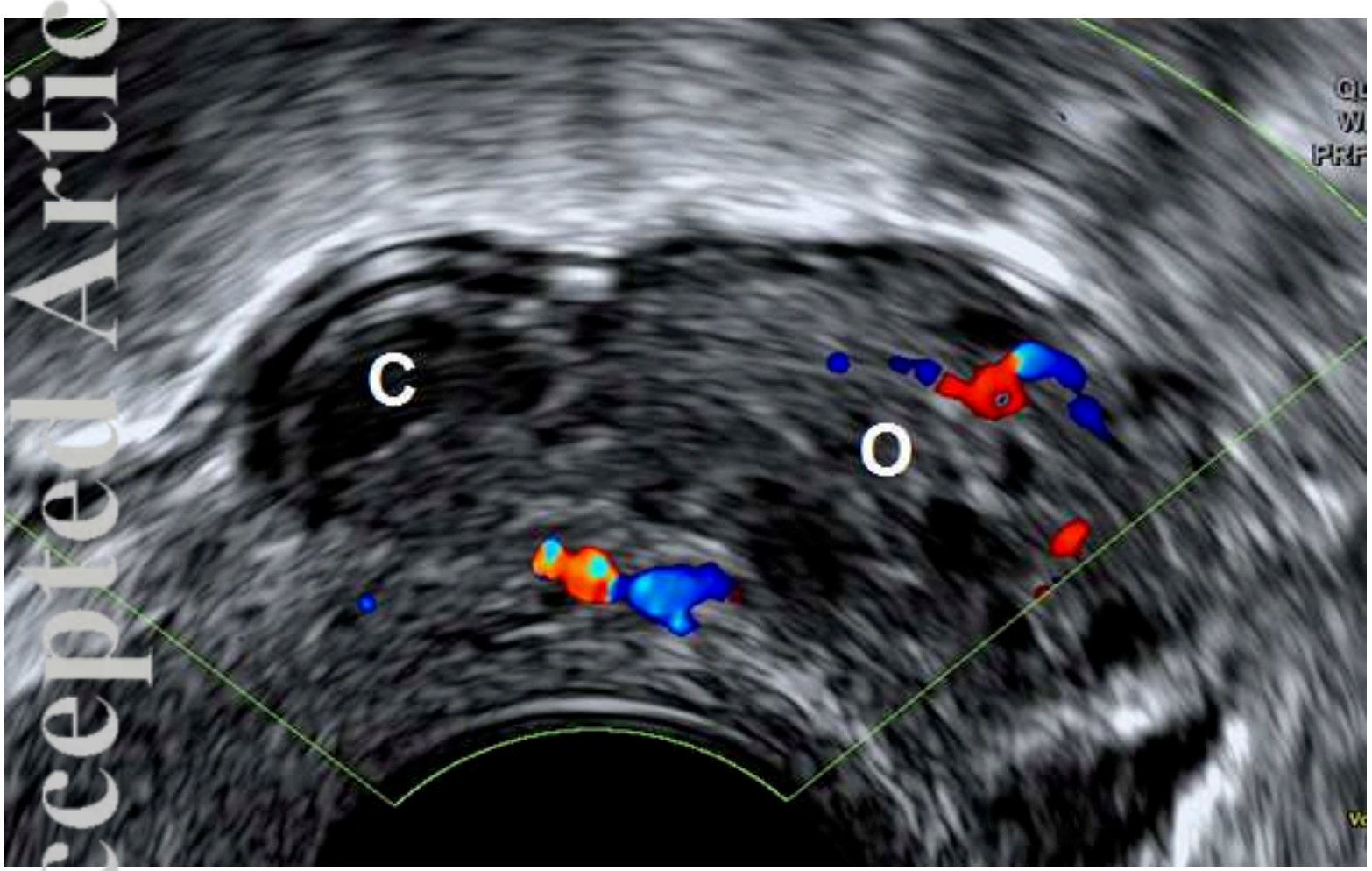

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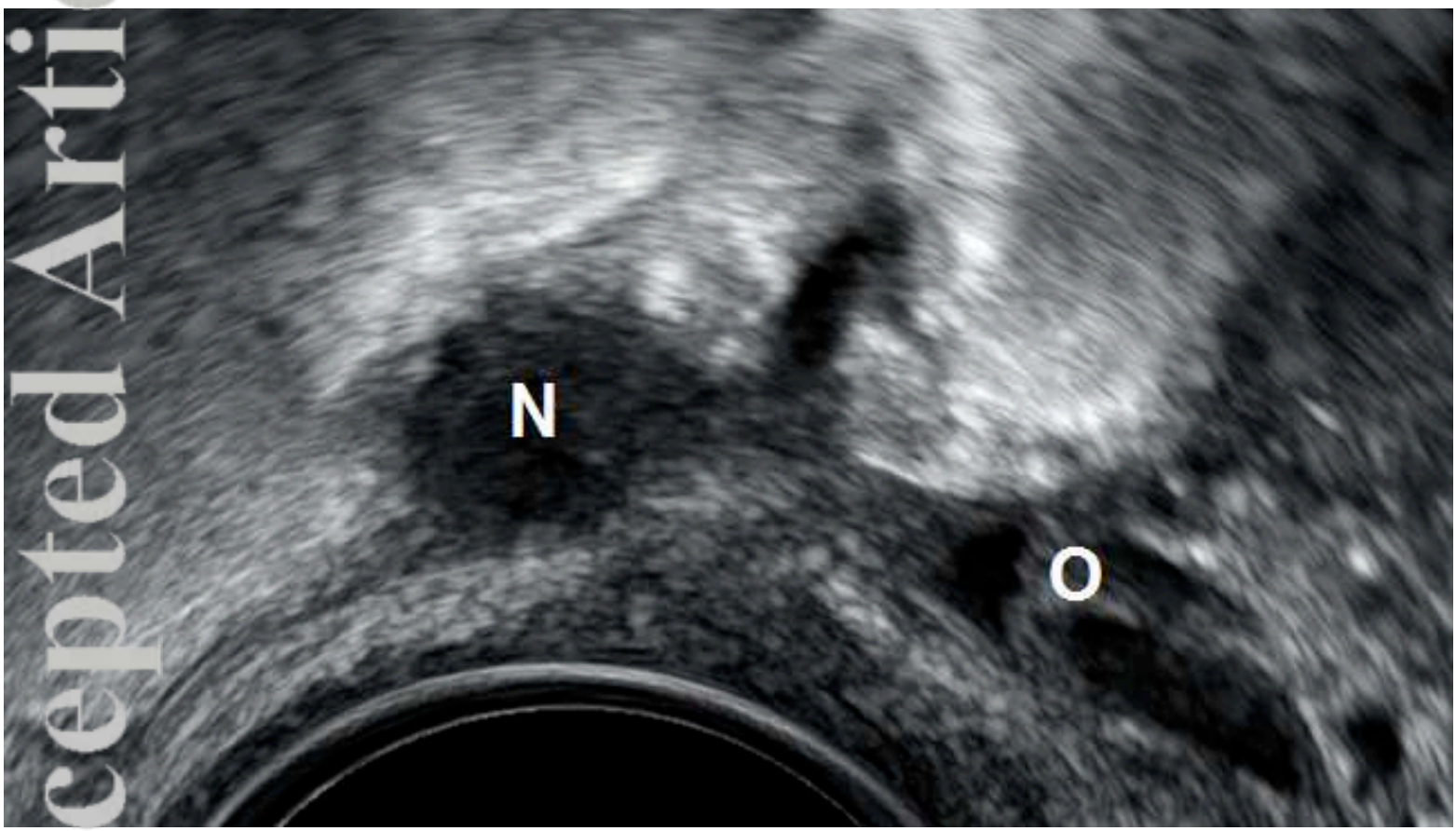

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