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Saline infusion sonohysterography in endometrial exploration

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ABSTRACT

Contrast substances have been an extremely important addition in the ultrasonographic examination of the female internal genital organs. Saline infusion sonohysterography consists of the transcervical instillation of fluid into the uterine cavity to improve endometrial visualization while performing a transvaginal ultrasound evaluation. Therefore, benign endometrial pathology such as hyperplasia, but most of all focal lesions like polyps, leiomyomas, or adhesions, as well as suspected malignant pathology such as endometrial cancer, can be better assessed during ultrasound examination. Saline infusion sonohysterography is an important tool for avoiding unnecessary biopsies in postmenopausal women with an apparent thicker endometrium; for women of fertile age, saline infusion sonohysterography can be used to select those females who require further therapeutic procedures, especially in infertility, caused by endometrial pathology. Sonohysterography is very well tolerated by patients, has a minimum degree of discomfort, can be performed without hospitalization and can be easily performed at a reduced cost.

Keywords: sonohysterography, saline infusion, endometrium, infertility, polyps, endometrial cancer

INTRODUCTION

As a first line for exploring abnormal uterine bleeding, transvaginal ultrasound is effective in characterizing focal endometrial lesions. However, the useful and easy instillation of saline, in conditions of minimal discomfort for the patient, increases the specificity of the method and directs the patient with this type of lesion to therapeutic hysteroscopy (1). The diagnosis of endometrial polyps is based on conventional ultrasonographic imaging completed by sonohysterography or hysteroscopy. In 2003, Timmerman et al. (2) stated that Doppler function highlighting of the single arterial pedicle (Figure 1) has a sensitivity for detecting endometrial polyps of 76.4%, a specificity of 95.3%, a positive predictive value (PPV) of 81.3% and a negative predictive value of 93,8%; extrapolating to detect any focal intracavitary pathology, the test reaches a PPV of 94.2%, which in the opinion of the authors, makes unnecessary the second-line diagnostic tests represented by sonohysterography and diagnostic hysteroscopy.

The simple measurement of endometrial thickness in women with abnormal uterine bleeding in the climax, selects patients at low risk of developing

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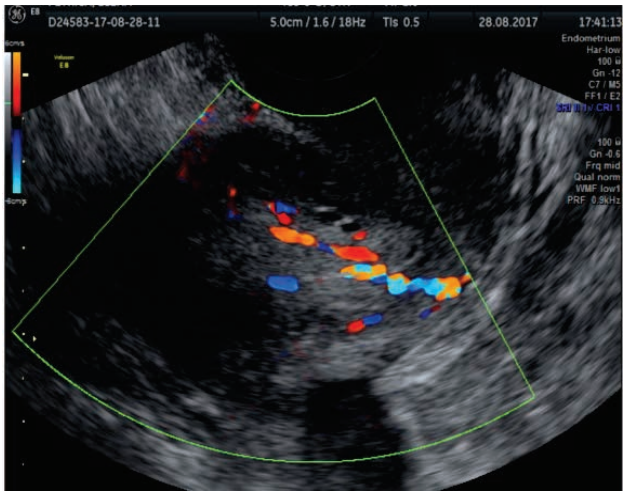

FIGURE 1. 2D color Doppler image of uterine longitudinal section showing a single arterial pedicle of a polyp. The endometrium in the secretory phase is thick, and the polyp is badly defined, thus color Doppler study becomes essential to the diagnosis (personal collection of Roxana Elena Bohiltea) (1)

endometrial cancer, the endometrium ≤ 4 mm decreasing the risk of this disease by a factor of 10 in both users and non-users of hormone replacement therapy; these patients do not require endometrial biopsy (3-8). The endometrial thickness ≥ 5 mm requires the assessment of endometrial morphology and vascularization using B mode and Doppler, followed by endometrial biopsy techniques, address the assessment of the risk of developing endometrial cancer (9-13). Given the fact that most causes of abnormal uterine bleeding in climax are focal lesions, about which Epstein (14) affirms that are mostly omitted by uterine curettage, it can be stated that patients with abnormal uterine bleeding in climax and endometrial thickness ≥ 5 mm optimally benefit from resection of focal lesions under direct hysteroscopic control; the diffuse character of the endometrial thickness proven by instillation of saline solution has the indication of performing a biopsy by aspiration or curettage.

ENDOMETRIAL THICKNESS EVALUATION

In postmenopause, the endometrial thickness ultrasonographically determined below 4 mm is used as a selection factor for patients who do not require endometrial biopsy (7,15,16). Cancer becomes significantly more frequent compared to benign lesions as the endometrial thickness approaches 20 mm, a value considered average for endometrial cancer in a study of 759 women with this diagnosis (7). The American College of Obstetricians and Gynecologists (ACOG) (17) and the Society of Radiologists in Ultrasound (SRU) (18) consider that endometrial thicknesses ≤ 4 mm, measured by transvaginal ultrasound (ACOG), respectively 5 mm (SRU), are effective as first line of diagnosis in postmenopausal women with bleeding. ACOG considers that at an endometrial thickness below 4 mm, the malignancy is very rare and ultrasound examination identifies other structural lesions. These recommendations are supported by a meta-analysis of 35 prospective studies that include almost 6,000 women with postmenopausal bleeding; the sensitivity and specificity of transvaginal ultrasound in detecting endometrial cancer at an endometrial thickness threshold of 4 mm are 96%, respectively 53%, and at a limit of 5 mm are 96%, respectively 61% (3). Increasing sensitivity is the main purpose of using this technique, given the priority goal of recruiting all cases of cancer. The low specificity is less important because a positive result is followed by endometrial biopsy performed prior to the final treatment. The authors of this analysis have calculated the probability of endometrial cancer based on the estimated risk associated with postmenopausal bleeding as equal to 1% in the case of an endometrial thickness less than 5 mm measured using transvaginal ultrasound. Subsequent meta-analyzes present different conclusions, the most representative of which is analyzing individual patient data from 13 studies including almost 3,000 women (8,9). This study reports the sensitivity of endometrial cancer detection by transvaginal ultrasound at an endometrial thickness of 4 mm and 5 mm, as 95% respectively 90%, at a limit of 3 mm, the sensitivity being 98%. The limitation of the meta-analysis was represented by the exclusion of many studies due to the lack of availability of individual patient data. Another meta-analysis including 57 studies with 9031 patients, 4 studies being of the highest quality and using a cut-off of endometrial thickness less than or equal to 5 mm, stated, based exclusively on the 4 studies, that a positive ultrasound result increases the probability of carcinoma from 14% to 31%, while a negative result reduces this probability to 2.5%, the conclusion of the meta-analysis being that the negative result (endometrium less than or equal to 5 mm) generally excludes endometrial neoplasia, but the ultrasonographic measurement of endometrial thickness cannot be used to rule out cancer (19).

A topic of current debate is the extent to which further explorations are required in case of accidental determination of increased endometrial thickness or the presence of intracavitary fluid in asymptomatic women. Bleeding is absent in approximately 5-20% of endometrial cancer cases. Ultrasound measurement of endometrial thickness appears to have a lower predictive value for endometrial neoplasia in asymptomatic women compared to those who present with bleeding. This conclusion is supported by a meta-analysis of 32 studies

including 11,000 asymptomatic postmenopausal women without hormone replacement therapy, the average endometrial thickness being 2.9 mm, the size of the endometrium over 5 mm showing a sensitivity of 83% and a specificity of 72% for the endometrial cancer detection, thus, lower values compared to those obtained in symptomatic women (20).

Persistence of bleeding even under conditions of an endometrium below 4 mm requires biopsy. The utility of a cut-off greater than 5 mm for asymptomatic women in climax is supported by the recent study by Jokubkiene et al. who found that 12% of 510 postmenopausal women, selected strictly gynecologically healthy and asymptomatic, had a sonographic endometrial thickness ≥ 5.0 mm; 67% (33/49) of those with endometrial thickness ≥ 5.0 mm, subjected to sonohysterography, showed intrauterine focal lesions, whose hysteroscopic resection revealed 2 cases (7%) of complex endometrial hyperplasia with atypia, without cases of malignancy, but with 2 serious complications of the endoscopic procedure. Sladkevicius et al. (21) and Andolf et al. (22) report similar incidences of 10% and 7%, respectively, of endometrial thickness over 5 mm in asymptomatic postmenopausal women. Given the large number of sonohysterography procedures and the risks of hysteroscopic resection that led to the diagnosis of two premalignant lesions whose risk of progression was 30%, Jokubkiene's study supports conservative management of the endometrium ≥ 5.0 mm in asymptomatic climax, the data presented justifying additional biopsy exploration when the 11 mm limit is exceeded in the absence of abnormal uterine bleeding.

A study published in 2014 by Dueholm et al. (23) integrates in a tested risk score 174 women with postmenopausal bleeding and endometrial thickness ≥ 5 mm, BMI calculation, endometrial thickness, Doppler evaluation of endometrial vascularization architecture and appearance of endometrial surface at sonohysterography (SHG); for a score ≥ 4, the sensitivity and specificity of endometrial cancer identification was 91% and 94%, respectively. Due to the high argumentation of the study and its ease of use, the score could be included in the algorithms for assessing the risk of endometrial cancer in postmenopause, in the context of the standardized description of the endometrium.

The thickness of the endometrium in most women on tamoxifen treatment is over 4 mm. In addition, when such women undergo biopsy curettage, despite the apparently thick endometrium, the amount of endometrial tissue obtained is minimal. This paradox may result from: (i) a change in endometrial consistency caused by tamoxifen; (ii) a change in the echogenicity of the myometrium underlying the endometrium, which thus appears similar and is incorporated into the measurement of the endometrium; or (iii) an inaccurate measurement due to image obliquity. Any deviation from a longitudinal (sagittal) section can cause an apparent increase in endometrial thickness. Due to tamoxifen, the cavity vacuum line echo is often lost and therefore cannot be traced from the cervix to ensure a perfectly longitudinal section of the endometrium. Moreover, cystic areas of the subendometrial area, which could be foci of adenomyosis reactivated by tamoxifen, alter the measurement. These cases optimally benefit from the instillation of intracavitary saline, the contrast medium thus created facilitating the correct measurement of the individual endometrial layers. Although high hopes were placed on the discriminatory capacity of uterine artery velocimetry and subendometrial circulation, studies have not confirmed the benefit of Doppler monitoring of these patients, whose endometrium of ≥ 5 mm should be biopsied.

3D ultrasonography (3D-US) (24-26), which visualizes any organ simultaneously in 3 orthogonal planes, reconstructs the uterus and the uterine cavity in the coronal plane and proves increasingly useful in the specific differentiation of forms of endometrial pathology, especially of malformations of the uterine cavity and endo-myometrial tumor pathology, as opposed to its use in capturing normal endometrial changes during the menstrual cycle, which do not benefit from additional information (27). According to the famous Professor Benacerraf BR, this technique has become an integral part of gynecological examination, generating valid reproducible measurements with wide clinical, educational and research utility (28).

SONOHYSTEROGRAPHY

Since the transabdominal sonography with saline instillation developed by Beyth in 1982, sonohysterography (SHG) has become an international standard in the exploration of the uterine cavity.

Sonohysterography represents the transvaginal ultrasound examination after fluid instillation in the uterine cavity as a negative contrast agent, saline solution, or gel (29-32). Unlike classical hysterosalpingography, which exposes the patient to allergic risks to iodine and irradiation, exploring the uterus exclusively antero-posteriorly, making the image difficult to interpret in the case of rotation, marked anteflexion or exaggerated retroflexion, failing to differentiate the septum from the bicorn uterus by the lack of visualization of the uterine contour, the instillation of saline increases the diagnostic accuracy of ultrasonography in detecting uterine pathology, except for uterine synechia in which hysteroscopy has better results.

The main indications for sonohysterography are abnormal uterine bleeding in premenopause and postmenopause, situations in which focal lesions differentiate from diffuse and transact subsequent behavior, and patients undergoing tamoxifen therapy with subendometrial sonolucency and occult polyps, being indicated in the annual screening of these patients. Distension of the uterine cavity is the most useful for assessing endometrial thickness in postmenopausal women, and is also used as a method of post-procedural control after ligation, reanastomosis or placement of tubal microinserts.

The main contraindications are pregnancy and active pelvic inflammatory disease. Complications consist in the impossibility of completing the procedure, sometimes cervical stenosis being overcome in outpatient conditions (7%), pelvic pain (3.8%), vagal symptoms (3.5%), post-procedural nausea and fever (1% and 0.8%, respectively) (33).

After the abandonment of contrast agents, among the many solutions tried, the saline solution seems to be optimal so far. In a comparative study between gel and saline, published in 2010, it is shown that the use of the gel increases and maintains slightly longer the uterine distension due to gas bubbles, to the detriment of image quality, in identical conditions of diagnostic sensitivity and comfort (34) (Figures 2 (a), (b) and Figure 3). At the same time, gel foam use is limited in exploring the endometrial details, the visualization being facilitated by using 3D mode that allows the visualization of the uterine contour in the coronal plane, without allowing the highlighting of the mucosal details (Figure 3) (35). Cavity deformity is better seen at the end of the procedure, when the cavity distension allows the detection of the focal lesions, highlighted by a fine layer of gel foam (Figure 4).

The optimal exploration window is, in the case of routine ultrasound examination, the early proliferative phase, respectively days 4-6 of the menstrual cycle, and respectively days 5-10 post progestin pill in the case of hormone replacement therapy. In

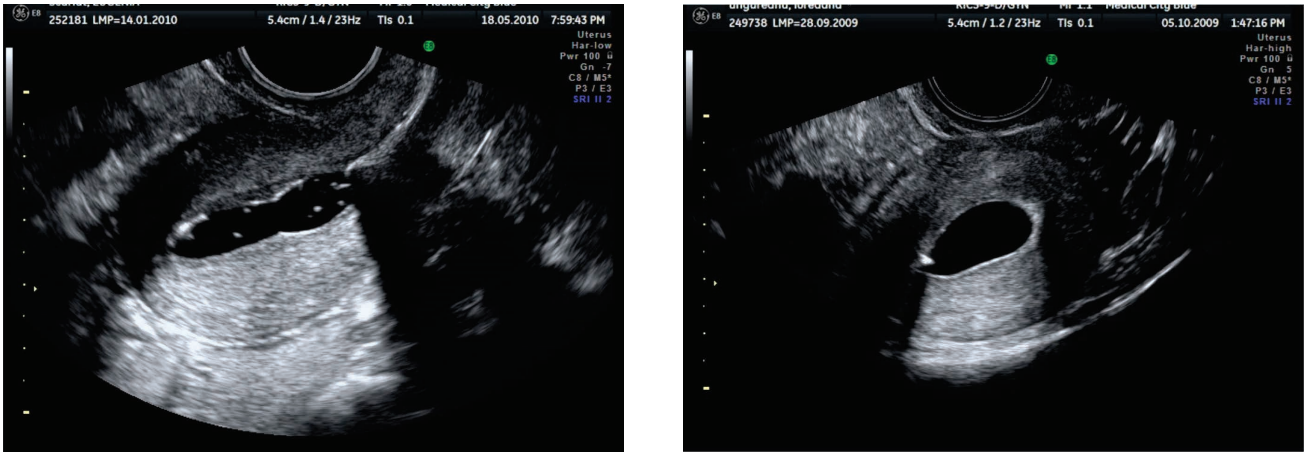

FIGURE 2. 2D longitudinal section (a) and transverse section (b) images of the uterus while performing a saline infusion sonohysterography (hyperechogenic thin endometrial layer is clearly visible) (personal collection of Roxana Elena Bohiltea)

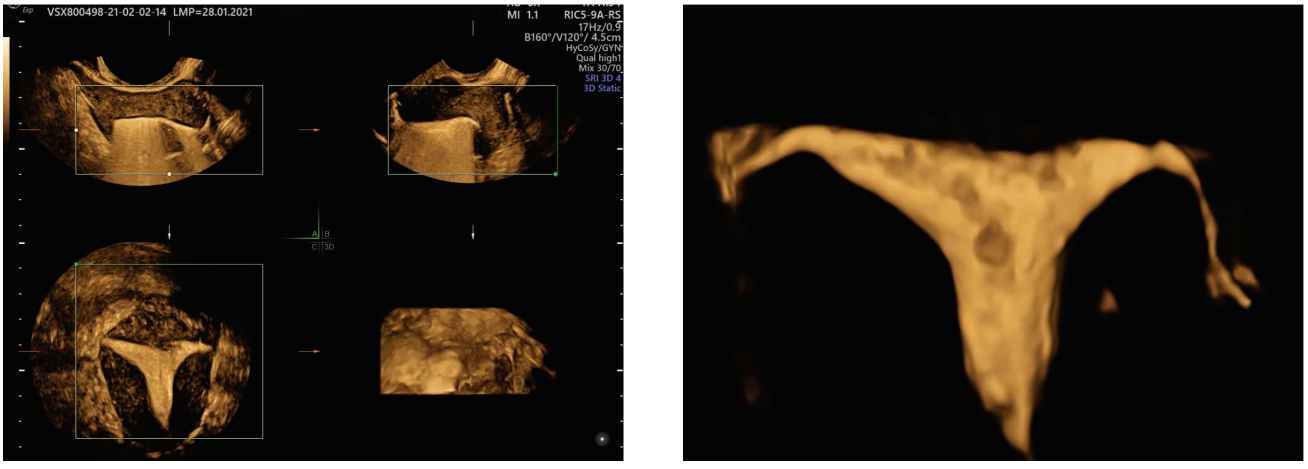

FIGURE 3. 3D reconstruction of the uterine cavity revealed by Hysterosalpingosonography (HyFoSy) in sepia mode; (a) the C plane shows uterine and endometrial cavities contour (b) 3D reconstruction of the cavity (personal collection of Roxana Elena Bohiltea)

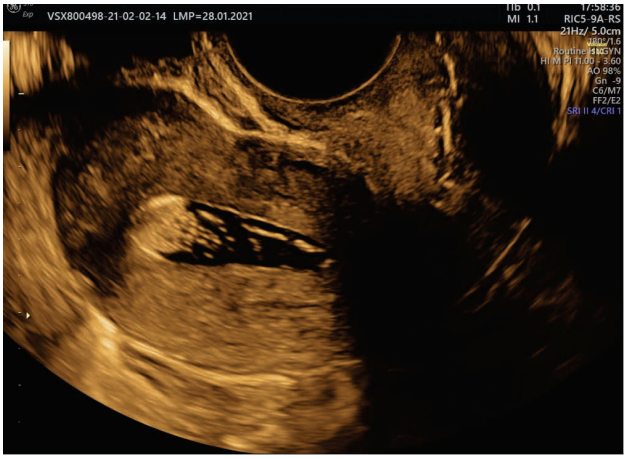

FIGURE 4. 2D endometrial cavity sepia mode imaging. The cavity contour is optimally visible at the end of the procedure, when the focal lesions are highlighted by a fine layer of substance (personal collection of Roxana Elena Bohiltea)

planning the procedure, without belonging to an unanimously accepted standard, it is recommended to check the existence of the pathogenic vaginal flora, including Chlamydia and the exacerbated load of Mycoplasma or Ureaplasma. The prior local gynecological examination usually establishes the position of the uterus and is aimed to detect possible subacute pelvic inflammation, which would contraindicate HSG. Carrying out the examination in optimal conditions and obtaining quality results involves emptying the bladder before starting the procedure, oral analgesics (Ibuprofen 600 mg) one hour before the examination, antiseptic vaginal toilet and positioning the patient with the pelvis elevated, ideally to an angle of 30° from the horizontal plane. Antibiotic prophylaxis consists in the administration of Doxycycline 100 mg orally one hour before the procedure to patients with a history of pelvic inflammatory disease. If fluid collections in the salpinx are found during the examination, Doxycycline 100 mg orally twice daily may be continued for five days to reduce the incidence of pelvic inflammatory disease (36).

SHG FINDINGS

In the examination of the uterine cavity, the evaluation of endometrial morphology and intrauterine lesions by sonohysterography, the International Endometrial Tumor Analysis (IETA) group provides the aspects that are common to the pre-existence of endocavitary fluid. Endometrial cavity distension is defined as optimal if the instilled substance clearly relaxes the cavity, suboptimal if the distension is mild or moderate and the lack of the substance in the cavity is mentioned as failure. Endometrial thickness, echogenicity and endo-myometrial junction are described using the designated terms. The endometrial surface can be smooth, the cavity appearing regular, with endometrial folds when it presents multiple folds and wavy areas with regular profile, polypoid when it has deep identities, the endometrium being described as irregular when the cavity has a cauliflower aspect.

Myometrial intracavitary lesions are defined by echogenicity, which may be homogeneous or heterogenous, and by grading established based on the proportion of the protruding lesion in the uterine cavity. Grading of Leone et al. used in hysteroscopy (37,38) comprises grade 0 (G0) represented by pediculated fibroids without intramural extension, located entirely inside the cavity; grade 1 (G1) designates sessile fibroids with an endocavitary location of more than 50% of their volume and grade 2 (G2) combined fibroids with less than 50% of the protruding volume in the cavity.

Endometrial polyps (Figure 5), the most common intracavitary pathology, appear as solid lesions with homogenous or heterogenous echogenicity, with regular or irregular contour, for surgical hysteroscopy, being necessary to specify the shape, position, and number of lesions. Synechia represents thick tissue bands that cross the endometrial cavity, usually isoechoic with the myometrium. In this case, the cavity is not completely distensible on sonohysterography. The color score and the presence of dominant vessels or other vascular patterns of the lesion enhance specificity of the method.

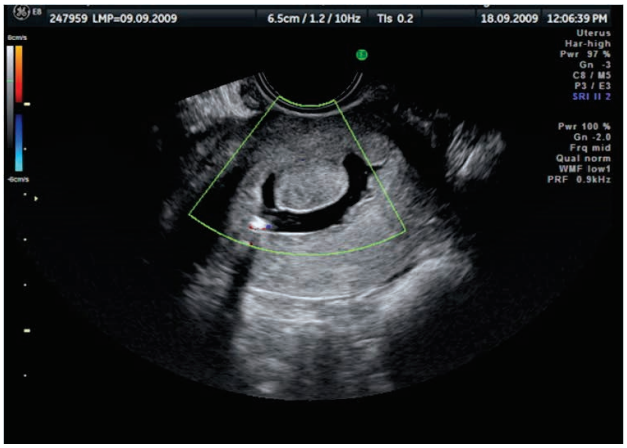

FIGURE 5. Saline infusion sonohysterography image of an endometrial polyp (personal collection of Roxana Elena Bohiltea)

SHG optimally evaluates the architecture of the endometrial cavity by detecting intracavitary lesions, and segmental-transverse scar defects after cesarean section (39-42), being considered a complementary technique to conventional transvaginal ultrasound and an alternative to hysteroscopy, minimally invasive, well tolerated, with reasonable costs and extremely rare complications. As previously presented, one of the great advantages of the

procedure is the optimal evaluation of submucosal leiomyomas, which can be characterized more correctly than using hysteroscopy, by size, degree of protrusion and vascularization. In the ISUOG 2014 Congress, Goldstein, an authority in the field of endometrial pathology, recommended the instillation of saline for the ultrasound study of the routine endometrium, to all menopausal women without fluid in the uterine cavity. Kaunitz AM (43) also recommends SHG to all women who need cavity assessment. SHG is less painful than hysteroscopy and can detect asymmetries or focal thickening of the endometrium, an important marker for endometrial neoplasia. The disadvantage of the technique consists in the lack of obtaining material for histological diagnosis, in conditions of slightly increased discomfort of the patient compared to the usual ultrasonographic exploration. A study of 113 patients aged 25-69 years with persistent abnormal uterine bleeding explored by endometrial biopsy after SHG, who subsequently underwent hysteroscopy or curettage or hysterectomy, revealed a sensitivity, specificity, positive and negative predictive value of biopsy association with SHG of 97%, 70%, 82% and respectively 94% (44). The combination of biopsy techniques with SHG allows the diagnosis of causes of abnormal uterine bleeding in most cases, excluding the need for invasive procedures such as hysteroscopy. The combination of techniques is more useful in women with symmetrical endometrial thickening (45,46).

In 2017, Bittencourt et al. (47) performed a meta-analysis on the diagnostic accuracy of sonic hysterography with saline to highlight endometrial polyps or submucosal fibroids, as a cause of abnormal uterine bleeding. The sensitivity and specificity of the procedure in the detection of polyps was 93%, respectively 81%, while the sensitivity and specificity of the technique in the diagnosis of submucosal fibroids is 94%, respectively 81%, an accuracy that supports ultrasound with or without instillation of solution in the first line exploration of abnormal uterine bleeding.

Clinical practice offers specific situations compared to the theoretical basis from which we start. Although the optimal window for endometrial evaluation in premenopause, as Goldstein established 20 years ago, is 4-6 days of the menstrual cycle, patients who go to an emergency hospital rarely fall into this range. In this context of suboptimal ultrasound exploration, the terms, definitions, and measurements established by the IETA group are of high importance in the etiological differentiation of bleeding causes. After the anamnesis, general and local physical examination, the first line of exploration of chronic abnormal uterine bleeding, both in premenopause, but especially in postmenopause is transvaginal ultrasound, the transabdominal approach being rarely used.

In this stage, the ultrasound investigation is expected to measure endometrial thickness and uterine size, to detect the existence of one or more structural causes of bleeding, to evaluate appendages and the presence of additional elements that could increase the risk of dilation and biopsic uterine curettage should be performed (intracavitary leiomyomas, deep myometrial invasion with increased risk of uterine perforation, uterine malformations, gestational trophoblastic disease). In the exploration of endometrial pathology, ultrasonography must first answer to 3 questions: is there any endometrial pathology? What is the probable etiological diagnosis of abnormal uterine bleeding (endometrial polyps, endometrial hyperplasia, endometrial carcinoma, endometritis, endometrial atrophy, adenomyosis, submucosal leiomyomas)? Does it require a biopsy?

In determining the causes of abnormal uterine bleeding, what should be taken into consideration is that in premenopause most uterine bleeding is dysfunctional (> 50%) or due to benign endometrial proliferation (30-50%), adenomyosis or uterine scar defects after cesarean section, endometrial cancer representing 1% of the causes, while in postmenopause, atrophy is responsible for 60-70% of cases, followed by polyps, hyperplasia or submucosal leiomyomas (20-40%) and endometrial cancer in 10% of cases. The current global trend is to use sonohysterography routinely in endometrial exploration of the causes of abnormal uterine bleeding. The separation of focal lesions from the global endometrial ones directs, as previously mentioned, the subsequent investigations. The endocavitary contour, respectively the irregular endometrial surface, is one of the highest predictive factors of malignancy.

CONCLUSIONS

Considering that transvaginal ultrasound is the first line in the exploration of uterine cavity, the adding of saline solution during the scan enhances significantly the capacity of pathologies detection of the method for postmenopausal women with abnormal uterine bleeding. Sonohysterography is successfully used to evaluate the endometrial morphology and to select the cases requiring biopsy, in women of fertile age who suffer from recurrent pregnancy loss, or in the fertility evaluation protocol for endometrial polyps diagnosis, submucous myomas location or intrauterine adhesions revealing. Sonohysterography offers a maximum benefit from a minimally invasive diagnostic method to an oriented treatment plan to all these women.

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