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Assessment of Perimenopausal Bleeding Using Three-Dimensional Hysterography, Hysteroscopy, and Histopathology

Waleed El-Khayat,[1] Fatmafaisal Ibraheem,[2] Amal Mohsen Ahmed,[1] Ashraf Abdelrahman Ramadan,[1]

Sara E Khalifa,[2,*] and Mohammed Faisal Ebrahim[2]

[1]Department of Obstetrics and Gynocology, Faculty of Medicine, Cairo University, Cairo, Egypt
[2]Department of Pathology, Faculty of Medicine, Cairo University, Cairo, Egypt

[*]*Corresponding author*: Sara E Khalifa, MD, Department of Pathology, Faculty of Medicine, Cairo University, Egypt. Tel: +2-27011516, E-mail: sarah.mekawy@kasralainy.edu.eg

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Abstract

Background: Abnormal uterine bleeding is a very common gynecological problem, especially in perimenopausal women. Intracavitary lesions have been reported in more than 40% of the referred patients.
Objectives: To compare the diagnostic accuracy of 3-dimensional sonohysterography (3D-SHG) versus hysteroscopy in the evaluation of uterine cavity in patients with perimenopausal bleeding and suspected intracavitary lesions, to evaluate the correlations between these findings and histopathological results, and to determine if 3D-SHG is superior or comparable to hysteroscopy in the diagnosis of these lesions.
Methods: A total of 50 women with perimenopausal bleeding and suspected intracavitary lesions, detected by either 2D transvaginal ultrasound or hysterosalpingography, were subjected to 3D saline-infusion sonohysterography (3D-SIS), office hysteroscopy, subsequent surgical procedures (i.e., fractional curettage, hysterectomy, polypectomy, or myomectomy), and finally histopathological examinations.
Results and Conclusions: Based on the findings, 3D-SIS is comparable to hysteroscopy in the diagnosis of intracavitary lesions in terms of sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy (97.83%, 100%, 100%, 80%, and 98%, respectively for 3D-SIS vs. 100%, 100%, 100%, 100%, and 100%, respectively for office hysteroscopy).

Keywords: Perimenopausal Bleeding, Intracavitary Lesions, Three-Dimensional Saline-Infusion Sonohysterography, Hysteroscopy, Histopathology

1. Background

Abnormal uterine bleeding (AUB) is the most common cause of many gynecological visits in the perimenopausal period. It can occur due to intracavitary lesions, which are either benign (e.g., leiomyoma, endometrial polyp, and endometrial hyperplasia) or malignant tumors (1). Therefore, it is very important to assess the uterine cavity for perimenopausal bleeding via either 2-dimensional transvaginal ultrasound (2D-TVS) or hysterosalpingography (HSG) in women with suspected intracavitary lesions (2).

Hysteroscopy is a high-quality tool for the evaluation of the interior of the uterus (3). Nevertheless, it is a relatively expensive and invasive procedure, which fails to provide information about the adnexa or myometrium; in fact, it only presents a subjective study of lesion size and depth of myometrial extension (4). This method is associated with many risks, such as uterine perforation and ascending genitourinary infection (5). Moreover, it is not always available in low-resource settings, and many gynecologists lack the expertise to interpret the findings (6).

Saline-infusion sonohysterography (SIS) is a minimally invasive, inexpensive, and relatively safe procedure, which can be used in the evaluation and detection of pelvic pathologies. However, this procedure fails to properly examine small localized lesions and does not allow differentiation between endometrial and myometrial abnormalities (7). Nevertheless, addition of 3D-TVS provides better visualization and improves the accuracy in the assessment of adnexa, pelvic pathologies, uterine contour, focal lesions, and myometrial invasion (8), as it allows simultaneous display of 3 perpendicular planes and provides access to planes which cannot be viewed via 2D sonohysterography (2D-SHG). Additionally, in 3D-SHG, after distending the uterine cavity with saline, the inner surface of both sides of the endometrium can be viewed (9).

In addition, histopathological studies facilitate definite diagnosis of intracavitary lesions. In many studies, histopathological analysis has been used as the gold standard for determining the accuracy of different imaging methods in the diagnosis of intracavitary lesions. Overall, the ability to distinguish between different conditions al-

lows physicians to determine the appropriate treatment method.

In this study, we aimed to compare the diagnostic values of 3D-SHG and hysteroscopy in the detection of uterine cavity lesions in patients with perimenopausal bleeding and suspected intrauterine lesions, identified via clinical tests, and/or 2D ultrasonography, and/or HSG studies. Moreover, we tried to determine if 3D-SHG is superior or comparable to hysteroscopy in the diagnosis of uterine cavity lesions by comparing the findings with histopathological results.

2. Methods

This prospective, comparative study was conducted on 50 patients with perimenopausal bleeding and suspected intrauterine lesions, examined via clinical tests, and/or 2D ultrasonography, and/or HSG studies. The subjects were selected among patients at the outpatient clinic of the Department of Obstetrics and Gynecology, Faculty of Medicine, Cairo University, Giza, Egypt.

The subjects were selected among patients above 40 years, who were in the perimenopausal stage. The exclusion criteria were as follows: 1) any general cause of bleeding, such as bleeding disorders, coagulation defects, liver cell failure, and use of drugs such as anticoagulants; and 2) any contraindications for SHG or hysteroscopy, including menstruation, pregnancy, marked cervical stenosis, recent or current pelvic inflammatory disease, severe vaginitis or cervicitis, endometrial infection, known cervical malignancies, excessive uterine bleeding, and recent uterine perforation.

The patients were informed about the purpose and methods of the study and signed the informed consent forms. The institutional review board of Kasr Al-Ainy School of Medicine approved this study. Each patient was subjected to full history-taking, full clinical assessment, abdominal examination, and pelvic analysis. Moreover, 3D-SIS was carried out, using a diagnostic ultrasound machine (Voluson 730) while the patient was in the lithotomy position with an empty bladder.

A sterile vaginal speculum was inserted, and the cervix was cleaned with an antiseptic solution. An intrauterine insemination catheter was used to inject the saline into the uterine cavity. Before insertion into the cavity, the catheter was prefilled with saline to minimize air artifacts. Then, the catheter was inserted into the uterine cavity, and the speculum was carefully removed; in the next step, the transvaginal probe was inserted into the posterior fornix of the vagina.

A plastic syringe, containing 20 mL of sterile saline solution, was attached to the catheter. The position of the catheter in the uterine cavity was established before saline instillation. Sterile saline was then slowly injected into the catheter under continuous sonographic visualization. Normally, 40 to 60 mL of fluid is required for uterine distention. Moreover, mode imaging was applied to evaluate endometrial thickness, echogenicity, and presence of endometrial lesions such as polyp, submucous myoma, hyperplasia, and carcinoma. Every lesion was evaluated in terms of site, size, shape, echogenicity, and relation to the uterine cavity. A 3D volume was generated by the automatic sweep of the mechanical transducer. The volumes were stored digitally and analyzed via multiplanar visualization.

Obstetricians and gynecologists, who were blind to the 3D-SHG results, performed office hysteroscopy (OH), using a rigid hysteroscope (continuous flow; 30° forward-oblique view), assembled in a diagnostic sheath (4-mm diameter) with a traumatic tip (Karl Storz Endoscopy, Tuttlingen, Germany). A high-intensity cold light source, as well as a fiberoptic cable, was used to illuminate the uterine cavity. Moreover, normal saline solution was used as the distention medium at 100 - 120 mmHg pressure, applied by an adjustable cuff blood pressure system to use the lowest pressure required for distending the uterine cavity.

Furthermore, the vaginoscopic “no touch” technique was adopted; however, no speculum or tenaculum was used. The hysteroscope with its light source and flowing fluid was gently introduced into the vagina (allowing for gradual distention) and was guided into the endocervical canal, following the small microcavity produced by the fluid in front of the endoscope. Upon entering the uterine cavity, a systematic inspection was conducted to evaluate uterine cornua, tubal ostia, uterine fundus, as well as lateral, anterior, and posterior uterine walls, for the presence of intrauterine lesions, such as polyps, myomas, hyperplasia, and carcinoma.

Endometrial curettage and other operative treatments (e.g., hysterectomy, myomectomy, or polypectomy) were performed on the patients. The specimens were fixed in 10% formalin solution and sent to the pathology laboratory, where gross dissection and tissue sampling were carried out at 3-mm thickness. The tissue sections were fixed for 24 hours in 10% neutral buffered formalin and were then dehydrated, cleared, and embedded in paraffin wax, according to routine processing procedures. The paraffin wax blocks were cut into 5-μ sections, mounted on glass slides, and stained by hematoxylin and eosin (H&E) for histological evaluation by two independent pathologists.

2.1. Statistical Analysis

Data are presented as mean $\pm$ standard deviation (SD), range, frequency, or percentage, when appropriate. Mc-

Nemar test was used to compare 3D-SHG, hysteroscopy, and pathological studies. Also, agreement was assessed using kappa statistics, and accuracy was measured by assessing sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy. P value less than 0.05 was considered statistically significant. All statistical calculations were performed using SPSS software, version 22 (SPSS Inc., Chicago, IL, USA).

3. Results

A total of 50 women within the age range of 41 - 52 years (mean, 44.9 ± 3.346 years) were enrolled in this study. The mean (SD; 95% CI) body mass index (BMI) was 29.26 (3.212; 24 - 40), the mean gravidity was 3.84 (2.324; 1 - 10), and the mean parity was 3.52 (2.188; 0 - 10). In cases with thickened endometrium, the mean endometrial thickness was 15.56 mm (4.875; 12 - 36). In terms of bleeding patterns, menorrhagia was the most common bleeding pattern (44%, 22 cases), followed by menometrorrhagia (36%, 18 cases), metrorrhagia (16%, 8 cases), and polymenorrhea (4%, 2 cases).

Based on the 3D-SHG findings (Figure 1), 20 (40%) cases had submucous myoma, 12 (24%) cases had endometrial polyps, 2 (4%) cases had both submucous myoma and endometrial polyp, 10 (20%) cases had endometrial hyperplasia, only 1 (2%) case had endometrial carcinoma, and 5 (10%) cases showed no abnormalities. According to the OH findings (Figure 2), 21 (42%) cases had submucous myoma, 13 (26%) cases had endometrial polyps, 1 (2%) case had both submucous myoma and endometrial polyp, 10 (20%) cases had endometrial hyperplasia, only 1 (2%) case had endometrial carcinoma, and 4 (8%) cases were hysteroscopically normal.

The definite diagnosis of intrauterine lesions was confirmed based on the histopathological study, which was considered as the gold standard for the diagnosis of these lesions (Figures 3-7). We found 22 (44%) cases of submucous myoma, 13 (26%) cases of endometrial polyps, 10 (20%) cases of endometrial hyperplasia, 1 (2%) case of endometrial carcinoma, and 4 (8%) cases of dysfunctional uterine bleeding.

We compared the 3D-SHG and OH findings with the results of histopathological studies, as the gold standard for the diagnosis of intrauterine lesions. Based on the findings, 3D-SHG could detect 12 cases of polyp, which were also confirmed via histopathological studies. However, it missed 1 case of polyp, which was diagnosed by histopathology (false negative). Also, 3D-SHG detected 2 cases of polyp associated with submucous myomas, which were not confirmed via histopathological studies (false positive).

On the other hand, OH detected 13 cases of polyp, which were confirmed by histopathology. Nevertheless, it reported 1 case of polyp, associated with submucous myoma, which was not confirmed by histopathology (false positive). All cases of submucous myoma, all cases of hyperplasia, and the single case of carcinoma, which were confirmed via histopathology, were also diagnosed by both 3D-SHG and OH studies. Therefore, OH could detect all lesions with only 1 false positive result, while 3D-SHS missed only 1 lesion (false negative) and reported 2 false positive results (Tables 1 and 2).

Table 1. True Positive Results on 3D-SHG and OH in Comparison with Definitive Diagnosis by HP

Intrauterine Lesion	3D-SHG, True Positive/All Positive	OH, True Positive/All Positive	HP, All Positive
Submucous myoma	22/22	22/22	22
Endometrial polyp	12/13	13/13	13
Hyperplasia	10/10	10/10	10
Carcinoma	1/1	1/1	1
Normal	4/4	4/4	4
Total	49/50	50/50	50

Abbreviations: 3D-SHG, 3D Sonohysterography; HP, Histopathology; OH, Office Hysteroscopy.

4. Discussion

Intrauterine lesions, such as submucous myoma, endometrial polyp, endometrial hyperplasia, and carcinoma, are common causes of abnormal uterine bleeding among perimenopausal women, referred to gynecological clinics (10). Therefore, it is important to diagnose these lesions accurately.

In the present study, all 50 patients were subjected to 3D-SIS and OH analyses. Both procedures were performed successfully for all the participants without any complications. The results were correlated individually with histopathological results. The final diagnosis was based on histopathological studies, as the gold standard for the diagnosis of intrauterine lesions. In this regard, Abou-Salem et al. (2010) and Khan et al. (2011) have also used histopathology as the gold standard (11, 12).

Distribution of abnormal findings varies in different studies. In the present study, submucous fibroids were the most common lesions. Similarly, submucous myoma was the most common intrauterine lesion in a study by Ebrashy et al. (2004) (13). On the other hand, polyps

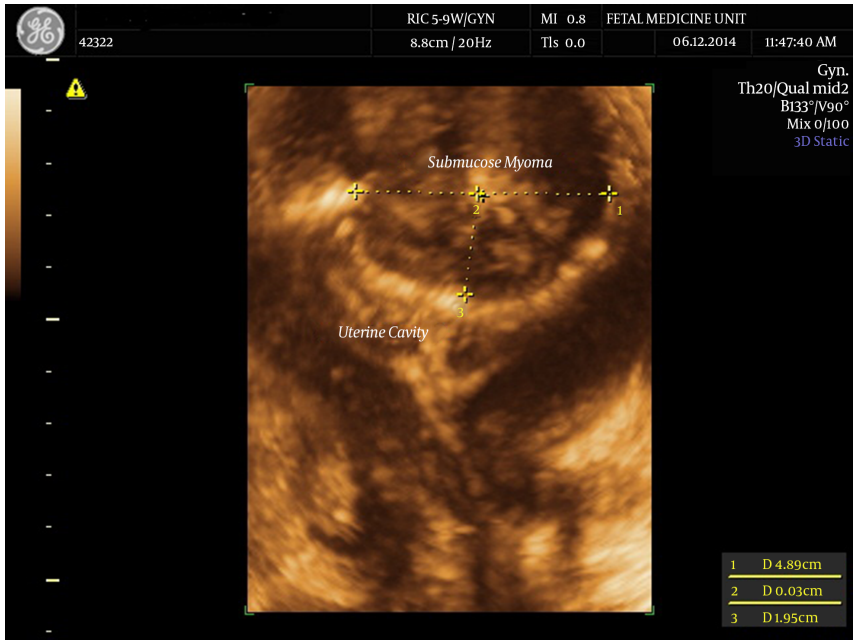

Figure 1. 3D-SHG Indicating a Submucous Myoma with More Than 50% Extension in the Uterine Cavity

Table 2. Comparison of Sensitivity, Specificity, PPV, NPV, and Overall Accuracy of 3D-SHG and OH in the Diagnosis of Intrauterine Lesions

Method	Lesion	Sensitivity	Specificity	PPV	NPV	Overall Accuracy
3D-SHG	Submucous myoma	100.00	100.00	100.00	100.00	100.00
	Endometrial polyp	92.31	94.59	85.71	97.22	94.00
	Endometrial hyperplasia	100.00	100.00	100.00	100.00	100.00
	Endometrial carcinoma	100.00	100.00	100.00	100.00	100.00
	All lesions	97.83	100.00	100.00	80.00	98.00
OH	Submucous myoma	100.00	100.00	100.00	100.00	100.00
	Endometrial polyp	100.00	97.30	92.86	100.00	98.00
	Endometrial hyperplasia	100.00	100.00	100.00	100.00	100.00
	Endometrial carcinoma	100.00	100.00	100.00	100.00	100.00
	All lesions	100.00	100.00	100.00	100.00	100.00

Abbreviations: 3D-SHG, 3-Dimensional Sonohysterography; NPV, Negative Predictive Value; PPV, Positive Predictive Value; OH, Office Hysteroscopy.

were the most prevalent lesions in studies by Epstein et al. (2001), Erdem et al. (2007), Yildizhan et al. (2008), Grimbizis et al. (2010), and Bingol et al. (2011) (14-18) on women with AUB (41%, 50%, 44%, 40%, and 38%, respectively); these variations might be attributed to ethnical or racial factors.

In the present study, OH studies could detect all cases of submucous myoma (44%), all cases of endometrial hyperplasia (20%), the single case of endometrial carcinoma (2%), and all cases of endometrial polyp (26%); however, 1 (2%) false positive result was reported. The diagnostic accuracy of hysteroscopy for polyps was 98% in comparison with histopathology, while there was no statistically significant difference (P = 0.999).

Accordingly, we concluded that the diagnostic accuracy of OH was almost 100% for all lesions in the present study. The high accuracy of OH (almost 100%) is in consistence with the results reported by Kelekci et al. (2005), Karageyim et al. (2010), and Bingol et al. (2011) (18-20). Moreover, considering the high accuracy of this method, it has been used in many studies as the gold standard to

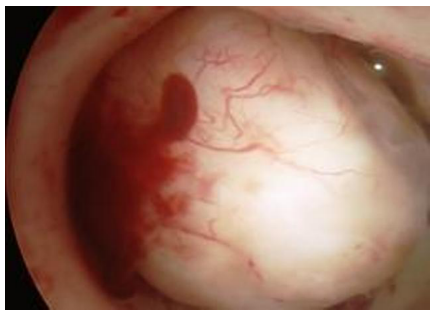

Figure 2. OH Indicating a Submucous Myoma

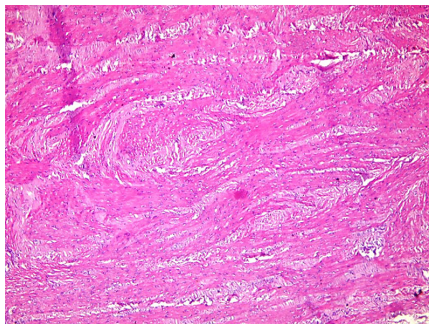

Figure 3. H & E Stained Image Indicating a Leiomyoma (× 200)

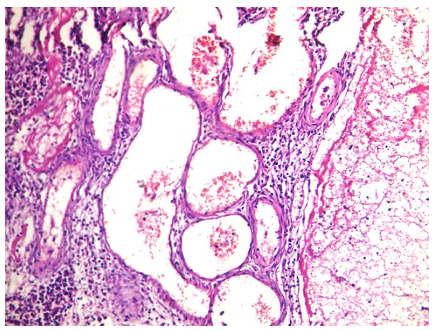

Figure 4. H & E Stained Image Indicating an Endometrial Polyp (× 200)

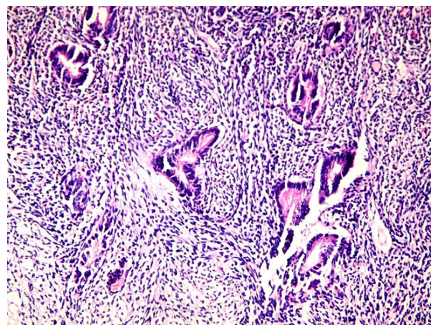

Figure 5. H & E Stained Image Indicating a Disordered Proliferative Endometrium (× 200)

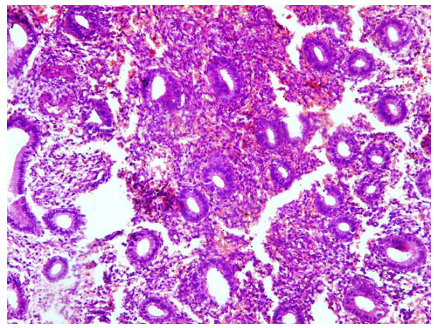

Figure 6. H & E Stained Image Indicating Simple Endometrial Hyperplasia (× 200)

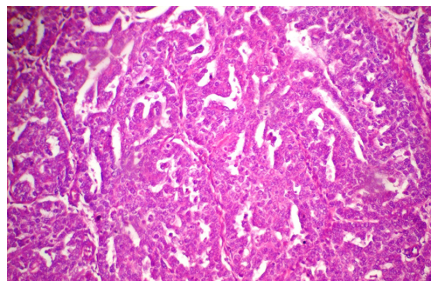

Figure 7. Endometrioid Carcinoma with a Villoglandular Variant Showing Long Delicate Papillary Fronds (H & E, × 100)

which other modalities are compared (15, 16, 21).

In the current study, 3D-SIS could detect all cases of submucous myoma (44%), all cases of hyperplasia (20%), and the single case of endometrial carcinoma (2%); it also diagnosed 12 (24%) cases of endometrial polyp. Nevertheless, 1 false negative result (2%) was reported due to missing 1 case of polyp. Also, 2 false positive results (4%) were reported due to the presence of intrauterine blood clots (confirmed by hysteroscopy and histopathology), which were misinterpreted as endometrial polyps; these findings were in line with the results reported by Elsayes et al. (2009) and Allison et al. (2010) (22, 23).

Based on the present findings, the diagnostic accuracy of 3D-SIS for polyps was 94% in comparison to histopathological studies; however, the difference was not statistically significant (P = 0.999). Accordingly, the diagnostic accuracy of 3D-SIS was almost 98% for all lesions. Moreover, the high accuracy of SHG for the diagnosis of intracavitary lesions, mainly polyps and submucous myomas, has been supported in some previous studies (14, 16-19, 21).

In patients with perimenopausal bleeding, the cutoff endometrial thickness was 12 mm, based on which presence of intrauterine lesions (such as polyp, hyperplasia, and carcinoma) was determined using both 3D-SHG and OH analyses. In 3D-SIS, the sensitivity, specificity, PPV, NPV, and accuracy were all 100% for submucous myoma, 92.31%, 94.59%, 85.71%, 97.22%, and 94% for endometrial polyps, respectively, 100% for endometrial hyperplasia, and 100% for carcinoma. Moreover, in OH, the corresponding values were 100% for submucous myoma, 100%, 97.30%, 92.86%, 100%, and 98% for endometrial polyps, respectively, 100% for endometrial hyperplasia, and 100% for carcinoma.

In the present study, the overall sensitivity, specificity, PPV, NPV, and accuracy were 97.83%, 100%, 100%, 80%, and 98% for 3D-SIS and 100% for OH studies. Although in the present study, there was a 2% difference in the overall sensitivity and accuracy for benign lesions (polyps), the difference was insignificant (P = 0.785). Besides, both methods could successfully detect the single case of malignancy (overall accuracy, 100% in both). Therefore, 3D-SHG did not miss the case of malignancy, which is a major concern, especially in perimenopausal women.

In addition, there was a significant agreement between 3D-SHG and OH in the diagnosis of intracavitary lesions (P = 0.032). Therefore, 3D-SHG is comparable to hysteroscopy (the gold standard in the evaluation of uterine cavities) in the diagnosis of intracavitary lesions among women with perimenopausal bleeding. Moreover, considering its other advantages, including safety, lack of complications, availability, limited experience requirements, low cost, and precise assessment of the entire pelvis, it can be used as an alternative to OH in the diagnosis of these lesions, especially in low-resource communities.

In agreement with the present results, several studies have investigated the diagnostic accuracy of SHG in comparison with hysteroscopy in the detection of intracavitary lesions, associated with different conditions. In this regard, infertility was assessed in a study by Ludwin et al. (2014) (24), recurrent spontaneous miscarriage was analyzed by Saravelos et al. (2008) (25), and abnormal uterine bleeding was examined by De Angelis et al. (2013) (26).

Also, Salim et al. (2005) (9) and Lee et al. (2006) (27) concluded that 3D-SHG is comparable to hysteroscopy and is a reproducible method in the classification of submucous fibroids. These results concur with those reported by Makris et al. (2007) (28), which revealed that 3D-SHG had a comparable accuracy to hysteroscopy in the diagnosis of congenital uterine anomalies.

In addition, Katsetos et al. (2013) (29) conducted a prospective randomized controlled cohort study to compare 3D-SHG and OH in terms of diagnostic accuracy, procedure duration, and patient discomfort among 49 women with abnormal uterine bleeding from different ethnical backgrounds. They concluded that 3D-SHG and OH are similar in terms of diagnosis of intracavitary lesions, pain, and procedure duration. However, patients' acceptability of SHG was significantly higher than OH.

The major limitations of hysteroscopy include experience requirements and subjective assessment of lesion size and depth of myometrial extension due to myoma (4). Meanwhile, the main advantage of sonographic methods is their potential to provide important information on the cavity. Moreover, adnexal masses and myometrial disorders, such as intramural fibroid and adenomyosis, can be detected, and the underlying symptomatology may be identified. In addition, SHG is a relatively short and inexpensive procedure, causing minimal discomfort for the patient. Therefore, 3D-SHG can be used as an alternative to hysteroscopy in the evaluation of uterine cavity.

4.1. Conclusion and Recommendations

Based on the findings, SIS is comparable to hysteroscopy in the diagnosis of uterine cavity lesions. Moreover, it may be used as the method of choice for the evaluation of uterine cavity among women with perimenopausal bleeding and suspected intracavitary lesions in low-resource communities. Although hysteroscopy remains the gold standard for the assessment of uterine cavity, it cannot replace histopathological studies.

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