# Undiagnosed endometrial abnormalities in women with normal hysterosalpingography scheduled for IVF: prospective evaluation of three-dimensional transvaginal ultrasound versus office hysteroscopy

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**Keywords:** Three-dimensional ultrasound, multi-slice view, office hysteroscopy, in vitro fertilization, cost modeling

***Abstract***

***Objectives:*** *To compare the diagnostic accuracy of three-dimensional transvaginal ultrasound (3D-US) to office hysteroscopy (OH) in the screening of uterine cavity with normal hysterosalpingography (HSG) findings for subtle endometrial abnormalities before in vitro-fertilization (IVF).*

***Methods:*** *A prospective cohort cost-modeling study was carried out in a University hospital. We included 120 infertile women with a normal uterine cavity on HSG scheduled for IVF. All cases were evaluated by 3D-US, and the results were compared with OH findings.*

***Results:*** *OH revealed cavitary endometrial lesions (CLs) in thirty-four women (28.3%). Endometrial polyps were the most common detected lesions (16, 47.1%). 3D-US had 88.2% sensitivity, 96.5% specificity, 90.9% positive predictive value, 95.4% negative predictive value, and 94.2% overall accuracy for CLs. The overall agreement between 3D-US and OH was near-perfect (κ=0.86, 95% CI=0.75-0.96). Irregular menstrual bleeds and prior endometrial procedures were significant predictors for CLs (aOR=24.96, 95% CI=2.71–230.04, P=0.005, aOR=9.16, 95% CI=2.13–39.3, P=0.002, respectively). A selective screening strategy discerning OH to women with these predictors and/or women with abnormal 2D-US would have an NPV of 92.8 % with substantial cost benefits.*

***Conclusions:*** *In the pre-IVF work up, 3D-US, a non-invasive imaging modality, seems to be nearly comparable to OH. Office hysteroscopy screening prioritizing women with abnormal 2D-US, irregular menstrual periods and/or prior endometrial traumatization could yield a satisfactory cost-effective approach for identifying endometrial lesions.*

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## Introduction

Evaluation of the endometrial cavity is an important step in the infertility workup, particularly if assisted reproductive therapy is planned. The aim is to identify possible endometrial abnormalities that may impair implantation.[1,2] Hidden endometrial abnormalities are present in 11 to 45% of women scheduled for in vitro fertilization (IVF).[3-6] Traditionally, two-dimensional transvaginal ultrasound (2D-US) and hysterosalpingography (HSG) are the primary methods for assessment of the endometrial cavity. However, these imaging modalities have shown high false-negative rates among infertile women, a finding that could confine their use to initial screening rather than definite diagnosis.[2,6-10]

Office hysteroscopy (OH) is the reference standard for the evaluation of the endometrial cavity. Evidence on the treatment of unsuspected hysteroscopically-diagnosed endometrial lesions, to improve IVF outcome, is still lacking.[11,12] A recent randomized controlled trial (RCT) that compared IVF outcomes among small numbers of treated as well as untreated lesions demonstrated similar clinical pregnancy and live birth rates.[13] In low income and resource countries, where governmental insurance provides the main coverage for IVF cycles, the psychological and financial consequences of failed IVF cycles are unjustifiable.[14]

Recently, there has been emerging evidence that the use of saline infusion in combination with 3D ultrasound imaging could present an alternative to OH.[8,11,15,16] With the advance of 3D software, the coronal view of the uterus can be exhibited in many displays: multi-planar view (MPV), surface rendering, and power Doppler modes. All have been studied before for the detection of the intrauterine lesions with satisfactory results.[15-17]

Our objective was to propose imaging-based strategies that may replace or minimize the use of OH before IVF for the detection of hidden intrauterine abnormalities. To achieve this purpose, we evaluated 3D-US using both multi-planar view (MPV) and multi-slice view (MSV) of the uterine cavity in comparison to OH, the gold standard, for diagnosis of cavitary endometrial lesions (CLs) in women scheduled for IVF. Also, we assessed an OH screening strategy, selectively comprised women with abnormal 2D TVUS and/or clinical predictors for CLs, in terms of diagnostic accuracy and cost.

## Materials and Methods

This was a prospective cohort study. The study's protocol was approved by The Research Ethics Committee of Faculty of Medicine, Assiut University. Women attending the infertility outpatient clinic and IVF center of a single university-affiliated hospital between July 2014 and October 2015 were considered for enrollment. Women were considered eligible if they were selected for IVF therapy, had a history of primary infertility, and had a normal uterine cavity on initial HSG done within one year before the enrollment.

Women with a known diagnosis of

uterine abnormality by prior OH after normal HSG were excluded from the study. After appropriate counseling, women were offered to participate in the study after written informed consent.

*Sonographic Examination*

Following the initial clinical assessment, all women were scheduled to have a sonographic examination within 48 hours of cessation of menstrual flow. Sonographic examinations were performed by the same sonographer using a Medison SonoAce X8 (Medison Co., Seoul, Korea) with a 3D/4D volumetric 12mm endocavitary, trans-vaginal, probe (3D4-9ES [4-9 MHz]).

Endometrial cavities were first evaluated using a 2D ultrasonographic view on two planes: sagittal and transverse. After that, 3D volumes were acquired from the mid-sagittal plane of the uterus while the entire uterus was included in the volume box. Both cervical and endometrial canals were completely visualized in continuity, and the probe was kept steady by the examiner. To generate the volume, 3D Static Mode was used with a maximum sweep angle of 120 degrees, and the subject was asked to hold her breath and to remain still. 3D volumes were obtained and stored digitally. The volumes were analyzed offline using MPV and MSV of the mid-coronal plane of the uterus. For the multi-planar display of the mid-coronal plane, Z technique was utilized as described by Abuhamad et al.[18] MSV then evaluated all coronal views. For each coronal view, parallel slices of 0.5 mm depth difference were studied simultaneously on the same screen.

The 3D scans were examined for endometrial abnormalities such as polyps, sub-mucosal myomas (SMM), intrauterine adhesions (IUA), and congenital anomalies. An endometrial polyp was identified as focal hyperechoic thickening of the endometrium, with a preserved myometrial-endometrial junction. A sub-mucous myoma (SMM) was defined as a mixed or hypoechoic lesion originating from the myometrium and interrupting myometrial-endometrial junction. Adhesions were defined as bands that separated the endometrial cavity and caused distorted or irregular endometrial line. For the diagnosis of a congenital uterine anomaly, outer and inner fundal contours and the length of the fundal indentation were analyzed. The American Society for Reproductive Medicine description of the anomalies was followed to categorize the findings.[19] For imaging analysis of the uterine morphology, standards in the literature were utilized to define each anomaly[20,21] appropriately.

*Office Hysteroscopy Examination*

Office Hysteroscopy was conducted on the same day of sonographic examination. Hysteroscopic examinations were done in the office 1-4 months before the IVF cycle by the same investigator (reproductive endocrinologist with more than ten years' experience in hysteroscopy) who was blinded to 3D-US results. Women were pre-medicated by vaginal misoprostol 200ug for cervical ripening 12 hours before the procedure. The procedure was performed utilizing a 3.5-mm outer diameter, single, continuous flow rigid hysteroscope with a 30-degree forward-oblique lens (2.7-mm in diameter) (Wolf Lumina®, Richard Wolf GmbH, Germany). Vaginoscopic approach ("no-touch" technique) was utilized without anesthesia or any cervical manipulations. Sterile normal saline solution 0.9% was used to distend the vagina and the uterus with the pressure kept between 50 and 100 mmHg.

During OH, the observations were explained to the subjects on set through a video screen. Participants were blinded to the sonographic results and were observed for 1-hour post-procedure.

*Inter/Intra-observer Agreement*

To calculate the inter-observer agreement for 3D-US diagnosis, two study investigators independently studied the digitally stored 3D volumes. They conducted another evaluation four weeks later for the calculation of the intra-observer agreement. The study investigators who evaluated 3D volumes were reproductive endocrinologists with five years' experience in 3D imaging.

*Statistical Analysis*

Statistical analysis was performed using STATA version 13 (STATA corp., College Station, TX, USA). Shapiro-Wilk test was used as a test of normality for continuous variables. Parametric variables were expressed as mean± standard deviation (SD), while skewed variables were described using the median and the inter-quartile range (IQR). Mann Whitney U test was used to compare the median of non-parametric variables. Chi-square and Exact Fisher's tests were used to compare proportions as appropriate.

Univariate logistic regression was conducted to identify potential clinical predictors of CLs. Independent variables that had P values $< 0.2$ were considered in multivariate logistic regression. Uncentered variance inflation factor (VIF) was used to assess collinearity; variables that had VIF $> 10$ were deemed to be collinear. Continuous variables were divided using cutoff points that were most informative in the regression model. Hosmer-Lemeshow Test was conducted for post-estimation of the model; a p-value> 0.5 supports goodness of fit.

The Cohen k was calculated to evaluate the level of agreement between 3D-US and OH. 0.41 to 0.60 was considered moderate, 0.61 to 0.80 was substantial, and 0.81 to 1.00 was described as perfect. Two-tailed McNemar test was conducted to compare proportions within the same cohort. Diagnostic accuracy of imaging modalities was expressed in terms of sensitivity, specificity, positive, and negative predictive values (PPV, NPV).

## Results

One hundred and twenty women met enrollment criteria and were recruited in this study. Their median (IQR) age was 30 (23.8 – 36) years, with 52.5% (N= 63) in their thirties and 25.8% (N= 31) in the late twenties. The median (IQR) duration of infertility was 6 (4 – 9.8) years. One-third of them reported prior IVF trials (40, 33.33%) with a mean (SD) number of trials of 1.68 ± 0.73. The indications for IVF treatment were a tubo-peritoneal factor (33.3%), anovulatory (28.3%), unexplained (16.7%), male infertility (15.8%) and combined factors (5.8%). The demographic and clinical characteristics of the study cohort are shown in Table 1.

**Table1: Characteristics of women with and without cavitary lesions**

| Patient characteristics | Overall (n=120) | Women without CLs (n=86) | Women with CLs (n=34) | P-value |
|---|---|---|---|---|
| **Female age, years**<br>**Median (IQR)** | 30 (23.8 - 36) | 29 (23 - 33.4) | 31.5 (27.4 - 37) | 0.009 |
| **Infertility duration, years**<br>**Median (IQR)** | 6 (4 - 9.8) | 5.5 (3 - 8) | 6 (4 - 11) | 0.11 |
| **BMI, kg/m$^2$**<br>**Median (IQR)** | 25 (23 - 28) | 25 (23 - 28) | 24 (22.8 – 27.3) | 0.35 |
| **Etiology of infertility (n, %)** | | | | |
| **Male factor** | 19 (15.8%) | 13 (15.1%) | 6 (17.6%) | 0.66 |
| **Ovulatory Dysfunction** | 34 (28.3%) | 25 (29.1%) | 9 (26.5%) | |
| **Tubo-peritoneal** | 40 (33.3%) | 26(30.2%) | 14(41.2%) | |
| **Unexplained** | 20 (16.7%) | 16 (18.6%) | 4 (11.8%) | |
| **Combined male and female** | 7 (5.8%) | 6 (7.0%) | 1 (2.9%) | |
| **Menstrual pattern (n, %)** | | | | |
| **Normal** | 87 (72.5%) | 65 (75.6%) | 22 (64.7%) | 0.26 |
| **Oligomenorrhea** | 19 (15.8%) | 17 (19.8%) | 2 (5.9%) | 0.06 |
| **Hypomenorrhea** | 1 (0.8%) | 0 ( 0) | 1 (2.9%) | N/A |
| **Heavy menstrual bleeding** | 6 (5%) | 2 (2.3%) | 4 (11.8%) | 0.09 |
| **Irregular menstrual periods** | 7 (5.8%) | 1 (1.2%) | 6 (17.6%) | 0.002 |
| **Prior IVF cycle(n, %)** | 40 (33.3%) | 26 (30.2%) | 14 (41.2%) | 0.29 |
| **Prior Endometrial procedure(n, %)** | 11 (9.2%) | 3 (3.5%) | 8 (23.6%) | 0.002 |

*CLs, endometrial cavitary lesions; BMI, body mass index; P value < 0.05 is considered significant*

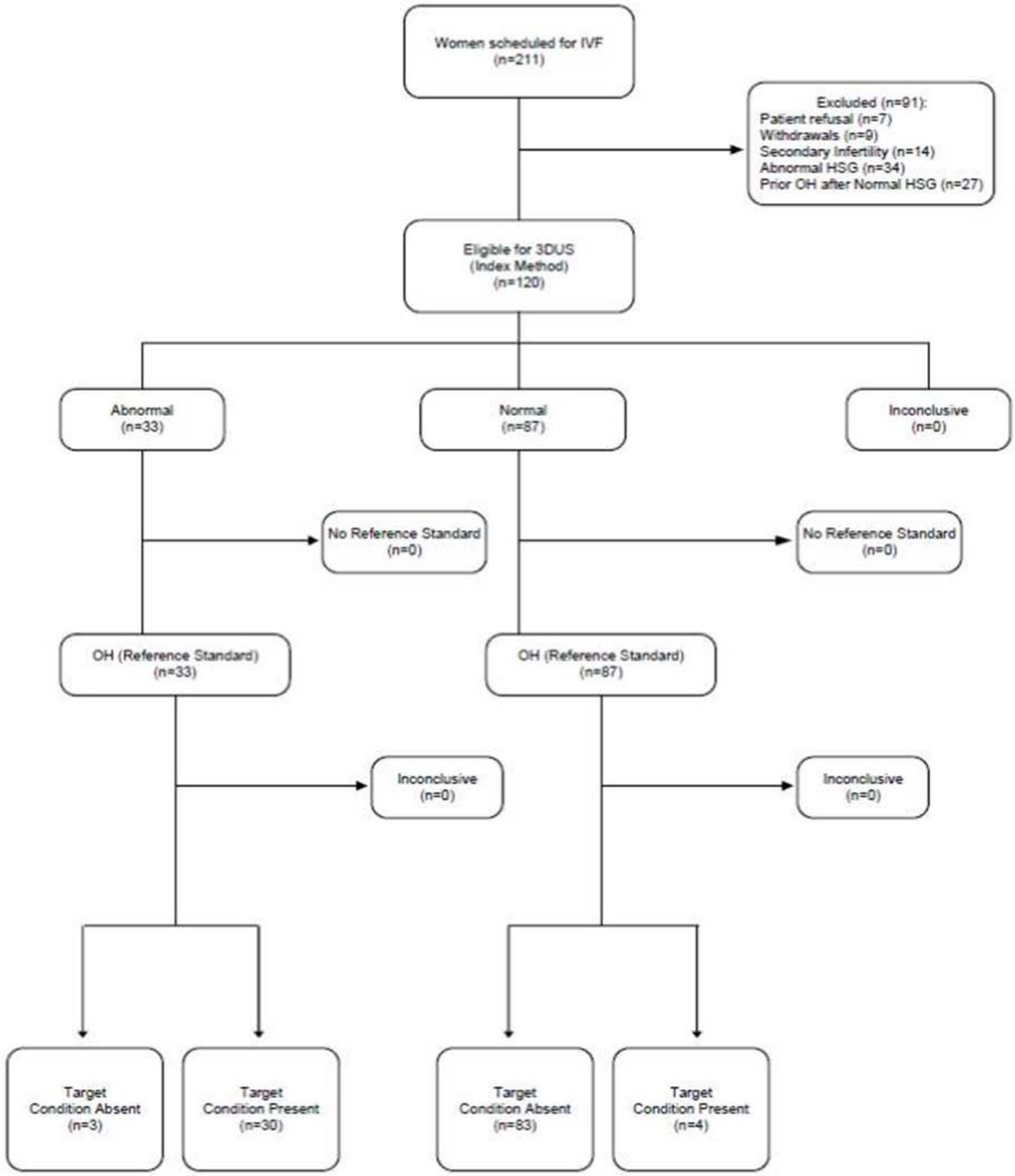


**Figure 1: STARD (Standards for the Reporting of Diagnostic Accuracy Studies) flow diagram showing cavitary lesions diagnosed during uterine cavity assessment using three-dimensional transvaginal ultrasound (index method) and office hysteroscopy (reference method).**

During OH, no participants asked to stop the procedure, and no complications were reported. At the hysteroscopic examination, 34 women (28.3%) had CLs (Figure 1). More abnormalities were reported among women with prior IVF failure compared to those scheduled for their first trial (14/40; 35% versus 20/80; 25%, respectively). However, this difference was not statistically significant (P=0.25). These abnormalities included polyps (16, 47.1%), submucous myomas (8, 23.5%), intrauterine adhesions (3, 8.8%), uterine septa (3, 8.8%) and arcuate uterus (4, 11.8%).


**Figure 2: 2D- and 3D-US images of sub-mucosal myoma.**

Of the CLs, 30 were diagnosed by 3D-US and 21 by 2D-US. Sensitivity, specificity, PPV, NPV and overall accuracy for 2D-US were 61.8%, 93%, 77.8%, 86% and 84.2% respectively. 2D-US showed perfect accuracy for SMM (Figure 2). 2D-US misdiagnosed 13 cases as normal uterine cavity; however, most of the missed lesions are minimal. Anatomical description of the 2D-misdiagnosed cases and their clinical presentations are shown in Table 2.

**Table 2: Correlating anatomy with clinical presentations of the lesions missed by 2D-US evaluation**

| The lesion | Anatomical description | Clinical presentations |
|---|---|---|
| **Polyps (n=5)** | Median (IQR), cm: 1.1 ( 0.7 – 1.3)<br>Mean ± SD, cm: 1.02 ± 0.28 | |
| | 0.8 cm low corporeal posterior polyp, oblong in shape. | Asymptomatic |
| | 1.1 cm utero-tubal polyp thin fusiform in shape. | History of prior polypectomy |
| | 0.6 cm utero-tubal polyp, oval in shape. | Asymptomatic |
| | 1.2 cm utero-tubal polyp, thin fusiform in shape | Irregular menstrual periods(metrorrhagia) |
| | 1.4 cm high corporeal , lateral wall polyp, rounded in shape | Irregular menstrual periods(metrorrhagia) |
| **IUA (n=2)** | Mid-corporeal, Moderate IUA. | Hypomenorrhea, History of prior myomectomy |
| | Low corporeal, Mild IUA appeared as filmy bands that started to be torn by the flow of the fluid during Office Hysteroscopy. | Asymptomatic |
| **Uterine Septum (n=2)** | 2 residual septa<br>1.6 cm residual septal length with a width of 2.1 cm<br>1.5 cm residual septal length with a width of 2.2 cm. | History of prior metroplasty |
| **Arcuate uterus (n=4)** | 4 cases of concave fundal depression | Asymptomatic |
| **Total missed lesions (n=13)** | | |

*2D-US; two-dimensional ultrasound, IUA; intrauterine adhesions*

The overall accuracy of 3D-US was 94.2%, and the results of the coronal view examination of the uterine cavity by 3D-US displays agreed with OH in 113 subjects: 83 with a normal uterine cavity and 30 with CLs. The overall agreement between these two methods was near-perfect (κ = 0.86, 95% CI = 0.75-0.96) (Table 3).

**Table 3: Diagnostic accuracy parameters of 3D-US in the diagnosis of cavitary lesions and level of agreement with OH**

| CL | Sensitivity | Specificity | PPV | NPV | AUC | κ value | 95% CI |
|---|---|---|---|---|---|---|---|
| **SMM** | 100 | 100 | 100 | 100 | 100 | 1.0 | 1.0-1.0 |
| **Polyps** | 81.3 | 99 | 92.9 | 97.2 | 96.7 | 0.85 | 0.70-0.99 |
| **IUA** | 66.7 | 98.3 | 50 | 99.1 | 97.5 | 0.56 | 0.11-1.0 |
| **Uterine Septum** | 100 | 100 | 100 | 100 | 100 | 1.0 | 1.0-1.0 |
| **Arcuate uterus** | 100 | 100 | 100 | 100 | 100 | 1.0 | 1.0-1.0 |
| **All** | 88.2 | 96.5 | 90.9 | 95.4 | 94.2 | 0.86 | 0.75-0.96 |

*3D-US, three-dimensional transvaginal ultrasound; CL, cavitary lesions; OH, office hysteroscopy; SMM, submucous myoma; IUA, intrauterine adhesions; AUC, accuracy; PPV, positive predictive value; NPV, negative predictive value*

For SMM, uterine septa, and arcuate uteri, 3D-US yielded 100% diagnostic accuracy and perfect agreement with OH (κ =1.00, 95% CI = 1.00-1.00)(Table 3). For uterine polyps (Figure 3), four cases were falsely diagnosed by 3D-US; three false negatives and one false positive. Nevertheless, 3D imaging exhibits a near-perfect agreement with OH (κ =0.85, 95% CI = 0.70-0.99) for diagnosis of polyps. The median (IQR) size of all polyps was 1.95 cm (1.6-2.28). 3D-US detected thirteen polyps (81.25%); their median (IQR) size was 2.1 cm (1.8-2.35). The three missed polyps were generally smaller in size (0.6, 0.8, and 1.1 cm) and were missed by 2D-US as well.

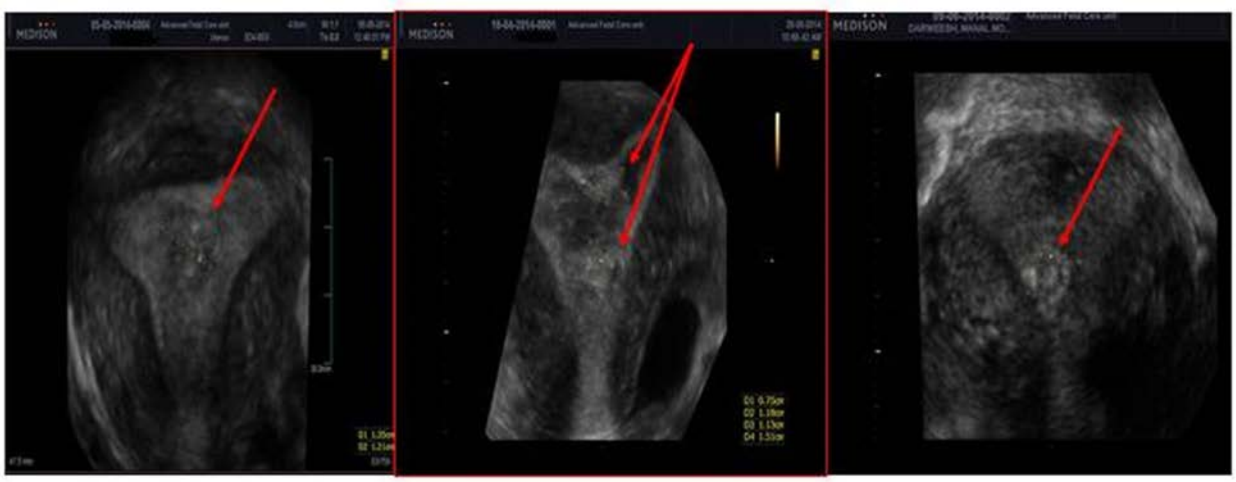


**Figure 3: Coronal plane of the uterus showing three cases of endometrial polyps.**

Three-dimensional US exhibits the lowest sensitivity and PPV in identifying intrauterine adhesions (IUA); moderate concordance with OH was reported (κ=0.56, 95% CI=0.11-1.0)(Table 3)(Figure 4). Based on the European

Society of Gynecological Endoscopy classification,[22] OH reported two moderate and one mild IUA. The latter case was missed by both 2D- and 3D-US.

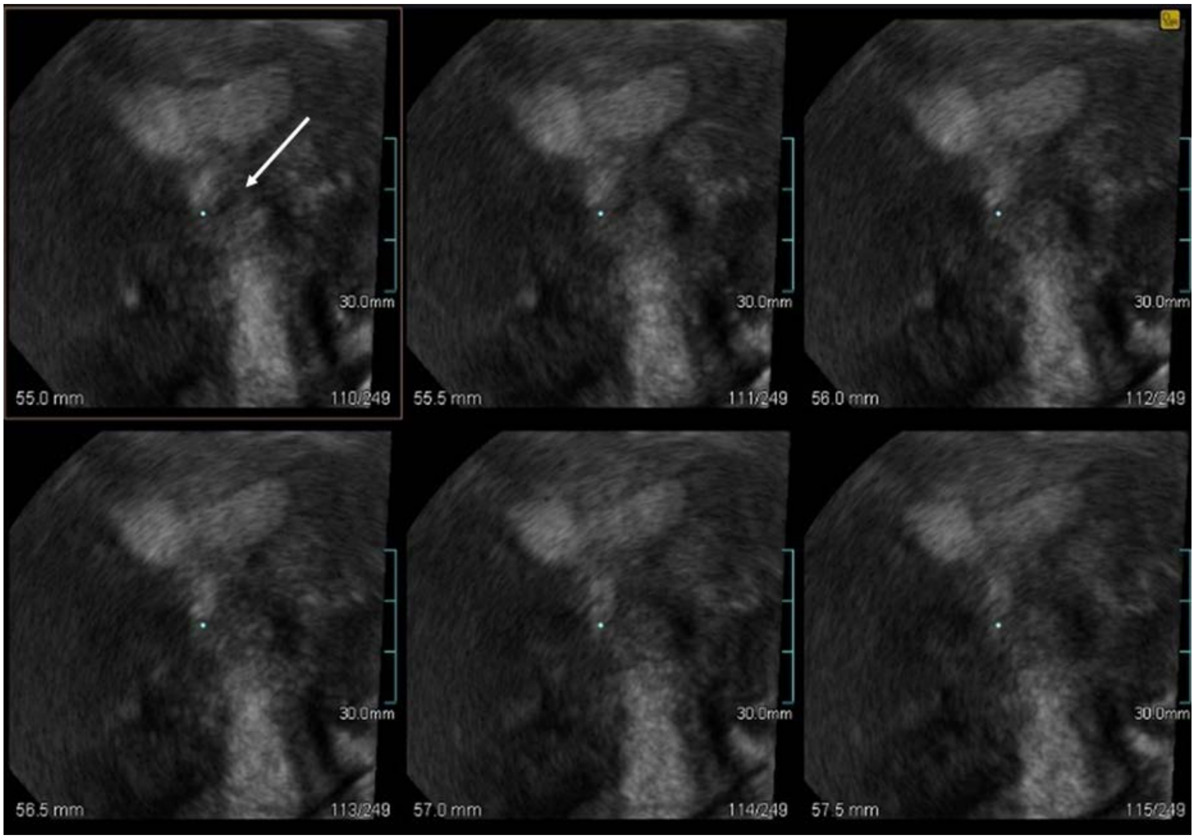


**Figure 4:Three-dimensional multi-slice view of the coronal plane of the uterus showing a case of moderate intrauterine adhesion (The Arrow)**

*Inter/Intra-observer Agreement*

In terms of inter-observer agreement, κ was 1.00 (95% CI= 1.00-1.00) for SMM, arcuate uterus and septate uterus; 0.83 (95% CI= 0.86-0.99) for polyps and 0.65 (95% CI= 0.29-1.00) for IUA. Kappa for intra-observer agreement was 1.00 (95% CI= 1.00-1.00) for SMM, polyps, arcuate uterus and septate uterus and 0.74 (95% CI= 0.39-1.00) for IUA. These results denote prefect inter/intra-observer agreement for 3D MPV and MSV in the diagnosis of SMM, polyps, arcuate uterus, and septate uterus and substantial inter/intra-observer agreement in the diagnosis of IUA.

*Prediction of CLs*

A univariate regression model was conducted to identify potential predictors of CLs (Table 4). Female age 30 years or more, irregular menstrual periods (metrorrhagia), heavy menstrual bleeding, and history of a prior endometrial procedure (hysteroscopic myomectomy, polypectomy, and metroplasty) were more common among women with CLs than women with normal uterine cavities. However, only irregular menstrual periods (aOR = 24.96, 95% CI=2.71 – 230.04, P =0.005) and a previous procedure (aOR = 9.16, 95% CI=2.13 – 39.3, P=0.002) were significant in multivariate analysis (Table 4).

**Table 4: Univariate and Multivariate regression model for testing possible predictors of the cavitary lesions**

| Predictor | Unadjusted odds ratio | CI | P value | Adjusted odds ratio* | CI | P value |
|---|---|---|---|---|---|---|
| Female age ≥ 30 years | 2.40 | 1.04 – 5.54 | 0.04 | | | |
| Infertility duration | 1.09 | 0.97 – 1.21 | 0.14 | | | |
| Body mass index | 0.93 | 0.80 – 1.09 | 0.34 | | | |
| Heavy menstrual bleeding | 5.6 | 0.98 – 32.16 | 0.05 | | | |
| Irregular menstrual periods | 18.21 | 2.1 – 157.88 | 0.008 | 24.96 | 2.71 – 230.04 | 0.005 |
| Prior IVF cycle | 1.62 | 0.71 – 3.68 | 0.25 | | | |
| Prior endometrial procedure | 8.51 | 2.1 – 34.46 | 0.003 | 9.16 | 2.13 – 39.3 | 0.002 |

** Multivariate analysis includes variables with P values < 0.2 in univariate analysis*

Based on our dataset, selective hysteroscopic evaluation of women, based on abnormal 2D-US and/or clinical predictors; irregular menstrual periods and prior endometrial procedure, would have an NPV of 92.8 % and would miss only six cases (6/34; 17.6 %). These six cases would include four arcuate uteri and two endometrial polyps (0.6 and 0.8 cm). This selective strategy would be comparable to the global screening of women using OH in diagnostic accuracy (McNemar P=0.61).

## Discussion

Adequate visualization of the endometrial cavity is required before embarking on IVF treatment. OH has been popularly assigned for this purpose however; it is not universally required before IVF treatment. Two recent well-designed RCTs demonstrated no differences in remote clinical outcomes following OH application in women enrolled for first and subsequent IVF cycles.[13,23] However, data still lacks the prevalence of CLs in women for IVF therapy, their anatomical and clinical behavior, and the fertility prospects of their uteri after surgical resection. Therefore, exploring alternatives to OH, which yield less financial burden and higher patient acceptability, is an area of research.

In this study, we evaluated the uterine cavity of women scheduled for IVF using combined 3D MPV and MSV to warrant better diagnostic performance. The 3D-US examination not only visualizes the uterine cavity abnormalities but also enables the clinician to examine the external contour and myometrial structure of the uterus.

Our findings for 3D-US diagnostic accuracy concurred with those reported by Van den Bosch et al. when examining the uterine cavity categorizing the results in their analysis as a normal or abnormal cavity. They reported sensitivity, specificity, and accuracy of 96%, 91%, and 93%, respectively.[24] Bocca et al. reported 100% detection rates for congenital anomalies, fibroids, and IUA. while 3D-US missed only one case of 38 polyps diagnosed in their cohort.[25]

We found that the highest accuracy of 3D-US was for diagnosing congenital anomalies and SMM. According to a meta-analysis reported by Saravelos et al., 3D-US is a definitive tool for diagnosing congenital anomalies.[26] Our findings for SMM are also comparable to those reached by Salim et al.[27]

Slightly higher accuracy parameters than ours were shown by studies adding saline infusion to the 3D scan. However, these reports did not include a description of the detected lesions. El-Sherbiny et al. examined 120 women in reproductive age by 3D saline infusion sonography (3D-SIS). They reported sensitivity, specificity, PPV, NPV, and overall accuracy of 94.2%, 98.5%, 98%, 95.7%, and 96.7% respectively.[28] In another study which included 180 infertile women with normal 2D-US and HSG, the accuracy parameters were; 92%, 100%, 100%, 98%, 98.8% respectively.[8]

Because of four false negatives, the overall agreement between 3D-US and OH was near-perfect. A substantial level of agreement (k=0.77; 95% confidence interval, 0.6–0.84) between 3D-SIS and OH was found in a study by Negm et al. when 146 women with recurrent implantation failure were assessed.[29]

Based on our results, the diagnostic performance of either 2D-US or 3D-US decreased when assessing small polyps one cm or less. This may be due to the absence of enhanced imaging by saline infusion in our design. A recent study concluded a similar trend of 3D-US for such polyp size.[30] Although evidence from basic science research supports that polyps may impair implantation,[11,31] clinical evidence argued that such small polyp size, not recognized by 3D-US, does not affect IVF outcome.[32-34] Analyzing the subgroup of asymptomatic IVF women in our cohort with normal 2D-US and with no clinical risk factors will show a similar prevalence (10%) of subtle, minimal lesions compared to what reported previously.[3,13] In this subpopulation, 3D-US added information only for the arcuate and septate uterus. Because the availability of 3D-US and familiarity with its use in IVF practice are not guaranteed, especially in low resource settings, we evaluated an alternative strategy that may minimize the use of OH for the detection of CLs. This strategy depends on the use of 2D-US, being more popular and readily available, along with clinical predictors that could enhance the diagnostic accuracy of this strategy.

In our study, both irregular menstrual periods (metrorrhagia) and prior endometrial traumatization were significant risk factors to have a CL. Abnormal anatomical finding, adhesions or residual septum have been described following hysteroscopic myomectomy and metroplasty, respectively.[35-37] Even though, after complete removal of the septum, adhesions, or septal remnants may occur.[38] Age was not recognized as a predictor in our cohort. Predictability of age for CLs in similar cohorts was controversial; El-mazny et al.[7] and Feghali et al.[39] found no association between a woman's age and the distribution of CLs. In contrast, Taskin et al. found that CLs were more prevalent in women aged 35 or more compared to the younger age group (45.4% vs. 27.9%, P= .002).[6]

Selective OH assessment discriminating women with abnormal 2D-US findings and/or significant clinical predictors would substantially decrease the cost per case detected to 37.4% of that cost if all women were screened with OH. This will help better allocate health resources in low resource and income settings. Moreover, most of the missed diagnoses by the selection would be arcuate uteri that have been reported not to affect implantation substantially.

The use of 3D combined displays for visualization of the uterus in IVF women as an alternative to OH presents a point of strength in this study. Another point is addressing a new clinical/imaging strategy in terms of costs and diagnostic accuracy, especially in the absence of a clear approach to screen IVF women with normal 2D-US who are clinically at risk to have a CL. However, the small sample size is a key limitation of our study. Another limitation is the lack of histopathology as a reference standard to detect chronic endometritis, a subtle endometrial abnormality that has been linked recently to recurrent implantation failure.[40]

## Conclusions

In conclusion, 3D-US provides an accurate, non-invasive alternative to OH for large cavitary lesions. It has the advantage of cost and patient convenience. This is of particular benefit in women with remote HSG as new lesions could develop over time.[41] Alternatively, a selective strategy that considers 2D-US in combination with clinical predictors may present an option to reduce the costs of the pre-IVF work up, particularly in low resource areas.

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