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ACCURACY OF TWO-DIMENSIONAL TRANSVAGINAL SONOGRAPHY AS A DIAGNOSTIC TOOL OF INTRAUTERINE PATHOLOGY IN SUB-FERTILE PATIENTS IN COMPARISON WITH DIAGNOSTIC HYSTEROSCOPY

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ABSTRACT

Background: endometrial pathologies are common in infertile women and adversely impact the reproductive outcome. **Materials and Methods**: this prospective study was conducted on 250 infertile women attending Albayda Fertility center/ Libya from January 2019 to July 2020. The diagnostic accuracy values of two-dimensional transvaginal sonography (2D TVS) in detection of intra-uterine lesions compared with a diagnostic hysteroscopy (DH) by receiver operating characteristic (ROC) curve analysis. **Results**: 2-D TVS had 70.2% sensitivity, 78.9% specificity, 70.9% positive predictive value (PPV), and 78% negative predictive value (NPV) for detection of endometrial pathology. Area Under the Receiver Operative Curve (AUROC) was; 0.745 (95% CI 0.681−0.810) for the accuracy of TVS compared to DH. **Conclusion**: transvaginal sonography had an acceptable accuracy for detection of uterine pathologies in infertile patients in comparison with diagnostic hysteroscope. Diagnostic hysteroscopy should be considered as an initial infertility workup before infertility treatment of patients with abnormal TVS findings.

KEYWORDS: Infertility, intrauterine pathology, transvaginal sonography, diagnostic hysteroscope, AUROC.

INTRODUCTION

The uterine cavity is the site of embryo implantation and the final site of embryo to grow. For implantation to succeed, the endometrium undergone complex cellular and morphological changes that underlie the functional transition from pre-receptive to receptive state.[1] From both natural cycles and in-vitro fertilization-embryo transfer (IVF-ET) techniques, the probability of successful embryo implantation rate is only approximately 30%.[2] The high rate of implantation failure is undoubtedly affected by different embryonic and/or endometrial factors. Embryos with chromosomal abnormalities[3] can be a cause of failed pregnancy. Hydrosalpinx was also found to be associated with a reduced chance of implantation after IVF/ET and an increased risk of pregnancy loss[4] acting either directly through its embryotoxic effect or through its adverse effect on the receptivity of the endometrium. Lifestyle and other causes, such as immunological factors, infections, hereditary and acquired thrombophilia could also be contributing factors for implantation failure.[5]

Up to 25-50% of infertile patients were found to have intrauterine structural lesions.[6] These abnormalities of the uterine cavity such as endometrial polyp, submucous myoma, intrauterine adhesion (IUA) and endometritis adversely affect reproductive outcomes.[7,8] They could result in infertility or miscarriage by interfering successful embryo implantation within the uterus by disrupting the uterine lining or by inhibiting sperm movement. Many studies reported that surgical treatment of these lesions, allows normal endometrial development and markedly improves the reproductive outcomes.[9-12] This could support the theory that achievement of normal endometrial receptivity might improve fertility. Therefore, accurate diagnosis of any endometrial pathology in the infertile patient is an important step during infertility work-up, either during initial evaluation or when any assisted reproductive technology (ART) procedure is scheduled in order to enhance the reproductive outcome.[8,13]

Two-dimensional transvaginal sonography (2D-TVS), hysterosalpingography (HSG), and hysteroscopy have been used to assess the uterine cavity; each has their own pros and cons. TVS is generally considered the first, non-invasive procedure for assessment of intrauterine lesions.[14] However, several intrauterine pathologies cannot be satisfactorily identified on two-dimensional transvaginal sonography.[15]

Hysteroscopy is currently considered the gold standard technique for the diagnosis of intrauterine pathologies.[16] As, it allows magnification and direct visualization of the intrauterine cavity as well as the treatment of many detected pathologies, making it more sensitive than the other diagnostic techniques; transvaginal sonography (TVS), hysterosalpingography (HSG) and saline infusion/gel instillation sonography (SIS/GIS).[17-20] However, TVS and HSG are still the most common first-line diagnostic procedures for evaluation of uterine cavity and tubal patency and hysteroscopy only indicated if pathology was suspected or detected by TVS or HSG.

The aim

Different types of uterine lesions (polys, fibroma, endometritis, congenital anomalies and acquired disease) can play an important role in female reproductive failures and various methods are used to diagnose these pathologies. This study aimed to compare the diagnostic values of 2-dimentional transvaginal ultrasonography with diagnostic hysteroscopy in detecting uterine cavity abnormalities in infertile women.

MATERIALS AND METHOD

The present study was a prospective comparative study conducted after obtaining the ethical approval from the Al-Mukhtar Committee for Bio-safety and Bioethics (MCBB) reference number (NBC: 007. H. 23. 6). All couples signed an informed consent form for participation in the study. Participants involved in this study were infertile women aged between 18 and 42 years recruited at Albayda Fertility Centre (afc.med.ly), Libya, between January 2019 and July 2020.

Patients with primary or secondary subfertility with different infertility aetiologies and with or without previous IUI and/or IVF trails and those with recurrent miscarriage and recurrent implantation failure (RIF) were eligible for participation in this study. Women on hormonal medications for at last 3 months and those with acute vaginal and cervical infection or bleeding for unknown causes were not included in the study.

The following data were obtained: age, obstetric, gynecologic and medical history, medications, surgical history, last menstrual period, preoperative and postoperative diagnoses, and operative findings.

Two-dimensional transvaginal ultrasound scan was performed for all the patients before they scheduled for the diagnostic hysteroscopy. The real-time ultrasound examination was done by a qualified physician on day two and repeated on day 8 to 10 of the menstrual cycle. High resolution two-dimensional ultrasound scan machine of either (Sonix ultrasound machines/BK ultrasound) or (SG health care Q40) was used after the patient has emptied her bladder. The sagittal view of uterus (from the fundus to the cervix) was first evaluated, then the probe was rotated slowly anticlockwise to visualize the transverse view of uterus. During the examinations, the uterine wall and cavity were meticulously observed by sliding, rotating, and tilting the transvaginal probe. This enables the clinician to determine the appearance and symmetry of the endometrium, myometrium, and junctional zone, for discovering any morphologic abnormalities such as Mullerian duct anomalies, fibroids, polyps, etc. Normal ultrasound findings: hyperechoic line at the middle of the uterus along with a homogeneous endometrial lining and district endometrial-myometrial margin (clear triple lie). Abnormal ultrasonic findings: heterogeneous echogenicity, polyp, presence of fluid in the uterine cavity or if the endometrium was divided in two areas; which suggest presence of uterine septum. Both ovaries were examined for any pathology and to evaluate the antral follicular count, the cul-de-sac also evaluated for the presence of any masses or fluid collection.

A diagnostic hysteroscopy (DH) was performed in Operation Theater under anesthesia (saddle block or spinal) in the proliferative phase for the detection and localization of any intra-uterine lesions. A high-intensity cold light source and fiberoptic cable were used to clarify the uterine cavity. The patient was placed in the lithotomy position and a pelvic examination was done to detect the size and direction of the uterus. After application of the Sims's speculum and disinfection of the cervix, a tenaculum was used to grasp the cervix. An expert gynecologist performed the DH by using a rigid hysteroscope (30 optic telescopes, KARL STORZ GmbH) & Co., Germany) assembled in a 6 mm diameter diagnostic sheath with an atraumatic tip. Normal saline was used as distending media for the procedure, and was delivered by a simple drip from a bag suspended 1 meter above the examination table.

At the entrance of uterine cavity, a through systematic inspection was done that included the uterine cornea, tubal ostia, uterine fundus, anterior, posterior and lateral uterine walls. During withdrawal of the instrument, the uterine cavity and endocervical canal were re-evaluated to identify any surface irregularity or other local pathology. The criteria taken for normal hysteroscopy were; normal uterine cavity (regular in shape and contour, no myoma, polyp, synechia, septum or clinical evidence of endometritis), and normal bilateral ostia. Any abnormality of uterine cavity, endometrium, and uterine ostia were noted and recorded on a special data form. Hysteroscopic examination findings were categorized as: normal, endometrial polyp, adhesions, endometritis, septum.

Corrective measures such as polypectomy, metroplasty, proximal ostia canalization or release of cervical canal stricture were taken accordingly. Endometrial biopsy was taken when indicted and sent for histopathology. At the end of the procedure, ultrasound scan was done to assess the presences of the normal saline in the Douglas pouch which indicates that at least one Fallopian tube was patent.

The patients were kept under observation for a minimum of two hours for full recovery and to assess any possible side effects and complications. Those women with suspected endometritis underwent an empirical antibiotic treatment with oral doxycycline and metronidazole for both couples and vaginal metronidazole.

Pregnancy that occurred spontaneously or following ovulation induction during the six months follow up period was recoded.

Statistical analysis

Statistical analysis was done using Statistical Package for Social Sciences (SPSS) version 26 (IBM). Continuous data were statistically described in terms of mean± SD (standard deviation) and categorical variables were presented in numbers and percentages (%). Qualitative variables were compared using Chi-square test/Fisher's exact test. Standard 2 × 2 tables were used to calculate sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive/negative likelihood ratio (+LR/−LR), and accuracy with 95% confidence intervals (CI) for ultrasound compared to diagnostic hysteroscopy for the diagnosis of intrauterine pathology in sub-fertile patients. Area Under Receiver Operating Characteristic curve analysis (AUROC)[21] was used to compare the diagnostic accuracy values of 2-DTVS in detection of uterine pathologies to that of DH. P-value of <0.05 was considered statistically significant.

RESULTS

During the study period, the eligible 250 infertile women were evaluated with both 2-Dimensional trans-vaginal ultrasound scan (2-D TVS) and diagnostic hysteroscopy (DH) and both procedures were completed successfully. No complications recorded during or after the procedures.

The age of the participants was ranged between 20 and 42 years and the mean and standard deviation of their BMI was 28.6 (5). Duration of infertility ranged between one and seventeen years and with a mean (SD) of 5.2 (3) years (Table 1). More than half of the couples (60%) were presented with primary infertility.

Table 1: Demographic data of the participants.

variable	Mean (standard deviation)	Range
Age (years)	33 (5.2) years	20- 42 years
BMI	28.6 (5) kg/m^2	15-43 kg/m^2
Infertility duration	5.2 (3) years	1-17 years

Figure 1 shows the causes of infertility in the included couples; female-related causes of infertility was reported in nearly half (46%) of the included cases, male causes of infertility was encountered in 16.9%. Combined male and female problems were responsible for nearly a quarter of the cases and no cause could be identified in 14% of the cases.

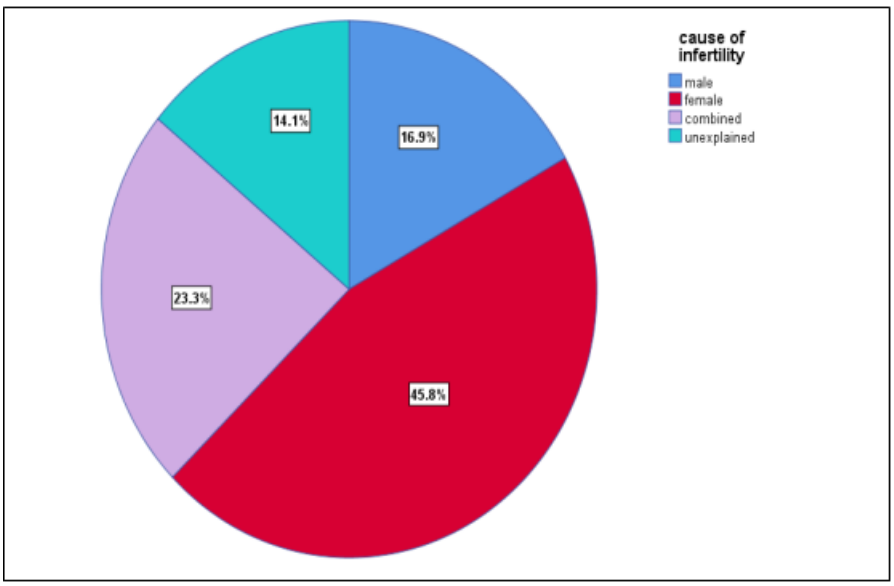

Figure 1: causes of infertility.

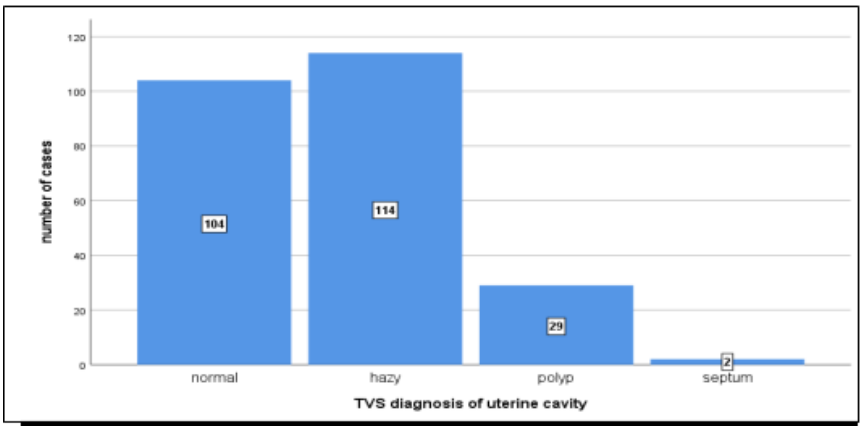

Figure 2: 2-D TVS assessment of uterine cavity of infertile women.

In the TVS examination, 104 (41.6%) cases were with normally looking endometrium and 146 (58.4%) had abnormal findings. 114 (45.6%) were having hazy endometrium (no specific abnormality could be identified), 29 (11.6%) cases were with polyp lesions, and only 2 (0.8%) patients were having septate and arcuate uterus (Figure 2).

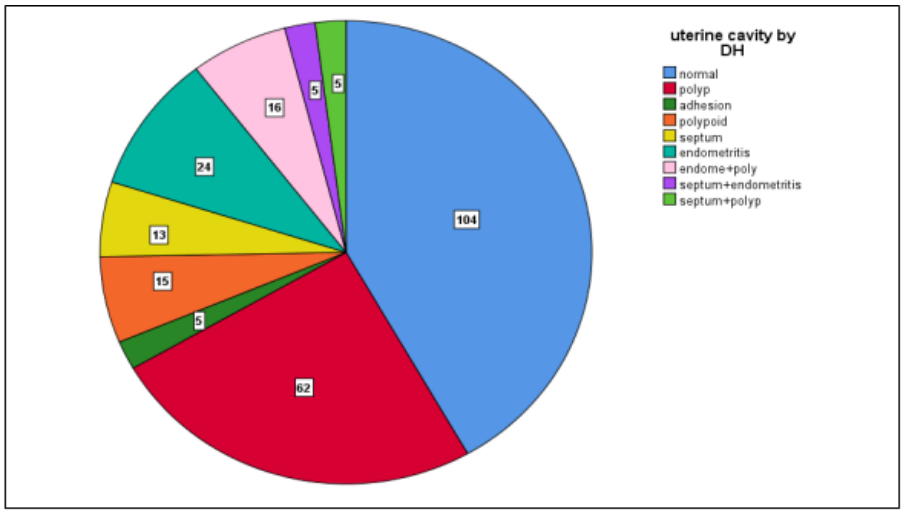

Figure 3: Endometrial cavity assessment by diagnostic hysteroscope.

Figure 3 demonstrated, the normal and abnormal findings found during the diagnostic hysteroscope; 146 (58.4%) had pathologic findings that included 62 (24.8%) single polyp lesions, 24 (9.6%) showed clinical evidence of endometritis, 4 (1.6%) Asherman's syndrome, 15 (6%) polypoid endometrium, 12 (4.8%) septate and arcuate uterus and 27 (10.8%) had more than one pathology.

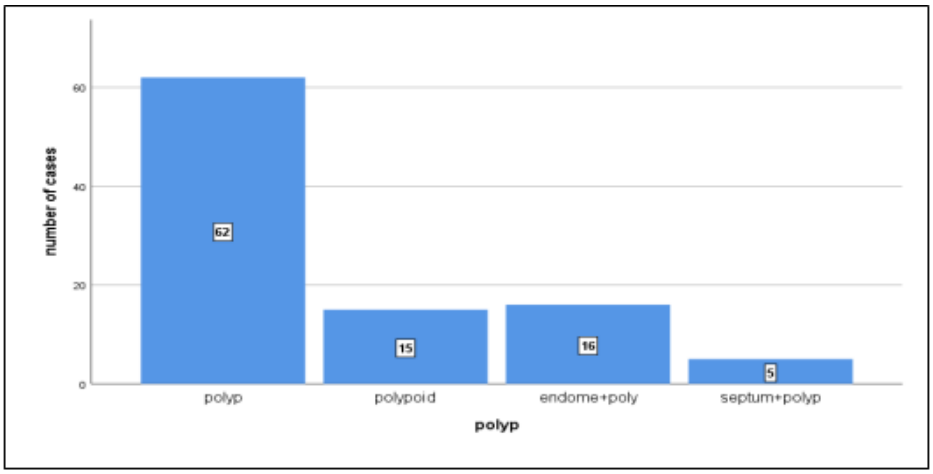

Figure 4: Hysteroscopic diagnosis of uterine polyp.

Endometrial polyp was the most common pathology diagnosed by hysteroscopy (98 cases); 62 was single polyp, 15 was multiple polypi, endometritis and poly were found in 16 cases and in 5 cases there was uterine septum and polyp (Figure 4). There was a significant difference between TVS and DH in the diagnosis of uterine polyp (38.6% Vs 11.6% respectively and with a Fishers Exact test; P<0.0001).

Considering hysteroscope as gold standard for uterine cavity assessment since it enables magnification and direct visualization of the uterine cavity[22], the diagnostic accuracy of 2-D TVS was compared to that of hysteroscopy. Using Chi-square test, DH was significantly more accurate than USS in the diagnosis of endometrial poly and uterine septum with Fishers-Exact test of (0.0001 and 0.003 respectively).

2-D TVS had 70.2% sensitivity, 78.9% specificity, 70.9% positive predictive value (PPV), and 78% negative predictive value (NPV) for detection of endometrial pathology.

Table 4: Diagnostic accuracy parameters of 2-D TVS compared with DH for diagnosis of intra-uterine pathologies in sub-fertile patients.

Parameter	Result
True Positive	73
True Negative	112
False Positive	30
False Negative	31
Sensitivity (95% CI)	70.19% (60.43-78.77%)
Specificity (95% CI)	78.87% (71.23-85.27%)
Positive Predictive Value (95% CI)	70.87% (61.10-79.41%)
Negative Predictive Value (95% CI)	78.32% (70.66-84.77%)
Positive Likelihood Ratio (95% CI)	3.32 (2.36-4.68)
Negative Likelihood Ratio (95% CI)	0.38 (0.28-0.51)
Accuracy (95% CI)	75.20% (69.32-80.47%)

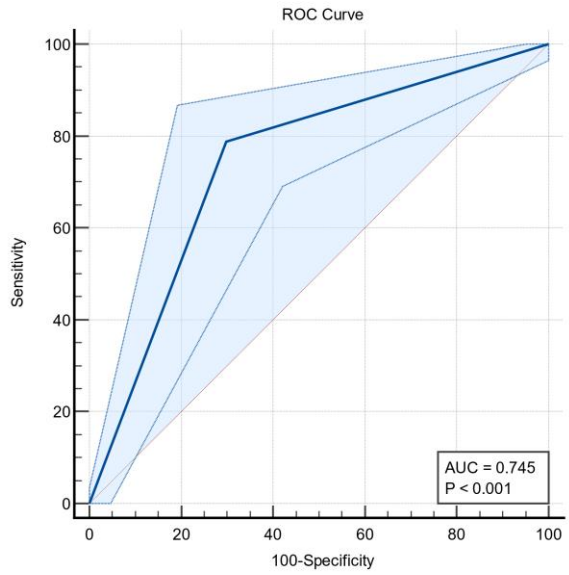

Figure 5: Area under ROC curve (AUC=0.74) for accuracy of 2-D TVS in compare to DH.

As shown in Figure 5; Area Under the Receiver Operative Curve (AUROC) was acceptable; 0.745 (95% CI 0.681−0.810) for the accuracy of TVS compared to DH.[21]

Endometrial biopsy done and sent for histopathological examination, polypectomy, metroplasty done for indicated cases during the hysteroscopic examination. Also, proximal ostia canalization and release of cervical stricture were performed when needed.

During a period of six months follow-up after hysteroscopy, 32 (12.8%) women got pregnant either spontaneously or after ovulation induction.

DISCUSSION

Intrauterine abnormalities are common findings in infertile women and adversely affect the reproductive outcomes.[6] Therefore, the accurate diagnosis of any intrauterine pathology is an essential step in the assessment of the infertile women. Different diagnostic

modalities used for assessment of uterine pathologies. In the current study, the accuracy of 2-dimentional transvaginal sonography was assessed in comparison with diagnostic hysteroscope that assumed to be a gold standard procedure for the diagnosis of intrauterine lesions.[16]

The diagnostic value of 2- dimensional transvaginal sonography (2-TVU) and diagnostic hysteroscopy (DH) for intrauterine pathologies were examined in this study in 250 infertile women. Generally, hysteroscopy seems to be better than TVS for most of the uterine pathologies evaluated, this result was in agreement with a study conducted on a pre- and post-menopausal woman with abnormal uterine bleeding.[23] With regard to infertility, a previous study reported intrauterine abnormalities detected during hysteroscopy in 15.1% sub-fertile women, in whom 2D-TVS was negative for intrauterine pathology.[24] This result supports the recommendation of using hysteroscopy for infertile women before ART especially for those with prior failed ART even with normal HSG and/or TVS.[6]

A previous study[16] used an office hysteroscope detected intrauterine lesion in only 15% of their infertile women. In contrast, in the present study, both TVS and DH results were in agreement in identifying abnormally looking endometrium; the prevalence was 58.4%. However, TVS could not identify the nature of the pathology in almost all cases with abnormally looking endometrium (hazy endometrium were found in 69% of cases with abnormally looking endometrium). Whereas, the magnification and direct visualization of the uterine cavity during the hysteroscopic procedure allowed detailed evaluation of the uterine cavity and enable the gynecologist to identify the nature of pathology. Another, advantages of the DH are the targeted biopsy sampling of any debatable lesion and also enable performing some interventions to improve fertility.[9,10]

Endometrial polyp; focal hyperplastic growth of endometrial glands and stroma, could be single or multiple lesions. In a review article, the prevalence of endometrial polyp mentioned to be ranged from 7.8% to 34.9%.[25] Endometrial polyp could be diagnosed with the use of high-resolution transvaginal ultrasound scan and appears as a hyperechoic lesion. In the current study, 29 (11.6%) cases were diagnosed as having endometrial polyp during TV scan. However, with the use of DH, 99 (39.6%) were having endometrial polyp. Endometrial polyps were the most common hysteroscopic abnormalities in our infertile patients and this was reported before.[26,27] Seventy-eight women were diagnosed to have endometrial polyp only; either single polyp or multiple polyps (63 and 15 respectively), 16 cases were having endometritis and polyp and both polyp and septum was found in 5 women.

There was a significant difference between TVS and DH in the diagnosis of uterine polyp (P<0.0001), this reflects the diagnostic accuracy of hysteroscopy over the ultrasound scan in discovery of endometrial polyp. Moreover, polypectomy was performed at the same setting during the hysteroscopic procedure, so hysteroscopy has both; diagnostic and therapeutic benefits. It was recommended to do hysteroscopic polypectomy as a therapy for infertile women.[28]

Chronic endometritis could not be identified at transvaginal sonography and only be suspected in complicated cases like intra-uterine adhesions or fluid collection in the uterine cavity (pyometria or haematometria).[29] Hysteroscopy is considered as the best technique to identify chronic endometritis through direct visualization of the endometrial cavity.[30] Chronic endometritis is characterized by the presence of red endometrium flushed with a white central point, either localized or scattered throughout the uterine cavity.[30] Chronic endometritis may also appear as friable whitish plaques.[31]

In the present study; out of 250 infertile women, forty-five cases (18 %) were found to have hysteroscopic morphological features of endometritis (the result was confirmed by histopathology in almost all the cases). Our result was a slightly higher than a prevalence of 15% of hystroscopically detected chronic endometritis found in infertile women.[24] In contradicts, endometritis prevalence in the current study was much lower than what was reported recently by[32] that showed, endometritis prevalence (51.7%) in infertile cases with unexplained infertility and (28.6%) in those with definite infertility causes. Endometritis adversely affects endometrial receptivity and this could explain the high prevalence of endometritis in infertile patients and those with implantation failure.[33] It was mentioned that, empirical antibiotic therapy was found to improve the hysteroscopic endometrial inflammatory features in more than 80% of cases.[24] Another study reported a clinical pregnancy rate of 61.3% after antibiotic treatment of infertile women with chronic endometritis.[32]

The cases of chronic endometritis (CE) in this study were subdivided into groups; endometritis alone in 24 cases, endometritis and endometrial polyp reported in 16 cases and six cases with endometritis and uterine septum. The coexistence of endometritis and endometrial polyp was reported before.[34] A recent study hypothesized that intrauterine abnormalities such as polyp induce endometrial inflammation, leading to chronic endometritis and they reported a high pregnancy rate after hysteroscopic surgery even without antibiotic therapy.[35] The same study[35] reported a high co-accordance of CE and uterine polyp and low co-occurrence of CE and septa and this was similar to our finding.

There was a great discrepancy between TVS and DH in the diagnosis of septate uterus [2 (0.8%) vs. 12 (4.8%) respectively] with Fishers Exact test (0.003). This result

was in contrast to the finding of[20] who reported an agreement between TVS and DH in the diagnosis of septate uterus. A study[36] conducted on infertile women reported a prevalence of uterine septa of 2% using DH and that was lower than half of our prevalence (4.8%).

In this study, the accuracy of TVS compared with hysteroscopy in the diagnosis of intrauterine lesion in infertile women was evaluated. In the present study, TVS sensitivity, specificity, PPV, and NPV were 70.19%, 78.87% %, 70.87%, and 78.32%, respectively. A higher specificity (100%) but a lower sensitivity (41.7%) was concluded by [6] that compared TVS and office hysteroscopy (OH) for assessment of uterine cavity pathologies in infertile patients scheduled for ART. Another study reported that the TVS sensitivity, specificity in diagnosis of uterine cavity pathology in infertile women in comparison to hysteroscopy as follow: PPV, and NPV were 91%, 83%, 85.4%, and 90%, respectively.[37] A study conducted on patients with recurrent implantation failure and recurrent abortion reported that DH was significantly more sensitive than 2D TVS for detection of uterine pathologies.[20] TVS is not as sensitive as DH hysteroscopy in detecting intrauterine pathologies.[38] Many studies therefore, recommend to do DH in infertile patients as an initial step before the treatment cycle even in case of normal hysterosalpingogram and/or TVS. However, the value of DH as a routine assessment of infertile women is still a debatable issue.

Area under the Receiver–operating characteristics curve (AUROC) was almost acceptable 0.745 (95% CI 0.681−0.810) for the accuracy [21] of two-dimensional trans-vaginal sonography compared with diagnostic hysteroscopy for detection of intrauterine pathologies in sub fertile patients. A study[20] conducted on patients with repeated implantation failures or recurrent pregnancy loss for detection of uterine pathologies reported that the area under the ROC curve (AUROC) was 0.71 for the accuracy of TVS compared to OH, a result lower than ours. The difference between our result and[20] could be due to different inclusion criteria of the participants.

From the above mentioned, in spite of the acceptable accuracy TV ultrasound, their predictive value remains limited and the findings that are suspicious in ultrasound should be confirmed by hysteroscopy. During DH, the uterine pathology could be identified, a directed biopsy could be done and also appropriate corrections could be performed at the same setting. All these advantages make the hysteroscopy a gold standard technique in the diagnosis and management of infertile women especially for those with suspected uterine pathology during TVS assessment of infertile women before scheduling them for infertility management. Another good advantage for infertile couples; is the occurrence of spontaneous pregnancy following hysteroscopy.[26,35]

During a period of 6 months of post-hysteroscopy follow up; 32 (12.8%) women got pregnant either spontaneously or after ovulation induction only. A study conducted before in our center[26] reported a lower pregnancy rate (6.1%) within three months of follow up and this lower pregnancy rate could be explained by a shorter period of follow up. Endometrial injury by fluid irrigation and mechanical manipulation of the endometrium may improve the endometrial receptivity as mentioned.[39,40] Fluid current may also help to release mild tubal blockage and just passing the cervical canal by the hysteroscope may help to release cervical stricture, these may also improve the pregnancy rate.

CONCLUSION

TVS had an acceptable accuracy for detection of uterine pathologies in infertile patients. DH should be considered as an initial infertility workup before infertility treatment of patients with abnormal TVS findings.

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