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## Original Research Article

# Prediction of chronic endometritis using 2D and 3D transvaginal ultrasound examination in infertile women

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### ABSTRACT

**Background:** Chronic endometritis is a pathology of continuous and hidden inflammatory process characterized by the infiltration of plasma cells into the endometrial stroma. Transvaginal bi-dimensional ultrasonography is in need to be evaluated in prediction of chronic endometritis in women with delayed pregnancy or infertility as a non-invasive, cheap, acceptable, and safe tool of diagnosis. Previously, 3D ultrasonography had been described as a novel for diagnosis of chronic endometritis and correlation of the images with hysteroscopic view results. Objectives were to predict the presence of chronic endometritis in infertile women during their reproductive age through examination of the uterine cavity by 2D and 3D transvaginal sonography to elicit proposed ultrasonographic signs of endometritis.

**Methods:** This observational prospective study took place at Shatby university hospital, Alexandria university and was done on two hundred infertile women. Women were assigned for ultrasonographic evaluation as a part of pre-treatment assessment. Detailed history was taken from all the patients included in the study. General examination and routine laboratory investigations were done according to hospital protocol. All patients were asked to do ultrasound examination immediately postmenstrual and at the time of ovulation. We used 2D transvaginal ultrasound to predict chronic endometritis, we searched for 1) presence of persistent endometrial focal or diffuse thickening postmenstrual, 2) presence of focal echogenic foci in the triple line endometrium during ovulation. The 3D ultrasonography was done as confirmatory examination. Office hysteroscopy as the main method for diagnosis of endometritis was performed to all patients either after menses if the first sign was detected or at the time of ovulation if the second sign was detected.

**Results:** The combination of persistent endometrial shreds and/or endometrial focal thickening or echogenicity can significantly predict presence of endometritis as the sensitivity and specificity of the combination were 94.90 and 81.37, respectively.

**Conclusions:** Bi-dimensional ultrasonography done to infertile women at 2 phases of the menstrual period can predict the presence of chronic endometritis as a subtle cause of infertility and might be an indication for hysteroscopic evaluation for these patients.

**Keywords:** 2D, 3D, Endometritis, Prediction, Transvaginal ultrasonography,

### INTRODUCTION

Chronic endometritis (CE) is a pathology of a continuous and hidden inflammatory process characterized by the infiltration of plasma cells into the endometrial stroma.<sup>1</sup> It is considered a silent lesion that cannot be detected clinically and has vague symptoms of continuous lower abdominal pain and irregular spotting during the menstrual cycle. Therefore its prevalence in the female

population is difficult to be estimated.<sup>2,3</sup> Among many cases of infertility, chronic endometritis is associated.<sup>4-6</sup> It was proved that many women suffering from recurrent implantation failure were diagnosed with chronic endometritis with minimal or absent signs of infection.<sup>7,8</sup>

Chronic endometritis is diagnosed by histopathology, hysteroscopic visualization, or bacterial culture. Hysteroscopy has a 40% sensitivity for detection of CE.

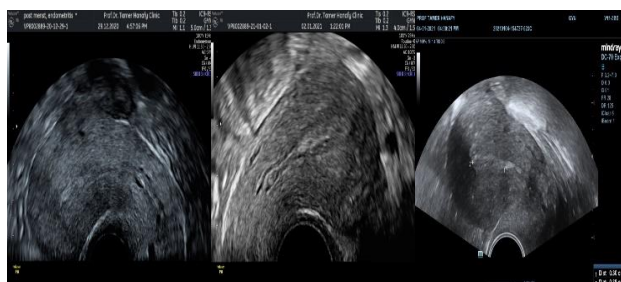
The diagnostic criteria include visualizing mucosal edema, endometrial hyperemia, and the presence of micro polyps.<sup>9,10</sup> As a non-invasive, cheap, acceptable, and safe tool of diagnosis, transvaginal bi-dimensional ultrasonography needs to be evaluated in prediction of chronic endometritis in women with delayed pregnancy or infertility. Previously, 3D ultrasonography had been described as a novel for diagnosis of chronic endometritis and correlation of the images with hysteroscopic view results.<sup>11</sup>

## METHODS

Two hundred patients were recruited in this study. All women were infertile and were assigned to do office hysteroscopy for infertility, abnormal uterine bleeding, and dysmenorrhea. Women were referred to the diagnostic imaging and interventional radiology department of Alexandria main and Shatby university hospitals as part of the pretreatment assessment protocol. All women were subjected to detailed history taking from all patients including age, duration of infertility, LMP and the regularity of menstruation, medical and surgical history, weight and BMI, detailed history of trials of assisted reproduction if present.

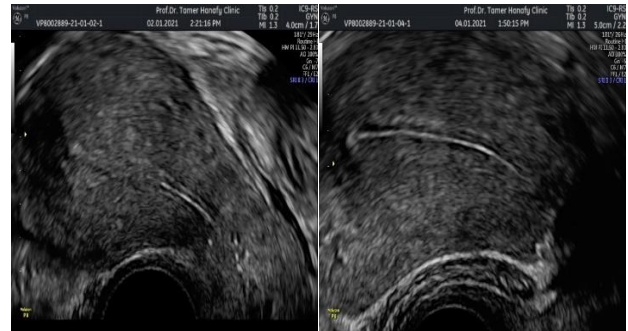
Also, general examination and routine laboratory investigations were done according to our hospital's protocol which includes CBC, FBS, PRL, TSH, AMH, FSH, E2, semen analysis. The USG evaluation of all patients was done either immediately after cessation of the menses (cycle day 5-8) or midcycle (cycle day 14-20) in patients with regular menstrual cycles. We used the Voluson P8 General Electric healthcare 2D/3D new version ultrasound device. TV ultrasonographic examination by the same sonographer (author) was done in both coronal and sagittal views. Transvaginal bi-dimensional ultrasound modality was used to confirm the presence of one or both new USG signs:

The presence of persistent endometrial focal or diffuse thickening postmenstrual. It resembles echogenic remnants of menstrual blood or tissues after the end of the menses (Figure 1).



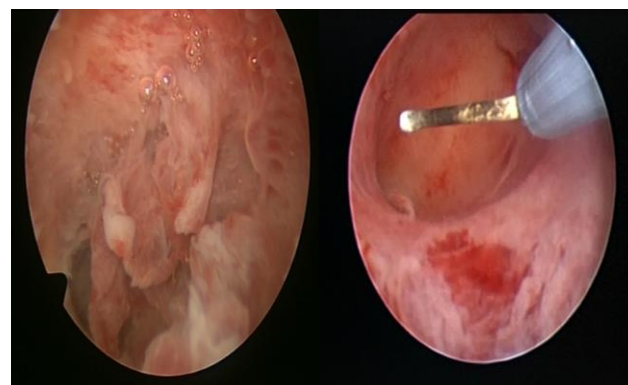
**Figure 1: Remnants of menstrual shreds.**

Presence of focal echogenic foci or minimal thickening in triple line endometrium during the ovulatory and early postovulatory phase (Figure 2).



**Figure 2: Heterogenous endometrium.**

The use of 3D was done as a confirmatory of the findings documented by 2D USG.



**Figure 3: 2 hysteroscopic findings of 2 cases of chronic endometritis.**

Following imaging, office hysteroscopy was done either immediately or in the following few days after USG examination to correlate both ultrasonographic signs of chronic endometritis with the hysteroscopic findings. We used The Karl Storz-Endoscope CAMPO TROPHYSCOPE® with a diameter of only 2.9 mm that allows an atraumatic primary approach and neither sterilization of the vagina or the cervix nor insertion of speculum or use of volsellum to grasp the cervical lip were done. As well, office hysteroscopy was done by the same physician. Chronic endometritis was diagnosed if one or more of the following hysteroscopic signs were found: endometrial hyperemia, micropolyp, inflammatory polyp, and endometrial glands ostia hyperemia.<sup>1-3</sup> Normal saline 0.9% was used as distension media.

All cases were treated by diclofenac sodium intramuscular injection (75 mg/ 3 ml) prior to the procedure and were given Azithromycin® 500 mg once daily for 5 days after the hysteroscopy. In cases where no typical hysteroscopic signs of endometritis were found we had to take endometrial biopsy by a grasper during the procedure and biopsy was sent for histopathologic examination to confirm the presence of plasma cells in the biopsy as a pathologic marker for endometritis.

### Statistical analysis

Statistical analyses were performed using Data fed to the computer and analyzed using IBM SPSS software package version 20.0. 2 Armonk, NY: IBM Corp 34 Comparisons between categorical variables were assessed using Chi-square test. Receiver operating characteristic curve (ROC) was used to determine the diagnostic performance of the markers, area more than 50% gives acceptable performance and area about 100% is the best performance for the test. Significance of the obtained results was judged the 5% level.

### RESULTS

The mean age of the study participants was 29.9±5.4. Most of females (80%) were nulliparas. The mean of the BMI of the study participants was 26.5±4. About two thirds of females (67%) had no persistent endometrial shreds, 56% of them had no US focal thickening or echogenicity and 51% had no hysteroscopic findings of endometritis. Plasma cells in in endometrial biopsy were found in 14.7% of females.

As shown in Table 1, persistent endometrial shreds and US focal thickening were used as assessment of presence of endometritis compared to hysteroscopy. The accuracy of persistent endometrial shreds and US focal thickening was 75 and 84, respectively. The differences between both methods and hysteroscopic findings were significant (<0.001 each).

**Table 1: Distribution of the studied cases according to different parameters (n=200).**

	No. (%)
<b>Age (years)</b>	
Mean±SD	29.9±5.4
Median (min.-max.)	30 (19-40)
<b>Parity</b>	
Nullipara	160 (80%)
Multipara	40 (20%)
Mean±SD	0.2±0.5
Median (min.-max.)	0 (0-2)
<b>BMI (kg/m<sup>2</sup>)</b>	
Mean±SD	26.5±4
Median (min.-max.)	25 (21-36)
<b>Persistent endometrial shreds</b>	
Absent	134 (67%)
Present	66 (33%)
<b>US focal thickening or echogenicity</b>	
Absent	112 (56%)
Present	88 (44%)
<b>Hysteroscopic findings of endometritis</b>	
Absent	102 (51%)
Present	98 (49%)
<b>Plasma cells in endometrial biopsy</b>	
Not done	164 (82%)
Absent	7 (3.5%)
Present	29 (14.5%)

**Table 2: Agreement (sensitivity, specificity and accuracy) for persistent endometrial shreds and US focal thickening (n=200).**

Hysteroscopic findings of endometritis					Sensitivity	Specificity	PPV	NPV	Accuracy
Absent (n=102)		Present (n=98)							
No.	%	No.	%						
Persistent endometrial shreds									
Absent	93	91.2	41	41.8	58.16	91.18	86.36	69.40	75.0
Present	9	8.8	57	58.2					
χ <sup>2</sup> (p)	55.030* (<0.001*)								
US focal thickening									
Absent	91	89.2	21	21.4	78.57	89.22	87.50	81.25	84.0
Present	11	10.8	77	78.6					
γ <sup>2</sup> (p)	93.207* (<0.001*)								

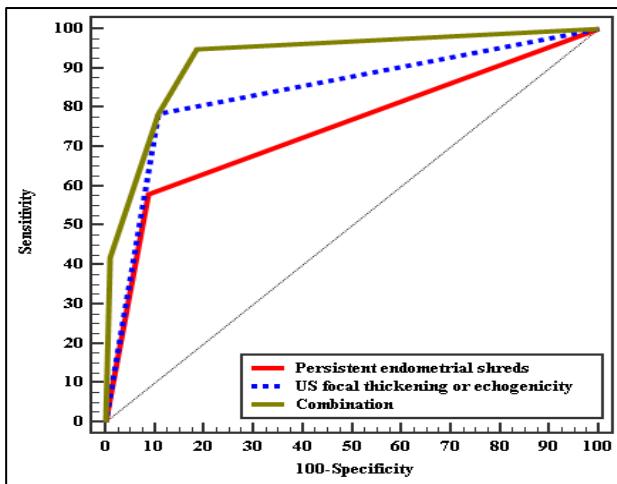
$\chi^2$ : Chi square test, PPV: Positive predictive value, NPV: Negative predictive value, p: p value for association between different categories, \*: Statistically significant at  $p \leq 0.05$

**Table 3: Agreement (sensitivity, specificity) for persistent endometrial shreds and US focal thickening to predict findings of endometritis.**

	AUC	P value	95% C.I	Cut off#	Sensitivity	Specificity	PPV	NPV
<b>Persistent endometrial shreds</b>	0.747	<0.001*	0.677-0.817	>0#	58.16	91.18	86.4	69.4
<b>US focal thickening</b>	0.839	<0.001*	0.780-0.898	>0#	78.57	89.22	87.5	81.2
<b>Combination</b>	0.922	<0.001*	0.883-0.961	>0.06#	94.90	81.37	83.0	94.3

AUC: Area Under a Curve, P value: Probability value, CI: Confidence intervals, NPV: Negative predictive value, PPV: Positive predictive value, \*: Statistically significant at  $p \leq 0.05$ , #Cut off was choose according to Youden index

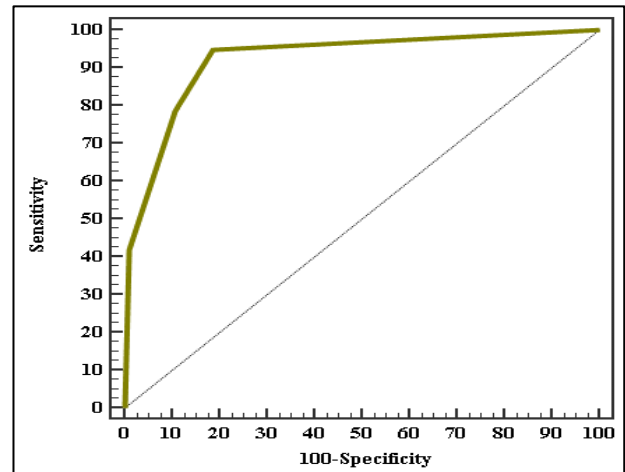
Agreement of (sensitivity, specificity and accuracy) for persistent endometrial shreds and US focal thickening roc curve analysis showed that persistent endometrial shreds and US focal thickening (Tables 2 and 3) can significantly predict findings of endometritis as diagnostic accuracy (AUC=0.747 and 0.839 (95% CI), respectively,  $p<0.001$ ). The cut off points which had the highest sensitivity and specificity of both were  $>0$  (sensitivity = 58.16 and 78.57 and specificity = 91.18 and 89.22, respectively).



**Figure 4: ROC curve for persistent endometrial shreds and US focal thickening to predict findings of endometritis.**

The roc curve in Figures 4 and 5 showed that combination of persistent endometrial shreds and US

focal thickening can significantly predict presence of endometritis as the largest area under the curve was 0.922,  $p<0.001$ . The sensitivity and specificity of the combination were 94.90 and 81.37, respectively (Table 4).



**Figure 5: ROC curve for combination of persistent endometrial shreds and US focal thickening to predict findings of endometritis.**

The hysteroscopy as an office procedure was very tolerable. We had difficulty in entry the internal os in 8 cases in whom we had to do dilatation in the operating theatre under anesthesia. No complications were encountered in any of our cases.

**Table 4: Agreement (sensitivity, specificity) for combination of persistent endometrial shreds and US focal thickening to predict findings of endometritis.**

Combination of	AUC	P value	95% C.I	Cut off#	Sensitivity	Specificity	PPV	NPV
<b>Persistent endometrial shreds and US focal thickening</b>	0.922	<0.001*	0.883-0.961	>0.06#	94.90	81.37	83.0	94.3

AUC: Area Under a Curve, P value: Probability value, CI: Confidence intervals, NPV: Negative predictive value, PPV: Positive predictive value, \*: Statistically significant at  $p\leq 0.05$ , #Cut off was choose according to Youden index

## DISCUSSION

Chronic endometritis is a sustained inflammation of the endometrial lining caused by several bacterial pathogens. Although chronic endometritis is mostly asymptomatic, however, repeated implantation failure, recurrent miscarriage, abnormal uterine bleeding, lower abdominal pain, and lower back pain could be the presenting complaints. Chronic endometritis diagnosis could be reached via hysteroscopy with endometrial biopsy.<sup>12</sup> The endometrial biopsy shows the presence of a large number of plasma cells among other types of inflammatory cells is diagnostic for chronic endometritis.<sup>13</sup>

Hysteroscopic markers of chronic endometritis include micro-polyps  $<1$  mm in size, edema of the endometrium, irregular (shaggy) endometrium, and hyperemic areas with prominent white glands.<sup>14,15</sup> Since establishing the diagnosis of chronic endometritis is not easy as it is mostly an asymptomatic lesion, trials to correlate detection of this lesion with ultrasonographic findings were done.<sup>3</sup> A study using 3D ultrasound Was done after a hysteroscopy to correlate findings and establish a diagnosis of endometritis. 3D views revealed the presence of several isoechoogenic round well-limited structures inside the endometrial cavity.<sup>11</sup>



To the best of our knowledge, no other studies compared hysteroscopic and sonographic findings regarding chronic endometritis detection. In this study, 200 infertile women were recruited which is a larger sample size compared to the earlier studies. Women underwent 2D ultrasonographic imaging at 2 different timing of the cycle to detect 2 specific abnormalities in the endometrial lining (presence of persistent focal or diffuse endometrial thickening postmenstrual and presence of focal echogenic foci on a triple line endometrium background during ovulatory phase). Office hysteroscopy was done to confirm or exclude the presence of chronic endometritis and we found high sensitivity and specificity of both signs in cases diagnosed as chronic endometritis. The remaining adherent endometrial shreds in the endometrium could be a result of the inflammatory process and the inability of the uterus to evacuate the uterine cavity during menses efficiently. The presence of echogenic endometrium among the normal triple line giving the shape of the heterogeneous pattern of endometrium could be related to the fluid content of the inflamed endometrium and its sonographic reflection which is different from the normal healthy endometrium.

A study examined the endometrial waves by ultrasound in women with CE and showed an altered EW pattern in both the mid-luteal and periovulatory phases. These altered waves might be responsible for and give an explanation of the symptoms related to CE such as pain and abnormal uterine bleeding.<sup>16</sup>

The real value of this study is to filter the cases who are in real need of hysteroscopic evaluation and that's to avoid unneeded interventions. In addition, the study gives an extra indication for cavity evaluation by office hysteroscopy notably before the IVF procedure.<sup>17</sup>

## CONCLUSION

Bi-dimensional ultrasonography done to infertile women at 2 phases of the menstrual period can predict the presence of chronic endometritis as a subtle cause of infertility and might be an indication for hysteroscopic evaluation for these patients.

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