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Original Research Article

## Can endometrial volume assessment predict the endometrial receptivity on the day of hCG trigger in patients of fresh IVF cycles: a prospective observational study

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### ABSTRACT

**Background:** Objective of present study was to evaluate the role of three dimensional (3D) endometrial volume measurement on the day of hCG trigger in predicting the endometrial receptivity. The present study is a prospective observational study conducted at assisted reproductive centre of a tertiary care hospital.

**Methods:** Endometrial volume was evaluated by three-dimensional ultrasound in 90 patients undergoing first cycle of IVF on hCG trigger day and was correlated with endometrial receptivity.

**Results:** Out of 90 patients studied 12 patients achieved pregnancy. A significant difference was found in mean endometrial volume on hCG trigger day among pregnant ( $5.33 \pm 2.14 \text{ cm}^3$ ) women compared to non-pregnant women ( $4.17 \pm 1.72 \text{ cm}^3$ ). Using Receiver operating characteristics (ROC) analysis the cutoff value for endometrial volume on hCG trigger day was  $3.50 \text{ cm}^3$  corresponding to sensitivity 75% and specificity 37.2%.

**Conclusions:** The endometrial volume on hCG trigger day was significantly higher in pregnant women as compared to non-pregnant.

**Keywords:** Endometrial volume, Endometrial receptivity, hCG trigger, *In-vitro* fertilization

### INTRODUCTION

The success of embryo implantation depends on the interaction of maternal and embryonic factors. The ability to identify a receptive uterus prospectively by a non-invasive method would have an invaluable impact on treatment efficiency and success rates following assisted reproduction. To assess uterine receptivity, one must take various factors into account. Current advances in transvaginal 3D ultrasonography have allowed us to examine in detail and visualize pelvic organ structures to analyse their volumes with great accuracy.<sup>1,2</sup> This enables us to quantify endometrial receptivity, because cycle outcome can be better related to a quantitative parameter

less prone to subjective variation. In addition, transvaginal 3D ultrasound is non-invasive, relatively inexpensive, and, most importantly, can provide information regarding whether to perform embryo transfer or to cryopreserve the embryos for future cycle. We aimed in this study to determine if, the measurement of endometrial volume by 3 DUS has role in predicting pregnancy.

### METHODS

Ethical approval was taken from the Institutes Ethics Committee prior to initiation of study. The design of the present study was done based on prospective

observational study. Women in the reproductive age group undergoing IVF at Assisted Reproductive Unit in Department of Obstetrics and Gynaecology at a tertiary care centre were enrolled in this study. The study was conducted over a period between 1<sup>st</sup> March 2015 and 30<sup>th</sup> July 2016.

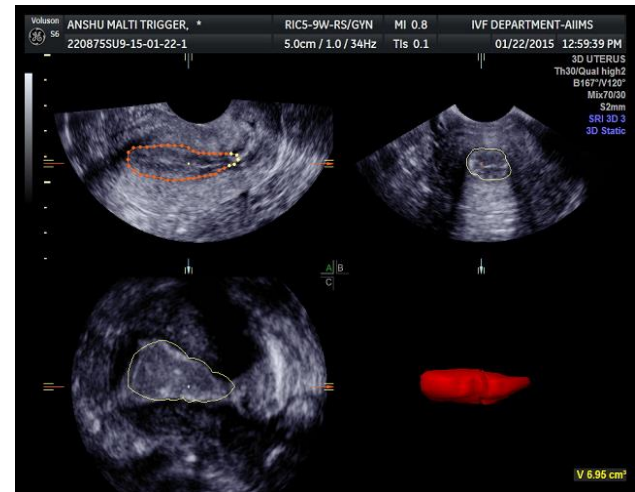
### Sample size

Ninety women undergoing first cycle of IVF were enrolled in this study. Women aged <40 yrs with BMI 18-28kg/m<sup>2</sup> undergoing first non-donor IVF cycle were included in the study those with prior failed IVF cycle, any history of granulomatous endometritis, history of intrauterine adhesions or polyp or myoma subjected to hysteroscopic surgical intervention were excluded. Pre IVF-assessment included baseline ovarian reserve using second day serum FSH, LH and serum AMH, the antral follicle count (AFC) and ovarian volume on 2nd or 3rd day of cycle. Women meeting eligibility criteria then underwent in-vitro-fertilization (IVF) or intracytoplasmic sperm injection (ICSI) depending on the indication. The patients were down regulated with the protocol used depending on the ovarian reserve of the patient.

For ovarian stimulation we either used the Gonadotropin-releasing hormone-agonist (GnRH) "long protocol" or flexible GnRH-antagonist regimen. In the long protocol, pituitary down-regulation was achieved with injectable GnRH-agonist, Leuprolide acetate (Luprofact; Bayer Zydus, Mumbai) 1 mg/day subcutaneous (s.c) from the midluteal phase prior to the treatment cycle. Gonadotropins, most commonly Recombinant Follicle Stimulating Hormone (Gonal F; Merck Serono, Italy) injected subcutaneously or rarely intramuscular Human Menopausal Gonadotropin (Humog; Bharat Serums and Vaccines Limited, Ambarnath) was used for ovarian stimulation after adequate downregulation was achieved i.e. serum estradiol <30pg/ml and luteinising hormone < 2IU/L. During stimulation the dose of Leuprolide acetate was reduced to 0.5 mg/day.

In the flexible GnRH-antagonist protocol Cetorelix acetate (Cetrotide; Merck Serono, Italy) 0.25 mg/day was administered s.c in the stimulated cycle when the diameter of leading follicle was 14 mm. Recombinant Human Chorionic Gonadotropin (hCG, Ovitrelle; Merck Serono, Italy) 250µg was administered s.c for inducing ovulation when 2-3 follicles were more than 18 mm in size. Oocyte retrieval was performed 34-36 hours after hCG administration under ultrasound guidance. Retrieved oocytes were fertilised either by conventional IVF or intracytoplasmic sperm injection (ICSI) technique. Embryos were cultured in sequential media using the "G-series" produced by Vitrolife (Goteborg, Sweden). On the morning of hCG trigger using 5-7 MHZ frequency vaginal probe by VOLUSON Scholar-6 GE MACHINE (Model: 083037002028313) 3D automated endometrial volume measurement was taken using VOCAL imaging

program (virtual organ computer aided analysis) using rotational method (30°) by a single trained observer and data recorded. For these rotational measurements, two calipers were placed at the upper and lower aspects of the endometrial cavity and the volume rotated about these to ensure they were appropriately sited and that all of the endometrium had been included. When the calipers were judged to be correctly positioned, the degree of rotation was determined by selecting the rotation angle and the manual mode of measurement entered. The junction between the myometrium and endometrium was then traced in a clockwise fashion using a track ball.



**Figure 1: Measurement of 3D endometrial volume by rotational method on hCG trigger day by 3D ultrasound.**

### Statistical analysis

An earlier study by Zollner et al showed that by 3D-ultrasound (multislice method) taken on day 3 among 125 patients underwent IVF, pregnancy rate was found to be 27.2% (95% CI: 19.5%-35.5%). Based on this information it was assumed that an expected minimum pregnancy rate of 20% would be obtained.<sup>3</sup>

Accordingly, a total of 90 patients (including 10% drop out rate) would be adequate enough that would be statistically significant at 5% level of significance with 80% power compared to the upper limit (35%) of confidence limits. This adjustment to sample size was made to have minimum sample size for the study. Baseline characteristics of continuous variables were expressed as mean±SD, frequency data were expressed in number, percent values.

Mean values of study variables that follows approximation to normal distribution were compared using t-independent test between pregnant and nonpregnant women. In case of non-normal distribution, median values were compared using non-parametric Mann-Whitney U test.

Frequency data were compared using Chi-square test or Fisher's exact test as appropriate. All data analysis was carried out using statistical product service solution (SPSS) version 20.0. A probability of  $p < 0.05$  was considered statistically significant. Receiver operating characteristics (ROC) analysis was carried out to find out the cut off value for endometrial volume on trigger day for predicting pregnancy status.

Based on significance of AUC cut off values based on LYUDEN index which was calculated as maximum

(sensitivity + specificity-1), pregnancy rate was compared between less than cut off value and more than cut off value for different study variables.

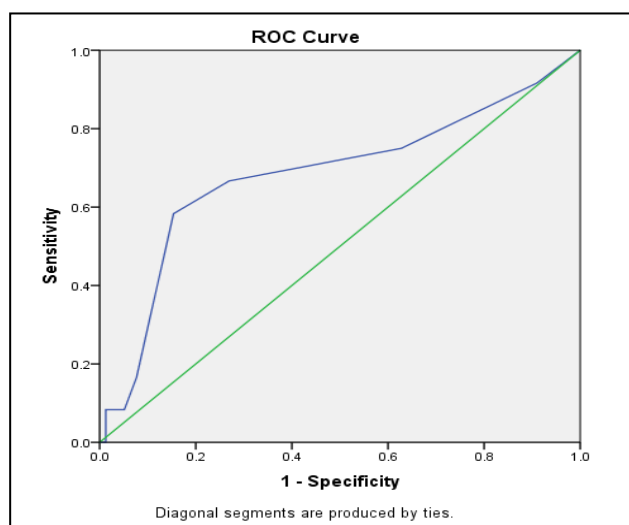
## RESULTS

Out of 90 patients studied 12 (13.3%; 95% CI:6.1%-19.9%) achieved pregnancy. There was no significant ( $P=0.425$ ) difference in age between pregnant ( $30.17 \pm 3.29$  years) and non-pregnant women ( $31.10 \pm 3.82$  years).

**Table 1: Comparison of study parameters between pregnant and non-pregnant women.**

Variables	Pregnant (n=12) (Mean±SD)	Non-pregnant (n=78) (Mean±SD)	P value
Age (years)	30.17±3.29	31.10±3.82	0.425
BMI (kg/m <sup>2</sup> )	24.67±4.25	24.79±3.58	0.911
AMH (ng/ml)	4.25±2.42	3.96±2.30	0.689
D2 FSH (mIU/ml)	6.76±1.28	6.86±1.23	0.672
D2 LH (mIU/ml)	4.59±1.18	4.71±1.19	0.572
Numbers of embryos transferred	3.25±0.96	2.96±0.92	0.319
EV on trigger day (cm <sup>3</sup> )	5.33±2.14	4.17±1.72	0.038

Similar trend was observed in body mass index ( $24.67 \pm 4.25$  kg/m<sup>2</sup> and  $24.79 \pm 3.58$  kg/m<sup>2</sup> for pregnant and non-pregnant women respectively ( $P = 0.911$ )). Baseline mean±SD of ovarian reserve day 2 serum LH ( $4.59 \pm 1.18$  and  $4.71 \pm 1.19$  mIU/ml), serum D2FSH ( $6.76 \pm 1.28$  and  $6.86 \pm 1.23$  mIU/ml) serum AMH ( $4.25 \pm 2.42$  and  $3.96 \pm 2.30$  ng/ml) for pregnant and non-pregnant are presented in (Table 1) and none was found to be with significant difference. However, a significant ( $P < 0.05$ ) difference was found in endometrial volume evaluated by 3 DUS on trigger day.



**Figure 2: ROC curve 1 for endometrial volume on trigger day**

The cut off value for endometrial volume on trigger day was found to be  $3.50 \text{ cm}^3$  with area under the curve 0.683 (ROC curve 1) with 95% confidence interval (0.494-0.872) and the AUC was statistically significant ( $p$  value-0.042), the sensitivity and specificity was found to be 75% and 37.2% respectively.

Of the 6 babies who required immediate resuscitation, one expired in immediate neonatal period due to birth asphyxia (intrapartum fetal distress at 32 weeks in woman with severe preeclampsia), one expired after 10 days due to metabolic complications and the rest four survived.

## DISCUSSION

Pregnancy outcome after in-vitro fertilization is multifactorial. The presumably dominant role of endometrial milieu continues to be an enigma and a research question that remains largely unanswered. Some studies have shown the thickness of the endometrium to be an important factor in predicting the outcome of IVF cycles other studies, however, have failed to show such a relation.<sup>4-12</sup> Also, there are studies that have reported no direct correlation between endometrial ultrasound parameters and pregnancy rate, even though a minimal endometrial mass was favorable for pregnancy to occur.<sup>2,13</sup> Schild et al. have demonstrated that the evaluation of endometrial thickness and volume on the day of oocyte retrieval by 3 DUS was not able to predict pregnancy and, moreover, the endometrial volume and thickness was even higher (but not significant) in non-

pregnant women.<sup>8</sup> In a prospective study by Raga et al pregnancy and implantation rates were significantly lower ( $P < 0.05$ ) in the group of patients with an endometrial volume  $< 2$  mL, with no pregnancy achieved with an endometrial volume  $< 1$  mL. Similar results were found by Yaman et al. they have shown that pregnancy rate in patients with an endometrial volume  $\geq 2.5$  mL was significantly higher than that in patients with an endometrial volume  $< 2.5$  mL ( $P < 0.012$ ), however their results have shown that neither endometrial volume nor endometrial thickness was directly correlated with pregnancy rate.<sup>2,13</sup> In a study by Zollner et al a threshold value of 2.5 mL for endometrial volume was predictive of failure to establish a pregnancy, with a negative predictive value of 91%. The positive predictive value, however was only 35% due to low overall pregnancy rates.<sup>3</sup> Based on this controversial literature, it is possible that a minimum endometrial mass could favor the pregnancy rate, but it is unlikely that a significant difference in endometrial thickness or volume really exists before embryo transfer.

Three-dimensional volumetry of the endometrium offers great potential in augmenting the information provided by 2D ultrasound in infertile patients. It is essential to identify objective measures of optimal uterine environment prior to embryo transfer in patients undergoing IVF. The study suggests that favourable results after IVF/ICSI can be expected with a threshold endometrial volume of  $3.5 \text{ cm}^3$  or more on the day of hCG trigger, any volume lower than  $3.5 \text{ cm}^3$  has a lower likelihood of successful implantation. 3D transvaginal ultrasound enables us to quantitatively predict endometrial receptivity and is less prone to subjective variation. Despite the low specificity it may be an important decision making tool in choosing whether to perform embryo transfer or cryopreservation.

## CONCLUSION

In our prospective observational study of ninety patients we found a significant correlation of 3DUS endometrial volume on the day of hCG trigger and pregnancy outcome. Further studies are required to validate findings.

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*Ethical approval: The study was approved by the Institutional Ethics Committee*

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