RESEARCH ARTICLE

Sonographic Folliculometry and Endometrial Echocomplex as an Evidence of Ovulation in Infertility Cases

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ABSTRACT

Objectives: To study the diagnostic accuracy of folliculometry and endometrial echo complex as an evidence of ovulation in infertility.

Materials and methods: This clinical study was conducted on 100 infertile women. The women were subjected to follicular monitoring by transvaginal sonography (TVS) from cycle day 8 or 10 of menstruation with 7.5 MHz vaginal probe of Siemens ultrasound machine. Evidence of follicular growth, ovulation, and morphology of endometrial echo complex with its thickness was noted. Endometrial biopsy was performed premenstrually as a day care procedure after excluding pregnancy.

Results: Out of 100 women, 81 cases were with evidence of ovulation on TVS and 68 were confirmed on histopathology. All the studied patients were also evaluated for endometrial thickness on the day of ovulation, echo complex of endometrium suggestive of ovulation was seen in 64 cases, out of these 59 cases were confirmed on histopathology. On histopathological study of 100 cases, we found 69 cases with secretory endometrium, 18 with proliferative endometrium, 10 patients with endometritis, one each with luteal phase defect, irregular shedding of endometrium, and hormonal imbalance.

Conclusion: We found folliculometry predicted ovulation 86% accurately with a specificity of 58.60% and sensitivity of 98.55%. Similarly, appearance of endometrium predicted ovulation 85% accurately with a specificity of 83.80% and sensitivity of 85.50%. Thus, TVS has undeniable advantages in terms of cost, time, acceptability, risk, convenience, and could easily diagnose signs of ovulation in cases of infertility. The TVS has quintessential role as the first diagnostic modality in patients presenting with infertility.

Keywords: Endometrial echo complex, Folliculometry, Infertility, Ovulation.

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INTRODUCTION

Reproduction and perpetuation are features of living beings. Inability to do so is not only called infertility but "infertility crisis" because of social, cultural, and psychological implications.[1]

In 2010, the World Health Organization defined infertility as "a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected intercourse" or after 6 months in patients over 35 years.[2] Primary infertility is failure to conceive at all, whereas secondary infertility is failure to conceive after having borne a child or abortion.[3]

The main causes of infertility include male factor, decreased ovarian reserve, ovulatory disorders, tubal injury, blockage or para tubal adhesions (including endometriosis with evidence of tubal or peritoneal adhesions), and uterine factors. An ovulation is most easily diagnosed and most effectively treatable cause of infertility.[4] Female infertility may occur due to disturbances involving any part of genital system or parts of central nervous system that control the ovaries hormonally.[5]

The advent of ultrasonography has provided clinicians with the opportunity to visualize the pelvic reproductive organ noninvasively. The use of ultrasound for diagnosis and treatment of infertility has progressed rapidly to become an integral part in the management of infertility with special reference to folliculometry. The TVS has become a popular test for assessment of follicular monitoring to detect ovulation. It has improved ultrasonic imaging over those taken via abdominal.

There are various signs on ultrasonography to document ovulation—disappearance or decrease in size of the dominant follicle, appearance of internal echoes within the follicle, collapse of the dominant follicle with crenation of the edges, presence of free fluid in a cul-de-sac, visualization of cumulus oophorus, visualization of corpus luteum, and thickened endometrium. As of now, no reproducible sonographic signs, however, have been shown to predict imminent ovulation reliably.[6]

Thus, today's question afloat is, can we develop a simple minimally invasive technique in an outpatient setting that is reliable, cost-effective, time-saving, and helps us in determining the diagnostic approach?

This study was thus conducted keeping in mind that TVS may be an answer to this burning question. This was a prospective study to document ovulation by TVS and endometrial biopsy for secretory changes on histopathology in cases of primary and secondary infertility. The present study was undertaken to compare the diagnostic accuracy of TVS with endometrial biopsy as an evidence of ovulation in cases of infertility.

MATERIALS AND METHODS

This comparative prospective study was conducted on 100 patients with primary or secondary infertility recruited from the Department of Obstetrics and Gynaecology, Shri Ram Murti Smarak Institute of Medical Sciences, Bhojipura, Bareilly, India, from May 2015 to May 2016 after obtaining necessary approval from the ethical committee. After taking written and informed consent and fulfilling the inclusion criteria, patients were included into the study.

Patients were assessed by thorough history regarding age, duration of marriage, educational status, socioeconomic status, menstrual history, medical illness, contraceptive used, sexual and married life, sexually transmitted diseases, pelvic surgery, or medical treatment, taken for any menstrual irregularity or infertility. General physical, systemic, and complete gynecological examination was done. They were investigated for routine blood and urine examination, husband semen analysis, Venereal Disease Research Laboratory, TVS folliculometry, and premenstrual endometrial biopsy.

Inclusion Criteria

Age 20 to 40 years, primary infertility, secondary infertility, no obvious menstrual abnormality, and no obvious pelvic pathology

Exclusion Criteria

Age >40 years, obvious menstrual abnormality, acute pelvic inflammatory disease, endometriosis, history of previous ovarian surgery, known case of thyroid dysfunction, hyperprolactinemia, and other obvious pelvic pathology.

The patients were subjected to follicular monitoring by TVS from day 8 to 10 of natural menstruation cycle with ultrasound machine using 6.7 MHz transvaginal transducers. Evidence of follicular growth and ovulation was noted. The evidence of ovulation on TVS was seen as a visualization of cumulus oophorus, crenation of edges of dominant follicle, decrease in size of dominant follicle, presence of internal echoes, presence of fluid in a cul-de-sac, visualization of corpus luteum, and thickened endometrium. An endometrial biopsy was performed as a day care procedure under sedation premenstrually after excluding pregnancy with full aseptic precaution.

Statistical Analysis

Statistical testing was conducted with Statistical Package for the Social Sciences version 24.0. Continuous variables are presented as mean ± standard deviation (SD) and categorical variables are presented as absolute numbers and percentage. The agreement between two tests (TVS and histopathology) was calculated using Kappa test. Follicular growth was analyzed by using analysis of variance test. Validity measures were calculated to analyze the diagnostic accuracy of TVS taking histopathology as a gold standard test. For all statistical tests, a p-value less than 0.05 was considered significant.

OBSERVATION AND RESULTS

Table 1 illustrates the distribution of patients according to the demographic variables, where mean age of presentation is 28.59 years and 66% of our patients were of primary infertility and 34% of secondary infertility. The mean of duration of marriage and infertility was 7.9 and 6.4 years respectively. Mean body mass index was 20.04 kg/m² and 55% belonged to low socioeconomic status.

Table 2 shows the distribution of cases according to sonographic evidence of ovulation and its comparison with an endometrial biopsy.

According to Graph 1, the overall sensitivity of TVS is 98.55%, specificity is 58.06%, and diagnostic accuracy is 86%.

Table 1: Descriptive statistics of sample size according to demographic variables

Variables	Mean ± SD
Age	28.59 ± 5.4 years
Type of infertility	66% primary, 34% secondary
Duration of marriage	7.90 ± 5.2 years
Duration of infertility	6.48 ± 4.4 years
Body mass index	20.04 ± 1.33 kg/m²
Socioeconomic status	55% low

SD: Standard deviation

Table 2: Distribution of cases according to sonographic evidence of ovulation and its comparison with endometrial biopsy

	Histopathology		
TVS	Ovulation	Anovulation	Total
Ovulatory cycle	68 (98.50%)	13 (42%)	81
Anovulatory cycle	1 (1.50%)	18 (58%)	19
Total	69	31	100
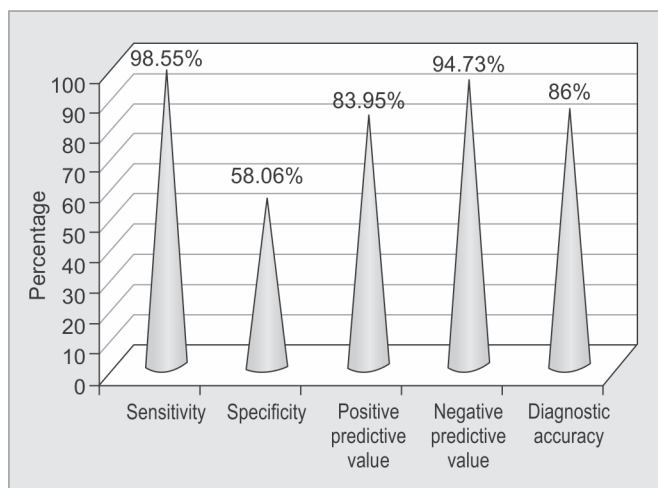
Graph 1: Validity measures according to sonographic evidence of ovulation and its comparison with endometrial biopsy

Table 3 reveals various signs on sonography to find out most sensitive specific signs to predict ovulation. We found that sensitivity of disappearance or decrease in the size of dominant follicle of TVS was better than other signs of ovulation, whereas the presence of crenation of edges of dominant follicle was found to be more specific with high positive predictive value (PPV). Fluid in the cul-de-sac was found more sensitive as well as specific as compared with other signs of ovulation.

Table 4 shows that maximum number of patients had an endometrial thickness between 10.1 and 12 mm, i.e., 60% on the day of ovulation. Mean endometrial thickness was 10.34 ± 1.22 mm.

Table 5 shows a histopathological study of premenstrual endometrium. We found 69% cases with secretory endometrium, 18% with proliferative endometrium, 10%

patients with endometritis (including 6% with tubercular endometritis), one each with luteal phase defect, irregular shedding of endometrium, and hormonal imbalance.

DISCUSSION

A diagnostic evaluation for infertility is indicated for a woman who fails to achieve a successful pregnancy after 12 months or more of unprotected intercourse. Anovulatory dysfunction is identified in approximately 15% of all infertile couples and accounts for up to 40% of infertile women.

Many diagnostic modalities are available and use of the invasive procedure is common. In recent years, TVS has become a major noninvasive vital tool to diagnose ovulation in cases of infertility. Folliculometry done from cycle day 8 to 10 (at the time of recruitment) showed that out of 100 women with infertility, 63% had dominant follicle of diameter 10.1 to 13 mm size and only 16% women had dominant follicle of 7 to 10 mm size.

In our study, we observed mean preovulatory diameter of Graafian follicle 16.91 ± 4.37 mm. The endometrial thickness at the time of this follicular size was 10.34 ± 1.22 mm. In stimulated cycles, follicle size can reach up to 22 to 25 mm before they ovulate or rupture. But we measured in natural cycles. The mean growth rate difference in early scans *vs* late scans was statistically significant with p-value <0.05.

All the studied patients following serial TVS folliculometry were subjected to premenstrual endometrial biopsy.

On histopathology, the secretory phase of endometrium was observed in 69 cases, proliferatory endometrium in 18 cases, luteal phase defect in one case,

Table 3: Comparison of TVS and endometrial biopsy as an evidence of ovulation in infertility cases

Signs of ovulation	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Visualization of cumulus	60.65% (47.30–72.66)	82.05% (65.89–91.80)	84.09% (69.32–92.84)	57.14% (43.27–70.03)
Crenation of edges of dominant follicle	56.52% (44.08–68.23)	96.77% (81.48–99.83)	97.50% (85.26–99.86)	50% (36.95–63.04)
Decrease in size of dominant follicle	94.20% (85.06–98.12)	77.40% (58.45–89.72)	90.27% (80.41–95.32)	85.71% (66.43–95.32)
Internal echoes	85.50% (74.49–92.46)	83.87% (65.52–93.90)	92.18% (81.99–97.08)	72.22% (54.56–85.20)
Fluid in cul-de-sac	94.20% (85.06–98.12)	83.87% (63.52–93.90)	92.85% (83.43–97.34)	86.66% (68.35–95.64)
Visualization of corpus luteum	26.08% (16.58–38.28)	87.09% (69.23–95.78)	81.81% (58.99–94.00)	34.61% (24.43–46.32)

NPV: Negative predictive value; CI: Confidence interval

Table 4: Distribution of cases according to endometrial echocomplex (endometrial thickness)

Endometrial thickness (mm)	No. of cases
<6	0
6.1–8	8
8.1–10	24
10.1–12	64
>12	5
Total	100

Table 5: Distribution of cases according to premenstrual histopathological examination (endometrial biopsy)

Histopathological pattern	No. of patients
Proliferative phase endometrium	18
Secretory endometrium	69
Endometritis (chronic/acute/tubercular)	10
Luteal phase defect	1
Irregular shedding of endometrium	1
Hormonal imbalance	1
Total	100

hormonal imbalance in one case, irregular shedding of endometrium in one case, and endometritis in 10 (tubercular endometritis in 6) of our studied population. In a similar study, Sharma et al[7] studied 50 cases of primary and secondary infertility and observed an ovulation in 28%, luteal phase defect in 20%, cystoglandular hyperplasia in 6%, tuberculous endometritis in 2.0%, and menstrual problems in 38%. A similar study done by Emokpae et al[8] showed that majority of cases showed secretory endometrium and 4% showed tubercular endometritis.

We had 6% patients of tubercular endometritis in our study showing tuberculosis as a major cause of infertility in this region. Various authors have done work on tuberculosis within infertility and found 5 to 10% involvement.[9]

In our setup, we sent two samples for evaluating genital tuberculosis apart from histopathology. They were stained for acid-fast bacilli on a smear of menstrual blood and *Mycobacterium* growth indicator tube test. We consider tuberculosis positive if either or all tests were positive.

Evidence of ovulation on TVS was seen as a visualization of cumulus oophorus, crenation of edges of dominant follicle, decrease in size of dominant follicle, presence of internal echoes, presence of fluid in a cul-de-sac, visualization of corpus luteum, and thickened endometrium.

We have tried to find out the diagnostic capability of each sign separately and then cumulatively to know the role of scanning in predicting ovulation.

In our study on folliculometry, we consider cycle ovulatory if growing dominant follicle along with any one or more signs of ovulation detected on sonography.

After analyzing the role of TVS to detect ovulation, we found TVS is 98.55 % sensitive and 58.06% specific. Thus, the difficulty in making an exact diagnosis with TVS is very less. A similar observation was encountered by other authors also. Leena et al[10] studied 100 patients with infertility, found ovulation in 73% by TVS and confirmed ovulation in 63 cases by histopathology. Similarly, Zandt-Stastny et al[11] also noted sonographic signs of ovulation in 73% of their studied subjects.

In the present study, particularly fluid in cul-de-sac was found to be more sensitive (94.20%) and specific (83.87%) as compared with other signs of ovulation. But cul-de-sac fluid may be associated with other conditions as acute pelvic inflammatory diseases, ruptured ectopic pregnancy, or ovarian hyperstimulation syndrome. Nongynecologic causes of cul-de-sac fluid include appendicitis, abdominal infections, nongynecologic intraabdominal cancers and intraabdominal bleeding from trauma, such as rupture of the spleen. Thus, fluid in a cul-de-sac along with other sonographic signs of ovulation was found to be sensitive, but not alone. As previous studies explain that fluid in a cul-de-sac is also associated with other

gynecological conditions, this sign of ovulation is not of much significance.

So, out of other signs of ovulation, we found the next most sensitive (94.20%) sign is "decrease in size of dominant follicle" and most specific (96.77%) sign is "crenation of edges of dominant follicle."

Thus, if we consider these signs for ovulation on TVS, we can get most sensitive and specific test to diagnose ovulation. So, considering the decrease in size of dominant follicle along with crenation of edges of follicle TVS is most sensitive (94.20%).

Ultrasound is an ideal imaging technique for locating follicles, monitoring subsequent growth, and documenting collapse or ovulation. Follicles are easily visualized. Maximum information is obtained because of high resolution and close proximity to pelvic organs. Optimum visualization of pelvic organs is almost guaranteed even under unfavorable conditions. The TVS can be extremely helpful in the group of women in whom endometrial biopsy has been attempted but has not been diagnostic. So, TVS can be used to obviate the need for a more invasive procedure like repeat endometrial biopsy.

The disadvantages of TVS are few. The tissue is not obtained during sonography so diagnostic confirmatory results are not obtained. Subjective errors can also occur. Folliculometric assessment of the patients requires repeated visits in the outpatient department (OPD), so it leads to undue inconvenience for the patients. The TVS folliculometry requires expertise, sometimes further making it less acceptable and less cost-effective. Some patients do not tolerate vaginal probe because of noncompliance.

The major problem for the gynecologists now is, How to approach infertility cases? What are the tools for investigating such cases? Which one is the best of all? But after the invention of a magnificent tool like TVS, the point to be discussed is whether an endometrial biopsy is needed in all infertility patients or if a better diagnostic aid is yet to be discovered, which could overcome the shortcomings of both TVS and endometrial biopsy.

Considering the above factors, there is still scope of research to develop a better diagnostic modality which would overcome the shortcomings of TVS and would be more acceptable and assessable diagnostic tool as well as specific (96.77%) for folliculometry.

CONCLUSION

From our study, the following points could be concluded:
- We found that TVS easily distinguished between ovulatory and anovulatory cycle. Our observations suggest that folliculometry is an almost noninvasive confirmatory device for ovulation detection. It can assess not only ovulation but also pelvic pathologies.

- The TVS has an undebatable role in the evaluation of a patient with infertility. We found the role of folliculometry is also undisputable in predicting ovulation with a sensitivity of 98.55%, specificity of 58.60%, and diagnostic accuracy of 86%.
- We found TVS highly sensitive but less specific for prediction of ovulation. But sonographically crenated margins of follicle in setting of other sign make TVS highly specific also.
- Despite being a test of negligible complication, there are few shortcomings of TVS as a diagnostic tool. At times, it requires comparatively more expertise, multiple OPD visits, inconvenience caused by vaginal manipulation, and nonvisualization of the ovary. Therefore, our research for a better diagnostic test for ovulation should continue.
- The TVS definitely enhances the diagnostic potential of sonographic assessment of ovulation except in a few difficult situations where the ovaries were not seen in ovarian fossa.
- The TVS has undeniable advantages in terms of cost, time, accessibility, risk, convenience, and additional information regarding myometrium and adnexa.

Although TVS has a quintessential role as the first diagnostic modality for these infertility patients, the endometrial and uterine cavity, however, demands further evaluation. The study was small and to formulate a definitive protocol, further multicentric studies with larger samples are required.

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