Original article

Uterine Biophysical Profile in IUI Cycles in Relevance to Hyaluronic Acid Pessaries

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Abstract:

- *Background***:** Intrauterine insemination overcomes sperm ascent barriers by depositing processed semen in the uterine cavity. The study aims to evaluate intravaginal hyaluronic acid's effect on endometrial receptivity using Doppler ultrasound and Uterine Biophysical Profile scores, and its role in enhancing pregnancy rates in IUI for infertile couples.

- *Methods:* This comparative prospective study was conducted at the High Institute of Infertility Diagnosis and Assisted Reproductive Technologies, Al-Nahrain University, from September 2021 to May 2022. Forty-nine infertile couples were randomly selected and divided into Group A (n=27) and Group B (n=22). Group A received daily 5mg HA pessaries (Ialugyn) from cycle day 7 until day 21. Serial ultrasound examinations monitored follicular development. The Uterine Biophysical Profile was assessed on the day of IUI, and pregnancy outcomes were evaluated 14 days post-IUI for comparison.

- *Result:* Demographic data and basal serum hormonal levels showed no significant differences (P>0.05) between groups. Uterine Biophysical Profile parameters remained unchanged. The total pregnancy rate was 18.3%, with no significant difference between study group (22.2%) and control group (13.6%), (p=0.440). The study group exhibited a higher pregnancy rate. A significant difference (p=0.042) in UBP was found between pregnant and non-pregnant women, with a cutoff value >16, 56% sensitivity, 72% specificity, 64% accuracy, and an AUC of 0.973.

- *Conclusions:* Intrauterine insemination with intravaginal HA improves endometrial receptivity and pregnancy rates, evidenced by the positive impact on Uterine Biophysical Profile score. The limited sample size might account for the non-significant increase in pregnancy rate.

- **Keywords:** Hyaluronic acid suppositories, intrauterine insemination, uterine biophysical profile.

INTRODUCTION

Infertility is a state of failure of a couple to conceive after a period of 12 months or more of unprotected coitus [1]. Intrauterine insemination (IUI) entails depositing processed sperm sample in the upper uterine cavity in order to overcome natural barriers to sperm ascent in the female reproductive tract [2]. Implantation is a multifaceted and complex process. A healthy embryo, a receptive endometrium, and a synchronized molecular interaction between the two, as well as immune tolerance/protection from the host, are required for successful implantation [3]. Window of implantation (WOI) described as a short phase of menstrual cycle, during which endometrium becomes optimally receptive to embryo, usually at mid–secretory phase (19-23) days [4]. Endometrial receptivity: means that the endometrium has matured to the point where it is completely ready to accept the properly developed implanting embryo. It is equivalent to the WOI [3]. A simple, noninvasive, and easy method for assessing ER is by using UBP (Uterine Biophysical Profile) scores, which based on seven parameters (endometrial thickness, appearance, blood flow, myometrium contractions, uterine artery pulsatile index, myometrium echogenicity, and myometrium blood flow) [5]. Hyaluronic Acid (HA) effect on endometrial receptivity: one of methods that used to increase ER is by use of hyaluronic acid (HA) supplement in embryo culture media [6]. Hyaluronic acid is a linear, anionic GAG (glycosaminoglycan), found mostly in soft connective tissues' extracellular matrix (ECM).
Hyaluronic acid plays important role in implantation, it act on providing greater viscosity conditions in both oviduct and uterus [7]. HA, increase in matrix and cell-cell adhesion [8]. The study's aim is to assess the effect of intravaginal hyaluronic acid on endometrial receptivity parameters by assessment of UBP score and assessing the role of vaginal HA in improving pregnancy rate in infertile couples undergoing IUI treatment.

PATIENT and METHOD

A Prospective comparative study done in high institute for infertility diagnosis and assisted reproductive technologies/Al-Nahrain University outpatient clinic Baghdad /Iraq, from 15/11/2021 up to 1/5/2022. Patients included in this study are those who are between 18 and 42 with Patent tubes, normal thyroid hormone, blood sugar, and prolactin hormone levels and a male partner with normal or subnormal semen analysis.
Patients excluded from this study are those with severe male factor infertility, moderate and sever endometriosis, intrauterine pathology (fibroid, polyp), and woman with pelvic adhesion, sever PID and bilateral tubal occlusion and endocrineopathies such as hyperprolactinemia, CAH, thyroid disease, and diabetes mellitus. A total 49 infertile women include in study, divided into two groups:
A) Group A (27 couples given Hyaluronic acid suppositories 5mg from day 8 until day 21 of cycle). They receive standard ovarian stimulation (letrozole and or gonadotrophin).
B) Group B (22 couples' control) in whom IUI done with standard ovarian stimulation without HA application.

At CD (2-3): After complete assessment by transvaginal ultrasound and hormonal assay, ovarian stimulation done by leterzole tab 2.5mg, given twice daily for 5 days.

At CD (7-8): Follow up by TVUS, if the largest follicle <10mm in diameter, FSH (follisurge) or human menopausal gonadotropin (hMG) 75 IU daily subcutaneous injection started.

At CD (9-10-11): TVUS to monitor follicular size and number, complete the stimulation by FSH injection for all patients in both groups in whom follicular growth need further stimulation, and with continuous TVUS monitoring for follicular growth and endometrial thickness and pattern. If ovulation confirmed by TVUS then patient prepared for IUI.

At day of IUI, vaginal ultrasound done with application of UBP score, IUI done, and Luteal phase supported by progesterone ampule given twice weekly, Pregnancy test done after 15 days to confirm pregnancy. The data were analyzed using Statistical Package for Social Sciences (SPSS) version 22.0 and Microsoft office 2007.Statistical data including frequency, mean and standard deviation were measured to describe the variables. The groups were compared by applying independent sample t-test (unpaired t-test between two groups) and chi square (for non-continuous data or percentage) and the degree of association between continuous variables was calculated by Pearson's correlation coefficient (r). The cut off value, sensitivity and specificity were calculated by using Receiver operative characteristics (ROC) curve. The result considered statistically significant when P value was less than 0.05.
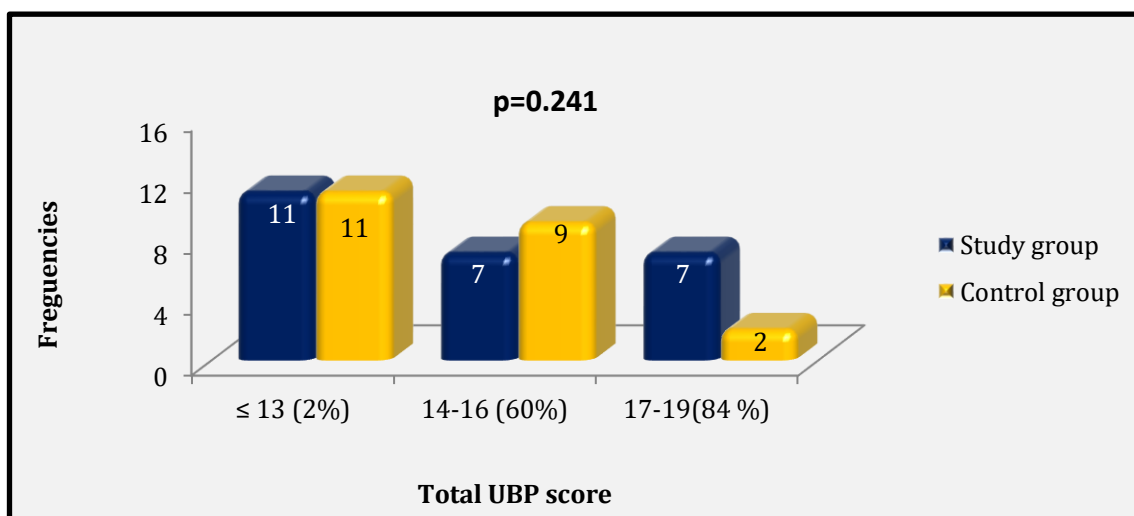
RESULTS

Comparison of uterine ultrasound biophysical profile between study and control groups

Table (1): Comparison of total UBP score between study and control groups.

Total score	≤ 13 (2%)	14-16 (60%)	17-19 (84%)	p value
Study group	11 (44%)	7 (28%)	7 (28 %)	0.241 NS
Control group	11 (50%)	9 (40.9%)	2 (9.1%)	

NS: Not significant (*p* value > 0.05)

Figure (1): Comparison of total UBP score between study and control groups.
Comparison of pregnancy outcome between study and control group

Six females who received hyaluronic acid pessaries out of twenty seven women became pregnant (22.2 %) while in control group, three women out of twenty two became pregnant (13.6 %), so there was no significant difference in pregnancy rate between study and control group (*p*=0.440) (Table 2 and figure 2 and figure 3).
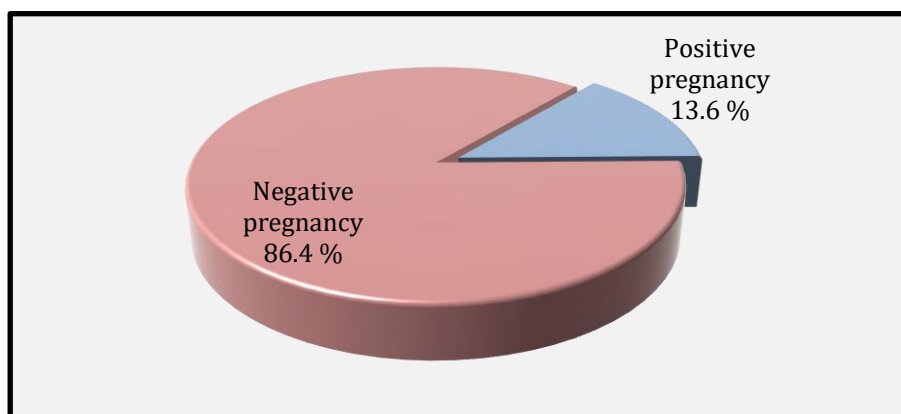
Table (2): Comparison of pregnancy rate between study & control groups

Parameter	Study group n. (%)	Control group n. (%)	p value
Positive pregnancy	6 (22.2 %)	3 (13.6 %)	0.440 NS
Negative pregnancy	21 (77.8 %)	19 (86.4 %)	

NS: Not significant (*p* value > 0.05).
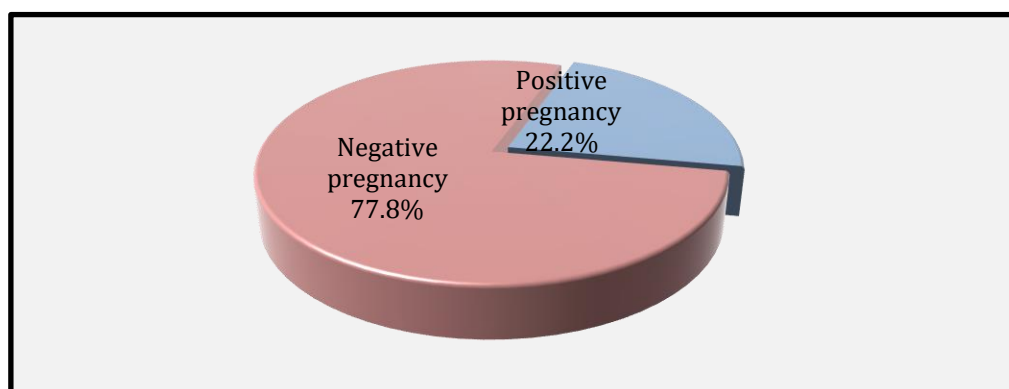
Figure (2): Pregnancy rate of study group

Figure (3): Pregnancy rate of control group

Comparison of total uterine biophysical profile between pregnant and non-pregnant females

According to result, there was significant difference in total uterine ultrasound biophysical profile (UBP) score between pregnant and non-pregnant females (p=0.042)

Table (3): Comparison of total UBP between pregnant & non-pregnant women

Parameter	Pregnant females	Non-Pregnant females	p value
Total uterine UBP score	15.22 ± 2.7	12.44 ± 3.7	0.042 S

IUI: Intrauterine insemination; NS: Not significant (p value > 0.05); S: p value ≤ 0.05 (significant).
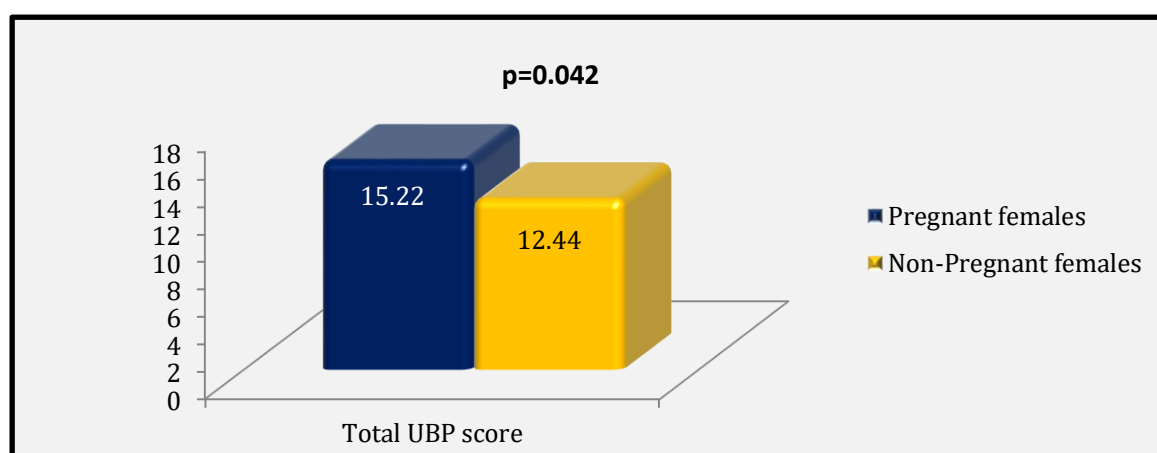

Figure (4): Comparison of total UBP between pregnant & non-pregnant females

Total uterine biophysical profile score as a predictor of positive pregnancy Receiver Operative Characteristic curve (ROC curve) has been used to calculate total UBP score cut-off value as a predictor of positive pregnancy with acceptable sensitivity, specificity, and accuracy. The results presented in (table 4) and figure 5, according to the results the cut-off value was ≥ 16 with sensitivity of 56 %, specificity of 72 %, accuracy of 64 % and area under the curve (AUC) equal to 0.973.

Table (4): ROC curve of total UBP as predictor of positive pregnancy

ROC curve characteristics	Results
Cut off value	≥ 16
Area under curve	0.727
p value	0.037
Sensitivity	56 %
Specificity	72 %
Accuracy	64 %
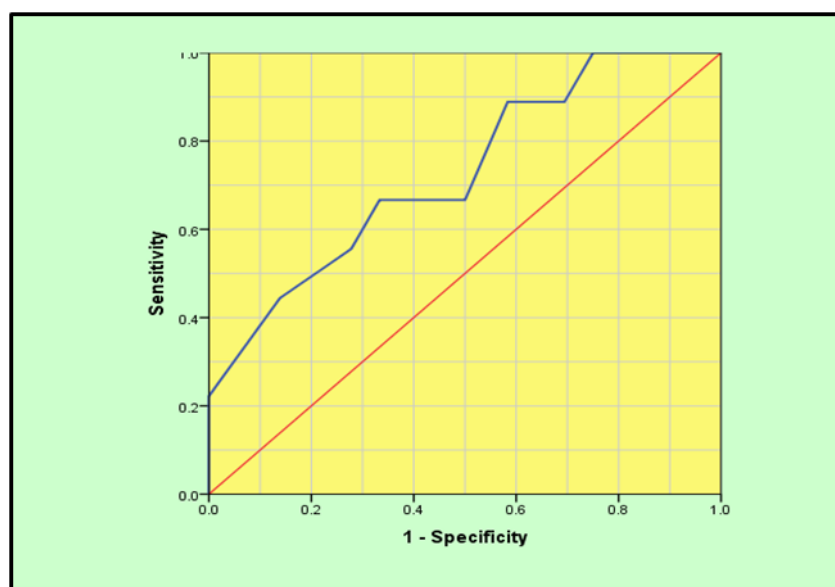
Figure (5): ROC curve of total UBP score as predictor of positive pregnancy.

DISCUSSION

This study investigated the value of intra-vaginal HA pessaries used in IUI cycle in an attempt to improve endometrial receptivity and pregnancy rate.

First table show that about 28% of women in study group have a total UBP score >17 and only 9.1% in control group have the same score.

Previous studies explain that scores greater than 17 have good implantation rate and high ER. In current study, the difference in mean total Uterine Biophysical Profile score between control and study groups indicate that using HA affect positively on total (UBP) but the difference was NS.

Non- significance in our result related to small sample size. The positive relation between HA and ER in this study agree with [9] who found that ER improve in ICSI cycle when HA pessaries used vaginally. Our finding disagrees with [10].

Biochemical pregnancy rate of infertile women participated in current study

A comparison of the pregnancy rates in the study and control groups: The percentage of positive biochemical pregnancy in the present research was greater in the study group than in the control group, 22.2% versus 13.6%, respectively, but the difference is NS. The possible explanation for this difference in pregnancy rate attributed to hyaluronic acid, which produce rise in both, thickness and blood flow of endometrium and hence higher UBP score and better endometrial receptivity and higher embryo implantation.

Comparison total uterine biophysical profile between pregnant and non-pregnant females

In all women participated in present research, there was a significant difference in the overall uterine ultrasonography biophysical profile (UBP) among pregnant and non-pregnant women (p=0.042). The mean UBP for pregnant was 15.22 and in non-pregnant was 12.44.

Our study strongly agree with the study that done by [11] on 51 infertile women, who found that UBP score above 15 have 100% pregnancy rate. While in women with UBP scores of <12 pregnancy rate was 0%. Meanwhile the study that done by [12], proved that mean total score of Uterine Biophysical Profile was significantly higher in women with positive pregnancy than in women with negative pregnancy.

Pregnant women have higher UBP score than non-pregnant women, this can be explained that high UBP score (Endometrium that is thick & have distinct five lines appearance, multi-focal vascularity within zone 3, homogenous myometrium, low UAPI, and presence of myometrium blood flow internal to arcuate vessels), associated with receptive endometrium. When ER rise, PR rise also. Our result agrees with [11-17].

5.3.3. Total uterine biophysical profile score as a predictor of positive pregnancy. The mean total score of Uterine Biophysical Profile was significantly greater in a female who had a positive pregnancy test than in women with negative pregnancy. The total UBP score cutoff value was >16 with an acceptable accuracy level of 64% (women with total UBP> 16 about 64% of them are pregnant) and (women with total UBP<16 about 64% of them not pregnant). The sensitivity (true positive) of that cutoff value was 56% and the specificity (true negative) was 72% and area under the curve equal to 0.727), indicating that UBP score can be used to predict pregnancy.

This result agrees with a study done in Erbil / Iraq by [11] on 51 infertile women, using total UBP score, for prediction of pregnancy, consider 15 as a cut-off value, sensitivity of 86.7% and a specificity of 100%. ROC (Receiver Operating Characteristic) curve, area under the curve was large (0.979, and the 95% CI was 0.944-1).

The study that done by [12], proved that Mean total score of UBP was significantly high in women with positive pregnancy. The total score cut off value was >17 with an acceptable accuracy level of 74.2. The sensitivity of that cutoff vale was 80 % and the specificity was 65.5%.

According to study conducted by [16] in spontaneous IUI cycles of 222 women, UBP score of 17–19 gave, 79% of conception and 7.6% conceived with a score of ≤13.
[15] found that pregnancy rate for patients with a score of 17–19 was 100% and a score of ≤13 was negative for pregnancy.

UBP scoring [11] is a simple method for prediction of ER and for prediction of pregnancy in ICSI cycle [13-14] and in IUI cycle [12,15-17].

CONCLUSION

Adding hyaluronic acid pessaries in ovarian stimulation–IUI cycles improve endometrial receptivity, implantation rate and pregnancy rate and this proved by its positive effect on Uterine Biophysical Profile, the score for predicting endometrial receptivity.

Conflicts of interest:
There are no conflicts of interest.

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