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# Using Uterine Biophysical Profile as a Predictor of Endometrial Receptivity and Pregnancy in Stimulated IUI Cycles

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## Abstract

Implantation failure and disorders of endometrial receptivity represent an essential cause of infertility; multiple parameters were needed to predict the uterine receptivity understanding that no sole parameter could predict the same. A score was termed as (Uterine Biophysical Profile) could be utilized as a predictor of endometrial receptivity. To evaluate the predictive potential of Uterine biophysical profile of both endometrial receptivity and pregnancy outcome in infertile women undergoing Intrauterine Insemination (IUI). The current cross-sectional study was conducted in the High Institute for Infertility Diagnosis and Assisted Reproductive Technologies in Al Nahrain University, Baghdad, Iraq from the 1st of Oct. 2018 till 1st of May 2019 involving seventy women of infertile couples with the same inclusion and exclusion criteria. Uterine biophysical profile was evaluated using a doppler ultrasound examination and then a score was calculated and correlated to pregnancy outcome. The mean Uterine Artery Pulsatility Index (UAPI) was significantly lower in women with positive pregnancy in comparison to women with negative pregnancy, 2.10±0.19 versus 2.47±0.65, respectively (P=0.032). Moreover, no women with Pulsatility Index (PI) score (0) succeeded to get pregnant and the higher the score, the higher the rate of pregnancy (P=0.006). Furthermore, Spearman correlation showed significant positive correlation between positive pregnancy outcome and UAPI (r=0.365; P= 0.002). The mean total score was significantly higher for pregnant women than in women with negative pregnancy, 18.27±1.33 versus 16.35±2.47, respectively (P= 0.005). The cutoff 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%. Uterine artery pulsatility index and total uterine biophysical score are the principal predictors of positive pregnancy outcomes in infertile women undergoing IUI.

**Keywords:** Uterine Biophysical Profile, Endometrial Receptivity, Pregnancy rate, Intrauterine Insemination.

## 1. Introduction

Infertility is a relatively common problem in developed as well as developing countries in which there is the failure of pregnancy by couples despite regular uninterrupted natural intercourse for at least 12 months (Vander Borght and Wyns [1]). The prevalence rate of infertility worldwide shows considerable variation; however, it is estimated to affect 15 % of couples globally (Agarwal, et al. [2]); and the regional variation among countries is a function of variation in predominant causes of infertility in a particular geographic area (Datta, et al. [3]). The opportunity of having live birth by infertile couples have been made very like following the invention and practicing assisted reproductive techniques (Almasi-Hashiani, et al. [4]). Intrauterine insemination (IUI) was one of the earliest methods in the field of assisted reproductive techniques (Allahbadia, GN [5]; Ombelet and Van Robays, [6]). Human implantation is an organized complex process involves an interaction between a receptive endometrium and a competent embryo. Diagnosis of endometrial receptivity (ER) has posed a task and so far, most offered tests have been subjective and lack of accuracy and significancy. Ultrasound is a non-invasive technique that can assess changes in the endometrium during stimulated cycles (Silva Martins, et al. [7]). Evaluation of uterine receptivity using a score determined on the basis of assessment of endometrial thickness, pattern, blood flow, myometrial contractions, pulsatility index of uterine arteries, myometrial echogenicity, and myometrial blood flow. This was termed as (Uterine Scoring System for Reproduction) or (Uterine Biophysical Profile) may be used as a predictor of implantation. To date, data regarding the validity of assessing each parameter as an indicative value for endometrial receptivity persist inconclusively and the impact of various ovarian stimulation protocols on endometrial receptivity has not been assessed in detail (Tiwary, et al. [8]).

## 2. Materials and Methods

The current cross-sectional study was conducted in the High Institute for Infertility Diagnosis and Assisted Reproductive Technologies in Al Nahrain University, Baghdad, Iraq from the 1st of October 2018 till the 1st of May 2019. The study was approved by institutional ethical approval committee and written consent was acquired from every couple participating in the study, involving seventy women of infertile couples with the same inclusion and exclusion criteria, received minimal ovarian stimulation (using Clomiphene Citrate and Human Menopausal Gonadotropin) protocol with IUI. Inclusion Criteria: Age 19-39 years; accepted seminal fluid analysis of male partners; with one or both patent tubes and no uterine anomalies. Exclusion Criteria: History of ovarian cyst or surgery; endometriosis; bilateral tubal disease; untreated endocrine, a medical or psychological disease that contrary to pregnancy. Uterine biophysical profile was evaluated using the Doppler ultrasound examination and then a score was calculated and correlated to pregnancy outcome. Cycle monitoring was done using Honda ultrasound to monitor follicular size and number and endometrial thickness and pattern by 2D transvaginal ultrasound probe done at CD2, CD7, and till the day of ovulation trigger every two days or daily. On the day of the trigger before the administration of hCG, transvaginal ultrasound (TVUS) was done measuring: number of follicles of 18-24mm in average diameter and endometrial thickness and pattern. On the day of IUI: Doppler ultrasound was performed in Ultrasound Clinic by radiology specialist using Voluson P8 from GE Healthcare USA, by 5-9 Mhz transducer for B mode and color imaging as well as pulsed Doppler spectral analysis to check ultrasound findings of ovulation, to detect the position of the uterus and simplify access to the cavity during IUI and to apply uterine biophysical profile (UBP) evaluation according to the UBP by Michael Applebaum (Navinchandra, et al.

[9]). According to Applebaum, the endometrial and peri-endometrial areas are divided in terms of endometrial vascularity into the following four zones:

1-**Zone 1**: A 2 mm thick area surrounding the hyperechoic outer layer of the endometrium

2-**Zone 2**: The hyperechoic outer layer of the endometrium

3-**Zone 3**: The hypoechoic inner layer of the endometrium

4-**Zone 4:** The endometrial cavity.

The UBP by Michael Applebaum is calculated by measuring seven parameters: (Navinchandra, et al. [9])

1. Endometrial thickness
2. Endometrial layering (i.e., a 5-line appearance)
3. Myometrial contractions (seen as endometrial motion)
4. Myometrial echogenicity
5. Endometrial blood flow
6. Gray-scale myometrial blood flow.
7. Uterine artery Doppler flow evaluation

**1-Endometrial thickness** was measured in a median longitudinal plane of the uterus as the maximum distance between the endometrial-myometrial junctions of the anterior to the posterior wall of the uterus

**2-Endometrial pattern** noticed was either distinct 5–line/trilaminar appearance which is hypoechoic endometrium with well-defined hyperechoic outer walls and a central echogenic line, or hazy 5- line/ trilaminar appearance endometrium which appeared as an endometrial pattern that was transitioning into an echogenic one at the myometrial and endometrial interface, but still had well-defined central echogenic line with hypoechoic areas between these lines, and endometrium with on layering which is a homogenous hyperechoic endometrium with a distracted central echogenic line.

**3-Myometrial contraction**: Myometrial contractions were monitored by two observers. Wave frequency was considered as the number of waves during 2 minutes period. Concentration on moderate and strong movement rather than weak one and those directed cranially was concerned.

**4-Subendometrial vessels** were usually visualized at the periphery of the endometrium. Sometimes they penetrated the hyper-echogenic endometrial edge or even reached the endometrial cavity. The blood flow velocity waveforms from the sub endometrial vessels were obtained by placing the Doppler gate over the color area and activating the pulsed Doppler function (El-Zenneni, et al. [10]).

**5-Pulsatility Index of Uterine Artery**: The Doppler gate was then placed over both uterine arteries lateral to the cervix and the same examination was repeated. (PI) were measured automatically by using the software program in the equipment, the average of both sides results was recorded. PI= (peak systolic velocity - end diastolic velocity)/mean velocity during the cycle.

**6-Uterine myometrial echogenicity** was assessed as uniform which is relatively (homogeneous) or non-uniform (coarse inhomogeneous).

**7-Myometrial vascularity** to the arcuate arteries can be seen power Doppler rather than color Doppler because power Doppler is more sensitive to detect flow in smaller vessels and low velocity flows, myometrial vascularity is seen in the outer part of the myometrium running parallel to the serosa. For each patient scoring, all parameters and calculation of the total score number which is out of twenty were done. Data were summarized, analyzed, and presented using statistical package for social sciences (SPSS) version 23 and Microsoft Office Excel 2010. Quantitative variables were expressed as mean and standard deviation (SD); whereas, categorical variables were expressed as number and percentage. Independent samples t-test was used to compare mean

values between two groups, while the Chi-square test was used to study associations between any two categorical variables. Receiver operator characteristic (ROC) curve analysis was used to identify cutoff values with corresponding accuracy, sensitivity, and specificity levels. The level of significance was set at $P \leq 0.05$.

## 3. Results

Overall the positive pregnancy outcome of the entire sample subjected to IUI was 15 out of 70 accounting for 21.4 %. The correlations of pregnancy outcome to demographic characteristics of infertile women involved in the current study are shown in Table 1. Positive pregnancy outcome was not correlated to any of the demographic characteristics of enrolled infertile women, Table 1. Correlations of pregnancy outcome to uterine biophysical profile score characteristics are shown in Table 2. Mean endometrial thickness did not affect positive pregnancy outcomes significantly (p = 0.350), so as endometrial thickness score (p = 0.649). In addition, Spearman correlation failed to show significant correlation between positive pregnancy outcome and endometrial score (r = 0.042; P = 0.733). Regarding endometrial layering, there was no significant association between pregnancy outcome and endometrial layering score (p = 0,382). Spearman correlation failed to show significant correlation between positive pregnancy outcome and endometrial layering score (r = 0.163P = 0.177). There was no significant association between myometrial contractions and pregnancy outcome (p = 0.610). Spearman correlation failed to show significant correlation between positive pregnancy outcome and myometrial contraction (r = 0.104; P = 0.390), Table 2. Mean UAPI was significantly lower in women with positive pregnancy in comparison to women with negative pregnancy, 2.10 ±0.19 versus 2.47 ±0.65, respectively (p= 0.032). Moreover, no women with PI score (0) succeeded to get pregnant and the higher the score, the higher the rate of pregnancy

(p= 0.006) Table 2 and Figure 3. Furthermore, Spearman correlation showed significant positive correlation between positive pregnancy outcome and UAPI (r = 0.365; p = 0.002). The pregnancy outcome was not significantly associated with myometrial blood flow in zone 3 (P = 0.248). Spearman correlation failed to show significant correlation between positive pregnancy outcome and myometrial blood flow in zone 3 (r = 0.197; p= 0.103). Finally, the mean total score was significantly higher in women with positive pregnancy than in women with negative pregnancy, 18.27 ±1.33 versus 16.35 ±2.47, respectively (p = 0.005) Table 2 and Figure 4. Therefore, the presence of a cutoff value for a total score to predict positive pregnancy outcomes and accordingly ROC curve analysis was carried out and the results are shown in Figure 2 and Table 3. The cutoff 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 %.

## *4. Discussion*

In the current study, mean endometrial thickness, endometrial layering, myometrial contractions, and zone three myometrial blood flow did not affect pregnancy outcome significantly, whereas, clinical pregnancy was significantly correlated to less uterine artery pulsatility index (UAPI). The mean total score of Doppler ultrasound was significantly higher in women with positive pregnancy than in women with negative pregnancy. The total score cutoff 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 %. On the contrary to our results, the pregnancy rates were higher in women with thick, distinct five-line endometrium and multifocal endometrial vascularity within zone 3, in a study assessing the role of endometrial ultrasound scoring in association with ART outcome (Khan, et al. [11]).

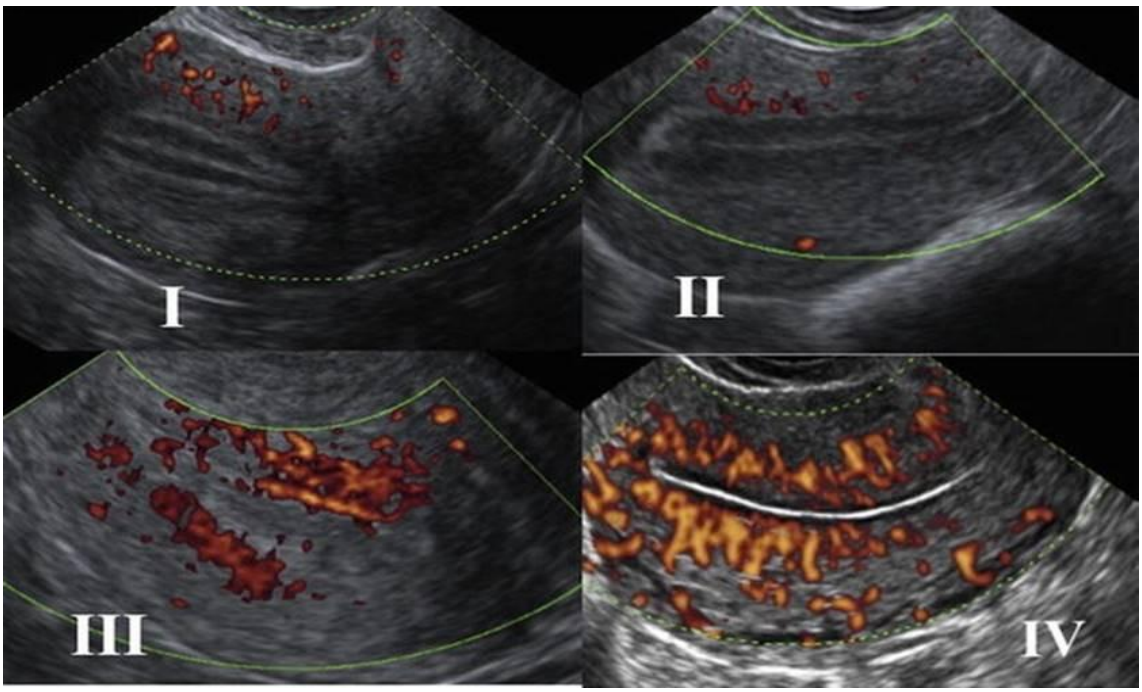


***Figure (1):*** Endometrial vascularity four zones (Bhadauria, et al. [12])

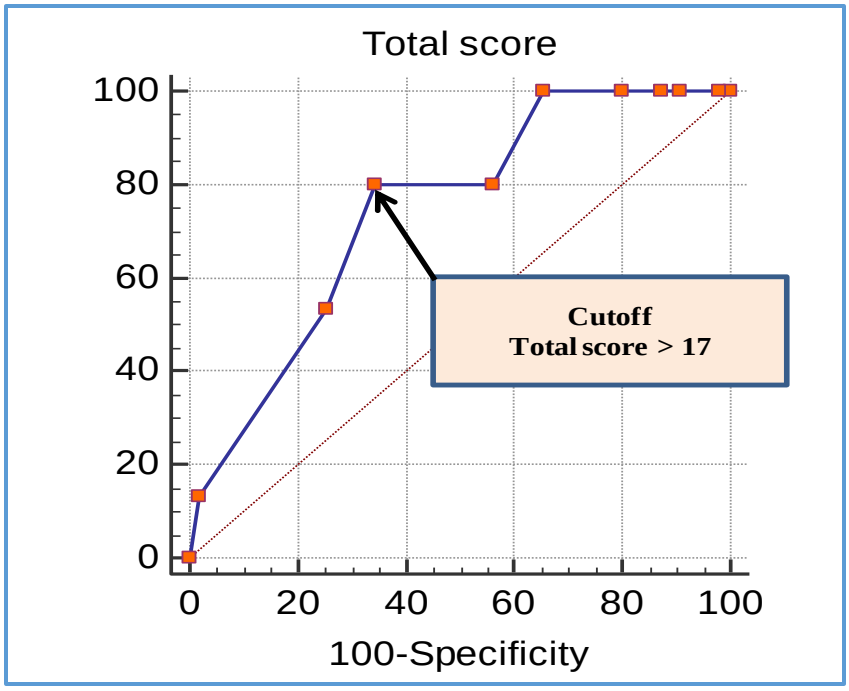


***Figure (2):*** Receiver operator characteristic (ROC) curve analysis to find the best total score cutoff value that can predict positive pregnancy outcome

***Table (1):*** Demographic characteristic of infertile women according to pregnancy outcome

| Characteristic | Negative pregnancy n = 55 | Positive pregnancy n = 15 | *P* | *R* | *P* |
|---|---|---|---|---|---|
| **Age (Years)** | | | | | |
| **Mean ±SD** | 27.07 ±4.98 | 26.20 ±4.25 | 0.538 † NS | --- | --- |
| **<35** | 50 (90.9) | 14 (93.3) | 1.000 € NS | --- | --- |
| **>35** | 5 (9.1) | 1 (6.7) | | | |
| **BMI (kg/m$^2$)** | | | | | |
| **Mean ±SD** | 25.15 ±2.99 | 25.39 ±2.55 | 0.782 ¥ NS | --- | --- |
| **Normal** | 27 (49.1) | 5 (33.3) | 0.455 ¥ NS | 0.068 | 0.575 β NS |
| **Overweight** | 23 (41.8) | 9 (60.0) | | | |
| **Obese** | 5 (9.1) | 1 (6.7) | | | |
| **Duration of infertility (years)** | | | | | |
| **Mean ±SD** | 4.84 ±2.86 | 5.30 ±2.23 | 0.565 † NS | --- | --- |
| **<5** | 28 (50.9) | 7 (46.7) | 0.690 ¥ NS | 0.019 | 0.878 β NS |
| **5-10** | 25 (45.5) | 8 (53.3) | | | |
| **>10** | 2 (3.6) | 0 (0.0) | | | |
| **Type of infertility** | | | | | |
| **Primary** | 41 (74.5) | 12 (80.0) | 0.923 € NS | --- | --- |
| **Secondary** | 14 (25.5) | 3 (20.0) | | | |
| **Cause of infertility** | | | | | |
| **PCOS** | 19 (34.5) | 8 (53.3) | 0.378 ¥ NS | --- | --- |
| **Combined** | 12 (21.8) | 3 (20.0) | | | |
| **Unexplained** | 24 (43.6) | 4 (26.7) | | | |

***n*: number of cases; BMI: body mass index; data were expressed as either mean standard deviation or number (%); †: independent samples t-test; ¥: Chi-square test; NS: not significant at $P \leq 0.05$**

***Table (2):*** Uterine biophysical profile score characteristics according to pregnancy outcome

| Characteristic | Negative pregnancy n = 55 | Positive pregnancy n = 15 | *P* | *R* | *P* |
|---|---|---|---|---|---|
| **Endometrial thickness** | | | | | |
| **Mean ±SD** | 8.77 ±1.20 | 9.09 ±0.96 | 0.350 † | --- | --- |
| **< 6 mm = 0** | 3 (5.5) | 0 (0.0) | 0.649 ¥ NS | 0.042 | 0.733β NS |
| **7-9 mm = 2** | 41 (74.5) | 12 (80.0) | | | |
| **10-14 mm = 3** | 11 (20.0) | 3 (20.0) | | | |
| **Endometrial layering** | | | | | |
| **No layering=0** | 3 (5.5) | 0 (0.0) | 0.382 ¥ NV | 0.163 | 0.177 β NS |
| **Hazy 5line appearance =1** | 9 (16.4) | 1 (6.7) | | | |
| **Distinct- 5line appearance =3** | 43 (78.2) | 14 (93.3) | | | |
| **Myometrial contractions in 2 min** | | | | | |
| **3=3** | 14 (25.5) | 2 (13.3) | 0.610 ¥ NV | 0.104 | 0.390 β NS |
| **4=3** | 32 (58.2) | 10 (66.7) | | | |
| **5=3** | 9 (16.4) | 3 (20.0) | | | |
| **Myometrial contractions in 2 min (score)** | | | | | |
| **3** | 55 (100.0) | 15 (100.0) | --- | --- | --- |
| **Myometrial Echogenicity** | | | | | |
| **Relatively Homogenous =2** | 55 (100.0) | 15 (100.0) | --- | --- | --- |
| **Uterine artery pulsatility index (UAPI)** | | | | | |
| **Mean ±SD** | 2.47 ±0.65 | 2.10 ±0.19 | 0.032 † S | --- | --- |
| **PI >2.5 = 0** | 24 (43.6) | 0 (0.0) | 0.006 ¥ HS | 0.365 | **0.002 β HS** |
| **PI 2.2-2.49 = 1** | 15 (27.3) | 6 (40.0) | | | |
| **PI <2.2 = 2** | 16 (29.1) | 9 (60.0) | | | |
| **Endometrial Blood flow within Zone 3** | | | | | |
| **Absent = 0** | 4 (7.3) | 0 (0.0) | 0.248 ¥ | 0.197 | 0.103 β |
| **Present but sparse = 2** | 15 (27.3) | 2 (13.3) | | | |
| **Present multifocal =5** | 36 (65.5) | 13 (86.7) | | | |
| **Myometrial Blood flow** | | | | | |
| **Present =2** | 55 (100.0) | 15 (100.0) | --- | --- | --- |
| **Total Uterine Biophysical Profile score =20** | | | | | |
| **Mean ±SD** | 16.35 ±2.47 | 18.27 ±1.33 | **0.005 † HS** | --- | --- |

***n*: number of cases, NV Non valid; data were expressed as either mean standard deviation or number (%); †: independent samples t-test; ¥: Chi-square test; NS: not significant at *P* ≤**

*Table (3):* Total score ROC curve characteristics

| Characteristic | Value |
|---|---|
| **Cutoff** | >17 |
| **AUC** | 0.742 |
| **95% CI** | 0.624 - 0.840 |
| **Accuracy** | 74.2 |
| ***P*** | <0.001<br>HS |
| **Sensitivity** | 80 % |
| **Specificity** | 65.5 % |

**AUC: area under curve; CI: confidence interval; HS: highly significant at $P \leq 0.01$**

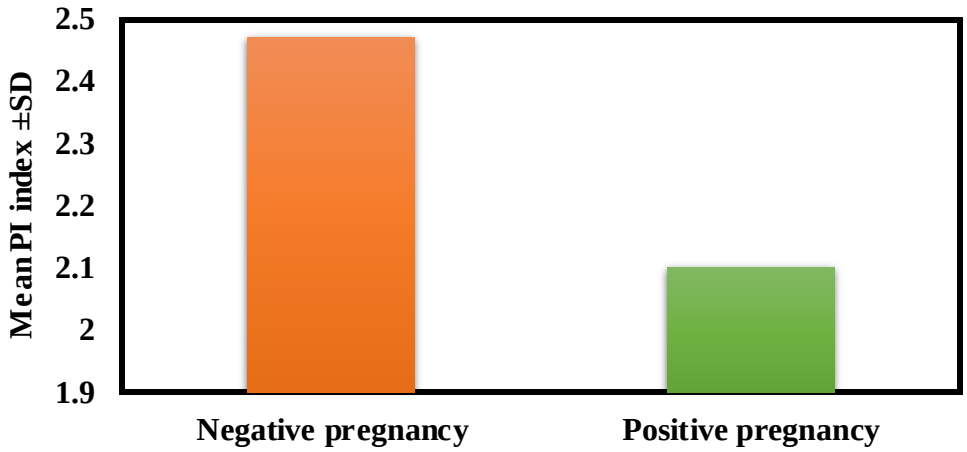


*Figure (3):* Mean PI index according to pregnancy outcome

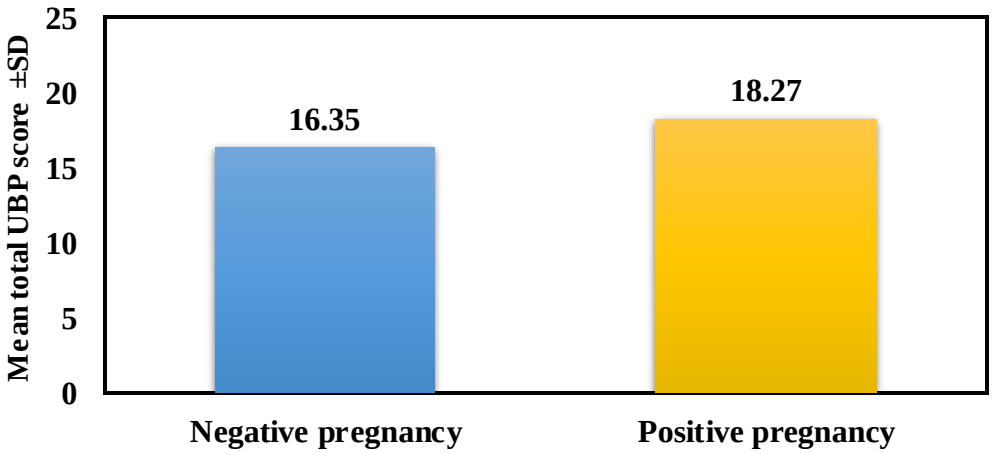


*Figure (4):* Mean UBP index according to pregnancy outcome

However, in agreement with our study, the latter study (Khan, et al. [11]) and other studies (Baruffi, et al. [13]; Aghahoseini, et al. [14]) found no significant association between myometrial blood flow and pregnancy outcome. (Khan, et al. [11]) also found a significant association between endometrial layering and pregnancy outcome, again in clear contradiction to our findings. The lack of a significant association between endometrial thickness and pregnancy outcome is in agreement with several other authors (Kolibiianahis, et al. [15]; Habibzadeh, et al. [16]) stated that women with endometrial thickness less than 6 mm have significantly lower pregnancy rate than women with an endometrial thickness higher than 6 mm; therefore, the lack of significant effect of endometrial thickness on the rate of pregnancy in our study may be explained by that most of women enrolled in the current study had an endometrial thickness of > 6 mm. Therefore, the overall score of endometrial and myometrial assessment should be considered rather than individual sonographic criteria when dealing with the prediction of positive pregnancy outcome as was the case in the current study in which the total ultrasound score was the main determinant with a cutoff value that had acceptable accuracy level. The current study result agreed by (Navinchandra, et al. [9]) study that found no significant effect of vascularity within zone 3 and pregnancy outcome. On the contrary to the study results, pregnancy rates were higher in women with thick, distinct five-line endometrium and multifocal endometrial vascularity within zone 3, in a study assessing the role of endometrial ultrasound scoring in association with ART outcome (Khan, et al. [11]). However, in agreement with the study, (Khan, et al. [11]; Baruffi, et al. [13]; Aghahoseini, et al. [14]) found no significant association between myometrial blood flow and pregnancy outcome. (Kim, et al. [17]; Khan, et al. [11]) found a significant association between endometrial layering and pregnancy outcome, again in clear contradiction to

present findings. (Masrour, et al. [18]) demonstrated that the endometrial blood flow was significantly greater in pregnant women and that the endometrial thickness and pattern of sonography did not have any predictive values for endometrial receptivity these results are similar to the current study concerning endometrial thickness and dissimilar to current results regarding sub endometrial vascularity and pregnancy. There was a negative correlation between pregnancy outcome and Uterine Artery Pulsatility Index (UAPI). Some authors have studied the difference in PI between pregnant and nonpregnant women following ARTs and have found, on the contrary to this study, no significant difference (Prasad, et al. [19]). However, other authors concluded that lower PI was correlated with positive biochemical pregnancy outcome in line with the findings of the current study (Navinchandra, et al. [9]; Martins, et al. [7]). These findings may relate to the hormonal status during ovarian controlled stimulation and the effects of relatively higher serum. Oestrogen promotes vascular smooth muscle relaxation and reduces sensitivity to adrenergic stimulation (Guedes-Martins, et al. [20]).


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## *Author Contribution*

Abunayla RSH, performed the study, Al-Anbari LA, Abood MS, and Husaini HAR, supervised the work.

## *Conflict of Interest*

The authors declare no conflict of interest.

## *Ethical Clearance*

The study was approved by the Ethical Approval Committee.

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## *Biography*

**Dr. Rawaa Saad Hasan Abunayla**

She graduated from Tikrit University, College of Medicine in 1996. Completed permanency in gynecology and Obstetrics in 2002. Received the Diploma in Obstetrics and Gynaecology in 2007 from Baghdad University, College of Medicine. She worked as a senior at Al Rumaitha General Hospital. Currently she is a student in the High Diploma in Clinical Infertility and ARTs in High institute for Infertility Diagnosis and ARTs Al Nahrain University, 2020.

**Dr. Lubna Amer Al-Anbari**

She received the M.B.CH.B., the Higher diploma from the college of medicine, University of Baghdad, in 2004, and 2011, respectively. She received the board in infertility from the Iraqi society of medical specialists in 2012. She published many kinds of research both local and international. She supervised many students. She held many academic positions.

**Dr. Muayad S. Abood**

He received the M.B.CH.B. from Al-Kufa University, the M.Sc., and the Ph.D. in Pharmacology from Al Nahrain University, in 1998, 2008, and 2014, respectively. He occupied several academic positions including the dean assistant for scientific affairs at Al Nahrain University. He has more than 10 published papers both local and international.

**Dr. Huda A. R. Hussaini**

She received the M.B.Ch.B: Babylon University, college of medicine, in 2000. The diploma in Radiology from the University of Baghdad in 2007. She is a fellow of the Iraqi Board for Medical Specialization, Council of Radiology since 2008. Currently, she is an assistant professor. Al Nahrain University, College of Medicine, department of surgery ( specialist radiologist ). She is a Member of staff in the high Institute of infertility diagnosis and ARTS. Including the ultrasound department in the institute since 2018. She has Participations in a lot of annual meetings, medical conferences. Seminars,

continuous learning, and thesis discussion. She is a member of the Iraqi medical association, the Iraqi Society of radiologist and medical imaging, Iraqi Journal of Embryos infertility researches, European Society for Hybrid, Molecular, and translation imaging. She published more than articles and has supervised many students.

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