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Dual trigger impacton Endometrial receptivity and uterine biophysical profile role in predicting the conception rate in infertile women in IUI cycle.

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ABSTRACT

Failure to conceive may be deeply upsetting and stressful, eventually leading to social, physical, and psychological implications. This study aimed to evaluate the impact of dual trigger on endometrial receptivity and the role of uterine biophysical profile in estimating the conception rate in women with primary or secondary infertility. A comparative prospective randomized clinical study was conducted at the High Institute for Infertility Diagnosis and Assisted Reproductive Technologies/ Al-Nahrain University, from October 2019 to April 2020. 90 infertile women who were attending the infertility diagnosis clinic of the institute was included in the study, receiving stimulated intrauterine insemination. Vaginal ultrasound was done for all women at the early and mid-follicular phase. The uterine scoring system for reproduction was assessed and total score of 20 was calculated and subsequently correlated to conception rate. A uterine scoring system for reproduction cut-off of 16 showed a sensitivity of 86.4% and a specificity of 75%. Patients with total score of 18, pulsatility index of lower than 1.79, and three or more endometrial contractions had the highest prevalence of successful pregnancy. Individual variables of endometrium (thickness, pattern, blood flow in zone 3, and myometrium features) had no statistical significance Applebaum's uterine score system for reproduction is a simple and non-invasive ultrasonic assessment. Low pulsatility index, endometrial contraction ≥3, and total score of 18 can point to the appropriate endometrial environment for implantation as well as the rate of conception.

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KEYWORD

Uterine Scoring System for Reproduction (USSR), Pregnancy rate, Endometrial thickness, Endometrial blood flow, Pulsatility index

1. Introduction

Infertility is a common problem of the reproductive system, defined as failure to obtain a healthy pregnancy after 12 months or more of regular, unprotected intercourse in women under 35 years of age, or within 6 months in women over 35 years of age, it affects up to 15% of couples **(ACOG ,2019[1]).**

Intrauterine insemination is the treatment of choice for infertile couples due to low costs, reduced invasiveness, and minimal clinical monitoring requirements, with cumulative live birth rate of 15 to 20% **(Allahbadia GN., 2017 [2])** . Dual trigger in stimulated intrauterine insemination was a matter of debate. It,s beneficial effect is based on the hypothesis that an increase in FSH in response to GnRHa causes oocyte meiosis and nucleus maturation, promotes LH receptor in granulosa cells, and increases cumulus cell expansion. Human chorionic gonadotropin(HCG) is a component of dual trigger that serve as a second rescue trigger in the event of a poor response to GnRH-a. It also has the potential to induce GnRH receptors in the endometrium and cause an increase in endometrial receptivity, enhanced angiogenesis, implantation parameter modification, and tissue remodeling **(Meyer et al.,2015[3]).** Although there is no precise way for predicting conception throughout any menstrual cycle, imaging female reproductive organs with transvaginal ultrasonography is quick, simple, non-invasive, and reproducible in analyzing female pelvic organs **(Chizen DR &Pierson RA , 2010[4]).**

Ultrasound examination of the endometrium had become a routine practice for the diagnostic purposes and treatment of infertility, with varied degrees of effectiveness to predict the possibility of conception in a spontaneous cycle, ovulation stimulation cycles and in vitro fertilization (IVF) cycles **(Shivtate et**

al .,2019[5]) . Many factors, including uterine receptivity play a role in successful implantation. Endometrial receptivity is described as a temporary, sporadic occurrence of a unique sequential receptivity factors that prepares the endometrium for embryonic implantation. It is the a short window of time during which the uterine surrounding is conducive to blastocyst adhesion and subsequent implantation **(Altema &Aghajanova L .,2019[6], Aynekin et al.,2022[23])**.

Adequate endometrial blood flow is needed for optimal endometrial growth and increased endometrial receptivity **(Khan et al .,2015[7])**.

Some sonographic findings are vitally necessary to examine the uterus, myometrium, endometrial thickness, appearance, and endometrial vascularity prior to implantation in order to get the best possible results. These findings are compiled into a uterine biophysical profile, which refers to an assessment of the uterus to implantation environment, and they are measured according to Applebaum's uterine scoring system for reproduction (USSR)**(Applebaum M .,1995[8]).**

Many factors, including age, the cause of infertility, estradiol levels, and stimulation strategy, can influence these outcomes **(Masrour, et al[9])**.

2. Materials and Methods

This prospective comparative clinical study was conducted in the High Institute for Infertility Diagnosis and Assisted Reproductive Technologiesl/Al Nahrain University, Baghdad, Iraq from the 1st of October 2019 till the 1st of April 2021. The study was approved by institutional ethical approval committee and each participant signed a written consent formsemen analysis and the females should have a normal thyroid function test and normal blood sugar levels. 90 women of infertile couples between 18-40 years with history of primary or secondary infertility who attending the infertility diagnosis clinic of the

institute were randomly divided into two group:

Group 1: 45 women undergo minimal ovarian stimulation with letrozol and HMG then ovulation triggered by dual trigger(triptolline 0.1 mg and ovitrelle 250µg).

Group 2: 45 women undergo ovarian stimulation and triggering of ovulation by rHCG (Ovitrelle 250 µg). After 36-42 hour IUI done in both group.

Inclusion Criteria: one or both patent tubes, normal uterine cavity.

Exclusion Criteria: Bilateral blocked tube ,endocrine or medical disease, mild endometriosis, male factors with exception of mild male factors

1- Controlled ovarian stimulation

The demographic criteria of all women was documented: age, BMI, type and cause of infertility including (PCOS, unexplained ,mild male factor, mild endometriosis)with baseline hormonal analysis (LH,FSH, Prolactin ,TSH)and Transvaginal ultrsound at cycle day2 ,and seminal fluid analysis according to WHO 2010 for male partners .

Controlled ovarian stimulation with letrozole (femara; Sanofi-Aventis ,France)2.5 mg twice daily from cycle day 3 to cycle day7 and HMG(Human Menopausal gonadotropin ;Menogon , Ferring pharmaceutical Switzerland)75 IU intramuscular injection was added based on ovarian response, monitoring by 2D Trans vaginal Honda Ultrasound prob, was conducted from CD7 every two to three days till two or three mature follicle of 18-22 mm in size are observed , then ovulation trigger was administrated.

45 women were received dual trigger(Ovitrelle Merck Serono and Triptorelin (decapeptyl) 0.1 mg Ferring Pharmaceutical Switzerland) subcutaneously , another 45women received recombinant rhCG, Ovitrelle 250 µg, Merck Serono) subcutaneously. For each group Intrauterine insemination was planned after 36-42 hour.

2- Transvaginal ultrasound and Doppler study

All the patients on the day of IUI, were examined by TVUS and Doppler study between 9.00 and 11.00 A.M by the same radiology specialist in Ultrasound Clinic. They took a 10-minute rest to minimize the effect of the exercise and avoid the circadian rhythmicity on uterine blood flow, after emptied their bladders, Doppler trasvaginal ultrasound(Voluson P8 /sony from GE Healthcare USA) was applied for assessment of endometrial parameters(thickness ,pattern , blood flow at zone 3 and mean UAPI ,myometrial contraction and echogencity).Endometrial thickness was obtained by a longitudinal view and measured at the maximal thickness between the endometrial- myometrial junctions. Endometrial pattern was observed either distinct triple pattern or hazy . Endometrial wave like motion was calculated over 2minute period and recorded. Uterine Artery Pulsatility Index UAPI is obtained by placing the Doppler gate over right and left uterine arteries lateral to the cervix, , the sample gate was 2 mm wide to cover the entire vessel, with an insonation angle of less than 30o. After acquiring three identical successive waveforms, the mean PI is calculated as the average of the left PI and right uterine artery PI, then mean PI was recorded automatically. In the same longitudinal image of the uterus, endometrial vascularity at zone 3 , myometrial echogencity and blood flow were observed. Applebaum's uterine biophysical profile total score was determined for each woman

(Applebaum ,1995[8]).

The following are the scores for each parameter: Each parameter is scored as follow; Endometrial thickness: <=0, 7-9mm=2, 10-14mm=3, more than 14=1. Endometrial layering: no layering=0, Hazy tri laminar appearance =1, Distinct-tri laminar line =3. Myometrial contraction (seen as wave

like endometrial motion)<3contraction in 2min(real time)=0, >3 contraction in 2min(real time)=3.

Myometrialechogencity:Coarse/inhomogenousechogenicity =1, Relative homogeneous echogencity=2. Uterine artery Doppler flow (pulsatility index PI) PI >3.0-2.5=0, PI <2.2-2.49=1, PI <less than 2.1-2.9=2 Endometrial blood flow within zone 3: Absent =0 ,Present ,but spare =2 ,Present multi focally =5 Myometrial blood flow internal to the arcuate vessles on gray scale:Absent=0,Present=1(Navinchandra,2016). For each women scoring all parameters and total score out of twenty was calculated.

3- Intrauterine Insemination

was done after aspiration of 0.5-1ml of prepared seminal fluid sample by 1ml syring attached to IUI catheter (Gynetics ,Belgium) and immediately the female was promptly inseminated in lithotomy position in an isolated room . After the procedure, each patient held in a supine position for 30 minute.

4- Luteal support

by progesterone vaginal suppositories(Cyclogest 400mg once daily started from the next day after IUI for 14 days. Biochemical pregnancy was defined by serum B-HCG level of 25 IU/ml or higher 14 days after IUI.

3. Statistical analysis

Microsoft Office Excel 2010 and (SPSS) version 23 were used to summarize, analyze, the data. Continuous data are expressed as mean ±SD for normal distribution of variables and Categorical data were expressed as number and percentage, independent samples t-test (two tailed)was used to compare mean values between two groups, Chi-square test was used to study the association between two categorical variables**.** Fisher,s exact test was used when the expected values of more than 20% of the cells of the table were less than 5. ROC curve analysis use to estimate the cutoff point of USSR above which the test result considered

positive in predicting the pregnancy. The two tailed p≤ 0.05 was the cutoff value of significance.

4.Results

1- The association between general characteristics and IUI cycle outcome

The overall conception rate was 22 out of 90 (24%) . The association of pregnancy outcome to general characteristics of infertile women are shown in (**Table-1**). No statistical significant differences between pregnant women and those not pregnant in all other characteristics .

2- The comparison in Doppler study finding between study groups

There were no statistical significant differences (P ≥ 0.05) in all Doppler findings of endometrium between the two groups as shown in **(Table-2)**.

3- The comparison in Doppler study finding according to pregnancy outcome

Table-3 show that women with mean PI 1.79 became pregnant , whereas women with a mean PI 2.2 did not(P= 0.001) .There was significant association between myometrial contraction in 2min and pregnancy outcome. Pregnant women had ≥ 3 contractions (50% P= 0.001).

There were no significant association was detected between the pregnancy outcome and endometrial thickness , pattern, blood flow at zone3, myometrial echogenicity and blood flow (P ≥ 0.05). The mean UBP score was 18.09 among pregnant women and 15.04 among those who not pregnant (P= 0.001).

4- SPSS output for the area under the curve(ROC curve analysis)

ROC (Receiver Operating Characteristic) curve analysis was constructed where mean PI and USSR score was used as a predictor for pregnancy outcome. The cut point of mean PI was 1.95 and for the total UBP score was 16 . Because the area under the curve for PI and total UBP

score was considerable , a high total score of UBP> 16 and a lower mean PI< 1.95 can be utilized to predict the outcome as presented in **(Table-4)** ,**(Figure-1)** and **(Figure 2)** . The highest sensitivity of 86.4% and a specificity of 75% when a cut –off value of 16 scores was considered. Other details are shown in **(Table-5)**.

Table(1): Association between general characteristics and IUI cycle outcome

Variable	IUI cycle outcome		*Total*)%(*n= 90*	*P*
	Pregnant)%(**n= 22**	**Not pregnant**)%(**n= 68**		
Type of infertility				
Primary	7 (17.5)	33 (82.5)	40 (44.4)	**0.17**
Secondary	15 (30.0)	35 (70.0)	50 (55.6)	
Cause of infertility				
Unexplained	16 (34.0)	31 (66.0)	47 (52.2)	**0.225**
PCOS	4 (17.4)	19 (82.6)	23 (25.6)	
Mild male factor	1 (8.3)	11 (91.7)	12 (13.3)	
Endometriosis	0 (0)	3 (100.0)	3 (3.3)	
Combined	1 (20.0)	4 (80.0)	5 (5.6)	
	Mean ± SD	**Mean ± SD**	**P - Value**	
Age (Year)	29.86 ± 5.8	29.02 ± 5.8	**0.559**	
BMI (kg/m2)	23.85 ± 4.3	25.46 ± 4.9	**0.146**	
Infertility duration (Year)	3.22 ± 2.5	4.03 ± 3.3	**0.232**	

*Significant difference between percentages using Pearson Chi-square test (χ^2-test) at 0.05 level.

#Significant difference between two independent means using Students-t-test at 0.05 level.

Table (2): The comparison in Doppler study finding between study groups

After 36 hours		Study group (Dual trigger)		Control (HCG only)		P value
		No	%	No	%	
Doppler Endometrial thickness (mm)	<10 mm	26	57.8	29	64.4	0.517
	=>10 mm	19	42.2	16	35.6	
	Mean± SD (Range)	9.11±1.81 (6-13)		9.00±2.11 (7-16)		0.797
Doppler Endometrial	Hazy	4	8.9	5	11.1	0.725
	Distinct	41	91.1	40	88.9	
Doppler MyomtrialEchogencit	Relative homogenous	45	100.0	45	100.0	-
	Not	-	-	-	-	
Myometrial Blood Flow	Present	45	100.0	45	100.0	-
	Not	-	-	-	-	
Endometrial Blood Flow	Spare	9	20.0	6	13.3	0.396
	Multifocal	36	80.0	39	86.7	
Myometrial Contraction	< 3	34	75.6	28	62.2	0.172
	> 3	11	24.4	17	37.8	
Doppler Mean PI	1-1.9	17	37.8	22	48.9	0.471
	2-2.9	24	53.3	21	46.7	
	3-3.9	4	8.9	2	4.4	
	Mean± SD (Range)	2.20±0.52 (1.32-3.1)		2.01±0.48 (1.05-3.2)		0.266
Doppler Total Score	8	2	4.4%	-	-	0.671
	10	2	4.4%	1	2.2%	
	12	5	11.1%	4	8.9%	
	14	10	22.2%	14	31.1%	
	16	15	33.3%	14	31.1%	
	18	11	24.4%	12	26.7%	
	Mean± SD (Range)	15.49±2.83		16.09±2.22		0. 266

		(8-19)	(11-20)	

*Significant difference between percentages using Pearson Chi-square test (χ2-test) at 0.05 level.

#Significant difference between two independent means using Students-t-test at 0.05 level.

Table (3): The comparison in Doppler study finding according to pregnancy outcome

Doppler study finding	**IUI cycle outcome**		**Total (%) n= 90**	**P - Value**
	Pregnant (%) n= 22	**Not pregnant (%) n= 68**		
Endometrial pattern				
Distinct	22 (27.2)	59 (72.8)	81 (90.0)	**0.072**
Hazy	0 (0)	9 (100.0)	9 (10.0)	
Myometrial echogenicity				
Relative homogenous	45 (100.0)	45 (100.0)	90 (100.0)	**1.0**
Myometrial blood flow				
Present	45 (100.0)	45 (100.0)	90 (100.0)	**1.0**
Endometrial blood flow in Z3				
Multifocal	21 (28.0)	54 (72.0)	75 (83.3)	**0.079**
Spare	1 (6.7)	14 (93.3)	15 (16.7)	
Contraction				
< 3	8 (12.9)	54 (87.1)	62 (68.9)	**0.001***
≥ 3	14 (50.0)	14 (50.0)	28 (31.1)	
	Mean ± SD	**Mean ± SD**	**P - Value**	
Endometrial thickness (mm)	9.5 ± 2.0	8.9 ± 1.9	**0.231**	
Mean PI	1.79 ± 0.46	2.2 ± 0.48	**0.001#**	
Total UBP score	18.09 ± 1.6	15.04 ± 2.3	**0.001#**	

* Significant difference between percentages using Pearson Chi-square test (χ2-test) at 0.05 level

#Significant difference between two independent means using Students-t-test at 0.05 level

Table (4): SPSS output for the area under the curve (ROC curve analysis)

Study group (Dual trigger) Test Result Variables	Area Under the Curve (AUC)	Std. Error	P value	95% Confidence Interval	
				Lower Bound	Upper Bound
Doppler Mean PI	0.783	0.070	0.007*	0.647	0.919
Doppler Total Score	0.834	0.060	0.001*	0.717	0.952

Table (5): Diagnostic accuracy of ultrasound examination of mean PI and total UBP score for prediction of pregnancy

Variable	Cut-off value	Sensitivity	Specificity	PPV	NPV	Accuracy
Mean PI	1.95	77.3%	72.1%	47.2%	90.7%	73.3%
Total UBP score	16	86.4%	75%	52.8%	94.4%	77.8%

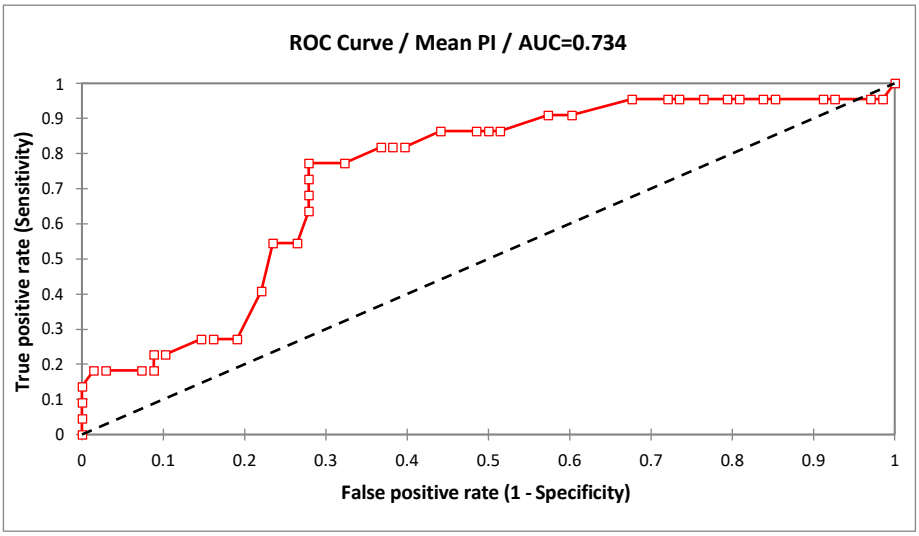

Figure (1): Receiver operator characteristic (ROC) curve analysis to find the mean PI cutoff value that can predict positive pregnancy outcome

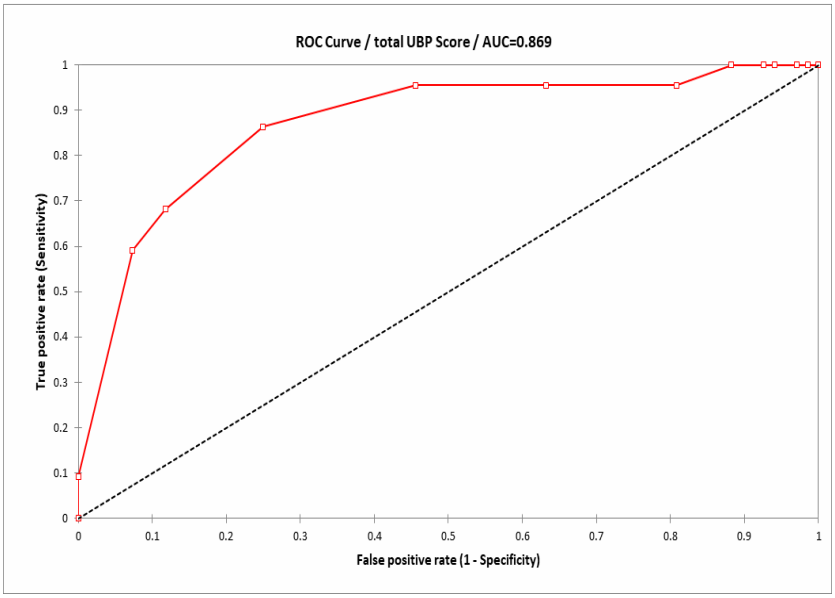

Figure (2): ROC curve for total UBP score in predicting successful pregnancy outcome

Discussion

The administration of dual trigger in COS/ IUI was a matter of debate . The beneficial effect of this intervention is based on the suggestion that FSH surge in response to GnRHa has positive effects on the oocyte meiosis resumption, nucleus maturation, promotes LH receptor in granulosa cells also increases the cumulus cells expansion. The hCG component has potentialy enhance the endometrial receptivity by inducing GnRH receptors, lead to prolongation of endometrial receptivity, increased angiogenesis, modulation of implantation parameters and tissue remodeling **(Meyer et al.,2015[3])**.

1- The association between general characteristics and IUI cycle outcome

Age is a major independent risk factor for clinical pregnancy, live birth and miscarriage. After age of 34, the clinical pregnancy results began to drop significantly **(Sun., et al .,2020[10])**. In this study positive pregnancy outcomes were not connected to women age, which is consistent with study findings by **(Isa et al ., 2014[11])**.

Although the average age in the study group was 29, most studies consider female age to be the most important factor in predicting pregnancy in Assisted Reproduction, as increasing age is linked to pregnancy failure, poor oocyte quality, poor fertilization and implantation rate as shown in study by **(Ahmed et al., 2015[12])**. There were no significant association between the other demographic characteristics and pregnancy outcome.

2- The comparison in Doppler study finding between study groups

In the current study, the majority of women had endometrial thickness between 8 - 9.5 mm, and there was no significant difference in mean endometrial thickness and layering pattern, endometrial blood flow in zone 3, myometrial echogencity and blood flow. These comparable to study by **(Tong et al .,2020[13])**.

3- The comparison in Doppler study finding according to pregnancy outcome

The uterine artery Doppler indices offer a good sensitivity and specificity for detecting high uterine blood flow impedance, which is one of the reasons of unexplained infertility. Uterine artery Doppler thus should be included in the assessment of unexplained infertility **(Prasad et al., 2017[14])**.

In the present study lower uterine artery pulsatility index PI≤ 1.7 was correlate to conception while PI of 2.2 or more was associate with pregnancy failure ,this agree with study by **(Guedes Martine et al .,2015 [15])**. These findings are explained by the fact that elevated blood estradiol levels produce dilatation of the vascular smooth muscle and decrease susceptibility to adrenergic stimulation

In this study the cut-off value of mean PI was 1.95 with sensitivity of 77.3% and specificity of 72.1% , these results are agree to study findings by **(Ali et al ., 2021[16])**. They discovered that the optimal uterine artery pulsatility index (PI) cut-off value was 1.95, with a

sensitivity of 95%, specificity of 86.7%, diagnostic accuracy of 91.42%. Endometrial thickness's ability to predict pregnancy outcome is currently being debated. There is no established endometrial thickness cut-off figure that can assist the clinician to counsel patients on pregnancy outcomes .This study's findings are consistent with research by **(Masrour et al., 2019[9])** who observed that endometrial thickness and pattern by sonography had little predictive value for endometrial receptivity and had little promise for predicting IUI success rate. The vast majority of the pregnancies in the present study occurring when the endometrial thickness was more than 9 mm.

There were no endometrial thicknesses less than 6mm (thin endometrium), and the greatest pregnancy rate was found when the endometrial thickness was <10mm.

Although adequate perfusion of endometrium is vital for successful implantation and conception, as all pregnant women in our study had a triple line pattern and good vascularity of endometrium at zone 3, so there was no statistical difference observed in the current study. Similar findings were achieved in research conducted by **(Liao et al.,2021[17])** who suggest that that endometrial blood flow are higher in pregnant women, and associated with successful pregnancy outcome, and pregnancies do not occur when endometrial blood flow is not detected. Another study Another study demonstrated that women with thick endometrium, distinct five lines, and multifocal vascularity inside zone 3 had a higher pregnancy rate **(Khan et al .,2015[7])**.

A few studies have examined the relationship between endometrial movements and pregnancy after an IUI cycle. Endometrial motions play a role in the pregnancy outcome by acting as mechanical variables. The current study supports the results of **(Swierkowski et al., 2017[18])** that uterine contractions on the day of IUI

are associated with a higher pregnancy rates and may be used as an appositive predictor of pregnancy following IUI. These findings , however, contrast those of **(Chung et al. ,2016[19])**, who discovered no significant link between myometrial contractions and pregnancy outcome. **(kim et al .,2015[20])** was the first study to show that more than 4 endometrial contractions per minute are positive predictors of pregnancy in IUI cycles, and may provide clinicians with useful relevant information about endometrium.

In the current study the USSRS score (uterine scoring system for reproduction) was computed and no women had a perfect score of 20 and the highest pregnancy rate associated with a total score of 18, Another study, which agrees with ours, was conducted by **(Navinchandra et al.,2016 [21])** and revealed that no woman had a perfect score of twenty, whereas the pregnancy rate for patients with a score of 17-19 was 100% and for those with a score of 14-16 was 50%. All of the women who had a score of 13 were negative for pregnancy. A higher USSR score resulted in a better conception outcome, making it a valid predictive parameter). In the current study, the cut-off value of total UBP score was 16 with sensitivity of 84% , specificity of 75% which is comparable to another study by **(Sedeq MG .,2022 [22])**.

6- Conclusion

The dual trigger improves endometrial receptivity by reducing the uterine artery pulsatility index without affecting other endometrial variables (thickness, pattern, and blood flow). Applebaum ,s scoring (USSRS) is highly predictive of a high conception rate in women with a history of infertility, and the total score is simple to compute. Endometrial receptivity, as defined by lower PI, endometrial contraction, and a high overall score, according to the current study, is strongly related with a positive pregnancy outcome.

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Author Contribution

Zeki Thaker, performed the study, AlAnbari LA, and AL Esawee , supervised the work .

Conflict of Interest

The authors declare no conflict of interest .

Ethical Clearance

The study was approved by the Ethical Approval Committee.

Financial Disclosure

There is no financial disclosure.

Ethical Clearance

The study was approved by the Ethical Approval Committee

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