

Role of uterine biophysical profile in predicting conception in a sample of infertile women attending an IVF center in Erbil

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Abstract

Background and objective: Failure to get pregnant can be profoundly disappointing, frustrating and eventually lead to a lot of social, medical, and psychological consequences like depression. This study aimed to evaluate the role of uterine biophysical profile in predicting conception in women with a history of infertility.

Methods: A prospective diagnostic accuracy study was conducted in Erbil, Iraqi Kurdistan region, in the Maternity Teaching Hospital from October 2019 to September 2020 on 51 women suffering from primary and secondary infertility. Vaginal ultrasound was performed for all the women at mid-cycle and before embryo transfer. The uterine scoring system for reproduction by Applebaum was calculated, and the total score was obtained. Its role in predicting conception was determined.

Results: A cut-off of 15 scores of the uterine scoring system for reproduction gave a sensitivity of 86.7% and a specificity of 100%. Factors found to be associated with high rates of pregnancy were endometrial thickness 10-14 mm ($P < 0.001$), distinct trilaminar layer ($P < 0.001$), abundant blood flow within zone 3 ($P < 0.001$), and uterine artery Doppler PI of < 2.19 ($P < 0.001$). The last two parameters gave a pregnancy rate of 100%.

Conclusion: Applebaum's uterine scoring system for reproduction is an easy, simple, noninvasive method for predicting pregnancy in women suffering from primary and secondary infertility. Both uterine artery Doppler PI and endometrial receptivity (including thickness, character, and vascularity) are two important parameters in predicting suitable environment for implantation and pregnancy outcome.

Keywords: Uterine scoring system for reproduction (USSR); Uterine biophysical profile; In-vitro fertilization (IVF); Intrauterine insemination.

Introduction

Infertility is defined as failure to conceive after 12 months or more of regular unprotected coitus. Failure to become pregnant after trying for a prolonged period can be disappointing, frustrating, and lead to many social, medical, and psychological consequences like depression and disappointment. It can be divisive to the couples involved. The formidable effect of infertility affects not only the lives of affected couples but also their families, relatives, and friends.¹

Although there is no definite procedure for

predicting felicitous conception during any given menstrual cycle, imaging with high-resolution transvaginal ultrasonography has licensed us to obtain more knowledge about female reproductive organs. It is quick, simple, inexpensive, noninvasive, and reproducible in assessing female pelvic organs.²

Examining the endometrium with ultrasound has become a standard procedure during the diagnostic workup and treatment of infertility. Ultrasonography has been used, with varying success grades, to correlate the prospect of

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pregnancy in the spontaneous cycle, ovarian stimulation-ovulation induction cycles, and in vitro fertilization (IVF) cycles. The focus of most imaging studies is to predict successful implantation, in which endometrial parameters including endometrial morphology, endometrial thickness, endometrial vascularity, and endometrial volume play a major role.³

Successful implantation during IVF and embryo transfer depends on many factors, including embryo quality and uterine receptivity. Endometrial receptivity is defined as a transient unique consecutive receptivity factor that makes the endometrium ready for embryonic implantation. It is the window of time when the uterine environment is facilitative to blastocyst assent and consequent implantation. Some sonographic findings become absolutely indispensable to evaluate the uterus, myometrium, endometrial thickness, appearance, and endometrial vascularity before implantation to obtain optimum results. These findings are compiled into uterine biophysical profile, which refers to an assessment of the uterus to produce a prosperous conception and implantation environment, and they are measured according to the uterine scoring system for reproduction (USSR) by M. Applebaum.⁴

This study aimed to evaluate the role of uterine biophysical profile assessment in predicting conception in women with a history of primary or secondary infertility and determine the parameters that can predict pregnancy.

Methods

A hospital-based prospective diagnostic accuracy study was conducted in 'Dr. Xawar in-vitro fertilization center' of the Maternity Teaching Hospital, Erbil, Kurdistan Region of Iraq, from October 2019 to September 2020. Fifty-one women with unexplained infertility (primary and secondary) undergoing IVF and intrauterine insemination in the age group of 22-45 years were included in the study.

The purpose of the study was explained to the participants, and verbal consent was taken from all participants. Ethical approval was obtained from the Ethics Committee of Hawler Medical University, College of Medicine. After standard diagnostic workup for infertility according to the center's regulations, transvaginal ultrasound was done in mid-cycle for those performing intrauterine insemination when the follicle reached 18 mm, and for those performing IVF before embryo transfer using GE ultrasound machine Voluson E6, IC5-9 Endo-vaginal probe. Transvaginal ultrasound was performed after the patient had emptied her bladder, and the examination was done in the lithotomy position. The endometrium was evaluated in both the sagittal and transverse planes. Measurement of endometrial thickness was obtained in the midline sagittal plane perpendicular to the long axis of the endometrium at the site of maximal thickness.

The thickness is measured to include both the anterior and posterior layers (full thickness measured from the myometrial-endometrial junction to the endometrial-myometrial junction). The visualized endometrial pattern was specified, whether it was layered or not. Then, on the longitudinal scan of the uterus, endometrial vascularization was assessed by placing the color gate over the thickest part of the endometrium to determine the presence or absence of color in the hypoechoic inner layer of the endometrium, which corresponds to zone 3. Then, a mid-sagittal section of the uterus and cervix was obtained. Zoom was used to enlarge the view of the cervix. The color flow was applied by tilting the transducer gently sideways to view the para-cervical region to identify the uterine artery at the level of the internal cervical os. The sampling gate was 2 mm to cover the whole vessel, with an angle of insonation less than 30°.

To verify that the examining vessel is uterine artery, the peak systolic velocity should be more than 50 cm/s.

After obtaining three identical consecutive waveforms, the mean PI is obtained as the average of the left PI and right uterine artery PI. Then myometrial echogenicity and myometrial blood flow internal to the arcuate vessels were evaluated and scored in the same longitudinal scan of the uterus. On the basis of the uterine biophysical profile, the USSR was done, and the total score as per Applebaum criteria⁴ was calculated, which included the following parameters:

Each parameter is scored as follows:

Endometrial thickness: < 7 mm = 0, 7 - 9 mm = 2, 10 - 14 mm = 3, > 14 mm = 1,

Endometrial layering: no layering = 0, hazy 5-line appearance = 1, distinct 5-line appearance = 3.

Myometrial contractions (appear as a wave-like motion of the endometrium): < 3 contractions in 2 minutes = 0, > 3 contractions in 2 minutes = 3.

Myometrial echogenicity: Coarse/ inhomogeneous echogenicity = 1, relatively homogeneous echogenicity = 2.

Uterine artery Doppler flow was measured by PI: PI > 3.0 = 0, PI < 2.5 - 2.99 = 0, PI < 2.2 - 2.49 = 1, PI < 2.19 = 2.

Endometrial blood flow within Zone 3: absent = 0, present but sparse = 2, present multifocally = 5.

Myometrial blood flow internal to the arcuate vessels: absent = 0, present = 2.

The endometrial vascularity is classified into these zones: Zone 1 -- 2 mm thick area surrounding the hyperechoic outer layer of the endometrium, zone 2 -- the hyperechoic outer layer of the endometrium, zone 3 -- the hypoechoic inner layer of the endometrium, zone 4 -- the endometrial cavity.

After 14 days of embryo transfer, serum B-HCG analysis was performed, and it was repeated on the 16th day. If it was positive, to confirm intrauterine pregnancy and to determine the number of gestational sacs present ultrasound examination was done 10–14 days later. Only clinical pregnancies defined by the presence of one or more gestational sacs or the histological confirmation of gestational product in miscarriages were considered.

Statistical analysis

Data were analyzed using the statistical package for the social sciences (SPSS, version 25). Categorical variables were presented in the form of frequencies and percentages, while numerical variables were summarized in the form of means and standard deviations (SDs). Mann Whitney test was used to compare the scores of USSR of pregnant women (success) and women who failed to become pregnant.

The Chi-square test of association was used to compare proportions. Fisher's exact test was used (instead of the Chi-square) when the expected values of more than 20% of the cells of the table were less than 5. ROC curve analysis was made to estimate a cut-off point of USSR score above which the test results can be considered 'positive' in predicting pregnancy. Youden's index was calculated (sensitivity + specificity -1), and its highest value was used to determine the cut-off point of the USSR score that gives the highest sensitivity and specificity. McNemar test was used (in the 2X2 table) when the results of ultrasound examination were compared with the pregnancy outcome (of the same patients); as in the following table:

Ultrasound finding	Pregnancy outcome	P (By McNemar)		
		Pregnancy	Failure	
Positive		TP	FP	TP+FP
Negative		FN	TN	FN+TN
Total		TP+FN	FP+TN	Grand total

TP=True positive; TN=True negative; FP=False positive; FN=False negative. Sensitivity = TP / (TP+FN)*100; Specificity = TN / (FP+TN)*100; Predictive value positive (PV⁺): TP / (TP+FP) * 100; Predictive value negative (PV⁻): TN / (FN+TN) * 100; Total agreement = (TP + TN) / Grand total. A P value of ≤ 0.05 was considered statistically significant.

Results

Fifty-one women were included in the study. Their mean age \pm SD was 34.78 ± 5.08 years, the median was 35 years, and the age range was 22 to 45 years.

Table 1 shows that the largest proportion (39.2%) of the sample were in the age group 35-39 years, but there was no significant association between age and the outcome ($P = 0.116$). The table also shows that the rate of pregnancy was 29.4%.

Table 2 shows that the endometrial thickness is significantly associated with the outcome ($P < 0.001$). The highest pregnancy rate (55%) was among women with endometrial thickness of 10-14 mm

(given three scores). More than half (59.1%) of the women with distinct trilaminar endometrium became pregnant, and the differences were significant ($P < 0.001$). All the women with PI of < 2.19 became pregnant, while none of the women with a PI of ≥ 2.5 became pregnant ($P < 0.001$). All the women with abundant endometrial blood flow became pregnant, while none of the women with absent endometrial blood flow became pregnant ($P < 0.001$). No significant association was detected between the outcome with: myometrial contraction / 2 minutes ($P = 0.446$), myometrial echogenicity ($P = 0.297$), and myometrial blood flow internal to the arcuate vessels ($P = 0.305$).

Table 1 Age distribution of the women and its association with the outcome

Age (years)	Outcome			P value
	Pregnancy	Failure	Total**	
	No. (%)	No. (%)	No. (%)	
<30	3 (42.9)	4 (57.1)	7 (13.7)	0.116*
30-34	4 (26.7)	11 (73.3)	15 (29.4)	
35-39	8 (40.0)	12 (60.0)	20 (39.2)	
40-45	0 (0.0)	9 (100.0)	9 (17.6)	
Total	15 (29.4)	36 (70.6)	51 (100.0)	

*By Fisher's exact test. **Column % had been calculated.

Table 2 Pregnancy rate by ultrasonographic findings

Ultra-sonographic findings	(Score)	N	Pregnancy No. (%)	Failure No. (%)	P value
Endometrial thickness (mm)					
7-9	(2)	26	4 (15.4)	22 (84.6)	
10-14	(3)	20	11 (55.0)	9 (45.0)	
>14	(1)	5	0 (0.0)	5 (100.0)	<0.001*
Endometrial layering					
No layering	(0)	2	0 (0.0)	2 (100.0)	
Hazy trilaminar	(1)	27	2 (7.4)	25 (92.6)	
Distinct trilaminar	(3)	22	13 (59.1)	9 (40.9)	<0.001*
Myometrial contraction / 2 minutes					
<3	(0)	28	7 (25.0)	21 (75.0)	
>3	(3)	23	8 (34.8)	15 (65.2)	0.446**
Myometrial echogenicity					
Coarse/heterogeneous	(1)	13	2 (15.4)	11 (84.6)	
Homogeneous	(2)	38	13 (34.2)	25 (65.8)	0.297*
Doppler flow evaluation (pulsatility index, PI) of the uterine artery.					
≥3	(0)	10	0 (0.0)	10 (100.0)	
2.5-2.99	(0)	16	1 (6.3)	15 (93.8)	
2.2-2.49	(1)	15	4 (26.7)	11 (73.3)	
<2.19	(2)	10	10 (100.0)	0 (0.0)	<0.001*
Endometrial blood flow in zone 3					
Absent	(0)	10	0 (0.0)	10 (100.0)	
Sparse	(2)	31	5 (16.1)	26 (83.9)	
Abundant	(5)	10	10 (100.0)	0 (0.0)	<0.001*
Myometrial blood flow internal to the arcuate vessels					
Absent	(0)	5	0 (0.0)	5 (100.0)	
Present	(2)	46	15 (32.6)	31 (67.4)	0.305*
Total		51	15 (29.4)	36 (70.6)	

*By Fisher's exact test. **By Chi-square test.

ROC (Receiver Operating Characteristic) curve analysis was done where the USSR score was used to predict the outcome, whether pregnancy or failure. The area under the curve was large (0.979, and the 95% CI was 0.944-1), indicating that the mentioned score can be used to predict the outcome, as presented in Table 3 and Figure 1.

the Youden's index (sensitivity + specificity -1) was used. The highest value of this index gave us a sensitivity of 86.7% and a specificity of 100% when a cut-off value of 15 scores was considered. Other details are presented in Table 4.

Table 3 SPSS output for the area under the curve (ROC curve analysis) and its related chart

Test Result Variable(s): Total score		Asymptotic 95% Confidence Interval		
Area	Std. Error	Asymptotic Sig.	Lower Bound	Upper Bound
0.979	0.018	< 0.001	0.944	1.000

Table 4 Validity of ultra-sonographic examination in predicting pregnancy

Ultra-sound finding	Pregnancy	Failure	Total	P value (McNemar)
Positive*	13	0	13	
Negative*	2	36	36	0.500
Total	15	36	51	
Sensitivity	Specificity	PV+	PV-	Agreement
86.7%	100.0%	100.0%	94.7%	96.0%

*A USSR score of 15 and more was considered positive (i.e., predicting pregnancy) based on the ROC curve analysis.

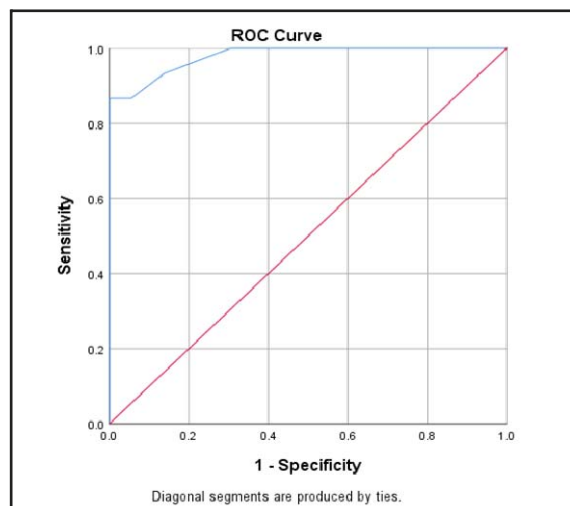


Figure 1 ROC curve analysis of USSR score in predicting conception

The mean USSR score was 16.5 among pregnant women and 9.9 among those with failure ($P < 0.001$), as presented in Figure 2.

It is evident in Table 5 that all the women with a score of 15 or higher became pregnant, while 0% and 15.4% of the women with scores of <12 and 12-14, respectively, became pregnant ($P < 0.001$).

Discussion

Infertility has a very bad impact physically and psychologically on the infertile individual. Infertility is a disease characterized by the failure to become pregnant after 12 months of regular and unprotected sexual intercourse in the fertile phase of the menstrual cycle. It is estimated to affect 8-12% of reproductive-aged couples worldwide.¹ Transvaginal sonography is the first imaging modality in assessing infertility management.

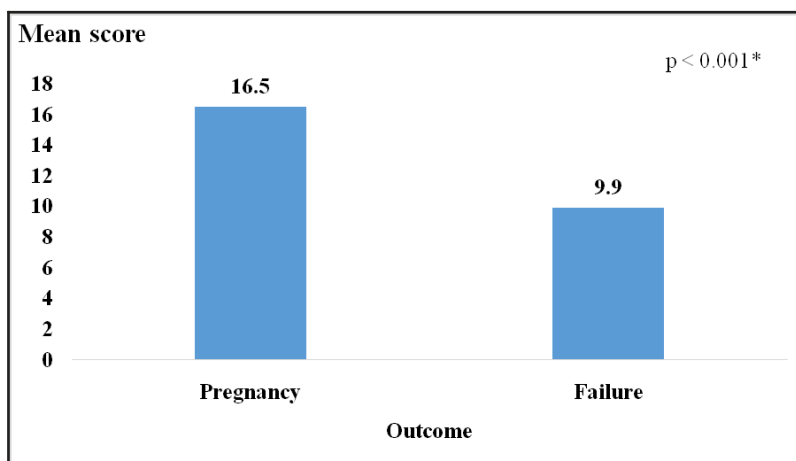
The uterine biophysical profile, which means assessment of the uterus to produce a successful conception and implantation environment analyzed by transvaginal ultrasound to predict positive pregnancy outcome. A total of 51 women were included in our study. The USSR was estimated, and no woman had a perfect USSR score of 20. The pregnancy rates among women with USSR scores of <12, 12-14, and ≥ 15 were 0%, 15.4% and 100%, respectively. According to a study conducted by Narendra Malhotra et al. in spontaneous cycles of 222 patients, the USSR score of 20 gave 80% of the pregnancy rate, while a score of 17-19 gave 79% of conception. While only 7.6% conceived with a score of ≤ 13.5 .⁵

While another study conducted by Pooja Gupta et al. on 55 women with unexplained primary infertility, the conception rates were 80%, 60%, 43.4%, and 8.3% among

Table 5 Pregnancy rate by total USSR score categories

Score	Pregnancy		Failure		Total		P value
	No.	(%)	No.	(%)	No.	(%)	
< 12	0	(0.0)	25	(100.0)	25	(100.0)	
12-14	2	(15.4)	11	(84.6)	13	(100.0)	
≥ 15	13	(100.0)	0	(0.0)	13	(100.0)	<0.001*
Total	15	(29.4)	36	(70.0)	51	(100.0)	

*By Fisher's exact test



*By Mann-Whitney test.

Figure 2 Mean USSR score by the outcome

women with USSR scores of 20, 17-19, 14-16, and ≤ 13 respectively.⁶

Another study, which is in agreement with our study, was conducted by Navinchandra et al. 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 women with a score of ≤ 13 were negative for pregnancy (the greater USSR score gave a better conception outcome, making it a reliable prediction parameter).⁷

The current study revealed that endometrial receptivity plays a crucial role in the implantation of an embryo. Endometrial receptivity is a temporary unique sequence of factors that make the endometrium receptive to embryonic implantation. It is the window of time when the uterine environment is conducive to blastocyst acceptance and subsequent implantation. In most reproductive medicine agencies, endometrial thickness and its pattern have been commonly used as noninvasive and reproducible methods for evaluating endometrial receptivity. The study revealed that endometrial thickness, endometrial layering, and endometrial blood flow in zone 3 were important parameters in detecting pregnancy outcomes.

The highest rate of pregnancy (55%) was obtained when the endometrial thickness was 10-14 mm, while no pregnancy was detected when the endometrial thickness was >14 . Also, distinct trilaminar endometrium was associated with high pregnancy outcome. This is in agreement with several studies that endometrial thickness and endometrial pattern are prognostic parameters for successful IVF outcome. Endometrial morphology, which shows a triple-line pattern with a moderate endometrial thickness (8-14mm), appeared to be associated with a good clinical outcome.⁸⁻¹²

Adequate perfusion to the endometrium, which means endometrial vascularization is vital to implantation. In our study,

the highest pregnancy rate (100%) was found when there was abundant blood flow in zone 3 of the endometrium. This is in agreement with another study done by Singh et al.¹³

In a prospective study, Wang *et al.* studied the endometrial thickness, blood flow, and endometrial echo pattern on transvaginal sonography of 182 women, and they observed a higher clinical pregnancy rate and implantation rate in women with detectable blood flow.¹⁴

Uterine artery Doppler indices have high sensitivity and specificity for diagnosing high uterine blood flow impedance. One of the etiologies of unexplained infertility may contribute to high uterine blood flow impedance diagnosed by uterine artery Doppler.¹⁵

Therefore, uterine artery Doppler should be included in the investigations of unexplained infertility. As it is observed in the current study that among 51 women with unexplained infertility, all the women with uterine artery PI of less than 2.19 became pregnant, while none of the women became pregnant with a uterine artery PI ≥ 2.5 . This agrees with a study by Ali et al. on 70 women divided into two groups. The control group included 30 fertile women, and the study group included 40 women with unexplained infertility.

They concluded that the best cut-off value of uterine artery pulsatility index (PI) was 1.95, with a sensitivity of 95%, specificity of 86.7%, diagnostic accuracy of 91.42%, positive predictive value of 90.47%, and negative predictive value of 92.86%.¹⁶

Another study by Khan et al. concluded that the pregnancy rates were higher in women with distinct five-line, thick endometrium and multifocal endometrial vascularity within zone 3. Despite the highest values for the other parameters, absent endometrial blood flow was associated with no conception.¹⁷

No pregnancy occurred with uterine PI values of more than 2.8. A maximum score of 20 was associated with a pregnancy rate

of 97.4 %, whereas scores of 13 or less resulted in no pregnancies;¹⁸ which agrees with our study.

The current study revealed no significant correlation between myometrial contraction in 2-minute, myometrial echogenicity, myometrial blood flow internal to arcuate vessels, and conception, another study conducted by Navinchandra et al. revealed a significant correlation between these parameters and conception.⁷

Conclusion

Applebaum's USSR scoring is highly indicative of good pregnancy outcomes in infertile women, and it is an easy method to perform and calculate the scores. As shown in our study, the highest scores are associated with the highest pregnancy rate. Also, the current study concluded that endometrial receptivity, including thickness, morphology, and endometrial vascularization, with uterine artery PI, are strongly correlated with successful pregnancy outcomes.

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Competing interests

The author declares that she has no competing interests.

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