Assessment of Applebaum Scoring in Endometrial Evaluation in Prediction of Implantation in Patients with Recurrent Pregnancy Loss

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Abstract

Background: Unexplained recurrent pregnancy loss (RPL) still poses a diagnostic and therapeutic challenge which can be quite distressing to the couples as well as to the gynaecologist. We aimed to study the prevalence of RPL at our tertiary care centre and to assess the efficacy of Applebaum scoring of endometrium for prediction of implantation in cases of unexplained RPL.

Materials and Methods: The study enrolled 43 cases with history of unexplained RPL in non pregnant state and their endometrial evaluation was done with TVS and colour Doppler. 37 patients were taken as controls which were comparable in terms of socio-demographic factors in the age group of 18-35 years. TVS was done on 12th day of menstrual cycle.

Results: The incidence of RPL at our center was found to be 3.68%. It was seen that pregnancy loss was more when endometrial thickness was <7mm or >14 mm. RPL was more when pulsatility index of uterine artery was >2.5 (p=0.004) which was statistically significant as compared to controls. It was observed that when total score was <13, the sensitivity and specificity of predicting implantation was 90.70% and 81.08% respectively.

Conclusion: Applebaum scoring system can be a good predictor in patients with recurrent pregnancy loss especially when no cause has been identified, accordingly therapeutic intervention can be directed to increase endometrial thickness, its vascularity as well as its receptivity.

Keywords: Applebaum Scoring; Endometrial Receptivity; Recurrent Pregnancy Loss.

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Received on: 23.05.2024

Accepted on: 03.07.2024

INTRODUCTION

RPL is a complex entity to resolve as its etiopathogenesis is still unclear involving a multifactorial mechanism including immunologic and genetic causes. Moreover, the criteria or diagnosis of RPL involve a lot of controversies as different societies opine differently. According to European Society for Human Reproduction and Embryology and the Royal College of Obstetricians and Gynaecologists, RPL refers to 2 or more consecutive miscarriages.[1] However, according to the American Society for Reproductive Medicine (ASRM), it is defined as two or more clinical pregnancy losses (documented by ultrasonography or histopathologic examination), but not necessarily

consecutive.[2] The incidence varies extensively (0.5-2.3%) because of variation in criteria used as well as the heterogeneity of population. Primary RPL refers to multiple losses in a woman with no previous viable infants, whereas secondary RPL refers to multiple losses in a woman who has already had a pregnancy beyond 20 gestational weeks[3]. RPL can be attributed to innumerable causes but still majority are unexplained or idiopathic.

For a pregnancy to continue till period of viability, process of implantation becomes a critical step for which endometrium undergoes a lot of physiological and immunological changes.[4,5,6]

To evaluate such changes, the role of TVS coupled with Doppler cannot be underestimated due to its easy availability, accessibility and cost effectiveness. Various researchers have evaluated ultrasonographic parameters and scoring systems to predict in infertility patients and one such scoring is applebaum scoring which has only been evaluated in infertile patients and there are very few studies in which endometrium has been evaluated in case of recurrent pregnancy loss. We attempt to undertake this study so as to determine the role of Applebaum scoring in prediction of implantation in patients with unexplained recurrent pregnancy loss.

MATERIALS AND METHOD

The study was conducted in the department of obstetrics and gynaecology along with radiology department at GSVM medical college, Kanpur from January 2020 to October 2021 in patients who came to our out patient department with history of unexplained recurrent pregnancy loss.

Inclusion Criteria: Group 1: Cases included patients with RPL between 18-35 years of age having >/= 2 consecutive or non consecutive pregnancy loss in non pregnant state.

Group 2: Controls included patients between 18-35 years of age in non pregnant state in whom history of RPL (primary or secondary), abnormal uterine bleeding and infertility were excluded.

Exclusion Criteria: Patients having endocrinological abnormalities like hypo/hyperthyroidism, diabetes mellitus, polycystic ovarian syndrome, inherited thrombophilias like anti-phospholipid antibody syndrome, uterine abnormalities like septate or bicornuate uterus, cervical incompetence. Enrolled patients evaluated by a thorough history, examination and following investigations were done like S. TSH, Oral glucose tolerance test with 75g glucose, Lupus anticoagulant, anti cardiolipin antibody, Beta 2 glycoprotein

1. Patients were evaluated with transvaginal ultrasonography along with colour Doppler on day 12 of menses using LOGIQP9 machine with 4-9 MHz probe. Patients were asked to lie down in lithotomy position after emptying the bladder. Maximum thickness of endometrium was measured from zona basalis of anterior wall of endometrial cavity till zona basalis of posterior wall and was designated as distinct 5 line appearance, hazy 5 line appearance or no layering. Hyperechogenic line in the centre represents uterine cavity, outer hyper echogenic lines represent zona basalis and relatively hypoechogenic areas in the middle represent zonal functionalis. Vascularity of the endometrium within zone 3 (hypoechoic layer) was assessed by doppler. Uterine artery pulsatility index was measured from flow velocity waveforms as systolic peak velocity minus diastolic peak velocity divided by mean of the two. No difference in uterine artery PI of left and right side was observed, so average PI was taken into consideration. Myometrium was examined for homogeneity and blood flow internal to arcuate vessels.

Each parameter of Applebaum was scored as follows:

1. Endometrial thickness
   a. <7 mm =0
   b. 7-9 mm = 2
   c. 10-14 mm = 3
   d. > 14 mm = 1

2. Endometrial layering
   a. No layering =0
   b. Hazy five-line appearance =1
   c. Distinct five-line appearance =3

3. Myometrial contractions (seen as wave-like endometrial motion high-speed playback from videotape)
   a. <3 contractions in 2 minutes (real-time) =0
   b. >3 contractions in 2 minutes (real-time) =3

4. Myometrial echogenicity
   a. Coarse/inhomogeneous echogenicity =1
   b. Relatively homogeneous echogenicity =2

5. Uterine artery Doppler flow
   a. PI>3.0 =0
   b. PI–2.5-2.99 =0
   c. PI–2.2-2.49 =1
   d. PI < 2.19 = 2

59

Kiran Pandey, Pavika Lal, Aishwina Anand *et al.* Assessment of Applebaum Scoring in Endometrial
Evaluation in Prediction of Implantation in Patients with Recurrent Pregnancy Loss

6. Endometrial blood flow within zone 3

    a.   Absent = 0

    b.   Present, but sparse = 2

    c.   Present multifocally = 5

7. Myometrial blood flow internal to the arcuate vessels seen on gray-scale examination

    a.   Absent = 0

    b.   Present = 2

RESULTS

The age group of patients in both cases and controls were in the range of 20-35 years. Of the 4129 patients who visited our gynaecological out patient department during the study period, 152 patients had history of recurrent pregnancy loss. The incidence of recurrent pregnancy loss at our center was found to be 3.68%.

Endometrial thickness was in the range 10-14 mm in 9.3% of group 1 patients compared with 48.6% of group 2 patients (Fig. 1). In our study 51.1% of patients had hazy 5 line appearance of the endometrium. Uterine artery pulsatility index was measured with value >3 seen in 48.8% of group 1 (Fig. 2). 44.18% and 51.1% of group 1 had no endometrial blood flow within zone 3 and no myometrial blood flow internal to arcuate vessels respectively. 65.1% of cases had inhomogeneous myometrium (Fig. 3). All these values were statistically significant. In our study it was reported that the incidence of recurrent pregnancy loss is higher in women with total Applebaum score of less than 13 as compared to individuals with a total score more than this value. The sensitivity of 90.70% and specificity of 81.08% showed that scoring method can be used for prediction of implantation in patients with recurrent pregnancy loss.
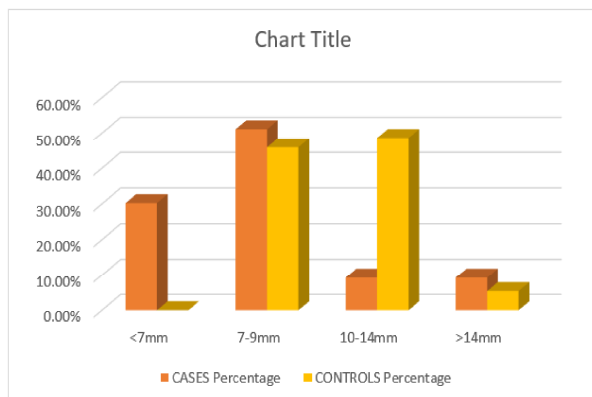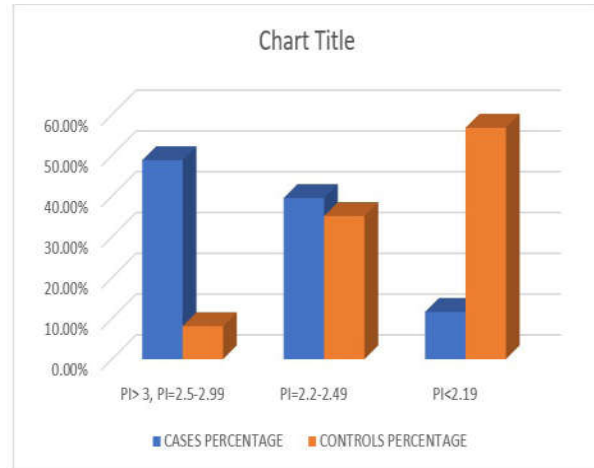

Fig. 2: Bar graph depicting percentage distribution of uterine artery Doppler among cases and controls

Fig. 3: Bar graph depicting percentage distribution of myometrial echogenecity among cases and controls.
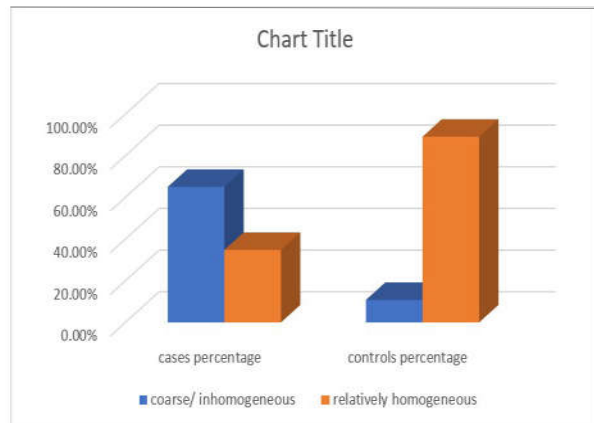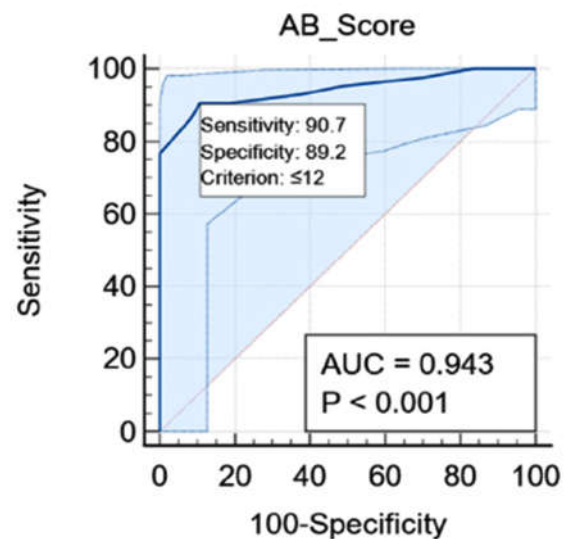

Fig. 1: Bar graph depicting percentage distribution of endometrial thickness among cases and controls

Fig. 4: area under the curve for total Applebaum score among cases and controls

Table 1: Comparison of endometrial parameters among cases and controls

Parameter	Cases		Controls		Odds ratio	95% Confidence interval	P-value
	No.	Percentage	No.	Percentage			
Endometrial thickness (10-14mm)	4	9.3	18	48.6	4.9	2.1-11.2	<0.001
Endometrial layering (no layering)	13	30.2	2	5.4	2.9	1.1-7.5	0.032
Uterine artery Doppler flow (PI<2.19)	5	11.6	21	56.75	3.6	1.5-8.7	0.004
Endometrial blood flow (absent)	19	44.18	1	2.7	9.6	2.23-45.5	0.004

Table 2: Comparison of myometrial parameters among cases and conytrols

Parameter	Cases		Controls		Odds ratio	95% Confidence interval	P value
	No.	Percentage	No.	Percentage			
Myometrial contractions (<3)	27	62.7	4	10.8	11.6	3.8-43.5	<0.001
Myometrial echogenicity (inhomogeneous)	28	65.1	4	10.8	13.2	3.3-52.6	<0.001
Myometrial blood flow (absent)	22	51.1	10	27.02	1.1	0.22-3.5	0.871

Table 3: Criterion values and coordinates for ROC curve for total applebaum scoring

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	-LR
<2	0.00	0.0 - 8.2	100.00	90.5 - 100.0	-	1.00
≤10	76.74	61.4 - 88.2	100.00	90.5 - 100.0	-	0.23
≤11	86.05	72.1 - 94.7	91.89	78.1 - 98.3	10.61	0.15
≤12	90.70	77.9 - 97.4	89.19	74.6 - 97.0	8.39	0.10
≤13	90.70	77.9 - 97.4	81.08	64.8 - 92.0	4.79	0.11
≤14	93.02	80.9 - 98.5	62.16	44.8 - 77.5	2.46	0.11
≤15	95.35	84.2 - 99.4	51.35	34.4 - 68.1	1.96	0.091
≤16	97.67	87.7 - 99.9	29.73	15.9 - 47.0	1.39	0.078
≤17	100.00	91.8 - 100.0	16.22	6.2 - 32.0	1.19	0.00
≤20	100.00	91.8 - 100.0	0.00	0.0 - 9.5	1.00	-

DISCUSSION

Unexplained RPL is a very challenging clinical scenario and since the process of implantation is a complex mechanism with enormous changes in the endometrial physiology along with immunomodulation, we undertook this study with an aim to evaluate the uterus by using applebaum scoring in such cases so that specific intervention can be directed to improve the pregnancy outcome.

4129 patients visited our gynaecological OPD during the study period, 152 patients were found to be cases of RPL. The incidence of RPL at our centre was found to be 3.68% which was higher than the incidence in the general population which may be because our centre is a tertiary care centre where patients are being referred.

In our study, it was reported that the incidence of recurrent pregnancy loss was more when endometrial thickness <7mm which was statistically significant (table 1). Similar finding was reported by Mohd Shoeb khan *et al*[7]. In his study, no pregnancy was reported when endometrial thickness was <7mm. When the thickness measured by ultrasound was <7mm, the functional layer was thin or absent, and the implanting embryo would be much closer

to the spiral arteries and higher vascularity and oxygen concentrations of basal endometrium. The high oxygen concentrations near the basal layers could be detrimental compared with usual low oxygen tension of surface endometrium. Noyes et al[8], Kovacs et al[9] reported that increased endometrial thickness was significantly associated with higher pregnancy rates. In a study conducted by Shu-Yin Tan et al[10] it was concluded that predictive accuracy of endometrial thickness to determine miscarriage before 12 weeks of gestation in participants was 68.1%. In a recent study, it was found that pregnancy was positively associated with increasing endometrial thickness.

In our study, it was found that women with recurrent pregnancy loss had hazy 5 line appearance of endometrium as compared to women with no history of recurrent pregnancy loss who had distinct 5 line appearance of the endometrium (table 1). Similar conclusions were drawn from a study conducted by Mohd Shoeb Khan et al[7]. Zhao et al. concluded that endometrial thickness and pattern independently affect pregnant outcomes.[11]

In our study the average PI of uterine artery was higher in patients with recurrent pregnancy loss as compared to those with no pregnancy losses (table 1). Diastolic blood flow may be categorized as reduced or absent blood flow velocity. Good uterine perfusion, as shown by full diastolic blood flow with low resistance during the early or mid secretory phases, correlates with conception. Ruiqing Tong et al it concluded that spiral artery blood flow parameters, and uterine artery blood flow parameters can be effective indices for evaluating endometrial receptivity.[12] In a study conducted by Mohd Shoeb Khan et al. it was concluded that average PI of uterine artery was higher in nonconception cycles as compared to conception cycles.[7] In their study, no conception was reported when PI was more than 2.8.

In our study, the incidence of recurrent pregnancy loss was significantly higher in patients with no demonstrable blood flow within zone 3 as compared to those with multifocal vascularity within zone 3 (table 1). Similar finding was reported by Chien et al[13], Shu-Yin Tan et al[10], and Maugey-Laulon et al.

In our study we found that non homogeneous myometrium had a significantly higher chance of RPL as compared to those with relatively homogeneous myometrium (table 2). Zhaojuan et al concluded that patients with non homogeneous myometrium on embryo transfer day usually have lower pregnancy rates.[14]

In a recent study, it was shown that combination of endometrial pattern and its thickness, and end diastolic blood flow of uterine artery was most effective for evaluation of endometrial receptivity.

Applebaum reported a pregnancy rate of 100% in females with a score of 20, 80% in females with scores of 17–19, and 60% in women with scores of 14–16. In our study it was reported that for a total score between 10-11, the sensitivity for predicting implantation decreased whereas specificity increased. For a total score between 15-20, the sensitivity for predicting implantation increased whereas specificity decreased. In our study it was found that the incidence of RPL was higher in women with total applebaum score of less than 13 as compared to individuals with a score more than this value. The sensitivity of 90.70% and specificity of 81.08% showed that scoring method can be used for prediction of implantation in patients with recurrent pregnancy loss. For a total score of <12, sensitivity of predicting implantation in case of recurrent pregnancy loss was 90.70% with similar specificity. (table 3)

CONCLUSION

RPL being an enigmatic entity involving a lot of controversies with respect to evaluation and management, Applebaum scoring system can prove to be a non invasive, cost effective intervention in patients with recurrent pregnancy loss to predict the implantation rate. The underlying cause being, the poor endometrial receptivity can be managed effectively by specific interventions that can be directed to increase endometrial thickness, its vascularity and thereby receptivity.

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