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Assessment of Sub-endometrial Blood Flow Parameters Following Oral Dydrogesterone versus Micronized Vaginal Progesterone in Women with Idiopathic Recurrent Miscarriage

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Authors' contributions

This work was carried out in collaboration among all authors. Author MIN designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors MKO and WMA managed the analyses of the study. Author AEM managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Recurrent pregnancy loss is an important reproductive health issue, affecting 2%–5% of couples. An unsupportive endometrium, leading to abnormal implantation, is considered to be one of the key factors contributing to idiopathic recurrent spontaneous miscarriage (IRSM). The aim of this work was to evaluate differences in uteroplacental blood flow and pregnancy outcome in women with idiopathic recurrent spontaneous miscarriage (IRSM) following administration of micronized vaginal progesterone versus oral dydrogesteron.
Materials and Methods: This prospective, randomized-controlled study comprised 90 pregnant women who came to outpatient clinic of obstetrics .All women had a singleton pregnancy with active cardiac pulsations at gestational age between 5-8 weeks Pregnant women in the study group were randomly distributed into :Group {A}: 30 pregnant women received 10 mg of oral

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dydrogesterone (Duphaston; Abbott Company) twice daily.Group {B}: 30 pregnant women received 200 mg micronized vaginal progesterone (Prontogest) twice-daily .Control group:30 pregnant women without history of recurrent miscarriage served as controls and they received folic acid as placebo.

Results: comparing the Doppler indices before progesterone supplementation, the mean resistance index (RI) was statistically significant less in the control group compared with both study groups (A&B) (P=0.012, P=0.005 respectively) .Moreover, pulsatility index (PI) was statistically significant less in the control group compared with both study groups (A&B) (P=0.026, P=0.05 respectively) .Paralleled to that, the S/D ratio was statistically significant less in control group compared with both group A &B (P=0.43, & P=0.019respectively) .In addition, the mean PSV was significantly higher in control group compared to group B (P=0.047) and was higher in control group than group A with nearly significant P value.

Conclusion: Considerable improvement in uteroplacental blood flow parameters of pregnant women with IRSM is evident with progesterone supplementation.

Keywords: Sub-endometrial blood flow; vaginal progesterone; oral dydrogesterone.

1. INTRODUCTION

Recurrent pregnancy loss is an important reproductive health issue, affecting 2%–5% of couples [1]. Recurrent spontaneous miscarriage is defined as three or more consecutive pregnancy losses within 20 weeks of gestation. In approximately 50% of these cases, the cause remains unsolved. An unsupportive endometrium, leading to abnormal implantation, is considered to be one of the key factors contributing to idiopathic recurrent spontaneous miscarriage (IRSM) [2]. Structural and functional modifications of the endometrial matrix and vasculature during the peri-implantation period to acquire a receptive state remain an active area of research [3]. The main event during this period is the trophoblastic cell invasion to the inner third of the myometrium and migration through the entire length of maternal spiral arteries. In addition, the vascular remodeling of these high resistance arteries in the maternal-fetal interface results in low resistance and high flow state in the intervillous space [4].

This is associated with a concomitant increase in uterine blood flow and perfusion that regulates uterine receptivity and is crucial for the normal pregnancy outcome [5,6].

Many published reports show that high blood flow resistance is associated with reduced conception and that women with lower Pulsatility Index (PI) values have the highest possibility of becoming pregnant . However, this is not a universally held opinion, as many investigators have not been able to document an association between abnormal uterine perfusion and pregnancy complications [7]. Dydrogesterone is a synthetic progestin and its chemical structure has a strong affinity for the P receptor (PR). The structure of dydrogesterone is similar to that of natural progesterone and is largely converted to its stable metabolite, 20-α-dihydrodydrogesterone [8].

The aim of this work was to evaluate differences in uteroplacental blood flow and pregnancy outcome in women with idiopathic recurrent spontaneous miscarriage (IRSM) following administration of micronized vaginal progesterone versus oral dydrogesteron.

2. SUBJECTS AND METHODS

This prospective, randomized-controlled study comprised 90 pregnant women who came to outpatient clinicof obstetrics department, Tanta University hospitalduring the period of research from November 2018 to November 2019.

Patients:

- Study groups
  Sixty pregnant women had history of recurrent spontaneous miscarriage (RSM).
- Control Group
  Thirty pregnant women without history of RSM.

All women had a singleton pregnancy with active cardiac pulsations at gestational age between 5-8 weeks.

Pregnant women in the study group were randomly distributed into:

- Group {A}: 30 pregnant women received 10 mg of oral dydrogesterone (Duphaston; Abbott Company) twice daily.

- Group {B}: 30 pregnant women received 200 mg micronized vaginal progesterone (Prontogest) twice-daily.
- Control group:30 pregnant women without history of recurrent miscarriage served as controls and they received folic acid as placebo.

Inclusion criteria: All Pregnant women aged from 23 to 35 years.with confirmed pregnancy in first trimester with confirmed date of last menstrual period and with singleton pregnancy.

Women had history of idiopathic recurrent spontaneous miscarriage(definedas recurrent loss of 'three or more consecutive pregnancies' with no obvious pathology can be identified.20,87.Documented embryonic cardiac activity. Women with BMI less than 30.

The exclusion criteria included the following:

- Pregnant women with uterine cavity abnormalities.
- Women with History of medical disorders such as diabetes, hypertension, thyroid disease, anemia, hyperprolactnamia, systematic lupus erythematous (SLE),antiphospholipid (APL) syndrome, or other recognized thrombophilia condition.
- Women received anticoagulant therapy or anti platelet e.g low dose aspirin .
- Women with contraindication to progesterone use.
- Women with threatened miscarriage.
- Pregnant women received any medication in the last 3 months.

Pregnant women fulfilled the inclusion criteria were subjectedto the following:

Complete history taken with special emphasis on:

- Personal history.
- Menstrual history, date of last menstrual period (LMP) for confirmation of gestational age.
- Past history of recurrent abortion. (Number, time, type of previous abortion & medical versus surgical evacuation).
- Past history forany medical disorder to excludethem.
- Previous operations.
- History of drug intake.
- Any pregnant woman complaint.

Clinical examinations were done including:

General examination including:

- Measurement of weight, height and body mass index (BMI)
- Assessment of vital signs (body temperature, pulse and blood pressure)to assess the hemodynamic status.

- Cardiac and chest examination.
- Abdominal examination.

Ultrasound Examination:

- The Equipment:

The ultrasound examination was done usinga 3.5- 5-MHz (Philips affinity 50G) trans-abdominal probe at the ultrasound unit of the Obstetrics department at Tanta University Hospitals.

All pregnant women underwent:

- Doppler velocimetry of the sub endometrial vessels:

All 90 pregnant women in study and control groupsunderwent measurement of endometrial blood flow parameters by Doppler indices. Baseline sub endometrial vessels Doppler indices including PI, resistance index (RI),Peak systolic velocity (PSV), end diastolic velocity (EDV) and systolic to diastolic (S/D) ratio were measured while confirming pregnancy at 5-8 weeks of gestation.

Intervention:

Then the 60 pregnant women with history of idiopathic recurrent miscarriage were randomly allocatedinto2subgroups:

- Group {A}: 30 pregnant women who received 10 mg of oral dydrogesterone (Duphaston; Abbott Company) twice daily.
- Group {B}: 30 pregnant women who received 200 mg micronized vaginal progesterone (Prontogest) twice-daily.

Follow up:

After 4 weeks, Doppler assessment was performed again and the indices were estimated. Then follow up of pregnancy for detection of obstetric problems as pre-eclampsia, antipar

tumhaemorrhage, and gestational diabetes. Oral dydrogesterone and micronized progesterone were continued upto 12weeks in groups A and B, respectively.

2.1 Statistical analysis

The sample size was calculated using Epi-Info software statistical package created by World Health organization and center for Disease Control and Prevention, Atlanta, Georgia, USA version 2002. The criteria used for sample size calculation (n>33) were 95% confidence limit, 80% power of the study.

Analysis of data were performed by SPSS v25 (SPSS Inc., Chicago, IL, USA). Quantitative parametric variables (e.g. age) were presented as mean and standard deviation (SD). Pearson's rho coefficient of correlation (r) was used to calculate the degree of correlation between 2 variables. P value < 0.05 was considered significant.

This table shows no statistically significant difference between the three groups regarding age (P=0.348) .As regard the parity in the control group was higher than that in the study group (A and B) (p=0.02) . Moreover, there was no statistically significant difference between the the control and study groups regarding to BMI (P =0 235) (Table 1).

3. RESULTS

3.1 Doppler Indices

This table shows that on comparing the Doppler indices before progesterone supplementation, the mean resistance index (RI) was statistically significant less in the control group compared with both study groups (A&B) (P=0.012, P=0.005 respectively) Moreover, pulsatility index (PI) was statistically significant less in the control group compared with both study groups (A&B) (P=0.026, P=0.05 respectively) .Paralleled to that, the S/D ratio was statistically significant less in control group compared with both group A &B (P=0.43, & P=0.019respectively) .In addition, the mean PSV was significantly higher in control group compared to group B (P=0.047) and was higher in control group than group A with nearly significant P value (P=0.059) .Also, the mean and EDV was significantly higher in control group compared to group A & B (P=0.41, & P=0.03 respectively) (Table 2).

3.1.1 Doppler results for group (A) after treatment

This study shows that following oral progesterone administration for 4 weeks, group A showed a highly significant reduction in both RI , PI, and S/D ratio as compared with their baseline levels (P<0.001 for all) (Table 3). Moreover, EDV and PSV were significantly increased in patients who received oral progesterone for 4 weeks (P<0.001 & p=0.02 respectively).

3.1.2 Doppler results for group (B) after treatment

This study shows that following vaginal progesterone administration for 4 weeks, group B showed a highly significant reduction in both RI , PI, and S/D ratio as compared with their baseline levels (P<0.001 for all).

Moreover, both PSV and EDV were significantly increased in patients who received vaginal progesterone for 4 weeks (P= 0.011 & P<0.001; respectively) (Table 4).

3.1.3 Doppler results for control group after Placebo treatment

This study shows that women in control group who received folic acid as placebo had decrease in RI and PI levels ,& S/D ratio compared to their levels at the beginning of study but without significance (P>0.05 for the 3 indices).Moreover, both PSV and EDV were non significantly increased in control group after 4 weeks (P>0.05 for both) (Table 5 & Fig. 1).

3.1.4 Outcome of pregnancy

This study shows that five miscarriages were recorded for group A (16.7%) and 7 for group B (23.3%). The number of ongoing pregnancies were 25 for group A (83.3%) and 23 in group B (76.7%). Without statistically significant difference (Table 6& Fig. 2) (P=0.519).

This study shows that the number of viable deliveries in group A was 23 (76.6%) compared to 21 (70%) at group B. Also, there was no statistically significant difference between the both studied groups (A & B) regarding number of viable deliveries (Table 10& Fig. 3) (P=0.559).

Table 1. Demographic data of all study groups and control group

		Study Groups Group {A} N=30	Group {B} N=30	Control Group N=30	P-value	Significance
Age (years)	Range	23–31	25-30	23–31	0.348	NS
	Mean ± SD	27±2.65	27±1.82	26.2±2.76		
Parity	1	27(90%)	24(80%)	18(60%)	0.02*	S
	2	3(10%)	6(20%)	12(40%)		
BMI (kg/m2)	Range	19-30	21-29.5	20-28.5	0 235	NS
	Mean ± SD	24.4±4.05	25.96±3.75	24.7±3.37		

Data expressed as mean± SD or Number (%) - P < 0.05: statistically significant

Table 2. Comparison between study and control groups regarding baseline Doppler indices before progesterone supplementation

		Study Groups		Control Group N=30	Sig. test	P-value
		Group {A} N=30	Group {B} N=30			
RI	Range	0.41-0.99	0.69-0.81	0.39-0.99	F=2.63	0.048
	Mean ± S. D	0.69 ±0.19	0.75±0.04	0.59 ±0.11		
p- value between gp A&B		0.111				
p- value between gp B&C			0.005*			
p- value between gp A&C		0.012*				
PI	Range	1.2–2.89	1.54-2.22	1.39–2.35	F=3.033	0.053
	Mean ± S. D	1.9 ± 0.58	1.87±0.23	1.66± 0.35		
p- value between gp A&B		0.779				
p- value between gp B&C			0.05*			
p- value between gp A&C		0.026*				
PSV	Range	20.4-42.4	23.05-38.7	25.5-50.15	F=1.299	0.278
	Mean ± S. D	32.76 ± 3.57	32.17±2.95	34.97 ±10.5		
p- value between gp A&B		0.746				
p- value between gp B&C			0.047*			
p- value between gp A&C		0.059				
S/D ratio	Range	1.7-4.9	1.87-4.7	2.18-3.44	F=2.842	0.064
	Mean ± S. D	3.39 ± 0.92	3.65±0.69	3.17± 0.12		

		Study Groups		Control Group N=30	Sig. test	P-value
		Group {A} N=30	Group {B} N=30			
p- value between gp A&B		0.198				
p- value between gp B&C			0.019*			
p- value between gp A&C		0.043				
EDV	Range	5.6 -14	8.27-12.6	8.4–16.93	F=1.589	0.085
	Mean ± S. D	10.63 ± 3.7	10.44±1.09	11.5± 5.74		
p- value between gp A&B		0.763				
p- value between gp B&C			0.03			
p- value between gp A&C		0.041				

- P < 0.05: statistically significant-RI, resistance index; PI, pulsatility index; PSV, peak systolic velocity; S/D, systolic/diastolic, EDV, end diastolic velocity; IRSM, idiopathic recurrent spontaneous miscarriage

Table 3. Doppler indices changes of group a before and after treatment with oral progesterone

Variable	Mean ± SD Before treatment	Mean ± SD After treatment	P- value	Significance
RI	0.69 ±0.19	0.57 ± 0.06	<0.001*	S
PI	1.9 ± 0.58	1.53 ±0.21	<0.001*	S
PSV	32.76 ± 3.57	35.19± 13.36	0.02*	S
S/D ratio	3.39 ± 0.92	2.8±0.6	<0.001*	S
EDV	10.63 ± 3.7	13.28 ± 3.89	<0.001*	S

P < 0.05: statistically significant (S)
-RI, resistance index; PI, pulsatility index; PSV, peak systolic velocity; S/D, systolic/diastolic, EDV, end diastolic velocity;
NS :non-significant; S:Significant

Table 4. Doppler indices changes of group B before and after treatment with vaginal progesterone

Variable	Mean ± SD Before treatment	Mean ± SD After treatment	P- value	
RI	0.75±0.04	0.70 ± 0.05	<0.001*	S
PI	1.87±0.23	1.55 ±0.55	<0.001*	S
PSV	32.17±2.95	35.22± 12.8	0.011*	S
S/D ratio	3.65±0.69	2.92±0.6	<0.001*	S
EDV	10.44±1.09	13.73 ± 2.96	<0.001*	S

P < 0.05: statistically significant (S)
-RI, resistance index; PI, pulsatility index; PSV, peak systolic velocity; S/D, systolic/diastolic, EDV, end diastolic velocity;
NS :non-significant; S:Significant

Table 5. Doppler indices changes of control group before and after treatment with placebo treatment

Variable	Mean ± SD Before treatment	Mean ± SD After treatment	P- value	Sig
RI	0.59 ±0.11	0.57 ± 0.27	0.49	NS
PI	1.66± 0.35	1.53 ±0.48	0.12	NS
PSV	34.97 ±10.5	35.67± 3.76	0.422	NS
S/D ratio	3.17± 0.12	2.82± 0.89	0.053	NS
EDV	11.5± 5.74	13.2 ± 2.09	0.054	NS

P < 0.05: statistically significant (S)
-RI, resistance index; PI, pulsatility index; PSV, peak systolic velocity; S/D, systolic/diastolic, EDV, end diastolic velocity;
NS :non-significant; S:Significant

This study shows that there was statistically significant difference between the patients who completed pregnancy and those who aborted in group A regarding all studied Doppler indices before and after progesterone supplementation (P<0.05) (Table 8).

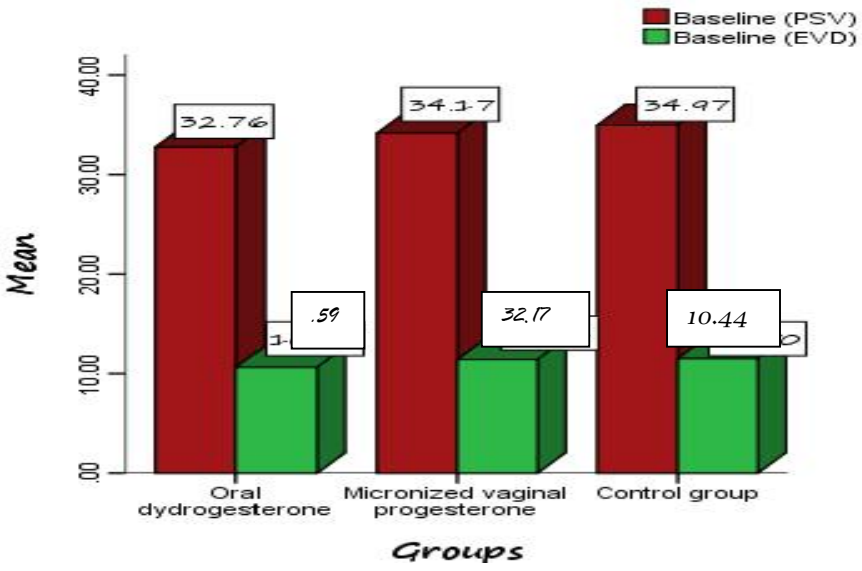
Receiver operating characteristic curve analysis of Doppler indices before therapy for predicting outcome of pregnancy: (Fig. 3)

This study illustrates the ROC plots to assess the diagnostic efficiency of Doppler indices including resistance index; pulsatility index; peak systolic velocity; systolic/diastolic ratio, and end diastolic velocity for predicting outcome of pregnancy.

ROC curve analysis showed that RI had significantly higher diagnostic accuracy than other indices in predicting outcome of pregnancy

ROC curve showed the optimum cutoff for resistance index was 0.775 for predicting miscarriage with sensitivity 88.5% and specificity 83.3%; an area under the ROC curve (AUROC) 0.905(95% CI: 0.827-0.983) (P<0.001).

Also, S/D ratio was found better predictor for abortion with an area under the curve 0.794(95% CI: 0.682-0.905) (P=0.001) and at cutoff value of 3.785, the sensitivity was 69.2% and the specificity was 83.3%.



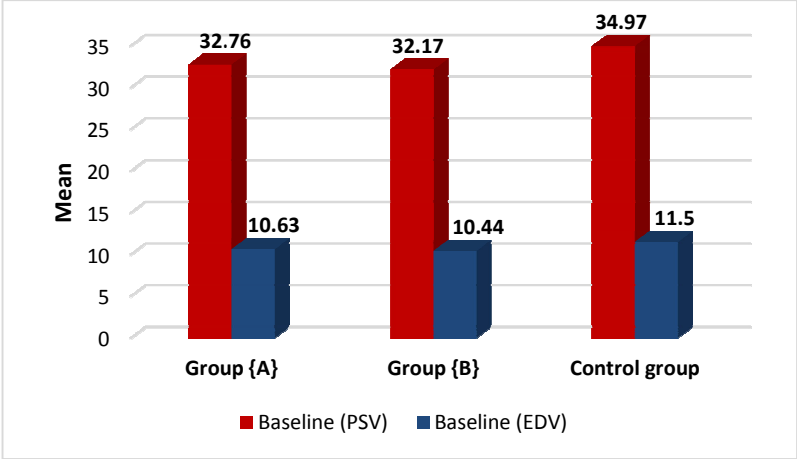


Fig. 1. Comparison between study groups and control group regarding baseline Doppler indices (PSV, EDV) before progesterone supplementation

While the cut off value of PI was 2.115 for predicting pregnancy outcome, the sensitivity was 85.9%, specificity was 58.3%; an area under the ROC curve (AUROC) 0.760(95% CI: 0.603-0.916) (P=0.004).

However both PSV and EVD were non-significant in predicting pregnancy outcome (P=0.119 & P=0.656; respectively).

Receiver operating characteristic curve analysis of Doppler indices after therapy for predicting outcome of pregnancy: (Fig. 4).

This study illustrates the ROC plots to assess the diagnostic efficiency of Doppler indices including resistance index; pulsatility index; peak systolic velocity; systolic/diastolic ratio, and end diastolic velocity after treatment for predicting outcome of pregnancy.

ROC curve analysis showed that RI had significantly higher diagnostic accuracy than other indices in predicting outcome of pregnancy ROC curve showed the optimum cutoff for resistance index was 0.685 for predicting miscarriage with sensitivity 71.8% and specificity 91.7%; an area under the ROC curve (AUROC) 0.856(95% CI: 0.748-0.965) (P<0.001).

Also, PSV and S/D ratio was found better predictor for abortion with an area under the curve 0.754(95% CI: 0.570-0.938) (P=0.005) & 0.744(95% CI: 0.625-0.863) (P=0.007);

respectively and at cutoff value of 40.25 for PSV, the sensitivity was 82.1% and the specificity was 66.7% whereas at cutoff value of 2.78 for S/D ratio, the sensitivity was 51.3% and the specificity was 100%

While the cut off value of EVD was 12.575 for predicting pregnancy outcome, the sensitivity was 47.4%, specificity was 91.7%; an area under the ROC curve (AUROC) 0.685(95% CI: 0.544-0.827) (P=0.039).

Table 6. Comparison between groups A and B regarding outcome after 28 weeks

Outcome		Study Groups		P-Value	Sig
		Group {A} N=30	Group {B} N=30		
Aborted	N %	5 16.7%	7 23.3%	0.519	
Completed	N %	25 83.3	23 76.7%		Non sig
Total	N %	30 100%	30 100%		

Table 7. Comparison between the groups A and B regarding regarding number of viable deliveries

Outcome		Study Groups		P-Value	Sig
		Group{A} N=30	Group{B} N=30		
Dead feti	N	7	9	0.559	
	%	3.3%	30%		
viable deliveries	N	23	21		Non sig
	%	76.7	70%		
Total	N	30	30		
	%	100%	100%		

Table 8. Comparison between aborted and completed IRSM cases regarding Doppler indices before and after progesterone supplementation in group A

Variable	Aborted Cases N=5	Completed Cases N=25	Sig. test	P- value	sig
Baseline (RI)	0.89 ±0.01	0.63 ± 0.15	t=11.768	<0.001**	S
Baseline (PI)	2.59± 0.03	1.71 ±0.39	t=14.791	<0.001**	S
Baseline (PSV)	24.6 ±6.7	30.79± 6. 13	t=3.875	0.001**	S
Baseline (S/D ratio)	4.38± 0.04	3.19± 0.88	t=6.780	<0.001**	S
Baseline (EDV)	10.14 ± 3.89	13.1± 0.2	t=-7.802	0.001**	S
RI after 4 weeks	0.71 ±0.04	0.56 ± 0.12	t=12.603	<0.001**	S
PI after 4 weeks	1.59 ±0.22	1.35± 0.17	t=9.228	0.003 **	S
PSV after 4 weeks	29.66± 3.43	42.8 ±8.94	t=8.165	0.001**	S
S/D ratio after 4 weeks	3.25± 0.05	2.27± 0.53	t=9.191	<0.001**	S
EDV after four weeks	14.64 ± 3.83	18.5± 2 45	t=2.888	0.019*	S

RI, resistance index; PI, pulsatility index; PSV, peak systolic velocity; S/D, systolic/diastolic, EDV, end diastolic velocity; NS: non-significant; S:Significant

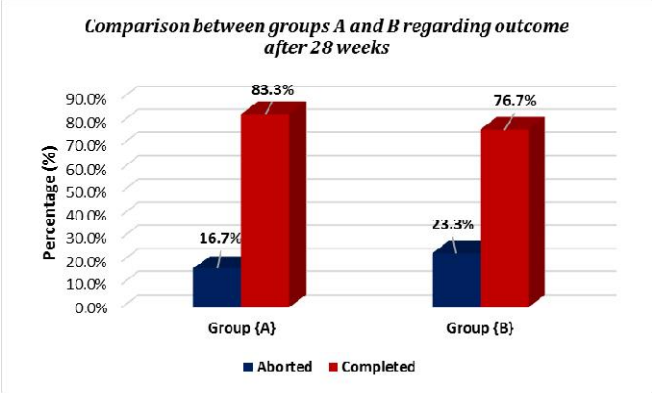


Fig. 2. Comparison between groups A and B regarding outcome after 28 weeks

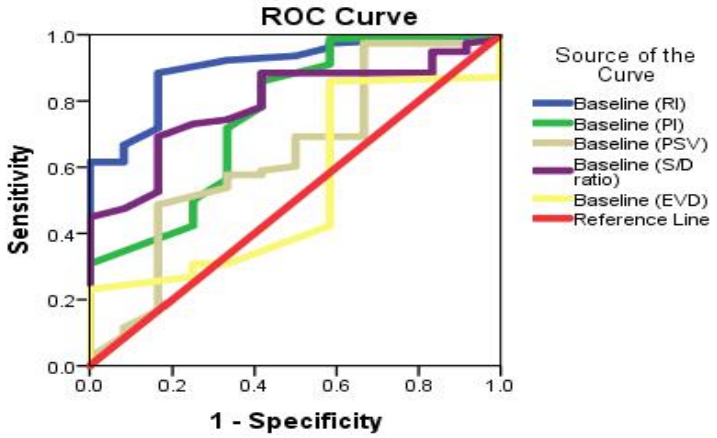


Fig. 3. ROC curve of dopplar indices at the beginning of study for predicting outcome of pregnancy

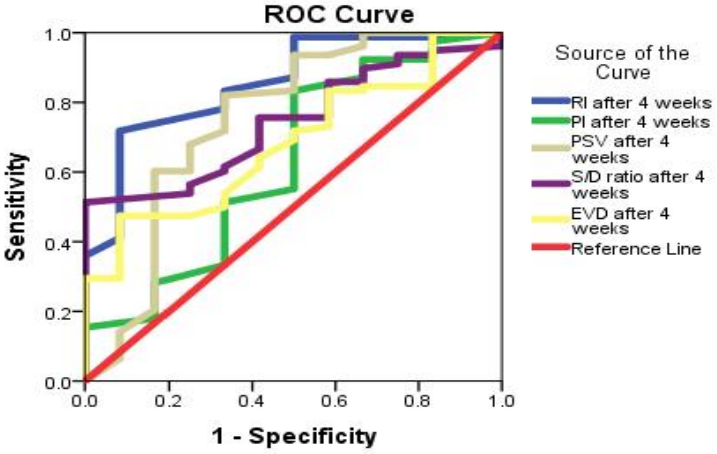


Fig. 4. ROC curve of dopplar indices after therapy for predicting outcome of pregnancy

However PI was non-significant in predicting pregnancy outcome (P=0.154).

4. DISCUSSION

On comparing the Doppler indices before progesterone supplementation, the mean resistance index (RI) was statistically significant less in the control group compared with both cases groups (A&B) (P=0.012, P=0.005 respectively). Moreover, pulsatility index (PI) was statistically significant less in the control group compared with both cases groups (A&B) (P=0.026, P=0.05 respectively). Paralleled to that, the S/D ratio was statistically significant less in control group compared with both group A &B (P=0.43, & P=0.019respectively). In addition, the mean PSV was significantly higher in control group compared to group B (P=0.047) and was higher in control group than group A with nearly significant P value (P=0.059). Also, the mean and EDV was significantly higher in control group compared to group A & B (P=0.41, & P=0.03 respectively) [9].

It was established that, the presence of good uterine and endometrial blood flow is an important prerequisite for successful implantation and continuation of pregnancy as shown by higher uterine artery blood flow resistance and lower endometrial blood flow in recurrent miscarriage cases and those patients with unexplained RPL may have abnormalities in the uterine and endometrial blood flow [10].

It can be explained by that a defective corpus luteum may produce low levels of progesterone, insufficient for endometrial ripening, implantation or placentation. Progesterone and dydrogesterone supplementation increase the subendothelial blood flow in women with RPL [11].

The uterine perfusion, in fact, regulates the endometrial receptivity and its alteration might be associated with pregnancy complication at an early stage [12].

Moreover, further studies also published that elevated uterine arterial impedance is associated with RPL and that women with recurrent pregnancy loss have a relatively increased level of PI in the uterine artery [13].

This study shows that women in control group who received folic acid as placebo had decrease in RI and PI levels ,& S/D ratio compared to their levels at the beginning of study but without significance (P>0.05 for the 3 indices).Moreover, both PSV and EDV were non significantly increased in control group after 4 weeks (P>0.05 or both).

Studies on endometrial blood flow comparing oral dydrogesterone with micronized vaginal progesterone administration in pregnant women with IRSM have not been found except by Ghosh et al. [14].

In agreement with our results, Ghosh and his co-workers, 2014 12 had reported improvement in endometrial blood flow in both the groups became apparent, with the Doppler indices comparable between the two groups (P<0.001for nearly all indices in both oral and vaginal progesterone groups) [15].

Moreover, in the control group they reported that all indices were not significantly changed after the same period of placebo therapy. This was similar to our results. This may be explained by that Doppler impedance indices change with advancing gestational age [16].

During pregnancy, there is modification of the vascular structure within the uterus leading to the development of neovascularization within the placenta and the fetus including redistribution of blood flow and alteration in circulating blood volume because vascular remodeling by trophoblast invasion occurs at placentation, causing a reduction in local arterial resistance [17].

On comparing the Doppler indices after administration of progesterone for four weeks; there was no statistically significant difference between the three studied groups regarding PI, S/D ratio, PSV , and EDV (P >0.05).Moreover, RI was showed to be decreased in group A who received oral progesterone and became non significantly different with control group(controls) (P >0.05), However, there was still a statistically significant difference in RI between IRSM cases in group B and both group A & controls (P< 0.001) after therapy.

Thus both oral and vaginal progesterone had nearly similar effects on Doppler indices with a slight better improvement of vascular impedance specially RI in cases who were treated with oral dydrogesterone [18].

These results were nearly in line with Ghosh and his co-workers, 2014 12 who reported that both

drugs were found to be effective in improving the endometrial blood flow parameters. While dydrogesterone was more effective in improving all Doppler indices including PI, RI, PSV, EDV and S/D ratio, micronized progesterone did not show any significant differences with respect to PSV [19]

As regard outcome of the study, five miscarriages were recorded for group A (16.7%) and 7 for group B (23.3%). The number of ongoing pregnancies were 25 for group A (83.3%) and 23 in group B (76.7%) without statistically significant difference ((P=0.519). Moreover, the number of viable deliveries in group A was 23 (76.6%) compared to 21 (70%) at group B. Also, there was no statistically significant difference between the both studied groups (A & B) regarding number of viable deliveries (P=0.559 [20].

Data from two recent systematic reviews and meta-analyses showed that dydrogesterone could be effectively used to prevent miscarriage in women with a history of idiopathic recurrent miscarriage [21].

Carp, 2015 181collated data from three studies, including 509 patients, and reported that the effect of dydrogesterone on the risk of miscarriage in women with recurrent miscarriage appears to be substantial. There was a statistically significant reduction in the OR for miscarriage after dydrogesterone compared to standard care of 0.29 (CI 0.13–0.65). The 23% miscarriage rate in control women (55/234) was reduced to 10.5% (29/275) after dydrogesterone administration (12.5% absolute reduction in the miscarriage rate).

Looking at clinical trial data, Kumar et al. 182 reported that the risk of miscarriage after three miscarriages was 2.4 times higher with placebo than dydrogesterone (RR 2.4; 95% CI 1.3–5.9). Both mean gestational age at delivery and birth weight were higher with dydrogesterone compared with placebo [22].

In another study, dydrogesterone was found to significantly reduce the rate of miscarriage versus no treatment (13% vs 29%; P = 0.028) with no reports of pregnancy complications or congenital abnormalities when given to women with history of idiopathic recurrent miscarriages [23].

There are few reports of side effects in mothers taking dydrogesterone. Some studies have reported drowsiness, nausea and vomiting, although such symptoms might be associated with the pregnancy itself [24].

A single-blind study by Yassaee et al. 184 that included 60 pregnant women with threatened miscarriage reported that progesterone suppositories (400 mg) reduced the number of miscarriages compared with control (6 vs 10 cases); however, this difference was not statistically significant .

In a single-center, randomized, double-blind study including 50 women with a previous diagnosis of inadequate luteal phase and threatened miscarriage, vaginal progesterone gel (Crinone 8%) was found to help in reducing the pain and the frequency of uterine contractions within 5 days of administration (P < 0.005), with a reduction in the rate of miscarriage after 60 days (P < 0.05), compared with placebo [25].

More recently, a large randomized trial found that micronized vaginal progesterone was no better than placebo for the treatment of threatened miscarriage. However, the authors cautioned that other formulations of progestational agents have different molecular structures and therefore potentially different mechanisms of actions and pharmacologic features [26].

The multicenter, randomized, double-blind, placebo-controlled PROMISE study exploring the effect of micronized vaginal progesterone (400 mg capsules) in women with a history of unexplained recurrent miscarriage (n = 836; 404 progesterone, 432 placebo) did not find any benefit of vaginal progesterone in improving rates of live birth, clinical pregnancy between 6 and 8 weeks of gestation, ongoing pregnancy at 12 weeks of gestation, miscarriage, ectopic pregnancy, stillbirth, neonatal survival, or neonatal congenital anomalies [27].

In contrast, in a similar study, Ismail et al. 187 reported that vaginal progesterone (400 mg pessaries) significantly reduced the rate of miscarriage compared with placebo (12.4% vs 23.3%; P = 0.001) in addition to an improvement in live birth rate (91.6 vs 77.4%) and continuation of pregnancy beyond 20 weeks (87.6 vs 76.7%), both of which were statistically significant (P < 0.05).

However, a recent Cochrane review, which included data from the Ismail study, demonstrated no difference between the incidences of recurrent miscarriage in patients receiving placebo (n=763) and patients receiving vaginal progestogen (n = 738), with a RR of 0.73 (95% CI 0.40–1.31) [28].

Although micronized progesterone has been used since the 1980s high doses are required when it is orally administered due to its low and variable bioavailability, resulting in side effects such as drowsiness, nausea, and headaches. For these reasons, micronized progesterone is now typically administered vaginally. This approach, in turn, carries its own disadvantages.the lower effect may be due to that intravaginal micronized progesterone may not be fully absorbed, may be washed out with vaginal bleeding, and may cause local irritation [29].

The difference in pharmacological action of these two types of progesterone may be explained due to differences in their signaling action after being bound to progesterone receptor (PR)-A or PR-B. Expression of eNOS and NO synthesis at the endothelial cell level essentially occurs through PR-A receptors [30].

Thus, it is hypothesized that the increased efficacy of dydrogesterone could be due to its enhanced affinity to PR-A receptors. Dysregulated eNOS synthesis may be prevented by myometrial quiescence and immunomodulatory changes on treatment with progesterone, especially with dydrogesterone and DHD [31].

The most frequently studied indices is uterine artery PI, Rifat, 2020 4who had focused on the early pregnancy period with a mean gestational age of nine weeks regarding identifying the best index and its cut-off value to be used as the screening test for early pregnancy failure revealed that the cut-off value for the PI of 2.64 was highly sensitive and specific for predicting the miscarriage with the area under the curve was 0.919 with a standard error of 0.03 (95% CI: 0.86-0.98), which implied that the PI could perfectly predict the occurrence of the adverse outcome among pregnant women with 91% sensitivity and 81% specificity for miscarriage [32].

Özkan et al. 179 reported that uterine artery PI cut off value of 2.03 could predict miscarriage occurrence with 88% sensitivity and 84% specificity while S/D ratio cut of value of 4.78 had 67% sensitivity and 91% specificity

Additionally, Wahab et al. [6] in their study found that the aborted patients had uterine artery PI more than 2.5 while those who attained term had the uterine artery PI value of 2.5 or less. However, the researchers could not predict the outcome of pregnancy depending on this cut-off value. However, they could not find any cut off values that could predict the occurrence of miscarriagedue to the small number of patients who became pregnant and reached term in their study [33].

This was the case with the other study that also failed to provide the cut-off for the indices since it was a cross-sectional study which was conducted among the high-risk pregnancies and lacked a control group and the follow-up to evaluate the pregnancy outcome of the enrolled women [34].

Thus, from all the above mentioned, it was concluded that progesterone supplementation caused improvement in uteroplacental blood flow parameters of pregnant women with IRSM. The use oral dydrogesterone is slightly more superior vaginal micronized progesterone. However, this study is limited by relatively small number of the studied patients [35].

5. CONCLUTION

Considerable improvement in uteroplacental blood flow parameters of pregnant women with IRSM is evident with progesterone supplementation .It was found that both oral and vaginal progesterone had nearly similar effects on Doppler indices in cases complaining from idiopathic recurrent spontaneous miscarriage with a slight better improvement of vascular impedance specially RI in cases who were treated with oral dydrogesterone.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT AND ETHICAL APPROVAL

As per international standard or university standard guideline participant consent and ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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