

RELATION BETWEEN VASCULER ENDOTHELIAL GROWTH FACTOR AND 3D DOPPLER ULTRASONOGRAPHY WITH SUBENDOMETRIAL WAVE LIKE MOVEMENT IN CASE OF UNEXPLAINED INFERTILITY

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ABSTRACT

Unexplained infertility remains a frustrating problem for the clinician and a distressing condition for the affected couples. Unexplained infertility has been defined as it is the infertility which no cause can be detected to explain the fertility problem in spite of conventional investigation for both partners.

to evaluate the Relation between Vasculer Endothelial Growth Factor (VEGF), sub endometrial wave like movement (JZC) and sub endometrial blood flow detected by 3D as indicator of uterine receptivity in spontnous and stimulated cycles in unexplained infertile women.

The sample size was calculated according to Jain et al., (2015) who reported that the level of VEGF in fertile women was 324 ± 20.50 and in infertile women the level was found to be 107.33 ± 24.96 . So, by adjusting the confidence interval to 95%, the power of the test to 90%, the ratio between groups was adjusted to 1:2. The sample size was found to be 96 cases divided into 32 controls (fertile women "group C") and 64 cases was divided also into two groups (infertile women with un-stimulated cycle (group A) and 32 cases infertile women with stimulated cycles chlomiphene citrate (group B).

This study was performed in the department and out patient clinic of obstetrics and gynecology at Al Zahraa university hospital from September 2016 to September 2019 on ninety six participants. Ninety six participants who qualified the exclusion and inclusion criteria were enrolled in this study: thirty two participants categorized in group (A) diagnosed as unexplained infertility with unstimulated cycle, thirty two participants categorized in group (B) diagnesd as unexplained infertility with stimulated cycle (clomiphene citrate) and thirty two participants normal fertile women categorized in group (C) seeking contraceptive means (control group). All participants on day 21 -22 day of cycle underwent in to 3D transvaginal ultrasound to detect subendometrial blood flow, subendometial wave like movement and on the same day venous blood sample was taken to measure VEGF.

Keywords: Unexplained infertility, Subendometrial blood flow, Endometrial receptivity, Junctional zone contraction .

RESULTS:

There was a statistically significant decrease in sub endometrial blood flow among infertile groups (A and B) than fertile group (C) p value <0.001 . The overall dynamic characteristics of uterine peristalsis between group A, B and C were different. The direction of the JZC in group C yielded large values from cervix to fundus in (87.4 %), and the

motion was more symmetrical than group A and B. Serum concentrations of VEGF during the secretory phases of the menstrual cycle in a group (A and B) was lower than group (C) fertile women $p < 0.001$. Roc curve is constructed to detect cut off point, sensitivity, specificity, AUC, positive predictive value and negative predictive value of VEGF in unexplained infertile women, it was found that the serum concentration of $< 200\text{pg/ml}$ was able to predict good endometrial receptivity with a sensitivity of 100% and a specificity of 96.8%. The positive predictive value of the test was found to be 98.4% and negative predictive value was 100%. The area under the curve was 0.970. There was positive relation between VEGF as regard Doppler blood flow study to sub endometrial region $r = 0.694$, p value 0.023.

Conclusion:

Transvaginal color Doppler examination of the subendometrial blood flow distribution provides a simple and effective method to evaluate endometrial receptivity. The junctional zone should be considered as a separate distinct functional unit within the uterus. There is enough evidence to suggest that it may have a central role in the processes of implantation. Serum VEGF levels were found to rise with increasing Doppler vascular penetration zones which implies that serum VEGF concentrations can be used as a marker of endometrial receptivity.

INTRODUCTION

Infertility in itself represents a wide spectrum of disorders explaining the inability to conceive in spite of conventional investigation for both partners. Series of investigations are required to depict the potential cause of infertility, yet there exist a small percentage (10-25%) of couples in which no obvious cause is delineated (*Speroff et al., 2012*).

Uterine receptivity is regulated by (1) markers as Vascular Endothelial Growth Factor. It is believed that VEGF, a mitogenic factor, is involved in angiogenesis process and thus in antral cavity formation (*Fanchin et al., 2017*). Trans-vaginal Color Doppler ultrasonography is used to assess endometrial and subendometrial flow and to evaluate the functional capacity and receptivity of the endometrium and in the prediction of successful implantation and revealing unexplained infertility problems (*Steer et al., 2015*). Endometrial receptivity can also be assessed by junctional zone contraction which found in superficial sub endometrial muscle layer, these waves are fundocervical, cervico fundal (which favourable for keeping pregnancy and conception) and haphazard or irregular. Movement with cervicofundal direction, movements of weak or moderate intensity, and higher number of endometrial contractions per minute should be considered favorable predictors of pregnancy. (*Nandi et al., 2015*).

The aim of this study was to evaluate the Relation between vascular endothelial growth factor (VEGF), sub endometrial wave like movement (JZC) and sub endometrial blood flow detected by 3D as indicator of uterine receptivity in spontaneous and stimulated cycles in unexplained infertile women.

Patients and Methods

This study was performed in the department and out patient clinic of obstetrics and gynecology at Al Zahraa university hospital from September 2016 to September 2019 on ninety six participant. Ninety six participants who qualified the exclusion and inclusion criteria were enrolled in the study.

They were classified in to: thirty two participants categorized in group (A) unexplained infertile women with unstimulated cycle, thirty two participants categorized in group (B) unexplained infertile women with stimulated cycle (clomiphene citrate) and thirty two participants normal fertile women categorized in group (C) seeking contraceptive means.

Before enrolling the study informed consent was taken from all patients. At the time of initial recruitment, the purpose of the study was adequately explained to each participant according to the ethical committee of Al Azher University for girls.

Groups (A and C) asked to come during mid luteal phase for examination While Patients in group (B) asked to come first in follicular phase and they were subjected to induction of ovulation with (clomiphene citrate) 50 milligram tablet twice per day for five days starting from second day of cycle. When graffian follicle reached to >18millimetre, HCG was given and then they were given cyclogest rectal suppository as luteal phase support then patient asked to come again on 21 -22 day of cycle for examination.

Inclusion Criteria for the infertility group:

- Age between 18-40 years old.
- Criteria for unexplained infertility: Normal semen analysis according to criteria in WHO 2018, normal ovulation with mid luteal serum progesterone 10 ng /ml, patent fallopian tubes and normal pelvic cavity diagnosed by hysterosalpingography and laparoscopy.
- Infertility either primary or secondary.

Inclusion Criteria for the control group:

- Age between 18-40 years old.
- Multiparous women.
- No hormonal contraception.
- Had baby at least 2 years.

Exclusion Criteria for both groups:

- Infertility due to ovarian factor.
- Infertility due to tubal disease.
- Infertility due to uterine or cervical cause.
- Infertility due to male factor.
- Pregnancy

Steps and Methods:

All women were subjected to: **Complete history taking:** personal history, menstrual history, obstetric history, past history and history of investigations (Semen analysis to exclude male factor of infertility. Hormonal profile at 3rd day of the cycle including FSH, LH, Estrone and prolactin. HSG to confirm the patency of the Fallopian tubes, and to exclude any structural abnormality of the uterus). **Complete examination:** General, abdominal and pelvic examination.

Then all women under went in to:

A - 3D Trans vaginal ultrasound examination was done on day 21 -22 day of cycle.

All examinations were performed with the scanner (MINDRAY DC 70) with 7.5 MHZ endocavitary transducer with pulsed colour Doppler and three D facility.

While the woman were in lithotomy position with empty bladder sliding the vaginal probe in to the vagina and placed in the anterior fornix, and the internal cervical os and the external one were identified, Uterine examination was performed to rule out any uterine anomaly that might interfere with pregnancy such as uterine septum, bicornuate uterus, and uterine myomas and to rule out any abnormalities.

Ultrasound measurement of endometrial thickness, pattern and blood flow of the subendometrial radial arteries was performed.

The subendometrial blood flow distribution pattern was determined by demonstrating pulsatile color signals in the subendometrial regions. The subendometrial area, summarized as follows: Zone 1, Zone 2 and Zone 3, poor, intermediate and good vascularity respectively. The blood flow distribution pattern was observed at the beginning and the end of the ultrasound examination.

Then junctional zone contraction was measured for five minutes. Wave types were described according to the classification system of *Ijland et al. (1996)* including five types of endometrial movement: no activity (N), waves from cervix to fundus (CF), waves from fundus to cervix (FC), opposing waves starting simultaneously at cervix and fundus (OP) and random waves starting at various foci (R).

B - Serological Investigations:

On the same day of 3D transvaginal ultrasound performing venous blood samples were collected from patients, Centrifugation was done to obtain at least 1ml of serum from each sample. The assay was done using DIACLONE VEGF-A BIOLISA Kit (quantitative) which measures free or active VEGF-A in serum. The antibodies used in this ELISA test were specific for human VEGF with no detectable cross-reactivity with placental growth

factor. Blood samples were immediately processed by centrifuge after clotting, and the supernatant serum was kept frozen at -70°C until assayed. Vascular endothelial growth factor was determined in duplicate by enzyme immunoassays (human VEGF) vascular endothelial growth factor antibodies, according to the manufacturer, are polyclonal and are able to detect any VEGF molecule present in the examined sample.

Statistical analysis

Data were collected, coded, revised and entered to the Statistical Package for Social Science (IBM SPSS) version 20. The data were presented as number and percentages for the qualitative data, mean, standard deviations and ranges for the quantitative data with parametric distribution and median with inter quartile range (IQR) for the quantitative data with non parametric distribution.

Chi-square test was used in the comparison between two groups with qualitative data and *Fisher exact test* was used instead of the Chi-square test when the expected count in any cell found less than 5.

The comparison between more than two groups with quantitative data and parametric distribution were done by using One Way Analysis of Variance (ANOVA) test and Kruskal-Wallis test was used in the comparison between more than two groups with quantitative data and non parametric distribution.

Spearman correlation coefficients were used to assess the significant relation between two quantitative parameters in the same group.

Receiver Operating Characteristic curve (ROC) Receiver operating characteristic curve (ROC) was used to assess the best cut off point for VEGF in unexplained infertile women with its sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and area under curve (AUC).

The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following:

- $P > 0.05$: Non significant (NS)
- $P < 0.05$: Significant (S)
- $P < 0.01$: Highly significant (HS)

RESULTS

Table (1): Comparison between group A, group B and group C as regards demographic data.

		Group A		Group B		Group C		Chi square test	
		No	%	No	%	No	%	χ^2	p value
Age	Mean \pm SD	30.13	3.38	28.84	2.49%	30.81	4.33	2.637	0.077
Parity	No	28	87.5%	28	87.5%	0	0.0%	67.200	<0.001
	Yes	4	12.5%	4	12.5%	32	100.0%		
BMI	Mean \pm SD	23.38	2.45	24.13	1.98	23.44	2.21	1.123	0.330

This table shows that there was no statistically significant difference regarding age, BMI between three groups. But there was a statistically significant difference

regarding parity between fertile and infertile groups.

Table (2): Comparison between group A, group B as regard parity, type and duration of infertility.

		Group A		Group B		Chi square test	
		No	%	No	%	χ^2	p value
Parity	No	28	87.5%	28	87.5%	0.000	0.995
	Yes	4	12.5%	4	12.5%		
Type of infertility	Primary	27	87.1%	20	65.6%	3.925	0.057
	Secondary	5	12.9%	12	34.4%		
Duration of infertility (yr)	Mean \pm SD	4.38	1.26	4.74	1.61	1.015	0.318

This table shows that there was no statistically significant difference regarding parity, type and duration of infertility between group A and group B (infertile groups).

Table (3): Comparison between group A, group B and group C as regards sonographic finding.

		Group A		Group B		Group C		Chi square test	
		No	%	No	%	No	%	χ^2	p value
Endometrial pattern	Hyper echoic	4	12.5%	5	15.6%	23	71.9%	35.355	<0.001
	Hypo echoic	25	78.1%	23	71.9%	5	15.6%		
	Triple line	3	9.4%	4	12.5%	4	12.5%		
Endometrial thickness (ml)	Mean \pm SD	5.16	1.27	7.50	1.57	9.2 2	2.71	34.991	<0.001
Direction of JZC	FC	22	68.8%	8	25.0%	4	12.5%	58.180	<0.001
	CF	0	0.0%	20	62.5%	28	87.4%		
	Opposing	3	9.4%	0	0.0%	0	0.0%		
	No movement	5	15.6%	3	9.8%	0	0.0%		
	Randomized	2	6.3%	1	3.1%	0	0.0%		
		Mean \pm SD		Mean \pm SD		Mean \pm SD		χ^2	p value
Frequency (waves/min)		3.15 \pm 0.94		4.39 \pm 1.52		2.24 \pm 0.78		29.405	<0.001
3D Doppler	ZONE 1	29	90.6%	25	71.9%	1	3.1%	80.725	<0.001
	ZONE 2	2	6.2%	5	21.9%	3	9.4%		
	ZONE 3	1	3.1%	2	6.2%	28	87.5%		

This table shows that there was a statistically significant difference regarding Sonographic finding among studied group (**p <0.001**).

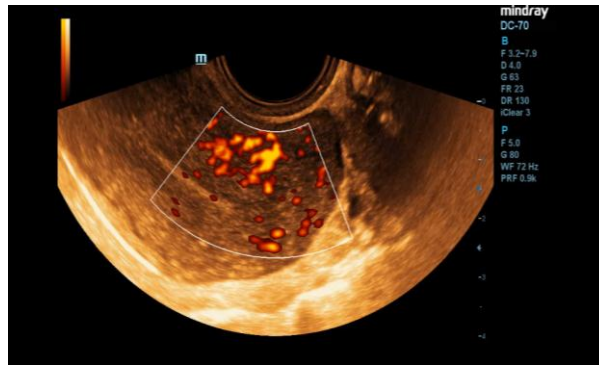


Fig (1): Doppler ultrasound image showing good endometrial vascularity group (C)

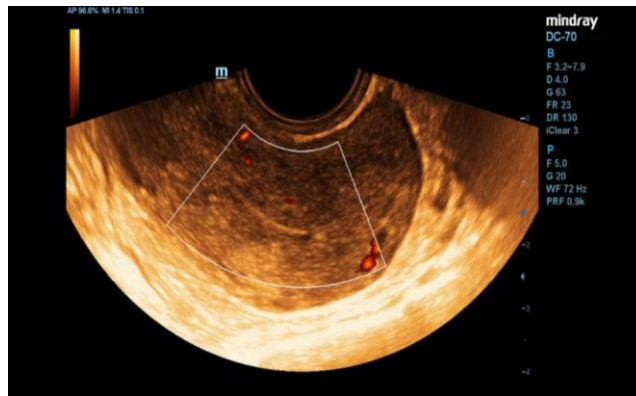


Fig (2): Doppler ultrasound image showing poor endometrial vascularity group (A)

Table (4): Comparison between group A, group B and group C as regards serological value of VEGF measured on 21 -22 day of cycle.

	Group A		Group B		Group C		one way ANOVA	
	Mean	SD	Mean	SD	Mean	SD	f/t**	p value
VEGF pg/ml	51.84	13.45	150.44	29.69	573.88	67.30	1320.474	<0.001

This table shows that there was a statistically significant increase in group C in comparison to group A& group B regarding VEGF measurement ($p < 0.001$).

Table (5): Cut of point, sensitivity and specificity of VEGF between patients group and Control group.

Cut off point	AUC	Sensitivity	Specificity	-PV	+PV
≤ 200	0.970	100.00	96.87	100.0	98.4

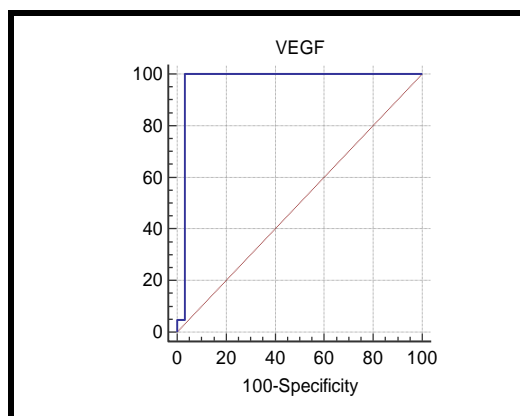


Fig (3): Roc curve is constructed to detect cut off point, sensitivity, specificity, AUC, positive predictive value and negative predictive value of VEGF in unexplained infertile women.

Table (6): Relation between VEGF as regard Doppler blood flow study to subendometrial region.

		Group A		Group B		Group C		One way ANOVA	
		VEGF		VEGF		VEGF			
		Mean	SD	Mean	SD	Mean	SD	f	P value
3D Doppler	Zone 1	49.00	13.56	141.57	30.33	494.33	0.00	36.694	0.023
	Zone 2	51.69	18.38	152.92	27.54	581.46	79.48		
	Zone 3	62.00	0.00	165.28	0.00	600.00	62.81		

This table shows that There was positive relation between VEGF as regard Doppler blood flow study to sub endometrial region p value 0.023.

Discussion

Unexplained infertility has been defined as it is the infertility which no cause could be detected to explain the fertility problem in spite of conventional investigation for both partners or the infertility problem continuous after correction of factors identified as probably responsible for infertility (*Riad and Hak, 2016*).

Angiogenesis is an essential prerequisite for human endometrial development and differentiation, further for the implantation of blastocyst and continuation of pregnancy. The absence of sub-endometrial perfusion is associated with non-conception cycles (*Ota et al., 2017*).

Ultrasonography includes its non-invasiveness, repeatability, real-time monitoring and predictability, however ultrasonographic findings indicating changed endometrial receptivity have not yet been acknowledged. The different sonographic markers of receptivity are endometrial thickness, pattern, echogenicity and colour Doppler study of uterine and endometrial blood flow (*Tekay et al., 2016*).

In the current study All women were in reproductive age (18 – 40 years) with no statistically significant difference between three groups as regard age, body mass index, while a statistically significant difference was present as regard parity between

fertile and infertile groups **as seen in table 1**. Also, no statistically significant difference was present between infertile groups (A and B) as regard parity, type and duration of infertility **as seen in table 2**.

The current study showed as regard endometrial thickness and pattern: there was a statistically significant decrease regarding endometrial thickness in group (A and B) than group (C) p value <0.001. Endometrial pattern was Hyper echoic in 71.9% in group C, hypo echoic in 87.1 and 71.9 in group A and B respectively **as seen in table 3**.

The current study was similar to study done by El-Mazny et al. (2013) who compared the endometrial thickness, pattern among parious women and women with unexplained infertility in mid luteal phase. They found that the endometrial thickness and pattern were significantly different between the two groups p value < 0.001.

On the contrary , Contort, Heng-Kien et al. (2014) disagree with the current study.They did a study on Six hundred twenty-three patients to detect association between pregnancy rate and endometrial measurements, and found that there was no statistically significant difference as regard endometrial thickness and pattern between fertile and infertile women.

The endometrium in the non-pregnant uterus shows distinct activity patterns throughout the menstrual cycle, which are called endometrial waves. These waves originate in the subendometrial myometrium and are influenced by steroids. The subendometrial activity might be initiated by pacemakers in the uterine muscle, providing the mechanical phenomenon of endometrial waves.A relative quiescence of the uterus and an adequate wave pattern in certain phases of the cycle are related to successful reproduction (*Bulletti et al., 2015; IJland et al., 2016*).

As regard Direction of junctional zone contraction: the current study showed that The overall dynamic characteristics of uterine peristalsis between group A, B and C were different. The direction of the JZC in group C yielded large values from cervix to fundus in (87.4 %), and the motion was more symmetrical than in group A and B. During secretory phase (mid luteal phase) in group (B), waves moving from the cervix to fundus dominated, comprising (62.5 %) of the wave types observed but less than group (C).While ‘no activity’, ‘fundo cervical’ and ‘opposing waves’ waves were more frequently observed in (group A) **as seen in table 3**.

Also, in the present study the frequency of junctional zone contraction in group C yielded smaller value than group A and B. Its mean \pm SD 2.24 \pm 0.78 While uterine prestalsis wave frequency was higher in group B than group A.Its mean \pm SD 4.39 \pm 1.52 **p value <0.001**.

On the same hand Bulletti et al. (2015) found that, luteal phase subendometrial contraction waves have been described as decreasing in frequency and intensity with the progression of the secretory phase as being directed predominantly from the cervical canal to the fundal part of the uterus. In fertile group wave moving from cervix to fundus (90%) while in infertile group wave seen from fundus to cervix in (87.5%). After ovulation, the endometrial wave-like activity decreases significantly to provide a quiet environment for embryo implantation.

As regard blood flow study to sub endometrium: it was found in the current

study that there was a statistically significant decrease in sub endometrial blood flow among infertile groups (A and B) than fertile group (C) $P < 0.001$. **zone 3** vascularity is seen in 87.5 % of group C and 3.1 % of group A and 6.2 in group B and **zone 1** vascularity seen in 90.6% of group A and 71.9 % of group B and 3.1% of group C. while **zone 2** vascularity seen in 6.2% of group A, 21.9 yn group B and 9.4% of group C as seen in table 3.

On the same hand Chien et al. (2016) found in their study on assessment of uterine receptivity by the endometrial subendometrial blood flow distribution pattern in women undergoing in vitro fertilization-embryo transfer noticed a significantly higher pregnancy and implantation rates in patients with increased vascularity i.e. when vascular penetration was seen till the innermost endometrial lining or inner-half of the endometrium as compared to the patients in which there was no detectable blood flow on Doppler imaging.

Similarly, Raine-Fenning et al. (2015) found that endometrial and subendometrial vascularity of women with unexplained infertility were significantly lower during the luteal phase of a natural cycle than that of normal fertile women $p < 0.001$.

As regard serological findings: it was found in the current study that serum concentrations of vascular endothelial growth factor during the secretory phases of the menstrual cycle in a group (C) fertile women was higher than groups (A and B) infertile groups $p < 0.001$ which had high significant (**Table 4**).

The crucial role of angiogenesis on human endometrium was hypothesised by **Klauber et al., (2016)** in their study on effect of inhibitors of angiogenesis on endometrial growth. An angiogenesis inhibitor AGM-1470 was injected in both pregnant and non-pregnant cycling women; in pregnant women it interference with decidualization, placental and yolk sac formation and embryonic vascular development. While in non –pregnant women it resulted in inhibition of endometrial maturation and corpus luteum formation.

The current study was similar to study done by El-Zenneni et al. (2015) who did study to asses subendometrial blood flows as well as the vascular endothelial growth factor as markers of endometrial angiogenesis and receptivity in women with unexplained infertility, they found that a significantly lower VEGF level, a significantly lower endometrial thickness and a significantly lower subendometrial blood flow among the unexplained infertile women when compared to their age matched Fertile Group.

The Doppler vascular penetration zones were taken as gold standard and cut-off value of serum VEGF. Using the Receiver operator curve (ROC), Roc curve is constructed to detect cut off point, sensitivity, specificity, AUC, positive predictive value and negative predictive value of VEGF in unexplained infertile women, it was found that the serum concentration of $< 200\text{pg/ml}$ was able to predict good endometrial receptivity with a sensitivity of 100% and a specificity of 96.8%. The positive predictive value of the test was found to be 98.4% and negative predictive value was 100%. The area under the curve was 0.970 as seen in (**Table 5**).

The current study not far from study done by Jain et al. (2015) who found that the Doppler vascular penetration zones were taken as gold standard and cut-off value of serum VEGF. Using the receiver operator curve (ROC), it was found that the serum concentration of 87pg/ml was able to predict good endometrial receptivity with a

sensitivity of 89.47% and a specificity of 87.8%. The positive predictive value of the test was found to be 77.27% and negative predictive value was 94.73%. The area under the curve was 0.943 with a standard error of 0.031, $p=0.000$.

The current study shows that there was positive relation between VEGF as regard Doppler blood flow study to sub endometrial region $r(36.694)$ p value (0.023) as seen in (Table 6).

On the same hand, the current study not far from study done by Jain et al. (2015), who conducted study on 60 Patients to see Doppler blood flow studies of the endometrium and its relation with Serum VEGF in Women with Unexplained Infertility and found that Doppler vascular penetration zones were identified as zone 1, zone 2 and zone 3 i.e. poor, intermediate and good vascularity respectively, a rise in the mean serum VEGF level was observed with the increase in the endometrial vascular penetration zones on Doppler i.e. from 37.67 ± 10.53 pg/ml in Zone 1 to 83.69 ± 19.86 pg/ml in Zone 2 to 215.07 ± 25.60 pg/ml in Zone3 ($p<0.05$).

Disclosure

Authors haven't received any financial aid from any of the companies and have no financial relation with any of the firms.

Conclusion

This study has shown that, Transvaginal color Doppler examination of the subendometrial blood flow distribution provides a simple and effective method to evaluate endometrial receptivity. The presence of subendometrial blood flow is indicative of good endometrial receptivity, whereas the absence of it represents a poor uterine environment. The junctional zone may be considered as a separate distinct functional unit within the uterus. There is enough evidence to suggest that it may has a central role in the processes of implantation. Expression of vascular endothelial growth factor in serum during luteal phase of the menstrual cycle suggests that vascular endothelial growth factor may promote the vascular growth, maintenance, and hyperpermeability required for adequate receptivity in the cycling human endometrium.

Conflict of interest

The authors report no conflict of interest.

REFERENCES

- Bulletti C, DeZiegler D, Polli V, Del Ferro E, Palini S and Flamingi C (2015):** Characteristics of uterine contractility during menses in women with mild to moderate endometriosis. *Fertil. Steril.*, 77, 1156±1161.
- Chien LW, Au HK, Chen PL, Xiao J and Tzeng CR (2016):** Assessment of uterine receptivity by the endometrial subendometrial blood flow distribution pattern in women undergoing in vitro fertilization embryo transfer. *Fert Steril.*; 78: 245–251.
- Choudhary M, Chowdhary J, Swarankar ML, Bharadwaj SL (2015):** Predictive value of subendometrial–endometrial blood flow assessment by transvaginal 3D power doppler on the day of HCG on clinical outcome of IVF cycles. *Int. J. Res. Med. Sci.*, 3: 3114.

- El-Mazny A, Abou-Salem N, Elshenoufy H (2013):** Doppler study of uterine hemodynamics in women with unexplained infertility. *Eur J Obstet Gynecol Reprod Biol.* 171(1):84–87.
- El-Zenneni R, Bettahar K, Grange G, Ohl J, Arbogast E, Moreau L (2015):.** Predictive value of transvaginal uterine Doppler assessment in an in vitro fertilization program. *Ultrasound Obstet Gynecol* 3:350–3.
- Fanchin R, De Ziegler D, Taieb J et al. (2017):** Human chorionic gonadotropin administration does not increase plasma androgen levels in patients undergoing controlled ovarian hyper-stimulation. *Fertil Steril.*, 73: 275-9.
- Heng-Kien RL, Holthaus S, d’Alquen J, Fimmers R, Dorn C, van der H, et al. (2014):** Quantitative assessment of subendometrial blood flow by three-dimensional ultrasound is an important predictive factor in an in vitro fertilization program. *Hum Reprod.* 15:89–94.
- Ijland MM, Evers JL and Hoogland HJ (2016):** Velocity of endometrial wavelike activity in spontaneous cycle. *Fertility and Sterility* 68, 72–75.
- Island M and Fufuda K (2016):** Uterine endometrial cavity movements and cervical mucus. *Hum. Reprod.*, 9: 1013-1016.
- Jain P, Paul S, Gupta U, Tuli A, Jain M (2015):** Doppler Blood Flow Studies of the Endometrium and Its Relation with Serum VEGF in Women with Unexplained Infertility. *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS).* 14(1): 74-78
- Klauber N, Rohan RM, Flynn E and D’Amato RJ (2016):** Critical components of the female reproductive pathway are suppressed by the angiogenesis inhibitor AGM-1470. *Nat Med*; 3(4):443–446.
- Nandi A, Gudi A, Shah A and Homburg R (2015):** An online survey of specialists’ opinion on first line management options for unexplained subfertility. *Hum Fertil*; 18:48–53
- Ota H, Igarashi S and Tanaka T (2017):** Morphometric evaluation of stromal vascularization in the endometrium in adenomyosis. *Hum Reprod*; 13:715–9.
- Raine-Fenning NJ, Campbell BK, Kendall NR et al. (2015):** Quantifying the changes in endometrial vascularity throughout the normal menstrual cycle with three dimensional power Doppler angiography. *Human Reprod.*, 19: 330-338.
- Riad ON and Hak AA (2016):** Assessment of endometrial receptivity using Doppler ultrasonography in infertile women undergoing intrauterine insemination. *Gynecol Endocrinol*; 30(1):70-73.
- Speroff L, Glass R, Kase N (2012):** *Clinical Gynecologic Endocrinology and Infertility*, 6th ed., 867-945.
- Steer CV, Campbell S, Pampiglione JS et al. (2015):** Transvaginal color flow imaging of the uterine arteries during the ovarian and menstrual cycles. *Hum Reprod.*, 5: 391–395.

Tekay A, Martikainen H and Jouppila P (2016): The clinical value of transvaginal colour Doppler ultrasound in assisted reproductive technology procedures. Hum. Reprod., 11, 1589–1590

العلاقة بين عامل نمو بطانة الوعاء الدموي والدوبلر التصويرى للأوعية الدموية فى أوعية بطانة الرحم وحركة الموجات فى الجزء من تحت بطانة الرحم فى حالات عدم الإنجاب غير معروف السبب

أ.د/مجدى عبد المحسن علما ، أ.م/ دعاء محمود عفت ، د/ إيمان محمد عبد العزيز

قسم امراض النساء والتوليد- كلية طب بنات الأزهر- جامعة الأزهر

يبقى العقم غير معروف السبب مشكلة محبطة للطبيب وحالة مؤلمة للزوجين المصابين ،

ومن اسباب العقم غير المسبب :-

١ . الاضطرابات الهرمونية مثل مرض خلل التبويض.

٢ . بطانة الرحم المهاجرة.

٣ . وجود الاجسام المضاده فى الحيوانات المنويه للرجال.

٤ . خلل فى مستقبلات بطانة الرحم .

٥ . أسباب مناعيه ومخاط عنق الرحم وعوامل نفسه .

ويتم تشخيص العقم غير المفسر من خلال عملية الإقصاء التى يتم اجراؤها على النمو المبين من قبل جمعية الخصوبه الأمريكيه عن طريق:-

- أخذ التاريخ الفحصى والمرضى للزوجين العقيمين .

- تحليل السائل المنوى وتقييم التبويض واختبار مابعد الجماع .

وتلعب بطانة الرحم دورا هاما فى تحديد الخصوبه لايمكن التقليل من شأنها حيث أنه خلال الدورة الشهرية يكون هناك زياده وسمك فى بطانة الرحم التى يمكن التحكم فيها مباشر او غير مباشر عن طريق المنشطات الإيجابية مثل (عامل نمو بطانة الرحم) .

وقد كان الهدف من هذه الدراسه هو تقييم العلاقة بين عامل نمو بطانة الوعاء الدموي و ٣ دوبلر بالموجات الفوق صوتيه مع موجة بطانة الرحم الفرعيه فى المرضى الذين يعانون من العقم غير المفسر فى دوره العاديه والدوره المحفزه .

و تمت هذه الدراسه بمستشفى الزهراء الجامعى بقسم النساء والتوليد حيث يتم تقسيم المرضى الى ثلاثة مجموعات مجموعته يعانون من العقم غير معروف السبب ومجموعه ياخذون منشط للتبويض ومجموعه لديهم دوره طبيعيه ، ويتم عمل متابعة للتبويض وعندما يصل حجم البويضه الى ٢٠ ميلليمتر يتم عمل 3D دوبلر وكذلك يتم قياس عامل نمو بطانة الاوعيه الدمويه ويتم مقارنة النتائج بين الثلاثه مجموعات. من خلال دراستنا، توصلنا إلى:-

١ . أن تدفق الدم للأوعية الدموية ببطانة الرحم مؤشر جيد لاستقبال الرحم.

٢ . يمكن استخدام عامل نمو بطانة الأوعية الدموية كمؤشر جيد لاستقبال الرحم.

٣ . يجب النظر إلى حركة الموجات فى الجزء أسفل بطانة الرحم لأن لها دور مهم جدا ف تأخر الإنجاب.