RESEARCH ARTICLE

Follicular fluid vascular endothelial growth factor in normal and hyperresponder females and how it is affected by the type of trigger

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Abstract

Objective: To study the type of trigger affecting the level of vascular endothelial growth factor in the follicular fluid of normal and hyper-responder females aiming to decrease the occurrence of ovarian hyper- stimulated syndrome.

Methods: A total of 87 females with infertility, attending the Al sadder center in AL-Najaf Al -Ashraf city, for IVF were included in the study. PCOS were present in 48 women and the remaining had other causes of infertility. All of them used antagonist protocol and gonadotrophin. Triggering of ovulation was induced by hCG in non PCOS and GnRH-agonist in PCOS. Transvaginal aspiration of the follicles and measurement of follicular fluid VEGF was done.

Result: A total of 87 infertile females were included in the study. They were divided in 2 groups; hyper -responders (48 cases)and normal responders 39 cases with male causes and tubal and unexplained etiology.

No significant difference was observed between the hyper responders and the normal responders regarding age and BMI, (P<0.313 and 0.721 respectively)

Using GnRH agonist as a trigger of ovulation in females with PCOS, lowering the level of VEGF, decreases the risk of developing OHSS.

Conclusion: using the GNRH agonist instead of hCG as a trigger in females with PCOS lowers the risk of developing OHSS.

Keywords: OHSS (ovarian hyperstimulated syndrome), VEGF (vascular endothelial growth factor), ART (assisted reproductive technology), GnRH (gonadotrophin releasing hormone), hCG (human chorionic gonadotrophin), PCOS (polycystic ovarian syndrome). (JPMA 71: S-56 [Suppl. 9]; 2021)

Introduction

Hyper response to ovarian stimulation can occur in females with polycystic ovarian syndrome (PCOS), a disorder encountered during the reproductive years, characterized by obesity, hyperandrogenism, insulin resistance and menstrual cycle abnormalities in the form of oligomenorrhea or amenorrhea which is due to an-ovulation, dyslipidaemia and hyperglycaemia.[1,2] Adolescents can also develop PCOs similar to adult females and meeting the Rotterdam criteria.[3,4] PCOS can be diagnosed by presence of 2 of 3 features which include: 1) oligo ovulation and or an-ovulation, 2) clinical signs and or biochemical markers of hyperandrogenism 3) unilateral or bilateral polycystic changes of the ovary on ultrasound.[5] The exact cause behind the development of PCOS is not well known. Cumulative causes include genetic, environmental and endocrine which may play a role in the development of this syndrome ; however, there is some evidence related to the syndrome to the disturbance in the blood flow of the ovaries and abnormal angiogenesis can lead to disorder of ovulation and subsequently menstrual abnormalities and subfertility in females with PCOS.[6] Angiogenic and antiangiogenic growth factors such as (vascular endothelial growth factor (VEGF) groups, angiopoitin, fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF) and thrombospondin (TSP-1)) are usually expressed in ovarian cycle.[7] Human VEGF is the most important angiogenic factor in cyclic new vessel formation and vascular permeability that affects endothelial proliferation and survival.[7] Recently some studies showed that the increase serum VEGF in PCOS in a female can cause increase in ovarian vascularisation and new vessel formation which leads to increased risk of development of OHSS.[8,9] Another study showed that increased levels of both serum and follicular VEGF in females with PCOS undergoing IVF.[10] It is also known that follicular fluid VEGF has a very important role in the process of maturation of the follicles and can affect the oocyte quality. Hence it can influence fertilization and development of the embryo in females with PCOS.[11,12] The objective of this study was to examine the type of trigger which can affect the level of VEGF in the follicular fluid in normal and hyper-responder females aiming to decrease the occurrence of OHSS.

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Patients and Methods

This cross sectional study included 87 females with infertility attending AL-Sadder infertility centre in AL-Ashraf, Al-Najaf, Iraq from October 2019 to November 2020. Male factor infertility was present in 26, 48 of them had polycystic ovarian syndrome, 5 had tubal factor infertility and 8 had unexplained infertility. Polycystic ovarian syndrome was diagnosed by the Rotterdam criteria[4] that involved clinical, biochemical and ultrasound tests. Exclusion criteria were females of age more than 40 years, presence of uterine fibroid, endometrial polyp or hydrosalpinx and women with abnormal ovarian reserve testing. Antagonist protocol was used in all patients. Pretreatment with oral oestrogen tablets was used for 10 days. Injection gonadotrophin for ovarian stimulation (either r- FSH or HMG) was administered by calculating the dose according to age and ovarian reserve. Flexible regime of antagonist with 0.25 mg of cetrotide daily was adopted, when the largest follicle was 14 mm in diameter. The patient was monitored by transvaginal ultrasound till these follicles reached 17 mm or more in diameter. Ovulation was triggered by giving either GnRH agonist (0.2 mg decapeptylR (triptorelene acetate)) when there were more than 18 follicles or using urinary hCG 10000 IU when the number of follicles were less than 18. Transvaginal ultrasound guided oocyte retrieval was performed 35 hours after trigger IVFIICSI after the sperm preparation. Progesterone supplementation in the form of intramuscular injection and embryo transfer was done on day 3 in the absence of signs and symptoms of ovarian hyperstimulation. Follicular fluid was collected by aspiration from a mature follicle (more than 16 mm diameter) and centrifuged for 10 minutes at 3000 g and stored for further assessment. VEGF was calculated by using ELIZA, in both normal and hyper responder patients.

Statistical analysis: Mean and standard deviation were calculated and comparison between means was done by t test and a P-value of less than 0.05 was considered significant.

Results

A total of 87 infertile females were included in the study. They were divided in 2 groups; hyper -responders (48 cases) and normal responders 39 cases with male causes and tubal and unexplained etiology.

Table-1 shows the demographic and clinical information of the included females. No significant difference was observed between the hyper responders and the normal responders regarding age and BMI, (P<0.313 and 0.721 respectively). The number of retrieved oocytes was more in PCOS mean 13.38±7.106, with no significant difference between the hyper-responders and the normal responders regarding age and BMI, (P<0.313 and 0.721) respectively. The number of retrieved oocytes were more in PCOS (mean 13.38±7.106) than the controls (mean 7.77±3.983) Number of mature oocytes was more in PCOS mean (10.60±7.031) than controls (5.79±3.643) with p<0.001. Number of transferred embryos was more in the control group compared to women with PCOS (p<0.362).

Table-1: Demographic characteristics and clinical information of the studied groups.

	Control Mean ± SD	Cases (PCOS) Mean ± SD	P-Value
Mean Age (year)	29.95±6.096	29.87 (4.897)	0.313
Mean BMI (kg/m^2)	26.32± 3.46	26.58 (2.52)	0.721
Mean retrieved oocytes	7.77± 3.983	13.38(7.106)	0.002
Mature oocytes	5.79± 3.643	10.60(7.031)	0.001
Mean number of embryos transferred	2.26±1.53	1.93 (1.65)	0.362

Table-2: VEGF in PCOS female and normal responder female.

	Control	PCOS	P-Value
Mean VEGF	45.74±35.88	38.60±37.025	0.301

VEGF: Vascular Endothelial Growth Factor. PCOS: Polycystic Ovarian Syndrome.

Table-2 shows the results of the use of agonist trigger in hyper responder females compared to the normal responder females using h-CG for triggering ovulation.

Discussion

VEGF has a significant role in regulating the female reproductive system. VEGF, a signal protein is produced by many cells that stimulate the formation of blood vessels. In the reproductive organs, it is mainly secreted from the white adipose tissue surrounding the ovaries and uterus and helps to maintain their functions. VEGF is increased in the follicular fluid of females with PCOS undergoing IVF, which is due to the effect of high dose of gonadotrophins used. In our study we found that VEGF in the follicular fluid is significantly lower in hyper responders than normal responder women and this was because of using agonist trigger instead of h-CG, but this finding is not similar to the studies by Agrawal et al.[10] and Artini et al.[11,12] who found VEGF to be elevated in follicular fluid of hyper-responder females undergoing IVF.

In our study the number of mature oocytes were higher in women with PCOS. This disagrees with Bokal et al.[10] who found smaller numbers of mature oocytes and decreased amount of follicular fluid related to the VEGF levels. This difference may be due to the presence of other substances as renin and angiotensin and estradiol levels

in the follicular fluid that may affect the oocyte maturation as quoted in the studies by Bokal et al.[10,13] In the current study, these follicular fluid substances were not estimated, which could influence the result. Our study found no statistical difference between the cases and controls regarding age and BMI which is similar to the results of other studies.[14] The number of transferred embryos was more in normal responders than in PCOS patients. This could be attributed to the policy of "freeze all in hyperresponder females to decrease the risk of developing OHSS".[14]

Conclusion

VEGF concentration is lower in hyperresponder females with agonist trigger than in normal responder females with h-CG trigger.

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Conflict of Interest: None.

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