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Original Research Article

Role of IGF_1, VEGF, Vit. D3 and Vit. B12 in high AMH level in Iraqi Infertile women as criteria to prepare them for IVF

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Abstract

High Anti-mullerian hormone (AMH) level is a view of PCOS which is a common metabolic dysfunction and heterogeneous endocrine disorder in women of reproductive age. Although women with high level of serum AMH usually characterized by increase LH/FSH ratio and increase number of oocytes retrieved during IVF, they are often of very poor quality, leading to lower aspect of fertilization cleavage and poor implantation rate and then high ratio of miscarriage rate. The aims of this study was to asses and compare serum vitamin D3 and hormonal profile in infertile women with normal AMH value and high AMH value, and use these data as criteria for treatment and IVF. Study samples taken from 70 infertile female patients and selected high AMH level patients and also performed ultra sound scan and found polycystic ovaries distributed on the periphery of the ovarian cortex (PCOS pattern ovaries), furthermore we collected 20 controls from normal AMH infertile women. The total number of infertile women equal to 90 women with history of infertility (more than one year) and high AMH level. Seventy women of high AMH level estimation of D3, B_{12}, IGF_1 and $VEGF_1$. Twenty women of normal AMH level estimation of D3, B_{12}, IGF_1 and $VEGF_1$. Vitamin D3 replacement significantly decreases serum level of VEGF correlating with decrease IGF_1 level in serum of women with highly level of AMH. This is a novel molecular explanation for the beneficial effects of Vit D3 supplementation. It is also suggest the need to investigate and evaluate the potential role of vitamin D3 in reducing the level of AMH in serum and reducing severity of OHSS in vitamin D3 deficient women with high AMH serum level.

Keywords: AMH, VEGF, IGF_1, Vit. D3, B12 & hormone profile

INTRODUCTION

Fertility is defined as the ability of an individual or couples to conceive and bear offspring (Makar and Toth, 2002). Infertility is the inability of couple to conceive or failure to achieve a clinical pregnancy after one year of frequent unprotected sexual intercourse (Templeton et al., 1996). However, the diagnosis of infertility does not mean that they cannot conceive a more precise diagnoses term would be "subfertility" or a diminished capacity to conceive. The main causes of female subfertility are ovulatory defect and pelvic disorders. While, there are

numerous factors of male infertility and female infertility. There are not mutually exclusive about 15% of couples have more than one causes of sub fertility. In approximately 20% of couples, the causes remains unknown classified as unexplained infertility (Fekkes et al., 2003). The term “infertile” describe condition of reduced fecundity whereas the absolute or irreversible complete inability to reproduce is defined as sterility which can be genetically or congenital to certain anomalies making the conception difficult or impossible (Himmel et al., 1997).

Infertility divided as primary infertility which is infertility in a couple who have never had a child. Secondary infertility is failure to conceive following a previous pregnancy (Hassan et al., 2015).

The technique of Assisted Reproduction Technologies (ART) consist of maneuver have been used for a couple of decades. Often the sperm or the eggs needed are retrieved from the testes or the ovaries, and to be fertilized in a clinical or laboratory setting. Some ART producers include; in vitro fertilization (IVF), intra-cytoplasmic sperm injection (ICSI), intrauterine insemination (IUI) and artificial insemination (AI) (Vernaeve et al., 2007). Artificial insemination has become an option for many infertile couples prior to considering more expensive assisted reproductive treatment such as in vitro fertilization with pre-implantation genetic diagnoses (PGD) (Hassan, 2016).

The first test tube baby occurred in 1978 (Louise Brown) by *in vitro* fertilization was born. Since that time, this producer has been used with increased success rates to produce offspring from couples have various infertility problems. The birth of the first baby conceived *in vitro*, opened up a completely new frontier in treatment of infertility (Jungwirth et al., 2015.

Infertility affects 15% of all couples. In 39% of these couples, the male generates semen analyzed as abnormal (male factor). In 41% of these couples, female factor. In 20% of these couples unexplained infertility (Buck Louis et al., 2014; Hassan et al., 2015; Hassan, 2016).

Aim of the study

Evaluate the effects of VEGF, IGF-1, Vit D3, and B12 on infertile women with high AMH level and Correlation between these factors.

MATERIAL AND METHODS

This randomized study done submitted on Jan 2016, resubmitted on March 2017, in Al-Nahrain University on High Institute of Infertility Diagnosis and Assisted Reproductive Technologies**.** Ninety infertile female in reproductive age (15-40) years old in (2-5) day of menstrual cycle. Blood samples taken from (70) infertile female patients and selected high AMH level patients and also performed ultra sound scan and found polycystic ovaries distributed on the periphery of the ovarian cortex (PCOS pattern ovaries), furthermore we collected 20 controls from normal AMH infertile women. Ninety infertile women divided into two groups. The cross sections which include twenty infertile female with normal AMH level called (group one) and seventy infertile women with high AMH called (group two).

The vitamin D3, IGF-1, VEGF, vitamin B12, and main infertility hormones (LH, FSH, Testosterone, Prolactin and E2) were estimated in both groups for all the infertile women in both groups.

RESULT

The present study evaluate the effect of D3, B_{12}, IGF_1 and $VEGF_1$ in infertile women with high AMH and poly cystic ovaries in reproductive age (15-40) years old. The total number of infertile women equal to 90 women with history of infertility (more than one year) and high AMH level. Seventy women of high AMH level estimation of D3, B_{12}, IGF_1 and $VEGF_1$. Twenty women of normal AMH level estimation of D3, B_{12}, IGF_1 and $VEGF_1$. Aspiration of blood sample from those patients done in (2-5) day of cycle

The table (1) shows person correlation of high AMH level of infertile women with other parameters (low Vitamin D3, high IGF1, high VEGF & different level of Vitamin B12). Person correlation of AMH with VitD3 equal -.344**, *P* value =.004, person correlation of AMH with VitB12 equal - .482**, *P* value =.000, and AMH with IGF1 equal 733**, *P* value =.000, and AMH with VEGF as person correlation equal to .887**, *P* value =.000.

The table 2 above shows Pearson correlation of normal AMH level of infertile women with other parameters (normal Vit D3, normal IGF1, normal VEGF and different level of Vit B12). Person correlation of AMH with VitD3 equal -.496*, *P* value = .026, person correlation of AMH with Vit.B12 equal .108, *P* value = .649, and AMH with IGF1 equal .008, *P* value = .974, and AMH with VEGF as person correlation equal to .577**, *P* value =.008.

The table above (3) shows the type of sensitivity of AMH with (LH, FSH, LH/FSH, Testosterone, PRL, E2) and *P* value of linear regression between AMH and the following variants (LH, FSH, LH/FSH, Testosterone, PRL, E2)

The comparison of result (N=70) there was high significant in AMH $P<0.01$ and Vit D3 $P<0.01$ but significant in Vit B12 P-value=0.024 $P<0.05$ significant and significant in IGF1 and VEGF the p-value=0.008, 0.049 $P<0.05$ > as shown in table (4).

Table 1. Showed the Person correlation between AMH with groups of results (n=70)

Result/AMH with groups	VitD3	VitB12	IGF1	VEGF
Pearson Correlation	-.344**	-.482**	.733**	.887**
P-value	.004	.000	.000	.000

Table 2. Table show Person correlation between AMH with groups of Control (n=20)

Control/AMH with groups	VitD3	VitB12	IGF1	VEGF
Pearson Correlation	-.496*	.108	.008	.577 **
P-value	0.026	0.649	0.974	0.008

* It means there was a correlation (- mean negative)
** It means there was a highly correlation

Table 3. Table show Linear Regression between other investigation with AMH

Variant parameters	P-value	Sig
LH	.025	S
FSH	.043	S
LHFSH	.152	NS
Testosterone	.008	S
PRL	.024	S
E2	.963	NS

S = It means significant
NS = It means not significant

Table 4. Table show Comparison of value of significany and p value in the group Result (N=70). N=Total number

	VEGF	IGF1	Vit B12	Vit D3	AMH
P-value	0.049	0.008	0.024	P<0.01	P<0.01
Sig	S	S	S	HS	HS

DISCUSSION

The study depends on the level of Anti-Mullerian hormone (AMH) as a main Gide of infertile women. When AMH level is high in serum of infertile women this mean poly cystic ovary (PCOS) (Hassan and Farag, 2019). Recent study has shown that AMH can be a very good predictor of ovarian reverse and the success rates of in vitro fertilization (IVF) (Melamed et al., 2008). Therefore in this study is to put a program for a preparing of infertile women to go to in vitro fertilization department by evaluating strategic role of some factors to form criteria for infertile women with high AMH level in serum to use that as a key for referring the patient to ART department.IGF-1 increase the sensitivity of ovaries to gonadotropin simulation and enhance follicular development (Yoshizawa et al., 1997).

There was a study aimed to identify the correlation between current tests used in assessment of ovarian reserve (AMH, FSH, LH and AFC) in different age group of infertile women (Ozkan et al., 2010).

The current study shows significant decrease in the serum level of vitamin D3 and this low level of D3 strongly correlated with increases serum level of AMH.

Consequently, IGF_1, and VEGF are present with high level in serum strongly correlated with increase serum level of AMH and specially VEGF level in serum highly significant increase with increasing level of AMH.

Moreover the serum level vitamin B12 in this study show no significant correlation with AMH level, but there is significant correlation with vitamin D3 level, when D3 level is so minimum, B12 decrease also. On the other hand this diminished level of vitamin D3 in serum of infertile women had significant relationship with VEGF inversely.

Additionally in this study the ratio of LH/FSH was very distinct relation with AMH level, when the serum AMH level increases the LH/FSH ratio increase consequently. So that increases level of LH in serum significant correlation with increase AMH level and LH/FSH ratio.

This review concluded VEGF may have important strategic role in the pathophysiology of PCOS and regulation of AMH level and is the key mediator in the pathogenesis of ovarian hyper stimulation syndrome (Wolpowitz and Gilchrest, 2006). Its role is perhaps not singular and several other factors play also role in bioavailability of hormones of infertility (Lerchbaum and Obermayer-Pietsch, 2012).

Finally, when AMH is normal value there is neither significant picture of changes in values of vitamin D3, Vit B12, IGF_1, and VEGF nor in LH, FSH, prolactin, testosterone and E2.

As a result of this study of Iraqi women with infertility, the increase of AMH level in serum mean low level of vitamin D3 highly significant (P-value<0.001) and the level of B12 not significant (P-value>0.05), whenever IGF_1 is significant (P-value <0.05) and VEGF level is highly significant (p-value <0.001) with increasing level of AMH.

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