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THE ROLE OF ADIPONECTINE HORMONE IN OBESE WOMEN WITH POLYCYSTIC OVARY SYNDROME ON OOCYTE AND EMBRYO QUALITY AFTER INTRACYTOPLASMIC SPERM INJECTION PROTOCOL

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BACKGROUND

Both Polycystic ovary syndrome and obesity are associated with specific reproduction health complications, including lower oocyte quality and pregnancy rates in assisted conception cycles which may be due to the endocrine- metabolic environment that may influence oocyte quality, and therefore embryo development. Adiponectin is a (Acrp30); 244-amino-acid-long polypeptide. It is an adipose tissue-derived protein whose serum concentrations, in contrast to leptin, are reported to be negatively correlated to body mass. Adiponectin had beneficial effects on the reproductive processes and an important relationship with the gonadotropins and other hormones. **Objective:** To determine the effect of adiponectine hormone in serum and follicular fluid in obese women with polycystic ovary syndrome and patients at day of ova pick up in assissing oocyte and embryo quality after intra_ cytoplasmic sperm injection. A total of 45 infertile obese women (30 women with Polycystic ovary syndrome and the other 15 women as a control-not PCOS) undergoing intracytoplasmic sperm injection cycle were prospectively recruited for this study in High Institute of Infertility and Assissted Reproductive Technology, Al-Nahrin University, Baghdad-Iraq; during the period from octobar 2016 to the end of February 2017. All patients underwent a long or short standard gonadotrophin releasing hormone agonist protocol(GnRH-a). Serum and follicular fluid of adiponectine levels were measured on the day of oocyte retrieval using by Enzyme linked immuno sorbent assay. The concentration of

serum and follicular fluid of adiponectine hormone was showed no significant differences between the polycytic ovarian syndrome and control group (P>0.05); however the serum level of the adiponectine hormone showed slightly decrease in polycystic ovary syndrome patients than in control patients(506.67 ± 42.74, 522.18 ± 44.01) ng/ml respectively. The concentration of Luteinizing hormone level in serum was highly significant increase in polycystic ovary syndrome patients than in control (7.823 ± 0.33, 3.717 ± 0.51) IU/ml respectively. The mean number of oocyte retrieved, mature oocyte(MII) were significantly increase in polycystic ovary syndrome patients than in control patients. We can conclude that the level of adiponectine hormone at day of oocyte retrieval in both serum and follicular fluid, has not have the benefit role in determination the quality of the oocyte and embryo after intra cytoplasmic sperm injection cycles.

KEYWORDS: Both Polycystic ovary Adiponectin injection cycles.

INTRODUCTION

Obesity has reached epidemic proportions in developing and developed countries. According to the practice committee of the American Society for Reproductive Medicine, obesity is the most common chronic disease in the U.S.[1] Despite worldwide awareness and international campaigns, the incidence of obesity is increasing, and obesity has been described as the new worldwide epidemic.[2] Polycystic ovary syndrome (PCOS) is a common endocrine disorder in women of reproductive age with primary manifestations of infertility, menstrual dysfunction and clinical or biochemical hyperandrogenism (hirsutism, acne and elevated androgen).[3] The etiology of PCOS is multifactorial, including both genetic and environmental issues. Although hyperandrogenism, ovarian dysfunction, abnormalities in the hypothalamic-pituitary axis, and excess insulin activity are known to be responsible for pathogenesis of the syndrome, the exact etiology has yet to be discovered.[4] PCOS is associated with metabolic aberrations including dyslipidemia and impaired glucose tolerance.[5] Obesity is a very common clinical feature in women affected by PCOS. More than 50-60% of PCOS women are obese.[6] The diagnosis of PCOS must be based on the presence of two of the three following criteria: oligo and/or anovulation, clinical and/or biochemical signs of hyperandrogenism, polycystic ovaries on ultrasonography and exclusion of related disorders.[7] Studies have shown that even in women who are ovulating regularly, overweight correlates with reduced conception rates[8], suggesting that obesity affects critical peri-conception events, such as oocyte and/or embryo quality. Although the mechanism

linking obesity to poor reproductive outcomes (oocyte maturity and/or embryo quality) is not well understood, various adipocytokines are thought to be involved.[7] Adiponectin is a member of the adipose-secreted proteins called adipocytokine. Adiponectin was discovered in 1995 after leptin. It is a protein of 244 amino acids (30 kDa) produced mainly by white adipose tissue but is also found in other tissues such as muscle and bone.[9] Adiponectin is also known as Acpr30 (adipocyte complement-related protein 30 kDa), apM1 (adipose most abundant gene transcript-1), or GBP 28 (gelatin-binding protein)[10] that modulates a number of metabolic processes, including fatty acid oxidation, glucose regulation.[11] The role of adiponectin has been studied in vitro on steroidogenesis of granulosa and theca cells and oocyte maturation in several species. In primary rat and human granulosa cells, adiponectin increases progesterone and estradiol secretions in response to IGF-1 (insulin-like growth factor 1).[12] Also In vitro, adiponectin has been shown to have anti-atherogenic effects[13], and a number of cell culture experiments and studies in animal models[14] have suggested that adiponectin has a potent insulin-sensitizing action. In humans, adiponectin levels were found paradoxically to be decreased in obese, compared with normal individuals[15], making it the only known adipocyte-specific hormone that is down-regulated in obesity. Moreover, decreased adiponectin levels are associated with coronary artery disease and increase significantly after weight reduction.[16] The aim of study was to determine the effect of adiponectine hormone on oocyte and embryo quality in patient with PCOS undergoing IVF/ICSI cycle and to find correlation between its concentration in serum and follicular fluid.

PATIENTS AND METHODS

A total of 45 infertile obese women(30 PCOS and 15 control) undergoing controlled ovarian hyperstimulation(COH) for ICSI were prospectively recruited for this study in High nstitute of infertility and assissted reporductive technology, Al-Nahrin University, Baghdad-Iraq during the period from October 2016 to the end of February 2017. Written informed consent was obtained from patients as well as control to participate in this study. The diagnosis of PCOS depend on Rotterdam' s criteria (2003).[7]

The inclusion criteria were

1) The patients who had diagnosed as PCOS in the presence of at least 2 of Rotterdam's criteria, based on Rotterdam consensus meeting (2003).

2) Patient age (18-40) years.

3) The patient's agreement to participate in the study. While the exclusion criteria were:

1) Evidence of endocrine abnormalities such as hyperprolactinemia, thyroid dysfunction and hypogonadotropic hypogonadism.
2) Cycles where no oocytes (empty follicles) were retrieved on the day of aspiration.
3) Patient aged more than 42 years.

Methods of measuring hormones in serum and follicular fluid

Serum levels of LH and FSH on day 3 of the menstrual cycle were determined by using enzyme linked immunosorbent assay (ELISA) technique (Germany). Serum and FF obtained on the day of oocyte retrieval were estimated for adiponectine levels by ELISA technique also using diagnostic kit (Germany).

Statistical analysis

The Statistical Analysis System- SAS (2012), Version 9 was used to effect of different factors in study parameters. Numeric variables were expressed as mean + standard error (SE), while nominal variables were expressed as number and percentage. Least significant difference –LSD or T-Test was used to significant compare between means and Chi-square test was used to significant compare between percentage in this study.

Pearson's correlation coefficient was used to evaluate correlation between numeric variables.

RESULTS

The 45 infertile obese women divided into 30 PCOS and 15 control groups. By comparing the levels of adiponectine hormone between two groups there were no significant difference ($p>0.05$) in the level of adiponectine in serum and follicular fluid Figure 1.

Clinical parameters (age, BMI, basal LH, and FSH) of this study with respect to the ICSI outcome, showed highly significant difference ($p<0.001$) in the level of basal LH and a significant increase in level of FSH between two groups (LH higher in PCOS group while FSH higher in control group), also significant increase in total number of oocyte retrieved and number of MII oocyte in PCOS than in control (Table 1).

Pearson's correlation analysis of associations between the FF and serum adiponectine and the clinical (age, BMI, basal LH and FSH) and treatment (oocytes (total, MII and fertilised oocytes) parameters (Table2), there was negative correlation between age, basal FSH, oocyte (total, MII and fertilised oocytes), number of embryo transferred with adiponectine FF, while

with serum adiponectine there was negative correlation with also total oocytes, basal FSH and number of embryo transferred. On the other hand with Grade 1 embryo and basal LH.

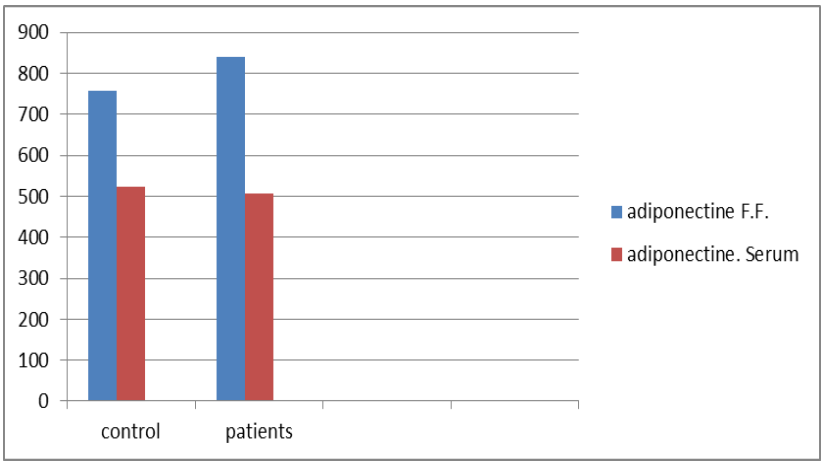

Figure. 1: Comparison between PCOS and control groups in level of Adiponectine hormone in follicular fluid (FF)and serum at day of oocyte retrival.

Table. 1: Comparison between PCOS and control in clinical and treatment parameters.

Parameters	Patients group		P-value
	PCOS	Control	
Age	31.03 ± 1.04	33.93 ± 0.98	0.0830 NS
BMI	33.86 ± 0.57	31.37 ± 0.57	0.0087*
Basal FSH IU/mL	5.571 ± 0.30	6.791 ± 0.61	0.0501*
Basal LH IU/mL	7.823 ± 0.33	3.717 ± 0.51	0.0001**
Total no.of oocytes retrieved	9.03 ± 1.15	5.67 ± 0.69	0.0501*
No.MI oocyte	1.366 ± 0.19	1.400 ± 0.32	0.925 NS
No.MII oocyte	5.233 ± 1.01	2.467 ± 0.36	0.0515*
No.Fertilised oocytes	4.33 ± 0.65	2.60 ± 0.28	0.0451*
No.ET	2.40 ± 0.23	2.33 ± 0.34	0.870 NS

All values expressed by mean± SE(stander error). BMI: body mass index. PCOS: Poly Cystic Ovary Syndrom, LH: Luteinizing Hormone. FSH: Follicle Stimulating Hormone, MI: Metaphase I, MII: Metaphase II oocytes. ET: Embryo Transferred. **P<0.001:highly significant *p<0.05:significant.NS: Non significant, No: number.

Table. 2: The correlation between follicular fluid (FF) and serum(S) Ghrelin with clinical and treatment parameters.

Parameters		Adiponectine. FF	Adiponectine. S
Age (years)	r	-0.23 NS	0.15 NS
	p	0.125	0.324
BMI(kg/m^2)	r	0.16 NS	0.03 NS
	p	0.274	0.816
oocte retrieved	r	-0.32 *	-0.04 NS
	p	0.03	0.787
No of MII	r	-0.31 *	0.01 NS
	p	0.032	0.915
Nunmber of embryo transferd	r	-0.02 NS	-0.06 NS
	p	0.861	0.672
Number of fertilised oocytes	r	-0.30 *	-0.01 NS
	p	0.044	0.934
Embryo G1	r	0.02 NS	-0.02 NS
	p	0.882	0.861
Basal FSH	r	-0.02 NS	-0.17 NS
	p	0.917	0.268
Basal LH	r	0.01 NS	-0.06 NS
	p	0.934	0.716

FF: Follicular Fluid. S: Serum. BMI: Body Mass Index. LH: Luteinizing Hormone. FSH: Follicle Stimulating Hormone. MII: Metaphase II. ET: Embryo Transferred. r: Correlation Coefficients. **p<0.001:highly significant. *p<0.05:significant.NS: Non significant.

DISSCUTION

The present study was designed to investigate the effects of obesity on ICSI success in women with PCOS, the results of the study indicated that the obesity is a very common problem among Iraqi females. In our study there was no significant differences(P>0.05) in mean age between PCOS group and control group**.** These results indicated that PCOS women had comparable age with control group to eliminate any variations that may affect the results of the measured biochemical parameters. The clinical importance of BMI on the outcome of ART treatments has been the subject of several investigations that have thus far yielded conflicting results. It is shown in the current study that there was a highly significant difference (P<0.001) in the body mass index (BMI) between control and PCOS groups. This data agree with the previous studies who suggest that the prevalence rate of obesity was higher in PCOS patients because it had a positive relation with insulin resistance.[17,18]

The mean serum level of basal LH in patient with PCOS in present study was highly significant elevated (P<0.001) when compared with normal controls group and basal Follicle

stimulating hormone level in PCOS patients was lower compared with that in control group; this result in agree with Yin, B., Hao, H. et al[19] whos showed the "Patients with polycystic ovary syndrome have successful embryo arrest." 667 subjects were enrolled, including 330 patients with PCOS and 337 subjects without PCOS. The subjects underwent in vitro fertilization/intracytoplasmic sperm injection and embryo transfer (IVF/ICSI-ET).

In this study there was significant increase in the number of retrieved oocyte and number of mature oocytes (MII oocyte)in PCOS group. This due to high number of antral follicles in PCOS patients that respond to hyperstimulation. While there was no significant difference in number of embryos transferred. These results agreed with Engmann *et al*[20] who found that the women with PCO produced more follicles, oocytes and embryos than the women with normal ovaries.

Adiponectine hormone However, the majority of studies have examined animal models and few have investigated outcomes after IVF/ICSI. There is also evidence that the expression of adiponectin and its receptors is regulated during follicular and oocyte growth and during early embryo development and implantation.[21,22]

The current study was showing that there's no significant difference between the two groups in both levels of adiponectine hormone (serum, follicular fluid) This result may be due to a small size number of the current study, However its inagree with Tao, T., Xu, B., & Liu, W.[23]; that investigated the "Ovarian HMW adiponectin is associated with folliculogenesis in women with polycystic ovary syndrome. the serum level of adiponectine hormone in PCOS patients was showing a slightly decline compared with the control group.

Richards et al.[24] reported that the addition of adiponectin to *in vitro* maturation media might improve the developmental competence of *in vitro* matured oocytes in human infertility care. Another effect of adiponectin is on embryo implantation. The adiponectin system was more abundantly expressed in human endometrium during the luteal period, which corresponds to the embryo implantation period.[25] The protein levels of adiponectin, AdipoR1 and AdipoR2 were found to be higher in the endometrium at the sites of embryo implantation compared to the interimplantation sites.[26] Adiponectin has anti-inflammatory and insulin sensitizing properties and is negatively associated with obesity.[27] Our study showed that highier FF adiponectin was negatively correlated with MII oocytes, number of embryo transferred and nomber of fertilized embryo.this in agree with others reported that an increasing FF

adiponectin tertile was negatively associated with embryo quality including viable cleavage morphology, successful blastulation and viable blastocyst morphology.[28] A study of 56 women found that adiponectin levels on the day before gonadotropin administration correlated with the number of oocytes retrieved and that adiponectin levels were higher in women who conceived.[29] Due to small number size of the cases we didnot found any correlation of adiponetin hormone with BMI as many researchers found that it had anegative correlation with BMI[30] conflicting results, additional studies are necessary to further distinguish the mechanisms by which adiponectin affects oocytes, embryo development, and implantation. Accurate and reliable research on the relationship of oocyte and embryo quality with adipocytokines was important. To determine the precise relationships between oocyte/embryo quality and adipocytokines, we analyzed the FF sample as a microenvironment directly affecting the quality of the embryo.

In conclusion, the level of adiponectine hormone was lower in PCOS than in control group and there was no significant difference in its level both in serum and FF, it has negative correlation between FF and number of total oocyte retrieved, MII,ET and number of fertilised oocytes. so it cannot be used as a strong test in predicting oocyte and embryo quality after intra cytoplasmic sperm injection cycles.

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