

Correlation of Recombinant FSH Doses with Follicular and Serum Level Resolvin E1 in Polycystic Ovarian Syndrome Women Undergoing ICSI

Muna Rasool Abdulzahraa Amal Abdulwahid Mohammed¹

¹AL-Nahrain University, High Institute for Infertility Diagnosis and Assisted Reproductive Technologies. Email: muna.rasool@ierit.nahrainuniv.edu.iq

KEYWORDS

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ABSTRACT

Background: Reproduction is a intricately structured process achieved by interaction of the higher centers in the brain, the gonads, and different body parts; Whereas infertility is a multifactorial pathological condition affecting approximately 10–15% of couples, especially in industrialized region. RESOLVIN E1 is a member of specialized pro resolving mediator family of bio active lipids. It has anti-inflammatory effects in various inflammatory diseases. A promising researches in their way to prove its positive role in reproduction through direct effect on folliculogenesis. It has a fundamental role in regulating follicular growth and maturation at central and peripheral levels highlighting its possible role in diagnosing and treating infertility problems. High level of RESOLVIN E1 which might play critical role in poly cystic ovarian syndrome due to its anti-inflammatory effects. Objectives: To investigate the correlation of serum and follicular RESOLVIN E1 to gonadotropin (recombinant FSH doses) in PCOS patient undergoing ICSI. Subject, Patients, Materials, and Method: A prospective cross-sectional study conducted in the high institute for infertility diagnosis and assisted reproductive technology /Al Nahrain University /Baghdad /Iraq, from November 2023 till March 2024. Twenty-nine infertile PCOS women who were undergoing intracytoplasmic sperm injection were enrolled in the study. Serum and follicular RESOLVIN E1 at day of oocyte pickup were measured using ELISA technique. Results: The current study shows significantly lower gonadotropins stimulation dose needed for PCOS females ($p < 0.001$). It also revealed no significant correlations between total gonadotropins dose with both serum and follicular fluids resolvin E1, while there were insignificant negative correlations between serum and follicular fluids resolvin E1 with patients' ages and body mass indices among PCOS females. Conclusions: There is no correlation between the serum and follicular RvE1 levels in PCOS infertile females.

1. Introduction

Introduction

Infertility is a global public health issue with a high impact on individuals of both sexes and it's ranked as the 5th highest serious global disability, higher social burden for women than men⁽¹⁾. It's a multifactorial pathological condition affecting approximately 10–15% of couples, especially in industrialized region⁽²⁾. It's characterized by the inability to conceive after 12 months or more of consistent unprotected sexual intercourse⁽³⁾. According to reports, around 33-41% of infertility cases are primarily caused by female factors, while male factors account for 25-39% of the problem⁽⁴⁾. Common reasons of female infertility include ovulation abnormalities such as polycystic ovary syndrome, hypothalamus dysfunction, premature ovarian insufficiency, tubal infertility, endometriosis, and uterine and cervical causes⁽⁵⁾. The World Health Organization categorized infertility into two groups in 2019; Primary and secondary infertility. Secondary infertility is the most common form among females with high rates of unsafe abortion and poor maternity care leading to post-abortive and postpartum infections⁽⁶⁾. Many assisted reproductive technologies (ART) have been developed since 1978⁽⁷⁾, It's a term refer to a range of medical procedures and techniques that aid in achieving pregnancy for couples who are facing difficulties conceiving naturally⁽⁸⁾. The main goal of these techniques is to the birth healthy child and reduces the risk of complications to the mother⁽⁹⁾. Many previous studies have proven that the in-vitro fertilization IVF protocol is the best for pregnancy and childbirth, and this technique involves the Controlled ovarian hyperstimulation (COH) that to increase the follicles, so increase the number of oocytes and subsequently the embryos to be selected and transferred⁽¹⁰⁾. It is worth noting, Gonadotropin-releasing hormone agonist (GnRH-a) has been proved to have an important role in controlling ovarian hyperstimulation among infertile patients undergoing ART procedure, as it prevents premature luteinizing hormone (LH) surge,

increases both the number of collected oocytes and pregnancy rates, and decrease the number of cancelled cycles. Yet (GnRH-a) increases the risk of ovarian hyperstimulation syndrome (OHSS) which is considered as a serious medical condition ⁽¹¹⁾. In ART, GnRH-a protocol is used to stimulates the release of large amount of FSH and LH. When GnRH agonist bind to the GnRH receptors in the pituitary, it stimulates the release of large amount of FSH and LH, together with the increase in the number of GnRH receptors, what is called the flare or upregulation effect ⁽¹²⁾. While Gonadotropin releasing hormone antagonist (GnRH-ant) used in COH it's causing rapid suppression of gonadotropins release. This protocol has fewer side effects, more convenient, shorter time, fewer injections in treatment for infertility patients ⁽¹¹⁾ and ability to inhibit the premature surge of LH during ovarian hyperstimulation ⁽¹³⁾, without increasing the incidence of ovarian hyperstimulation syndrome, and negatively impacting both the pregnancy rate and live birth rate compared to GnRH agonist long protocol ⁽¹¹⁾. Polycystic ovarian syndrome (PCOS) is a common hormonal and metabolic disorder affecting around 6-20% of women in their reproductive years⁽¹⁴⁾. its impact on fertility, linked to higher risks of developing type 2 diabetes, cardiovascular disease, endometrial cancer ⁽¹⁵⁾, and its often accompanied by obesity ⁽¹⁶⁾, Additionally, PCOS involves chronic inflammation resulting partly from excess visceral adipose tissue and its pro-inflammatory mechanisms ⁽¹⁷⁾.The inflammatory response to infection involves many mediator molecules. These mediators comprise four different subgroups: the resolvins (Rvs), lipoxins (LXs), protectins (PDs) and maresins (Masr) and are depicted as SPMs: specialized pro-resolving mediators ⁽¹⁸⁾.There are many crucial roles of SPMs such as Resolution of inflammatory processes ⁽¹⁹⁾ and triggering events that lead to tissue regeneration and homeostasis. its contribute to halting neutrophil infiltration, promoting macrophage-dependent phagocytosis of these neutrophils, reducing pro-inflammatory chemokines and cytokines, decreasing prostaglandins and platelet-activating factor production while activating anti-inflammatory signaling pathways ⁽²⁰⁾.Resolvin E1 (RvE1) is a member of family pro resolving lipid mediators with anti- inflammatory properties⁽²¹⁾. Studies have revealed that RvE1 inhibits the production of pro-inflammatory mediators, actively promotes the resolution of inflammation by enhancing the clearance of inflammatory cells and debris ⁽²²⁾, especially studies have revealed. In the case of PCOS, a pro-inflammatory state was detected, and a high pro-inflammatory mediator/SPM ratio was documented in serum ⁽²³⁾, this dual action makes RvE1 a promising candidate for the development of novel anti-inflammatory therapies ⁽²⁴⁾.Research exploring the potential role of RvE1 as a biomarker in infertility it's a positively related to oocyte competence and may improve oocyte quality by improving viability, inhibiting apoptosis of surrounding cumulus cells (CCs) ⁽²⁵⁾ and through its anti-inflammatory and resolution-promoting properties⁽²⁶⁾.Therefore, RvE1 may be adopted as a potential exclusive biomarker for oocyte selection and serve as a promising intervention to improve the IVF success rate after being thoroughly investigated and rigorously testified in the future⁽²⁷⁾. Several studies have begun to elucidate the possible link between RvE1 levels and fertility outcomes; it's associated with certain reproductive disorders and impaired fertility and may influence reproductive health and potentially serve as a valuable indicator in the assessment and management of infertility. In the context of reproductive physiology, inflammatory processes can impact the ovarian microenvironment and follicular development, potentially influencing oocyte maturation and overall quality. As a result, the anti-inflammatory effects of RvE1 have sparked curiosity regarding its potential role in mitigating inflammatory-related impacts on oocyte quality ⁽²⁶⁾.

2. Methodology

This study is a cross-sectional study performed in the High Institute for Infertility Diagnosis and Assisted Reproductive Technologies of Al-Naharin University, from November 2023 till March 2024. This study includes ⁽²⁹⁾PCOS infertile Iraqi women between 18 to 42 years scheduled for ICSI program; The baseline fertility assessment was done for all couples starting from history, physical examination, hormonal assays in addition to the semen analysis for male partners. All the 29 infertile females enrolled in a flexible antagonist protocol, were received recombinant human follicular stimulation hormone (Gonal-F subcutaneous injection/75 IU vial) on the cycle day2-3 with a dose

(75-300IU) , the starting dose was individualized for each patient according to the age, BMI, and previous response of ovulation induction, then the dose was adjusted according to the ovarian response evaluated by transvaginal ultrasonography and serum E2 hormone level ⁽²⁸⁾ till the leading follicle reached 12-14 mm in diameter, at that time Cetrotide (GnRH antagonist) was given with a dose of 0.25 mg subcutaneously in a dose of (0.25 mg) daily to down regulate the pituitary gland, until the day of trigger ⁽²⁹⁾. The ovulation was triggered by giving human chorionic gonadotropin (hCG), (Ovitrelle 6500 IU) subcutaneously when at least 2-3 leading follicles reached 17-18 mm. After 35-36 hrs. following the trigger, the oocyte retrieval was done under transvaginal ultrasound guidance ⁽³⁰⁾. Serum and follicular fluid samples were taken at the day of oocyte retrieval and kept in deep freezer (-20C) to be used for the measurement of RvE1 level, The level of RvE1 measured in private laboratory.. blood samples from all infertile woman was done on day of oocyte retrieval by serum separator tube (SST) and samples were allowed to clot at room temperature for 15 mins then centrifuged at 2000-3000 RPM for 20 minutes. The serum that obtained from centrifugation was stored at -20C in a deep freezer and used after that to measured RvE1 level, while determination of RvE1 levels in the follicular fluid (FF), each follicle was recovered in a different tube during individual aspiration. To avoid contamination from blood, flush medium, or mixed follicular fluid, only the second retrieved leading follicle's fluid was collected. Thus, one follicular fluid sample per patient was used for analysis. Samples were centrifuged at 2000g for 10 min, and the supernatants were stored in the freezer at -20°C for further analysis. RvE1 in serum and follicular fluid was measured using an enzyme-linked immunosorbent assay (ELISA) technique using a diagnostic kit (cat. No. YLA4192Hu, SHANGHAI YL Biological Technology) that provides quantitative determination of RvE1 concentration in serum, and follicular fluid.

3. Results and Discussion

The demographic features of twenty -nine infertile female are shown in Tables

1. The mean age is (30.31). The mean BMI in study group is (27.45), while the duration of infertility was (8.45) and the percentage of infertility type in this study were (93.1%) for primary type and(6.9%) for secondary one.

Table 1. Demographic Features Of PCOS Infertile Females

Demographic features		PCOS females N.=29
Age (years) (Mean±SE)		30.31 ± 1.08
BMI (Kg/m ²) (Mean±SE)		27.45 ± 0.43
Duration of infertility (years) (Mean±SE)		8.45 ± 0.73
Type of infertility N. (%)	Primary	27 (93.1 %)
	Secondary	2 (6.9 %)

Table 2. Total Gonadotropins Stimulation Dose In PCOS Infertile Females

Parameter	PCOS females (Mean \pm SE)
Gonadotropins dose (IU)	1088 \pm 28.27

Table3. Serum And Follicular Fluids Resolvin E1 Levels In PCOS Infertile Females

Parameter	PCOS females (Mean \pm SE)
Serum resolvin E1 (pg/ml)	80.96 \pm 6.94
Follicular fluids resolvin E1 (pg/ml)	163.93 \pm 12.69

On the other hand table 4 revealed no significant correlations between total gonadotropins dose with both serum and follicular fluids RvE1 among PCOS infertile females..

Table 4. Correlations Between Serum And Follicular Fluids Rve1 With Total Gonadotropins Dose Among PCOS Infertile Females

Parameters		PCOS females	
		Serum Resolvin E1	F. F Resolvin E1
Total gonadotropins dose	r	-0.042	-0.104
	p value	0.828 NS	0.590 NS

r: Pearson's correlation coefficient; NS: Not significant ($p > 0.05$)

The efficacy of reproduction and oocyte quality is significantly influenced by the maternal age ⁽³¹⁾, rather than to reduced uterine function, decreased embryo quality and hormonal disturbances ⁽³²⁾. As mentioned in Table (1), Most of the Patients enrolled in this study within average reproductive age. However in this study, none of the participants had a BMI indicating underweight. As shown in Table 1, the duration of infertility in the present research ranged from two to eighteen years, with a mean value of 8.80 year, this length duration of infertility can affect the success rate of IVF, as Van Loendersloot's study showed a negative correlation between the length of infertility and the success rate of ICSI, this implies that as the duration of infertility increases, the likelihood of achieving pregnancy with ICSI diminishes. On the other hand, the reason for the length period of infertility may be due to: delay females marriage and cost of fertility treatment which hinder the infertile couples from seeking medical solutions ⁽³³⁾. As declared in Table (2), for PCOS females, the dosage of

gonadotropins stimulation was significantly less this is consistent with Hassan's study⁽³⁴⁾. The examination of the cumulative dose of gonadotropin administered in the aforementioned investigation yielded similar findings to the present study, 1663.20 ± 615.2 for PCOS women. According to the gonadotropin stimulation procedure that was employed in the current investigation, Behery (2019) emphasized crucial information. It is stated in that the antagonist protocol is the recommended stimulation strategy for PCOS patients undergoing ICSI due to its ability to decrease the occurrence of OHSS without negatively impacting the success of conception⁽³⁵⁾. Based on the data in Table (3), the mean value of RvE1 in FF was much higher than that in serum. explain the reason behind the elevation of RvE1 value in FF as follows, peripheral blood exudations and cumulus cells (CC) secretion both raise the amount of RvE1 in FF. RvE1 inhibits cell apoptosis after interacting to ChemR23 (a G protein-coupled receptor), which increases the survivability and proliferation of CCs⁽³⁶⁾. This, in turn, encourages CCs to produce more RvE1 as a positive feedback loop, taking into consideration the increased numbers of growing follicles due to ovarian stimulation drugs usage. RvE1 is a essential for the maintenance of tissue homeostasis and the resolution of inflammation⁽³⁷⁾. The current study marked out that the levels of RvE1 in serum and FF were slightly lower among females with PCOS which may indicate the dysregulation the resolution of inflammation in PCOS infertile women . The capacity of RvE1 to inhibit inflammation, decrease tumors proliferation, and augment the effectiveness of chemotherapy in cancer models indicates its potential for controlling the inflammatory components of ovarian illnesses such as PCOS⁽³⁸⁾.

4. Conclusions

To the base of our knowledge, this is the first study investigating serum and follicular Resolvin E1 level in PCOS infertile women undergoing ICSI program.

There is no correlation between total dose of gonadotropin and serum and follicular levels of RvE1.

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