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Dependence of Ferritin Indices and Embryo Yield in in Vitro Fertilization

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Abstract: The aim of the study was to investigate the relationship between ferritin levels in blood and follicular fluid and the quality of embryos obtained during in vitro fertilization (IVF) procedures. The study included 65 women aged 25 to 39 years with a diagnosis of infertility who underwent ovulation stimulation and ovarian puncture as part of standard IVF protocols. The participants were divided into two groups depending on the strategy of iron medication use: group 2A (iron + stimulation) and group 2B (iron - break - stimulation). Ferritin levels in blood and follicular fluid were analyzed comparatively, and the correlation between ferritin levels and the quality of embryos obtained was investigated. The results showed that high ferritin levels in follicular fluid correlated with an increase in the number of high quality embryos in group 2A, but excess iron could lead to a decrease in embryo quality. In group 2B, where ferritin levels were lower, there was a higher frequency of good quality embryos. The study confirms the importance of optimizing iron levels to improve IVF success and embryo quality.

Keywords: ferritin, in vitro fertilization, follicular fluid, iron, infertility, embryos, ovulation stimulation, oxidative stress, embryo quality, reproductive health.

I. Introduction

Oncoming out with cases of infertility where the woman may have various reproductive disorders, IVF comes across as one of the most dependable therapeutic options for doctors. Despite undeniable progress in reproductive medicine IVF has shown tremendous discrepancy in its results given the variability in the clinical course in the balance of various factors, including the quality of oocytes, hormone levels, and health status of a body of a patient.

Ferritin, a protein that buffers iron, is a biochemical compound, which according to some is thought to be a potential marker. Iron is very crucial and paramount for the metabolic processes such as the synthesis of DNA, cell division, and energy metabolism for oocyte maturation and embryo formation. Disorders of iron metabolism can have deleterious effects on ovum quality and may result in disturbances in the success of fertilization and embryo development as shown from individual reports. The present study will address the divariable relationship for the ferritin levels in blood and follicular fluid for the patients and the characteristics of the resulting embryos in IVF. Primarily, the aim of the current work is to find an evaluation of ferritin as a

marker that could raise its impact on the success of this procedure, with an aim to suggest a corrective measure for possible improvements to favorable fertility therapy.

Ferritin is so intracellularly as an intracellular iron storage protein that it represents a good marker for the metabolic situation of iron in the body. This protein is crucial for maintaining intracellular iron homeostasis, thereby protecting the cell from its toxic effects, by preventing the formation of free radicals.[1] For women of reproductive age, ferritin expression may be more important because iron is necessary for processes such as cellular respiration, DNA synthesis, cell division and defense as an antioxidant[2], which are essential for favorable oogenesis and embryogenesis.

The fact that the iron level has both good and bad effects on the fertility parameter is well established. Iron deficiency, commonly meaning anemia, directly influences ovarian function. It causes menstrual irregularities, decreases ovulatory capacity, and damages egg quality. Studies have shown that women with anemia and ferritin levels have poorer oocyte quality and lower embryo numbers in an in vitro-fertilization (IVF) cycle compared to those with normal ferritin levels.[3] On the other hand, an increased supply of iron from causes such as hemochromatosis or iron overload due to chronic inflammation is another enemy to fertility. Plethoric iron formation leads to free radical formation and the rapid development of reactive oxygen species, resulting in oxidative stress. Oxidative stress affects mitochondria first; enhancing lipid peroxidation, enzyme inactivation, endoplasmic reticulum stress, DNA damage, and, in turn, apoptosis; also it interferes with the recovery of ovarian cell and affects follicular health, leading to oocyte maturation.[4]

Follicular fluid plays an essential role in creating a favorable microenvironment for oocyte growth and maturation. It consists of nutrients, hormones, proteins, antioxidants, etc., each of which plays a marked role in oocyte maturation and therefore fertilization. Ferritin levels in the follicular fluid suggest the state of ovarian iron metabolism at the local level and can be a hint to the quality of maturing oocytes. Several studies showed that ferritin levels in the follicular fluid correlate with the success rate of IVF treatment.[5] For instance, higher ferritin levels were found to be correlated with a greater number of good quality oocytes, thereby producing a surge in more viable embryos. Extremely high levels of ferritin in the follicular fluid are correlated to the poor quality of embryos, thus showing the necessity for maintaining an iron balance.

Ovulation stimulation protocols used in IVF cycles affect iron metabolism and ferritin levels in women. Studies show that stimulation leads to an increase in ferritin levels in follicular fluid, which is associated with increased metabolic activity in the ovaries.[6] However, the degree of increase in ferritin can vary depending on the patients' baseline iron status. Women with iron deficiency prior to stimulation are more likely to have low ferritin levels in follicular fluid, which adversely affects the quality of oocytes. To correct this condition, it is recommended to take iron preparations before or during stimulation. At the same time, in women with normal iron

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[1] Kovalenko Y.A., Malko Anna Vladimirovna, Ryazantsev I.I., Trunyan D.G., Filippov E.F., Krutova V.A. Influence of the age of patients on the quality of the received oocytes, embryos and outcomes of programs of assisted reproductive technologies // Kuban Scientific Medical Bulletin. 2018. №1.

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[4] Haga P. Plasma ferritin concentrations in preterm infants in cord blood and during the early anaemia of prematurity // Acta Paediatrica. 1980. Vol. 69. P. 637.

[5] Shao J., Richards B., Kaciroti N., Zhu B., Clark K. M., Lozoff B. Contribution of iron status at birth to infant iron status at 9 months: data from a prospective maternal-infant birth cohort in China // European Journal of Clinical Nutrition. 2021. Vol. 75, no. 2. P. 364-372.

[6] Nefedova A. V., Pestova T. I., Rusakova M. D., Bryukhin G. B. Influence of ovulation stimulation and conditions of embryo culturing on the outcome of in vitro fertilization in women of different age groups // Man. Sport. Medicine. 2011. №26 (243).

levels, excessive iron supplementation can lead to excessive ferritin accumulation, which is also associated with an increased risk of oxidative stress.

Studies show that the approach to iron supplementation plays an important role in IVF outcomes. For example, the use of iron preparations in combination with antioxidants can minimize the risk of oxidative stress and improve follicular fluid parameters. In addition, strategies that provide a break between iron supplementation and the start of stimulation may promote more stable ferritin levels and optimize reproductive outcomes.

Based on published data, it has been established that ferritin levels not only affect oocyte quality, but also have significance at the stage of embryo formation and evaluation. High ferritin levels in follicular fluid are associated with improved cell division rates and blastomere quality. This is because iron is actively involved in the processes of cell metabolism and mitosis.[7] However, excessive iron accumulation and associated oxidative stress can impair embryo quality by reducing implantation capacity. In particular, embryos developing under conditions of excessive oxidative stress are more likely to exhibit abnormal compactization and morphological defects.

Despite the availability of data on the role of ferritin in the IVF process, many questions remain incompletely understood. For example, there is a need to determine the optimal ferritin levels that provide the best IVF outcomes. Also, an important area of research is the development of individualized iron correction strategies to improve the success of infertility treatment. Literature evidence supports that ferritin is an important indicator that can be used to predict embryo quality and IVF success.

II. Aim of the work

The current study performed at the IVF clinic "Siz ona bulasiz" was aimed at studying the relationship between ferritin levels in blood and follicular fluid and the characteristics of embryos obtained during the IVF cycle.

III. Materials and methods

The study included 65 women diagnosed with infertility, and their ages ranged between 25 and 39 years. All patients included in the treatment were subjected to IVF under standard ovulation stimulation protocols. Inclusion criteria were women of reproductive age diagnosed with infertility of varied etiologies, with no serious somatic diseases and no previously reported serious complications of IVF protocols. Patients suffering from severe anemia (hemoglobin <70 g/L), chronic inflammatory diseases, or any conditions that could affect ferritin levels or the outcome of IVF were excluded.

Participants were allocated into two groups based on the mode of preparation. Study 2A comprised women who had iron preparations starting simultaneously with the initiation of ovulation stimulation (n=29). Group 2B comprised those patients who took iron preparations two months before the stimulation was started (n=36). Blood and follicular fluid samples from the same day of ovarian puncture were subsequently taken to assess for ferritin levels. Ferritin in the blood acted as a systemic indicator of iron stores, while ferritin concentration in the follicular fluid served as an indicator of local iron metabolism in the ovaries. Measurement of ferritin was done by enzyme-linked immunosorbent assay (ELISA), ensuring high accuracy and reproducibility of the measurements.

IV.Results

Puncture was performed, after which the number of retrieved oocytes and the quality of embryos formed were assessed. Embryo quality was classified according to international grading standards: "excellent" embryos (uniform blastomeres with no fragmentation), "good" embryos (minimal fragmentation from 0–20%), and poor quality embryos (exceedingly fragmented,

[7] Bergh C., Wennerholm U.-B. Long-term health of children conceived after assisted reproductive technology // Upsala Journal of Medical Sciences. 2020. Vol. 125, no. 2. P. 152-157.

beyond 50%). Descriptive statistics and correlation methods were used to analyze the collected data. The analysis of paired comparisons of ferritin levels in groups was performed using Student's t-test, while Pearson's correlation coefficient was applied to determine the correlation between ferritin levels and embryo morphological characteristics. The difference was considered statistically significant at $p<0.05$.

In this way, the materials and methods were oriented toward investigating the multifaceted relationship between the level of ferritin and in vitro fertilization (IVF) results while laying emphasis on both systemic and local indicators of iron status and their effects on embryo quality.

Table 1. Comparative Characterization Of Ferritin Indices In Blood And Follicular Fluid In Women During Ovarian Puncture And Oocyte Collection

	Ferritin at the time of the puncture	
	in blood	in follicular fluid
2a iron + stimulation, n=29	85,5±6,7	171,3±13,7
2 iron-2 months break-stimulation, n=36	70,8±2,4	56,1±3,0
P	<0,05	<0,001

Ferritin levels displayed a statistically significant difference between groups 2A (iron + stimulation) and 2B (iron - break - stimulation). In group 2A, blood ferritin levels were 85.5 ± 6.7 µg/L, significantly higher than those of group 2B (70.8 ± 2.4 µg/L, $p<0.05$). This indicates that iron-containing preparations administered in conjunction with ovulation stimulation enhance blood ferritin levels. Moreover, the concentration of ferritin in follicular fluid was recorded to be higher in group 2A than in group 2B (group 2A: 171.3 ± 13.7 µg/L; group 2B: 56.1 ± 3.0 µg/L, $p<0.001$). This confirms that iron accumulation in the system directly affects local parameters in the ovaries.

Table 2. Correlative Characterization Of The Number And Quality Of Embryos Obtained As A Function Of Ferritin Indices

		Ferritin			
		KG	1 gr	2A gr	2B gr
Number of embryos.		0,10	-0,09	0,03	-0,04
Stage and quality/ grade of embryos	excellent	0,52	-0,04	-0,09	0,03
	good	-0,55	-0,23	0,32	-0,09
	poor quality	-0,21	-0,09	-0,22	-0,08
	Compactized	-0,02	0,03	0,17	0,11

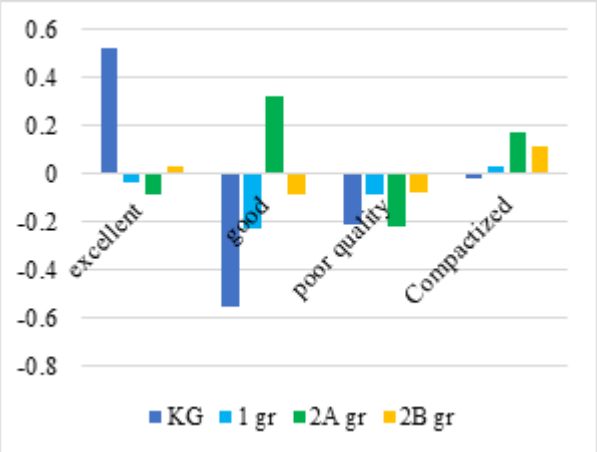

Figure 1 - Correlative characterization of the number and quality of embryos obtained as a function of ferritin indices

The analysis showed differences in the number and quality of embryos obtained from women with different ferritin levels. Group 2A showed a weak positive correlation between blood ferritin level and number of embryos (r = 0.10), whereas in group 2B the correlation was negative (r = -0.09). This may be due to the fact that excessive iron accumulation in the ovaries (in group 2A) may create a favorable environment for cell division. In group 2A, the ferritin level in follicular fluid was positively correlated with the number of perfect embryos (r = 0.52), whereas no such relationship was observed in group 2B (r = -0.04). In group 2A, there was a weak negative correlation with the number of good embryos (r = -0.23), whereas in group 2B the correlation was positive (r = 0.32). Ferritin levels were insignificantly correlated with the number of poor quality embryos in both groups (r = -0.21 for 2A and r = -0.22 for 2B), indicating a weak effect of ferritin on the formation of poor quality embryos.

DISCUSSION

The obtained results indicate that ferritin levels in blood and follicular fluid significantly affect the processes of embryo formation and embryo quality during in vitro fertilization. The differences observed between groups 2A and 2B suggest that the modes of administration of iron preparations influence iron metabolism in the woman's body directly, thus influencing the success of IVF procedures.

Higher levels of ferritin in blood and in follicular fluid were seen in group 2A where iron preparations were administered simultaneously with ovulation stimulation. This could probably have been due to synchronizing ovarian function with heightened iron availability, creating conditions for enhanced local metabolism within the follicles. High levels of ferritin in follicular fluid favor a relatively good microenvironment for oocyte maturation, which is supported by the positive correlation between ferritin levels and the number of good embryos in this group. However, excess iron might work in both ways: increased iron concentrations could, by increasing the reactive oxygen species, contribute toward oxidative stress that could impede cell division and reduce embryo quality. This could provide an explanation for the decrease in the good quality embryo percentages observed at increased ferritin levels in group 2A.

Meaning ferritin levels were significantly lower in blood and follicular fluid in group 2B where a break of two months was allowed between iron supplementation and ovulation stimulation. This avoided excess iron accumulation, thereby probably reducing exposure of developing cells to oxidative stress. However, lower ferritin levels may also have limited iron availability for metabolic functions relevant to oocyte maturation, which would lead to fewer good embryos, although the percentage of good quality embryos was higher in this group than in group 2A.

Hence, it can be stated that iron balance is a key parameter deciding the fate of in vitro fertilization. Quite obviously, iron deficiency and iron excess have opposing effects on the quality of oocytes and embryos. Iron deficiency limits the resources that are required in metabolic and antioxidant defense tasks, while iron excess creates an atmosphere of oxidative stress and damage to cells. These results agree with previous studies that show the need for ferritin and iron level monitoring in women undergoing IVF. The levels of ferritin in follicular fluid might be an important predictor for oocyte and embryo quality and for the implantation process. Particular attention should be paid to individual iron adjustments for the women, based on different levels of iron stores, to minimize the risks of adverse effects of both iron deficiency and excess.

The present study confirmed the importance of ferritin levels in blood and follicular fluid as significant factors affecting the number and quality of embryos in in vitro fertilization. The use of different strategies to correct iron levels before and during ovulation stimulation was found to result in significant differences in the metabolic processes occurring in follicles. Women who received iron supplementation concurrently with ovulation stimulation had higher ferritin levels in blood and follicular fluid, which was positively correlated with the number of perfect embryos. However, excessive iron accumulation in the ovaries was associated with a risk of

oxidative stress, which may reduce the quality of the resulting embryos. In contrast, a strategy involving a two-month break between iron supplementation and the start of ovulation stimulation avoided excessive ferritin accumulation, which contributed to an improved rate of good quality embryos, although the total number of excellent embryos was lower.

CONCLUSION.

Thus, careful monitoring of iron and ferritin levels in patients is necessary to maximize the effectiveness of IVF. Optimization of these parameters may include individual correction taking into account the initial iron status, stimulation methods and potential risks. The results obtained have important scientific and practical significance, as they can be used to develop new approaches to prepare women for in vitro fertilization procedures. Future research should focus on determining accurate target ferritin values and evaluating the long-term outcomes of individualized iron correction strategies. This will improve the success of infertility treatment and outcomes of IVF programs.

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