Oxidative Stress Markers in IVF Patients and Their Association with Pregnancy Results

IVF Hastalarında Oksidatif Stres Belirteçleri ve Bunların Gebelik Sonuçlarıyla İlişkisi

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ABSTRACT Objective: Oxidative stress has been well recognized as a component in the pathogenesis of many diseases, including female infertility. In this study, we aimed to investigate serum paraoxonase (PON1), arylesterase and myeloperoxidase (MPO) activities, and lipid hydroperoxide (LOOH) levels as oxidative stress markers along with their relationship with the pregnancy rate in women undergoing in vitro fertilization (IVF) treatment. **Material and Methods:** Serum samples of 179 subjects were collected immediately before starting ovarian stimulation and on ovum pick-up (OPU) day during IVF treatment. Stimulation protocol and starting doses were determined individually. When the leading follicle reached at least 17 mm in size, recombinant human chorionic gonadotropin (Ovitrelle, 250 mcg, Serono) was administered for ovulation induction. Serum basal/salt-stimulated paraoxonase, arylesterase activities, myeloperoxidase activity, and lipid hydroperoxide levels were compared between two samples. Subjects were also divided into two groups according to the presence of pregnancy, and the groups were compared in terms of oxidative stress markers studied. **Results:** Serum MPO activity and LOOH levels were significantly higher on ovum pick up day ($p<0.05$, $p<0.001$, respectively), while basal/salt-stimulated paraoxonase and arylesterase activities were significantly lower ($p=0.012$, $p=0.041$, respectively) than those before ovarian stimulation. Serum LOOH levels on OPU day were significantly higher in non-pregnant group than pregnant one ($p<0.001$). Although basal/salt-stimulated paraoxonase, arylesterase and myeloperoxidase activities were higher in the non-pregnant group compared to the pregnant group, it was not statistically significant ($p>0.05$). **Conclusion:** Ovarian stimulation during IVF treatment resulted in increased oxidative stress and decreased PON1 activity. However, changes in the studied parameters were not found to be significantly associated with the pregnancy results. Further studies are required to clarify our results.

Key Words: In vitro fertilization; lipid peroxides; peroxidase; PON1 protein, human

ÖZET Amaç: Oksidatif stresin, kadın infertilitesi de dahil olmak üzere bir çok hastalığın patogenezinde yer aldığı gösterilmiştir. Bu çalışmada, in vitro fertilizasyon (IVF) tedavisi uygulanan kadınlarda oksidatif stres belirteçlerinden serum paraoksonaz (PON1), myeloperoksidaz (MPO), aril esteraz aktiviteleri ile lipid hidroksiperoksid (LOOH) düzeylerini ve bu belirteçlerin gebelik oranlarıyla ilişkisini araştırmayı amaçladık. **Gereç ve Yöntemler:** Yüz yetmiş dokuz olgunun serum örnekleri ovaryan stimulasyona başlanmadan hemen önce ve tedavi esnasında yumurta toplama günü (OPU) alındı. Stimulasyon protokolü ve başlangıç dozları bireysel olarak belirlendi. Dominant folikül boyutu en az 17 mm'ye ulaştığında, ovulasyonu tetiklemek için rekombinant human korionik gonadotropin (Ovitrelle, 250 mcg, Serono) uygulandı. Alınan iki örnekte serum bazal/tuz-stimule PON1, aril esteraz ve MPO aktiviteleri ile LOOH düzeyleri karşılaştırıldı. Olgular ayrıca gebelik durumuna göre de iki gruba ayrıldı ve çalışılan oksidatif stres belirteçleri iki grup arasında karşılaştırıldı. **Bulgular:** Bazal/salt-stimüle PON1 ve aril esteraz aktiviteleri OPU günü ovaryan stimulasyon öncesine göre istatistiksel olarak anlamlı düşük bulunurken (sırasıyla p=0,012, p=0,041), serum MPO aktivitesi ve LOOH düzeyleri anlamlı yüksek bulundu (sırasıyla p=0,036, p=0,001). Gebe olmayan grupta OPU günü serum LOOH düzeyleri gebe olanlara göre anlamlı derecede yüksekti ($p<0,001$). Bazal/tuz-stimüle PON1, arilesteraz ve MPO aktiviteleri gebe olmayan grupta gebe olanlara göre daha yüksek olsa da, bu yükseklik istatistiksel olarak anlamlı değildi ($p>0,05$). **Sonuç:** IVF tedavisi uygulanan kadınlarda tedavi sırasındaki ovaryan stimulasyon artmış oksidatif stress ve azalmış PON1 aktivitesine neden olmaktadır. Ancak, bu parametrelerdeki değişiklikler ile gebelik sonuçları arasında anlamlı bir ilişki bulunmamıştır. Sonuçların netleşmesi için daha ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: İn vitro fertilizasyon; lipid peroksitler; peroksidaz; PON1 proteini, insan

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Reactive oxygen species (ROS) resulting from normal cell metabolism are important molecules that may either be harmful or beneficial to living bodies. It has been shown that ROS are physiological in the female reproductive tract.[1,2] However at excessive levels, ROS can result in pathologies affecting female reproduction.[3] ROS produced within the follicle especially during the ovulatory process have an important role in embryo formation and quality.[4] On the other hand, oxidative stress imbalance in the ovarian follicular fluid environment has a detrimental effect on oocyte and embryo development, pregnancy outcome and endometriosis-associated infertility.[5-8]

Oxidative stress has been well recognized as a component in the pathogenesis of many diseases, including female infertility,[1,6,7,9,10] but reports about the effects of oxidative stress on infertility and in vitro fertilization (IVF) treatment are conflicting.

Paraoxonase-1 (PON-1) is a glycoprotein of 43–45 kDa, and its gene is located on the long arm of chromosome-7.[11] PON-1, which has PON and arylesterase activities, is a high-density lipoprotein (HDL)-bound antioxidant enzyme that protects low-density lipoprotein cholesterol (LDL-C) and HDL cholesterol (HDL-C) against oxidative damage, and these activities have been found to be inversely associated with oxidative stress.[12-14] Serum PON1 activity was found to be decreased in endometriosis and in subfertile men.[15,16]

Myeloperoxidase (MPO) is an oxidative enzyme found in phagocytes, and it is an essential part of the anti-microbial system and inflammatory regulation[17]. MPO is a heme enzyme that uses the oxidizing potential of superoxide and hydrogen peroxide to convert chloride ion to hypochlorous acid (HOCI) and other ROS.[17]

To the best of our knowledge, the relationship between IVF results and activities of PON1, MPO and lipid hydroperoxidase (LOOH) levels in serum has not yet been investigated. In this study, we measured serum paraoxonase, MPO and arylesterase activities, and LOOH levels as oxidative stress markers in women undergoing IVF, and investigated the correlation between these parameters and pregnancy results after treatment.

MATERIAL AND METHODS

The study was performed in Istanbul Memorial Hospital IVF Center, Istanbul, Turkey. Laboratory tests were carried out in the Biochemistry Laboratory of Harran University, Sanliurfa, Turkey.

One hundred seventy nine women aged between 22-42 years undergoing IVF were enrolled in the study. According to the presence of pregnancy, the subjects were divided into two groups as pregnancy negative (n=99) and positive (n=80) groups. The subjects were otherwise healthy. The women underwent a general biochemical study as well as the standard infertility work-up before IVF. Two groups were compared in terms of oxidative stress markers.

The study protocol was conducted in accordance with the Helsinki Declaration as revised in 2000, and approved by the local ethics committee of Yuzuncu Yil University, Medical Faculty. All subjects were informed about the study, and their written consents were obtained.

OVARIAN STIMULATION PROTOCOL

Each patient was evaluated sonographically for ovarian reserve at the beginning of the stimulation cycle. The type of stimulation protocol and starting doses were determined individually for each patient. Dose adjustment was done according to the ovarian response. When the leading follicle reached at least 17 mm in size, recombinant human chorionic gonadotropin (HCG) (Ovitrelle, 250 mcg, Serono) was administered for ovulation induction. Oocyte retrieval was performed 36 hours after HCG administration. Intracytoplasmic sperm injection was performed in all oocytes. One or two best quality embryos were transferred on days 2-5 after oocyte retrieval. Pregnancy was diagnosed by serum HCG on the 14th day after OPU, and confirmed by ultrasonographic appearance of gestational sac with heart beat.

STATISTICAL ANALYSIS

The results are expressed as the mean±standard deviation. The paired sample t test was used to compare PON1 levels, myeloperoxidase activity, and

TABLE 1: Comparison of some characteristics of the two groups.

Parameters	Pregnancy positive (n=80)	Pregnancy negative (n=99)	p
Age (years)	33.21±4.90	34.61±4.82	0.123
BMI (kg/m2)	25.76±4.46	26.12±4.82	0.617
Endometrium on HCG day(mm)	10.47±1.87	9.82±1.83	0.021
E2 level on HCG day (pg/mL)	1792±1157	1567±1075	0.184
Oocyte number retrieved	10.65±7.27	8.02±6.76	0.014
MII oocyte number	7.53±4.91	5.47±4.53	0.004
Mean number of embryos	6.55±4.45	4.43±3.64	0.001
Duration of infertility (year)	5.75±3.35	7.08±5.19	0.057
Duration of induction (days)	8.22±1.69	8.20±1.73	0.970
Total gonadotropin dose (IU)	2020±947	2007±842	0.925
Embryo transfer day	3.92±1.01	3.89±0.90	0.876

BMI: Body mass index; MII: Mature oocyte; HCG: Human chorionic gonadotropin; NS= Non significant.
Values are presented as mean ± standard deviation.

TABLE 2: Paraoxonase, arylesterase, myeloperoxidase activities and oxidative stress levels before and after ovarian stimulation during in vitro fertilization treatment.

Parameters	Before stimulation (n=179)	After stimulation (n=179)	p
Paraoxonase (U/L)	226.36±79.23	214.70±79.25	0.036
Salt stimulated paraoxonase (U/L)	475.08±296.53	405.64±254.71	0.012
Arylesterase (kU/L)	233.64±36.51	222.18±35.51	0.041
Myeloperoxidase (U/L)	28.98±11.35	34.55±14.18	0.036
Lipid hydroperoxide	4.03±0.65	4.22±0.80	0.001

Values are presented as mean ± standard deviation.

LOOH levels before and after the IVF treatment. Student's t test was used to compare PON1, myeloperoxidase activity and LOOH levels in pregnancy positive and negative groups. The results were considered to be statistically significant when the p value was less than 0.05. The data were analyzed using the SPSS® for Windows computing program (Version 11.0).

RESULTS

Some characteristics of the subjects in the pregnancy positive and negative groups are presented in Table 1. There were no significant differences between the two groups for age and body mass index of the patients (p>0.05) (Table 1).

After ovarian stimulation treatment, serum MPO activity and LOOH levels were significantly higher (p=0.036, p=0.001, respectively), while basal/salt-stimulated paraoxonase and arylesterase activities were significantly lower (p=0.012, p=0.041, respectively) (Table 2).

After the ovarian stimulation, serum LOOH levels on OPU day were significantly higher in non-pregnant group compared to pregnant group (p<0.001). Although basal/salt-stimulated paraoxonase, arylesterase and myeloperoxidase activities were higher in non-pregnant group, it was not statistically significant (p>0.05).

DISCUSSION

In this study, we aimed to investigate serum paraoxonase, MPO and arylesterase activities, and LOOH levels as oxidative stress markers in women undergoing IVF. Additionally, association between these parameters and pregnancy results of IVF treatment were also investigated. The results of the current study indicated that serum MPO activity and LOOH levels were significantly increased, and

paraoxonase, arylesterase activities decreased in women undergoing IVF treatment. After dividing the subjects according to the presence of pregnancy, we observed that serum LOOH levels were significantly increased in pregnancy negative subjects compared to the pregnancy positive subjects. However, we did not observe any significant differences in other parameters between pregnancy positive and negative subjects. To the best of our knowledge, the current study is the first one on this issue, and we hope that our results provide important data.

Oxidative stress has been associated with numerous adverse health effects including atherosclerosis,[18] pre-eclampsia,[19] and male and female infertility.[20] It has also been considered as a major causative factor in etiologies such as polycystic ovary syndrome, endometriosis, tubal, peritoneal and unexplained infertility.[21]

Free radicals and other damaging ROS, such as the superoxide anion, are produced in oxidative metabolic and physiological processes, and it is well known that oxidative stress increases during normal pregnancy.[22] All living aerobic cells are normally exposed to ROS, and oxidative stress arises as a consequence of excessive production of ROS and impaired antioxidant defense mechanisms.[23] Numerous studies have demonstrated the presence of ROS in the female reproductive tract; ovaries,[24] fallopian tubes[25] and embryos.[26] However, excessive ROS levels have been speculated to be an increased risk for poor oocyte quality.[27] At the end of our study, no significant difference was found between the oxidative stress markers of pregnancy positive and negative subjects.

Several studies have examined the role of oxidative stress and pregnancy complications. Vural et al.[28] demonstrated that plasma ascorbic acid (vitamin C) and α-tocopherol (vitamin E) levels were significantly lower in women with recurrent spontaneous abortions. Furthermore, Oyawoye et al. have reported the total antioxidant capacity levels to be lower in the case of inferior oocyte and embryo formation.[1] Some others showed that high levels of antioxidants present in follicular fluid may be responsible for controlled generation of ROS and lipid peroxidation, thereby resulting in the formation of good quality oocytes and embryos and an improved fertilization rate.[29]

The IVF is characterized by decreased antioxidant levels and increased lipid peroxidation levels in the follicular fluid[4]. Low intrafollicular oxygenation has been associated with decreased oocyte developmental potential, as reflected by increasing frequency of oocyte cytoplasmic defects, impaired cleavage and abnormal chromosomal segregation in oocytes from poorly vascularised follicles.[30] Levels of ROS in the follicular fluid are positively correlated with pregnancy in patients undergoing IVF.[10] Increasing ROS concentration plays a physiological role in sperm–oocyte fusion,[31] and improves mouse and human blastocyst development.[32] These observations suggest that a limited amount of oxidative stress is essential for embryo development.

Reports about the effects of oxidative stress on infertility and IVF treatment are conflicting. Some studies have shown that higher antioxidant capacity level increases fertilization potential in women undergoing IVF.[1,9] Some other investigators reported higher ROS levels in women undergoing IVF.[7,10] In our study, serum MPO activity and LOOH levels showing oxidative stress were found significantly higher, while basal/salt-stimulated paraoxonase and arylesterase activities representing antioxidant activity were significantly lower. Attaran et al.[10] reported even a beneficial role for ROS, with higher levels in follicular fluid in IVF conception cycles compared with non-conception cycles. However, the authors did not report any association between total antioxidant capacity and conception. Similarly, we also did not find any significant association between the antioxidant markers and pregnancy results. Pasqualotto et al.[7] reported that women who became pregnant by IVF had higher levels of lipid peroxidation than those who did not. Other studies suggested that oocyte maturity did not vary with the changing levels of ROS and lipid peroxidation.[6]

On the other hand, Aurrekoetxea et al.[33] evaluated serum oxidizability and antioxidant status in women undergoing an IVF cycle to assess the pos-

sible relationship of the oxidizability indexes with the pregnancy rate. Treatment with IVF induced the production of ROS, which was reflected in a serum less protected against oxidation. The results also suggested a role for ROS in the occurrence of conception in IVF. Ovarian stimulation during IVF therapy produces a perturbation in the oxidant-antioxidant balance that causes the serum to be less protected against oxidation.

The association between PON1 activity and female infertility is unknown. PON1 has been shown to prevent LDL and HDL oxidation. It is also responsible for antioxidant effect of HDL.[34] PON1 activity was significantly lower after ovarian stimulation in the present study. We suggest that decreased PON1 activity must be related to enhanced production of oxidative stress. In addition, it has been previously shown that PON1 activity was decreased in some diseases because of oxidative stress pathogenesis under oxidative stress and inflammatory conditions such as diabetes, coronary artery disease, and endometriosis.[16,34] Serum PON1 expression is down-regulated by oxidative stress.[35] Marsillach et al.[36] observed elevated serum oxidative stress that was significantly correlated with an increase in serum PON1 activity without any evidence of a proinflammatory reaction. They suggested a protective role of PON1 against inflammation in this clinical setting.

Our study indicated that ovarian stimulation during IVF treatment was associated with increased oxidative stress and decreased PON1 activity. This association may be helpful to understand some undetermined points of pathogenesis of infertility and IVF treatment. However, changes in the studied parameters were not found to be significantly associated with the pregnancy results. Further studies are required to clarify the results.

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