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Research Article

Circulating Presepsin Levels in Women with Recurrent Implantation Failure

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Abstract

Aim: The aim of this study is to investigate the serum and follicular fluid (FF) presepsin (PSPN) levels of patients undergoing IVF/ICSI with the diagnosis of recurrent implantation failure (RIF).

Methods: Twenty five women with RIF who failed to achieve a pregnancy after three fresh or frozen embryo transfer cycles with at least one or two good-quality embryos transferred were included. Ten infertile women with unexplained infertility were accepted as control group. They were treated according to a standard antagonist protocol with individually dosed recombinant FSH starting on day 2 - 3 of the menstrual cycle. During oocyte pick up serum and follicular fluid samples were collected. PSPN levels were measured by using the Rel Assay Human ELISA kit.

Results: Serum PSPN levels were significantly higher in the RIF group compared to FF levels (18.1 ± 1.23 mg/L vs 11.3 ± 2.21 mg/L). When RIF and control group were compared between themselves in terms of serum PSPN levels, there was no difference between them (18.1 ± 1.23 mg/L vs. 16.7 ± 4.2 mg/L). However, the control group's FF-PSPN levels were significantly higher than the RIF group (17.4 ± 3.25 mg/L vs 11.3 ± 2.21 mg/L).

Conclusion: Significantly decreased FF-PSPN levels in RIF cases suggest insufficient inflammatory activity during follicle development.

Keywords: *RIF; PSPN; Serum; Follicular Fluid*

Introduction

Despite the transfer of four good quality embryos in at least three fresh or frozen cycles, the inability to conceive is considered to be recurrent implantation failure (RIF). It is one of the leading infertility issues in reproductive biology [1]. The underlying mechanism of RIF is unknown. In addition to the age of the patients, egg and sperm quality, endometrial tissue having sufficient thickness and receptive properties also play an important role in etiology. The completion of the genetic and molecular development of the eggs obtained in spontaneous or induced cycles is essential for a healthy pregnancy. In order for an egg to complete its developmental capacity, molecular steps must be performed perfectly after the LH peak [2]. One of the pathways activated after the LH peak is the inflammatory pathway. Adequate inflammatory reactions in the follicle and serum are essential for a healthy ovulation. Because ovulation is a specialized kind of inflammatory process. Presepsin is a specialized marker of inflammation discovered in 2005. Presepsin (PSPN) is also called as soluble CD14 subtype [3,4]. Presepsin is a novel biomarker of inflammation and its diagnostic capacity in reproductive biology is still in an investigation. In the inflammatory process that is not linked to infection, presepsin rises systemically. Although presepsin levels in serum and follicular fluids of some infertile cases were examined, this marker was not studied in RIF cases.

Aim of the Study

The aim of this study is to investigate the serum and follicular fluid presepsin levels of patients undergoing IVF/ICSI with the diagnosis of RIF.

Materials and Methods

Twenty five women with RIF who failed to achieve a pregnancy after three fresh or frozen embryo transfer cycles with at least one or two good-quality embryos transferred were included. Ten infertile women with unexplained infertility were accepted as control group. They were registered at the Istanbul Bahcesehir University Medical park Hospital IVF Center, between January 2020 and June 2020. Women were treated according to a standard antagonist protocol with individually dosed recombinant FSH starting on day 2 - 3 of the menstrual cycle. Gonadotrophin-releasing hormone antagonist was started on the 5th or 6th day of stimulation. When at least three follicles reached 16 - 17 mm in diameter, maturation of follicles was induced with recombinant hCG (Ovitrelle, Merck-Serono, 250 mg, Modugno, BA, Italy). Egg collection was performed 36 hours after hCG application. Ovarian follicles were aspirated using a single-lumen, 17-gauge needle (Cook Medical, Bloomington, IN, USA) guided by trans-vaginal ultrasonography. During oocyte pick up serum samples were also collected. All samples were frozen until analyzed and stored at -20°C. Presepsin levels were studied in frozen serum and follicular fluid samples collected from patients with the diagnosis of RIF and control group. PSPN levels was measured by using the Rel Assay Human PSPN ELISA kit. The measurement was made in accordance with the working procedures defined in the kit catalogue. Absorbance measurements were taken with a Microplate Reader. The minimum detection limit of PSPN was 0.02 mg/L.

Statistical analysis

The normality distribution of data was tested with the Kolmogorov-Smirnoff test. The continuous variables were analyzed by means of analysis of variance test with post hoc Tukey procedure and Mann-Whitney U test. Data are presented as the means ± SD. A *p* value of <.05 was considered statistically significant.

Results

There was no significant difference between the groups in terms of age, duration of infertility and other demographic features. BMI of RIF cases were higher than the BMI of control group. The rFSH doses used were similar between the two groups. Serum PSPN levels were significantly higher in the RIF group compared to FF levels (18.1 ± 1.23 mg/L vs 11.3 ± 2.21 mg/L). When RIF and control group were compared between themselves in terms of serum PSPN levels, there was no difference between them (18.1 ± 1.23 mg/L vs. 16.7 ± 4.2 mg/L). However, the control group's FF-PSPN levels were significantly higher than the RIF group (17.4 ± 3.25 mg/L vs 11.3 ± 2.21 mg/L).

Discussion

In recurrent implantation failure, the search for solutions still continues, but no significant progress is detected. Although genetic tests and local interventions to the endometrium are found to be a solution to some cases, many patients still cannot become pregnant. In this study, we focused our attention on the intra-follicular dynamics. To achieve a healthy pregnancy, an embryo that has completed both metabolically and genetically development is needed. In order to complete the development of the follicle, it needs the LH peak and subsequently activated inflammatory pathways [1,2]. Intra-follicular inflammatory pathways are coordinated systems with multiple functions. First of all, these pathways cause weakening in the follicle wall and subsequently rupture and ovulation [3,4]. However, inflammation is necessary for the oocyte in the follicle to complete its development. Presepsin is one of the new inflammatory molecules. In our study, the decrease of FF-PSPN levels in RIF cases compared to serum levels suggests that there may be an inflammatory defect limited to follicle. The fact that the FF-PSPN levels of the control group cases were significantly higher than the FF-PSPN levels of the RIF group supports our view.

In fact, ovulation is a kind of inflammatory process [1,2]. Thanks to the inflammation, the follicle completes the meiosis, is ready to be ejected with cumulus cells, the follicle wall becomes easier to rupture and a healthy ovulation occurs. In RIF cases, follicle fluid inflamma-

tory markers have not been studied to date. This is the first study to investigate the PSPN levels in serum and FF of RIF patients. As a result of the data we obtained, we came to the following opinion. A decrease in FF-PSN levels may prevent follicle quality and thus attachment to the endometrium, leading to RIF. For this reason, the inflammatory defect that we encounter at the follicle level can be a new and important data in the RIF etiology. This issue needs to be revealed with larger series of studies.

Conclusion

Significantly decreased FF-PSPN levels in RIF cases suggest insufficient inflammatory activity during follicle development.

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