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Could Antimullerian Hormone Play a Role in Fertilization Failure in ICSI Application

Tulay Irez[1, *], Onur Güralp[2], Hakan Yelke[3], Semra Kahraman[4]

[1]Department of Histology and Embryology, Medical Faculty, Istanbul Yeni Yuzyil University, Istanbul, Turkey

[2]Department of Gynaecology & Obstetrics, Medical Faculty, University of Oldenburg, Oldenburg, Germany

[3]Department of IVF and Gynetics Center, Sisli Memorial Hospital, Istanbul, Turkey

[4]Department of Gynecology and Obstetrics and IVF and Gynetics Center, Sisli Memorial Hospital, Istanbul, Turkey

Email address:

ireztulay@yahoo.com (T. Irez), dronur@hotmail.com (O. Güralp), hyelke@yahoo.com (H. Yelke), semkahraman@gmail.com (S. Kahraman)

[*]Corresponding author

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Abstract: Aim: Failed fertilization (FF) occurs in approximately 2–3% of ICSI cycles and is mainly due to lack of oocyte activation. The reasons of total fertilization insufficiency in ICSI applications can be listed as mitosis errors, sperm aster formation defects, sperm decondensation defects, PN formation defects and oocyte activation defects. In this study, sperm functions, oocyte morphology, hormone levels and possible effects of gonadotropins used in the treatment were investigated retrospectively. Material and Methods: In this study, semen parameters and sperm functions, oocyte morphology, basal hormone values and treatment processes of 32 fertilization failure cases and 91 fertile controls were compared. Results: It was found that age of female and male, basal FSH value and gonadotropin used in the treatment process were higher in total fertilization failure cases compared to fertile controls ($p = 0.004$, $p = 0.041$, $p = 0.008$, $p = 0.004$). Basal AMH level, total oocyte count, M2 oocyte count, quality oocyte count and normal ZP percentage were lower in fertilization failure cases ($p = 0.002$, $p = 0.000$, $p = 0.000$, $p = 0.008$, $p = 0.000$). There was no statistically significant difference between the two groups in terms of sperm functions. Conclusions: It was understood that high FSH and low AMH levels and high-dose gonadotropin treatment in cases with optimal sperm quality may cause oocyte cytoplasmic and zona pellucida abnormalities, and it should be discussed as a cause of fertilization failure.

Keywords: Antimullerian Hormone, Oocyte Abnormalities, Fertilization Failure

1. Introduction

With ICSI, the sperm is inserted directly into the oocyte cytoplasm and IVF failure is treated in this way. However, in some patients, insufficient fertilization is seen in all ICSI-treated eggs. After ICSI oocyte activation is characterized by a two-stage increase pattern of intracellular Ca^{2+} concentrations. The first Ca^{2+} increase (triggers) originates from the oocyte cortex following sperm-oocyte membrane interaction and follows a series of shorter Ca^{2+} transient amplitudes (oscillators) that continue for 3-4 hours (oscillator) after 30 minutes [1]. Oscillator function is due to the release of a sperm-associated oocyte activation factor that requires oocyte to sustain recurrent Ca^{2+} releases from intracellular stores [2]. Inadequacies in this oocyte-related osillator function have been shown as a result of auxiliary oocyte activation studies [3].

Genetic parameters in many sperm-related studies in cases of fertilization insufficiency and Torra-Massana M. et al. (2019) have shown that phospholipase C zeta 1 mutations are associated with insufficiency [4]. Fertilization deficiency is frequently observed in globozoospermic cases and studies have reported a multigenic defect due to acrosomal insufficiency in globozoospermic cases [5]. Therefore, Therefore, it is aimed to perform a retrospective study in young women with FF and patients with semen parameters within the acceptable range.

The role of AMH in influencing oocyte quality and oocyte

activation mechanism in fertilization is unknown. Recently Zhang et al. suggested that AMH improved oocyte quality by upregulating GDF9 and BMP15 expressions in oocyte in vitro maturation studies [6]. Furthermore, it is found that different AMH levels could predict the quality of oocytes, the presence of postmaturity and nucleoli Z score, early cleavage, and ICSI outcomes [7]. Therefore, much information is needed to be explained about the contribution of Antimullerian hormone to oocyte quality, oocyte cytoplasmic maturation and fertilization mechanism.

The aim of this study was to examine hormonal and clinical parameters in women and sperm function parameters in men and to examine the chance of predicting TFF before the day of ICSI in patients with acceptable semen analysis findings in two consecutive fertilization failure cycles.

2. Material and Methods

This is a retrospective study with a cross-sectional design at Sisli Memorial IVF Clinic was performed from May 2013 to July 2018 Patient all data were collected from data base of the clinic with the permission of Sisli Memorial Hospital menagement. Because we performed a retrospective analysis of an established clinical procedure in our unit, institutional review board approval was deemed unnecessary. The study population included infertile women 25–37 years old of age who went through serum hormone level tests as well as oocytes retrieval to examine oocyte quantity and quality as a part of IVF procedures. Ovarian stimulation in patients consisted of antagonist protocols were used. Follicular development was monitored and when the maximal diameter of three leading follicles exceeded 18 mm, 10000 IU hCG (Pregnyl 5000 IU Amp. Organon) was given intramuscularly. After 36 hours, follicles were aspirated under transvaginal ultrasound guidance with a single lumen aspiration needle. 2 hours post-collection, the oocytes were denuded of their surrounding cumulus cells with hyaluronidase (Vitrolife, Sweden) and mechanical pipeting, which allows a precise determination of nuclear maturation status and oocyte morphology. 91 fertil controls and 32 total fertilization failure in last two cycles, cases with sperm function test results included the study. Routine semen analysis was done by light microscopy according to strict criteria. Morphology was evaluated by Diff Quick staining technique. Serum AMH, E2, Inhibin B and FSH levels were measured on 3th day during the menstrual cycle and HCG day E2 level using ELISA (Beckman/Coulter, USA). Oocyte and zona morphology and maturation level was determined from photographs taken on the day of oocytes retrieval using Nikon eclipse Ti-U software. Dark and irregularities with thick and thin zona pellucida were evaluated as zona anomalies. Patients with no serum AMH data, azoospermia and no mature oocytes retrieved were excluded. Sperm analysis and the sperm function tests are routine procedures in IVF center. The data were analyzed with SPSS 17.0 package program.

3. Results

When the data of the groups are examined in the study; total fertilization failure was observed in women and men ages were higher (Table 1). Basal FSH was found to be higher in the FF group and AMH was lower than in fertile controls (Table 1). In the fertilization insufficiency group, more gonadotropin was used for treatment (Table 1). When the oocyte parameters were examined, the average oocyte count and M2 oocyte count were lower in the FF group. In addition, zona pellucida morphology was found to be worse in FF group (Table 2). In Table 3, semen analysis and sperm membrane integrity, DNA fragmentation and sperm maturation analyzes were similar in both groups.

Table 1. *Comparison of clinical parameters of fertile control cases and total fertilization failure cases.*

Patients (n)	Fertil controls (91)	Fertilization Failure (TFF) (32)	p
Age of women (years)	30,86±3,99	33,5±5,12	0,004
Age of men (years)	34,88±4,50	36,93 ±5,04	0,041
BMI (kg/m^2)	25,31±4,45	26,80±3,95	0,09
Duration of infertility (years)	6,88±4,04	7,96±4,75	0,224
Basal FSH (IU/ml)	5,25±2,05	7,80±2,05	0,008
Basal LH (IU/ml)	4,09±2,16	3,71±2,47	0,437
Basal E2 (pMol/ml)	39,27±18,32	43,28±14,89	0,302
Inhibin B	77,31±59,57	66,21±46,79	0,397
AMH (ng/ml)	3,83±2,86	1,87±1,74	0,002
Endometrial Thickness (mm)	10,25±2,11	8,72±2,56	0,110
HCG day E2 (pmol/ml)	1899,5±1097,26	1871,4±1803,1	0,961
Gn (U)	1971,79±817,37	2725,15±11,27	0,004

Table 2. *The number of mature or immature oocytes, high quality oocytes and zona pellucida abnormalities in fertil or fertilization failure patient groups.*

Patients (n)	Fertil controls (91)	Fertilization failure (32)	P
Total oocytes	9,64±3,47	4,48±4,30	0,000
M2 oocytes	7,63±3,65	3,19±3,23	0,000
M1 oocytes	0,16±0,52	0,29±0,73	0,313
GV	1,06±1,54	0,51±0,88	0,063
High quality M2	5,08±3,53	2,77±3,06	0,008
Normal Zona Pellucida	7,46±3,69	2,67±2,89	0,000

Table 3. *Sperm parameters and function tests of the groups.*

	Fertil controls	Fertilization failure	p
Concentration (mil/ml)	51,71±38,96	65,30±59,60	0,313
Total motility (%)	21,70±15,72	19,53±13,61	0,726
Mot A (%)	12,32±12,84	11,15±11,84	0,766
Mot B (%)	6,42±4,94	4,61±3,33	0,214
Morphology (%)	3,01±2,79	4,91±3,84	0,052
HOS (+)(%)	62,27±22,60	76,80±19,86	0,183
AO test (+) (%)	40,61 ±18,69	36,25±16,74	0,668
Chromatin condensation (%)	23,80±19,97	15,66±10,01	0,502

4. Discussion

In this study, it was found that the age of the women was higher, the serum AMH level was below 2 ng / dl, the number of oocytes was less than 5 and the number of M2 oocytes was less than 4 and the number of low zona pellucida normal oocytes in cases with fertilization deficiency.

Because of the many factors involved in the fertilization process, it may be observed that there are patients who have been exposed to complete insemination failure despite the presence of a normal spermatozoon [8-10]. The frequency of total fertilization failure cycles was reported to be ∼1–3 % and also characterized by very low oocyte counts [11-13]. In such cases, repeated ICSI treatment has proven to be beneficial however, some patients will have to face repeated fertilization failure despite normal sperm parameters and good ovarian response [3, 12, 13].

Successful fertilization is observed in cases with normal oocyte maturation. The proper response of oocyte cytoplasm to sperm PLCζ signals is a very important step for fertilization [14]. The ability to produce sequential cytoplasmic calcium releases during fertilization requires several cytoplasmic changes: rearrangement of the endoplasmic reticulum (ER), increase in the number of IP3 receptors, changes in the biochemical properties of receptors (sensitivity to IP3), an increase in the concentration of calcium ions stored in the endoplasmic reticulum (ER) and redistribution binding ER proteins [15-19]. Studies on non-fertilized oocytes in IVF / ICSI cycles have shown the presence of abnormal spindles and interphase microtubes indicating that deficiencies in ooplasmic and nuclear components may be a cause of failed fertilization [20, 21].

Anti-Müllerian hormone (AMH) is a glycoprotein growth factor secreted by granulosa cells [22]. The normal expression pattern of AMH is found to be low in the primary follicles, followed by large pre-antral and small antral follicles, followed by a decrease in follicle growth. Based on this expression pattern, it was suggested that the concentration of serum AMH would reflect the number of follicles that grew early as the follicle pool decreased with decreasing growth [23-25]. Previous studies have investigated AMH gene expression levels in granulosa cells and their correlation with oocyte quality, but the results are inconsistent and contradictory [26-28]. Studies also show that AMH gene expression levels in CCs correlate with AMH concentration in the respective follicular fluid (FF). Anti-mullerian hormone (AMH) is thought to reflect the growth of follicles and the ovarian function [29-31]. In a study conducted by Borges et al. In 2017, it was suggested that serum AMH levels affect the results of ovarian hyperstimulation, it is a useful indicator of oocyte quality and ovarian response to fertilization, but AMH levels do not impair embryo development [32]. In the study of Gupta et al, (2017) it was suggested that antimullerian hormone had an effect on oocyte quality (28). Borges et al suggested that serum levels of AMH are a useful predictor of ovarian response to COS, oocyte quality, and fertilization [32].

Traditionally, the most important measurement in the assessment of ovarian function has been age-independent baseline follicle-stimulating hormone (FSH) levels [31]. Age-specific baseline FSH levels predicted the retrieval of fewer than or equal to four oocytes, with a positive predictive value of 19.5% and a negative predictive value of 88% [31]. According the study of Fang and Abdalla (2015, 2004) basal FSH levels combined with age (age-specific FSH levels) can be used as a more accurate marker for the ovarian response in women with normal ovarian reserves undergoing IVF-ET, particularly in women ≤ 37 years old [30, 33]. In our study, the mean female age in the patient groups was 30.86 in the fertile group and 33.5 in the ff group. In contrast, the mean FSH value was 5.25 and 7.80. According to the number of M2 oocytes, the average oocyte in the ff group was below 4. In this case, the increase in the basal FSH value in the young patient group has affected the number and quality of oocytes. According to the studies Zona Pellucida dysmorphology is associated with markedly diminished pregnancy and implantation rates in IVF [34]. There is no consensus on the effects of oocyte morphological anomalies on fertilization, embryo quality and pregnancy outcomes [35]. There are also studies showing that abnormal oocytes do not affect fertilization, embryo quality and pregnancy outcomes negatively [36, 37-40].

In conclusion, in the presence of optimal sperm parameters, low M2 oocyte count, age-inappropriate FSH elevation and low AMH values should be investigated in cases of fertilization failure.

Conflicts of Interest

Authors declare that there is not any conflict of interest.

Author Contribution Statement

Design of the study: T. I, O. G, S. K.
Laboratory documentation: H. Y.
Statistics: O. G.

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