Original Article

Unexplained Total Fertilization Failure after Intracytoplasmic Sperm Injection Cycles: A Case-Control Study on Predictive Factors and Retreatment Prognosis

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Abstract

Background: The aim of our study was to detect the rate of unexplained total fertilization failure (TFF) after intracytoplasmic sperm injection (ICSI) and identify its risk factors and retreatment prognosis.

Materials and Methods: In this retrospective case-control study, we searched the computerized database of the Royan Institute (Tehran, Iran) from March 2015 to March 2019 and retrieved all cases diagnosed with TFF after ICSI. TFF cases that did not have any recognized risk factors were classified as unexplained (subgroup A). Cases with recognized risk factors were classified as subgroup B. The control group was randomly selected from infertile couples who underwent ICSI cycles with fertilization of at least one oocyte during the same time interval. Characteristics and treatment outcomes of the cases with unexplained TFF (subgroup A) were compared to the control group, and to the other TFF cases (subgroup B).

Results: Out of 18,750 couples who underwent ICSI cycles, 296 (1.58%) experienced TFF for the first time. Of these, 49 (16.5%) couples were diagnosed as unexplained TFF (subgroup A) and 247 (83.5%) were placed in subgroup B, TFF with expected risk factors. Multivariable logistic regression analysis showed that the total number of mature oocytes (P<0.001), duration of infertility (P=0.043), and women's body mass index (BMI, P<0.001) were significant predictive factors for unexplained TFF. In the ICSI cycle after TFF, clinical pregnancy and live birth rates in subgroup A were higher than subgroup B. Although differences between these groups were not statistically significant (P=0.14 and P=0.07, respectively), this finding could be clinically important.

Conclusion: Unexplained TFF following ICSI is a rare event significantly related to a lower number of mature oocytes, longer duration of infertility and higher female BMI. It has a good prognosis in retreatment cycles in comparison with expected TFF cases. Clinicians should take this into consideration for patient counseling and management.

Keywords: Case-Control Study, Fertilization, Intracytoplasmic Sperm Injection, Retreatment

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Introduction

Total fertilization failure (TFF) is a problem for patients and a major challenge for physicians (1). Fertilization via *in vitro* fertilization (IVF) is the result of complex molecular reactions between sperm and oocytes, and any breakdown in this process leads to TFF, which occurs in 5-10% of IVF cycles (2) and in 1-3% of intracytoplasmic sperm injection (ICSI) cycles (3, 4).

ICSI was initially used to bypass all physiological sperm screening mechanisms. This procedure can result in fertilization in couples diagnosed with severe male factor infertility. Despite recent advances in ICSI, the fertilization rate remains around 50-70% and does not differ from standard IVF in non-male factor cases (2). It is proposed that factors other than sperm binding and penetration are involved in limiting the fertilization rate (5). Significant risk factors for TFF include total immotility of spermatozoa, azoospermia and other surgically retrieved sperm conditions (6), oocyte activation deficiencies that can be caused by both sperm or oocyte related factors, cytoplasmic immaturity and spindle abnormalities (7, 8) as well as low oocyte yield, oocyte aneuploidy, fragile oocytes, defects in the *in vitro* sperm/oocyte medium (9), and operator proficiency for ICSI (5).

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Prediction of TFF is complex and sometimes one good quality oocyte and one retrieved sperm from a globozoospermia case can result in successful fertilization; however, TFF can also occur in couples with apparently normal gametes (5). Although many researchers have examined the rate of TFF and its related risk factors, no study has compared the prognosis after a retreatment ICSI cycle in expected versus unexplained TFF cases. We designed the present study to evaluate the occurrence rate of unexplained TFF after an ICSI cycle in patients treated at the Royan Institute (Tehran, Iran) and to identify its risk factors and prognosis in one subsequent cycle.

Materials and Methods

The Scientific Council and Ethics Committee of the Royan Research Institute approved this retrospective study protocol (IR.ACECR.ROYAN.REC.1398.112). We searched a computerized database of 18 750 ICSI cycles performed at the Royan Institute from March 2015 to March 2019 for cases diagnosed with TFF. The following cases were excluded: donor oocyte (donor sperm is illegal in our center); embryo transfer (ET) failure due to arrest of embryo development (uncleaved embryo); and cycles that lacked sperm or oocyte retrieval. Finally, a total of 296 cycles with TFF (the absence of two pronuclei [2PN] embryos 16-18 hours after all injected oocytes) were retrieved and subsequently placed in two subgroups. The TFF cases without any recognized risk factors were classified as unexplained TFF (subgroup A) while the other TFF cases with recognized risk factors (azoospermia, women over 40 years of age, and less than five retrieved oocytes) were placed in subgroup B. The control group was randomly selected from infertile couples who underwent ICSI cycles with fertilization of at least one oocyte during the same time interval. Patients diagnosed with azoospermia were not included in the control group. The occurrence rates of unexplained TFF and its risk factors were assessed. In addition, the outcome of ET cycles and the recurrent rate of TFF following a second ICSI cycle were compared in subgroups A and B among TFF cases readmitted for subsequent ICSI cycles.

Characteristics of the couples in the study included age and body mass index (BMI); cause, type, and duration of infertility. Data on baseline follicle stimulating hormone (FSH), luteinizing hormone (LH) and anti-Müllerian hormone (AMH) were collected from the patients' records.

Controlled ovarian hyperstimulation (COH) was performed using long gonadotropin releasing hormone (GnRH) agonist or antagonist protocols. Details of these protocols have been reported previously (10). Oocyte pick up (OPU) procedures were performed by transvaginal ultrasound-guided aspiration 34-36 hours after the final oocyte triggering. Semen samples were collected by masturbation after 3-4 days of abstinence on the day of the OPU. For each semen sample, separate gradients for each 1.5 ml volume were prepared with 1.5 ml of each custom-made SupraSperm® solutions (100% lower and 50% upper, Origio A/S). Sperm concentration and motility were assessed after mixing. A total of 1.5 ml of the liquefied semen sample from the top of the prepared gradient was dispensed, and the gradient was centrifuged at 525 RFC for 10 minutes. The supernatant was removed and re-suspended in 5 ml HampsF_{10} Alb (10%) plus medium for 5 minutes. Next, the supernatant was aspirated. This washing procedure was repeated once more before we determined sperm concentration and motility in the washed sample.

The final pellet was used for ICSI. Sperm morphology was evaluated by Papanicolaou staining according to World Health Organization (WHO; 2010) guidelines for male infertility workup and strict criteria on sperm morphological assessment (11). Routine oocyte and embryo quality assessments at our institute have been explained elsewhere in detail (12). The oocyte maturity rate was defined as the number of metaphase II (MII) oocytes divided by the total number of retrieved oocytes per patient. ICSI was performed according to a standard protocol by the same team of embryologists who used the same technique and culture conditions for all patients. Fertilization was defined as the presence of 2PN and two polar bodies at 16-18 hours after ICSI. ET was performed on the second, third or fifth day after ICSI. Vaginal progesterone suppositories (Cyclogest, 400 mg) were administered twice per day for luteal phase support. ICSI cycle characteristics included ovarian stimulation duration; total dose and type of gonadotropin; time from triggering to ovum pickup; and ICSI performance. Total number of retrieved and MII oocytes, total sperm count, sperm morphology, and progressive motility were obtained from patients' charts. Chemical pregnancy was determined by serum beta-human chorionic gonadotropin (β-hCG) levels (Elecsys reagent kit, Roche Cobas) performed 14 days after ET. Clinical pregnancy was defined as the presence of a gestational sac with a fetal heartbeat observed by ultrasound four weeks after ET. Live birth was defined as the delivery of a live fetus, irrespective of the duration of the pregnancy.

Statistical analysis

Data analysis was carried out using SPSS software, version 21 (SPSS Inc., Chicago, IL, USA). Normality distributions for continuous variables were determined using the Kolmogorov-Smirnov test. Data are presented as mean ± standard deviation (SD) or median (min-max), where applicable. Mean differences between the unexplained TFF and control groups and between TFF subgroups A and B were compared using the student's t test. The Mann-Whitney U test was applied for the comparison of median values. Both univariate and multivariable logistic regression analyses were performed to detect predictive factors for unexplained TFF. The odds ratio (OR) and 95% confidence interval (CI) for significant variables were also calculated. The Hosmer-Lemeshow test was used to confirm the goodness-of-fit of the logistic regression model. $P<0.05$ were considered to be statistically significant.

Results

In total, 18 750 ICSI cycles were performed between March 2015 and March 2019 at the Royan Institute. Of these, 296 (1.58%) couples experienced TFF for the first time; 49 (16.5%) were diagnosed with unexplained TFF (subgroup A) and 247 (83.5%) with TFF with recognized risk factors (subgroup B).

A comparison of basic characteristics between patients with unexplained TFF and control patients showed no significant differences with respect to age and baseline hormone levels (FSH, LH and AMH); however, women's BMI (P<0.001), infertility duration (P=0.02), and cause of infertility (P=0.03) were significantly different between the groups (Table 1). Despite a similar distribution of standard COH protocols between the two groups, both total gonadotropin doses and duration of stimulation were higher in women with unexplained TFF than in the controls. Moreover, the number of mature oocytes and the oocyte maturity rate in the unexplained TFF group were significantly lower than in the control group. In terms of sperm characteristics, although total sperm count (P=0.21) and progressive motility (P=0.22) did not differ significantly between groups, the level of normal sperm morphology (P=0.050) in the unexplained TFF group was lower than in the controls. A further investigation compared mean time intervals between oocyte triggering to puncture and between oocyte retrieval to sperm injection between the groups. No statistically significant differences in oocyte triggering to puncture (P=0.9) and oocyte retrieval to sperm injection (P=0.3) were observed (Table 1).

Multivariable logistic regression analysis using stepwise backward selection demonstrated that the total number of MII oocytes (P<0.001), duration of infertility (P=0.043) and women's BMI (P<0.001) were significant risk factors for unexplained TFF, but cause and duration of infertility, total gonadotropin dose, total number of MII oocytes, and normal sperm morphology were not (Table 2). A low chi square value (1.28, df: 8, P=0.99) from the Hosmer-Lemeshow test showed that the model was a satisfactory fit for the data.

Table 1: Comparison of patients' basic and controlled ovarian stimulation cycle characteristics between the unexplained TFF and control groups

Characteristics	Unexplained TFF group (n=49)	Control group (n=100)	P value	OR* (95% CI)
Female age (Y)	33.4 ± 4.3	33.1 ± 1.9	0.66	1.02 (0.91-1.15)
BMI (kg/m^2)	25.7 ± 3.27	22.8 ± 2.7	<0.001	1.39 (1.21-1.60)
Basal LH (IU/L)	5.820 ± 4.339	5.2 ± 3.4	0.36	1.04 (0.95-1.13)
Basal AMH (ng/mL)	3.444 ± 3.015	3.5 ± 1.3	0.89	0.98 (0.82-1.18)
Basal FSH (IU/L)	6.195 ± 2.372	6.2 ± 3.2	0.94	0.99 (0.88-1.11)
Causes of infertility			0.03	
Ovulatory factor	1 (2.0)	25 (25)		Reference group
Tuboperitoneal factor	3 (6.1)	3 (3)		0.12 (0.01-1.14)
Unexplained factor	13 (26.5)	15 (15)		3.16 (0.50-20.0)
Male factor	26 (53.0)	38 (38)		2.74 (0.84-8.93)
Mixed (both female and male factors)	6 (12.2)	19 (19)		2.16 (0.76-6.15)
Duration of infertility (Y)	6.6 ± 4.0	5.03 ± 3.2	0.020	1.14 (1.03-1.25)
COH protocol				
Standard long GnRH agonist	31 (63.2)	67 (67)	0.65	Reference group
GnRH antagonist	18 (36.7)	33 (33)		1.17 (0.57-2.40)
Duration of stimulation (days)	11.7 ± 2.4	10.7 ± 2.3	0.01	1.20 (1.03-1.39)
Total gonadotropin dose (IU)	2216 ± 905	1912 ± 796	0.03	1.0 (1.00-1.002)
Total retrieved oocyte count	8.9 ± 3.9	9.6 ± 3.0	0.25	0.93 (0.84-1.04)
Number of MII oocytes	5.6 ± 3.5	8.0 ± 2.8	<0.001	0.75 (0.66-0.86)
Oocyte maturity rate	0.6 ± 0.3	0.8 ± 0.1	<0.001	0.037 (0.007-0.17)
Total sperm count (million)	47.9 ± 29.8	41.8 ± 25.3	0.21	1.007 (0.99-1.02)
Normal sperm morphology (%)	4.2 ± 2.9	5.3 ± 3.0	0.050	0.25 (0.14-0.46)
Progressive motility (%)	20.0 ± 10.1	23.6 ± 18.8	0.22	1.02 (0.99-1.04)
Time interval between oocyte retrieval and sperm injection (hours)	1.21 ± 0.71	1.10 ± 0.6	0.34	0.60 (0.13-2.77)

Data are presented as mean ± SD or n (%). OR; Odds ratio, CI; Confidence interval, *; These results were obtained from univariate logistic regression analysis, TFF; Total fertilization failure, BMI; Body mass index, LH; Luteinizing hormone, AMH; Anti-Müllerian hormone, FSH; Follicle stimulating hormone, COH; Controlled ovarian hyperstimulation, GnRH; Gonadotropin releasing hormone, and MII; Metaphase II.

Table 2: Multivariable logistic regression analysis with unexplained TFF as the outcome of interest

Risk factors	OR	95% CI	P value
Number of mature oocytes	0.72	0.603, 0.874	<0.001
Women's BMI	1.54	1.281, 1.862	<0.001
Duration of infertility	1.15	1.004, 1.322	0.043

TFF; Total fertilization failure, BMI; Body mass index, OR; Odds ratio, and CI; Confidence interval.

In the follow-up, out of 49 patients diagnosed with unexplained TFF, 17 patients were referred again for an ICSI treatment cycle. Of these, 5 (29.4%) had recurrent TFF. Out of the 12 patients who had ET, 3 (27.3%) had clinical pregnancies and live births. By comparison, out of the 247 couples diagnosed with expected TFF, 61 patients were referred for an ICSI treatment cycle. Of these, 20 (32.8%) had recurrent TFF and 41 patients had ET. The analysis indicated that the recurrence rate was similar between the groups (P=0.79, Table 3).

Table 3: Comparison of readmission and recurrence rates between TFF subgroups

	Unexplained TFF (Subgroup A) (n=49)	Expected TFF (Subgroup B) (n=247)	P value
Readmission for ICSI cycle after TFF	17 (34.7)	61 (24.7)	0.10
TFF recurrence rate	5/17 (29.4)	20/61 (32.8)	0.79

Data are presented as n (%). TFF; Total fertilization failure and ICSI; Intracytoplasmic sperm injection.

Table 4: Comparison of basic and controlled ovarian stimulation cycle characteristics of patients who underwent ART cycle after the first TFF

Characteristics	Unexplained TFF (subgroup A) (n=17)	Expected TFF (subgroup B) (n=61)	P value
Female age (Y)	32.3 ± 5.2	34.4 ± 5.0	0.14
Male age (Y)	35.2 ± 5.2	39.3 ± 6.7	0.02
Female BMI (kg/m^2)	26.9 ± 2.51	27.19 ± 4.5	0.85
Male BMI (kg/m^2)	26.3 ± 6.1	28.9 ± 6.5	0.04
Male smoker	5 (29.4)	19 (31.1)	0.57
Basal LH (IU/L)	3.8 ± 1.7	4.9 ± 4.1	0.28
Basal AMH (ng/mL)	1.9 ± 1.8	2.4 ± 3.9	0.60
Basal FSH (IU/L)	5.8 ± 2.5	7.0 ± 3.6	0.21
Cause of infertility			<0.0001
Ovulatory factor	2 (12)	13 (21.4)	
Tuboperitoneal factor	0 (0)	1 (1.6)	
Unexplained factor	8 (47)	4 (6.5)	
Male factor	6 (35)	21 (34.4)	
Mixed (both female and male factors)	1 (6)	22 (36.1)	
Duration of infertility (Y)	5.7 ± 3.8	7.7 ± 6.1	0.19
COH protocol			0.88
Standard long GnRH agonist	6 (35.3)	24 (39.3)	
GnRH antagonist	11 (64.7)	37 (60.7)	
Duration of stimulation (days)	10.7 ± 2.0	10.6 ± 2.83	0.83
Total gonadotropin dose (IU)	2053 ± 807	1747 ± 1086	0.29
Total retrieved oocyte count	8.0 ± 4.2	4.8 ± 4.4	0.01
Number of MII oocytes	5.6 ± 3.334	3.9 ± 3.8	0.10
Oocyte maturity rate	0.9 ± 0.2	0.7 ± 0.2	0.02
Oocyte activation (yes)	3 (17.6)	7 (11.4)	0.37
Total sperm count (million)	52.7 ± 29.9	35.6 ± 33.1	0.06
Normal sperm morphology (%)	2.0 ± 1.1	1.2 ± 1.1	0.01
Progressive motility (%)	32.1 ± 17.3	18.7 ± 16.2	0.004
Physiological ICSI	1 (5.88)	2 (3.27)	0.52
Number of transferred embryos	2.6 ± 2.5	1.5 ± 1.6	0.14
Positivity β-hCG/ET	4/12 (33.3)	6/41 (14.6)	0.20
Clinical pregnancy/ET	3/12 (27.3)	4/41 (10)	0.14
Live birth rate/ET	3/12 (27.3)	3/41 (7.5)	0.07

Data are presented as mean ± SD or n (%). TFF; Total fertilization failure, BMI; Body mass index, LH; Luteinizing hormone, AMH; Anti-Müllerian hormone, FSH; Follicle stimulating hormone, COH; Controlled ovarian hyperstimulation, MII; Metaphase II, ICSI; Intracytoplasmic sperm injection, GnRH; Gonadotropin releasing hormone, β-hCG; Beta-human chorionic gonadotropin, and ET; Embryo transfer.

A comparison of baseline characteristics and COH cycle outcomes for subgroup A and B patients who had a second ICSI cycle after the first TFF is presented in Table 4. The analysis showed no significant difference between the unexplained TFF (subgroup A) and expected TFF (subgroup B) in terms of female age and BMI, basal serum LH, FSH and AMH levels, duration of infertility, COH protocol, and total dose of gonadotropins used. Notably, mean male age (P=0.02) and BMI (P=0.04) in subgroup A were significantly higher than in subgroup B. The majority of couples in subgroup A had unexplained factor infertility compared to mixed factor infertility in subgroup B (P<0.001). The couples in subgroup A had significantly higher numbers of retrieved and MII oocytes, as well as higher levels of progressive motility and normal sperm morphology. The rates of oocyte activation and physiological ICSI did not significantly differ between the two subgroups. Finally, ET outcomes were compared between the TFF subgroups. Although clinical pregnancy and live birth rates in the unexplained TFF (subgroup A) were higher than in the expected TFF (subgroup B), these differences were not statistically significant between the groups (P=0.14 and P=0.07, respectively, Table 4).

Discussion

The results of the present study indicated that TFF occurred in 1.58% of all ICSI cycles during the four-year study period. This finding is in line with previous reports, range 1 to 5%, and those reported by Goksan Pabuccu et al. (13) 4.3%, Esfandiari et al. (14) 3.6%, and Bhattacharya et al. (4) 1%. The TFF recurrence rate (32%) in the current study was slightly higher than those previously reported, 15 to 30% (2, 5, 13). As not all the patients with a diagnosis of TFF in our study were referred for a second treatment cycle, the calculated recurrence rate may have been slightly under or overestimated. In addition, we note that unexplained TFF was rare (0.26%). Shinar et al. (15) reported that the rate of TFF in patients under 40 with at least five MII oocytes was 0.7%. It is interesting that the rates of readmission for a second treatment cycle and repeated TFF in both subgroups of patients (unexplained and expected) were similar (range: 25 to 35%). The results of a previous study showed that repeated TFF occurred in 13% of treatment cycles during the second ICSI attempt. Although the rate of referral for a second cycle in patients with expected TFF was lower in the unexplained group (24 vs. 34%) and was not statistically significant, this finding could be clinically significant. Most couples who experience TFF following an ICSI cycle with azoospermia or where the woman is of advanced age and diminished ovarian reserve are reluctant to begin retreatment.

In the present study, male factors, unexplained factors and longer durations of infertility were more common among couples with unexplained TFF compared to controls. These results are comparable to those reported by Shinar et al. (15). The higher mean BMI in patients with unexplained TFF might explain the higher level of gonadotropin consumption and longer duration of ovarian stimulation in these patients compared to controls. The results of a large cohort study indicated that, in comparison with women of normal weight, overweight women (BMI>25<30 kg/m^2) had significantly fewer retrieved oocytes (16). In another large cohort study, overweight women (BMI>25<30 kg/m^2) had significantly lower fertilization rates compared to women of normal weight (16, 17). These data suggest that weight reduction may be advisable for patients with unexplained TFF to improve the outcomes of subsequent ICSI treatments.

Pregnancy results in patients who underwent a second ICSI/ET cycle in both TFF subgroups were similar; however, differences between the two groups in terms of live birth rates were clinically significant. Rates in the unexplained TFF group were three times higher than in the expected TFF group. In our opinion, the results of the present study give us the opportunity to make better decisions in counseling and in selection of an appropriate clinical approach to these patients.

Our results indicate that total sperm count and progressive motility rate had no significant relationship with unexplained TFF, whereas sperm morphology was significantly related in univariate regression analysis. In agreement with our findings, previous research has indicated that total sperm motility has no effect on ICSI results; however, fertilization is decreased or fails when few spermatozoa are available for injection, particularly when nonviable sperm are injected (6). The effects of semen origin on fertilization have been extensively studied, with no significant differences observed in fertilization and clinical outcomes of ICSI cycles (18). Univariate analysis in the current study showed that patients with unexplained TFF had a lower level of normal sperm morphology compared to the control group. However, in the multivariate logistic regression model, these sperm characteristics were not significant predictors of unexplained TFF following ICSI. Recently, Krog et al. (19) concluded that female factors (low number of retrieved oocytes, female smoking, and non-tubal infertility) and an apparently minor sperm factor (low number of progressive motile spermatozoa) were independent predictors of TFF.

Some researchers suggest that ICSI success rates are independent of typical semen analysis and largely depend on the total number of retrieved oocytes (20). In the present study, the number of MII oocytes was the most important factor in predicting unexplained TFF following ICSI. Esfandiari et al. (14) found that ≤2 total MII oocytes was one of the most significant risk factors for TFF. Melie et al. (21) reported that the risk of TFF increased when the number of retrieved oocytes was less than two. Flaherty et al. (3) showed that the risk of TFF decreased from 37 to 0.8% when the total number of retrieved oocytes increased from one to more than five. We therefore consider that less than five total retrieved oocytes is a major risk factor for TFF. Interestingly, although the total number of retrieved oocytes in the unexplained TFF group was similar to the

control group, the number of MII oocytes in this group was significantly lower.

Most TFF cases can be explained by factors such as sperm abnormalities (azoospermia, nonviable, immotile) and oocyte abnormalities (number, maturity, and morphology). However, in some TFF cases, there is no observed abnormality. In these unexplained TFF cases, technical conditions are reported to be involved. One of the most common technical causes of TFF is the failure properly to insert sperm into the oocyte cytoplasm; therefore, choosing the right injection site may increase the number of euploid embryos (22). In the present study, we evaluated the first occurrence of unexplained TFF following ICSI using the same embryologist team at the Royan Institute. We evaluated technical factors, time intervals (hours) between oocyte triggering and puncture, and between oocyte retrieval and sperm injection. We found no relationship between these factors and unexplained TFF. Interestingly, Zhang et al. (23) evaluated the relationship between general and partial time intervals, from serum β-hCG to sperm micro-injection, and ICSI outcomes (fertilization rate, available embryo rate and clinical pregnancy rate). Similar to our findings, they found no relationship between the time interval from oocyte pickup to ICSI and fertilization and clinical pregnancy rates. As a new finding, they reported that an extended time interval between denudation (DN) and ICSI was associated with a higher rate of fertilization than a short DN-ICSI interval, but there was a significant decrease in the clinical pregnancy rate when the interval was over four hours (24). Further studies are warranted to confirm this finding.

Based on recent studies, some couples who undergo ICSI are unable to achieve successful fertilization due to unexplained reasons. In these challenging cases, the ICSI cycles are generally associated with fertilization rates of 70 to 80% and TFF rates of 1 to 3% (24). In the current study, we found that couples with unexplained TFF who undergo an ICSI cycle after the first TFF have higher levels of oocyte maturity, normal morphology, and progressive motile sperm compared to those with expected TFF, which may explain the better pregnancy outcomes in this group. A strength of our study is that this is the first study to compare two subgroups of patients with TFF. To strengthen our conclusions, we suggest that more prospective studies should be undertaken in this area.

Conclusion

The results of the current study show that unexplained TFF following ICSI is a rare event that is significantly related to a lower number of mature oocytes, longer duration of infertility and higher female BMI. It has a good prognosis in retreatment ICSI cycles when compared with expected TFF cases. Clinicians should take this into consideration during patient counseling and management.

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Authors' Contributions

P.M., F.Gh.; Designed the study, drafted and revised the manuscript, participated in the conception of the study, and data interpretation. Z.Z.; Contributed to data acquisition and drafted and revised the manuscript. S.V.; Performed data analysis and revised the manuscript. All authors read and approved the final manuscript.

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