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RESEARCH PAPER

Total fertilization success and embryo formation in ART treatments; does it have any predictive value?

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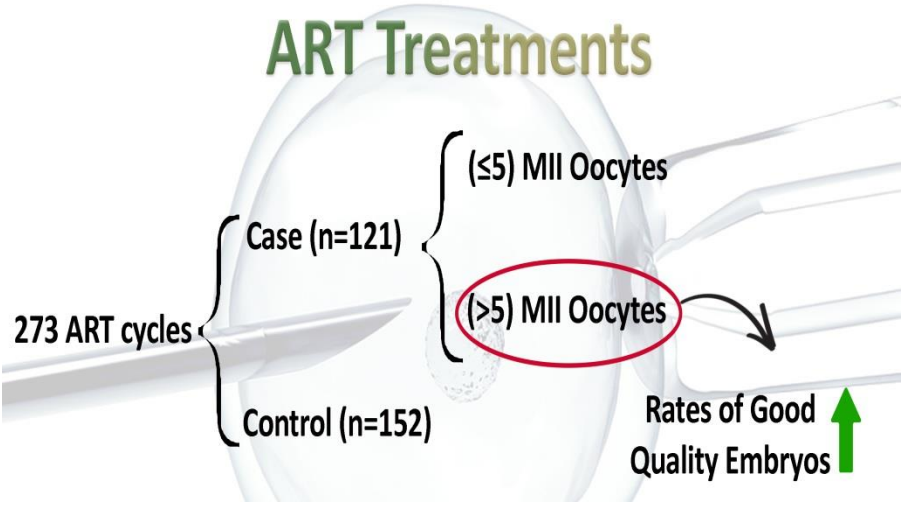
Highlights

- There was no difference among the female age, duration and cause of infertility, number of ART cycles and AMH levels in patients with TFS and TEF and other patients.
- Serum levels of E2, number of COCs, MII oocytes and transferred embryos were higher in patients with TFS and TEF.
- High-quality embryo chemical and clinical pregnancy rates were similar in patients with TFS and TEF and other patients.
- The rates of good quality embryos, chemical and clinical pregnancy were higher in patients with TFS and TEF and>5 MII oocyte.

Graphical Abstract



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Abstract

This retrospective study was aimed to investigate the characteristics of cycles with 100% achievement in laboratory procedures to determine the predictors of cycles with total fertilization success (TFS) and following total embryo formation (TEF). 273 ART cycles were categorized into two groups of the case (n= 121) and control (n=152). Inclusion criteria for case group were; cycles that a total number of MII oocytes were fertilized, and a total of fertilized oocytes developed into the embryos. Demographic variables, ART cycle characteristics and clinical outcomes were assessed and compared between groups. In subcategorizing, the case group was divided into two groups; A) patients with five or fewer (≤5) MII oocytes (n=94); B) patients with more than five (>5) MII oocytes (n=27). Clinical outcomes were assessed between subgroups of A, B and control. Man-Whitney U test, independent sample test and chi-square test were applied wherever appropriate to compare between two groups. P-value less than 0.5 were considered significant. Serum levels of E2, number of COCs, MII oocytes and transferred embryos differed between the groups (P< 0.0001 and P= 0.001). There was a trend manner in increasing the rate of ICSI in case group rather than controls (76.9% vs. 67.1%, respectively; P= 0.081). Furthermore, data sub-analysis showed that the rates of good quality embryos, chemical and clinical pregnancies were higher in subgroup B rather than the other subgroup; however, the differences were not significant (P= 0.07, 0.71 and 0.07, respectively). To increase the likelihood of a successful pregnancy in ART cycles, higher good quality embryos and appropriate number of available embryos for transfer could play an important role.

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Introduction

In vitro fertilization (IVF) has become a promising optionthat helped many infertile couples to realize their dream of having children. However, the most important concern in IVF programs is unsuccessful implantation after embryo transfer (1). It has been estimated that implantation failure occurs in 85% of the transferred embryos (2). In 2012 in Europe, assisted reproductive technology (ART) cycles including 139978 of IVF and 312,600 of theintracytoplasmic sperm injection (ICSI) resulted in 29.4 and 27.8% of clinical pregnancy rates per aspiration, respectively (3). Several clinical and non-clinical parameters predicting the implantation and pregnancy outcomes during IVF treatments including female age, duration of subfertility, type of subfertility, indication for IVF, basal FSH, number of oocytes retrieved, method of fertilization (IVF or ICSI), number of embryos transferred, uterine receptivity, gamete and embryo qualities and transfer efficiency (4, 5).

Moreover, in the case of apparently normal sperm quality, total fertilization failure (TFF) occurs in 5-15% of the couples undergoing the IVF treatment. TFF cycles may be explained by lack of penetration of the zona pellucida (ZP), an oocyte activation failure, or a defect in the oocyte integrity (6). However, ICSI can bypass those barriers and can be an effective way to overcome the TFF or low fertilization rates (6, 7). Although, generally accepted that the indication for ICSI is a severe male factor or previous fertilization failure following IVF (8), but it has been frequently performed alone or in combination with IVF in couples with other etiologies of infertility (9, 10). Reports regarding the benefits of ICSI in non-male factor cases have shown controversial results. Some studies have shown a higher fertilization rate and lower fertilization failure by using ICSI (11, 12). Whereas the other studies do not support the advantages of ICSI in the prevention of TFF (13), and its influences on the other clinical outcomes, such as the embryo quality, implantation and clinical pregnancy rates (14, 15). Regarding the possible factors influencing the success of ART cycles, this study assessed the characteristics of cycles with 100% achievement in laboratory procedures to determine which factors may be predictive of cycles with total fertilization success (TFS) and following total embryo formation (TEF).

Materials and Methods

Study design

In this retrospective study, laboratory and clinical data from patients undergoing ART programs from March 2016 to April 2017 were analyzed. Cycles with severe male factor (sperm concentration < 4×10^6/ ml), frozen and surgically retrieved spermatozoa, also donation and surrogacy cycles were excluded from the study. The eligibility criteria for selecting the case group were the patients with the same number of MII oocytes, fertilized oocytes and developed embryos. Demographic variables, ART cycle characteristics and clinical outcomes were assessed in the case group and compared with the controls. In subcategorizing, the case group was divided into two groups: A) the patients with five or fewer (≤5) MII oocytes; B) the patients with more than five (>5) MII oocytes. The clinical outcomes were assessed between subgroups A, B and control. This study was approved by the author's institute ethics committee.

Ovarian stimulation and IVF/ICSI procedure

Ovarian stimulation was achieved by long pituitary down-regulation using a combination of a gonadotrophin-releasing hormone (GnRH) agonist or antagonist and FSH (Gonal-F; Serono, Geneva, Switzerland). The recombinant hCG (rhCG; IBSA Co, Switzerland) was administered when the maximum diameter of leading follicles was exceeded 18 mm, followed 36 h later by oocyte retrieval. The retrieved cumulus-oocyte complexes (COCs) were incubated at 37 °C in 6% CO2 and 95% air until undergoing IVF or ICSI. In cycles with a plan of ICSI, the COCs were denuded of their cells by 30-60 s exposure to HEPES buffered medium containing 80 IU/mL hyaluronidase (Irvine Sci, CA, USA) followed by pipetting the COCs with a pasture pipette. ICSI procedure was performed as described previously (16).

Fertilization and embryo assessments

Oocytes were checked for signs of fertilization 18-20 h after insemination or 16-18 h after injection. Fertilization was approved by the presence of two pronuclei (2PN) and two polar bodies. 2 days of embryos were graded as follows: Grade A: equal size blastomeres without fragmentation, Grade B: slightly unequal blastomere, up to 10% cytoplasmic fragments. Grade C: unequal-sized blastomeres up to 50% fragments and large granules. Grade D: unequal blastomeres with significant fragmentation and large black granules (17). Grades A and B were regarded as high-quality embryos. In the all of the culture steps, the oocytes and embryos were incubated on the 5% O_2 and 6% Co_2. Results of chemical pregnancy were determined 14 days after embryo transfer (ET) on day 2. Furthermore, the clinical pregnancy was defined as fetal heartbeat rate (FHR) confirmation by sonography.

Statistical analysis

The data were presented as median (min-max) and mean ± SD for quantitative and percentage for qualitative data. Man-Whitney U test, independent sample test and chi-square test were applied wherever appropriate to compare between two groups. All hypotheses were considered two-tailed and a significant level was defined at $P \leq 0.05$.

Results

Table 1 summarized the demographic, laboratory and cycle characteristics of the patients with TFS and TEF (case group) and control group. There were no significant differences in female age, duration and cause of infertility, the number of ART cycles and also in levels of AMH between the groups. Although, the levels of serum E_2, the number of COCs, MII oocytes and transferred embryos differed between the groups ($P< 0.0001$ and $P= 0.001$, Table 1). However, the method of fertilization was not significantly differed between groups, but there was a trend in increasing the rate of ICSI in the case group rather than control (76.9% vs. 67.1%, respectively; $P= 0.081$). The rates of high-quality embryos (A + B), chemical and clinical pregnancy showed no significant differences between the groups (Table 2). According to Table 3, data subanalysis showed that the rates of good quality embryos, chemical and clinical pregnancy were higher in subgroup B rather the other subgroup; however, the differences were not significant ($P= 0.07$, 0.71, and 0.07, respectively).

Table 1. Comparison of demographic, laboratory and cycle characteristics between two study groups.

Variables	Case group	Control group	P-value
NO. of cycles	121	152	
Female age *	32.8± 4.75	31.1 ± 4.47	0.521
Duration of infertility	8 (1-25)	7 (1-24)	0.171
Cause of infertility (%)			
Male factor	38.8	43.4	
PCOs	7.4	15.1	
TF	9.9	5.9	0.066
OF	16.5	8.6	
Endometriosis	4.1	2.6	
Male and female factor	16.2	14.5	
Unexplained	7	9.9	
Serum E_2	1100 (121-6021)	1385 (147-9891)	<0.0001
AMH	2.4 (0.2-20)	2.75 (0.6-11.6)	0.148
NO. of ART cycle	1.18± 0.8	1.47± 0.7	0.402
NO. of COCs	4 (1-14)	8 (2-44)	<0.0001

Table 1. Continue.

NO. of MII oocytes	**2 (1-13)**	**7 (2-39)**	**<0.0001**
NO. of immature oocytes	0 (0-6)	1 (0-14)	0.331
Method of fertilization (%)			
IVF	23.1	32.9	0.081
ICSI	76.9	67.1	
NO. of transferred embryo *	1.72± 0.46	1.92± 0.48	0.001

Data are presented as median (min-max) except * presented as mean± SD. PCOs: polycystic ovarian syndrome, TF: tubal factor, OF: ovarian factor, E2: estradiol, AMH: anti-mullerian hormone, ART: assisted reproductive technology, COCs: cumulus-oocyte complex, MII: metaphase II, IVF: in vitro fertilization, ICSI: intracytoplasmic sperm injection.

Table 2. Clinical outcomes of ART cycles in case and control groups.

Variables	**Case group**	**Control group**	**P-value**
Fertilization rate *	100	63.9± 21.6	<0.0001
Embryo formation rate *	100	88.8± 19.2	<0.0001
Good quality embryos rate (%)	86.8 (105.121)	85.5 (130.152)	0.987
Chemical pregnancy rate (%)	32.2 (39.121)	35.5 (54.152)	0.608
Clinical pregnancy rate (%)	18.2 (22.121)	20.4 (31.152)	0.758

* Data are presented as mean± SD.

Table 3. Clinical outcomes of ART cycles in subgroup A (≤ 5 MII oocyte), subgroup B (> 5 MII oocyte) and control group.

Variables (%)	**Subgroup A (≤ 5 MII oocyte)**	**Subgroup B (> 5 MII oocyte)**	**Control group**	***P*-value**
Good quality embryos	83 (78/94)	100 (27/27)	85.5 (130/152)	0.07
Chemical	30.9 (29/94)	37(10/27)	35.5 (54/152)	0.71
Clinical pregnancy	13.8 (13/94)	33.3(9/27)	20.4 (31/152)	0.07

Discussion

This retrospective cohort study on 273 IVF/ICSI treatments is the first study on the TFS and following TEF cycles for finding the probable predictive factors and enhancing the chance of success in clinical outcomes. However, data do not show any significant differences in the pregnancy rates of these cycles compared to control (Table 2). The female age was considered as one of the strongest factors in predicting pregnancy chances after IVF treatments (4, 18). Moreover, the oocyte morphological quality could be related to advanced maternal age (19). However, this study group was not significantly differed in the female age from the control group. In one study, the embryo quality was introduced as the better predictor of pregnancy rather than the number of transferred embryos and female age (20). Two other factors associated with pregnancy rates are the duration and cause of infertility (21). In the present study, these two late factors were matched between case and control groups, so they cannot be the predictive factors for TFS and TEF in ART programs.

AMH is a member of the transforming growth factor-β superfamily produced exclusively by granulosa cells, which declines with age, and is widely considered as a sensitive marker of ovarian reserve (22, 23). The predictive ability of AMH for pregnancy outcomes is age-dependent (24), so AMH linearly reflects oocyte quantity and quality, both declining related to the advancing female age (25). The presented data confirmed no significant differences in the AMH levels between the groups (Table 1). Based on the above-mentioned studies regarding that the AMH is age-dependent, such results will be expected from the analysis due to the similar mean of female age in both groups. Furthermore, the results of the studies are inconsistent in the association of

AMH with implantation, pregnancy and live birth rate in assisted reproduction [26, 27]. A recent meta-analysis of 5,373 women examining the association of AMH with implantation and clinical pregnancy showed that its predictive accuracy for these parameters is poor (28).

As shown in Table 1, the serum E_2 levels and the number of retrieved COCs and MII oocytes were significantly lower in the case group compared to the control group. Serum E_2 plays an important role in follicular and oocyte maturation, and also in uterus preparation for embryo implantation (29). Moreover, it was mentioned that usually, serum E_2levels in hCG administration day could predict the approximate number of COCs in that cycle (30). There was a debate on the impact of elevated E_2levels on the quality and outcomes of the cycles. Some studies showed that supraphysiological E_2 levels do not adversely affect the quality of developing oocytes and embryos (31). Whereas, numerous studies have shown lower pregnancy and implantation rates in relation to elevated levels of E_2caused by disrupted endometrial receptivity (32). In the group with lower levels of E_2, the results showed significantly higher fertilization and embryo formation rates without a concomitant rise in chemical and clinical pregnancy outcomes.

There are some studies on the association between the number of oocytes retrieved and pregnancy (21, 33). The availability of an optimum number of MII oocytes improves the likelihood of generating good quality embryos and consequently achieving successful outcomes (34). Sharma and colleagues reported a higher cumulative conception rate in patients with more than five retrieved oocytes (35). In the case group of this study, there were higher rates of fertilization and embryo formation despite the fewer number of retrieved COCs and MII oocytes retrieved. However, the chemical and clinical pregnancy was insignificantly lower when compared to the control group. In a subanalysis, the group with TFS and TEF was divided into two subgroups regarding the number of retrieved oocytes. Data showed a significantly higher clinical pregnancy rate in TFS and TEF patients with more than five oocytes in comparison to the other groups (33.3% vs. 13.8%, and 20.4%, P= 0.07). Moreover, the number of embryos transferred was influenced on IVF success, as the patients with more than two embryos available for transfer had significantly higher pregnancy chances (35). The number of embryos transferred in the case group was significantly lower and subsequently, chemical and clinical pregnancy showed a lower rate. In the TFS and TEF group, the number of cases with only one embryo available for transfer was higher compared to the control group due to the higher number of cycles with only one retrieved oocyte. So, according to the lower number of available embryos for transfer in each cycle, the lower clinical pregnancy rate is reliable and predictable. For resolving this problem, the chemical and clinical pregnancy rates were separately analyzed in subgroups in order to the number of MII oocytes. In regards to the relationship of the method of fertilization with a chance of pregnancy, some studies reported a lower pregnancy rate in ICSI rather than IVF programs (30), although the other studies showed insignificant differences (36). Also, the results showed no significant differences in performed fertilization method.

Concluion

In conclusion, the data do not show any specific parameter that could be influenced by TFS and TEF. However, according to our findings, the cycles with the higher-good quality embryos and the appropriate number of available embryos for transfer will have a better prognosis for the pregnancy success.

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