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Investigating Prognostic Factors for Assisted Reproductive Technology Outcomes in Qadir-Mother and Child Hospital of Shiraz, Iran

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Abstract

Background: Assisted reproductive technology (ART) helps infertility treatment. In this study, the researchers tried to find several prognostic factors for ART success.

Methods: Data of 189 couples that had undergone ART at Qadir-Mother and Child hospital, were retrospectively explored. Cycles were classified as succeeded/failed and female/male/combined causes. Three classes of ovarian response based on the number of retrieved oocytes were determined. Duration of ovarian stimulation, dosages of gonadotropins, and sperm parameters were evaluated. Chi square, t-test and Pearson correlation were used for the analysis.

Results: Couples with male factor infertility had a higher success rate. Female age had a negative correlation with follicle count (r = -0.25), retrieved oocytes (r = -0.25), fertilized oocytes (r= -0.2), and clinical pregnancy (r = -0.21). Female age was negatively correlated with AMH, although not significant. The fertilization rate had a reverse correlation with the basal FSH (r = -0.22, P= 0.01) and LH (r= -0.18, P= 0.05). Finally, ART success rate was positively correlated with the number of follicles before (r = 0.18, P = 0.05) and after retrieval (r = 0.15, P = 0.05) and fertilized oocyte (r = 0.23, P = 0.01).

Conclusions: Female age, the number of mature follicles before retrieval, the number of retrieved oocyte, and fertilized oocytes are predictive factors in ART outcomes.

Keywords: Assisted Reproductive Technology, Infertility, Ovarian Response

1. Background

Increased prevalence of infertility in the last twenty years has caused the wide usage of assisted reproductive technologies (ART) in many countries, including Iran. After each failed ART attempt, pregnancy rate in the subsequent attempts decreases with the most remarkable decrease after the third attempt (1). In addition to factors depending on female reproductive system, such as female age (2), identification of other factors in this area may help individualize the diagnostic and therapeutic program.

Upon presentation of an infertile couple to an infertility center, a particular therapeutic plan would be set. Determining factors include etiological factors and individual demographic-history, physical examinations, and laboratory characteristics. Individually tailored ovarian stimulation with the aim of obtaining the best oocytes in quality and count is needed. Embryos obtained from successful fertilization of retrieved oocytes will be transferred to the uterus for implantation. All of the mentioned steps have their exclusive character and connection to others, which should be considered for a successful result.

2. Objectives

In the present study, the researchers evaluated several pre-treatment characteristics, demographic data, ovulation induction, fertilization, and implantation results of several ART cycles to identify important factors that are correlated with ART outcomes for a better prediction of the possibility of success.

3. Methods

This was a retrospective study performed on the recorded data of 189 couples that had undergone ART cycle

at Qadir-Mother and Child hospital affiliated to Shiraz University of Medical Sciences, from 2010 to 2012. Although all participants remained anonymous, a consent form was obtained previously to access their documentations and the study protocol conformed to the ethical guidelines of the 1975 declaration of Helsinki and was approved by the institutional ethics committee of Shiraz University of Medical Sciences (ethics code: IR.sums.rec.1392.6867).

All of the couples were divided according to the causes of their infertilities to male factor infertility (MFI) (106 couples in this study) (involving structural abnormalities, sperm production disorders, ejaculatory disturbances, and immunologic disorders), Female factor infertility (FFI) (75 couples in this study) (involving ovulatory disorders, endometriosis, pelvic inflammatory disease and damage to fallopian tubes or uterus) or combined with the presence of both female and male factors (eight couples in this study).

Infertility was defined as failure of pregnancy after one year of unprotected intercourse (3). Primary infertility was defined when the couple did not have even a single prior pregnancy and secondary infertility was diagnosed when infertility occurred following one or more previous pregnancies (4). The follicles were counted by transvaginal ultrasound (TVS) scan and the numbers were documented in charts during each ART cycle. The numbers of the retrieved oocytes were also counted and documented by embryologists after each ovum pick up. Fertilization rate was defined as the percentage of transformation of the sperm exposed oocytes to two pronuclei stage embryo in 16 to 18 hours after IVF/ICSI (5). The ART success was defined by the achievement of a clinical pregnancy with detection of gestational sac and fetal heart at four to five weeks after embryo transfer by TVS.

Hormonal assay for the following hormones was performed: follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), prolactin (PRL), anti mullerian hormone (AMH), estradiol (E2), dehydroepiandrosterone sulfate (DHEAS), total testosterone (T), and luteinizing hormone (LH). The enzyme linked immunosorbent assay (ELISA) method was used for the measurement of FSH, PRL, TSH, T and E2 (Monobind ,U.S.A.), AMH (Beckman ,U.S.A) and DHEAS (DRG,Germany). Enzyme linked fluorescent assay (ELFA) was used for the measurement of LH (Vidas Biomerio, France).

The ovarian responses were graded to three classes, according to the number of the retrieved oocytes: poor ovarian response was defined as ≤ 3 retrieved oocyte, normal ovarian response was four to ten retrieved oocytes and high ovarian response was ≥ 10 retrieved oocytes (6).

Duration of ovarian stimulations, dosages of the used gonadotropins, and sperm parameters were extracted from the charts and were analyzed. Couples, who benefited from egg or embryo donation, were not enrolled in this study. Moreover, patients, who delivered an uncompleted form, in each part of the content, were excluded from this study.

3.1. Statistical Analysis

Statistical analysis was performed by statistics package for social sciences version 19.0 (SPSS Inc, New York, USA, 2010). Bivariate analyses (chi square and t-tests) were conducted to assess the relationship between all independent variables and cycle outcomes. Correlations were tested by Pearson correlation test based on 95% and 99% confidence. $P < 0.05$ and $P < 0.01$ were considered as representing statistically significant differences.

4. Results

4.1. Characteristics According to ART Outcomes

Among 189 surveyed cycles, 94 cycles that led to clinical pregnancies were considered as successful ART outcome and 95 cycles failed. Among the succeeded cycles, 25 (26.6%) were FFI against 50 (52.6%) in the failed cycles. Furthermore, 65 (69. 2%) couples of the succeeded group were MFI against 41 (43.2%) among failed cycles. This observation indicates that the couples with MFI had a higher probability of pregnancy by ART. There were four couples with combined causes of infertility in both of the succeeded and failed groups that were not included in this section.

Among succeeded cycles, 33 (35.1%) couples had one to three years and 25 (26.6%) couples had three to six years of primary infertility. However, 25 (26.6%) had primary infertilityof $>$ 6 years and 11 (11.7%) had secondary infertility. Among the failed cycles, the most prevalent type of infertility was primary infertility of $>$ 6 years with 37 (38.9%) couples, followed by 26 (27.3%) couples with one to three years and 20 couples (21%) with three to six years of primary infertility. The less frequent kind of infertility among failed cycles was secondary infertility in 12 (12.6%) couples.

Table 1 shows the mean of female age, male age, total dose of administered gonadotropin, duration of ovarian stimulation, number of follicles prior to retrieval, retrieved and fertilized oocytes, number of transferred embryos, fertilization rate and duration of primary and secondary infertility, compared between succeeded cycles and failed cycles.

4.2. Characteristics of MFI and FFI Groups

In the present study, the researchers surveyed documentations of 189 ART cycles. Initially, this study investigated for correlation between certain parameters in couples defined as FFI (75 cycles) and MFI (106), separately. In

Table 1. Compared Parameters Between the Succeeded and Failed Cycles[a]

Characteristics	Successful Cycles	Fail Cycles	P-Value
Female age (y)	30.8 ± 4.9	33.3 ± 6.3	0.003
Male age (y)	35.3 ± 5.9	37.18 ± 7.389	0.052
Total dose of administered gonadotropin (IU)	3289 ± 1725	3919 ± 2082	0.025
Duration of ovarian stimulation (d)	9.4 ± 2.19	9.7 ± 2.3	0.279
Number of follicles prior to retrieval	12.5 ± 5.7	10.3 ± 5.8	0.011
Number of retrieved oocytes	11.7 ± 6	9.7 ± 6.6	0.033
Number of fertilized oocytes	7.5 ± 4.3	5.5 ± 4	0.001
Number of the transferred embryos	2.76 ± 0.67	2.6 ± 0.8	0.076
Fertilization rate (%)	66 ± 23	60 ± 24	0.089
Mean of duration of primary infertility (y)	5.46 ± 3.9	7.4 ± 5.9	0.016
Mean of duration of secondary infertility (y)	4.5 ± 3.3	4.9 ± 3	0.74

Abbreviation: IU, international unit.
[a] Values are expressed as mean ± SD

the female factor infertility group, the female age had a significant negative correlation with follicle count before retrieval (r = -0.25, P-value < 0.001), number of retrieved oocytes upon ovarian stimulation (r = -0.25, P-value < 0.001), fertilized oocytes (r = -0.2, P-value = 0.001), and ART success rate (r = -0.21, P-value = 0.008). Moreover, female age was negatively correlated with AMH, although this correlation was not significant. Number of retrieved and fertilized oocytes, although being non-significant, were negatively correlated with serum testosterone level and estradiol, and positively correlated with AMH. This research checked the female basal FSH level, LH, PRL, T, E2, and AMH. None of the mentioned hormone levels were correlated with ART success rate. Fertilization rate had a reverse correlation with basal FSH (r = -0.22, P-value = 0.003) and LH (r = -0.18, P-value = 0.048). Finally, ART success rate was positively correlated with the number of follicles (r = 0.18, P-value = 0.04), retrieved oocytes (r = 0.15, P-value = 0.032), and fertilized oocytes (r = 0.23, P-value ≤ 0.001).

The FSH, LH, and semen parameters (volume, count, morphology, and motility) of the male partner in MFI group were analyzed to find any correlation with fertilization rate and ART success rate. Fertilization rate was negatively correlated with basal FSH (r = -0.16, P-value = 0.05). The ART success rate was positively correlated with sperm motility (r = 0.14, P-value = 0.02). Moreover, different sperm parameters were analyzed for the detection of possible correlations between them. Sperm motility was positively correlated with sperm morphology (r = 0.26, P-value < 0.001).

4.3. Characteristics According to Ovarian Response

In the second step, the researchers classified the participants according to their ovarian responses. Overall, 22 (11.7%) females were classified as poor ovarian response, 82 (43.6%) as normal ovarian response, and 84 (44.6%) as high ovarian response. In one cycle, number of the retrieved oocytes was not documented. Data showed that higher number of follicles caused statistically higher number of retrieved oocytes (P-value = 0.00) and the highest number of retrieved oocytes was obtained when the female age was statistically lower (P = 0.002).

The ART cycle outcomes were analyzed with respect to the causes of infertility and to the ovarian responses that are shown in Table 2. The highest success rate was obtained in the high response group (52/84 = 61.9%) followed by normal (36/82 = 43.9%) and poor response (6/22 = 27.2%). As previously mentioned, MFI was associated with higher success rates and it is shown in Table 2 that in this study the prevalence of MFI was 61.9% among the high response group that probably helped for better outcomes, while the majority of couples with FFI emerged as poor responders (68.1%).

5. Discussion

The present study on 189 ART cycle outcomes and their characteristics, attempted to identify prognostic clinical factors and patient characteristics for ART success. In this study, MFI was associated with higher success rates. This superiority could be attributed to the fact that intracytoplasmic sperm injection (ICSI) had helped considerably for the treatment of MFI. Also, most of the males classified as MFI in this study had partners with high ovarian responses and higher success rates.

This research observed that in the succeeded cycles, the mean female age, mean duration of infertility, and mean

Table 2. ART Success According to Ovarian Response and Female/Male/Combined Infertility[a]

	Ovarian Response								
	Poor ($\leq$ 3 Retrieved Oocytes)			Normal (4-10 Retrieved Oocytes)			High ($\geq$ 10 Retrieved Oocytes)		
	Succe.	Fail.	Tot.	Succe.	Fail.	Tot.	Succe.	Fail.	Tot.
FFI	1 (6.6)	14 (93.4)	15/22 (68.1)	11 (33.3)	22 (66.7)	33/82 (40.2)	13 (48.1)	14 (51.8)	27/84 (32.1)
MFI	5 (71.4)	2 (28.6)	7/22 (31.8)	23 (50)	23 (50)	46/82 (56)	37 (71.2)	15 (28.8)	52/84 (61.9)
Combined factor	0 (0)	0 (0)	0 (0)	2 (66.7)	1 (33.3)	3/82 (3.6)	2 (40)	3 (60)	5/84 (5.9)
Total	6/22 (27.2)	16/22 (72.7)	22	36/82 (43.9)	46/82 (56)	82	52/84 (61.9)	32/84 (38)	84

[a] The sum of succeeded or failed cycles is shown in columns and the sum of FFI, MFI and combined factor infertility in each ovarian response group are shown in rows. Values are expressed as numbers (%).

total dosage of administered gonadotropin, were statistically lower compared to the failed cycles. Conversely, the mean number of follicles prior to retrieval and number of retrieved and fertilized oocytes were statistically higher in succeeded cycles. Fertilization rate was slightly higher in succeeded cycles compared to failed cycles. However, the difference was not statistically significant, indicating that other variants enrolled in the next steps may affect ART outcomes. Likewise, ART outcomes are positively correlated with the number of follicles before retrieval and retrieved oocytes, and negatively correlated with gonadotropin dosage. Observed correlations are consequences of female age. Accordingly, for younger females with higher follicle count, lower dosage of gonadotropin was administered and still more oocytes were retrieved and better outcomes were obtained. These results highlight the impact of maternal age on all steps of ART and fit very well with the literature (7, 8).

The current data show that the couples with fewer years of infertility had a higher chance of successful ART cycles (since the majority of succeeded cycles had one to three years primary infertility while the majority of failed cycles had > 6 years infertility). This observation is in concordance with the second result showing lower mean duration of primary and secondary infertilities among the succeeded cycles compared with the failed cycles and is in agreement with the literature (9).

Mean male age was not statistically different between succeeded and failed cycles yet when this parameter was checked only in the MFI group, it was statistically lower in succeeded cycles (34.92 ± 6.23 versus 37.95 ± 7.45, P-value = 0.026). The current data indicate that when the cause of infertility is directly male partner, younger participants have more chance of success. Although several evidences in the literature argue that male age does not affect ART outcomes (10, 11), yet the current observations were in agreement with some limited work, illustrating the role of male age on ART outcomes (12).

Various ovulation induction protocols for poor responders and advanced age females are based on higher dosage of gonadotropins and in most cases need longer duration of stimulation (13). As the data indicates, for these patients, even by applying this kind of protocol, less number of oocytes were retrieved and fertilized and lower fertilization rates were obtained.

All together, the researchers identified female age, number of follicles prior to retrieval, number of retrieved oocytes and fertilized oocytes for the female partner and sperm motility for the male partner as significant predictors of ART success. The current results and those of others indicate that all of these characteristics and in a bold importance, the female age, should be monitored very carefully during an ART cycle.

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Footnotes

Authors' Contribution: This study was planned and conceived by Bahia Namavar Jahromi. Ardeshir Bahmanimehr contributed to conduction and data analysis. Zahra Anvar reported on the final data and wrote the manuscript. Najmeh Moein-Vaziri assisted in the manuscript preparation and edition.

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