Journal of Obstetrics, Gynecology and Cancer Research | ISSN: 2476-5848

Investigating the Factors Affecting the ICSI (microinjection) Success in Infertile People Referred to an Infertility Treatment Center in Western Iran from 2011 to 2017

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Article Info

10.30699/jogcr.5.3.115

Received: 2020/06/01;
Accepted: 2020/08/03;
Published Online: 30 Nov 2020;

Use your device to scan and read the article online

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ABSTRACT

Background & Objective: Various parameters can affect the success of intra cytoplasmic sperm injection (ICSI). This study aims to compare the results of fertility in formerly infertile couples who underwent ICSI considering different parameters.

Materials & Methods: In this retrospective study, 261 cases of infertile couples who referred to Motazedi Infertility Center in Kermanshah, and had successful ICSI from 2011 to 2017, were examined. Statistical analysis was performed after collecting the data.

Results: The highest ICSI success rates were in the age range of 31-40 years (58.2%), and 21-30 years (55.8%), in men and women, respectively. Regarding the duration of infertility, the highest success rate was observed in couples who were infertile for less than five years (51.8%). In this study, all the patients' endometrial thicknesses were normally higher than 4 mm. In terms of the number of embryos formed, the success percentage was 68% with three formed embryos. The hormonal variations and distribution percentages were as following: AMH ranging from 1.01 to 5 ng/mL (55.6%), TES ranging from 0 to 50 nmol/L (53%), TSH ranging from 1.01 to 5 µU/mL (81.6%), FSH ranging from 5.01 to 10 IU/L (58.9%), PRO ranging from 5.01 to 10 ng/mL (24%), LH ranging from 1.01 to 5 IU/L (46.7%), and DHEA-S ranging from 1.01 to 5 ng/mL (18.9%).

Conclusion: According to the results, it seems that the success of ICSI technique in infertile couples depends on some parameters including variations in reproductive hormones, number of embryos, couples' ages, and duration of infertility.

Keywords: Assisted reproductive technology, ICSI, Infertility, Western Iran

Introduction

Infertility is one of the couples' issues all around the world which can be caused by either one of the partners. Their lack of childbearing naturally leads them to ask for the help of modern fertility techniques in this field **(1)**. Intra cytoplasmic sperm injection (ICSI) is one of these methods used when the sperm quality is not good or the conditions for the sperm reaching the egg in the uterus are not provided **(2)**. Although ICSI was initially utilized in 1992 to treat infertile men **(3)**, its application is not only limited to them. For about two decades, the percentage of using this technique has increased in many infertility treatments centers in Europe, America, and other countries **(4, 5)**. The percentage of utilizing ICSI technique for factors other than male infertility was high in infertility centers. On the other hand, the concerns regarding its usage have increased since this technique is expensive and time consuming and can create damage to gametes **(6-8)**. Many studies have shown that using ICSI in non-male infertility did not improve the desired clinical results **(9-11)**. In non-severe male infertility, like mild oligospermia, the outcome of fertilization and pregnancy after ICSI is unclear compared to conventional in vitro fertilization (IVF) methods. Randomized studies conducted on sibling oocytes have demonstrated contradictory results **(12, 13)**.

Furthermore, other studies have proven that there is no difference between ICSI and conventional IVF methods in embryo quality, implantation, pregnancy, or live birth rate **(14, 15)**.

However, a variety of indicators, including maternal age, unexplained infertility, number of oocytes and their quality, and previously failed fertilization, affect the ICSI success rate and greatly influence the chances of successful fertilization and embryo formation **(16)**. These indications have been extensively studied and formed international guidelines so that treatment centers can implement standard treatment methods **(17)**. Despite the increase in the application of this technique in infertility treatment centers, there are still controversies about the using this technique, and little is known about the benefits of applying ICSI in the treatment of non-male factor infertility. Given the status quo, evaluating the factors affecting ICSI success among infertile people in medical centers is needed to obtain definitive results. The current study aims to investigate a randomized controlled clinical trial, compare the results of ICSI in infertile couples, and test possible differences between the results. In other words, this study aims to compare several parameters, including age, hormonal variations, changes in endometrial thickness, and the number of embryos formed as a result of ICSI in couples who referred to Motazedi Treatment Center in Kermanshah, Iran, for treatment.

Materials and Methods

In this retrospective study, 261 cases who had a successful ICSI at Motazedi Hospital in Kermanshah, Iran, from 2011 to 2017, were examined in terms of age, hormonal variations, duration of marriage and infertility, type of infertility, endometrial thickness, and the number of embryos formed. This study was ethically approved by the Ethics Committee of the Kermanshah University of Medical Sciences, Iran. The records of patients referred to this infertility center were collected via the electronic systems available. The patients' data, such as age, gender, body mass index (BMI), and the number of antral follicles, laboratory test results including levels of anti-müllerian hormone (AMH), testosterone (TES), thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), prolactin (PRO), luteinizing hormone (LH), and dehydroepiandrosterone sulfate (DHEA-S), and details of their husbands' semen analyses, including sperm count, motility, and morphology, were collected from their records.

Eligibility Criteria

Eligible couples referred to the infertility center from 2011 to 2017 were selected for screening.

Inclusion Criteria

Inclusion criteria included

- Infertile couples who dealt with infertility for at least a year and referred to the infertility center to be treated with ICSI.
- Infertile couples who planned for the first or second IVF/ICSI cycle.
- Men who did not have severe infertility.
- Women treated with gonadotrophin-releasing hormone agonist (GnRH-a) or gonadotrophin-releasing hormone antagonist (GnRH-ant).
- Patients who did not have a history of obstetric surgery.

Exclusion Criteria

Exclusion criteria were

- Infertile couples whose data were incomplete and did not have a successful ICSI.
- Infertile couples with underlying diseases, like diabetes, hypertension, anemia, liver and kidney diseases, and various cancers.
- Infertile couples who took a variety of medications other than fertility drugs.
- Women without oocytes.
- Men without sperm.

Stimulation Protocol and Embryological Methods

Ovarian stimulation with GnRH-a was performed on the 21stday of the menstrual cycle before super-ovulation and the third day of the next menstrual cycle after injecting human menopausal gonadotropin (HMG) (150-225 IU). The patients were given 1000 units of Human chorionic gonadotropin (HCG) when at least two follicles reached 18 mm in diameter. The oocyte retrieval was done 36-39 hours later under light anesthesia using vaginal ultrasound. For the ICSI cycle, the surrounding cumulus was removed to assess oocyte maturation two hours after the recovery. Oocytes in metaphase stage II were injected with the husband's sperm at least an hour after the removal of cumulus cells. Oocytes that were not fully mature were discarded. The fertilization was evaluated 16-18 hours after the inoculation.

Embryo Quality

Cleaved embryos were considered high quality embryos (Grade I or II) when they were observed with four cells on the second day and seven to eight cells on the third day, with less than 20% fragmentations and without any morphological abnormalities. In this clinic, the number of embryos transferred to mothers depended on the maternal age such that two embryos were transferred to mothers under 35 years of age, and three embryos were transferred to mothers over 35 years old. However, if a patient had low or poor-quality embryos, the embryos were transferred on the second day of the luteal phase. The ratio of good embryos was calculated by dividing the number of good embryos by the number of cleaved embryos. In order to reduce the effect of the minimum number of embryos, only four cleaved embryos were used in the data analysis.

Hormonal Markers

Serum concentrations of AMH, TES, TSH, FSH, PRO, LH, and DHEA-S were measured by the relevant kits in the laboratory of the same infertility center. According to the measurements made for different hormones, various groupings were considered for them.

Thus, AMH, TES, TSH, FSH, PRO, LH, and DHEA-S were divided into groups of six, five, five, four, nine, five, and three, respectively.

Statistical Analysis

Data analyses were carried out by SPSS 22 (SPSS Inc., Chicago, IL., USA). Data values were reported as M±SEM. The chi-square test was used to analyze the associations between nominal qualitative variables, and the Spearman correlation coefficient was used to rank quantitative or qualitative variables. P-values less than 0.5 were considered significant.

Results

The Couples' Age

The patients underwent ICSI between the ages of 21 to 60 years. To better investigate the association between the couples' age and ICSI success, the female population was divided into five groups, and the male population was classified into four groups (Figure 1) (Tables 1, 2). The highest success rate was observed in men aged 31-40 years and a mean age of 34.64±5.77 (58.2%), and women aged 21-30 years and a mean age of 25.47±5.78 (55.8%). The results indicated a statistically significant difference between the couples' age and pregnancy rates.

Table 1. The men's age range and the ICSI success rate

Men's age		Frequency	Percentage distribution	P-value
Range	21.00 - 30.00	64	25.5	
	31.00 - 40.00	146	58.2	
	41.00 - 50.00	39	15.5	
	51.00 - 60.00	2	0.8	
	Total	**251**	**100.0**	**0.01**

Table 2. The women's age range and the ICSI success rate

Women's age		Frequency	Percentage distribution	P-value
Range	<= 20.00	3	1.2	
	21.00 - 30.00	140	55.8	
	31.00 - 40.00	92	36.7	
	41.00 - 50.00	15	6.0	
	51.00 - 60.00	1	0.4	
	Total	**251**	**100.0**	**0.01**

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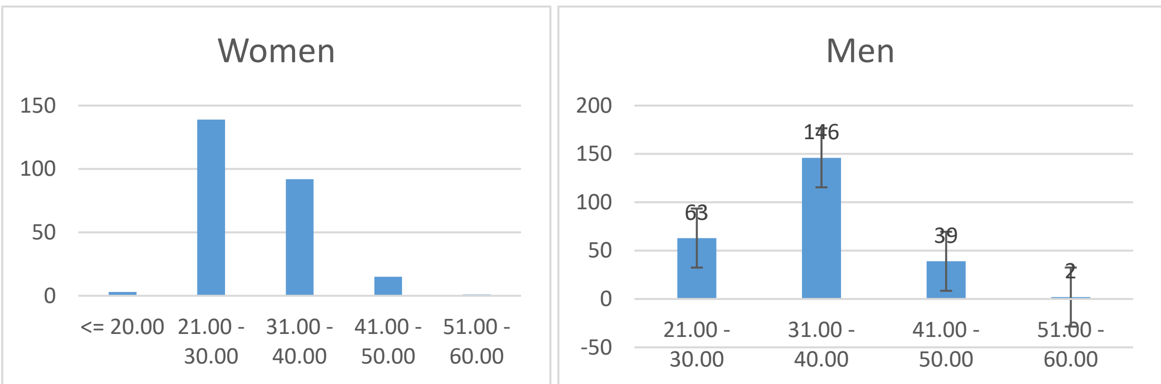

Figure 1. The age range of these men and women and its association with the ICSI success rate. The highest success rate was observed in men aged 31-40 years and a mean age of 34.64±5.77 (58.2%), and women aged 21-30 years and a mean age of 25.47±5.78 (55.8%).

Duration of Infertility

The data collected from the infertile couples referred to this infertility center during the mentioned period demonstrated that their maximum infertility duration was 25 years. As shown in Table 3 and Figure 2, the couples were divided into five groups considering the duration of infertility. Among these groups, the highest success rate was reported in infertility of fewer than five years (51.8%). However, a statistically significant difference was observed between the duration of infertility and ICSI success.

Table 3. Examining the duration of infertility and the ICSI success rate

Duration of infertility (y)		Frequency	Percentage distribution	P-value
Range	<= 5.00	130	51.8	
	5.01 - 10.00	89	35.5	
	10.01 - 15.00	21	8.4	
	15.01 - 20.00	8	3.2	
	20.01 - 25.00	3	1.2	
	Total	**251**	**100.0**	**0.001**

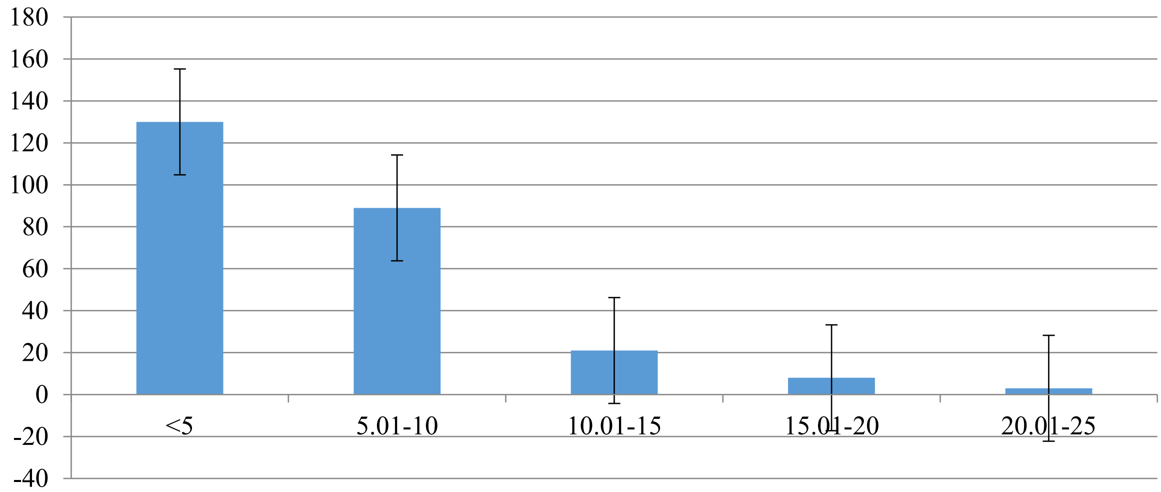

Figure 2. Examining the duration of infertility and its association with ICSI success rate. Among these groups, the highest success rate was reported in infertility of fewer than five years (51.8%).

Endometrial Thickness

In the present study, all the patients' endometrial thicknesses were normal and higher than 4 mm.

The Number of Formed Embryos

To evaluate the number of embryos formed and ICSI success, the Smirnov-Kolmogorov test was used to examine the data. As can be seen in Table 4 and Figure 3, the number of embryos formed for each patient was placed in its related group, and the number of groups associated with this parameter was five. In this study, the success rate in the number of embryos formed was three, with a 68% success. The ICSI result showed a statistically significant relationship.

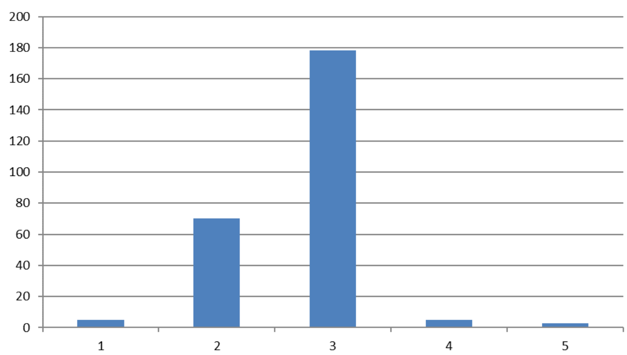

Figure 3. Evaluating the number of embryos formed

Hormonal Variations

In the current study, hormonal variations of AMH, TES, TSH, FSH, PRO, LH, and DHEA-S were examined.

AMH Variations

AMH was tested in the patients and recorded as M±SEM. The results of which are shown in Table 5. As can be seen in this Table, the maximum and minimum serum AMH levels in the patients were reported to be 11<AMH<20 ng/mL. To best categorize these levels, they were divided into five groups. Most of the patients had serum AMH levels in the range of 1.01-5 ng/mL, with a 55.6% distribution. The data indicated no statistical difference between the serum AMH levels and the ICSI success rate.

Table 4. **The number of embryos formed**

Number of embryos formed		Frequency	Percentage distribution	P-value
Range	1	5	0.38	
	2	70	29.88	
	3	178	68.19	
	4	5	1.14	
	5	3	0.38	
	Total	**261**	**100**	**0.0001**

Table 5. **The AMH variations**

AMH		Frequency	Percentage distribution	P-value
Level	0.11 - 1.00	6	2.8	
	1.01 - 5.00	119	55.6	
	5.01 - 10.00	18	8.4	
	10.01 - 15.00	53	24.7	
	15.01 - 20.00	18	8.4	
	Total	**214**	**100**	**0.32**

TES Variations

The maximum and minimum serum TES levels in the patients were reported to be 0<TES<250 nmol/L. These serum TES levels were divided into five groups. As shown in Table 6, most of the patients had serum TES levels in the range of 0-50 nmol/L, with a 53% distribution. The data showed a statistical difference between the serum TES levels and the ICSI success rate.

Table 6. **The TES variations**

TES		Frequency	Percentage distribution	P-value
Level	0 -50.00	127	53	
	50.01 -100.00	72	30	
	100.01 -150.00	14	5.8	
	150.01 - 200.00	18	7.5	
	200.01 - 250.00	8	3.3	
	Total	**240**	**100**	**0.01**

TSH Variations

The maximum serum TSH level in the patients was 15 µU/mL. These serum TSH levels were classified in five groups. As noted in Table 7, most of the patients had serum TSH levels ranging from 1.01 to 5 µU/mL, with a distribution of 81.6%. The data indicated a statistical difference between these serum TSH levels and the ICSI success rate.

FSH Variations

The serum FSH levels in the patients were reported to be 0<FSH<20 IU/L. These FSH levels were categorized into four groups for a more accurate assessment. As demonstrated in Table 8, most of the patients had serum FSH levels in the range of 5.01-10 IU/L, with a distribution of 58.9%. The data showed a statistical difference between the serum FSH levels and the ICSI success rate.

PRO Variations

The serum PRO levels in the patients were reported as 0<PRO<45 ng/mL. These PRO levels were categorized into nine groups for a more accurate evaluation. As shown in Table 9, most of the patients had serum PRO levels ranging from 5 to 10 ng/mL, with a 24% distribution. The data demonstrated a statistical difference between the serum PRO levels and the ICSI success rate.

Table 7. **The TSH variations**

TSH		Frequency	Percentage distribution	P-value
Level	<= 0.10	12	4.7	
	0.11 - 1.00	14	5.5	
	1.01 - 5.00	205	81.6	
	5.01 - 10.00	14	5.5	
	10.01 - 15.00	6	2.3	
	Total	**251**	**100**	**0.02**

Table 8. **The FSH variations**

FSH		Frequency	Percentage distribution	P-value
Level	0 - 5.00	61	23.6	
	5.01 - 10.00	152	58.9	
	10.01 - 15.00	35	13.5	
	15.01 - 20.00	10	3.8	
	Total	**258**	**100**	**0.01**

Table 9. **The PRO variations**

PRO		Frequency	Percentage distribution	P-value
Level	0 – 5	20	8.16	
	5.01-10	59	24	
	10.01 - 15.00	44	17.9	
	15.01 - 20.00	54	22	
	20.01 - 25.00	34	13.8	
	25.01 - 30.00	14	5.7	
	30.01 - 35.00	10	4	
	35.01 - 40.00	4	1.63	
	40.01 -45.00	6	2.44	
	Total	**245**	**100**	**0.01**

LH Variations

The serum LH levels in the patients were reported to be 11<LH<20 IU/L. These LH levels were categorized into five groups for a more accurate evaluation. As demonstrated in Table 10, most of the patients had serum LH levels in the range of 1.01-5 IU/L, with a distribution of 45.8%. The data showed a statistical difference between the serum LH levels and the ICSI success rate.

DHEA-S Variations

The serum DHEA-S levels in these patients were reported as 11<DHEA-S<20 ng/mL. The DHEA-S levels were categorized into three groups for a more accurate evaluation. As shown in Table 11, most of the patients had serum DHEA-S levels in the range of 1.01-4 ng/mL, with a 68% distribution. The data indicated a statistical difference between the serum levels of DHEA-S and the ICSI success rate.

Table 10. The LH variations

LH		Frequency	Percentage distribution	P-value
Level	0.11 - 1.00	15	5.8	
	1.01 - 5.00	117	45.8	
	5.01 - 10.00	82	32	
	10.01 - 15.00	31	12	
	15.01 - 20.00	10	4	
	Total	**100**	**100**	**0.02**

Table 11. The DHEA-S variations

DHEA-S		Frequency	Percentage distribution	P-value
Level	.11 - 1.00	54	24.5	
	1.01 - 4.00	150	68	
	4.01 - 20.00	16	7	
	Total	**220**	**100**	۰,۰۱

Table 12. The results of hormonal tests of women referred to the infertility center

	Total	Abnormal	Normal
AMH	214	38 (82%)	176 (18%)
TES	240	46 (19.2%)	194 (80.8%)
FSH	258	51 (19.7%)	251 (80.3%)
TSH	251	28 (11%)	223 (88.84%)
Prolactin	245	57 (23%)	188 (78%)
LH	255	45 (18%)	210 (82%)
DHEA-S	220	16 (7%)	204 (93%)

Discussion

The results showed that ICSI-related indicators, including the variations in AMH, TES, TSH, FSH, PRO, LH, and DHEA-S, couples' age, duration of infertility, and the number of embryos formed, were effective in the ICSI success rate. In the present study, the data associated with these indicators were evaluated using the records of 261 patients referred to the infertility center over 6 years. These cases were selected based on the inclusion criteria with the utmost care and sensitivity so that the obtained data is reliable and usable for women of childbearing age. These data showed that 214 patients had serum AMH levels in the range of 11<AMH<20 ng/mL. Among these people, 119 patients (55.6%), had the AMH levels in the range of1.01-5 ng/mL, and 6 patients (2.8%) had the AMH levels in the range of 1-11 ng/mL. We hope that this study can be used by physicians as a reliable reference for the correct interpretation of the data.

Some studies have shown that AMH levels may be affected by race, ethnicity, and geographical location (18-20). However, in 2016, Du et al. stated that the maximum and minimum AMH levels in different age groups were 6.23 ng/mL and 1.09 ng/mL, respectively **(21)**. Moreover, other studies reported AMH levels in various age groups as 0.95±0.14 - 4.94±0.17, 3.24±123 - 3.91±1.37, and 0.46±0.59- 2.5±2.0 ng/mL **(22-24)**. This is while the difference in AMH levels may be mainly due to the sample size in the studies, women's health status, economic and nutritional status, and the like. Additionally, menopausal age has been reported differently in various parts of the world **(25, 26)**, which may indicate differences in AMH levels at various ages. This is while many efforts have been made to identify patients based on a good prognosis of AMH levels **(27, 28)**. Our study has concluded that AMH can be a reliable indicator for predicting success in ICSI in the Iranian society, with the range of 1.01-5 ng/mL. Another parameter evaluated in this study was the determination of FSH and LH levels in the patients. As shown in Tables 7 and 9, the maximum and minimum serum levels of FSH and LH were reported to be 0<FSH<20 IU/L and 11<LH<20 IU/L, respectively. Out of these patients, 258 and 255 individuals had serum levels of FSH and LH, respectively, of which 152 (58.9%) had the serum FSH levels in the range of 5.01-10 IU/L, and 10 patients (3.8%) had the serum FSH levels in the range of 15.01-20 IU/L. Moreover, serum LH levels ranged 1.01-5 IU/L in the majority of patients (117 patients or 45.8%), and 10 patients (4%), had serum LH levels in the range of 15.01-20 IU/L. A study conducted by Cochrane found that changes in progestogens or estrogens in GnRH antagonist-treated women affected assisted reproductive technology (ART) outcomes (29). In a 2016 study conducted on healthy women in the reproductive age range, their FSH and LH levels were 6.30+1.95<FSH<11.79+12.43 IU/L and 4.17+2.07 <LH<5.83+5.76 IU/L, respectively, which are in line with the ranges of our study (21). In a 2005 study done by Bjercke *et al.*, **(30)** the levels of FSH and LH in women with successful ICSI were 3.5±1.6 IU/L and 1.9±1.2 (IU/L), respectively. This is consistent with our results on the levels of FSH and LH. Furthermore, in a 2015 study conducted by Kolibianakis on women treated successfully with Corifollitropin alfa and beta using ICSI, the authors reported FSH and LH levels of approximately 10 and 5 IU/L, respectively **(31)**, which are consistent with the results of this study. Additionally, in 2017, Tannuset al. reported that FSH and LH levels were almost 7 and 4.5 IU/L in women aged 35-40 years old treated with GnRH-a and HCG, respectively **(32)**.

Regarding the results of TES evaluation, 214 patients had testosterone levels of 0<TES<250 nmol/L. Among these patients, serum TES levels ranged 0-50 nmol/L in127 individuals (53%) and 200.1-250 nmol/L in 8 individuals (3.3%). The level of this hormone was reported in some studies in the two groups treated with and without oral contraceptives with mean ranges of 1.15<TES<91 nmol/L and 1.04<TES<1.11 nmol/L **(33)**, which, in this study, considering our wide range of data, was in the range of 0-50 nmol/L. This range is consistent with our results. In other studies, the levels of this hormone in patients with polycystic ovary syndrome and primary ovarian insufficiency were reported 1.2±1.8 and 0.6±0.8 nmol/L, respectively **(34)**, which is in the range of our study. In another study conducted on healthy women in the reproductive age range of 20-55 years, the maximum and minimum TES levels in different groups ranged from 15.24±33.50 nmol/L and 13.72±18.97 nmol/L **(21)**, which are consistent with the range of our study, with most patients being in the 0-50.00 nmol/L range. The serum TSH levels were reported in the 1<TSH<15 µU/mL range in 251 patients. About 205 individuals (81.6%) had the serum TSH levels in the 1.01-5 (µU/mL) range, and 6 individuals (2.3%) had the serum TSH levels in the 10.01- 15 µU/mL range. Many studies have shown that serum TSH levels do not change much during pregnancy, ranging 3.38-35 µU/mL **(35-37)**. This range is in line with the majority of the patients' serum TSH levels, ranging 1.01-5.00 µU/mL.

In the current study, serum PRO levels of 245 patients were in the range of 0<PRO<45 ng/mL of whom about 59 patients (24%) had 5.01-10 ng/mL PRO in their serum, and 4 people (1.63%) had the serum PRO levels in the range of 35.01-40 ng/mL. However, some studies have demonstrated that the rate of this hormone was 14.9±17.5 ng/mL (34), which is consistent with the range of our study. This is while in some other studies, they reported that the levels of this hormone in pregnant women were 36<PRO<372 ng/mL **(35, 38)**, which are less consistent with the results of our study. The serum levels of DHEA-S were reported in our study. In this regard, 220 patients were in the range of 11<DHEA-S<20 ng/mL. Among these, 150 patients (68%) had serum DHEA-S levels in the range of 1.01-4.00 ng/mL, and 16 patients (7%) had serum DHEA-S levels in the range of 4.01-20.00 ng/mL. In contrast, other studies have reported that the level of this hormone was 102±207 ng/mL **(34)**, which is not in line with the range of our study and is not consistent with our data. In the current study, the number of embryos formed in 261 patients was examined, and the range of embryos formed in them was reported as 1<the number of embryos<5. Of these, the highest number of patients, i.e. 178 (68.19%) had three fetuses. Most studies have shown that most of the patients who underwent ICSI were in this range **(33, 39, 40)**.

Conclusion

Based on the results of the present study, parameters, such as variations in reproductive hormones, number of embryos, couples' age, and duration of infertility, can affect the success rate of the ICSI technique in infertile couples. The results of this study can be considered as a reliable reference for the correct interpretation of the data in the successful implementation of the ICSI technique.

Acknowledgments

We would like to thank Miss Farzaneh Esmaeili for her excellent help in collecting data.

Conflict of Interest

The authors declared no conflict of interest.

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How to Cite This Article:

Bakhtiari M, Babaei T, Safarpour M, Esmaeili M, Esmaeili M, Asgari R et al . Investigating the Factors Affecting the ICSI (microinjection) Success in Infertile People Referred to an Infertility Treatment Center in Western Iran from 2011 to 2017. J Obstet Gynecol Cancer Res. 2020; 5 (3) :115-125