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Evaluation of factors predicting pregnancy by comparing successful IVF cycles with previous failed ones of the same patients in the same year

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Abstract

Aim: In this study, we aimed to examine the factors predicting pregnancy by comparing successful in vitro fertilization/ intracytoplasmic sperm injection (IVF)/(ICSI) fresh cycles with previous failed ones of the same patients in the same year.

Materials and Methods: The study consisted of two groups, failed (n:283) and successful IVF fresh cycles (n:283) that applied one after another within the same year, thusly each woman acted under her own control. IVF treatment indications, antral follicle count, ovulation induction protocol type, initial and total gonadotropin dose, progesterone, and estradiol (E2) levels on the trigger day, the number of oocytes retrieved and mature oocytes, number of Grade 1, Grade 2, Grade 3 embryo, day of embryo transfer (ET), endometrial thickness on trigger and oocyte pick-up (OPU) day, embryo-fundus distance and beta-human chorionic gonadotropin (B-hCG) levels on the 10th day after the ET were measured. The same luteal phase support was administered in both groups.

Results: Totally 566 cycles and 283 women were included in the study. There was a significant difference in luteinizing hormone (LH) levels on OPU day and number of grade 1 ET between the two groups, LH levels on OPU day and number of grade 1 ET were higher in successful IVF fresh cycles group ($p<0.05$).

Conclusion: Low serum LH levels on OPU day was associated with decreased pregnancy results. Increased IVF success was observed in grade 1 ET cycles.

Introduction

The multi-step IVF/ICSI procedures (i.e., controlled ovarian stimulation (COS), oocyte retrieval, oocyte fertilization and ET), complicate the process of achieving a pregnancy. IVF ongoing pregnancy rates change between 8.6 and 46.2% per cycle [1,2].

The most common reasons for treatment discontinuation after failed IVF cycles in Turkey were: financial problem (41%) and hopeless (22.9%) [3]. Considering these variables, success rates and costs of IVF, the factors affecting the pregnancy have become essential problems to be solved. On top of these, psychological problems such as depression and anxiety are witnessed in patients exposed to failed cycles [4]. Although these factors are not fully comprehended, it is known that a fair number of independent variables do contribute to the very processes. Prognostic variables are as follows: maternal age, embryo quality, duration of infertility, ovulation induction protocol, indications of IVF and endometrial pattern [5-7].

The most critical factor impacting embryo quality enabling IVF success is maternal age. Indeed, it is a fact that the risk of aneuploidy increases as maternal age increases. Aneuploidy is not the only age-related adverse effect, reduced oocyte yield, smaller embryo cohorts and impaired endometrial thickness are amongst the other disadvantages seen in advanced age. In addition, it was found that embryo-endometrium asynchronization was higher in advanced maternal age, likely 68.1% in women >35 years old [8,9].

Taking into account that maternal age is the key factor that comes into play in pregnancy success, in the current study, we excluded the age factor through selecting women

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with two IVF-ET fresh cycles applied in the same year one another where one was failed and the other was successful.

To this end, in the present study, we intended to delve into the factors influencing the pregnancy success by examining the failed and successful IVF/ICSI fresh cycles of the same patients who applied to the IVF clinic within the same year.

Materials and Methods

Study design and study population

This was a retrospective study conducted at the IVF clinic of Etlik Zübeyde Hanım Women's Health Training and Research Hospital of Ankara, Turkey. All the recorded data pertaining to a total of 566 cycles and 283 women who applied to the IVF clinic between 2010-2022 were analyzed. The protocol was approved by the Local Ethical Committee (06. 22.2022/ 90). The study consisted of two groups, women with failed IVF/ICSI fresh cycles (n:283) and successful IVF/ICSI fresh cycles (n:283) that applied one after the other in the same year to the hospital, thereupon it would be fair to state that each woman acted under her own control.

The history of chronic diseases, patients who received mild or natural cycle protocols, freeze-thawed cycles, the cases with more than one embryo transfer, multiple pregnancies, the use of preimplantation genetic diagnosis, oocyte and embryo recipients were all excluded.

IVF treatment indications (male factor, DOR and others), antral follicle count, ovulation induction protocol type, initial and total gonadotropin dose, progesterone, and E2 levels on the trigger day, the number of oocytes retrieved as well as the number of mature oocytes, the number of Grade 1, Grade 2, Grade 3 embryo [10], day of ET, endometrial thickness on the trigger and OPU day, embryo-fundus distance and B-hCG levels on the 10th day after the ET were all studied.

Hormone levels were analyzed in our laboratory using the IMMULITE 2000 Immunoassay System (Siemens, Berlin, Germany). The detection limits were detected as 0.1-200 mIU/mL for LH, 5-3000 pg/mL for E2, 0.1-10.000 mIU/mL for B hCG, 0.05-60 ng/mL for progesterone. The inter-assay and intra-assay coefficients of variation were figured out as 1.4%˜2.71% for LH, 1.54%˜2.01% for E2, 2.31%˜3.96% for B hCG, 2.1%˜2.61% for progesterone, respectively. The same luteal support was administered in both groups. The primary outcomes of this study were to compare embryo quality, total antral follicle count and type of ovulation induction protocol between cycles of the patients.

COS protocol

Microdose flares up and long luteal protocols were used for patients with diminished ovarian reserve (DOR), whereas for the other indications antagonist and long luteal protocols were applied.

COS was initiated with gonadotropin (recombinant follicle-stimulating hormone (FSH), Gonal-F® Merck, Germany) or human menopausal gonadotropin (hMG), Menopur®, Ferring Pharmaceuticals, Germany) between 150 to 300 IU daily. Gonadotropin releasing hormon (GnRH) antagonist (141 Cetrotide®, Merck, Germany) and GnRH agonist (Gonapeptyl®, Ferring Pharmaceuticals, Germany) were used for preventing LH surge. Dose of ovarian stimulation protocols were determined according to patient characteristics or responses during previous cycles. In all patients hCG trigger (Ovitrelle®, Merck, Germany) was used when at least three follicles were over 17-18 mm in diameter. OPU was performed 35-36 hours later, via transvaginal aspiration under ultrasound guidance. Oocytes were incubated as cumulus complex at 37 0C 5% CO2 and 5% O2 for two hours before denudation for ICSI. Denudation was complated by both hyaluronidase (Hyase 10X, Vitrolife, Sweeden) and mechanical technique. Denuded oocytes were morphologically appraised as described by the guidelines of the European Society of Human Reproduction and Embryology. The ICSI was perfomed just after the denudation. Fertilisation was confirmed by the presence of two pronuclei 18-20 hours after the ICSI. One step culture protocol (G-TL, Vitrolife, Sweeden) used for the embryo culture under oil at 37 0C 5% CO2 and 5% O2 incubator (Miri, ESCO Medical, Turkey) conditions. The embriyos were transferred to the uterus on day 3 or day 5 [10]. Luteal phase support was provided with intramuscular (100 mg daily) progesteron (Progestan®, Koçak Pharma, Turkey) and oral (10 mg 3 times a day) dydrogesteron (Duphaston®, Abbott, Turkey) until 12 weeks of gestational age in all patients.

Statistical analysis

This study performed all the statistical analyses using IBM The Statistical Package for Social Sciences (SPSS) Version 20.0 (IBM Corp., Armonk, NY). For descriptive statistics, mean and standard deviation (X ± SD), number (n) percent (%) representation was used and the non-parametric variables, the "Wilcoxon" test (Z-table value) method was utilized with a view to comparing the values of two dependent groups. All analyzes were evaluated within the 95% confidence interval. P value under 0.05 was considered as "statistically significant".

Results

Totally 566 cycles and 283 women were enrolled into the study. The mean age of women were 32.92±5.41 years. The distribution of IVF treatment indications are given in Table 1.

The comparisons between groups did not reveal any significant differences in ovulation induction protocol and induction type (p = 0.751, p = 0.435 respectively) (Table 2).

There were no significant differences in total antral follicle count, initial and total gonadotropin dose, E2 level-progesterone level-endometrial thickness on the trigger day and follicle count > 17 mm between the two groups (p=0.929, p=0.487, p=0.917, p=0.190, p=0.217, p=0.760 and p=0.694 respectively) (Table 3).

We realized no significant differences in E2 level- progesterone level-endometrial thickness on the OPU day and ET day, total oocyte retrieved, the number of Grade 2 and Grade 3 embryo, the day of embryo transfer, the distance of embryo-fundus between the two groups (p=0.425,

Table 1. Distribution of IVF treatment indications.

Variables	Failed cycles		Pregnant cycles	
	n	%	n	%
Male factor				
No	182	64.3	183	64.7
Yes	101	35.7	100	35.3
Tubal factor				
No	262	92.6	265	93.6
Yes	21	7.4	18	6.4
Diminished ovarian reserve				
No	25	21.9	28	24.8
Yes	89	78.1	85	75.2
Unexplained infertility				
No	167	59.0	172	60.8
Yes	116	41.0	111	39.2

Table 2. Comparison of ovulation induction protocol and induction type.

Variables	Failed cycles		Pregnant cycles		p
	n	%	n	%	
Ovulation Induction P.					
Micro dose flare up	19	7.8	17	6.7	
Long luteal	115	47.1	114	45.1	0.751
Antagonist	110	45.1	122	48.2	
Ovulation Induction T.					
recFSH + HMG	105	42.2	116	45.3	
recFSH	134	53.8	125	48.8	0.435
HMG	10	4.0	15	5.9	

P: protocol, T: type, rec FSH: recombinant follicle stimülating hormone, HMG: human menopausal gonadotropin.

p=0.621, p=0.763, p=0.965, p=0.310, p=0.401, 0.638, 0.521, 0.199, p=0.278 and p=0.401 respectively) (Table 3). There existed a significant difference in LH levels on the OPU day and number of grade 1 ET between the two groups, LH levels on OPU day and number grade 1 ET were higher in IVF cycles group (p=0.037, p=0.000 respectively) (Table 3).

Discussion

To the best of our knowledge, our study is the first to examine the factors predicting pregnancy by comparing successful in vitro fertilization/ intracytoplasmic sperm injection (IVF)/(ICSI) cycles with previous failed ones of the same patients in the same year. In this study, we observed that low serum LH levels on OPU day were ascribed to the decreased pregnancy success whilst grade 1 ET was linked to the increased pregnancy success. The most important factors for IVF failure were maternal age, obesity, immune factors and thrombophilias [11]. One remarkable feauture of our study was that each woman acted as her own control which leads to exclude these adverse factors. LH activity is not only crucial for the folliculogenesis but also plays a central role in the maintenance of corpus luteum, oocyte quality, embryo implantation, and synchronization between the embryo and the endometrium, thereby endometrial receptivity and pregnancy success [12-14]. Taking a closer look at the relevant line of the literature, it appears that the underlying mechanism of how low LH levels reduce the pregnancy success is not fully clear. The main hypothesis of association of low LH level with decreased pregnancy could be the theory of "favorable LH window". Each patient had a unique LH threshold and when excessive or inadequate LH level was occurred; the adverse effects in folliculogenesis, oocyte quality and quantity, endometrial receptivity and implantation were seen. Previous studies have shown that the LH threshold was between 0.5 and 1.2 mIU/mL [15-17]. It is controversial that high or low LH levels are associated with pregnancy success in the bulk of literature. In a study by Benmachiche, low LH levels on the day of trigger are with decreased ongoing pregnancy [18]. On the other hand, Depalo declared that positive pregnancy tests were seen more frequently in those with low LH levels on the day of trigger [19]. Relatively recent two independent studies unearthed that low LH levels seem to reduce mature oocyte counts [20,21]. In contrast, we did not determine a decreased mature oocyte counts in low LH level group which was in agreement with the study by Andersen et al. [22]. A number of studies have hitherto unveiled that low LH levels are connected with endometrial receptivity rather than oocyte quality and quantity [15,16]. In addition to these, Luo Y shared that low LH's detrimental effect is discovered merely in fresh ET cycles, not in freeze thaw ET cycles, in this direction LH levels gain a more important role on the endometrium and corpus luteum function [23]. Along similar lines, Garcia-Velasco JA discerned that diminishing implantation rate by profound pituitary suppression that occurred with low LH levels can be rescued with LH add-back strategy [24]. In the present study, it was identified that the rate of Grade 1 ET was higher in the successful cycle's group. Embryo quality mainly depends on gamete quality and the culture conditions [25]. In detail of maternal perspective, oocyte quality is related to oogenesis which begins in fetal period and ends during final oocyte maturation and accomplishment of second meiotic division. LH plays a part during oocyte competence, maturation, and meiosis. The LH signal declines cyclic nucleotide (cAMP and cGMP) levels in the preovulatory follicle. Thence, reduced cyclic nucleotide levels in the oocyte activate the maturation promoting factor (MPF). The activated MPF completes meiosis I and meiosis II. Also, oocyte quality and even embryo quality can be improved by in vitro maturation (IVM) manipulation of LH signal [26]. The main weaknesses of this study were its retrospective design and we did not identify the paternal factors that affect the embryo quality.

Conclusion

Low serum LH levels on OPU day was held responsible for the decreased pregnancy success whereas a significant positive correlation was ascertained between the number of grade 1 ET and pregnancy. Studies of the more comprehensive sort are required to better corroborate the results of our study.

Table 3. Comparison of laboratory data and IVF cycle characteristics.

Variables	Failed cycles		Pregnant cycles		Statistical analysis* P value
	$\bar{x}$±SD	Median [Min-Max]	$\bar{x}$±SD	Median [Min-Max]	
Total antral follicle count	14.58±8.46	13.0 [2.0-44.0]	14.45±8.05	13.0 [2.0-36.0]	Z=-0.089 p=0.929
Initiation doses of stimulating agents	233.39±85.56	225.0 [50.0-600.0]	235.61±85.51	225.0 [25.0-450.0]	Z=-0.695 p=0.487
Total doses of stimulating agents	2270.54±1007.63	2025.0 [525.0-6000.0]	2241.00±957.69	2025.0 [625.0-6750.0]	Z=-0.105 p=0.917
E2 levels on trigger day	2506.57±1568.04	2079.0 [181.0-10361.0]	2396.19±1578.19	2020.0 [312.0-9530.0]	Z=-1.310 p=0.190
Progesteron levels on trigger day	0.97±0.74	0.8 [0.2-5.3]	0.86±0.53	0.8 [0.1-2.9]	Z=-1.235 p=0.217
Follicle count > 17 mm	3.33±2.64	3.0 [0.0-23.0]	3.29±2.40	3.0 [0.0-13.0]	Z=-0.393 p=0.694
Endometrial thickness on trigger day	10.04±1.95	10.0 [5.0-16.0]	10.09±1.94	10.0 [5.6-16.0]	Z=-0.306 p=0.760
E2 levels on OPU day	1671.15±1072.30	1365.3 [160.0-5990.0]	1620.98±1140.22	1375.2 [71.0-8497.4]	Z=-0.797 p=0.425
LH levels on OPU day	1.33±2.45	0.4 [0.0-23.1]	1.68±2.71	0.4 [0.0-22.5]	Z=-2.084 p=0.037
Progesteron levels on	7.46±6.22	5.9 [0.3-60.0]	7.04±4.51	5.9 [0.5-21.9]	Z=-0.494 p=0.621
Endometrial thickness on OPU day	9.78±2.11	9.6 [1.1-15.0]	9.86±2.21	10.0 [4.5-17.3]	Z=-0.301 p=0.763
Total oocyte retrieved	12.74±7.90	11.0 [1.0-43.0]	12.52±6.75	12.0 [2.0-34.0]	Z=-0.471 p=0.638
Grade 1 embryo	0.74±0.78	1.0 [0.0-3.0]	0.97±0.84	1.0 [0.0-3.0]	Z=-3.582 p=0.000
Grade 2 embryo	0.40±0.61	0.0 [0.0-3.0]	0.37±0.59	0.0 [0.0-3.0]	Z=-0.642 p=0.521
Grade 3 embryo	0.20±0.42	0.0 [0.0-2.0]	0.16±0.42	0.0 [0.0-2.0]	Z=-1.285 p=0.199
Day of embryo transfer	3.85±1.05	3.0 [2.0-6.0]	3.94±1.03	3.0 [2.0-6.0]	Z=-1.085 p=0.278
Progesteron levels on embryo transfer day	63.54±48.46	59.1 [1.8-282.0]	67.81±49.61	60.0 [0.1-271.9]	Z=-1.016 p=0.310
E2 levels on embryo transfer day	1482.08±1318.45	1165.5 [47.4-10566.0]	1483.55±1230.15	1277.0 [11.0-8171.8]	Z=-0.044 p=0.965
Endometrial thickness on embryo transfer day	10.37±2.45	10.0 [1.3-17.4]	10.22±2.08	10.0 [6.0-20.6]	Z=-0.839 p=0.401
Distance of embryo-fundus	9.11±3.97	9.3 [0.0-19.0]	9.57±4.02	9.3 [0.5-25.0]	Z=-0.840 p=0.401

*Wilcoxon test (Z-table value) statistics, LH: luteinizing hormone, E2: estradiol, OPU: oocyte pick up.

Ethical approval

This study was approved by the local ethics committee of Etlik Zübeyde Hanım Women's Health Training and Research Hospital (Date: 22.06.2022/2022/90).

Peer review

Externally peer-reviewed.

Authors' contributions

Conception/Design of Study- K.E., N.T.S., E.U.Ö., S.Ö., S.D., İ.K., Y.EÜ.; Visualization, Investigation, Supervision, Writing-review & editing-K.E., N.T.S., S.Ö.; Investigation, Conceptualization, Writing-review & editing- K.E., N.T.S., E.U.Ö.; Investigation, Conceptualization, Writing - original draft; Supervision- K.E., S.D., İ.K., YEÜ.

Conflict of interest

There is no conflict of interest among the authors.

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