



# 10-year Analysis of Assisted Reproductive Technique Outcomes at a University Hospital

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## Abstract

**Objective:** Our aim is to investigate the 10-year results of assisted reproductive technique (ART) cycles in our in vitro fertilization (IVF) clinic and to evaluate the effects of treatment protocols on ART outcomes.

**Methods:** Medical records of 2.795 IVF cycles of 1.964 infertile couples who were admitted to our IVF unit between 1998 and 2007 were evaluated retrospectively. A short or long protocol was performed with a gonadotropin-releasing hormone (GnRH)-analog and a GnRH-antagonist. Factors that may affect ART success or failure were evaluated and interpreted.

**Results:** The pregnancy rates per IVF cycle and per transfer were 21.07% and 24.4%, respectively. The highest pregnancy rate was attained when the cause of infertility was unexplained ( $p<0.001$ ). Treatment with the long protocol resulted in a higher pregnancy rate than treatment with either the short or the long the antagonist protocol ( $p<0.001$ ). The pregnancy rate was higher when the third-day step-down protocol was applied, compared with any of the fifth-day step-down, continuous-dose, and step-up protocols. The number of cycles, duration of infertility, age, follicle stimulating hormone level on the 3<sup>rd</sup> day of menstruation, E2 level measured on the day of human chorionic gonadotropin, total gonadotropin dose, total number of oocytes collected, and number of total embryos transferred affected the success rate of ART per cycle.

**Conclusion:** Unexplained infertility, use of the long protocol, application of the third-day step-down protocol, and application of intracytoplasmic sperm injection and luteal support are associated with higher pregnancy rates. The number of oocytes collected, number of embryos transferred, and the quality of the transferred embryos are important factors affecting pregnancy rates.

**Keywords:** Assisted reproductive technology, pregnancy, infertility

## INTRODUCTION

Infertility is defined as failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse. Infertility affects 10%-15% of couples in the reproductive age group (1). According to the findings of the Infertility Diagnosis and Treatment Group of the World Health Organization, the cause of infertility was attributed to the female in 37% of cases, the male in 8%, and the couple in 35%, while in 5% of cases, a cause was not found (unexplained infertility). Over the course of the study, 15% of the couples conceived (2). Female infertility

may be caused by tuboperitoneal factors (25%-30%), ovulatory dysfunction (15%-20%), or cervical and uterine factors (5%-10%) (2).

A variety of treatment modalities are offered to infertile couples. In vitro fertilization (IVF) and embryo transfer (ET) is one such technique. It is generally applied after other treatment methods, but in some cases, it may be the first option. In 1978, Steptoe and Edwards obtained a single preovulatory human oocyte by a natural cycle, conducted IVF and transferred the resulting embryo to the uterus in the blastocyst stage, resulting in a term delivery



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(3). Over the years, significant improvements have been made to the techniques of ovulatory stimulation, oocyte collection, oocyte and embryo culture, embryos cryopreservation, and ET (4). IVF is a controlled ovarian stimulation performed by external gonadotropin administration, oocyte collection under transvaginal ultrasonography (USG), fertilization in the laboratory, and transcervical transfer of embryos to the uterus.

The aim of this study was to investigate the results of assisted reproductive technique (ART) cycles in our IVF unit and to investigate the factors confounding ART outcomes.

## METHODS

In this study, 2,795 ART cycles performed in 1964 infertile couples were evaluated retrospectively in a 10-year period between January 1998 and December 2007. Indications for initiation of treatment of patients were classified as tubal factors, male factors, unexplained infertility, and ovarian failure. The study was conducted according to the Helsinki Declaration.

Patient histories were taken. Gynecological examinations were performed. Following gynecological examination, transvaginal USG was performed. Sperm analysis was performed prior to ART. In order to determine the ovarian reserve, venous blood was sampled on the third day of menstruation (early follicular phase); follicle stimulating hormone (FSH), luteinizing hormone (LH), and estradiol levels were measured using enzyme immunoassay kits. Hysterosalpingography was routinely performed prior to treatment.

A short or long protocol was performed with a gonadotropin-releasing hormone (GnRH)-analog and a GnRH-antagonist.

1. Long protocol: Administration of a GnRH-analog was started on the 21<sup>st</sup> day of the menstrual cycle, and gonadotropin was added on the second to third day of the next cycle and continued until the day of human chorionic gonadotropin (HCG) administration.

2. Short protocol: Administration of a GnRH-analog was started on the first day of the menstrual cycle, and gonadotropin was added on the second to third day of the cycle and was continued until the day of HCG administration.

On the third day of ovulation induction, age and body mass index was taken into consideration, and 225-300 IU gonadotropin was started. Follicular development was followed by daily E2 evaluations and by transvaginal USG. It was decided that the dose of E2 in the late follicular phase should be increased by 50% compared with the previous day, and follicles increased by 1-3 mm/day. When at least 2 follicles passed 16 millimeters, and the E2 per follicle exceeded 150 pg/dL, for the LH peak 5,000

or 10,000 IU HCG was administered. Follicle aspiration was performed 36 hours after HCG administration. The follicles were collected with the help of transvaginal USG. Each follicle of 11 millimeters and above was aspirated.

Follicle aspiration was performed with transvaginal ultrasound. The vaginal mucosa was cleaned with warm saline prior to the procedure. Follicular aspiration was performed under intravenous analgesia. Follicle aspiration was performed by entering the vaginal side walls and fornices with a single-lumen aspiration needle, which could be attached to the vaginal ultrasound by an adapter. After this examination, the sperm were made ready for insemination or intracytoplasmic sperm injection (ICSI) by swim-up or rotating according to their density.

As luteal-phase support, oral, vaginal, or muscular progesterone supplementation or muscular HCG was administered up to 12 weeks of gestation.

Pregnancy was determined by serum  $\beta$ -HCG measurements at 12 days after ET. In patients with  $\beta$ -HCG levels above 10 mIU/mL, measurements were monitored at 7-14-day intervals. Clinical pregnancy was defined as the presence of at least one gestational sac with fetal cardiac activity, detected by transvaginal USG.

Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, (number: 4467, date: 05.02.2008).

## Statistical Analysis

SPSS Statistics, Version 17 (SPSS Inc.; Chicago, IL, USA) was used for statistical analysis. In the biostatistical analysis of the study, variables were defined by the mean, standard deviation, frequency, and percentages, and the chi-square and Fisher exact tests were used to compare frequencies and percentages. The Mann-Whitney U test was used for non-parametric variables. In order to compare the mean of the variables with the normal distribution, a t-test was used in the two groups. Multivariate stepwise logistic regression analysis was used for regression analysis.  $P < 0.05$  was considered as statistically significant.

## RESULTS

A total of 1964 cases were evaluated. The total number of cycles was 2,795. A total of 2,405 ETs were performed. The total number of pregnancies was 589. The pregnancy rate per cycle was 21.07%. The rate of pregnancy per ET was 24.4%.

Cases of patients admitted to our inpatient clinic due to infertility were examined according to their etiological factors: 1,982 (70.9%) had a male factor, 487 (17.4%) had a tuboperitoneal factor, 282 (10.1%) had unexplained infertility, and 44 (1%) had

ovarian failure. In these groups, the rates of pregnancy per cycle were 22.5% in the male factor group (41.9% in ET), 18.6% in the tuboperitoneal factor group (21.5% in ET), 31.5% in the unexplained infertility group (35% in ET), and 10.7% (13.6% pregnancy rate per ET) in the ovarian failure group. In the group with unexplained infertility, the pregnancy rate per cycle was significantly higher than that in the other groups ( $p < 0.001$ ).

In 2.795 cycles, the GnRH-analog long protocol was used in 1.713 cycles, the GnRH-analog short protocol in 954 cycles and the GnRH-antagonist protocol in 128 cycles. The pregnancy rates per cycle in these groups were 24.3%, 16.0%, and 14.8%, respectively. In the GnRH-analog long protocol group, the pregnancy rate was found to be significantly higher than that in the other groups ( $p < 0.001$ ).

In 1.105 cycles, a step-down gonadotropin protocol was applied with dose reduction on the third day. A total of 281 (25.4%) pregnancies were obtained in this group. In 152 cycles, a stepwise decreasing gonadotropin protocol was applied, and dose reduction was applied on the fifth day. A total of 29 (19.1%) pregnancies were obtained in this group. In 1,390 cycles, a fixed-dose gonadotropin protocol was applied, and 258 (18.6%) pregnancies were obtained in this group. The step-up gonadotropin protocol was applied in 148 cycles. A total of 21 (14.2%) pregnancies were obtained in this group. The pregnancy rates per cycle in the third-day decreasing group were found to be significantly higher than those in the other group treatment protocols ( $p < 0.001$ ).

Out of 2.795 cycles, 1.051 (37.7%) cycles were treated with human menopausal gonadotropin (HMG), 1.566 (56%) with pure FSH, 113 (4%) with urinary FSH, and 65 (2.3%) with different drugs. The pregnancy rates per cycle in these groups were 21%, 21%, 23.8%, and 18.4%, respectively. There were no statistically significant differences in pregnancy rates according to these ratios ( $p > 0.05$ ).

A GnRH-analog was used in 2,656 (95.4%) cycles and GnRH-antagonists in 129 (4.6%) cycles. The pregnancy rate per cycle was 21.4% and 14.7%, respectively. Pregnancy rates among the GnRH-analog and GnRH-antagonist groups were significantly higher in the Leuprolid asetat group ( $p = 0.002$ ). In addition, when only GnRH-analog agents were compared, pregnancy rates were significantly higher in the Leuprolid asetat group ( $p = 0.002$ ).

Oral progesterone, intramuscular (IM) progesterone, HCG, and vaginal progesterone were used as luteal-phase support. Pregnancy rates per cycle were 24.1% in the group using oral progesterone, 26.7% in the IM progesterone group, 24.9% in the

vaginal progesterone group, 24.2% in the HCG group, and 24.1% in the HCG and progesterone group. There were no statistically significant differences between the groups ( $p > 0.05$ ).

No difference was found in LH, PRL, E2, and thyroid stimulating hormone levels between the clinically positive and negative patients. Infertility duration, age, and the FSH level on the third day of menstruation were higher in the group that did not achieve clinical pregnancy (Table 1).

The total number of ART cycles, serum E2 level on the day of HCG administration, total gonadotropin dose, total number of oocytes collected, number of oocytes used for ICSI, number of oocytes used for IVF, total number of oocytes fertilized for ICSI, total number of oocytes fertilized for IVF, number of total embryos transferred, number of grade 1 embryos transferred, number of grade 2 embryos transferred, number of metaphase 2 oocytes, and number of prophase 1 oocytes (germinal vesicle) were significantly higher in the group that achieved clinical pregnancy (Table 2).

In logistic regression analysis, the number of transferred embryos [ $p = 0.06$ , odds ratio (OR): 1.38] was found to be poorly correlated with pregnancy success, although not statistically significant; the relation between the use of the ICSI method ( $p = 0.03$ , OR: 1.13) and pregnancy success was found to be the most statistically significant, among all the variables tested (Table 3).

## DISCUSSION

The rate of pregnancy per ART cycle in our clinic was 21.1%. The rate of pregnancy per ET was 24.4%. These rates are close to those reported by the European Society of Human Reproduction and

	<b>Clinical pregnancy negative (n=1.375)</b>	<b>Clinical pregnancy positive (n=589)</b>	<b>p value</b>
Age	33.43±4.82	31.84±3.98	<b>&lt;0.001</b>
Infertility duration (years)	8.91±3.23	7.80±2.84	<b>&lt;0.001</b>
BMI (kg/m <sup>2</sup> )	25.70±4.87	24.17±4.66	<b>&lt;0.001</b>
FSH (mIU/mL)	7.98±3.43	6.75±3.23	<b>&lt;0.001</b>
LH (mIU/mL)	5.57±2.66	5.62±2.76	0.794
Estradiol (pg/mL)	54.87±12.54	49.66±12.98	0.227
Prolactin (ng/mL)	20.96±7.44	20.94±6.98	0.994
TSH (µIU/mL)	2.14±1.12	2.13±1.32	0.930
Total number of cycles	1 (1-2)	1 (1-2)	<b>0.028</b>
BMI: Body mass index, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, TSH: Thyroid stimulating hormone			

Embryology (ESHRE) for ET in 2005 (28.8%) (5). The society for ART (SART) reported in 2001 that the pregnancy rate per ET was 40% (6). The success rate of our clinic is consistent with the pregnancy rate reported by ESHRE, but lower than that reported by the SART.

	<b>Clinical pregnancy negative (n=2.206)</b>	<b>Clinical pregnancy positive (n=589)</b>	<b>p value</b>
Induction duration (days)	8.64±2.32	8.76±1.54	0.154
LH level at HCG day (mIU/mL)	3.46±1.55	3.84±1.67	0.550
Estradiol level at HCG day (pg/mL)	1853.37±846.44	2230.20±987.22	<b>&lt;0.001</b>
Progesterone level at HCG day (ng/mL)	1.22±0.66	0.94±0.55	0.563
Endometrial thickness at HCG day (mm)	10.42±2.67	10.52±2.33	0.794
Total number of oocytes	8 (5-11)	11 (7-15)	<b>&lt;0.001</b>
Number of fertilized oocytes	3 (4-6)	5 (3-7)	<b>&lt;0.001</b>
Number of transferred blastocysts	0 (0-1)	0 (0-1)	0.811
Number of metaphase 1 oocytes	0 (0-1)	0 (0-1)	0.862
Number of metaphase 2 oocytes	2 (1-3)	2 (1-4)	<b>&lt;0.001</b>
Number of prophase 1 (germinal vesicle) oocytes	0 (0-1)	0 (0-1)	0.065
Total number of transferred embryos	2 (1-4)	4 (2-6)	<b>&lt;0.001</b>
Number of transferred grade 1 embryos	1 (0-2)	2 (1-3)	<b>&lt;0.001</b>
Number of transferred grade 2 embryos	1 (0-2)	2 (1-3)	<b>&lt;0.001</b>
Number of transferred grade 3 embryos	0 (0-1)	0 (0-1)	0.294
Number of transferred grade 4 embryos	0 (0-1)	0 (0-1)	0.332
Number of postmature oocyte	3 (1-5)	5 (3-8)	<b>&lt;0.001</b>

LH: Luteinizing hormone, HCG: Human chorionic gonadotropin

A variety of reasons may account for this difference. These include differences in ovulation induction protocols, variability between patient groups, and different ET techniques of physicians working in our IVF unit. Pregnancy rates per cycle are different between patient groups and between different treatment protocols. Male factor infertility was the major etiological reason for patient admission to our IVF unit. This was followed by tuboperitoneal factors and unexplained infertility. When the pregnancy rates per cycle according to etiological factors were evaluated, we found that the highest success rate was with unexplained infertility [31.5% (pregnancy rate per ET 35%)] group. This was followed by male factor [22.5% (pregnancy rate 41%)] and tuboperitoneal factor [18.6% (21.5% per ET)]. Qublan et al. (7) reported 891 ART cycles with the following etiologies: Male factor (17.8%), endometriosis (17.6%), tubal factor (31.6%), and unexplained infertility (41.1%). They found that patients with unexplained infertility had higher pregnancy rates.

There are many reports suggesting that there is no difference in randomized studies comparing ART protocols. Similar

	<b>OR</b>	<b>p</b>
Number of transferred embryos	1.38 (0.98-1.94)	0.062
ICSI method	1.13 (1.01-1.26)	<b>0.031</b>
Number of fertilized oocytes	2.26 (1.04-4.87)	<b>0.045</b>
Age	1.34 (0.98-1.85)	0.061
Infertility duration	0.94 (0.79-1.12)	0.559
Induction duration	2.10 (0.96-4.56)	0.067
LH level at HCG day	0.79 (0.58-1.08)	0.143
Estradiol level at HCG day	1.02 (0.74-1.40)	0.904
Endometrial thickness at HCG day	1.35 (0.67-2.72)	0.392
Number of transferred blastocysts	0.39 (0.02-2.20)	0.287
Number of metaphase 1 oocytes	0.97 (0.93-1.01)	0.255
Number of metaphase 2 oocytes	0.77 (0.44-1.34)	0.398
Number of prophase 1 (germinal vesicle) oocytes	0.80 (0.28-2.30)	0.686
Total number of transferred embryos	1.43 (0.92-2.23)	0.105
Number of transferred grade 1 embryos	1.31 (0.90-1.90)	0.147
Number of transferred grade 2 embryos	1.33 (0.94-1.89)	0.109
Number of transferred grade 3 embryos	0.76 (0.33-1.75)	0.534
Number of transferred grade 4 embryos	0.26 (0.04-1.62)	0.152
Number of postmature oocyte	0.80 (0.35-1.83)	0.605

ICSI: Intracytoplasmic sperm injection, LH: Luteinizing hormone, HCG: Human chorionic gonadotropin, OR: Odds ratio

pregnancy rates have been found in clinical studies comparing standard long GnRH-analog protocols with GnRH-antagonist protocols (8,9). In a clinical study comparing the GnRH-antagonist protocol with the standard long GnRH-analog protocol, Firouzabadi et al. (10) did not find a clinically significant difference between these two groups. Al-Inany and Aboulghar (11) compared GnRH-analog long protocol cycles with GnRH-antagonist cycles and found that the GnRH-antagonist group had significantly lower pregnancy rates than the GnRH-analog group (10). However, studies have also found the GnRH-antagonist group to be more successful (11,12). In a meta-analysis comparing the GnRH-analog long agonist protocol with the short GnRH-analog protocol, higher pregnancy rates were obtained with the GnRH-analog long protocol (13). We used the long GnRH-analog protocol, the short GnRH-analog protocol, and the GnRH-antagonist protocols, and the long GnRH-analog protocol was more successful. We have used the short GnRH-analog and GnRH-antagonist protocols frequently in patients with poor responses. Therefore, lower success rates may have been achieved.

A meta-analysis comparing urinary FSH with purified FSH in the literature showed similar pregnancy rates (14). In a study comparing urinary FSH with purified FSH, no significant difference was found between the two groups in terms of the clinical pregnancy rate and mean number of collected oocytes (15). However, in the meta-analysis of a large number of different studies, purified FSH was associated with a higher pregnancy success rate than urinary FSH (16). In a study comparing urinary FSH with purified FSH, the clinical pregnancy rate per ET was higher in the purified FSH group (17). In a meta-analysis of five similar studies, urinary FSHs were found to be more successful (18). In a study comparing HMG with purified FSH, the live birth rate with HMG was significantly higher (19). These results show that there is no consensus on the superiority of any drug against another. In our retrospective study, we found that there was no difference in pregnancy rates between pure gonadotropins and urinary gonadotropins.

A wide variety of agents have been proposed in the literature for luteal-phase support after ET. These include progesterone, HCG, and GnRH analogs. In a meta-analysis of 30 randomized studies comparing the use of progesterone and the use of supplemental HCG in the literature, it was found that vaginal use of progesterone was associated with a higher implantation rate than oral use (20). It was determined that IM use of progesterone was associated with higher clinical pregnancy rates, compared with non-use, and no difference was found between oral and vaginal progesterone use. It was observed

that HCG administration was associated with higher clinical pregnancy rates, compared with those in the untreated group and the groups treated with oral progesterone, and there was no difference between vaginal and IM use of progesterone (20). The efficacy of HCG compared with progesterone showed similar results, but it has been suggested that HCG increases the ovarian hyperstimulation syndrome risk (21). It has been reported that IM progesterone use results in higher pregnancy success rates than vaginal progesterone use (20). In our study, we found that there were no differences between the various routes of administration of HCG and progesterone after ET.

Increased treatment cycles of ART appear to be associated with poor prognosis and increased maternal age (22,23). In a retrospective study by Martin-Johnston et al. (22) with 2.167 ART cycles, pregnancy rates decreased significantly after the second cycle, and even this decrease was more prominent after 3-5 cycles. They observed that the probability of success decreased with each new treatment cycle. The most significant reduction in pregnancy rates occurred after the third cycle. Therefore, patients who experience three failed cycles should be informed about other treatment options. In a study by Silberstein et al. (23), pregnancy rates and implantation rates decreased in second cycle and reach a plateau in 3-5 cycles. In our study, we found that increasing the number of cycles decreased the ART success and pregnancy rate per cycle.

The gonadotropin dose used is also an important factor affecting the pregnancy rate. We found that increasing the dose of gonadotropin negatively affects pregnancy outcomes. The response to gonadotropin treatment is an indication of the ability of the ovaries to develop follicles directly. In a retrospective study by Martin et al. (24), they found an inverse relationship between the gonadotropin dose and pregnancy rates. This study shows that success in ART cycles depends on the ability of the ovaries to develop an appropriate follicle. The high-dose gonadotropins used are indicative of the inability of the ovaries to develop follicles.

We showed that the number of oocytes collected, number of embryos transferred, and the quality of the transferred embryos are important factors affecting conception. We found that the number of collected oocytes, the number of embryos transferred, and the quality of the transferred embryos increased pregnancy rates. Kably Ambe et al. (25) found in their study that the number of collected oocytes, especially when this number was above 13, was associated with high pregnancy rates, in support of our findings.

## CONCLUSION

In summary, the number of ART cycles performed, duration of infertility, maternal age, FSH level on the third day of menstruation, E2 level measured on the day of HCG, total gonadotropin dose, total number of oocytes collected, number of oocytes used for ICSI, number of oocytes used for IVF, total number of oocytes fertilized by ICSI, total number of oocytes fertilized as a result of IVF, number of total embryos transferred, number of grade 1 embryos transferred, number of metaphase 2 oocytes, number of prophase 1 oocytes (germinal vesicles) affect the success of ART per cycle. The limitation of our study is its retrospective design. Future prospective randomized trials with large patient populations evaluating ART success are needed.

### Ethics

**Ethics Committee Approval:** Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, (number: 4467, date: 05.02.2008).

**Informed Consent:** Informed consent is not obtained due to the retrospective nature of this study.

**Peer-review:** Externally and internally peer-reviewed.

### Authorship Contributions

Concept: G.A., T.E., Design: G.A., Data Collection or Processing: G.A., Analysis or Interpretation: B.A.Ç., Literature Search: B.A.Ç., Writing: G.A., B.A.Ç.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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