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What are the factors affecting IVF success in women with hypogonadotropic hypogonadism?

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Abstract. – OBJECTIVE: This study aimed to investigate *in vitro* fertilization (IVF) outcomes in women with hypogonadotropic hypogonadism (HH) and unexplained infertility and investigate factors affecting the pregnancy rate among HH patients.

MATERIALS AND METHODS: This retrospective cohort study was conducted at Zeynep Kamil Maternity and Children's Diseases Training and Research Hospital, Turkey, a tertiary care referral center. The medical records of 143 women who underwent IVF treatment at this hospital between 2015 and 2020 were reviewed. Sixty-three had hypogonadotropic hypogonadism (HH) and 74 had unexplained infertility. Demographics, hormonal profile, IVF cycle characteristics, and pregnancy rates were recorded. The factors affecting the ongoing pregnancy rates were evaluated among HH patients.

RESULTS: Anti-Mullerian hormone (AMH) levels were lower among women with HH compared to those with unexplained infertility (1.64±1.2 *vs.* 3.0±2.13). IVF cycle characteristics and ongoing pregnancy outcome (20.28% *vs.* 22.97%) were similar between the groups; however, the total dose of human menopausal gonadotrophin (HMG) used (5127.74±1845.8 *vs.* 2035.71±1387.45) was higher in the HH group. Increased estradiol level (2596.35±1085 *vs.* 1869.9±1203.4), endometrial thickness (10.82±1.74 *vs.* 8.43±2.33), higher number of total oocytes retrieved (12.14±4.34 *vs.* 8.43±5.44) were correlated with higher ongoing pregnancy rates among the HH group.

CONCLUSIONS: IVF success rates were similar between the HH and unexplained infertility groups. Although AMH level was not a prognostic factor for IVF success, higher doses of HMG were needed to achieve pregnancy in the HH group. The factors affecting the ongoing pregnancy rates in the HH group were higher estradiol level, increased endometrial thickness, and a higher number of oocytes retrieved.

Key Words:
Hypogonadotropic hypogonadism, Infertility, ART, Pregnancy.

Introduction

Hypogonadotropic hypogonadism (HH) is defined as gonadal failure due to abnormal gonadotropin levels and characterized by ovulation disorders and estrogen deficiency[1]. HH patients require hormonal therapy to have regular cycles and sustain normal bone mass. Some scholars[2] report that ovulation was achieved in 95% of women with the administration of exogenous gonadotropins or pulsatile GnRH. Many women need *in vitro* fertilization (IVF) depending on their reproductive desires[1,3-4]. However, assessing the ovarian response is challenging because the usual predictors of ovarian reserve such as antral follicle count (AFC), basal serum Follicle-Stimulating Hormone (FSH) and estradiol levels could be unreliable in these patients[5,6]. Anti-Mullerian hormone (AMH) is a promising marker in predicting ovarian response[6]. The factors mainly affecting the IVF success and the most efficient method to achieve pregnancy are still unclear[4,7]. Also, the data for reproductive outcomes among women with HH undergoing IVF is limited.

This study aimed to investigate IVF outcomes in women with hypogonadotropic hypogonadism and unexplained infertility and investigate the factors affecting the pregnancy rate among women with hypogonadotropic hypogonadism.

Materials and Methods

This retrospective cohort study was conducted at Zeynep Kamil Maternity and Children's Diseases Training and Research Hospital, Turkey, a tertiary care referral center. The medical records of 143 women who underwent IVF treatment at this hospital between 2015 and 2020 were reviewed. Sixty-nine had hypogonadotropic hypogonadism

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Table I. Demographics and hormonal profile between the groups.

	Hypogonadotropic hypogonadism (n= 69)	Unexplained infertility (n= 74)	p
Age	31.1±4.66	31.93±4.95	0.423
FSH	0.80±1.00	6.1±2.67	***0.001****
E2	16.49±3.8	51.16±13.23	***0.000****
LH	0.47±0.74	4.48±2.3	***0.000****
PRL	12.0±8.87	16.28±7.21	0.651
TSH	2.17±1.4	2.08±1.32	0.370
AMH	1.64±1.2	3.0±2.13	***0.040****
AFC	7.04±3.63	10.61±4.44	0.104

*Independent samples *t*-test.

and 74 had unexplained infertility. The diagnosis of HH was based on the absence of withdrawal bleeding following progesterone challenge, and serum levels of FSH < 2.0 IU/L and LH< 1.0 IU/L. All HH patients had primary amenorrhea.

Blood samples to measure FSH, LH, and estradiol were obtained from a peripheral vein and serial transvaginal ultrasound examinations were performed to assess follicular response. Human menopausal gonadotropin (HMG) was used for controlled ovarian hyperstimulation in both groups. Oocytes were retrieved by transvaginal ultrasonography 36 hours after the oocyte maturation induction by 10,000 IU human chorionic gonadotropin (hCG).

The study was approved by the Local Ethics and Clinical Investigation Committee of Zeynep Kamil Maternity and Children's Diseases Training and Research Hospital and performed per the Helsinki Declaration. All analyses were performed using the SPSS v20 program (SPSS Inc, Chicago, IL, USA). Descriptive statistics were presented as mean ± standard deviation for normally distributed data. The relationship between the categorical variables was examined using the Chi-square test. The Kolmogorov-Smirnov test was used to assess the normality of data. The student's *t*-test was used to evaluate normally distributed data. The results were assessed with a confidence interval of 95%, and $p<0.05$ was considered statistically significant.

Results

The demographics and hormonal profile of the patients are presented in Table I. As expected, FSH, LH and estradiol levels are significantly different between the groups. AMH levels of HH patients are lower compared to those with unexplained infertility. IVF cycle characteristics and pregnancy success rates are presented in Table II. The total dose of HMG used in an IVF cycle was higher in the HH group, while IVF success rates were similar. Factors influencing IVF success in HH patients are presented in Table III.

Table II. IVF cycle characteristics and pregnancy rates.

	Hypogonadotropic hypogonadism (n= 69)	Unexplained infertility (n= 74)	p
HMG dose	5127.74±1845.8	2035.71±1387.45	***0.001****
E2 level before HCG	1966.14±1358.18	1679.72±947.91	0.06
End Line	9.71±2.13	10.63±7.39	0.110
Oocyte number	8.38±5.3	8.09±4.31	0.086
M2 number	5.10±3.9	5.84±3.25	0.224
Positive ß-HCG	20/69 (28.9%)	29/74 (39.18%)	0.758
Clinical pregnancy	15/69 (21.73%)	23/74 (31.08%)	0.803
Ongoing pregnancy	14/69 (20.28%)	17/74 (22.97%)	0.598

*Chi-square test.

Table III. Differences in parameters between ongoing pregnant and non-pregnant patients with hypogonadotropic hypogonadism.

	Ongoing pregnancy		p
	Yes (n=14)	No (n=37)	
A Age	29.14±3.43	31.16±4.46	0.162
FSH	1.11±1.2	0.85±1.06	0.167
E2	23.8±12.02	72.7±225.16	0.325
LH	0.446±0.48	0.64±0.9	0.814
PRL	13.52±12.72	12.95±8.64	0.520
TSH	2.54±1.97	2.13±1.10	0.889
AMH	2.19±1.85	1.52±0.99	0.669
AFC	7.57±3.05	7.48±3.8	0.890
HMG dose	4315.38±1266	5122.31±1921.3	0.058
E2 level before HCG	2596.35±1085	1869.9±1203.4	0.031*
End Line	10.82±1.74	8.43±2.33	0.042*
Oocyte number	12.14±4.34	8.43±5.44	0.015*
M2 number	7.57±4.05	5.59±3.57	0.132

*Mann-Whitney U test.

Discussion

In our study, AMH levels were significantly lower, and antral follicle count was insignificantly lower in HH patients compared to those with unexplained infertility. However, there was no difference regarding retrieved and MII oocytes between the groups. This finding demonstrates that lower AMH levels are not correlated with total and mature oocytes retrieved in HH patients. Chan et al[3] found that lower AMH levels in HH patients increased with HMG ovarian stimulation. This study[3] reported that serum AMH and AFC should not serve as prognostic markers of fertility in HH patients. Therefore, the AMH level is not a reliable factor for ovarian response in HH patients who underwent COH.

Our study revealed that IVF cycle characteristics and pregnancy outcome were similar between the groups; however, the total administered HMG dose differed. Similarly, Ulug et al[2] reported that there were no differences in terms of the pregnancy rates between the HH and tubal factor infertility groups. A meta-analysis[8] revealed that fertilization, implantation, and live birth rates were similar among HH patients compared to patients with infertility due to other causes.

We demonstrated that the factors affecting the ongoing pregnancy rates were estradiol level on the day of HCG trigger, endometrial thickness and total oocytes retrieved among HH patients undergoing IVF cycles. Higher estradiol level may be related to increased endometrial thickness and, as a consequence, better ongoing pregnancy rates. Also, the higher oocytes retrieved correlated with better ongoing pregnancy rates in women with HH. Banu et al[9] reported that age was not a prognostic factor in IVF success in women with HH, similar to our results.

Conclusions

IVF success rates were similar between patients with HH and unexplained infertility. Although AMH level was not a prognostic factor for IVF success, higher HMG doses were needed in the HH group. The factors affecting the ongoing pregnancy rates in the HH group were higher estradiol level, increased endometrial thickness and the higher oocytes retrieved.

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Conflict of Interests

The authors declare no conflict of interest.

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