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Low Antimullerian Hormone Levels Improve Fertility Outcome in Patients with Polycystic Ovary Syndrome

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ABSTRACT

***Background**: It was known thatpolycystic ovary syndrome (PCOS) patients have high AMH levels.The aim of this study is to show whether low AMH levels are associated with better clinical pregnancy rates in patients with PCOS.*

***Methods**: This retrospective study was performed on 443 patients with PCOS referred to BAU MedicalparkGoztepe Hospital IVF Clinic from January 2015 to October 2020. Participants ranged in age from 18 to 40, had their first two IVF trials, had performed frozen-thawed embryo transfer (FET) cycle at day 5.The diagnosis of PCOS was made using the Rotterdam criteria. Data related to patients' AMH were compared with each other, and based on the value, participants were divided into two groups: the first group was AMH≥7 (N = 49); The second group was AMH <7 (N = 394).*

***Results**: The pregnancy test was positive for 288 (65%) participants. Of these participants, 214 had livebirth, 71 had miscarriages, and 3 had stillbirths. There was no significant difference in age and BMI between the two groups. There were no significant differences between the two groups in the number of stimulation days, the total number of oocytes, and MII oocytes. The numbers of frozen embryos were higher in the AMH≥7 group (p = 0.005). The positive pregnancy results were significantly higher in the AMH<7 group than in the AMH≥ 7 group (P= 0.02). There was no significant difference in live birth, stillbirth, and miscarriage rates between the two groups.*

***Conclusion**: Low levels of circulating AMH are associated with better clinical pregnancy rates in patients with PCOS.*

Keywords
AMH, ICSI, PCOS.

Introduction

Anti-mullerian Hormone (AMH) is a member of the beta-transporter growth factor family and a glycoprotein dimer [1]. It is secreted from the primary follicles' granulosa cells, small antral, and preantral (4-6 mm) of the ovary and is not secreted from follicles larger than 8 mm [1,2]. The serum concentration of AMH depends on the number of small follicles and their ovarian reserves. AMH has recently been considered as a novel marker of ovarian function [2]. AMH secretion in polycystic ovaries or folliculogenesis failure leads to excessive accumulation of small antral and preantral follicles in these patients.

Polycystic Ovary Syndrome (PCOS) is the most prevalent endocrine dysfunction in childbearing age women. PCOS is one of the most common causes of infertility in women, affecting about 9-10% of childbearing age women [3]. The exact cause of this syndrome is still unknown. According to Rotterdam diagnostic criteria, at least

two of the three menstrual irregularity, hyperandrogenism, and polycystic ovary morphology syndromes on ultrasound indicate PCOS [3]. Serum AMH levels in patients with PCOS are two to three times higher than in normal individuals due to increased small follicles [3,4]. Also, the granulosa cells of a patient with PCOS produce more AMH [5]. Studies have shown a significant positive relationship between ovarian sensitivity and AMH levels in healthy women, not seen in patients with PCOS [6,7]. Also, because patients with PCOS have high AMH levels, they may be resistant to ovarian stimulation with gonadotropins and appear to require higher therapeutic doses [6-8].

Measurement of serum AMH concentration before starting treatment may be used as a predictor of treatment success and determine the drug's starting dose[8]. The present study investigates the effect of AMH in PCOS patients and compares their pregnancy outcomes after ICSI.

Materials and Methods

This retrospective study was performed on 443 patients with PCOS referred to BAU MedicalparkGoztepe Hospital IVF Clinicfrom January 2015 to October 2020. The study was performed according to the guidelines of the Helsinki Declaration on human experimentation and was approved by the Local Ethics Committee.

Participants ranged in age from 18 to 40, had their first two trials, had performed frozen thawed embryo transfer (FET) cycle at day 5. The diagnosis of PCOS was made using the Rotterdam criteria. Data related to patients' AMH were compared with each other, and based on the value, participants were divided into two groups: the first group was AMH≥7 (N = 49); The second group was AMH <7 (N = 394). The cause of infertility in all participants was only PCOS, and there was no additional infertility cause among the participants. In all cases, the Intracytoplasmic sperm injection (ICSI) technique was used. People with hyperprolactinemia and thyroid dysfunction were excluded from the study.

GnRH-antagonist protocol was utilized for ovarian stimulation in all patients. Gonadotropin stimulation was started by applying recombinant follicle stimulating hormone (rFSH) (Gonal-F, Merck Pharmaceutical Group Inc, Turkey) and/or human menopausal gonadotrophin (hMG) (Merional, IBSA Pharmaceutical Group Inc.) as the initial dose on the second or third day of the menstrual cycle in all women. Serial vaginal ultrasonography was used to monitor ovarian response. In order to prevent premature luteinisation, 0.25 µg GnRH antagonist (Cetrotide 250µg, Merck Serono, Turkey) was added daily when the leading follicle reached a diameter of 14 mm. When the mean diameter of two or three leading follicles reached 17 mm or more, triptoreline acetate (Gonapeptyl 0.1mg/ml, Ferring, Turkey) was used to trigger ovulation. The oocyte pick-up was carried out after trigger success, at a minimum of 35 and a maximum of 36 hours after administration. All embryos of patients were cryopreserved at day 5. In preparation for FET, patients were started on estradiol valerate 2 mg tablet (Estrofem tablet, three times daily), roxithromycin 300 mg tablet (Rulid tablet, once daily), acetylsalicylic acid 100 mg tablet (Coraspin tablet, once daily), and folic acid 5 mg tablet (Folbiol tablet, once daily) on the second day of menstruation. Patients continued to receive these treatments until the 12th day of menstruation. Progesterone initiation was begun after detecting 8-mm endometrium thickness and observing the characteristic “triple line” pattern. Progesterone(progestan ampule 50mg, twice daily), was given through intramuscular applications to induce endometrial secretion to transfer the thawed embryo. As a rule of thumb, normal transfers were planned on the 18th or 19th days of the menstrual cycle, corresponding to 5 days of embryo development. Embryo transfers were performed under ultrasound guidance using a soft tip catheter (Cook Medical, USA) on the sixth day of progesterone administration. One or two blastocyst embryo transfer was performed at the stage of top quality or good quality embryos according to Gardner and Schoolcraft blastocyst grading system. Estradiol and progesterone supplementation were continued until the day of the pregnancy test, carried out 10 days after the embryo transfer. If the test was positive, estradiol and progesterone was maintained due to 10th gestational week.Clinical pregnancy was defined as ultrasound detecting the gestational sac after embryo transfer. Regardless of the menstrual cycle, serum levels of AMH were measured by enzyme-linked immunosorbent assay (ELISA) at ReproSource (Woburn, MA).

The results of the Kolmogorov-Smirnov test show that none of the quantitative variables have a normal distribution. The Mann-Whitney test is then used for further analysis. Chi-square test and Fisher's exact test are used to investigate the relationship between qualitative variables in the two groups. Statistics for categorical (qualitative) variables were presented as frequency and (n (%)), and for numerical (quantitative) variables as a minimum, maximum, mean, and standard deviation (mean ± sd). The data analysis was made with the SPSS 26 program, and a 95% confidence level was selected. $P < 0.5$ was considered statistically significant.

Results

Participants were divided into two groups based on AMH values: AMH under seven (AMH<7) and AMH seven and above (AMH≥7), with 394 in the first group and 49 in the second group. Among the participants, the minimum age was 19, and the maximum age was 39 years. The mean BMI of the participants was 25.6, with a standard deviation of 2.9. The minimum AMH of the participants was 3, and the maximum was 20 with a mean of 5.2 and a standard deviation of 2.2. The number of Stimulation days was a minimum of 7 and a maximum of 14. The mean total number of oocytes was 16.7 with a standard deviation of 8.3, and the mean number of MII oocytes was 13.04 with a standard deviation of 6.5. Descriptive statistics of these variables are given in Table 1.

Descriptive statistics of pregnancy-related variables are given in Table 2. The pregnancy outcome was positive for 288 (65%) participants. Of these participants, 214 gave livebirth, 71 had miscarriages, and 3 had stillbirths. 214 participants had one gestational sac, and 49 participants had two gestational sacs. Also,

219 participants had one fetal heart rate, while 44 participants had two fetal heart rates.

Table 1: Descriptive Statistics of Demographic variables.

Variable	N	Minimum	Maximum	Mean	Std.
Age	443	19	40	29.5	4.3
BMI	443	19	35	25.6	2.9
AMH	443	3	20	5.2	2.2
Duration of Stimulation	443	7	14	10.2	0.6
Total Number of Oocytes	443	3	40	16.7	8.3
Number MIIOocytes	443	2	36	13.04	6.5
Frozen embryo numbers	443	0	9	2.5	1.6

Table 2: Descriptive statistics of pregnancy-related variables.

Variables	Frequency	Percent
Pregnancy		
Negative	155	35.0
Positive	288	65.0
Pregnancy Result		
Live	214	48.3
Dead	3	.7
Misscariage	71	16.0
Negative	155	35.0
SAC		
0	180	40.6
1	214	48.3
2	49	11.1
FHR		
0	180	40.6
1	219	49.4
2	44	9.9

Table 3: Mann-Whitney test for quantitative variables.

	AMH<7 (N=394)	AMH≥7 (N=49)	*Z*	*p-value*
AGE	29.5 (4.4)	29.4 (3.4)	-0.018	0.9
BMI	25.6 (2.9)	25.5 (2.8)	-0.02	0.9
AMH	4.5 (0.7)	10.4 (3.1)	-11.7	0.000
Stimulation Duration	10.2 (0.5)	10.3 (1.1)	-1.8	0.06
Total Number of Oocytes	16.7 (8.5)	17.4 (7.02)	-0.7	0.4
Number of MII Oocytes	13.07 (6.7)	12.7 (5.1)	-0.14	0.8
Frozen embryo numbers	2.6 (1.6)	2.1 (1.9)	-2.8	0.005

The results of the Mann-Whitney test for quantitative variables of the two groups are given in Table 3. There was no significant difference in age and BMI between the two groups. There were no significant differences between the two groups in the number of stimulation days, the total number of oocytes, and MII oocytes. The numbers of frozen embryos were higher in the AMH≥7 group ($p = 0.005$).

Table 4 shows the Chi-square test and Fisher's exact test for qualitative variables. As the results show, the positive pregnancy results were significantly higher in the AMH<7 group than in the AMH≥ 7 group (P= 0.02). There was no difference between live birth, stillbirth, and miscarriages between the two groups. There was a significant difference between the number of sacs and fetal heart rate of the two groups (p= 0.02 and p= 0.04, respectively).

Table 4: Chi-square test and Fisher's exact test for qualitative variables.

	AMH≥7(N=49) Fequency (%)	AMH<7 Fequency (%)	P-value
PREGNANCY			0.02
NEGATIVE	24 (49)	131 (33.2)	
POSITIVE	25 (51)	263 (66.8)	
PREGNANCY_RESULT			0.1
Live	18 (36.7)	196 (49.7)	
stillbirth	0	3 (0.8)	
Miscarriage	7 (14.3)	64 (16.2)	
Negative	24 (49)	131 (33.2)	
SAC			0.02
0	28 (57.1)	153 (38.6)	
1	15 (30.6)	199 (50.5)	
2	6 (12.2)	43 (10.9)	
FHR			0.04
0	28 (57.1)	152 (38.6)	
1	17 (34.7)	202 (51.3)	
2	4 (8.2)	40 (10.2)	

Discussion

This study investigates the association between serum AMH levels in women with PCOS and their pregnancy outcome after ICSI. Pregnancy outcome isan essential clinical measure in choosing ARTtreatments, and the results of the present study showed that women with PCOS with higher serum AMH levels had poorer pregnancy outcomes than women with lower serum AMH levels.

In our retrospective study of women with PCOS who underwent ICSI, the clinical pregnancy rate (CPR) was significantly higher in the group with low AMH serum than in the group with high AMH serum. A similar trend was observed in the rate of live births and miscarriages; however, these differences were not significant. As far as we know, this study was unique in that it exclusively examined the effect of ICSI in PCOS patients with varying AMH levels. Other studies have examined AMH and ART outcomes in patients with PCOS, but none have examined ICSI exclusively [7,9,10]. Also, the results of these studies are contradictory in some cases. In some studies, there was a positive relationship between AMH levels and clinical pregnancy rate [7,9], and in others, there was an inverse relationship between AMH serum levels and clinical pregnancy rate [10]. The exact reason for these conflicting results is not clear, but the difference in the size of the sample population could be one of the reasons. Also, the age difference between the two AMH groups could be the reason for these differences observed in Kaya et al. [9]. Xi et al. [10], as in our study, found no age difference between the two AMH groups, and the result of this study is consistent with our findings, which could be a good explanation for the conflicting results between these studies.

AMH plays a role in regulating ovary folliculogenesis [11] and is known as one of the main features of PCOS severity [8]. The follicular arrest can lead to a two to fourfold increase in serum AMH levels, and it has been shown that AMH production by granulosa cells within the follicle increases severalfold [12,13]. Increased AMH reduces the FSH sensitivity of granulosa cells and causes follicular arrest [14]. Studies have also shown a positive correlation between AMH levels and hyperandrogenemia [3,7,15,16]. This condition can cause the accumulation of intraovarian androgens [17,18]. Because androgens play an important role in the early stages of follicular stimulation [19,20], they can increase AMH production in the ovaries. These mechanisms may play a role in the phenotypes of PCOS anovulation and hyperandrogenism. As studies have shown, hyperandrogenic phenotypes are associated with lower CPR and ivebirthrate(LBR) [21,22]. It has also been shown that an increase in androgens is associated with a decrease in oocyte quality and fertility rate [23]. In addition to androgens, luteinizing hormone (LH) is directly associated with elevated AMH levels in patients with PCOS [12]. These could be mechanisms associated with the follicular arrest directly related to reduced clinical pregnancy rates at high AMH levels.

The results of related studies may vary in the population of people without PCOS. A meta-analysis in 2015 showed that AMH was a poor marker of ART outcome in women without PCOS, while in patients with PCOS, AMH had a higher predictive power [9]. More recent studies have compared the direct effects of PCOS phenotypes and AMH levels on pregnancy outcomes through ART. In a study, AMH was a significant predictor of pregnancy outcomes in only one of the four PCOS phenotypes but not in other phenotypes and the general PCOS population [22]. Another study showed that hyperandrogenic phenotypes of PCOS have much lower LBR rates than other phenotypes [21]. Further studies on the types of PCOS phenotypes can more accurately determine the association between AMH and ART outcomes in patients with PCOS.

Limitations

The limitations of this study are its retrospective nature and the limitations of patient data to a single clinic. In future studies, it is suggested that PCOS phenotypes and AMH levels be examined separately.

Conclusion

In conclusion, this study found that patients with PCOS had a significantly higher clinical pregnancy rate in the lower AMH group than in the high AMH group. The results of this study indicate the potential benefit of AMH in PCOS patients beyond a basic diagnostic criterion in the treatment and selection of ART methods. PCOS is a heterogeneous and multifaceted disorder that requires further studies to examine its various phenotypes in ART outcomes and the effect of serum AMH levels on them. Such findings could help to develop better strategies to increase the chances of live birth in PCOS patients.

References

1. Gürbüz T, Gökmen O, Güngör ND. Polikistik over sendromu bulunan kadınlarda glikoz potasyum oranının tanısal değerinin insülin ile karşılaştırılması. Cukurova Medical Journal. 2021; 46: 381-386.
2. Homburg R, Crawford G. The role of AMH in anovulation associated withPCOS: a hypothesis. Human Reproduction. 2014; 29: 1117-1121.
3. Athanasia Piouka, Dimitrios Farmakiotis, Ilias Katsikis, et al. Anti-Mullerian hormone levels reflect severity of PCOS but are negatively influenced by obesity: relationship with increased luteinizing hormone levels. American Journal of Physiology-Endocrinology and Metabolism. 2009; 296: E238-E243.
4. Sezai Sahmay, Begum Aydogan Mathyk, Nigar Sofiyeva, et al. Serum AMH levels and insulin resistance in women with PCOS. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2018; 224: 159-164.
5. Henri Sova, Leila Unkila-Kallio, Aila Tiitinen, et al. Hormone profiling, including anti-Müllerian hormone (AMH), for the diagnosis of polycystic ovary syndrome (PCOS) and characterization of PCOS phenotypes. Gynecological Endocrinology. 2019; 35: 595-600.
6. Stracquadanio ML, Ciotta, Palumbo M. Relationship between serum anti-Mullerian hormone and intrafollicular AMH levels in PCOS women. Gynecological Endocrinology. 2018; 34: 223-228.
7. Reshef Tal, David B Seifer, Moisey Khanimov, et al. Characterization of women with elevated antimüllerian hormone levels (AMH): correlation of AMH with polycystic ovarian syndrome phenotypes and assisted reproductive technology outcomes. American journal of obstetrics and gynecology. 2014; 211: 59. e1-59. e8.
8. Christos Vosnakis, Neoklis A Georgopoulos, David Rousso, et al. Diet, physical exercise and Orlistat administration increase serum anti-Müllerian hormone (AMH) levels in women with polycystic ovary syndrome (PCOS). Gynecological Endocrinology. 2013; 29: 242-245.
9. Kaya C, Pabuccu R, Satıroglu H. Serum antimüllerian hormone concentrations on day 3 of the in vitro fertilization stimulation cycle are predictive of the fertilization, implantation, and pregnancy in polycystic ovary syndrome patients undergoing assisted reproduction. Fertility and sterility. 2010; 94: 2202-2207.
10. Xi W, Gong F, Lu G. Correlation of serum Anti-Müllerian hormone concentrations on day 3 of the in vitro fertilization stimulation cycle with assisted reproduction outcome in polycystic ovary syndrome patients. Journal of assisted reproduction and genetics. 2012; 29: 397-402.
11. Visser JA, Shreshtha Sagar, Amrita Chaurasia, et al. Anti-Mullerian hormone: a new marker for ovarian function. Reproduction. 2006; 131: 1-9.

12. Pellatt L, Laurine Hanna, Mark Brincat, et al. Granulosa cell production of anti-Mullerian hormone is increased in polycystic ovaries. The Journal of Clinical Endocrinology & Metabolism. 2007; 92: 240-245.
13. Pellatt L, Rice S, Mason HD. Anti-Müllerian hormone and polycystic ovary syndrome: a mountain too high? Reproduction. 2010; 139: 825-833.
14. Jonard S, Dewailly D. The follicular excess in polycystic ovaries, due to intra-ovarian hyperandrogenism, may be the main culprit for the follicular arrest. Human reproduction update. 2004; 10: 107-117.
15. Priya Bhide, Roy Homburg. Antimüllerian hormone and polycystic ovary syndrome. Fertility and sterility. 2011; 96: 230-235.
16. Pascal Pigny, Emilie Merlen, Yann Robert, et al. Elevated serum level of anti-mullerian hormone in patients with polycystic ovary syndrome: relationship to the ovarian follicle excess and to the follicular arrest. The Journal of Clinical Endocrinology & Metabolism. 2003; 88: 5957-5962.
17. Grossman MP, Steven T Nakajima, Mary E Fallat, et al. Müllerian-inhibiting substance inhibits cytochrome P450 aromatase activity in human granulosa lutein cell culture. Fertility and sterility. 2008; 89: 1364-1370.
18. Laura Pellatt, Suman Rice, Nafi Dilaver, et al. Anti-Müllerian hormone reduces follicle sensitivity to follicle-stimulating hormone in human granulosa cells. Fertility and sterility. 2011; 96: 1246-1251. e1.
19. Vendola KA, Zhou J, Adesanya OO, et al. Androgens stimulate early stages of follicular growth in the primate ovary. The Journal of clinical investigation. 1998; 101: 2622-2629.
20. Weil S, Vendola K, Zhou J, et al. Androgen and follicle-stimulating hormone interactions in primate ovarian follicle development. The Journal of Clinical Endocrinology & Metabolism. 1999; 84: 2951-2956.
21. Michel De Vos, Stéphanie Pareyn, and Panagiotis Drakopoulos, et al. Cumulative live birth rates after IVF in patients with polycystic ovaries: phenotype matters. Reproductive biomedicine online. 2018; 37: 163-171.
22. Ramezanali F, MahnazAshrafi, MandanaHemat, et al. Assisted reproductive outcomes in women with different polycystic ovary syndrome phenotypes: the predictive value of anti-Müllerian hormone. Reproductive biomedicine online. 2016; 32: 503-512.
23. Qiao J, Feng HL. Extra-and intra-ovarian factors in polycystic ovary syndrome: impact on oocyte maturation and embryo developmental competence. Human reproduction update. 2011; 17: 17-33.