

AMH, Induction Protocols, Age and Total Motile Sperm Count Do Not Affect the Success of Pregnancy in Intrauterine Insemination: A Single Center Retrospective Study

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Abstract

Objective: The objective of this study is to further examine the effects of basal anti-mullerian hormone (AMH), induction protocols used in Controlled Ovarian Stimulation (COS), age and total motile sperm count (TMSC) on the pregnancy rate obtained through Intrauterine Insemination (IUI).

Materials and Methods: 242 infertile couples were enrolled in our study and the factors affecting the pregnancy rate as a result of IUI treatment were examined retrospectively. The values corresponding to Basal AMH, the age of women, induction protocols used in COS and TMSC of patients who got pregnant and who did not were compared. For COS procedure, CC, Letrozole and additionally gonadotropin was applied in combination with the aforementioned drugs. 17 patients of 242 were inseminated during their natural menstrual cycle. The results are provided in percentages, standard deviation and mean values, furthermore the effects of the examined parameter (mentioned above) on the rate of pregnancy were measured by regression analysis. According to their qualifications, data obtained were compared in Independent T test and Pearson Chi-square test. If the P value is lower than 0,05, statistically it is accepted as significant.

Results: As a result of IUI treatment, in 44 out of 242 patient (18,2%), the pregnancy was obtained. When the mean values of Basal AMH are considered, there were no significant difference between the values for patients who got pregnant and who did not. (Mean \pm Standard Deviation for patients who got pregnant and who did not are respectively $2,14 \pm 0,93$ and $2,11 \pm 0,76$). There is also no significant difference in the mean values of AMH regarding pregnancy ($p = 0,924$). During the natural menstrual cycle ($n = 17$) and in the group treated with Letrozole ($n = 5$), no pregnancies were observed. The highest rate of pregnancy is observed in the groups treated with Letrozole + HMG (33,3%) and Letrozole + FSH (27,9%). Pregnancy rate is not dependent on the used drug. Between the age of 18-25 in women, the rate of pregnancy is the highest, (30,6%) with older age, the rate of pregnancy decreases. Pregnancy rates were not different in the age groups. In the washed semen used for IUI, the mean value for TMSC was 80,69 million/liter. TMSC value is not significant on the rate of pregnancy ($p = 0,635$).

Conclusion: The most important factor affecting pregnancy might be the age. Basal AMH and the type and combination of COS drugs and TMSC seem to make no significant difference in IUI treatment. As is IUI treatment is easy and compared to IVF cheaper, yet the field calls for new strategies and researches to increase pregnancy rates.

Keywords: IUI; AMH; COS; IVF

Introduction

Infertility is defined as inability to get pregnant after regular and unprotected sexual intercourse for one year or more and affects about one-tenth of married couples [1]. Intrauterine insemination (IUI) is the injection of semen from the spouse into the uterus of the infertile woman according to the estimated ovulation time after increasing the number and quality of the volume. This method is an inexpensive, easy and patient-friendly option. The rationality of the IUI is based on the combination of eggs and a large number of quality sperm at the fertilization site. Unexplained infertility, male subfertility, minimal-mild endometriosis, physical insufficiency or psychological problems because of the treatment of couples who cannot have sexual intercourse is widely used as a first-line treatment [2-5]. Anovulation occurs in 21% of infertile women. 4 - 7% of reproductive women have polycystic ovary syndrome (PCO) and these anovulatory women have difficulty in getting pregnant [6]. Regulation of ovulation with controlled ovarian stimulation (COS) increases the rate of conception [7].

Although widely used, the optimal treatment method for COS + IUI is still under discussion. The protocols used for COS are selected according to the age of infertile women, ovarian reserve, body mass index and response to previous treatment protocols. In this study, we retrospectively investigated the effects of drug protocols used for COS, basal (2 - 4 days of menstruation) Anti-Mullerian Hormone (AMH) value, age and post-wash total mobile sperm count on pregnancy rate in infertile couples decided to undergo COS + IUI.

Materials and Methods

242 infertile couples who applied to a private IVF center between 2018 - 2019 were included in our study. Patients who decided to undergo IUI were between 18 - 43 years old. Patient distribution for IUI; unexplained infertility (n = 125), polycystic ovary syndrome (n = 84), male subfertility (n = 4), vaginismus (n = 5), endometriosis (n = 2), and other reasons (n = 22). The other factors were consisted of IUI for recurrent pregnancy loss (n = 1), PCO + tubal factor (n = 5), poor response to IVF (n = 3), tubal factor (n = 5), age factor (n = 8) decision. The financial impossibility for IVF was effective in guiding the last group to the IUI. Medications used for COS include Clomiphene Citrate (CC), Letrozole, Recombinant Follicle Stimulant Hormone (FSH), Human Menopausal Gonadotropin (FSH + LH). According to the protocol, the drugs were administered alone or in combination. The dose and type of drugs were determined according to the patient.

COS method

COS treatment for IUI was started on the 2nd or 3rd day of menstruation. Letrozole was started on the second day of menstruation for PCOS and given 5 mg for 5 days. 75 - 150 U doses were added on day 5. In the unexplained infertility group, stimulation was started on the 2nd or 3rd day of menstrual period according to age, ovarian reserve and response to previous cycles, if any. 75 - 150U gonadotropin was chosen as the initial dose. HMG was preferred for patients with low ovarian reserve (LOR) and advanced age. Some patients who underwent IVF with an antagonist cycle returned to IUI due to poor response. Combined protocols were preferred to reduce cost and number of injections. When the leading follicle reached 18 - 20 mm, HCG was administered and 36 hours later IUI was performed with 1 ml of sperm solution prepared by gradient method.

Determination of pregnancy

Serum β -HCG was measured 12 days after insemination. Values above 10 mIU/mL were considered positive and called for follow-up every other day. In case of an increase in β -HCG, patients were called for ultrasonographic examination 10 days later.

Data were analyzed with IBM SPSS V23. Independent samples t-test was used to compare the data for normal distribution. All categorical data were analyzed by Pearson chi-square test. Independent logistic regression analysis was performed to determine the independent factors affecting pregnancy. Significance level was taken as $p < 0.05$. Informed consent was not obtained since the study is retrospective.

Results

Overall pregnancy rate was 18.2% (44/242) in patients who underwent IUI independent from the method. According to the current literature, basal AMH, age, type of drug used for COS, post-wash total motile sperm count, and pregnancy rates were correlated with pregnancy rates. We evaluated the results with questions and answers.

Do AMH values affect IUI pregnancy rates? For example, does the pregnancy rate increase in patients with AMH above 2.3?

	Mean (SD)	p
Non-pregnant	2,11 (0,76)	0,924
Pregnant	2,14 (0,93)	

Table 1: Comparison of AMH levels according to pregnancy status.

There was no difference between mean AMH values according to pregnancy status (p = 0.924). The mean value was found to be 2.11 in those without pregnancy and 2.14 in those with pregnancy.

	OR (%95 CI)	p
AMH (> 2,3)	0,579 (0,133 - 2,519)	0,466

Table 2: Logistic regression analysis of the effect of AMH on pregnancy.

The effect of AMH above 2.3 was not statistically significant (p = 0.466).

Which medication group used for COS in IUI result in a better pregnancy rate? Is there a difference in pregnancy rates in different drug protocols such as CC, letrozole, CC + FSH etc?

	Negative*	Positive*	p
CC	30 (88,2)	4 (11,8)	0,217
CC+FSH	27 (81,8)	6 (18,2)	
CC+FSH+LH	12 (85,7)	2 (14,3)	
Natural cycle	17 (100)	0 (0)	
Letrozole	5 (100)	0 (0)	
Letrozole + FSH	47 (72,3)	18 (27,9)	
Letrozole + FSH + LH	6 (66,7)	3 (33,3)	
FSH	33 (82,5)	7 (17,5)	
FSH+LH	21 (84)	4 (16)	

Table 3: The status of pregnancy according to medications.

*: n (%).

Conception was not dependent on the medication used ($p = 0.217$). The rate of conception was 11.8% in CC, 18.2% in CC + FSH, 14.3% in CC + FSH + LH, 27.9% in letrozole + FSH, 33.3% in letrozole + FSH + LH group 17.5% in FSH and 16% in FSH + LH group.

Which age group (18 - 25, 25 - 30, 30 - 35, 35 - 40, > 40 years) has the higher pregnancy rate is higher with IUI? Is conception dependent on age?

Age	Negative*	Positive*	p
18 - 25	34 (69,4)	15 (30,6)	0,150
25 - 30	69 (83,1)	14 (16,9)	
30 - 35	53 (86,9)	8 (13,1)	
35 - 40	30 (85,7)	5 (14,3)	
> 40	12 (85,7)	2 (14,3)	

Table 4: Status of pregnancy according to age groups.

*: n (%).

Conception was not dependent on age groups ($p = 0.150$). Pregnancy rate between 18 - 25 years is 30.6%, 16.9% among 25 - 30 years, 13.1% among 30 - 35, 14.3% among 35 - 40 and 14.3% among over 40 years old.

The analysis reveals whether pregnancy depends on age groups. According to the results, pregnancy is not dependent on age groups. In paired comparisons, there was no difference between the pregnancy rates of 18 - 25 and 25 - 30 age groups ($p = 0.082$). The 13.7% difference is not statistically significant. The confidence interval was calculated as (-0.0146784; 0.289574) and there is no significant difference in this range since it includes the value of 0. There is a 17.5% difference between the pregnancy rates of 30.6% and 13.1% and the p value of this difference is obtained as 0.034. The difference between them without making any correction is said to be statistically significant, but this decision is based on $p = 0.05$ and is incorrect. However, when the Bonferroni correction is applied, we divide the value of 0.05 into 10, which is the binary comparison number, and the new p value is obtained as 0.005. This now orders that all binary comparisons should be decided according to 0.005. Therefore, 0.034 value is not statistically significant compared to the new p value.

Does total motile sperm count (TMSC) affect pregnancy rate? [TMSC = sperm count (million) x motility (%)]

The mean total sperm count after the gradient was 87.54 million/ml, the average motility was 89.23%, and the total number of mobile sperm was 80.69 million/ml.

	OR (%95 CI)	p
TMSS	0,999 (0,993 - 1,004)	0,635

Table 5: The logistic regression analysis of the total motile sperm count effect on pregnancy.

TMSS value did not have a significant effect on pregnancy ($p = 0.635$).

Discussion

This retrospective cohort study showed that the use of medications used for the COS protocol alone or in combination in patients with IUI was not superior to each other in achieving pregnancy. In addition, baseline AMH, female age, TMSS, and IUI cycles did not make any difference in terms of pregnancy rates.

There is a great deal of information that AMH makes good predictions of pregnancy in assisted reproductive techniques [8,9]. Although AMH is widely used for the determination of ovarian reserve, it does not always provide accurate predictions due to variability in its measurement. Since the cut-off values of AMH vary according to age, age-specific AMH values were studied to predict ovarian response. Addition of age-specific AMH values to the IUI stimulation protocol had little effect on the results [10]. In our series, only 2019 AMH values of our patients were available and AMH values for the IUI outcome did not make a significant difference in these patients (Table 1). The mean AMH values between pregnant and non-pregnant were similar (2.14 ng/mL, 2.11 ng/mL, respectively). There is strong evidence that AMH is not a good predictor of pregnancy in COS + IUI patients. Several studies have been conducted on the cut-off value of AMH for the association with pregnancy rate in ART. In our study, we could not show the relation of pregnancy rate for this cut-off value of AMH by regression analysis (Table 2). Treatment with COS + IUI results in a two-folds higher pregnancy rate than those with only IUI [11].

A meta-analysis has shown that superovulation with gonadotropins + IUI has a pregnancy rate of approximately 2 times higher than that of timed coitus [12]. The effectiveness of COS drug protocol is very important for in IUI. Of course, the drug to be selected should be individualized and the target should be achieved by making the necessary adjustments according to the patient response. The ovarian stimulation strategy for IUI is a very valuable method for achieving maximum pregnancy rates, especially in patients with irregular or anovulatory patients where ovulation is unpredictable. Patient-friendly drug protocols have been developed for COS in less time and in less expensive ways. The addition of gonadotropins to CC or Letrozole for COS saves time and costs. Ideally, to demonstrate that a COS protocol is better in a particular group of patients, the results should be compared with COS with different drugs in the same patient, but in practice it is difficult to do so. Our study shows that drug protocols for COS do not provide superiority in terms of pregnancy rates in patients with IUI decision. According to the success rates given in the literature for IUI (7 - 20%), we can say that the COS protocols initiated by considering the patient's characteristics are optimal because of our success rate close to the upper limit [13]. However, it is seen that one of the COS protocols applied for IUI is not superior to the other (Table 3). The fact that no pregnancy can be achieved in the natural cycle and Letrozole group may be related to the low number of patients.

There are conflicting reports on whether maternal age has an effect on pregnancy rates in the treatment of infertile couples with assisted reproductive techniques. Some authors report that age has no effect on pregnancy rates [14], while others have emphasized that age is a good predictor of IUI success [15,16]. Our study showed that pregnancy rates in IUI treatment decreased significantly with age, but did not show a statistical significance (Table 4). Overall pregnancy rate is significantly lower in advanced age group.

A Cochrane review published this year compared sperm preparation techniques for IUI. Gradient, swim-up, centrifuge and simple washing techniques did not make any difference in terms of pregnancy rates; however, there is no strong evidence that it is superior to each other according to clinical pregnancy and ongoing pregnancy criteria. The live birth rate of these techniques has not been reported [17]. The mean TMSC value in our IUI patients is 80.69 million/ml. TMSC was not found to be effective on pregnancy rates.

Limitation of the Study

The limitation of this study may be differences that do not reach statistical significance due to the small sample size. Because of the heterogeneous patient group, the effectiveness of the parameters examined may be less than expected.

Conclusion

Pregnancy rates decrease significantly in COS + IUI treatment with age, but there is no statistically significant difference between age groups. Basal AMH, COS protocols, and post-wash TMSC did not make a significant difference in pregnancy rates. Medications used for basal AMH, COS in IUI may be more effective in collecting eggs, but it can be said that it does not change the pregnancy rate.

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