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Live Birth Rate following Intrauterine Insemination in Women with Low or Very Low Level of Serum Anti-müllerian Hormone

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Abstract

Background: While anti-Müllerian hormone (AMH) level allows quantitative evaluation of ovarian reserve, its predictive value for live births following assisted reproductive technology cycles has remained controversial. The aim of the present study was to assess the importance of AMH in predicting live birth following intrauterine insemination (IUI) in the case of low or very low ovarian reserve.

Methods: In this retrospective cohort study, 123 patients with AMH≤1 ng/ml, who underwent a total of 137 IUI cycles were enrolled and evaluated for live birth rate. Patients were divided into two groups based on serum AMH levels: group 1 with low level of AMH (0.4-1 ng/ml, n=83, cycles: 95) and group 2 with very low level of AMH (≤0.4 ng/ml, n=40, cycles: 42). The results were compared between the two groups. Main outcome was the pregnancy rate.

Results: The rates of biochemical pregnancy, clinical pregnancy and live birth in all patients were 11%, 8% and 7.3%, respectively. The two groups showed no significant difference in the rates of biochemical pregnancy (10.4% vs. 14.3%, p=0.3), clinical pregnancy (6.3% vs. 11.9%, p=0.2) and live birth (6.3% vs. 9.8%, p=0.5). In univariate regression analysis, baseline characteristics and ovarian stimulation parameters showed no significant relationship with the rates of pregnancy and live birth.

Conclusion: In women with AMH≤1 ng/ml, serum levels of AMH did not appear to reflect pregnancy outcomes and live births following IUI. It can be concluded that in women with low or very low levels of AMH, there is chance of pregnancy, and live birth following IUI.

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Introduction

Nowadays, the age of marriage and childbearing seems to have been increasing. On the other hand, there is a decline in fertility with aging which is a reflection of the diminished ovarian reserve. In recent years, anti-Müllerian hormone (AMH), a glycoprotein secreted from granulosa cells of small follicles in the ovary, has been particularly important in identifying ovarian reserve (1). In assisted reproductive technology (ART), this hormone is able to detect ovarian reserve and predict ovarian response to hormone stimulation (2). However, there is no consensus on the ability of this marker to predict live birth (3, 4). Various studies have shown different thresholds for low and very low AMH levels and their association with reduced chance of pregnancy (5, 6).

It is challenging to offer the type of ART procedure to patients with low ovarian reserve and there are few studies on live birth rates in women with very low AMH following IVF/ ICSI cycles suggesting acceptable pregnancy rates (7-10). However, there are controversies regarding the ability of the serum level of AMH to predict IUI results. While some studies showed no significant association between pregnancy and serum AMH values, others indicated such association (4,11, 12). To the best of our knowledge, no study has specifically examined pregnancy outcomes following IUI in individuals with serum AMH≤1ng/ml level. The aim of the present study was to evaluate live birth rate in women with low AMH (0.4-1) or very low AMH (≤0.4) following IUI treatment.

Materials and Methods

Study design

This retrospective cohort study was designed to evaluate intrauterine insemination (IUI) outcomes in women with low ovarian reserve. For this, the medical records of women undergoing IUI cycles at Mehr Medical Institute (Rasht, Iran) from September 2016 to March 2017 were investigated. Based on previous studies, AMH levels between 0.4-1 and ≤0.4 ng/ml were considered as low and very low levels of AMH respectively (9).

AMH measurements

Before the start of the ovarian stimulation cycle, blood samples were collected on the third day of menstruation and serum was separated and frozen in aliquots at -22ºC for future analysis with measurement being performed by enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions (Beckman Coulter, France). The intra-assay and inter-assay coefficient of variants were 5% and 7.4% respectively.

IUI protocol

Clomiphene citrate (50 mg, Iran Hormone, Iran) and letrozole (2.5 mg, Iran Hormone, Iran) were given for 5 days from day 3 of the menstrual cycle. Recombinant FSH (CinnaGen, Iran) or human menopausal gonadotropin (Menotropin, pharmatech GmbH, Germany) was administered daily from day 8 of the cycle until the day of hCG injection. Ovarian follicle status was assessed using ultrasonography.

After observing at least one follicle ≥20 mm, hCG (5000 IU, Darou Pakhsh, Iran) was administered, and IUI was performed 36 to 40 hours later. Endometrial thickness was measured on the day of hCG administration. Luteal phase support was achieved using 400 mg/day vaginal progesterone (Fertigest, Abureihan, Iran).

Serum β-human chorionic gonadotropin (βhCG) was assessed 18 days after the insemination. A biochemical pregnancy was defined as βhCG concentration>25 mIU/ml. A clinical pregnancy was defined as the presence of gestational sac with fetal cardiac activity, two weeks after a positive βhCG

test. If clinical pregnancy continued after 12 weeks, ongoing pregnancy was considered. The birth of at least one live baby was considered a live birth.

Statistical analysis:

All analyses were performed using the Statistical Package for Social Sciences software version 21 (SPSS Inc., Chicago, IL, USA). Categorical variables were expressed as percentages and continuous variables were expressed as means ± SD or as medians and ranges. Comparison of variables was performed with Chi-square test for categorical variables or Mann-Whitney test and student t-test for continuous variables with non-normal and normal distribution respectively. Regression test was used to evaluate the relationship of baseline characteristics and ovarian stimulation factors with pregnancy and live birth rates. All tests were two-sided with P values less than 0.05 being considered as statistically significant.

Results

Patient-related characteristics have been presented in Table 1. A total of 1588 IUI cycles were evaluated, of which 143 cycles (9%) with an AMH level of ≤1 ng/ml were identified. Six cycles were excluded for the following reasons: inappropriate sperm sampling on IUI day (n = 2), conversion of IUI cycle to ICSI due to high number of follicles and patient's consent to ICSI (n = 2) and no follow up response (n=2). A total of 123 patients undergoing 137 IUI cycles were included in the present study.

Patient's mean age was 34.78 ± 5.5 years and mean of AMH level was 0.6±0.3 ng/ml. Biochemical pregnancy, clinical pregnancy and live birth rates were respectively 11%, 8% and 7.3%. The women were divided into two groups according to their AMH levels including 40 patients (42 cycles) with extremely low AMH levels (≤0.4 ng/ml) and 83 patients (95 cycles) with low AMH levels (0.4–1.0 ng/ml). Table 1 summarizes patients' demographic characteristics in the two groups. There were no significant differences with regards to the patient's age at first cycle, type of infertility, etiology of infertility and total gonadotropin dosage.

Table 1. The baseline and ovarian stimulation characteristics in the two studied groups

	Extremely low serum AMH level (≤0.4ng/ml)(n=40)	low serum AMH level (0.4-1 ng/ml) (n=83)	P value
Number of cycles	42	95	
Age (year)	35.5±6.4	34.5±5	0.4
FSH (mIU/ml)	7.8±5.1	6.9±3.1	0.3
Duration of infertility (year)	2.2±1.5	3.8±2.9	0.002
Type of infertility (%)			
Primary	19 (51.4%)	52 (58.4%)	0.6
Secondary	18 (48.6%)	37 (41.6%)	
Total gonadotropin dosage (IU)	614.3±383.2	628.4±230.8	0.2
No of follicles ≥14mm	2.1±0.8	2.3±0.9	0.17
Endometrial thickness (mm)	7.6±1.5	8.3±1.6	0.01

Duration of infertility (p=0.002) and endometrial thickness (p=0.01) were significantly different between the two groups. Differences in the rates of biochemical pregnancy (p = 0.3), clinical pregnancy (p = 0.2) and live birth (p = 0.5) were not statistically significant between the two groups of very low and low AMH levels (Table 2). Following univariate regression analysis, none of the baseline and ovarian stimulation variants showed significant relationship with pregnancy rate and live birth rate (P <0.2).

Table 2. Pregnancy outcome in the two studied groups

Outcome / Group	All patients	Extremely low serum AMH level (≤0.4ng/ml)	Low serumAMH level (0.4-1 ng/ml)	P value
Chemical pregnancy per cycle (%)	15/137(11)	6/42 (14.3)	9/95 (10.4)	0.3
Clinical pregnancy per cycle (%)	11/137(8)	5/42 (11.9)	6/95 (6.3)	0.2
Live birth per cycle (%)	10/137(7.3)	4/41 (9.8)	6/95 (6.3)	0.5

Discussion

The present study did not demonstrate the importance of serum AMH levels for prediction of live births in women with low or very low ovarian reserve. No differences in pregnancy and live births rates were found between women with very low (≤ 0.4 ng/ml) and low AMH (0.4-1 ng / ml) level. Women with very low AMH had a live birth rate of 9.5%. Two cases of pregnancy showed undetectable serum AMH level. Therefore, it seems that one with low or very low levels of AMH does not necessarily have low-quality oocytes and is likely to have a live birth following IUI. Various studies have also suggested that serum AMH levels may not reflect the quality of the oocytes or predict the success rate following ICSI/IVF cycles (13, 14).

Studies that have specifically examined the chance of pregnancy in women with low or very low levels of AMH following IVF/ICSI cycles show inconsistent results. In a retrospective cohort study on 156 women with low or very low levels of AMH, the rate of live births in women with AMH≤ 0.4 ng/ml was significantly lower compared to women with AMH= 0.4-1 ng/ml (9). By contrast, in another study on 181 women with AMH≤1 ng/ml undergoing 769 IVF/ICSI cycles, patients with very low AMH levels had similar and acceptable pregnancy rates compared to those with low AMH levels and it has been concluded that AMH should not be a criterion for excluding patients from repeated IVF cycles (8). Similarly, Weghofer *et al.* showed that low level of AMH was not a suitable criterion for excluding the patient from the treatment process (7).

In another study, the pregnancy rate and time to pregnancy following timed coitus with or without superovulation were evaluated in young women under 35 years with low AMH level (<25th percentile) and it was shown that this method was highly effective in this group of patients; however, for women with longer infertility or very low levels of AMH, more advanced therapies should be considered (15).

There are different opinions regarding the ability of the serum level of AMH to predict IUI results. Tremellen & Kolo assessed if AMH, as an ovarian reserve marker, is associated with a chance of live birth and miscarriage following IUI and found that AMH was strongly correlated with AFC and was

therefore a good measure of ovarian reserve. On the other hand, there was no significant difference in the rates of live birth and abortion in the four AMH quartile groups. Thus, it was concluded that AMH was not an appropriate measure of ovarian reserve quality (4). A study by Freiesleben *et al.* showed that there were no significant difference in median value of AMH between pregnant and non-pregnant women following IUI (11). Contrary to these studies, in a study by Li *et al.* on the role of AMH levels in predicting live birth after IUI, women with live birth had significantly higher AMH levels than women with IUI failure (12). In Wang *et al.* study, low levels of AMH were associated with a decreased chance of clinical pregnancy following IUI (16). As far as we know, no study has specifically examined pregnancy outcomes following IUI in individuals with an AMH≤ 1ng/ml level. In Tremellen & Kolo study, live birth rate for the first quartile of AMH was estimated to be 9.6% at a mean AMH of 3±2 ng/ml (4). In our study, with a mean AMH level of 0.6±0.3 ng/ml, the live birth rate was 7%.

In women with AMH≤1 ng/ml, serum levels of AMH do not appear to be capable of predicting live births following IUI. In our study, univariate regression analysis did not show significant association of AMH and ovarian stimulation factors with pregnancy and live birth rates.

The more challenging question is whether the proposed IUI method is relevant to these patients in the first step. Should these patients be removed from the IUI list or can the patient be given the opportunity to test this method? Given the facts that IUI method seems to be less invasive, less expensive with low dose of gonadotropin, it seems that women with very low level of AMH can also benefit from IUI. However, many factors need to be taken into consideration and careful consultation with the patient is required before any decisions can be made.

References

1. La Marca A, Sighinolfi G, Radi D, Argento C, Baraldi E, Artenisio AC, et al. Anti-Müllerian hormone (AMH) as a predictive marker in assisted reproductive technology (ART). Hum Reprod Update 2010; 16(2):113-30.
2. Nardo LG, Gelbaya TA, Wilkinson H, Roberts SA, Yates A, Pemberton P, et al. Circulating basal anti-Müllerian hormone levels as predictor of ovarian response in women undergoing ovarian stimulation for in vitro fertilization. Fertil Steril 2009; 92(5):1586-93.
3. Riggs R, Kimble T, Oehninger S, Bocca S, Zhao Y, Leader B, et al. Anti-Müllerian hormone serum levels predict response to controlled ovarian hyperstimulation but not embryo quality or pregnancy outcome in oocyte donation. Fertil Steril 2011; 95(1):410-2.
4. Tremellen K, Kolo M. Serum anti-Mullerian hormone is a useful measure of quantitative ovarian reserve but does not predict the chances of live-birth pregnancy. Aust N Z J Obstet Gynaecol 2010; 50(6):568-72.
5. La Marca A, Giulini S, Tirelli A, Bertucci E, Marsella T, Xella S, et al. Anti-Müllerian hormone measurement on any day of the menstrual cycle strongly predicts ovarian response in assisted reproductive technology. Hum Reprod 2006; 22(3):766-71.
6. Gleicher N, Weghofer A, Barad DH. Anti-Müllerian hormone (AMH) defines, independent of

age, low versus good live-birth chances in women with severely diminished ovarian reserve. Fertil Steril 2010; 94(7):2824-7.

7. Weghofer A, Dietrich W, Barad DH, Gleicher N. Live birth chances in women with extremely low-serum anti-Mullerian hormone levels. Hum Reprod 2011; 26(7):1905-9.

8. Kedem A, Haas J, Geva LL, Yerushalmi G, Gilboa Y, Kanety H, et al. Ongoing pregnancy rates in women with low and extremely low AMH levels. A multivariate analysis of 769 cycles. PLoS One 2013; 8(12):e81629.

9. Reijnders IF, Nelen WL, IntHout J, van Herwaarden AE, Braat DD, Fleischer K. The value of Anti-Müllerian hormone in low and extremely low ovarian reserve in relation to live birth after in vitro fertilization. Eur J Obstet Gynecol Reprod Biol 2016; 200:45-50.

10. Łukaszuk K, Kunicki M, Liss J, Bednarowska A, Jakiel G. Probability of live birth in women with extremely low anti-Müllerian hormone concentrations. Reprod Biomed Online 2014; 28(1):64-9.

11. Freiesleben N, Rosendahl M, Johannsen TH, Løssl K, Loft A, Bangsbøll S, et al. Prospective investigation of serum anti-Müllerian hormone concentration in ovulatory intrauterine insemination patients: a preliminary study. Reprod Biomed Online 2010; 20(5):582-7.

12. Li HW, Yeung WS, Lau EY, Ho PC, Ng EH. Evaluating the performance of serum antimullerian hormone concentration in predicting the live birth rate of controlled ovarian stimulation and intrauterine insemination. Fertil Steril 2010; 94(6):2177-81.

13. Lie Fong S, Baart EB, Martini E, Schipper I, Visser JA, Themmen AP, et al. Anti-Müllerian hormone: a marker for oocyte quantity, oocyte quality and embryo quality? Reprod Biomed Online 2008; 16(5):664-70.

14. Smeenk JM, Sweep FC, Zielhuis GA, Kremer JA, Thomas CM, Braat DD. Antimüllerian hormone predicts ovarian responsiveness, but not embryo quality or pregnancy, after in vitro fertilization or intracyoplasmic sperm injection. Fertil Steril 2007; 87(1):223-6.

15. Koo HS, Song IO, Cha SH, Park CW, Kim HO. The likelihood of achieving pregnancy through timed coitus in young infertile women with decreased ovarian reserve. Clin Exp Reprod Med 2018; 45(1):31-7.

16. Wang MH, Chen CH, Wang CW, Hsu MI, Tzeng CR. A higher anti-Müllerian hormone level is associated with an increased chance of pregnancy in patients undergoing controlled ovarian stimulation and intrauterine insemination. J Obstet Gynaecol 2015; 35(1):64-8.